Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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Safety and Activity of Anti-PD-L1 (BMS-936559) in Patients With Advanced Solid Tumors

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Protocol Amendment 1 36 pages	Clinical Protocol MDX1105-01 Amendment 1 Summary of Change A Phase 1, Open-label, Multicenter, Dose-escalation Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors	September 5, 2008	**77**
Protocol Amendment 2 38 pages	Clinical Protocol MDX1105-01 Amendment 2 Summary of Change A Phase 1, Open-label, Multicenter, Dose-escalation Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors	August 18, 2009	**113**
Protocol Amendment 3 2 pages	Clinical Protocol MDX1105-01 Amendment 3 Summary of Change A Phase 1, Open-label, Multicenter, Dose-escalation Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors	October 2, 2009	**151**

Protocol Amendment 4 8 pages	Protocol CA210001 (MDX1105-01): A Phase 1, Open-Label, Multicenter, Dose-Escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors Amendment 4	March 2, 2010	**153**
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Protocol Amendment 7 6 pages	Protocol CA210001 (MDX1105-01): A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors Amendment 7	September 21, 2011	**173**
Protocol Amendment 8 5 pages	Protocol CA210001(MDX1105-01): A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors Amendment 8	March 14, 2012	**179**
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Rev Protocol 5 107 pages	Clinical Protocol CA210001 (MDX1105-01) A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors Revised Protocol 5	June 16, 2010	**545**
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Clinical Protocol MDX1105-01

A Phase 1, Open-label, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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SYNOPSIS

TITLE

A Phase 1, Open-label, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

MDX1105-01

OBJECTIVES

The primary objective is to determine the safety profile of MDX-1105, the maximum tolerated dose (MTD), and the dose-limiting toxicity (DLT) of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

The secondary objectives are to: 1) evaluate preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) characterize the immunogenicity of MDX-1105; and 3) characterize the preliminary multidose pharmacokinetic (PK) profile of MDX-1105.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], or epithelial ovarian cancer [epOC]) will be enrolled in the study.

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Five dose levels are planned and include: 0.3, 1, 3, 10, and 15 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 0.3 mg/kg/dose administered as an intravenous (i.v.) infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's dosing in the previous cohort. One subject will be enrolled in each cohort until 1 subject experiences a ≥ Grade 2 drug-related adverse event, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 3 or 6 subjects. This lower dose level will be considered the MTD if ≤ 1 in 6 subjects has a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced.

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT, enrollment will be stopped and the data will be reviewed by the Medarex Medical Monitor before any subject continues in the study.

A DLT is defined as a ≥ Grade 3 drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are drug-related adverse events that occur after Cycle 1. *Delayed DLTs will not be used to determine the MTD for dose escalation.* Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval.

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle). Subjects with initial progressive disease (PD) based on sum of the longest diameter (SLD) or development of new lesions at the end of a cycle, but with otherwise stable or improved performance and clinical status, will continue to be treated with study drug for 1 additional cycle. At the next scheduled imaging evaluation, if there is further increase in the SLD, or development of additional new lesions, then PD has been confirmed and the subject will stop treatment and complete the off-treatment procedures. If the SLD remains the same or decreased and no additional new lesions develop and the subject is otherwise stable or improved in performance and clinical status, then PD has not been confirmed and the subject will continue to be treated with study drug for 1 additional cycle until the next scheduled imaging evaluation.

In the absence of confirmed disease progression, subjects who discontinue MDX-1105 treatment should continue in the study until at least 70 days following the last dose of MDX-1105 or the next scheduled visit has been performed which ever is longer. Subjects who discontinue MDX-1105 because of a treatment-related adverse event will remain in the study and continue to be followed until 70 days following the last dose of MDX-1105 or until stabilization or resolution of the event, whichever is longer. Subjects who discontinue MDX-1105 administration due to an adverse event and who have a demonstrated complete response (CR), partial response (PR), or stable disease (SD) will remain in the study and be followed every 3 months for up to 6 months until relapse, confirmed disease progression, or initiation of new therapy, whichever occurs first.

Subjects who achieve a confirmed CR will not receive further cycles of MDX-1105 and will be followed every 3 months for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects with a response of PR/SD will continue to receive MDX-1105 treatment until achievement of a confirmed CR, confirmed disease progression, development of a ≥ Grade 3 CTCAE, or intolerability to therapy. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but should be given no later than 21 days. No subject will be permitted dose escalations or de-escalations. The maximum duration of study drug treatment for a subject is 2 years. Those subjects who continue to receive clinical benefit after 2 years of therapy (subjects with CR, PR, or SD) will be followed every 3 months from the last day they received study drug for 6 months until relapse, confirmed disease progression, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. The maximum total study participation duration for a subject is 2.5 years.

STUDY POPULATION

Up to 40 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors, of one of the following pathological documented types: RCC, NSCLC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

MDX-1105 will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 17 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, 10, and 15 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, flow cytometry, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety and immunogenicity. Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other immune-related adverse events (irAEs). Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

An irAE is a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serological and immunological data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

EFFICACY EVALUATIONS

The efficacy endpoint is the best observed response rate (BORR) as determined by the Investigator timepoint tumor evaluations. Tumor response status will be assessed using RECIST with modifications.

Independent confirmation of responses may be requested at the discretion of the Sponsor, Medarex.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

For Cycle 1, Day 1, serum concentrations of MDX-1105 will be assessed pre-dose within 30 minutes before and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. For Days 2, 3, 4, 8, and 42, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 17, samples will be drawn every 14 days before and immediately after the infusion is completed. The samples will be collected within 30 minutes before each MDX-1105 infusion and immediately after the infusion is completed. For the Off Study Visit, a single sample will be drawn.

Post-infusion samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on the days of infusion.

STATISTICAL METHODS

The sample size for this study is not determined from power analysis. A total of up to 40 subjects with measurable advanced or recurrent solid tumors are enrolled in this study, based on the ATD for dose escalation and safety evaluation requirements.

Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.

The efficacy parameter, the BORR, will be summarized using descriptive statistics. All safety and pharmacokinetic parameters will be summarized using descriptive statistics.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BORR	Best observed response rate
CMV	Cytomegalovirus
CR	Confirmed response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
HuMAb	Human monoclonal antibody
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NSCLC	Non-small cell lung cancer
epOC	Epithelial ovarian cancer
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PK	Pharmacokinetic
PPD	Purified protein derivative
PR	Partial response

Abbreviation	Term
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RENCA	Mouse renal cell carcinoma
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Off Study[1]
		Cycle 1 (±1 Day)								
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	
Visit	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**	**9**	**10**	**11**	
Informed Consent/HIPAA[3]	•									
Inclusion/exclusion criteria	•									
Demographics/medical history[4]	•									
Baseline signs and symptoms	•[5]									
Pregnancy test[6]	•	•			•		•			•
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•[8]
Vital signs[9]	•	•		•	•	•	•	•	•	•
ECOG performance status	•	•[10]		•	•[10]	•	•[10]	•	•	•
Physical examination[11]	•	•		•	•	•	•	•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[12]	•[13]								•	•[14]
Bone scan (if clinically indicated)[15]	•[13]								•	•[16]
ECG (12-lead)	•[13]								•	•
Hematology	•	•[17]		•[17]	•[17]	•[17]	•[17]	•[17]	•[17]	•
Serum chemistries	•	•[17]		•[17]	•[17]	•[17]	•[17]	•[17]	•[17]	•
Immune safety assays[18]	•								•	•
Tumor or other biopsy	•[19]									
Hepatitis B and C testing	•									
Urinalysis	•	•		•	•	•	•	•	•	•
Flow cytometry[20]	•								•	•

continued

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Off Study[1]
		Cycle 1 (±1 Day)								
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42**[2]	
Visit	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**	**9**	**10**	**11**	
PBMC (cryopreserved)		•[21]								•
Serum sample for immunogenicity		•[22]							•	•
MDX-1105 infusion		•			•		•			
Concomitant medications	•	•	•	•	•	•	•	•	•	•
Adverse events		•	•	•	•	•	•	•	•	•

TABLE 1 FOOTNOTES:

1. Off-Study evaluations are to be performed at the time of completion or early withdrawal from the study.
2. To be done within Days 38 to 42. Evaluations will be used to determine whether to initiate a new cycle of treatment.
3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of all study treatment and procedures. May be signed before Day -28.
4. To include collection of prior medication and prior/concurrent medical conditions.
5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).
6. Serum β-HCG pregnancy test within 7 days before the first infusion and urine pregnancy test at all other indicated timepoints before infusion and at the Off-Study Visit for women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.
8. A single serum sample for pharmacokinetic sampling will be drawn during the Off-Study Period.

(continued)

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TABLE 1 FOOTNOTES: *(continued)*

9. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and/or the subject is stabilized.
10. ECOG Performance Status to be assessed before each infusion.
11. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. Height will be measured at Screening only. Weight to be taken at the Screening Visit and only before each initial infusion of each cycle (Note: Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).
12. Tumor Imaging (CT/MRI of chest/abdomen/pelvis required). The same technique (CT/MRI) used at baseline should be utilized throughout the study.
13. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
14. To be performed if not done within the preceding 28 days.
15. Bone scan will be repeated every other cycle (end of Cycle 2, 4, 6, etc.) if positive at baseline. If positive at baseline the bone scan must be performed to confirm CR or PR. Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
16. To be performed if clinically indicated.
17. During the study Treatment Period, hematology and serum chemistry results will be evaluated by both local and central laboratories. The results of hematology and clinical chemistry **must be reviewed before dosing.** Local labs may be drawn up to 48 hours before infusion to meet this requirement.
18. Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, C-Reactive Protein (CRP), Antinuclear Antibody (ANA) titer and pattern. The following tests, may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50. To be collected at Screening, end of Cycle 1, and at the Off-Study Visit.

(continued)

TABLE 1 FOOTNOTES: *(continued)*

19. Optional tumor or other (e.g., inflamed tissue) biopsies (requiring additional consent and targeting anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the study as clinically indicated. Optional tumor biopsy for research purposes requires a separate consent. Immunohistochemistry (IHC) for PD-L1 expression may be done on tumor samples collected during or before this study.

20. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD19, CD20, CD56 [NK]).

21. Sample collected prior to study drug administration.

22. Serum sample for immunogenicity evaluation will be collected within 30 minutes before infusion.

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Table 2: Time and Events Schedule for Cycles 2-17

Examination	Treatment Period				Off Study[1]	Complete Response F/U[2] Continued Clinical Benefit F/U[3]
	Cycles 2-17 (±1 Day)					
Timepoint (Day)	**1**[4]	**15**	**29**	**42**[5]		
Urine pregnancy test[6]	•	•	•		•	
Serum sample for pharmacokinetics[7]	•	•	•		•[8]	
Vital signs[9]	•	•	•	•	•	•
ECOG performance status	•	•[10]	•	•	•	•
Physical examination[11]	•	•	•	•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[12]				•	•[13]	•
Bone scan (if clinically indicated)[14]				•	•	•[15]
ECG (12-lead)				•	•	
Hematology		•[16]	•	•	•	•
Serum chemistries		•	•	•	•	•
Immune safety assays[17]				•	•	
Tumor or other biopsy[18]						
Urinalysis		•	•	•	•	•
PBMC (cryopreserved)	•[19]				•	
Flow cytometry[20]				•	•	
Serum sample for immunogenicity				•	•	
MDX-1105 infusion	•	•	•			
Concomitant medications	•	•	•	•	•	•
Adverse events	•	•	•		•	•

Footnotes can be found on the following page.

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Table 2 Footnotes:

1. Off-Study evaluations are to be performed at the time of completion or early withdrawal from the study.
2. For subjects who achieve a confirmed CR and stop therapy, follow-up will be every 3 months for 6 months until relapse, initiation of new therapy, or a total of 6 months follow-up, whichever occurs first. Evaluations will be performed at each visit.
3. For those subjects who continue to have clinical benefit (CR, PR, SD) after 2 years of therapy, follow up will be every 3 months for 6 months until documented progression/relapse (PD), initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Evaluations will be performed at each visit. Subjects who discontinue MDX-1105 administration due to an adverse event and who have a demonstrated complete response (CR), partial response (PR), or stable disease (SD) will remain in the study and be followed every 3 months for up to 6 months until disease progression or initiation of new therapy, whichever occurs first.
4. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. Day 1 of each new cycle will have only the pregnancy testing and study drug infusion.
5. To be done within Days 38 to 42.
6. For women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.
8. A single serum sample for pharmacokinetic sampling will be drawn during the Off-Study Period.
9. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and/or the subject is stabilized.
10. ECOG Performance Status to be assessed before each infusion.
11. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. Weight to be taken only before each initial infusion of each cycle (**Note:** Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).

(continued)

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Table 2 Footnotes *(continued)*

12. Tumor Imaging (CT/MRI of chest/abdomen/pelvis required). The same technique (CT/MRI) used at baseline should be utilized throughout the study.
13. To be performed if not done within the preceding 28 days.
14. Bone scan will be repeated every other cycle (end of Cycle 2, 4, 6, etc.) if positive at baseline. If positive at baseline, the bone scan must be performed to confirm CR or PR.
15. To be performed if clinically indicated and if not done within the preceding 28 days.
16. During the study Treatment Period, hematology and serum chemistries will be evaluated by both local and central laboratories. The results of hematology and clinical chemistry **must be reviewed before dosing.** Local labs may be drawn up to 48 hours before infusion to meet this requirement.
17. Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, C-Reactive Protein (CRP), Antinuclear Antibody (ANA) titer and pattern. The following tests, may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50. To be collected at the end of each cycle and at the Off-Study Visit.
18. Optional tumor or other (e.g., inflamed tissue) biopsies (requiring additional consent and targeting anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor biopsy for research purposes requires a separate consent. IHC for PD-L1 expression may be done on tumor samples collected during or before this study.
19. Sample collected for Cycles 2 and 3 only, prior to study drug administration.
20. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD19, CD20, CD56 [NK]).

Table 3: Pharmacokinetic Sampling Schedule

Minutes	Cycle 1[1]					Cycle 2-17[2]	Off Study[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
		●	●				●
0 to -30 (preinfusion)	●			●	●	●	
60 (end of infusion)	●			●	●	●	
90	●						
120	●						
180	●						
300	●						

1. Serum samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. For Days 2, 3, 4, 8, and 42, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.
2. For Cycles 2-17, samples will be drawn every 14 days before and at the end of each infusion. The samples will be collected within 30 minutes before each MDX-1105 infusion and immediately after infusion is completed.
3. A single sample will be taken Off Study.

1. INTRODUCTION AND RATIONALE

1.1. Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens, and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of costimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by costimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

MDX-1105 is a fully human monoclonal antibody (HuMAb) of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. Its interaction with the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Four tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1/2 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel targeted therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR]

Temsirolimus). Subjects with advanced RCC will relapse on these newer agents and therefore other novel targeted agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006. The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival, and new patients should not be given this drug. Thus novel targeted therapies are needed.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006. The majority of new MEL cases (95%) are diagnosed early as localized tumors and curable. However, approximately 5% to 10% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and therefore novel agents are needed.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006. The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis. Thus novel agents are needed.

1.2. PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,4,5,6,7,8,9,10] For example, in renal cell

carcinoma, high intratumoral expression levels of PD-L1 are related to tumor aggressiveness. Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in post-operative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both PD-L1^{+} and PD-L1^{-} tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell costimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity. PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1

in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody. Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. [32] Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-1$^{-/-}$ mice. In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition. Anti-PD-L1 monoclonal antibody (mAb) together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma (RENCA) kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD-1 blockade.[33,34] Using a murinized anti-mouse PD-1 antibody, Medarex showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition (TGI) in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD-L1 (and/or PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, MDX-1105 represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3. Summary of MDX-1105 Preclinical Studies

MDX-1105 is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. MDX-1105 was selected to inhibit the interaction of PD-L1 with its receptor PD-1. MDX-1105-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using MDX-1105 can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived

antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of MDX-1105 shows that the antibody is not capable of inducing antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDCC) with PD-L1 positive cells. In addition, incubation of MDX-1105 at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. MDX-1105 was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or as weekly doses (times 5) at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4. Rationale for MDX-1105

1.4.1. Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in-vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 15 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol MDX1105-01 will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level (NOAEL) considerations from preclinical toxicology studies, where MDX-1105 doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2. Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

Initial safety experience of single dose administration of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer in Protocol MDX-1106-01, as of 15 April 2008, has shown no DLTs at the 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg dose levels. A related serious adverse event (colitis) has been reported in a subject who has received 5 doses of 1 mg/kg over 32 weeks.

Twenty-one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with MDX-1105 will be closely monitored in Protocol MDX1105-01.

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Only 17/88 (19.3%) subjects with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective is to determine the safety profile of MDX-1105, the maximum tolerated dose (MTD), and the dose-limiting toxicity (DLT) of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

2.2. Secondary Objectives

The secondary objectives of the study are to 1) evaluate preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105, 2) characterize the immunogenicity of MDX-1105, and 3) characterize the preliminary multidose pharmacokinetic profile of MDX-1105.

3. OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the PD-L1. Up to 40 subjects with measurable advanced or recurrent solid tumors (RCC, NSCLC, MEL, or epOC) will be enrolled in the study.

An accelerated titration design (ATD)[37] will be utilized for this Phase 1 study. Five dose levels are planned and include: 0.3, 1, 3, 10, and 15 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 0.3 mg/kg/dose administered as an i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's dosing in the previous cohort. One subject will be enrolled in each cohort until 1 subject experiences a ≥ Grade 2 drug-related adverse event, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 3 or 6 subjects. This lower dose level will be considered the MTD if ≤ 1 in 6 subjects has a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced.

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT, enrollment will be stopped and the data will be reviewed by the Medarex Medical Monitor before any subject continues in the study.

A DLT is defined as a ≥ Grade 3 drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are drug-related adverse events that occur after Cycle 1. *Delayed DLTs will not be used to determine the MTD for dose escalation.* Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval.

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the

first dose of the next cycle). Subjects with initial progressive disease (PD) based on sum of the longest diameter (SLD) or development of new lesions at the end of a cycle, but with otherwise stable or improved performance and clinical status, will continue to be treated with study drug for 1 additional cycle. At the next scheduled imaging evaluation, if there is further increase in the SLD, or development of additional new lesions, then PD has been confirmed and the subject will stop treatment and complete the off-treatment procedures. If the SLD remains the same or decreased and no additional new lesions develop and the subject is otherwise stable or improved in performance and clinical status, then PD has not been confirmed and the subject will continue to be treated with study drug for 1 additional cycle until the next scheduled imaging evaluation.

In the absence of confirmed disease progression, subjects who discontinue MDX-1105 treatment should continue in the study until at least 70 days following the last dose of MDX-1105 or the next scheduled visit has been performed which ever is longer. Subjects who discontinue MDX-1105 because of a treatment-related adverse event will remain in the study and continue to be followed until 70 days following the last dose of MDX-1105 or until stabilization or resolution of the event, whichever is longer. Subjects who discontinue MDX-1105 administration due to an adverse event and who have a demonstrated complete response (CR), partial response (PR), or stable disease (SD) will remain in the study and be followed every 3 months for up to 6 months until relapse, confirmed disease progression, or initiation of new therapy, whichever occurs first.

Subjects who achieve a confirmed CR will not receive further cycles of MDX-1105 and will be followed every 3 months for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects with a response of PR/SD will continue to receive MDX-1105 treatment until achievement of a confirmed CR, confirmed disease progression, development of a $\geq$ Grade 3 CTCAE, or intolerability to therapy. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but should be given no later than 21 days. No subject will be permitted dose escalations or de-escalations. The maximum duration of study drug treatment for a subject is 2 years. Those subjects who continue to receive clinical benefit after 2 years of therapy (subjects with CR, PR, or SD) will be followed every 3 months from the last day they received study drug for 6 months until relapse, confirmed disease progression, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. The maximum total study participation duration for a subject is 2.5 years.

4. STUDY POPULATION

Up to 40 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors, of one of the following histologically confirmed types: RCC, NSCLC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

4.1. Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA Authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;
2. Life expectancy ≥ 12 weeks;
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 1);
4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, including, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic taxane-based therapy.

   For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after standard therapy (may include high-dose interleukin-2). All melanomas regardless of primary site of disease will be allowed.

   For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic platinum-based therapy.

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2);

6. May have been treated with up to 3 previous systemic therapies for advanced/recurrent disease or have become intolerant to a systemic therapy;
7. Prior treated brain metastases must be without MRI evidence of progression for at least 8 weeks and off steroids for at least 4 weeks before study drug administration to be eligible;
8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;
9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
10. At least 28 days since the last chemotherapy, immunotherapy, biological or investigational therapy, radiation, or at least 2 weeks from approved tyrosine kinase inhibitor (TKI) therapy (Sunitinib, Sorafenib) before the first dosing of MDX-1105 and have recovered from any toxicity associated with such treatment;
11. Systemic or topical corticosteroids must be discontinued at least 4 weeks before study drug administration;
12. Prior major treatment-related surgery completed at least 4 weeks before study drug administration;
13. Screening laboratory values must meet the following criteria:

WBC	≥ 3000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X ULN
ALT	≤ 2.5 X ULN
Bilirubin	< 1.5 mg/dL (unless diagnosed with Gilbert's syndrome)

No known positivity for human immunodeficiency virus (HIV) (no laboratory testing is required), no active infection with Hepatitis B or Hepatitis C;

14. Women must meet 1 of the following criteria: post-menopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. Women of child bearing potential must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug; and

15. Men must agree to the use of male contraception during the study Treatment period and for at least 180 days after the last dose of study drug.

4.2. Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody;
3. Any other malignancy, excluding basal or squamous cell carcinoma of the skin, cervical carcinoma in situ, or localized prostate cancer, from which the subject has not been disease-free for at least 5 years;
4. Active infection (viral, bacterial, or fungal) requiring i.v. systemic therapy within 28 days prior to the first dose of MDX-1105;
5. Evidence of bleeding diathesis or coagulopathy;
6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo;
7. Recent history of attenuated viral vaccination within 30 days prior to the first dose of study drug;
8. Known current drug or alcohol abuse;
9. Apparent active or latent tuberculosis (TB) infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of infections infiltrate; recent unexplained changes in fever/chill patterns;
10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
11. Concurrent medical condition requiring the use of immunosuppressive medications, or systemic or topical corticosteroids. Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;

12. Use of other investigational drugs (drugs not marketed for any indication) within 30 days before study drug administration;
13. Psychiatric illness or social situation that would preclude study compliance; or
14. Pregnant or nursing.

5. RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6. ASSIGNMENT TO STUDY

The investigative site will contact Medarex for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by Medarex. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7. DOSAGE AND ADMINISTRATION

7.1. Physical Description of Study Drug

MDX-1105 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 10 mg of MDX-1105 (10 mg/mL).

7.2. Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (cGMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.3. Storage

MDX-1105 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1105 include laboratory coats and gloves. Note: once MDX-1105 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for MDX-1105 supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any

anti-microbial preservative or bacteriostatic agent. No incompatibilities between MDX-1105 and polyolefin bags have been observed.

7.4. Study Drug Preparation

1. Allow the appropriate number of vials of MDX-1105 to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the MDX-1105 solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of MDX-1105 solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)
4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume is more than 60 mL, no additional dilution is necessary.
5. Prepare the MDX-1105 solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX-1105 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX-1105 and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.
6. Mix by GENTLY inverting several times. DO NOT shake.
7. Filter the dose through a sterile 0.2 μM-in-line filter.
8. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
9. Record the time MDX-1105 was prepared on the i.v. bag label.

Do not enter into each vial more than once.

Do not prepare MDX-1105 for infusion in glass syringes.

7.5. Study Drug Administration

MDX-1105 will be administered at a dosage of 0.3, 1, 3, 10, or 15 mg/kg/dose and administered as an i.v. infusion controlled by a volumetric pump over 60 minutes, with an adequate normal saline flush at the end of the infusion.

MDX-1105 should be administered under the supervision of a physician or other study personnel experienced in the use of i.v. agents.

1. Attach the i.v. bag containing the MDX-1105 solution to the infusion set, 0.2 μM in-line filter, and infusion pump.
2. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
3. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Do not administer study drug as an i.v. push or bolus injection.

7.6. Drug Accountability

Medarex, Inc. is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by Medarex or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Medarex at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

All used and partially used study drug will be destroyed by the site, in accordance with the site's SOPs or at a central depot.

7.7. Infusion Delays and Missed Doses

There must be a minimum of 14 days between study drug infusions. In exceptional circumstances an infusion may be delayed for up to 7 days. Infusions that can not be administered in that timeframe will be considered a missed dose, and the subject should come in for their next, regularly scheduled visit. The next scheduled visit should occur according to the subject's next regularly scheduled visit relative to Day 1. A subject will be considered to have discontinued study drug if he/she misses 3 consecutive doses.

8. TOXICITY AND MANAGEMENT

8.1. Dose Escalation

The first cohort of 1 subject will receive 0.3 mg/kg/dose administered as an i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's dosing in the previous cohort. One subject will be enrolled in each cohort until 1 subject experiences a ≥ Grade 2 drug-related adverse event, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 3 or 6 subjects. This lower dose level will be considered the MTD if ≤ 1 in 6 subjects has a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced.

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be treated at the MTD or at the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT, enrollment will be stopped and the data will be reviewed by the Medarex Medical Monitor before any subject continues in the study.

8.2. Dose-limiting Toxicity

A DLT is defined as a ≥ Grade 3 drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event) using NCI CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are drug-related adverse events that occur after Cycle 1. *Delayed DLTs will not be used to determine the MTD for dose escalation.* Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval.

All adverse events that meet DLT criteria**,** as well as any unexpected toxicity (regardless of attribution), must be reported to Medarex, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3. Stopping Rules for Dose-limiting Toxicity and Delayed Dose-limiting Toxicity

The dose-escalation schema will proceed based upon the occurrence of a ≥ Grade 2 drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval.

Considering the anticipated half-life of the molecule, dose-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

8.4. Stopping Rules for the Expansion Cohort

For the expansion cohort (10 subjects), if 3 or more subjects experience a DLT, enrollment in the expansion cohort will be stopped and the data will be reviewed by the Medarex Medical Monitor before any subject continues in the study.

8.5. Infusion Reactions

Since MDX-1105 contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-L1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT.

Prophylactic premedication may be given anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (Version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) at least 30 minutes before additional MDX-1105 administrations.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDS), narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the MDX-1105 infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol/acetaminophen; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further MDX-1105 will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), paracetamol (acetaminophen) and/or corticosteroids should be administered at least 30 minutes before additional MDX-1105 administrations. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of MDX-1105. Begin an i.v. infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. MDX-1105 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.6. Possible Toxicities

There is no clinical experience with MDX-1105 to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm:** Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and Tumor Necrosis Factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with MDX-1105, and has not been seen in preclinical testing.
- **Tumor lysis syndrome (TLS)**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal (GI) bleeding.
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs):** Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that mixed syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and

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colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of irAEs is currently hypothetical, as no subjects have been treated with MDX-1105 to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, Ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). A management algorithm for high-grade irAEs in this current study is provided in the Investigator Brochure. **All irAEs should be managed according to this algorithm.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105 program.

9. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10. CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.

b. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.

c. Concomitant use of other ccRCC/MEL/epOC cytotoxic chemotherapy, investigational agents, growth factors, cytokines, and RT may not be used while the subject is on the study. Radiation therapy for bone pain will be discussed with the Medical Monitor. No other investigational therapies for any reason shall be administered while the subject is in the study.

d. Subjects on immunosuppressive doses of oral or parenteral corticosteroids must be tapered off the medication 4 weeks before the first dose of MDX-1105 and must remain off all oral and parenteral corticosteroids while the subject is on the study (unless used for the treatment of infusion reactions).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11. STUDY EVALUATIONS

11.1. Study Procedures by Visit

11.1.1. Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic (PK) Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for PK assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and ECG performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days prior to the administration of MDX-1105 need not be repeated**.**

All subjects (withdrawn or completed) will have final evaluations and procedures performed (Off Study Visit).

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11.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions).
- Baseline signs and symptoms: Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (to be taken within 7 days before the first infusion; for all women of childbearing potential; serum pregnancy test must be negative to continue).
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead Electrocardiogram (ECG)
- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistries: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine

Glucose

Lactate dehydrogenase (LDH)

Total protein

Urea nitrogen (BUN)

Uric acid

- Electrolytes (including sodium, potassium, chloride, and bicarbonate)
- Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.

  Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings
- Hepatitis B and C testing

- Immune Safety Assays: Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, C-Reactive Protein (CRP), Antinuclear Antibody (ANA) titer and pattern.

  The following tests may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.
- Optional tumor or other (e.g., inflamed tissue) biopsies (requiring a separate informed consent and targeting anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor biopsy for research purposes requires a separate consent.
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD19, CD20, CD56 [NK]).
- Concomitant medications

11.1.3. Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start MDX-1105 treatment within 0 to 28 days of Screening. Subjects will receive 3 doses of MDX-1105 every 14 days during each cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1105 will be determined by the response assessment (described below). Results of assessments must be reviewed and

documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 1 or more day) or missed doses, see Section 7.7 for administration details. A subject who misses a dose during Cycle 1 only, not due to a DLT, will be replaced.

11.1.3.1. Cycle 1

Cycle 1 will begin with the first i.v. infusion of MDX-1105 (Day 1, Visit 2) and will continue through to the end of Visit 11. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment within Days 38 to 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained pre-infusion and post infusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis)
- Bone scan (if clinically indicated). Bone scan does not have to be performed if positive at baseline.
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue)
- Serum samples for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. (Post-infusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days).
- Serum sample for immunogenicity
- Flow cytometry
- Cryopreserved peripheral blood mononuclear cells (PBMCs): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity testing will be governed by type of tumor and availability of test antigens.

- Clinical laboratory tests ([local and central laboratories]; the results of hematology and clinical chemistry **must be reviewed before dosing**. Local labs may be drawn up to 48 hours before infusion. Samples should be drawn from a site other than the infusion site [i.e., contralateral arm]) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Clinical chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.3.2. Cycle 2 to 17

Following Cycle 1, subjects with SD or PR will receive additional cycles of MDX-1105 (Cycles 2 to 17) until CR, confirmed PD, development of a ≥ Grade 3 (CTCAE) intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 17 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (changes to dose will only be made if there has been ≥ 10% weight change since the previous cycle)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Bone scan, if clinically indicated

- Cryopreserved PBMCs (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm)
- Serum sample for immunogenicity
- Tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and clinical chemistry **must be reviewed before dosing**. Local labs may be drawn up to 48 hours before infusion. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm).
  - Hematology with differential (as outlined in Section 11.1.2)
  - Clinical chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.4. Off Study Visit

For each subject, an Off Study visit will be scheduled at the first occurrence of one of the following (whichever occurs first for a subject):

- study completion (up to 2.5 years after the first dose of study drug)
- study withdrawal
- treatment discontinuation before the end of a treatment cycle, or
- Confirmed PD

If a subject is prematurely withdrawn during a cycle of treatment, these procedures will be performed as soon as possible relative to the day of treatment discontinuation.

If a subject is withdrawn before completing the study as defined below, the reason for withdrawal will be documented on the CRF and in the source document. All subjects will be followed to collect adverse events and concomitant medication use every 2 weeks for 70 days following the last dose of MDX-1105 or until resolution/stabilization of any adverse event suspected to be related to MDX-1105 treatment. All study subjects (completed or early

withdrawal as defined below) should have the following evaluations and procedures completed when they go off study:

- Urine pregnancy test for women of childbearing potential
- Serum sample for pharmacokinetic assessment of MDX-1105
- Vital sign measurements
- ECOG performance status
- Physical examination
- Tumor imaging if not done within the preceding 28 days.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- 12-lead electrocardiogram
- Clinical laboratory tests as outlined in Section 11.1.2
- Immune safety assays
- Flow cytometry
- Cryopreserved PBMCs (as outlined in Section 11.1.3.1).
- Serum sample for immunogenicity
- Concomitant medications
- Adverse event assessment

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if withdrawn from the study, the reason for withdrawal. At the end of Cycle 1, the subject completion status for each subject, as defined below, will be documented on the CRF.

Subject Completion Status at the end of Cycle 1

- **Early Withdrawal:** subjects who discontinue from the study before Day 42. Subjects who discontinue for reasons other than a DLT will be replaced.
- **Completed:** subjects who receive all 3 doses of MDX-1105 during Cycle 1 and complete all evaluations at the end of Cycle 1.

If, for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reason for early withdrawal will be documented:

- Adverse event(s)
- Protocol violation

- Subject withdrew consent
- Subject is lost to follow-up
- Death
- PD
- Other

11.1.5. Complete Response/Continued Clinical Benefit Follow-up

Subjects who achieve a confirmed CR will not receive further cycles of MDX-1105 and will be followed every 3 months for 6 months until relapse, initiation of new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue MDX-1105 administration due to an adverse event and who have a demonstrated CR, PR, or SD will remain in the study and be followed every 3 months for up to 6 months until relapse, confirmed disease progression, or initiation of new therapy, whichever occurs first.

Subjects who continue to have clinical benefit (CR, PR, SD) after 2 years of therapy will be followed every 3 months from the last day they received study drug for 6 months until relapse, confirmed disease progression, initiation of a new therapy, or total of 6 months follow-up, whichever occurs first.

Subjects (confirmed CR or continued clinical benefit as defined above) will have the following evaluations and procedures completed at each visit (see Table 2):

- Vital sign measurements
- ECOG performance status
- Physical examination
- Tumor imaging
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2
- Concomitant medications
- Adverse event assessment

11.2. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1105: vital sign measurements, clinical laboratory tests, flow cytometry, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of

MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other immune-related adverse events (irAEs). Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety and immunogenicity.

11.2.1. Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of MDX-1105-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the MDX-1105 drug itself, and is characterized by antibodies that the subject may develop that react with MDX-1105. These may result in more rapid clearance of MDX-1105 from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with MDX-1105 at a later date.

11.3. Efficacy Evaluations

11.3.1. Efficacy Parameter

The efficacy parameter is the best observed response rate (BORR) as determined by the Investigator timepoint tumor evaluations. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent confirmation of responses may be requested at the discretion of Medarex.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically

observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of MDX-1105 and more likely capture its true potential to induce clinical responses.

11.4. Pharmacokinetic Evaluations

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

Blood samples for the analysis of serum concentrations of MDX-1105 will be drawn in all subjects according to the schedule listed below and in Table 3 of the Time and Event Schedule. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1. Cycle 1

- **Day 1:** pre-dose (within 30 minutes before infusion), and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, 8, and 42:** single serum samples will be taken on each day.
- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and at the end of each MDX-1105 infusion.

11.4.2. Cycles 2-17

- **Days 1, 15, and 29:** serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3. Off-Study Visit

- A single serum sample will be taken.

12. ADVERSE EVENT REPORTING

Clinical events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE,

Version 3.0.[38] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later). For all follow-up periods beyond 70 days from the last dose of study drug, only adverse events deemed by the Investigator to be related to MDX-1105 should be reported.

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug – related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as “not related” or “related”. The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted
7 Study drug dosage adjusted

12.2. Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serological and immunological data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Immune-related adverse events will be evaluated as described for adverse events (Section 12.1) and will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.4), even if the nature of the adverse event is not deemed serious.

12.3. Serious Adverse Events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure subject safety, each serious adverse event must also be reported to Medarex within 24 hours of learning of its occurrence.

All adverse events that potentially meet DLT criteria, as well as any unexpected toxicity must be reported to Medarex within 24 hours. Medarex or designee will communicate serious adverse events, DLTs, and other toxicities to the study sites as required by regulatory authorities. A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; hospitalization to facilitate the work up of a $\leq$ Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.4. Instructions for Rapid Notification of Serious Adverse Events

12.4.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she provided informed consent and HIPAA authorization, while receiving study treatment, or during the 70 days following study drug administration or follow-up must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk, or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring greater than 70 days from the last dose of MDX-1105 must be reported if deemed related to study drug. The report must include the event term, subject identifier, attribution, description, concomitant medication used to treat the event, and any other relevant information. Follow-up information about previously reported serious adverse events must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert

may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.4.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to Medarex or its designee. The monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and fax confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.4.3. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, Medarex considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.4.4. Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1105 and must not continue in the study. The Off-Study Visit assessments will be completed, and the subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period) at any

time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, such pregnancies should be followed (to term) to determine the outcome.

12.4.4.1. Reporting of Pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Medarex and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Medarex according to Serious Adverse Event reporting procedures described in Section 12.4.2.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.4.5. Contact Persons and Numbers

The Medarex Central Emergency Contact telephone and serious adverse event telefax numbers are listed on the cover page of the protocol.

13. STATISTICAL METHODS

13.1. Sample Size Determination

The sample size of up to 40 subjects is based on an accelerated titration dose-escalation design, not a power analysis. Up to 6 subjects will be enrolled at the following dose levels: 0.3, 1, 3, 10, and 15 mg/kg/dose. A total of 16 subjects (6 in dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD, or the highest dose studied. If no DLTs occur, a total of 20 subjects will be needed to finish the study.

13.2. Study Populations

13.2.1. Safety Population

The safety population includes all subjects who receive at least 1 dose or any partial dose of MDX-1105.

13.2.2. Per-protocol Population

The per-protocol population includes all subjects dosed at the MTD (or the highest dose tested if the MTD is not determined) in the safety population who have the correct disease diagnosis, valid baseline tumor assessment showing measurable disease, and at least 1 valid post-baseline tumor assessment. Any subject who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the per-protocol population. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population.

13.2.3. Pharmacokinetic Population

The pharmacokinetic population includes all subjects in the safety population who complete all 3 infusions in Cycle 1 and have completed the pharmacokinetic assessments up to Day 42 of that cycle.

13.3. Statistical Considerations

The Biostatistics group at Medarex, Inc. or its designees will analyze the data collected in this study.

All data will be listed individually by subject. Continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency and percentage.

The baseline value for an analysis variable is the last measurement before study drug administration.

Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05

13.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.3.2. Extent of Exposure

The total dosage (mg), total number of doses, and total number of treatment cycles will be summarized by dose level using descriptive statistics.

13.3.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant medications will be summarized by dose level using descriptive statistics. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study.

13.3.4. Safety

The safety analysis will be conducted on the safety population. The following safety parameters will be evaluated:

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0 to categorize a preferred term and a system organ class for each adverse event. The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE version 3.0), irAEs, TEAEs, and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Physical Examinations

Abnormal findings in physical examinations will be summarized by dose level using descriptive statistics.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level using descriptive statistics.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE 3.0 Grade will be assigned to some of the laboratory parameters, which are included in "CTCAE version 3.0". Central laboratory values will be listed. Laboratory values which are outside normal range will be flagged as H (above high normal limit) or L (below lower normal limit) in the listings. The NCI CTCAE 3.0 Grade will also be flagged in the listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

Diagnostic Tests

Diagnostic tests results will be summarized by dose level using descriptive statistics.

Immunogenicity

Immunogenicity measurement for human anti-human antibodies (HAHA) will be summarized appropriately.

13.3.5. Efficacy

The efficacy analysis will be conducted on the per-protocol population.

The efficacy endpoint is the BORR, as determined by the Investigator timepoint tumor evaluations. The BORR will be summarized using descriptive statistics by response level: CR, PR, SD, and PD.

13.3.6. Pharmacokinetic

Plasma concentrations of MDX-1105 will be determined by a validated method at the times listed in the time and events schedule tables.

Definition and Calculation of PK Parameters

The following pharmacokinetic parameters will be estimated and reported:

$AUC_{0\rightarrow t}$ Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).

$AUC_{0\rightarrow \infty}$ Area under the curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z).

λ_z Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of $\log_e$ (concentration) vs time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time and (iii) the correlation coefficient r of regression must be ≥ 0.95.

C_{max} Maximum plasma concentration observed post-dose.

t_{max} Time at which the C_{max} occurs.

$t_{½}$ Elimination half-life, determined as $0.693/\lambda_z$.

The pharmacokinetic parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

13.4. Missing-Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

13.5. Statistical Software

The estimation of pharmacokinetic parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher.

14. ETHICAL ASPECTS

14.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Medarex SOPs. These are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Notes of Clarification added Washington 2002 and Tokyo 2004).

The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

14.2. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to Medarex or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Medarex, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC must be given to Medarex before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the

IRB's Health and Human Safety (HHS) Assurance number must be supplied to Medarex or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

14.4. Informed Consent

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Medarex supplies a proposed ICF that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Medarex or its designee before submission to the IRB/IEC and a copy of the approved version must be provided to the Medarex monitor after IRB/IEC approval.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Medarex before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Medarex monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or

4. Addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Medarex in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, Medarex should be notified and the IRB/IEC for the center should be informed within 1 working day.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization [CRO]); and
2. Minor changes in the packaging or labeling of study drug.

15.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Medarex representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Medarex monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so

that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Medarex or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Medarex will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.4. Auditing Procedures

In addition to the routine monitoring procedures, Medarex, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Medarex, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Medarex immediately that this request has been made.

15.5. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Medarex. Authorship

will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Medarex statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Medarex.

Medarex must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Medarex personnel.

15.6. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Medarex or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Medarex (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Medarex, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7. Discontinuation of Study

Medarex reserves the right to discontinue any study for any reason at any time.

15.8. Data Management

15.8.1. Data Collection

Investigators must enter the information required by the protocol onto the Medarex CRFs that are printed on "no carbon required" (NCR) paper. Medarex monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required clarifications or additions. The CRFs will be forwarded to Medarex, or its designee, with 1 copy retained at the investigational site.

15.8.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

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Subsequently, the information entered into the database will be systematically checked by Data Management staff following Medarex, or its designee, data management procedures. Obvious errors will be corrected by Medarex personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Medarex study team.

16. REFERENCES

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17. APPENDICES

Appendix 1: ECOG Performance Status

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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Appendix 2: RECIST With Modification

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently. (Adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The (SLD) for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint), All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria

for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having "symptomatic deterioration."

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.

continued

Definitions *(continued)*

Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not "selected" images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis (ADEM)
IgA nephropathy
Addison's disease
Inflammatory bowel disease
Alopecia universalis
Interstitial cystitis
Ankylosing spondylitis
Lambert-Eaton Myasthenia Syndrome
Antiphospholipid antibody syndrome (APS)
Lupus erythematosus
Aplastic anemia
Lyme disease - chronic
Asthma
Meniere's Syndrome
Autoimmune hemolytic anemia
Mooren's ulcer
Autoimmune hepatitis
Morphea
Autoimmune hypophysitis
Multiple sclerosis
Autoimmune hypoparathyroidism
Myasthenia gravis
Autoimmune myocarditis
Neuromyotonia
Autoimmune Oophoritis
Opsoclonus myoclonus syndrome (OMS)
Autoimmune orchitis
Optic neuritis
Autoimmune thrombocytopenic purpura
Ord's thyroiditis
Behcet's disease
Pemphigus
Bullous pemphigold
Pernicious anemia
Celiac disease
Polyarteritis nodusa
Chronic fatigue syndrome
Polyarthritis
Chronic inflammatory demyelinating polyneuropathy
Polygrandular autoimmune syndrome
Chung-Strauss Syndrome
Primary biliary cirrhosis
Crohn's disease
Psoriasis
Dermatomyositis
Reiter's syndrome
Diabetes mellitus type 1
Rheumatoid arthritis
Dysautonomia
Sarcoidosis
Eczema
Scleroderma
Sjögren's syndrome
Epidermolysis bullosa acquista
Stiff-Person Syndrome
Gestational pemphigoid
Takayasu's Arteritis
Giant Cell Arteritis
Ulcerative colitis
Goodpasture's syndrome
Vitiligo
Graves' disease
Vogt-Kovanagi-Harada disease
Guillain-Barré syndrome (GBS)
Vulvodynia
Hashimoto's disease
Wegener's granulomatosis
Kawasaki's Disease

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MEDAREX

Protocol Number: MDX1105-01
Version: Amendment 1
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Document Status: Final
Date: 5 September 2008

Clinical Protocol MDX1105-01 Amendment 1

Summary of Change

A Phase 1, Open-label, Multicenter, Dose-escalation Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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Confidential

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Primary Change

The primary change in Amendment 1 is the removal of the Off-Study Visit and the addition of (up to) 3 Follow-up Visits.

Reason for change: The change in visit structure and sequence was implemented to clarify the plan for subject flow through the protocol, as well as to provide for additional testing of ECGs, pharmacokinetics, and immunogenicity as requested by the FDA. For subjects that will not initiate new treatment cycles, the Follow-Up 1 visit will be performed after the required scans are done, and will collect equivalent history, physical examination, and laboratory information that would be collected at the first visit of a succeeding treatment cycle. In addition, the Follow-Up 2 visit provides an opportunity to collect adverse event, as well pharmacokinetic and immunogenicity data on subjects through the 70 days it is expected to take to clear MDX-1105 from the blood. Subjects who had progressed and started other therapies will also be asked to come to this visit to collect these blood samples and information.

Global Changes

- The title was updated to reflect that this study is a multicenter study. The title now reads: A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors. This change appears on the title page, and in the synopsis.
- 'Best observed response rate' changed to 'Best overall response rate'.
- Targeted agents replaced with novel agents.
- The dosage range of paracetamol (325 to 1000 mg) that may be given as pretreatment after experiencing an infusion reaction has been specified.

The majority of other changes reflect modifications to the Medarex protocol template. The changes to the protocol template do not affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

These changes, along with changes resulting from minor typographical errors or defining acronyms for the first time, are not summarized within the section changes, as they are not expected to affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Section Changes

The following changes (indicated with a ~~strikeout~~ (delete text) or shaded areas (new text) have been made as Amendment 1 to the Protocol for Study MDX1105-01.

Title Page

Added additional Sponsor contact information:

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Reason for change: Administrative change and to provide additional contact information.

Page 5, Synopsis: Objectives

Changed primary objective to read:

The primary objective of this study is to assess the safety and tolerability~~determine the safety profile of MDX-1105; the maximum tolerated dose (MTD),and the dose-limiting toxicity (DLT)~~ of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

Reason for change: Clarification of primary objective.

Page 5, Synopsis: OVERVIEW OF STUDY DESIGN

Added new second paragraph to read:

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 17 6-week cycles), and Follow-up (up to 6 months). Each treatment cycle is comprised of 3 doses of study drug administered on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Reason for change: Clarification of study design.

Pages 5 and 6, Synopsis: OVERVIEW OF STUDY DESIGN, Dose Escalation

Revised second sentence in second paragraph to read:

Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dosing in the previous cohort.

Revised third sentence in second paragraph to read:

One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level.

Revised seventh and eighth sentence in second paragraph to read:

If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has ~~3 or~~ 6 subjects. ~~This lower dose level will be considered~~ The MTD is the highest dose studied where ~~if~~ ≤ 1 in 6 subjects ~~has~~ experiences a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

Reason for change: Clarification of timing of dose escalation and MTD.

Added new text at end of Dose Escalation subsection to read:

If 4 or more delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed if there has been ± 10% weight change since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Reason for change: Administrative changes to reflect consistency with Medarex revised protocol template.

Page 6, Synopsis: OVERVIEW OF STUDY DESIGN, Expansion Cohort

Revised stopping rules for the Expansion Cohort.

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT or 4 or more subjects experience a delayed

DLT, enrollment will be held ~~stopped and the data will be reviewed by the Medarex Medical Monitor before any subject continues in this study~~ pending completion of a safety analysis by the Investigator and the Medarex Medical Monitor and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).

Reason for change: Clarification of stopping rules for delayed DLT, safety monitoring, and enrollment continuation in the Expansion Cohort.

Moved definitions of DLT and delayed DLT to SAFETY EVALUATIONS

Reason for change: Administrative changes to reflect consistency with Medarex revised protocol template.

Page 6, Synopsis: OVERVIEW OF STUDY DESIGN, Administration of Additional Treatment Cycles and Follow-up Period

Replaced text as follows:

~~Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle). Subjects with initial progressive disease (PD) based on sum of the longest diameter (SLD) or development of new lesions at the end of a cycle, but with otherwise stable or improved performance and clinical status, will continue to be treated with study drug for 1 additional cycle. At the next scheduled imaging evaluation, if there is further increase in the SLD, or development of additional new lesions, then PD has been confirmed and the subject will stop treatment and complete the off-treatment procedures. If the SLD remains the same or decreased and no additional new lesions develop and the subject is otherwise stable or improved in performance and clinical status, then PD has not been confirmed and the subject will continue to be treated with study drug for 1 additional cycle until the next scheduled imaging evaluation.~~

~~In the absence of confirmed disease progression, subjects who discontinue MDX-1105 treatment should continue in the study until at least 70 days following the last dose of MDX-1105 or the next scheduled visit has been performed which ever is longer. Subjects who discontinue MDX-1105 because of a treatment-related adverse event will remain in the study and continue to be followed until 70 days following the last dose of MDX-1105 or until~~

~~stabilization or resolution of the event, whichever is longer. Subjects who discontinue MDX-1105 administration due to an adverse event and who have a demonstrated complete response (CR), partial response (PR), or stable disease (SD) will remain in the study and be followed every 3 months for up to 6 months until relapse, confirmed disease progression, or initiation of new therapy, whichever occurs first.~~

~~Subjects who achieve a confirmed CR will not receive further cycles of MDX-1105 and will be followed every 3 months for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects with a response of PR/SD will continue to receive MDX-1105 treatment until achievement of a confirmed CR, confirmed disease progression, development of a ≥ Grade 3 CTCAE, or intolerability to therapy. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but should be given no later than 21 days. No subject will be permitted dose escalations or de-escalations. The maximum duration of study drug treatment for a subject is 2 years. Those subjects who continue to receive clinical benefit after 2 years of therapy (subjects with CR, PR, or SD) will be followed every 3 months from the last day they received study drug for 6 months until relapse, confirmed disease progression, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. The maximum total study participation duration for a subject is 2.5 years.~~

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 17 (with up to 3 doses per cycle). Following each cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 days after the last dose of the prior treatment cycle and no later than 21 days after the last dose to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed if there has been ± 10% weight change since the previous cycle.

Subjects who meet the following conditions will be treated in additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from

treatment is likely; 3) PD that is confirmed and then worsens; 4) development of a ≥ Grade 3 study drug-related CTCAE; 5) other intolerability to therapy; or 6) receipt of the maximum number of cycles.

- Subjects with progressive disease (PD) that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit for approximately 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

Reason for change: The flow of text has been changed to improve clarity.

Page 7, Synopsis: Duration and Treatment/Study Participation

Added new section to read:

The expected maximum duration of study drug treatment for a subject is approximately 2 years.

The expected maximum duration of a subject's participation in this study is approximately 2.5 years.

Reason for change: Administrative changes to reflect consistency with Medarex revised protocol template.

Page 7, Synopsis: Study Population

Revised section to read:

Up to 40 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors, of one of the following ~~pathological~~ histological documented types: RCC, NSCLC, MEL, or epOC.

Reason for change: Consistency within document.

Page 7, Synopsis: Safety Evaluations

Inserted DLT text to this section and revised section to read:

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, flow cytometry, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety and immunogenicity. ~~Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other immune-related adverse events (irAEs). Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.~~

~~An irAE is a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serological and immunological data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.~~

Dose-Limiting Toxicity

A DLT is defined as a study drug-related ≥ Grade 3 adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient (resolving within 6 hours of onset) Grade 3 infusion adverse event) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are ~~drug-related~~ adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to ~~determine~~ estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. ~~If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval.~~

Immune-related Adverse Events

An immune-related adverse (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic~~al, and,~~ immunologic~~al~~ and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other immune-related adverse events (irAEs). Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

Reason for change: Defined 'transient', clarified the definition of delayed DLTs, and removed stopping rules for delayed DLTS as these rules are now under OVERVIEW OF STUDY DESIGN. Clarification of data to be used to support irAE diagnosis.

Page 8, Synopsis: Exploratory Immune Function Evaluations

Added new section to read:

Samples will be collected for cryopreservation of lymphocytes and plasma and stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens, and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Reason for change: Clarification of exploratory evaluations

Page 8, Synopsis: Pharmacokinetic Evaluations

Revised third paragraph (Cycles 2-17) to read:

For Cycles 2 to 17, samples will be drawn every 14 days, 30 minutes before the administration of MDX 1105, ~~before~~ and immediately after the infusion is completed. ~~The samples will be collected within 30 minutes before each MDX-1105 infusion and immediately after the infusion is completed.~~

Reason for change: Administrative changes to reflect consistency with Medarex revised protocol template.

Revised fourth paragraph to read:

Single samples will also be collected at Follow-Up Visits 1 and 2. ~~For the Off Study Visit, a single sample will be drawn.~~

Reason for change: Reflects change in study design.

Pages 11 through 20, Time and Event Schedule: Tables 1 and 2

Revised the Tables 1 and 2 to read as follows on next pages:

Reason for changes: Replaced with new tables to reflect changes in study design.

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (±1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4]	•											
Baseline signs and symptoms	•[5]											
Pregnancy test[6]	•	•			•		•			•		
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[11]	•[12]								•		•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (±1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Brain CT scan/MRI[11,13]	•[12]								•	•	•	•
Bone scan (if clinically indicated)[14]	•[12]								•	•[14]	•[14]	•[14]
ECG (12-lead)	•[12]	•[15]								•		
Hematology	•	•[16]		•[16]	•[16]	•[16]	•[16]	•[16]		•	•	•
Serum chemistry	•	•[16]		•[16]	•[16]	•[16]	•[16]	•[16]		•	•	•
Immune safety assays[17,18]		•								•	•	
Optional tumor or other biopsy	•[19]											
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry[20]		•								•		
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•[21]								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (±1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for immunogenicity		•[22]								•	•	
MDX-1105 infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
Off Treatment/Study Procedures [23]												
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

1. Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

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Table 1 Footnotes *(continued)*

4. To include collection of prior medication and prior/concurrent medical conditions.
5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).
6. Serum β-HCG pregnancy test within 7 days before the first infusion and urine pregnancy test at all other indicated timepoints before infusion for women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.
8. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes post infusion and longer if necessary until the subject is stabilized.
9. ECOG Performance Status to be assessed before each infusion.
10. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and only before each initial infusion of each cycle (Note: Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).
11. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
12. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

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Table 1 Footnotes *(continued)*

13. Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 2 months (and NOT required for subjects with epOC). Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or as clinically indicated. If required, subsequent brain CT scans/MRI should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2 and 3.
14. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days. Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
15. To be performed pre- and post-infusion.
16. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
17. To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibody titer and pattern.
18. The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.
19. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression may be done on tumor samples collected during or before this study.
20. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
21. Sample collected pre-infusion.
22. Serum sample for immunogenicity evaluation will be collected within 30 minutes before infusion.

Table 1 Footnotes *(continued)*

23. When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.

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Table 2: Time and Events Schedule for Cycles 2-17

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-17 (±1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Urine pregnancy test[4]	•	•	•		•		
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]	•	
Bone scan (if clinically indicated)[12]				•	•[10]		
ECG (12-lead)	•[13]				•		
Hematology	•[14]	•[14]	•[14]		•		
Serum chemistry	•[14]	•[14]	•[14]		•	•	•
Immune safety assays[15,16]	•				•	•	
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry[19]	•						
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

Table 2: Time and Events Schedule for Cycles 2-17

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-17 (±1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
							continued
Serum sample for immunogenicity	•				•	•	
MDX-1105 infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
Off Treatment/Study Procedures [20]							
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

1. Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject has permanently discontinued study drug treatment. **Subjects who discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given 14 days (and no later than 21 days) after the last dose of the prior treatment cycle.
3. The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
4. For women of childbearing potential.
5. Pharmacokinetic sampling to be performed according to Table 3.

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Table 2 Footnotes *(continued)*

6. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes post infusion and longer if necessary until the subject is stabilized.
7. ECOG Performance Status to be assessed before each infusion.
8. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken only before each initial infusion of each cycle (**Note:** Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).
9. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
10. To be performed if clinically indicated and if not done within the preceding 28 days.
11. Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain scans should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2 and 3. If positive at baseline, the brain scan must be performed to confirm CR or PR.
12. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated.
13. To be performed pre- and post-infusion.
14. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
15. To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibodytiter and pattern.
16. The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.
17. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression may be done on tumor samples collected during or before this study.

Table 2 Footnotes *(continued)*

18. Sample collected for Cycles 2 and 3 (pre-infusion) and at Follow-Up Visit 1.
19. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
20. When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.

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Page 21, Pharmacokinetic Sampling Schedule: Table 3

Replaced Off-Study Visit with Follow-up Visits 1 and 2, and replaced off-Study Visit in footnote 3 with Follow-up Visits 1 and 2

Reason for changes: Reflect changes in study design.

Replaced 180 minute timepoint with 240 minute timepoint, and delete 300 minute timepoint

Reason for changes: Consistency within the document.

Page 22, Section 1.1: Background

Revised second sentence in second paragraph to read:

The binding of PD-L1 to ~~Its interaction with~~ the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses.

Reason for change: Information clarified.

Revised last sentence of third paragraph to read:

Four tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1~~/2~~ pathway is important for tumor progression.

Reason for change: Information clarified to be consistent with textual context.

Page 25, Section 1.2: PD-1/PD-L1 Pathway and Immune Responses

Revised last sentence of fifth paragraph to read:

This suggests that PD-1/PD-L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

Reason for changes: Clarified that PD-L2 is an alternate receptor.

Page 27, Section 2.1 Primary Objectives

Revised as per Synopsis changes.

Reason for changes: Consistency within document.

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Page 27, 28, 29, and 30, Section 3: Overview of Study Design

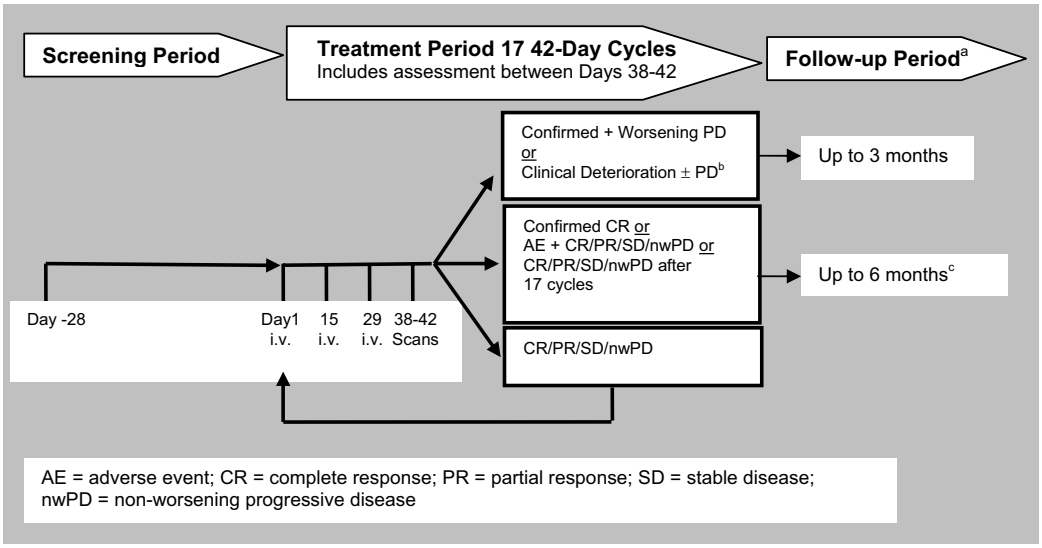
Revised as per Synopsis changes.

Reason for changes: Consistency within document.

Page 30, Section 3, Overview of Study Design

Add schematic study design:

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months F/U)



[a] For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug, the subject should be followed to resolution/stabilization of: 1) ongoing study drug-related adverse events; 2) new study drug-related adverse events that occur within the 90-day period; and 3) adverse events that led to the discontinuation. A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit. Only study drug-related serious adverse events will be collected > 90 days after the last administration of study drug.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow up visits should be done unless precluded by disease progression or clinical deterioration.

[c] Follow-up should continue until relapse, initiation of a new therapy, or a total of 6 months (3 months for confirmed PD), whichever comes first.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 31, 32, and 33, Section 4.1: Inclusion Criteria

Revised inclusion criteria to read:

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2~~or 1~~ (Appendix 1);

4. MEL: …relapsed after at least 1 prior standard therapy….

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;

6. May have been treated with up to ~~3~~ 5 previous systemic therapies for advanced/recurrent disease or have become intolerant to a systemic therapy;

7. Prior treated brain metastases must be without magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least ~~4~~ 2 weeks before study drug administration to be eligible;

11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

~~11. Systemic or topical corticosteroids must be discontinued at least 4 weeks before study drug administration~~

12. Prior ~~major treatment related~~ surgery that required general anesthesia must be completed at least 14 days ~~4 weeks~~ before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

13.

AST	≤ 2.5 X ULN without hepatic metastasis, ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 X ULN without hepatic metastasis, ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)~~< 1.5 mg/dL (unless diagnosed with Gilbert's syndrome)~~

~~No known positivity for human immunodeficiency virus (HIV) (no laboratory testing is required), no active infection with Hepatitis B or Hepatitis C.~~

Reason for changes: Criteria were deleted or modified to more specifically explain inclusions.

Pages 33, and 34, Section 4.2: Exclusion Criteria

Revised exclusion criteria to read:

2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);

3. ~~Any other~~Prior malignancy ~~excluding~~ active within the previous 2 years except for locally curable cancers that have been adequately treated, such as basal or squamous cell ~~carcinoma of the~~ skin cancer, superficial bladder cancer or ~~cervical~~carcinoma in situ of the cervix or breast, or localized prostate cancer~~, from which the subject has not been disease-free for at least 5 years~~;

4. Active infection (viral, bacterial, or fungal)~~ requiring i.v. systemic therapy within 28 days prior to the first dose of MDX-1105~~:

    a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of MDX-1105;
    b. Known history of infection with Human Immunodeficiency Virus
    c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)

6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;

7. Recent history of attenuated viral vaccination within 28~~30~~ days prior to the first dose of study drug;

9. Apparent active or latent tuberculosis ~~(TB)~~ infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectiou~~n~~s infiltrate; recent unexplained changes in fever/chill patterns;

11. Concurrent medical condition requiring the use of immunosuppressive medications~~, or systemic or topical corticosteroids~~ or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses > 10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be

continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;

12. Use of other investigational drugs (drugs not marketed for any indication) within 28~~30~~ days or at least 5 half-lives (whichever is longer) before study drug administration;

Reason for changes: Criteria were modified to more specifically explain exclusions.

Page 35, Section 7.1: Physical Description of the Study Drug

Revised section to read:

MDX-1105 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of MDX-1105 (10 mg/mL).

Reason for change: Correction of total amount (in mg) of MDX-1105 in each vial.

Pages 35, 36, and 37, Section 7.4: Study Drug Preparation and Administration

Combined Sections 7.4 (Study Drug) and Section 7.5 (Study Drug Administration).

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 37, Section 7.6: Dose Adjustments, Infusion Delays, and Missed Doses

Revised section title and text to read:

Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for MDX-1105 except for weight changes (± 10%) at the beginning of each cycle. There must be a minimum of 14 days between study drug infusions. ~~In exceptional circumstances an infusion may be delayed for up to 7 days. Infusions that can not be administered in that timeframe will be considered a missed dose, and the subject should come in for their next, regularly scheduled visit. The next scheduled visit should occur according to the subject's next regularly scheduled visit relative to Day 1. A subject will be considered to have discontinued study drug if he/she misses 3 consecutive doses.~~ In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1. A subject will be considered to have discontinued study drug if they miss 2 consecutive doses within a cycle.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 37 through 42, Section 8: Toxicity and Management

Same changes made in Section 8.1, 8.2, 8.3 and 8.4 as in Synopsis.

Reason for Change: Consistency with change to synopsis.

Pages 39 and 40, Section 8.5: Infusion Reactions

Revised last sentence of first paragraph to read:

All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and must be reported to Medarex within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

Reason for change: Provide detailed information on the type of events that require rapid notification in addition to serious adverse events. Administrative change to reflect consistency with Medarex revised protocol template.

Revised second paragraph to read:

Prophylactic premedication (e.g. acetaminophen or diphenhydramine) may be given before infusions, if indicated by a prior infusion reaction, anytime after the first dose of Cycle 1.

Reason for change: Clarification of premedications permitted and when to administer these medications.

Changed the last sentence under Grade 2 symptoms and add a new sentence to read:

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) ~~and/or corticosteroids~~ should be administered at least 30 minutes before additional MDX-1105 administrations. If necessary (persistent mild or moderate infusion reactions), corticosteroids (up to 25 mg of SoluCortef or equivalent) may be added. Remain at bedside and monitor subject until recovery from symptoms.

Reason for change: Clarification of premedications permitted and when to administer these medications.

Page 41, Section 8.6: Possible Toxicities

Changed third sentence in bulleted item, Immune-related Adverse Events to read:

The spectrum of irAEs is currently hypothetical, as no subjects have been treated with MDX-1105 to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, limited experience with human subjects treated with anti-PD-1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response.

Reason for change: Additional information provided.

Page 42, Section 8.7: Stopping Rules for Clinical Deterioration

Added new section to read:

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to stop treatment should be discussed with the Medarex Medical Monitor.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction

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- Development of new central nervous system (CNS) metastases
- Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

Reason for change: Guidance for investigators added regarding subjects with clinical deterioration.

Page 43, Section 10: Concomitant Therapy

Revised items c, d, and e to read:

c. Concomitant use of other ccRCC/MEL/epOC/NSCLC cytotoxic chemotherapy, investigational agents, growth factors, cytokines, and RT may not be used while the subject is on the study. ~~No other investigational therapies for any reason shall be administered while the subject is in the study.~~

d. No other investigational therapies for any reason shall be administered while the subject is in the study.

e. Subjects on immunosuppressive ~~doses of~~ oral or parenteral corticosteroids must be tapered off immunosuppressive doses (>10 mg/day of prednisone or equivalent) of the medication 2~~4~~ weeks before the first dose of MDX-1105 and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required~~used~~ for the treatment of infusion reactions, irAEs, or other adverse events).

Reason for change: Clarification of steroid use and consistency with inclusion and exclusion criteria.

Page 44, Section 11: Study Evaluations

Revised to include changes in the Synopsis and Time and Event Schedule.

Reason for change: Consistency with changes to the Synopsis and Time and Event Schedule.

Page 50, Moved and revised text for Completion of Cycle 1 and Study Completion to new Sections 11.1.5 and 11.1.6 (See below).

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 50, Section 11.1.5: Cycle 1 Treatment Completion

Moved and revised from previous Section 11.1.4 to read:

~~**Subject Completion Status at the end of Cycle 1**~~

- ~~**Early Withdrawal:** subjects who discontinue from the study before Day 42. Subjects who discontinue for reasons other than a DLT will be replaced.~~
- ~~**Completed:** subjects who receive all 3 doses of MDX-1105 during Cycle 1 and complete all evaluations at the end of Cycle 1.~~

Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 3 doses of MDX-1105 in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 50 and 51, Section 11.1.6: Study Participation

Added new section to read:

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up

- Death
- Other

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 51, Section 11.2.3: Exploratory Immune Function Evaluations

Added new section to read:

Samples will be collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Reason for change: Consistency with synopsis.

Page 53, Section 11.4.3: Follow-up Evaluations

Revised section to read:

~~A single serum sample will be taken~~ (in reference to Off-Study Visit).

Follow-up Visits 1 and 2: single serum samples to be taken.

Reason for change: Consistency with synopsis.

Page 53, Section 12: Adverse Event Reporting

Moved subsections for Immune-Related Adverse Event and Contact person within this section.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 53, Section 12.1: Definitions

Deleted last sentence of first paragraph.

~~For all follow-up periods beyond 70 days from the last dose of study drug, only adverse events deemed by the Investigator to be related to MDX-1105 should be reported.~~

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template providing clarification on serious adverse event information to be collected.

Delete 'study drug dosage adjusted' as an option for 'Actions Taken' subsection.

Reason for change: Administrative change to reflect dosing options for this protocol.

Pages 54, and 55, Section 12.1.1 Safety Reporting for Adverse Events

Added new section to read:

All adverse events occurring within 90 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only treatment-related serious or other clinically significant adverse events will be collected for all subjects 90 days after the administration of the last dose of study drug.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template and coordination of follow up with visit schedule.

Page 55, Section 12.2: Serious Adverse Events

Deleted text in first paragraph:

~~Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure subject safety, each serious adverse event must also be reported to Medarex within 24 hours of learning of its occurrence.~~

~~All adverse events that potentially meet DLT criteria, as well as any unexpected toxicity must be reported to Medarex within 24 hours. Medarex or designee will communicate serious adverse events, DLTs, and other toxicities to the study sites as required by regulatory authorities.~~

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 55 and 56, Section 12.3.1: Reporting Responsibilities

Revised section to read:

Any serious adverse event occurring in a subject after he/she provided informed consent and HIPAA authorization, while receiving study treatment, or during the ~~70~~ 90 days following study drug administration ~~or follow-up~~ must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond ~~70~~90 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk (SAE reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring greater than ~~70~~90 days from the last dose of MDX-1105 must be reported if deemed related to study drug. The report must include the event term, subject identifier, attribution, description, concomitant medication used to treat the event, and any other relevant information. Follow-up information about previously reported serious adverse events must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 57, Section 12.5: Pregnancy

Revised first paragraph to read:

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential

must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1105 and must not continue in the study. ~~The Off-Study Visit assessments will be completed, and~~The subject will be followed to determine the outcome of the pregnancy.

Reason for change: Consistency with the revised study design.

Revised last line in third paragraph to read:

When possible, partner's ~~such~~ pregnancies should be followed (to term) to determine the outcome.

Reason for change: Consistency with the revised study design.

Page 58, Section 12.6 Immune-Related Adverse Events

Revised section to read:

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

~~Immune-related adverse events will be evaluated as described for adverse events (Section 12.1) and will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.4), even if the nature of the adverse event is not deemed serious.~~

Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

Reason for change: Consistency within document to reflect previous changes.

Page 58, Section 12.7: Rapid Notification of Adverse Events of Importance

Added new section to read:

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 60, 61, and 62 Section 13.3.4: Safety

Deleted version of MedDra used.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Changed Physical Examinations subsection to read:

Abnormal findings in physical examinations will be ~~summarized by dose level using descriptive statistics.~~recorded as adverse events or baseline medical history and will be included in the respective summaries.

Reason for change: Change in CRF design.

Added new subsections to read:

Flow Cytometry

Flow cytometry results will be summarized by dose level using descriptive statistics or as otherwise appropriate.

Immune Safety Evaluations

Immune safety tests results will be summarized by dose level using descriptive statistics.

Exploratory Immune Function

The effects of MDX-1105 on humoral and cellular immune responses to tumor antigens (when available) and a panel of recall nontumor antigens will be assessed. Parameters to be examined

will include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment will be assessed. These parameters will be summarized by dose level using descriptive statistics, and may be reported as part of a separate document.

Reason for changes: Completeness.

Page 63, Section 14.1: Ethics and Good Clinical Practice

Revised section to read:

This study must be carried out in compliance with the protocol and in accordance with Medarex SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the ~~following documents:~~ International Conference on Harmonisation Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). ~~Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Notes of Clarification added Washington 2002 and Tokyo 2004).~~

The protocol and any amendments and the subject informed consent will receive ~~Institutional Review Board/Independent Ethics Committee (~~IRB/IEC~~)~~ approval/favorable opinion ~~before~~ prior to initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 65, Section 15.1 Protocol Amendments

Revised first paragraph list number text to read:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve ~~for~~ safety monitoring.

Revised third paragraph list number text to read:

- Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization [CRO]); and
- Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 66, Section 15.3: Recording of Data and Retention of Documents

Added new third paragraph to read:

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 68, Section 15.8.1: Data Collection

Added new second paragraph to read:

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 69, Section 15.8.2: Data Management and Quality Control

Added new third paragraph to read:

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Appendix 3: Alphabetized conditions

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

MEDAREX

Protocol Number: MDX1105-01
Version: Amendment 2
Development Phase: Phase 1
IND Number: 101,850
Document Status: Final
Date: 18 August 2009

Clinical Protocol MDX1105-01 Amendment 2

Summary of Change

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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PRIMARY SUBSTANTIVE CHANGES

The primary substantive changes are:

- Inclusion of subjects with colorectal adenocarcinoma (CRC) as another indication to be studied in the protocol.
- Removal of the highest dose level (15 mg/kg) to be tested; only 4 doses of MDX-1105 (0.3, 1, 3, and 10 mg/kg) are to be studied.
- Addition of expansion cohorts at the MTD or a lower dose for all 5 indications and addition of 2 additional expansion cohorts for melanoma at doses other than the primary expansion dose.
- Reporting period for adverse events was changed from 90 days following the last dose of study drug to 70 days following the last dose of study drug.
- Added requirement for permission to collect slides or tissue samples from pre-enrollment tumor biopsies, if available for examination of tumor markers and inflammatory infiltrates.
- Expanded the text describing the statistical analysis and summarization of efficacy and safety parameters.

GLOBAL CHANGES

The following changes were made to the synopsis, Time and Events schedules, and/or the body of the protocol.

1. Clarified cycle number (only 16 cycles in total, therefore Cycles 2-17 in Amendment 1 of the protocol were changed to Cycles 2-16).
2. Added CRC as another indication to be studied in the protocol.
3. Removed the highest dose level (15 mg/kg); only 4 dose levels (0.3, 1, 3, and 10 mg/kg) are to be studied.
4. Clarified dose escalations or de-escalations as being required only if a 10% or greater change in weight (increase or decrease) occurred.
5. Added 5 primary expansion cohorts (one in each of the 5 indications), resulting in an increase from 40 to 130 in the maximum number of subjects to be enrolled.
6. Added 2 additional expansion cohorts of subjects with melanoma (at doses other than the primary expansion dose).
7. Added blood tests for CEA and CA-19-9 for subjects with CRC and CA-125 for subjects with epOC.
8. Changed AE reporting time period from 90 days following the last dose of study drug to 70 days following the last dose of study drug.

Reason for substantial and global changes:

1. Change in total number of cycles and AE reporting period implemented for consistency across studies and drugs within Medarex, Inc.
2. Early positive trend in CRC with another related Medarex product supported adding CRC as additional indication.
3. Dose of 15 mg/kg removed for consistency across studies and drugs within Medarex, Inc.
4. Clarified conditions for dose escalations/de-escalations.
5. Total number of subjects per cohort at the primary expansion dose was increased (up to 16 subjects [dose-escalation plus expansion] within each cohort) to gain additional safety and tolerability information as well as provide an initial estimate of efficacy.
6. Analyses for CEA and CA-19-9 were added to test for these specific biomarkers in subjects with CRC and for CA-125 in epOC.
7. Description of statistical analyses expanded for clarity.
8. Text added to allow for collection of pre-study slides/tissue samples for use in future research.

SECTION CHANGES

The following changes (indicated with a ~~strikeout~~ (deleted text) or shaded areas (new text) have been made as Amendment 2 to the Protocol for Study MDX1105-01. Changes resulting from minor typographical or grammatical errors, or defining acronyms for the first time, are not summarized within the section changes noted below as they are not expected to affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

SECTION 1.1, INTRODUCTION AND RATIONALE

Change last sentence in fifth paragraph to read:

Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival~~, and new patients should not be given this drug~~. Thus novel therapies are needed for this subject population.

Change sixth paragraph to read:

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (~~95~~85%) are diagnosed early as localized tumors and curable. However, approximately ~~5% to 10~~15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and ~~therefore~~are in need of additional novel anticancer agents ~~are needed~~for treatment.

Change last sentence in seventh paragraph to read:

However about 50% to 75% of cases will relapse and have a poor prognosis~~. Thus~~; these subjects need additional options for treatment on relapse.

Add paragraph to read:

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006. The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

Reason for changes: Background information added for new CRC indication; need for additional treatment options emphasized; clarifications to text.

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SECTION 1.4.1, Dose Selection

Change the last sentence in the first paragraph to read:

In general, efficacy is expected to manifest at a dose between 1 and ~~15~~10 mg/kg. This may vary with repeated or combination treatments.

Reason for change: Maximum dose of 10 mg/kg to be studied based on nonclinical and clinical findings within the MDX-1105 program, findings across another and mechanistically related monoclonal related antibody therapy program within Medarex, Inc., in general, the evaluation that repeated doses up to 10 mg/kg will provide sufficient levels to allow for potential therapeutic effects to emerge.

SECTION 1.4.2, Safety Considerations

Change the first and second sentence in second paragraph; and third sentence in third paragraph to read:

~~Initial safety experience~~As of 14 April 2008, there were no DLTs reported after single dose administration of ~~MDX-1106 (an anti-PD-1 antibody) to subjects with cancer in Protocol MDX-1106-01, as of 15 April 2008, has shown no DLTs at the~~ 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, ~~and~~ or 10 mg/kg ~~dose levels~~of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer (Protocol MDX-1106-01). A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg of MDX-1106 over 32 weeks.

~~Only 17/88 (19.3%)~~ Seventeen subjects (17/88, 19.3%) with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations.

Reason for change: Update section with more recent safety information; clarifications of text; minor editorial changes.

SYNOPSIS and SECTION 2, STUDY OBJECTIVES

Add sentence to the primary objective to read:

The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

Add an additional secondary object to read:

The secondary objectives are to~~: 1)~~ evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) ~~characterize the~~ immunogenicity of MDX-1105; ~~and~~ 3) ~~characterize the~~ preliminary multidose pharmacokinetic profile of

MDX-1105; and 4) histologic, serologic, and cellular immune correlates of toxicity and/or clinical activity.

Reason for change: Addition of new CRC indication; secondary objective No. 4 added to provide additional safety/efficacy information; minor editorial changes.

SYNOPSIS and SECTION 3, OVERVIEW OF STUDY DESIGN

Change first and second paragraph to read:

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1). ~~Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], or epithelial ovarian cancer [epOC]) will be enrolled in~~) membrane receptor on T lymphocytes and other cells of the ~~study~~immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to ~~17~~16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Reason for change: List of indications moved to primary objectives; clarification of definition of PD-L1; clarification of text and minor editorial changes; global change to number of cycles.

SYNOPSIS, SECTIONS 3.1 and 8.1, DOSE ESCALATION

Change first sentence in second paragraph of Synopsis (Dose Escalation) and Section 3.1, and first sentence in the first paragraph of Section 8.1 to read:

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose ~~administered as an intravenous (i.v.) infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29)~~level.

Change third paragraph of Synopsis (Dose Escalation) and Section 3.1, and the first five sentences in the second paragraph of Section 8.1 to read:

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects ~~has~~experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD , the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. ~~The MTD is the highest~~

~~dose studied where ≤ 1 in 6 subjects experiences a DLT.~~ Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

Change fourth paragraph of Synopsis (Dose Escalation) and Section 3.1 to read:

If ~~4~~2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

Add fourth and fifth paragraph to Section 8.1 to read:

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Reason for change: Changes to holding of accrual with delayed DLTs to increase subject safety; clarifications of text around dose escalations/de-escalations and to improve readability and consistency within the document; minor editorial changes.

SYNOPSIS and SECTION 3.2, EXPANSION COHORTS

Change section to read:

~~A total of 16 subjects (6 in the dose-escalation cohort + 10 in the~~To further characterize safety and efficacy, up to 7 expansion cohort)s will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified~~. For~~) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohort~~, if 3 or more~~ s. If none of the first 5 subjects ~~experience~~ have a DLT ~~or 4 or more subjects experience a delayed DLT~~by the end of Cycle 1, enrollment ~~will be held pending completion of a safety analysis by the Investigator and~~ to the ~~Medarex Medical Monitor and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).~~primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.

b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Reason for change: Increase the expansion cohorts with regard to number of cohorts tested (all 5 indications at the primary expansion dose level and additional MEL expansions at two other dose levels) and number of subjects per cohort (up to 16 subjects [dose-escalation plus expansion] within each cohort) in order to gain additional safety and tolerability information as well as provide an initial estimate of efficacy.

SYNOPSIS and SECTION 3.2.1, INITIATION OF THE PRIMARY EXPANSION COHORTS

Add new section to read:

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Reason for Change: Increase the safety and efficacy information for each indication at the highest dose level tested.

SYNOPSIS and SECTION 3.2.2, INITIATION OF THE ADDITIONAL MELANOMA EXPANSION COHORTS

Add new section to read:

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.

If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.

If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.

Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Reason for change: Gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy; provide instruction for enrollment of subjects into MEL expansion cohorts.

SYNOPSIS, SECTIONS 3.2.3, and 8.4, STOPPING RULES FOR THE EXPANSION COHORTS

Add new section to Synopsis and add Section 3.2.3, to read:

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Change Section 8.4 to read:

~~For the expansion cohort (10 subjects), if 3 or more subjects experience a DLT or 4 or more subjects experience a delayed DLT, enrollment will be held pending completion of a safety analysis by the Investigator and the Medarex Medical Monitor, and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).~~

Enrollment may be held in all expansion cohorts if the rate of DLTs is ≥ 33% across all 5 indications at the MTD dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate will be calculated based on the total number of subjects in a cohort (dose-escalation plus expansion). New enrollment should be held in the dose level where DLTs are ≥ 33% and at any higher dose level that might also be enrolling at that point in time (lower dose level expansion may continue). Subjects who are tolerating a study drug dose level that is being reviewed due to DLTs that occurred in other subjects will not be automatically precluded from continued dosing during this safety review, and will be allowed to continue dosing for as long as is tolerated unless the safety review mandates dose reduction. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for apply to DLTs.

Reason for change: Provide guidance on the stopping rules for enrolling subjects into the expansion cohorts.

SYNOPSIS and SECTION 3.3, ADMINISTRATION OF ADDITIONAL TREATMENT CYCLES

Change second paragraph of Synopsis (Administration of Additional Treatment Cycles) to read:

The maximum number of cycles to be administered to an individual subject in this study is ~~17~~16 (with up to 3 doses per cycle). ~~Following~~ At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than ~~14~~14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle ~~and no later than 21 days after the last dose~~ to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been ~~±~~a 10% or greater change in weight ~~change~~ (increase or decrease) since the previous cycle.

Reason for change: Clarify dosing time windows; clarification of text regarding cycles; global change regarding dose adjustments.

Change first bulleted in Synopsis (under Administration of Additional Treatment Cycles) to read:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) ~~progressive disease (PD) that is confirmed and then worsens; 4)~~development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); ~~5~~4) other intolerability to therapy; or ~~6~~5) receipt of the maximum number of cycles.

Reason for change: Clarification and consistency across sections.

Change Section 3.3 to read:

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments **must** be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is ~~17~~16 (with up to 3 doses per cycle). Following each treatment cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to MDX-1105 that

precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 ± 2 days after the last dose of the prior treatment cycle but no later than 28 ± 2 days. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive MDX-1105 therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

  Subjects with PD should be managed in the study as follows:

  – PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the Medarex Medical Monitor as described in Section 8.7.

  – PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.

    - If, at each subsequent imaging evaluation (Cycle 3 or later)**, there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.

- If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to MDX-1105 that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

Reason for change: Expand and clarify criteria for additional cycles of treatment; global change to total number of cycles allowed.

SYNOPSIS and SECTION 3.4, FOLLOW-UP PERIOD

Change Synopsis and first paragraph in Section 3.4 (Follow-up Period) to read:

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1~~ (7 days after the last visit of the last treatment cycle)~~. Completion of subsequent follow-up visits ~~(Follow-up Visits 2 and 3)~~ will depend on the status of the subject at the end of ~~treatment~~the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit ~~for approximately 6 months~~ until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

Add additional sentence to end of first paragraph, Section 3.4:

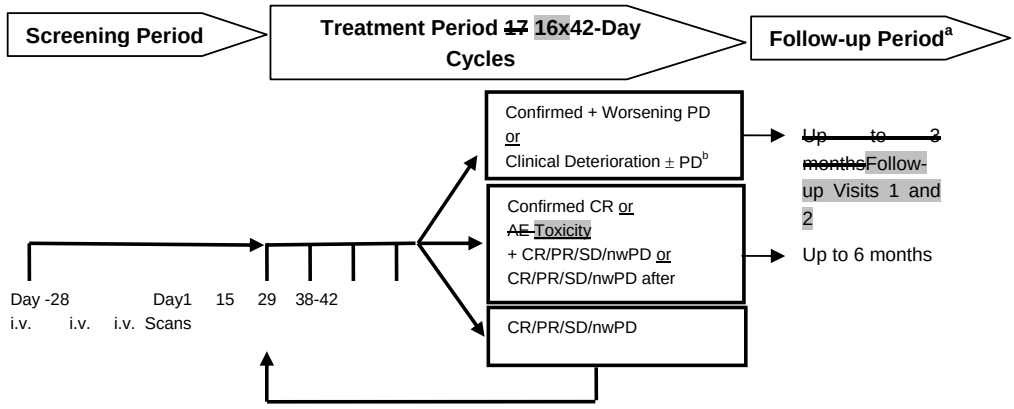
Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

Reason for change: Clarifications to text; minor editorial changes.

SECTION 3, OVERVIEW OF STUDY DESIGN

Change Figure 1 to read:

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



~~AE = adverse event;~~ CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects ~~who discontinue from the study within 90 days after the administration of the~~, all adverse events occurring within 70 days of last dose of study drug~~, the subject~~ should be reported and study drug-related AEs should be followed to resolution~~/~~ or stabilization ~~of: 1) ongoing study drug-related adverse events; 2) new study drug-related adverse events that occur within the 90-day period; and 3) adverse events that led to the discontinuation. A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit. Only study drug~~. After 70 days of last dose of study drug, only treatment-related serious adverse events ~~will be collected > 90 days after the last administration of study drug~~or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

~~[c] Follow-up should continue until relapse, initiation of a new therapy, or a total of 6 months (3 months for confirmed PD), whichever comes first.~~

Reason for change: Consistency across sections; clarifications to text; minor editorial changes.

SECTION 4.1, INCLUSION CRITERIA

Change criteria 4, 7, 10, and 13 to read

4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable

to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, ~~including~~such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic ~~taxane-based~~ therapy.

For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior ~~standard~~ systemic therapy (may include high-dose~~ interleukin~~IL-2). All melanomas regardless of primary site of disease will be allowed.

For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic ~~platinum-based~~ therapy.

7. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging ~~(~~[MRI~~) evidence of progression~~] with contrast – preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;

10. At least 28 days since the last chemotherapy, immunotherapy, biological or investigational therapy, ~~radiation,~~ or ~~at least 2 weeks from~~ approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of MDX-1105 and have recovered from any toxicity associated with such treatment;

13. Screening laboratory values must meet the following criteria:

WBC ≥ ~~3000~~2000/μL

Reason for change: No. 11 clarification of imaging methods; No. 13. screening laboratory value for WBC changed for consistency across studies; other clarifications of text, minor editorial changes; global addition of CRC indication.

Section 4.2, Exclusion Criteria

Change criteria 3 to read:

3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been ~~adequately treated~~apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;

Reason for change: Clarification of text.

SYNOPSIS, and SECTION 7.4, STUDY DRUG PREPARATION AND ADMINISTRATION

Change first paragraph and steps 4 and 5 of Section 7.4 to read:

MDX-1105 (0.3, 1, 3, and 10~~, or 15~~ mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to ~~17~~16 cycles). The following steps outline the procedures to be followed for the preparation and infusion of MDX-1105.

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary.

5. Prepare the MDX 1105 solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX 1105 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX 1105 10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

   If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted MDX-1105 is needed. In this case, all drug should be infused in 60 minutes.

Reason for change: Clarifications of text and minor editorial changes; global changes to number of cycles and top dose level.

SECTION 7.6, DOSE ADJUSTMENTS, INFUSION DELAYS, AND MISSED DOSES

Change first 2 sentences to read:

There will be no dose adjustments allowed for MDX-1105 except for weight changes (~~a~~ a 10~~%)~~% or greater change in weight [increase or decrease]) at the beginning of each cycle. ~~There must be a minimum~~If a subject is eligible to receive additional cycles, the first dose of ~~14~~ the next cycle should be given no earlier than 14 ± 2 days ~~between study drug infusions~~and no later than 28 ± 2 days after the last dose of the prior treatment cycle.

SECTION 8.2, DOSE-LIMITING TOXICITY

Change third paragraph to read:

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. ~~If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).~~

Reason for change: Clarification to text regarding time windows for dosing and delayed DLTs; global change to dose adjustment wording.

SECTION 8.7, STOPPING RULES FOR CLINICAL DETERIORATION

Change last sentence of second paragraph to read:

The decision to continue or stop treatment should be discussed with the Medarex Medical Monitor and will be documented in the study files.

Reason for change: Clarification of documentation of stopping rules.

SECTION 10, CONCOMITANT THERAPY

Change items c and d to read:

~~c. Concomitant use of other ccRCC/MEL/epOC/NSCLC cytotoxic chemotherapy, investigational agents, growth factors, cytokines, and RT may not be used while the subject is on the study. Radiation therapy for bone pain will be discussed with the Medical Monitor.~~

~~d. No other investigational therapies for any reason shall be administered while the subject is in the study.~~

c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.

d. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.

Reason for change: New point "c" replaces original c and d; clarification of allowed palliative therapy.

SECTION 11.1.2, SCREENING PERIOD

Change the following bulleted items to read:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions);

  ~~Baseline signs and symptoms:~~ Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF

- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject;
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Serum β-HCG pregnancy test (~~to be taken within 7 days before the first infusion;~~ for all women of childbearing potential; serum pregnancy test must be negative to continue);
- ~~Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent;~~

Reason for Change: Final bullet replaced by new bullets 2 through 5 clarifying biopsy information; clarification of timing of serum pregnancy test so that it may be done at the same time as other Screening tests; minor editorial changes.

SECTION 11.1.3, TREATMENT PERIOD

Change section to read:

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start MDX-1105 treatment within ~~0 to~~ 28 days of Screening. Subjects will receive ~~3 doses~~1 dose of MDX-1105 every 14 days ~~during each~~ for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1105 will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by ~~1~~2 or more days) or missed doses, see Section 7.~~7~~6 for administration details. A subject who misses a dose during Cycle 1~~ only,~~ not due to a DLT, will be replaced.

Reason for change: Clarifications of text and minor editorial changes; global change to dose adjustment.

SECTION 11.1.3.1, CYCLE 1

Change last sentence of first paragraph to read:

The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment ~~within~~between Days 38 ~~to~~and 42.

Change the following bulleted items to read:

- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects;

Reason for change: Addition of blood tests for biomarkers; clarifications of text and minor editorial changes.

SECTION 11.1.3.2, CYCLES 2-16

Change the following bulleted items to read:

- Weight (changes to study drug dose will only be made if there has been a ~~≥~~10% or greater ~~weight~~ change in weight [increase or decrease] since the previous cycle);
- ~~Optional cryopreserved~~Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1);

- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects;

Reason for change: Addition of blood tests for biomarkers; clarification to dose adjustments; minor editorial change.

SECTION 11.1.4, FOLLOW-UP

Change the following bulleted items to read:

- ~~Urine~~Serum β-HCG pregnancy test;
- 12-lead ECG
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects

Reason for change: Change from urine to serum pregnancy test for increased subject safety; addition of tumor-specific therapy to visit; clarification of ECG; addition of blood tests for biomarkers.

SYNOPSIS and SECTION 11.2, SAFETY EVALUATIONS

Change Synopsis to read:

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, ~~flow cytometry~~pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Change Section 11.2 to read:

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1105: vital sign measurements, clinical laboratory tests, flow cytometry, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Reason for change: Flow cytometry removed from safety parameters and added to exploratory parameters; pregnancy testing added to safety parameters; clarification of text.

SYNOPSIS and Section 11.2.3, EXPLORATORY IMMUNE FUCTION EVALUATIONS

Change Synopsis to read:

Samples will be collected, and evaluated for ~~cryopreservation of~~lymphocyte phenotype, and cryopreserved lymphocytes and plasma ~~and~~ will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. ~~Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.~~

Change first paragraph of Section 11.2.3 to read:

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

- **Reason for change:** Flow cytometry moved to exploratory parameters from safety parameters; addition of text to allow for collection of slides or tissue samples from pre-enrollment tumor biopsies; clarification of evaluations; minor editorial changes.

SYNOPSIS and SECTION 11.4, PHARMACOKINETIC EVALUATIONS

Change Synopsis to read:

For Cycle 1, Day 1, blood samples for assessment of the serum concentration~~s~~ of MDX-1105 will be ~~assessed pre-dose~~ drawn within 30 minutes before ~~and~~infusion, at the end of ~~the~~ infusion, and at 30, 60, 120, and 240 minutes ~~post~~ after infusion. For Days 2, 3, 4, and 8, ~~and 42,~~ a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to ~~17~~16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-up Visits 1 and 2.

~~Post-infusion samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on the days of infusion.~~

Change second paragraph of Section 11.4 to read:

Blood samples for the analysis of serum concentrations of MDX-1105 will be drawn in all subjects according to the schedule listed below and in Table 3~~ of the Time and Event Schedule~~. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

Reason for change: Day 42 PK blood sample collection deleted as that visit is for imaging only and is not a standard clinic visit; clarifications of text; minor editorial changes; global change to number of cycles allowed.

SECTION 11.4.1, CYCLE 1

Change bulleted items to read:

- **Day 1:** pre-dose (within 30 minutes before infusion), ~~and~~ at the end of ~~the~~ infusion, and at 30, 60, 120, and 240 minutes ~~post~~after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- Days 2, 3, 4, and 8, ~~and 42~~: single serum samples will be taken on each day.

Reason for change: Day 42 PK blood sample collection deleted as that visit is for imaging only and is not a standard clinic visit; minor editorial changes.

SECTION 12.1.1 SAFETY REPORTING FOR ADVERSE EVENTS

Change second paragraph and bulleted item to read:

For subjects who discontinue from the study within ~~90~~70 days after the administration of the last dose of study drug:

- Only treatment-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects ~~90~~70 days after the administration of the last dose of study drug.

Reason for change: Clarifications of text; global change to number of days for collection of AEs.

SECTION 12.3, RAPID NOTIFICATION OF SERIOUS ADVERSE EVENTS

Change title to read:

12.3 ~~Instructions for~~ Rapid Notification of Serious Adverse Events

Reason for change: Editorial change.

SECTION 12.6, IMMUNE-RELATED ADVERSE EVENTS

Add text to end of section to read:

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105 program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

Reason for change: Clarification to text to increase the oversight of subject safety.

SYNOPSIS and Section 13.1 SAMPLE SIZE DETERMINATION

Change Synopsis and Section 13.1 to read:

~~The sample size for this study is not determined from power analysis.~~ A total of up to ~~40~~ 130 subjects ~~with measurable advanced or recurrent solid tumors~~ are to be enrolled in this study based on the ~~ATD~~study design for dose escalation ~~and~~, safety evaluation, and anti-tumor activity evaluation requirements.

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size ~~at the MTD or highest dose level~~of each expansion cohort is determined by a power analysis. It is assumed that the ~~patients~~subjects would have no response if they would not have received any

therapy and that BORR for ~~patients~~subjects in the ~~MTD or highest dose level~~ expansion cohort would be 10%. Based on this assumption, a sample size of 16 ~~patients in the MTD or highest dose level~~ subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Change Synopsis to read:

Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.

~~The efficacy parameter, the BORR, will be summarized using descriptive statistics. All safety and pharmacokinetic parameters will be summarized using descriptive statistics.~~

Efficacy and safety parameters will be summarized by dose and by indication using descriptive statistics. For BORR in each expansion cohort, a one-sided exact Bionomial text will be performed and the 95% confidence intervals will be determined. Time to response and duration of response will be summarized for those subjects with confirmed responses. For the expansion cohorts, efficacy analyses will only be applicable to cohorts that enroll at least 16 subjects. The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests, immune safety assays, ECOG, physical examination, vital signs, ECGs, and immunogenicity results will be summarized using descriptive statistics.

Reason for change: Revisions to include additional information on the statistical analyses to the Synopsis; editorial changes because of the extra expansion cohorts; other minor editorial changes.

Section 13.2.2, Per-protocol Population

Change last sentence of section to read:

A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population with the exception of those withdrawn for rapid progression after receiving only 2 or 3 doses.

Reason for change: Clarification of Per-protocol Population criteria.

Section 13.2.3, Pharmacokinetic Population

Change section to read:

The pharmacokinetic population includes all subjects in the safety population who complete all 3 infusions in Cycle 1 and have completed the pharmacokinetic assessments ~~up to Day 42~~ of that cycle.

Reason for change: Day 42 PK blood sample collection deleted as that visit is for imaging only and is not a standard clinic visi**t**

Section 13.2.4, Safety

Change second and last sentence of third paragraph of Adverse Events to read:

The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, treatment-related serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized.

The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE version 3.0), ~~irAEs, TEAEs,~~ and additional grouping by severity and relationship to study drug. ~~Individual listings of adverse events will be provided.~~

Change last sentence of Clinical Laboratory Tests to read:

Laboratory values which are outside normal range will be flagged as H (above high normal limit)~~or~~), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE 3.0 Grade will also be flagged in the listings.

Reason for change: Revisions to include additional information on the statistical analyses to the Synopsis; clarification of laboratory flags to be used in listings; other minor clarifications.

SYNOPSIS and SECTIONS 11.3.1 (Efficacy Parameter) and 13.3.5 (Efficacy)

Change Synopsis to read:

The primary efficacy endpoint is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator ~~tumor~~ evaluations for each indication. Tumor response status will be assessed using RECIST with modifications.

Independent ~~confirmation of responses~~ review of tumor assessments may be requested at the discretion of ~~the Sponsor,~~ Medarex.

The secondary efficacy parameters include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with confirmed responses.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and

documented before initiating a new cycle of treatment with MDX-1105; Tumor response status will be assessed using RECIST with modifications, as well as by tumor-specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9).

Change first paragraph of Section 11.3.1 to read:

The primary efficacy endpoint is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator ~~tumor~~ evaluations for each indication. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent ~~confirmation of responses~~ review of tumor assessments may be requested at the discretion of ~~the Sponsor,~~ Medarex.

Change Section 13.3.5 to read:

The ~~efficacy analysis will be conducted on the per protocol population.~~

~~The~~ primary efficacy endpoint is the BORR~~,~~ during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator ~~tumor~~ evaluations~~. The~~ for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of Medarex. In each expansion cohort, a one-sample exact Binomial test will be performed for the BORR and the 95% confidence intervals will be determined.

The secondary efficacy endpoints include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), progression-free survival, and the time to response and duration of response for those subjects with confirmed responses. All the secondary efficacy parameters will be summarized using descriptive statistics ~~by~~for each expansion cohort. Progression-free survival will be summarized using Kaplan-Meier survival methods. Time to response ~~level: CR, PR, SD,~~ and ~~PD~~duration of response will be summarized for those subjects with confirmed responses.

For the expansion cohorts, efficacy analyses will only be applied to the cohorts that enroll at least 16 subjects.

Reason for change: Clarification of secondary endpoints; clarification of assessments and inclusion of tumor-specific antigen levels; expanded description of statistical analyses for efficacy parameters; minor editorial changes.

SYNOPSIS and SECTION 13.3.7, EXPLORATORY IMMUNE FUNCTION STUDIES

Change Synopsis to read:

EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Samples will be collected, and evaluated for ~~cryopreservation of~~lymphocyte phenotype, and cryopreserved lymphocytes and plasma ~~and~~ will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. ~~Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.~~

Move Exploratory Immune Function Studies and Flow Cytometry from Safety (Section 13.3.4) to Section 13.3.7.

Reason for change: Assessments moved from safety as they should be considered as exploratory.

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
~~Baseline signs and symptoms~~	~~•~~											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[11]	•[12]								•	•[14]	•	•
Brain CT scan/MRI[11,13]	•[12]								•[14]	•[14]	•[14]	•[14]
Bone scan (if clinically indicated)~~[17]~~[15]	•[12]								•[15]	•[15]	•[15]	•[15]
Response assessment									•			
ECG (12-lead)	•[12]	•~~[17]~~[16]								•		
Hematology	•	•~~[17]~~[17]			•~~[17]~~[17]	•~~[17]~~	•~~[17]~~[17]	•~~[17]~~		•	•	•
Serum chemistry	•	•~~[17]~~[17]			•~~[17]~~[17]	•~~[17]~~	•~~[17]~~[17]	•~~[17]~~		•	•	•
Immune safety assays~~[17, 17]~~		•								•	•	
Optional tumor or other biopsy	•[18]~~[17]~~											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry~~[17]~~		•								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		• ~~[17]~~								•		
Serum sample for immunogenicity		• ~~[17]~~								•	•	
MDX-1105 infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
~~Off Treatment/Study Procedures~~ ~~[17]~~												
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

continued

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Table 1 Footnotes:

1. Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. If a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.
4. To include collection of prior medication and prior/concurrent medical conditions.
5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).
6. ~~Serum β-HCG pregnancy test with 7 days before the first infusion and urine pregnancy test at all other indicated timepoints before infusion for women of childbearing potential.~~ Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.
8. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.
9. ECOG Performance Status to be assessed before each infusion.

continued

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TABLE 1 FOOTNOTES *(continued)*

10. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and ~~only~~ before ~~each initial~~ the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

11. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

12. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

13. Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days ~~2 months~~ (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or ~~if~~ as clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be ~~should be~~ repeated at every cycle ~~(end of Cycle 2, 4, 6, etc.)~~ during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

14. To be performed if clinically indicated and if not done within the preceding 28 days.

~~14~~15. If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated ~~if~~ and not done within the preceding 56 ~~28~~ days. Bone scan will not be required at the end of Cycle 1 if positive at ~~Baseline~~ Screening, unless clinically indicated.

~~15~~16. To be performed pre- and postinfusion.

~~16~~17. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.

~~17~~ ~~To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibody titer and pattern.~~

continued

TABLE 1 FOOTNOTES *(continued)*

~~18.~~ ~~The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSa antibody (Ro), anti-islet cell antibody; anti-SSB antibody (la), anti-neutrophil cytoplasm antibody, antithyroglobulin andtibody, C3 and C4, anti-LKM antibody, and CH50.~~

18. Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

19. CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

~~20.~~ ~~Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include by may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD14, CD16+56 [NK]).~~

~~21.~~ ~~Sample collected pre-infusion.~~

~~22.~~ ~~Serum sample for immunogenicity evaluation will be collected within 30 minutes before infusion.~~

~~23.~~ ~~When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.~~

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Table 2: Time and Events Schedule for Cycles 2-~~17~~16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-~~17 (±~~16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
~~Urine pregnancy~~Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]	•	
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•[15]	•[15]		•	•	•
Serum chemistry	•[15]	•[15]	•[15]		•	•	•
Immune safety assays[~~16,17~~]	•				•	•	
Tumor-specific blood tests[18]	•				•	•	•
Optional tumor or other biopsy[19]							
Urinalysis	•	•	•		•	•	•
~~Cryopreserved PBMC (research samples for exploratory immune function evaluation)~~	•[~~20~~]				•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

continued

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Table 2: Time and Events Schedule for Cycles 2-~~17~~16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-~~17 (±~~16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
~~Flow cytometry~~[21]	•						
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[22]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•				•	•	
MDX-1105 infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
~~Off Treatment/Study Procedures~~[23]							
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

1. Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject ~~has~~ will permanently ~~discontinued~~ discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given ~~14~~no sooner than 14 ± 2 days (and no later than ~~21~~28 ± 2 days) after the last dose of the prior treatment cycle.

continued

Approved v1.0 930041402 1.0

Table 2 Footnotes *(continued)*

3. The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
4. ~~For~~Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
5. Pharmacokinetic sampling to be performed according to Table 3.
6. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes post infusion and longer if necessary until the subject is stabilized.
7. ECOG Performance Status to be assessed before each infusion.
8. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken ~~only~~ before ~~each initial~~the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note:** Dose adjustments will only be made if there has been ≥a 10% ~~weight~~ or greater change in weight [increase or decrease] since the previous cycle).
9. The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.
10. To be performed if clinically indicated and if not done within the preceding 28 days.
11. Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or ~~as~~PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans ~~should~~/MRI will be repeated ~~every other cycle (end of~~after Cycle ~~2,~~ 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-~~Up~~up Visits 2 and 3. ~~If positive at baseline, the brain scan must be performed to confirm CR or PR.~~
12. If the bone scan is positive at ~~baseline~~Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.
13. At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation.

~~12~~14. To be performed pre- and post-infusion.

continued

Approved v1.0 93004402 1.0

Table 2 Footnotes *(continued)*

~~14~~15. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.

~~15. To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibodytiter and pattern.~~

~~16. The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.~~

16 CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

17. Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

~~18.~~ Sample collected for Cycles 2 and 3 only~~(pre-infusion) and at Follow-Up Visit 1.~~

~~19. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK])~~.

~~20. When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.~~

Table 3: Pharmacokinetic Sampling Schedule

~~Minutes~~**Sample collection time points**	**Cycle 1**[43]					**Cycle 2-~~17~~**[44]**16**[45]	**Follow-up Visits 1 and 2**[46]
	Day 1	**Days 2-4**	**Day 8**	**Day 15**	**Day 29**	**Days 1, 15, 29**	
~~Non-infusion days~~Any time during the visit		•	•				•
~~-~~30 to ~~-30(pre-~~0 minutes before infusion~~)~~	•			•	•	•	
~~60 (~~At the end of infusion~~)~~	•			•	•	•	
~~90~~30 minutes after the infusion	~~•~~						
~~120~~60 minutes after the infusion	•						
~~240~~120 minutes after the infusion	•						
240 minutes after the infusion	•						

43. ~~Serum~~Blood samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before ~~and~~ infusion, at the end of ~~the~~ infusion, and at 30, 60, 120, and 240 minutes ~~post~~after the infusion. For Days 2, 3, 4, and 8, ~~and 42,~~ a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.

44. ~~For Cycles 2-17, samples will be drawn every 14 days, 30 minutes before the administration of MDX-1105 and at the end of each infusion.~~

45. For Cycles 2-16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX-1105 and at the end of each infusion.

46. A single sample will be taken at Follow-up Visits 1 and 2.

MEDAREX

Page: 1 of 2
Protocol Number: MDX1105-01
Version: Amendment 3
Development Phase: Phase 1
IND Number: 101,850
Document Status: Final
Date: 02 October 2009

Clinical Protocol MDX1105-01 Amendment 3

Summary of Change

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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The following changes have been made to the Time and Events Schedule as Amendment 3 to the Protocol for Study MDX1105-01.

TABLE 1: Time and Events Schedule for Cycle 1 (Page 14)

- Added hematology and serum chemistry to be performed on Day 8.

TABLE 3: Pharmacokinetic Sampling Schedule (Page 23)

- Added blood sample to be drawn 30 minutes after the infusion on Day 1.

Reason for changes: Inadvertently deleted hematology and serum chemistry timepoint in Amendment 2. Pharmacokinetic sampling 30 minutes after infusion on Day 1 was missing from Table 3 (Note: timepoint was presented in Footnote 1 of Table 3)

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Page: 1
Protocol Number: CA210001 (MDX1105-01)
IND Number: 101,850
EUDRACT Number NA
Date: 02-Mar-2010

Protocol CA210001 (MDX1105-01): A Phase 1, Open-Label, Multicenter, Dose-Escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Amendment Number 04
Site Number: All

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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The protocol was amended to incorporate information and processes resulting from the acquisition of Medarex, Inc. by Bristol-Myers Squibb Co (BMS). New and revised protocol sections were incorporated to provide more clarity to investigators and where applicable to provide investigators with new instructions. Statistical sections are revised to match BMS template and to assure all statistical analyses in the protocol are consistent with BMS statistical principles. In addition, changes were made to two of the inclusion criteria. Inclusion criterion #6 that limits previous systemic therapies to 5 is removed because the intention of this requirement was to make sure patients enrolled in this study have acceptable performance status, which is already covered inclusion criterion #3. The washout period since the last chemotherapy, immunotherapy, biological therapy, or approved TKI therapy specified in inclusion criterion #10 is changed from 28 days to 14 days or 5 half lives (whichever is longer) to implement appropriate washout periods that address a wide range of half-lives.

All changes are summarized below.

Major Changes to the Protocol:

- Section 2.2: Secondary Objective #3 is modified to indicate pharmacokinetics evaluation is not preliminary. Secondary Objective #4 is moved into Exploratory Objectives.

- Section 2.3: Exploratory Objectives are added to evaluate the association between biomarkers and clinical activities and toxicities.

- Section 4.1: remove the inclusion criterion #6 in previous protocol version that limits the systemic therapies to 5.

- Section 4.1: inclusion criteria #14 is modified to indicate appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject.

- Section 4.1: in inclusion criterion #10, washout requirement for prior therapies is changed from 28 days to 14 days or 5 half-lives (whichever is longer).

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- Section 4.2: add two exclusion criteria #15 and #16 to exclude prisoners or subjects who are involuntarily incarcerated, or subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

- Section 7.7: the following is deleted "A subject will be considered to have discontinued study drug if they miss 2 consecutive doses within a cycle."

- Section 11.3.1: primary efficacy endpoint is changed from Best Overall Response Rate to Objective Response Rate.

- Section 11.4: PK parameters are changed to AUC(0-T), AUC(INF), Cmax, Tmax, T-HALF, Vss and CLT.

- Section 13.2.1: definition of Safety Population is modified.

- Section 13.2.2: section title is changed from Per Protocol Population to Efficacy Population and definition is updated.

- Section 13.2.3: definition of Pharmacokinetic Population is updated to include subjects who receive BMS-936559 (MDX-1105) and have concentration-time data.

- Section 13.2.4: this new section is added to define Immunogenicity Population.

- Section 13.3: this new section is added to define safety, efficacy and PK endpoints, while Section 13.3 in previous protocol revision (Statistical Considerations) is deleted.

- Section 13.4: this new section is added to describe safety analyses, efficacy analyses, PK analyses, immunogenicity analyses and exploratory analyses.

- Sections 13.4 (Missing Data Handling) in previous protocol revision is deleted because it should be defined in Statistical Analysis Plan (SAP).

- Sections 13.5 (Statistical Software) in previous protocol revision is deleted because it should be described in SAP.

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Other Changes to the Protocol:

- Throughout the protocol, the protocol number is changed from MDX1105-01 to CA210-001 (MDX1105-01), drug name is changed from MDX-1105 to BMS-936559 (MDX-1105), and Medarex is changed to Bristol-Myers Squibb Co. or BMS.

- On cover page, Medical Monitor's contact information is changed and Central Emergency Phone Number is changed.

- Synopsis is updated to reflect the changes made in study objectives, endpoints and statistical analysis in the protocol.

- Abbreviations table is updated.

- Section 3.2.3: this section is moved to 3.5.2.

- Section 3.5: this new section combines the stopping rules in sections 3.5.2, 8.3, 8.4, and 8.7.

- Section 3.5: this is a new section added to address post study access to therapy.

- Section 4: add text to emphasize subjects must meet all criteria to enter into the study.

- Section 4.1: add text to specify that the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject.

- Section 7: add text and new section (7.1) to define investigational product.

- Section 7.4: add language about the storage of investigational product.

- Section 7.8: this is the new section added for the destruction of study drug.

- Section 7.9: this is the new section added to specify study drug should not be returned.

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- Section 8.1: the following text is deleted "A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be treated at the MTD or at the highest dose studied if the MTD is not identified." because the statement is not correct. Total of 80 patients from 5 cancer types will be treated at MTD.

- Section 11.1.7: this is the new section added to specify when subject must be discontinued from the treatment.

- Section 12: the following text is deleted from the previous protocol version "Clinical events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF."

- Section 12.1: definition of adverse event in this section is modified using BMS language.

- Section 12.1: the following text is deleted "Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them."

- Section 12.2: section title and content are modified to clarify the reporting procedures for non-serious adverse events.

- Section 12.3: the section is replaced with BMS language about the definition of SAE.

- Section 12.4: this is the Section 12.3 in the previous protocol version, where subsections 12.3.1, 12.3.2, and 12.3.3 are deleted and BMS language about when and how to report SAE is added.

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- Section 12.5: modify the section to clarify on reporting overdose as an SAE.

- Section 12.6: this section is added to clarify when laboratory test abnormalities should be reported as adverse events.

- Section 12.7.1: clarify pregnancy reporting procedure.

- Section 13: section title is changed from Statistical Methods to Statistical Considerations.

- Section 13.1: sample size determination is added.

- Section 13.2: section title is changed from Study Populations to Populations for Analysis.

- Section 14.1: add language that requires reporting potential serious breach of the conditions and principles of GCP in connection with the study or the protocol to BMS.

- Section 14.3: this section is replaced with BMS language about IRB/IEC review and approval.

- Section 14.4: this section is replaced with BMS language about informed consent procedure.

- Section 15.1: modify the section to clarify that the study shall be conducted as described in this approved protocol. Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation, except where necessary to eliminate an immediate hazard(s) to study subjects. In such case, investigator has to submit deviation or change to IRB/IEC review and approval and inform BMS and regulatory authorities.

- Section 15.3: this is the new section added about investigational site training.

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- Section 15.4: modify the section with BMS language about recording of data and retention of study documents.

- Section 15.6: the section is replaced with BMS language to clarify that the data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA).

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

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Approved v1.0 930043154 1.0
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AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA210001 (MDX1105-01)
Site Number:
Amendment Number: 04

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Page:	1
Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	16-Jun-2010

Protocol CA210001 (MDX1105-01): A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Amendment Number 05
Site Number: All

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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to address recent potential safety issues that have occurred and will include: 1) an update on infusion reactions and instruction on consequent pre-medication requirements and 2) an update on the irAEs of endopthalmitis and Myasthenia Gravis and benefit of management with immunosuppressive agents.

1) This amendment institutes a requirement for all subjects treated at the 10 mg/kg dose of BMS-936559 (MDX-1105) - regardless of whether the subject has been treated or has experienced infusion reactions previously - to be pre-medicated with acetaminophen and diphenhydramine for each dose. This requirement is based upon reports of infusion reactions described below. The amendment will also clarify the management of infusion reactions.

It has been observed that of the 46 subjects having received at least one dose of BMS-936559 (MDX-1105) at the 10 mg/kg dose level, 9 subjects have reported infusion reactions (4 Grade 1, 4 Grade 2, and 1 Grade 3). All of the subjects recovered with symptomatic treatment and 8 of the 9 were able to tolerate completion of infusion without further reaction. One subject discontinued due to recurrence of symptoms upon resuming infusion. Two subjects of 18 at the 3 mg/kg dose level also reported Grade 2 infusion reactions. These subjects also responded to treatment and tolerated completion of infusion without incident.

As an outcome, to minimize the risk of infusion reaction, the protocol will require all subjects receiving the 10 mg/kg dose to be pre-medicated with both acetaminophen and diphenhydramine. An investigator letter advising of the potential safety concern and detailing the specifics of pre-medication was issued on June 2, 2010 and this amendment is revised to be consistent with that guidance.

2) The amendment also provides information on two high Grade irAEs (immune-related adverse events) of Grade 4 pan-endophthalmitis and Grade 3 Myasthenia Gravis which have been reported in this study at the 3 mg/kg and the 10 mg/kg doses, respectively. In conjunction with these events, the benefit of prompt intervention with immunosuppressive agents such as corticosteroid in these settings is addressed.

Changes to the Protocol:

1) Cover page: medical monitor is changed to Stacie Goldberg
2) Synopsis, Time & Events Schedule Table 1, ECOG performance status, hematology and serum chemistry are unchecked at Day 42 and checked at day 36. Tumor Imaging is checked at Follow-up visit 3.

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3) Section 7.5, Study Drug Preparation and Administration, a new paragraph is added with instruction to pre-medicate the subjects receiving 10 mg/kg dose prior to the start of infusion of BMS-936559 (MDX-1105).
4) Section 8.3, Infusion Reactions, this section is replaced with the description of infusion reactions reported in the study so far, provide instructions to pre-medicate subjects receiving the 10 mg/kg dose, how to grade and treat infusion reactions and when patients can be re-treated following infusion reactions.
5) Section 8.4, Possible Toxicities, Bullet 8, 9 and 10, modify the section with currently reported immune-related adverse events (iRAE) in the anti-PDL-1 program and also provided with a algorithm to manage the reported iRAEs.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

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Dana-Farber v. BMS, IPR2023-00252
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AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA210001 (MDX1105-01)
Site Number:
Amendment Number: 05

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Page:	1
Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	20-Oct-2010

Protocol CA210001 (MDX1105-01): A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Amendment Number 06
Site Number: All

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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment includes the following: 1) to characterize the dose response relationship in melanoma (MEL) and non-small cell lung cancer (NSCLC) cohorts , and 2) evaluation of three new expansion cohorts of 10 mg/kg of BMS-936559 administered every 14 days in subjects with gastric carcinoma (GC), pancreatic carcinoma (PC) and breast cancer (BC).

Preliminary clinical activity data demonstrates that BMS-936559 elicits anti-tumor activity across a broad range of tumor indications including MEL (across dose levels at 1 mg/kg, 3 mg/kg, and 10 mg/kg) as well as RCC and NSCLC at 10 mg/kg. To date, there has been no observed dose response relationship. To further characterize safety, tolerability, and preliminary efficacy data in subjects with NSCLC with pre-specified tumor histologies as well as to explore multiple dose levels in subjects with NSCLC; three expansion cohorts are included in this amendment.

Based on the estimated half-life of BMS-936559 and the estimated prolonged receptor occupancy of BMS-936559 on T cell receptors, it is reasonable to expect that the range of clinically active doses includes dose levels lower than the dose of 1 mg/kg which has previously shown anti-tumor activity in melanoma. Therefore two additional cohorts of subjects with MEL are included in this amendment beyond the single subject previously tested at 0.3 mg/kg in the dose escalation phase

To assess anti-tumor activity in other potential indications, expansion cohorts will be added at the 10 mg/kg dose for subjects with gastric carcinoma (GC), pancreatic carcinoma (PC) and breast cancer (BC).

Other changes to the protocol include the following: 1) inclusion of extensive PK samples for 10 subjects at each dose level administered; 2) inclusion of an exploratory analysis using an immune-based response criteria based on modifications to the Response Evaluation Criteria In Solid Tumors (RECIST v 1.0); 3) modification to the drug preparation and administration guidelines to include instructions for the 0.1 and 0.3 mg/kg dose levels; 4) an allowance for reinitiating study therapy for subjects that demonstrate disease progression during the follow-up phase either after having achieved

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a confirmed complete response to therapy or after completion of all 16 treatment cycles with ongoing stable disease; 5) minor changes to eligibility criteria

Changes to the Protocol:

1) Section synopsis, objectives, Protocol section 2.0 Study Objectives: a) Updated text with other tumor indications. b) A new secondary objective was added to characterize the dose response relationship. Exploratory objective modified to include additional analysis parameters.
2) Synopsis, Overview of Study Design: language was added describing the allowance for subjects entering the follow-up phase to restart study medication upon disease progression. Follow-up period increased to 1 year to support re-initiation therapy.
3) Synopsis, dose escalation, Protocol section 3.1 Dose Escalation: language was added specifying that the 0.1 and 0.3 mg/kg dose levels did not impact the dose escalation plan for this study and qualifying that subjects in the 0.1 and 0.3 mg/kg dose levels will not be subject to the no intrapatient dose escalations.
4) Synopsis, expansion cohorts, Protocol section 3.2, Expansion Cohorts: language was added specifying the inclusion of 8 new expansion cohorts (3 cohorts in NSCLC, 2 cohorts in MEL and 1 cohort each in GC, PC and BC). The language also clarifies which cohorts had completed enrollment prior to this amendment and which cohorts were added as a direct result of this amendment. Language was included specifying that NSCLC cohorts and the MEL cohorts will each be randomized during enrollment.
5) Synopsis, Initiation of the Primary Expansion Cohorts, Protocol section 3.2.1, initiation of the primary expansion cohorts: language was added clarifying how the various expansion cohorts were initiated. The primary expansion cohorts were considered the primary MTD expansion cohorts. The initial melanoma expansion cohort was considered the non-MTD expansion cohorts. The newly added cohorts under this amendment are considered the additional expansion cohorts. Language was added to describe the initiation of the new expansion cohorts.
6) Synopsis, Administration of Additional Treatment Cycles, Protocol section 3.3, administration of additional treatment cycles: the criteria by which subjects are allowed to continue additional cycles of study therapy clarified.
7) Synopsis, Follow-up Period, Protocol section 3.4, and Follow-up Period: Follow-up period modified to 1 year to allow re-initiation therapy. A new section of Re-initiation of study therapy for subjects in follow-up period was included.
8) Synopsis, Duration of Treatment/study participation: Modified maximum study drug treatment time and study participation time.

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9) Synopsis, Study Population, Protocol section 4, Study Population: the total number of expected subjects was revised. Also, the number of subjects that have enrolled to date was specified.
10) Synopsis, Dosage and Administration: modified to include instructions for all anticipated dose levels.
11) Synopsis, Efficacy Evaluations, Protocol section 11.3, Efficacy Evaluations: revised based on the inclusion of additional cohorts and inclusion of immune-related response criteria analysis.
12) Synopsis, Exploratory Immune Function and Other Biomarker Evaluations, Protocol section 11.2.3, Exploratory Immune Function Evaluations: modified to collect additional exploratory samples for analysis under the amendment 6.
13) Synopsis, Pharmacokinetic Evaluations, protocol section 11.4, Pharmacokinetic Evaluations: modified to include the anticipated time points for collection and the parameters under evaluation.
14) Synopsis, Statistical Methods, protocol section 13, Statistical Considerations: revised based on the anticipated analyses and the number of expansion cohorts and tumor types.
15) Synopsis, Abbreviations: updated with additional abbreviations.
16) Synopsis, Table 1 and 2 along with foot notes was modified to include a) additional biomarker sample collection schedule b) follow-up period 3, 4 and 5 c) to modify the follow-up period to 1 year.
17) Synopsis, Table 3: Pharmacokinetic Sampling Schedule: modified to include intensive PK collection time points.
18) Protocol section 1.1, Background: modified to introduce the background of the additional tumor indications. Also updated with references as end notes.
19) Protocol section 1.4.1, Dose Selection: language was added to introduce two lower dose cohorts of 0.1 mg/kg and 0.3 mg/kg to achieve adequate pharmacokinetic profile.
20) Protocol section 1.4.2: a) title was modified to summary of the safety b) section modified to include the current summary of the safety data and a reference to safety information in the investigator's brochure.
21) Protocol section 3.6, Post Study Access to Therapy: modified to update the language to provide study treatment access via extension of the study.
22) Protocol section 4.1, Inclusion Criteria: a) inclusion # 3 was modified to eliminate inclusion of subjects with baseline ECOG of 2. b) inclusion # 4 was modified to include more expansion cohorts and washout period information. c) inclusion # 6 was added to collect archived or tumor tissue for correlative studies. d) inclusion # 11 modified to change the washout period time for previous therapy.

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23) Protocol section 4.2, Exclusion Criteria: exclusion # 16 was added to specify the vaccination requirement prior to initiation of study therapy.

24) Protocol section 5, Randomization and Blinding: was modified to specify that subjects enrolled in the new NSCLC and new MEL cohorts will be randomized to one of the dose levels included.

25) Protocol section 7.2, Non-investigational Product: a new section with non-investigation product definition was added.

26) Protocol section 7.5, Ordering Study Drug: a new section to provide information regarding the ordering of the study drug was added.

27) Protocol section 7.7, Study Drug Preparation and Administration: a) was modified to include instructions and guidance for study drug preparation for all anticipated dose levels. b) dose range information for the use diphenydramine was updated.

28) Protocol section 7.9, Dose Adjustments, Infusion Delays and Missed Doses: was modified to include additional language about maximum dosing delays and the allowance for subjects in the 0.1 and 0.3 mg/kg dose levels to be escalated to 1 mg/kg as described earlier in the amendment.

29) Protocol section 8.1, Dose Escalation: modified to add language specifying that the 0.1 and 0.3 mg/kg dose levels did not impact the dose escalation plan for this study.

30) Protocol section 8.3, Infusion reactions: a) Updated safety information related to infusion reaction. b) Modified information for the subjects with infusion reactions, premedication dose range for diphenhydramine and treatment guidelines to the investigator upon the occurrence infusion reaction.

31) Protocol section 8.4, Possible Toxicities, last bullet: updated number of subjects under treatment information.

32) Protocol section 10, Concomitant Therapy: modified to include language regarding clinically indicated infectious disease vaccinations and other language was clarified.

33) Protocol section 10.1 Treatment of Isolated Lesions section was added.

34) Protocol section 11.1, study procedures by visit: Updated the following sections:

   a) Protocol section, 11.1.3, Treatment Period: modified to correct protocol section references.

   b) Protocol section 11.1.3.1, Cycle 1: modified to update table and section references, additional exploratory sample collection schedules, response and adverse event assessments.

   c) Protocol section 11.1.3.2, Cycle 1: modified to updated language to collect additional exploratory samples.

   d) Protocol section 11.1.4, Follow-up: modified to include correct references.

   e) Protocol section 11.1.6, Study Participation: modified to update the follow-up language.

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35) Protocol section 11.2.1, Immunogenicity: modified to update the sample collection language.

36) Protocol section 11.4, Pharmacokinetic Evaluations: modified to include description of sample processing and PK parameters under evaluation.

37) Protocol section 12, Adverse Event reporting: modified to match standard sponsor template language.

   a) Protocol section 12.3, Rapid Notification of Serious Adverse Events: modified to change the contact person to which clinical site report adverse events of special interest and to include an additional type of event that requires reporting to BMS within 24 hours.

   b) Protocol section 12.8, Rapid Notification of Serious Adverse Events of importance: modified adverse events reporting language with BMS clinical team contact.

38) Protocol section 13, Statistical Considerations, 13.1, sample size determination: revised to include sample size estimates based on the anticipated toxicity and the number of anticipated expansion cohorts.

   a) Protocol section 13.2.2, All Enrolled Population: this section was added to define the All Enrolled Study Population.

   b) Protocol section 13.2.2, All Treated Population: this section was added to define the All Treated Study Population.

   c) Protocol section 13.2.3, Response Evaluable Population: this section was modified to include clarifying the analysis that will be conducted on this response evaluable study population.

   d) Protocol section 13.2.5, Exploratory Biomarker Population: this section was added.

   e) Protocol section 13.3.1, Safety Endpoints: modified language to include language regarding adverse event definitions and adverse event criteria used.

   f) Protocol section 13.3.2, Efficacy Endpoints: this section was modified to clarify the efficacy parameters that will be conducted.

   g) Protocol section 13.3.3, Pharmacokinetic Endpoints: modified to include additional parameters that will be summarized under this amendment.

   h) Protocol section 13.4.1, Demographics and Baseline Characteristics: this section was modified to specify the data types that constitute these parameters, and how they will be summarized.

   i) Protocol section 13.4.2, Safety Analysis: this section was modified to include language regarding adverse event definitions and the different sub-types of adverse events.

   j) Protocol section 13.4.3, Efficacy Analysis: modified to clarify the efficacy parameters that will be conducted.

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k) Protocol section 13.4.4, Immunogenicity Analysis: modified to include correcting and clarifying text on how immunogenicity data will be summarized.

l) Protocol section 13.4.5, Pharmacokinetic Analysis: modified to include correcting and clarifying text on types of analyses and pharmacokinetic parameters that will be summarized under this amendment.

m) Protocol section 13.4.6, Exploratory Biomarker Analysis: modified to include correcting and clarifying text on the parameters to be analyzed and the types of analyses to be conducted.

39) Protocol section 15.4, Recording of Data and Retention of Documents: modified to include correcting and clarifying text related to keeping the records of non investigational products.

40) Protocol section 16, References: new references with corresponding endnotes were added to the protocol reference section.

41) Protocol Appendix 2 and 3: modified as per the new sponsor template language. Re numbered appendices.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

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AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA210001 (MDX1105-01)
Site Number:
Amendment Number: 06

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Page:	1
Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	21-Sep-2011

Protocol CA210001 (MDX1105-01): A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Amendment Number 07

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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to revise the dosing solution preparation and storage guidelines as requested in the August 10, 2011 teleconference and August 17, 2011 partial hold removal letter from the U.S. Food and Drug Administration (FDA). The protocol has now been updated to provide, separate instructions for preparation of the 0.1 and 0.3 mg/kg dosing solutions which, in contrast to the 1, 3, and 10 mg/kg dosing solutions, require both a BMS-provided vehicle for dilution and normal saline.

In addition, the toxicity and events of special interest section have been revised to be consistent with the current version of the Investigator Brochure. Also, modifications to the inclusion/exclusion criteria have been provided to better capture potential study candidates with gastric and breast cancer and to better define baseline cardiac and pulmonary status. Updates have also been provided to include the current potential drug induced liver injury (DILI) language from the FDA as well as updates to the current template language for women of childbearing potential. Also, endpoints have been modified to more closely match objectives and pharmacokinetics and anti drug antibody collections have been modified based on the preliminary analyses of initial samples.

The above noted changes to the protocol will not impact the scientific integrity of the study and facilitate accrual and study conduct.

Changes to the protocol:

Major Changes:

1) Protocol section 4.1, inclusion criteria: Revised the inclusion criteria to better capture potential study candidates with gastric and breast cancer patients.
2) Protocol section 4.2, exclusion criteria: Revised the exclusion criteria to maintain more explicit guidelines regarding baseline cardiac and pulmonary status.
3) Protocol section 7, dosage and administration: Revised dosage and administration section.
4) Protocol section 12.8, updated the potential drug induced liver injury (DILI) language as per the new guidelines from health authority.
5) Protocol sections 8.4 and 12.6, revised the toxicity and events of special interest section to align with current data and updated Investigator brochure guidance.

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Minor changes:

1) Cover page, updated revised date, revised protocol number and amendment number.
2) Synopsis, objectives, safety evaluations, dose-limiting toxicity, biomarkers, protocol section 2.3, exploratory objectives, protocol section 12.6, immune related adverse events: Removed reference to the text 'irAE' and immune related toxicity section.
3) Synopsis, overview of the study design, table, figure 1, pharmacokinetic evaluations, Protocol section 3.2 expansion cohorts, table 4, figure 1, section 3.3 administration of additional treatment cycles: Removed reference to previous amendment 06. Updated text with amendment 07 reference.
4) Synopsis, duration of treatment/study participation: Updated study duration time to 5 years.
5) Synopsis, study population, protocol section 4, study population: Updated with number of subjects that have enrolled to date.
6) Synopsis, dosage and administration: Modified drug product dilution information.
7) Synopsis, efficacy evaluations, statistical methods and statistical analysis: Updated statistical sections for the alignment of objectives with endpoints and analyses. Modify the table to add immunogenicity sample collection column.
8) Synopsis, Immunogenicity analysis, protocol section 11.2.1, immune safety, section 13.4.4 immunogenicity analysis: Updated text human anti human antibody to anti drug antibody.
9) Synopsis, table 1 and 2, time and events schedule for cycles 1, 2-16 (Table 1 and 2): Updated response assessment requirement in follow-up period. Modify foot note to collect additional serum sample for immunogenicity analysis.
10) Synopsis, time and events schedule, Table 2, aligned the PK sample collections in table 3 with the text in the section 11.4 and added additional response assessments in follow-up period and immunogenicity sample collections in Table 2.
11) Synopsis, time and events schedule, Table 2A, added new time and events schedule will be updated (Table 2.A) for subjects treated under re-initiation of the study therapy.
12) Synopsis, time and events schedule, Table 3: Updated foot note 'e' as subjects who had screening baseline hemoglobin levels less than 10 g/dL will be excluded from collecting intensive PK sampling.
13) Protocol section 1.1, background: Updated with new tumor indications.
14) Protocol section 1.4.2, summary of safety: Updated with the current safety data.

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15) Synopsis and Protocol section 3.1, dose escalation, section 3.3 administration of additional treatment cycles, section 8.1, dose escalation, section 11.1.3, treatment period, section 11.1.3.2, cycle 2 to 16: Dose adjustments for > 10% change in weight allowed at any dose rather than just at the beginning of the cycle. Updated throughout protocol.

16) Protocol section 3.3, administration of additional treatment cycles: Modified required treatment days for additional treatment cycles. Removed section 8.7 reference.

17) Protocol section 4.1, inclusion criteria: Modified reference to amendment number for collecting tumor tissue samples. Bullet 14, updated language to collect samples at screening and at treatment.

18) Protocol section 4.2, exclusion criteria: Revised cardiac and pulmonary exclusion criteria. Corrected language for the exclusion criteria 4.

19) Protocol section 4.3, Women of child bearing potential; Language revised to comply with the core protocol template language.

20) Protocol section 6, assignment to study: Updated language to collect the data from the screen failure subjects into clinical database.

21) Protocol section 8.3, infusion reactions: Updated the section with current infusion reactions data and maximum study drug infusion time duration.

22) Protocol section 8.4, possible toxicities: Modified the section to update the data based on the current safety data available in the clinical database.

23) Protocol section 10, concomitant therapy: Updated to add language to include the prohibition Denosumab therapy.

24) Protocol Section 11.1.3.1, cycle 1: Bullet 12, updated with table 3 reference. Bullet 20 modified text Serum for quantitative PCR to Blood sample for quantitative PCR. Bullet 18, 19 and 20 removed references to amendment 06.

25) Protocol Section 11.1.3.1, cycle 2 to 16: Bullet 12, updated with table 3 reference. Bullet 14 and 15, removed references to amendment 06 and for cycle 2 collections.

26) Protocol Section 11.1.4, follow-up: Bullet 2, updated with table 3 reference.

27) Protocol section 11.4, Pharmacokinetic Evaluations: Modified to include language regarding the exclusion of subjects from intensive pharmacokinetic (PK) sampling, for subjects who had screening baseline hemoglobin levels less than 10 g/dL. Modified the language to align text with table 3.0. Removed the references to amendment 06.

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28) Protocol section 12.9, Other Safety Considerations: Modified the section number to 12.9.

29) Protocol section 11.2, Safety Evaluations, 11.3 Efficacy Evaluations, 13.2 population for analysis, 13.3 End point definitions and 13.4 Analysis: Updated statistical sections for the alignment of objectives with endpoints and analyses.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

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AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA210001
Site Number:
Amendment Number: 07

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Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	14-March-2012

Protocol CA210001(MDX1105-01):

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Amendment Number 08
Site Number: All

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Route 206 & Province Line Road
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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

Modifications to inclusion/exclusion criteria have been provided to facilitate enrollment of study candidates with breast and non-small cell lung cancer. Some typographical errors have been corrected and updated pregnancy reporting timelines have been incorporated.

Preliminary data generated from the CA210-001/MDX1105-01 study protocol has demonstrated objective responses (OR) as measured by RECIST 1.0 in multiple tumor types. To date, OR appear durable. It is therefore of clinical interest for the development of BMS-936559 to collect survival data as an exploratory endpoint. Collecting survival data on the number of subjects that have enrolled in this study will allow for exploratory correlations of dose and candidate predictive biomarkers with survival data and enable decision making for dose and schedule in subsequent clinical studies. In addition to inclusion of an exploratory objective of overall survival, additional exploratory objectives have been added to evaluate PDL-1 expression in tumors as well as to evaluate the level of PD-L1 receptor occupancy in peripheral blood.

Changes to the Protocol:

1) Protocol cover page, the revised date was updated to 14 March 2012, the revised protocol and amendment number was revised to 08.
2) Protocol synopsis, Objectives, exploratory objectives added for survival, evaluation of PDL-1 expression in tumors, and evaluation of PD-L1 receptor occupancy.
3) Protocol synopsis, Overview of Study Design, the inclusion of collection of survival data was specified
4) Protocol synopsis, Overview of Study Design, Dose Escalation and Expansion Cohorts, the subject replacement criteria was changed to ‘may be replaced’
5) Protocol synopsis, Survival Follow-up Period, section was added to the protocol describing the survival follow-up period
6) Protocol synopsis, Duration of Treatment/Study Participation, section was revised to include the additional survival component of the study
7) Protocol synopsis, Efficacy Evaluations, section was revised to include an exploratory analysis for overall survival
8) Protocol synopsis, Exploratory Immune Function and Other Biomarker Evaluations, section was revised to include evaluation of receptor occupancy.

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9) Protocol synopsis, Statistical Methods, Efficacy Analyses, section was updated to include an analysis for overall survival by Kaplan-Meier
10) Protocol synopsis, Statistical Methods, Biomarkers, section was updated to further clarify the types of biomarkers that will be evaluated as well as clarification on the expectation for exploratory interim analyses for decision making
11) Protocol synopsis, Table 1: Time and Events, footnotes were updated to include latest pregnancy reporting requirements and to correct some footnote references
12) Protocol synopsis, Table 2: Time and Events, table was updated to include Survival Visits and footnotes were updated to include latest pregnancy reporting requirements
13) Protocol synopsis, Table 2A: Time and Events, footnotes were updated to include latest pregnancy reporting requirements and to correct some footnote references
14) Protocol synopsis, Table 3: PK/PD, table was updated to include the actual sampling schedule, after Cycle 4, that is captured in the lab manual
15) Protocol Section 2.3, Exploratory Objectives, title was changed to plural and language was added to include exploratory objectives for survival, evaluation of PDL-1 expression in tumors, and evaluation of PD-1 receptor occupancy
16) Protocol Section 3, Overview of Study Design, the inclusion of collection of survival data was specified
17) Protocol Section 3.1, Dose Escalation and Section 3.2, Expansion Cohorts, the subject replacement criteria was changed to 'may be replaced'
18) Protocol Section 3.6, Survival Follow-up Period, section was added to the protocol describing the survival follow-up period
19) Protocol Section 3.7, Post Study Access to Therapy, section was renumbered
20) Protocol Section 4.1, Inclusion Criteria, maximum number of prior lines of therapy requirement for NSCLC subjects was removed (criteria #4); maximum number of prior lines of therapy requirement for subjects with BC was removed (criteria #4); criteria #5 requirement for evidence of disease progression since last anti-tumor therapy was removed; criteria #7 was removed as a placeholder after becoming not applicable after amendment #4; subsequent inclusion criteria were renumbered as a result; criteria #8 was changed to permit enrollment of patients whose only site of measurable disease is one that has been irradiated so long as there has been subsequent progression at that site.
21) Protocol Section 4.2, Exclusion Criteria, criteria #7 was changed to remove coagulopathy; criteria #8, Appendix reference was updated
22) Protocol Section 8.1, Dose Escalation and Section 11.1.3, Treatment Period, the subject replacement criteria was changed to 'may be replaced'
23) Protocol Section 11.1.6, Survival Follow-up, section was added to the protocol describing the survival follow-up phase and the types of data/assessments that will be

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collected

24) Protocol Section 11.1.7, Study Participation and Section 11.1.8, Discontinuation of Subjects from Treatment were renumbered due to addition of Survival Section

25) Protocol Section 11.2.3, Exploratory Immune Function Evaluations, section was revised to clarify the types of exploratory biomarker analyses that will be conducted to support the exploratory objectives under altered section 2.3

26) Protocol Section 11.3, Efficacy Evaluations, section was revised to include an exploratory analysis for overall survival

27) Protocol Section 13.3.3, Pharmacokinetic Endpoints, the section was updated to specify serum analyses

28) Protocol Section 13.4, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936559

29) Protocol Section 13.4.3, Efficacy Analyses, section was revised to include the analyses for overall survival and to clarify how efficacy analyses will be presented by tumor type

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

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AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA210001
Site Number: all
Amendment Number: 08

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MEDAREX

Protocol Number: MDX1105-01
Version: Amendment 1
Development Phase: Phase 1
IND Number: 101,850
Document Status: Final
Date: 05 September 2008

Clinical Protocol MDX1105-01 Amendment 1

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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If any Medarex contact information is changed during the course of the study, this will be done by Medarex, with written notification to the Investigator(s), and will not require (a) protocol amendment(s).

Replace all previous version(s) of the protocol with this revised Protocol Amendment No. 1

Property of Medarex, Inc.
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Bloomsbury, NJ 08804

Confidential

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SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

MDX1105-01

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

The secondary objectives are to: 1) evaluate preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) characterize the immunogenicity of MDX-1105; and 3) characterize the preliminary multidose pharmacokinetic profile of MDX-1105.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], or epithelial ovarian cancer [epOC]) will be enrolled in the study.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 17 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Five (5) dose levels are planned: 0.3, 1, 3, 10, and 15 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 0.3 mg/kg/dose administered as an intravenous (i.v.) infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs). If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. The MTD is the highest dose studied where ≤ 1 in 6 subjects experiences a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 4 or more delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been ± 10% weight change since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohort

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT or 4 or more subjects experience a delayed DLT, enrollment will be held pending completion of a safety analysis by the Investigator and the Medarex Medical Monitor and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 17 (with up to 3 doses per cycle). Following each cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 days after the last dose of the prior treatment cycle and no later than 21 days after the last dose to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been ± 10% weight change since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) progressive disease (PD) that is confirmed and then worsens; 4) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 5) other intolerability to therapy; or 6) receipt of the maximum number of cycles.
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit for approximately 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

The maximum duration of a subject's participation in this study is approximately 2.5 years.

STUDY POPULATION

Up to 40 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors, of one of the following histological documented types: RCC, NSCLC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

MDX-1105 will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 17 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, 10, and 15 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, flow cytometry, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related ≥ Grade 3 adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient (resolving within 6 hours of onset) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The efficacy endpoint is the best overall response rate (BORR) as determined by Investigator tumor evaluations. Tumor response status will be assessed using RECIST with modifications.

Independent confirmation of responses may be requested at the discretion of the Sponsor, Medarex.

EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Samples will be collected for cryopreservation of lymphocytes and plasma and stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

For Cycle 1, Day 1, serum concentrations of MDX-1105 will be assessed pre-dose within 30 minutes before and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. For Days 2, 3, 4, 8, and 42, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 17, samples will be drawn every 14 days, 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-Up Visits 1 and 2.

Post-infusion samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on the days of infusion.

STATISTICAL METHODS

The sample size for this study is not determined from power analysis. A total of up to 40 subjects with measurable advanced or recurrent solid tumors are enrolled in this study, based on the ATD for dose escalation and safety evaluation requirements.

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size at the MTD or highest dose level cohort is determined by a power analysis. It is assumed that the patients would have no response if they would not have received any therapy and that BORR for patients in the MTD or highest dose level cohort would be 10%. Based on this assumption, a sample size of 16 patients in the MTD or highest dose level cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.

The efficacy parameter, the BORR, will be summarized using descriptive statistics. All safety and pharmacokinetic parameters will be summarized using descriptive statistics.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BORR	Best overall response rate
ccRCC	Clear cell renal cell carcinoma
CMV	Cytomegalovirus
CR	Confirmed response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PPD	Purified protein derivative

Abbreviation	Term
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (±1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4]	•											
Baseline signs and symptoms	•[5]											
Pregnancy test[6]	•	•			•		•			•		
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[11]	•[12]								•		•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	**Screening**	**Treatment Period**								**Follow-up Period**[1]		
		Cycle 1 (±1 Day)								**Follow-up**		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42**[2]	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Brain CT scan/MRI[11,13]	•[12]								•	•	•	•
Bone scan (if clinically indicated)[14]	•[12]								•	•[14]	•[14]	•[14]
ECG (12-lead)	•[12]	•[15]								•		
Hematology	•	•[16]		•[16]	•[16]	•[16]	•[16]	•[16]		•	•	•
Serum chemistry	•	•[16]		•[16]	•[16]	•[16]	•[16]	•[16]		•	•	•
Immune safety assays[17,18]		•								•	•	
Optional tumor or other biopsy	•[19]											
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry[20]		•								•		
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•[21]								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (±1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for immunogenicity		•[22]								•	•	
MDX-1105 infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
Off Treatment/Study Procedures [23]												
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

1. Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

(continued)

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Table 1 Footnotes *(continued)*

4. To include collection of prior medication and prior/concurrent medical conditions.

5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).

6. Serum β-HCG pregnancy test within 7 days before the first infusion and urine pregnancy test at all other indicated timepoints before infusion for women of childbearing potential.

7. Pharmacokinetic sampling to be performed according to Table 3.

8. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes post infusion and longer if necessary until the subject is stabilized.

9. ECOG Performance Status to be assessed before each infusion.

10. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and only before each initial infusion of each cycle (Note: Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).

11. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

12. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

(continued)

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Table 1 Footnotes *(continued)*

[13]. Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 2 months (and NOT required for subjects with epOC). Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or as clinically indicated. If required, subsequent brain CT scans/MRI should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2 and 3.

[14]. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days. Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.

[15]. To be performed pre- and post-infusion.

[16]. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.

[17]. To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibody titer and pattern.

[18]. The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.

[19]. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression may be done on tumor samples collected during or before this study.

[20]. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).

[21]. Sample collected pre-infusion.

[22]. Serum sample for immunogenicity evaluation will be collected within 30 minutes before infusion.

(continued)

Table 1 Footnotes *(continued)*

[23.] When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.

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Table 2: Time and Events Schedule for Cycles 2-17

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-17 (±1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Urine pregnancy test[4]	•	•	•		•		
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]	•	
Bone scan (if clinically indicated)[12]				•	•[10]		
ECG (12-lead)	•[13]				•		
Hematology	•[14]	•[14]	•[14]		•		
Serum chemistry	•[14]	•[14]	•[14]		•	•	•
Immune safety assays[15,16]	•				•	•	
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry[19]	•						
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-17

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-17 (±1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for immunogenicity	•				•	•	
MDX-1105 infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
Off Treatment/Study Procedures [20]							
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

1. Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject has permanently discontinued study drug treatment. **Subjects who discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given 14 days (and no later than 21 days) after the last dose of the prior treatment cycle.
3. The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
4. For women of childbearing potential.
5. Pharmacokinetic sampling to be performed according to Table 3.

(continued)

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Table 2 Footnotes *(continued)*

6. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes post infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes post infusion and longer if necessary until the subject is stabilized.
7. ECOG Performance Status to be assessed before each infusion.
8. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken only before each initial infusion of each cycle (**Note:** Dose adjustments will only be made if there has been ≥ 10% weight change since the previous cycle).
9. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
10. To be performed if clinically indicated and if not done within the preceding 28 days.
11. Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain scans should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2 and 3. If positive at baseline, the brain scan must be performed to confirm CR or PR.
12. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated.
13. To be performed pre- and post-infusion.
14. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
15. To be performed pre-infusion. Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibodytiter and pattern.

(continued)

Table 2 Footnotes *(continued)*

16. The following tests are among those that may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.
17. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression may be done on tumor samples collected during or before this study.
18. Sample collected for Cycles 2 and 3 (pre-infusion) and at Follow-Up Visit 1.
19. Flow cytometry assessments will include but are not necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but may not be limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
20. When a subject is withdrawn from study drug treatment, but will remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study entirely (during the Treatment or Follow-up Period), all evaluations associated with the subject's last study visit should be performed and the Study Discontinuation CRF should be completed including the reason for study withdrawal.

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Table 3: Pharmacokinetic Sampling Schedule

Minutes	Cycle 1[1]					Cycle 2-17[2]	Follow-up Visits 1 and 2[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
Non-infusion days		•	•				•
0 to -30 (pre-infusion)	•			•	•	•	
60 (end of infusion)	•			•	•	•	
90	•						
120	•						
240	•						

1. Serum samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. For Days 2, 3, 4, 8, and 42, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.
2. For Cycles 2-17, samples will be drawn every 14 days, 30 minutes before the administration of MDX-1105 and at the end of each infusion.
3. A single sample will be taken at Follow-up Visits 1 and 2.

1. INTRODUCTION AND RATIONALE

1.1. Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens, and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

MDX-1105 is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Four tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus).

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Subjects with advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival, and new patients should not be given this drug. Thus novel therapies are needed.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (95%) are diagnosed early as localized tumors and curable. However, approximately 5% to 10% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and therefore novel agents are needed.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis. Thus novel agents are needed.

1.2. PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,4,5,6,7,8,9,10] For example, in renal cell

carcinoma, high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[7] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in post-operative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both PD-L1$^+$ and PD-L1$^-$ tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co-stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity.[14] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[32] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. [32] Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[33] In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[6] Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD-1 blockade.[33,34] Using a murinized anti-mouse PD-1 antibody, Medarex showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD-L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, MDX-1105 represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3. Summary of MDX-1105 Preclinical Studies

MDX-1105 is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. MDX-1105 was selected to inhibit the interaction of PD-L1 with its receptor PD-1. MDX-1105-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using MDX-1105 can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the

immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of MDX-1105 shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of MDX-1105 at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. MDX-1105 was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4. Rationale for MDX-1105

1.4.1. Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in-vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 15 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol MDX1105-01 will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where MDX-1105 doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2. Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

Initial safety experience of single dose administration of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer in Protocol MDX-1106-01, as of 15 April 2008, has shown no DLTs at the

0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg dose levels. A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg over 32 weeks. Twenty-one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with MDX-1105 will be closely monitored in Protocol MDX1105-01.

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Only 17/88 (19.3%) subjects with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

2.2. Secondary Objectives

The secondary objectives of the study are to: 1) evaluate preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) characterize the immunogenicity of MDX-1105; and 3) characterize the preliminary multidose pharmacokinetic profile of MDX-1105.

3. OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (RCC, NSCLC, MEL, or epOC) will be enrolled in the study.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 17 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study

drug administered on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Five dose levels are planned: 0.3, 1, 3, 10, and 15 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 0.3 mg/kg/dose administered as an i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. The MTD is the highest dose studied where ≤ 1 in 6 subjects experience a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 4 or more delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been ± 10% weight change since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohort

A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion cohort, if 3 or more subjects experience a DLT or 4 or more subjects experience a delayed DLT, enrollment will be held pending completion of a safety analysis by the Investigator and the

Medarex Medical Monitor and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments **must** be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 17 (with up to 3 doses per cycle). Following each cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 (and no later than 21) days after the last dose of the prior treatment cycle. No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been ± 10% weight change since the previous cycle.

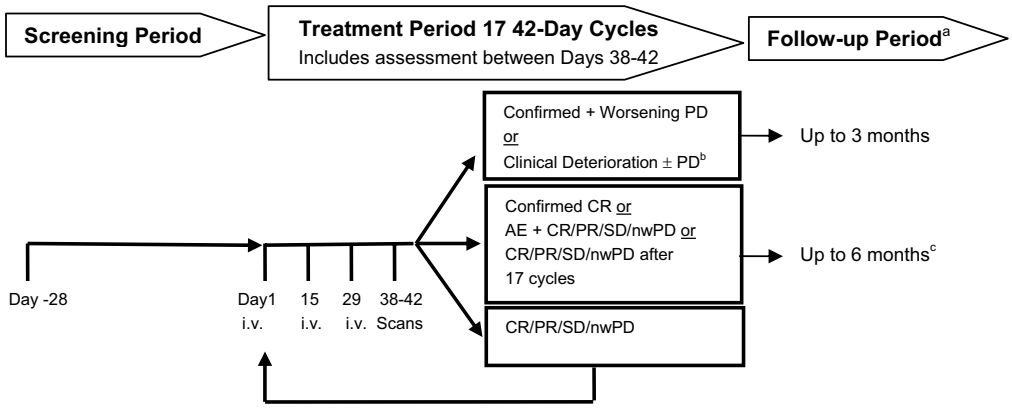
- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) progressive disease (PD) that is confirmed and then worsens; 4) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 5) other intolerability to therapy; or 6) receipt of the maximum number of cycles.
- Subjects with stable or improved clinical status, but the response evaluation at the end of Cycle 2 or later demonstrates evidence of PD (based on sum of the longest diameter [SLD] or development of new lesions at the end of a cycle), should continue to be treated with study drug until their next scheduled imaging evaluation. If, at the next or any subsequent imaging evaluation, there is no further increase in the SLD and no additional new lesions develop, and the subject's clinical status remains stable or has improved, treatment should be continued, even if PD is confirmed. If, at any subsequent imaging evaluation there is further progression (i.e., increase in the SLD or development of additional new lesions) or clinical deterioration, then the subject must discontinue study drug. In the absence of clinical deterioration or toxicity, subjects are expected to move directly to the next cycle. Follow up visits should be done unless precluded by disease progression or clinical deterioration.

Stopping treatment for clinical deterioration should be guided by clinical observations outlined in Section 8.7 and Investigator judgment.

Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent Follow-up Visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit for approximately 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. The flow of subjects through the study is diagrammed in Figure 1 below.

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



AE = adverse event; CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug, the subject should be followed to resolution/stabilization of: 1) ongoing study drug-related adverse events; 2) new study drug-related adverse events that occur within the 90-day period; and 3) adverse events that led to the discontinuation. A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit. Only study drug-related serious adverse events will be collected > 90 days after the last administration of study drug.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow up visits should be done unless precluded by disease progression or clinical deterioration.

[c] Follow-up should continue until relapse, initiation of a new therapy, or a total of 6 months (3 months for confirmed PD), whichever comes first.

4. STUDY POPULATION

Up to 40 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors, of one of the following histologically confirmed types: RCC, NSCLC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

4.1. Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA Authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;
2. Life expectancy ≥ 12 weeks;
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1);
4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, including, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic taxane-based therapy.

   For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and

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disease refractory to or relapsed after at least 1 prior standard therapy (may include high-dose interleukin-2). All melanomas regardless of primary site of disease will be allowed.

For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic platinum-based therapy.

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;
6. May have been treated with up to 5 previous systemic therapies for advanced/recurrent disease or have become intolerant to a systemic therapy;
7. Prior treated brain metastases must be without magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;
8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;
9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
10. At least 28 days since the last chemotherapy, immunotherapy, biological or investigational therapy, radiation, or at least 2 weeks from approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of MDX-1105 and have recovered from any toxicity associated with such treatment;
11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;
12. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;
13. Screening laboratory values must meet the following criteria:

WBC	≥ 3000/μL
Neutrophils	≥ 1500/μL

Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis
	≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 X ULN without hepatic metastasis
	≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 X ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

14. Women must meet 1 of the following criteria: post-menopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. Women of child bearing potential must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug; and
15. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2. Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);
3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been adequately treated, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;
4. Active infection (viral, bacterial, or fungal):
   a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of MDX-1105;
   b. Known history of infection with Human Immunodeficiency Virus
   c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)
5. Evidence of bleeding diathesis or coagulopathy;

6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;
7. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;
8. Known current drug or alcohol abuse;
9. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;
10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
11. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses >10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;
12. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;
13. Psychiatric illness or social situation that would preclude study compliance; or
14. Pregnant or nursing.

5. RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6. ASSIGNMENT TO STUDY

The investigative site will contact Medarex for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by Medarex. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7. DOSAGE AND ADMINISTRATION

7.1. Physical Description of Study Drug

MDX-1105 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of MDX-1105 (10 mg/mL).

7.2. Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.3. Storage

MDX-1105 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1105 include laboratory coats and gloves. Note: once MDX-1105 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for MDX-1105 supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between MDX-1105 and polyolefin bags have been observed.

7.4. Study Drug Preparation and Administration

MDX-1105 (0.3, 1, 3, 10, or 15 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 17 cycles).

1. Allow the appropriate number of vials of MDX-1105 to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the MDX-1105 solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of MDX-1105 solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume is more than 60 mL, no additional dilution is necessary.
5. Prepare the MDX-1105 solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX-1105 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX-1105 and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.
6. Mix by GENTLY inverting several times. DO NOT shake.
7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
8. Record the time MDX-1105 was prepared on the i.v. bag label.
9. Attach the i.v. bag containing the MDX-1105 solution to the infusion set, 0.2 μm in-line filter, and infusion pump.
10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Do not enter into each vial more than once.

Do not prepare MDX-1105 for infusion in glass syringes.

Do not administer study drug as an i.v. push or bolus injection.

7.5. Drug Accountability

Medarex, Inc. is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by Medarex or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Medarex at the end of the study. The Drug Accountability Log will record the study drugs received, dosages

prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs) or at a central depot.

7.6. Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for MDX-1105 except for weight changes (± 10%) at the beginning of each cycle. There must be a minimum of 14 days between study drug infusions. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1. A subject will be considered to have discontinued study drug if they miss 2 consecutive doses within a cycle.

8. TOXICITY AND MANAGEMENT

8.1. Dose Escalation

The first cohort of 1 subject will receive MDX-1105 0.3 mg/kg/dose administered as an i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29). Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dosing in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. The MTD is the highest dose studied where ≤ 1 in 6 subjects experiences a DLT. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced.

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A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be treated at the MTD or at the highest dose studied if the MTD is not identified.

8.2. Dose-limiting Toxicity

A DLT is defined as a ≥ Grade 3 study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient (resolving within 6 hours of onset) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis. If 4 or more such delayed DLTs are noted, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

All adverse events that meet DLT criteria**,** as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to Medarex, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3. Stopping Rules for Dose Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a ≥ Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

8.4. Stopping Rules for Expansion Cohorts

For the expansion cohort (10 subjects), if 3 or more subjects experience a DLT or 4 or more subjects experience a delayed DLT, enrollment will be held pending completion of a safety analysis by the Investigator and the Medarex Medical Monitor, and a decision will be made (with subsequent IRB and FDA notification) as to whether enrollment may continue at the current dose, or a new expansion cohort will be initiated at a lower dose. (Other subjects who have received treatment at the higher dose without complication may continue dosing at the same dose level).

8.5. Infusion Reactions

Since MDX-1105 contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-L1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and must be reported to Medarex within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

Prophylactic premedication (e.g., acetaminophen or diphenhydramine) may be given before infusions, if indicated by a prior infusion reaction, anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional MDX-1105 administrations.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the MDX-1105 infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further MDX-1105 will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or

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equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional MDX-1105 administrations. If necessary (persistent mild or moderate infusion reactions), corticosteroids (up to 25 mg of SoluCortef or equivalent) may be added. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of MDX-1105. Begin an i.v. infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. MDX-1105 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.6. Possible Toxicities

There is no clinical experience with MDX-1105 to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm:** Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and Tumor Necrosis Factor. Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure.

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Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with MDX-1105, and has not been seen in preclinical testing.

- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs):** Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of irAEs is currently hypothetical, as no subjects have been treated with MDX-1105 to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, limited experience with human subjects treated with anti-PD-1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

  Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). A management algorithm for high-grade irAEs in this current study is provided in the Investigator Brochure. **All irAEs should be managed according to this algorithm.**

Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105 program.

8.7. Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to stop treatment should be discussed with the Medarex Medical Monitor.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

9. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10. CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.

b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.

c. Concomitant use of other ccRCC/MEL/epOC/NSCLC cytotoxic chemotherapy, investigational agents, growth factors, cytokines, and RT may not be used while the subject is on the study. Radiation therapy for bone pain will be discussed with the Medical Monitor.

d. No other investigational therapies for any reason shall be administered while the subject is in the study.

e. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of MDX-1105 and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11. STUDY EVALUATIONS

11.1. Study Procedures by Visit

11.1.1. Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1105 need not be repeated**.**

11.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions);
- Baseline signs and symptoms: Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF;
- Inclusion/exclusion criteria;
- Serum β-HCG pregnancy test (to be taken within 7 days before the first infusion; for all women of childbearing potential; serum pregnancy test must be negative to continue);
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure;
- ECOG performance status;
- Physical examination (to include height and weight);

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- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study;
- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study;
- Bone scans (if clinically indicated);
- 12-lead ECG;
- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings
  - Hepatitis B and C testing;
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at

other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent;

- Concomitant medications.

11.1.3. Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start MDX-1105 treatment within 0 to 28 days of Screening. Subjects will receive 3 doses of MDX-1105 every 14 days during each cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1105 will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 1 or more day) or missed doses, see Section 7.7 for administration details. A subject who misses a dose during Cycle 1 only, not due to a DLT, will be replaced.

11.1.3.1. Cycle 1

Cycle 1 will begin with the first i.v. infusion of MDX-1105 (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment within Days 38 to 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained pre-infusion and post infusion as defined in the Time and Events Schedule (Table 1);
- ECOG performance status (to be conducted before infusion on infusion days);
- Physical examination;
- Weight;
- Tumor imaging (CT/MRI chest/abdomen/pelvis);
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated;
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated;

- Optional tumor or other biopsy (as outlined in Section 11.1.2);
- 12-lead ECG;
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue);
- Serum samples for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. (Post-infusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days);
- Serum sample for immunogenicity;
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]);
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens;
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site [i.e., contralateral arm]) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- Immune Safety Assays: Rheumatoid Factor, Adrenocorticotropic hormone, Thyroid Stimulating Hormone, Free T4 Level, C-Reactive Protein, Antinuclear Antibody titer and pattern;

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;

- MDX-1105 infusions;
- Concomitant medications;
- Adverse event assessment;

11.1.3.2. Cycle 2 to 17

Following Cycle 1, subjects in stable condition will receive additional cycles of MDX-1105 (Cycles 2 to 17) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 17 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2;
- ECOG performance status;
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue);
- Physical examination;
- Weight (changes to study drug dose will only be made if there has been a ± 10% weight change since the previous cycle);
- 12-lead ECG;
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis);
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated;
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days;
- Optional cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1);
- Serum sample for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm);
- Serum sample for immunogenicity;
- Optional tumor or other biopsy (as outlined in Section 11.1.2);

- Flow cytometry;
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)
- MDX-1105 infusions;
- Concomitant medications;
- Adverse event assessment.

11.1.4. Follow-up

There are 3 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Urine pregnancy test;
- Serum sample for immunogenicity;
- Serum samples for pharmacokinetic evaluation of MDX-1105;
- Vital sign measurements;

- ECOG performance status;
- Physical examination;
- ECG
- Tumor imaging;
- Brain scan (MRI preferred) as clinically indicated;
- Bone scan if clinically indicated and not done within the preceding 28 days;
- Clinical laboratory tests as outlined in Section 11.1.2;
- Optional biopsies and/or cryopreserved PBMC as outlined in Sections 11.1.2 and 11.1.3.1;
- Flow cytometry;
- Concomitant medications;
- Adverse event assessment.

11.1.5. Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 3 doses of MDX-1105 in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6. Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up

- Death
- Other

11.2. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1105: vital sign measurements, clinical laboratory tests, flow cytometry, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety and immunogenicity.

11.2.1. Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of MDX-1105-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the MDX-1105 drug itself, and is characterized by antibodies that the subject may develop that react with MDX-1105. These may result in more rapid clearance of MDX-1105 from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with MDX-1105 at a later date.

11.2.3. Exploratory Immune Function Evaluations

Samples will be collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3. Efficacy Evaluations

11.3.1. Efficacy Parameter

The efficacy parameter is the best overall response rate (BORR) as determined by the Investigator tumor evaluations. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent confirmation of responses may be requested at the discretion of Medarex.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of MDX-1105 and more likely capture its true potential to induce clinical responses.

11.4. Pharmacokinetic Evaluations

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

Blood samples for the analysis of serum concentrations of MDX-1105 will be drawn in all subjects according to the schedule listed below and in Table 3 of the Time and Event Schedule. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1. Cycle 1

- **Day 1:** pre-dose (within 30 minutes before infusion), and at the end of the infusion, and at 30, 60, 120, and 240 minutes post infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, 8, and 42:** single serum samples will be taken on each day.

- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and at the end of each MDX-1105 infusion.

11.4.2. Cycles 2-17

- **Days 1, 15, and 29:** serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3. Follow-Up Visits

- **Follow-up Visits 1 and 2:** single serum samples to be taken.

12. ADVERSE EVENT REPORTING

Clinical events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, version 3.0.[37] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug – related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

- **Not related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

- **Related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted

12.1.1. Safety Reporting For Adverse Events

All adverse events occurring within 90 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only treatment-related serious or other clinically significant adverse events will be collected for all subjects 90 days after the administration of the last dose of study drug.

12.2. Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; hospitalization to facilitate the work up of a $\leq$ Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3. Instructions for Rapid Notification of Serious Adverse Events

12.3.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she provided informed consent and HIPAA authorization, while receiving study treatment or during the 90 days following study drug administration must be reported. The timeframe for reporting after discontinuation of study

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drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 90 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring greater than 90 days from the last dose of MDX-1105 must be reported if deemed related to study drug. The report must include the event term, subject identifier, attribution, description, concomitant medication used to treat the event, and any other relevant information. Follow-up information about previously reported serious adverse events must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to Medarex or its designee. The field monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and fax confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.3.3. Contact Persons and Numbers

The Medarex Central Emergency Contact telephone and serious adverse event fax numbers are listed on the cover page of the protocol.

12.4. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, Medarex considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5. Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1105 and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1. Reporting of Pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Medarex and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Medarex according to Serious Adverse Event reporting procedures described in Section 12.3.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.6. Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

12.7. Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

13. STATISTICAL METHODS

13.1. Sample Size Determination

The sample size of up to 40 subjects is based on an accelerated titration dose-escalation design, not a power analysis. Up to 6 subjects will be enrolled at the following dose levels: 0.3, 1, 3, 10, and 15 mg/kg/dose. A total of 16 subjects (6 in dose-escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD, or the highest dose studied. If no DLTs occur, a total of 20 subjects will be needed to finish the study.

To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) in an expansion cohort: Up to 16 subjects

will be enrolled in the expansion cohort. In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size at the MTD or highest dose level cohort is determined by a power analysis. It is assumed that the patients would have no response if they would not have received any therapy and that BORR for patients in the MTD or highest dose level cohort would be 10%. Based on this assumption, a sample size of 16 patients in the MTD or highest dose level cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

13.2. Study Populations

13.2.1. Safety Population

The safety population includes all subjects who receive at least 1 dose or any partial dose of MDX-1105.

13.2.2. Per-protocol Population

The per-protocol population includes all subjects dosed at the MTD (or the highest dose studied if the MTD is not identified) in the safety population who have the correct disease diagnosis, valid baseline tumor assessment showing measurable disease, and at least 1 valid post-baseline tumor assessment. Any subject who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the per-protocol population. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population.

13.2.3. Pharmacokinetic Population

The pharmacokinetic population includes all subjects in the safety population who complete all 3 infusions in Cycle 1 and have completed the pharmacokinetic assessments up to Day 42 of that cycle.

13.3. Statistical Considerations

The Biostatistics group at Medarex, Inc. or its designees will analyze the data collected in this study.

All data will be listed individually by subject. Continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency and percentage.

The baseline value for an analysis variable is the last measurement before study drug administration.

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Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05.

13.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.3.2. Extent of Exposure

The total dosage (mg), total number of doses, and total number of treatment cycles will be summarized by dose level using descriptive statistics.

13.3.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications will be summarized by dose level using descriptive statistics. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study.

13.3.4. Safety

The safety analysis will be conducted on the safety population. The following safety parameters will be evaluated:

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a preferred term and a system organ class for each adverse event. The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and

proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE version 3.0), irAEs, TEAEs, and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Physical Examinations

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history and will be included in the respective summaries.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level using descriptive statistics.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE 3.0 Grade will be assigned to some of the laboratory parameters, which are included in "CTCAE version 3.0". Central laboratory values will be listed. Laboratory values which are outside normal range will be flagged as H (above high normal limit) or L (below lower normal limit) in the listings. The NCI CTCAE 3.0 Grade will also be flagged in the listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

Flow Cytometry

Flow cytometry results will be summarized using descriptive statistics or as otherwise appropriate.

Diagnostic Tests

Diagnostic tests results will be summarized by dose level using descriptive statistics.

Immune Safety Evaluations

Immune safety tests results will be summarized by dose level using descriptive statistics.

Immunogenicity

Immunogenicity measurement for human anti-human antibodies (HAHA) will be summarized appropriately.

Exploratory Immune Function

The effects of MDX-1105 on humoral and cellular immune responses to tumor antigens (when available) and a panel of recall nontumor antigens will be assessed. Parameters to be examined will include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment will be assessed. These parameters will be summarized by dose level using descriptive statistics, and may be reported as part of a separate document.

13.3.5. Efficacy

The efficacy analysis will be conducted on the per-protocol population.

The efficacy endpoint is the BORR, as determined by the Investigator tumor evaluations. The BORR will be summarized using descriptive statistics by response level: CR, PR, SD, and PD.

13.3.6. Pharmacokinetic

Plasma concentrations of MDX-1105 will be determined by a validated method at the times listed in the time and events schedule tables.

Definition and Calculation of Pharmacokinetic Parameters

The following pharmacokinetic parameters will be estimated and reported:

$AUC_{0\rightarrow t}$ Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).

$AUC_{0\rightarrow \infty}$ Area under the curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z).

λ_z Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of $\log_e$ (concentration) vs time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time and (iii) the correlation coefficient r of regression must be ≥ 0.95.

C_{max} Maximum plasma concentration observed post-dose.

t_{max} Time at which the C_{max} occurs.

$t_{½}$ Elimination half-life, determined as $0.693/\lambda_{z.}$

The pharmacokinetic parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

13.4. Missing-Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

13.5. Statistical Software

The estimation of pharmacokinetic parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher.

14. ETHICAL ASPECTS

14.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Medarex SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

14.2. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to Medarex or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Medarex, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC must be given to Medarex before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to Medarex or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

14.4. Informed Consent

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Medarex supplies a proposed ICF that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Medarex or its designee before submission to the IRB/IEC and a copy of the approved version must be provided to the Medarex monitor after IRB/IEC approval.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Medarex before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Medarex monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Medarex in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, Medarex should be notified and the IRB/IEC for the center should be informed within 1 working day.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization [CRO]); and
2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Medarex representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Medarex monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the

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protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Medarex or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Medarex will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.4. Auditing Procedures

In addition to the routine monitoring procedures, Medarex, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Medarex, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Medarex immediately that this request has been made.

15.5. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Medarex. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Medarex statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Medarex.

Medarex must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Medarex personnel.

15.6. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Medarex or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Medarex (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Medarex, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7. Discontinuation of Study

Medarex reserves the right to discontinue any study for any reason at any time.

15.8. Data Management

15.8.1. Data Collection

Investigators must enter the information required by the protocol onto the Medarex CRFs that are printed on "no carbon required" paper. Medarex monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to Medarex, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.8.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following Medarex, or its designee, data management procedures. Obvious errors will be corrected by Medarex personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Medarex study team.

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17. APPENDICES

Appendix 1: ECOG Performance Status

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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Appendix 2: RECIST With Modification

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently. (Adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint), All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria

for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having "symptomatic deterioration."

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.

continued

Definitions *(continued)*

Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not "selected" images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polygrandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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MEDAREX

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Clinical Protocol MDX1105-01 Amendment 2

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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If any Medarex contact information is changed during the course of the study, this will be done by Medarex, with written notification to the Investigator(s), and will not require (a) protocol amendment(s).

Replace all previous version(s) of the protocol with this revised Protocol Amendment No. 2

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SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

MDX1105-01

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) immunogenicity of MDX-1105; 3) preliminary multidose pharmacokinetic profile of MDX-1105; and 4) histologic, serologic, and cellular immune correlates of toxicity and/or clinical activity.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.

b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansions

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Melanoma Expansions

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once

enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.

- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at

the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

The maximum duration of a subject's participation in this study is approximately 2.5 years.

STUDY POPULATION

Up to 130 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

MDX-1105 will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, and 10 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of Medarex.

The secondary efficacy parameters include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with confirmed responses.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with MDX-1105; Tumor response status will be assessed using RECIST with modifications, as well as by tumor-specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9).

EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

For Cycle 1, Day 1, blood samples for assessment of the serum concentration of MDX-1105 will be drawn within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-up Visits 1 and 2.

STATISTICAL METHODS

A total of up to 130 subjects are to be enrolled in this study based on the study design for dose escalation, safety evaluation, and anti-tumor activity evaluation requirements.

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that BORR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.

Efficacy and safety parameters will be summarized by dose and by indication using descriptive statistics. For BORR in each expansion cohort, a one-sided exact Bionomial text will be performed and the 95% confidence intervals will be determined. Time to response and duration of response will be summarized for those subjects with confirmed responses. For the expansion cohorts, efficacy analyses will only be applicable to cohorts that enroll at least 16 subjects. The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests, immune safety assays, ECOG, physical examination, vital signs, ECGs, and immunogenicity results will be summarized using descriptive statistics.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BORR	Best overall response rate
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1

Abbreviation	Term
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[11]	•[12]								•	•[14]	•	•
Brain CT scan/MRI[11,13]	•[12]								•[14]	•[14]	•[14]	•[14]
Bone scan (if clinically indicated)[15]	•[12]								•[15]	•[15]	•[15]	•[15]
Response assessment									•			
ECG (12-lead)	•[12]	•[16]								•		
Hematology	•	•[17]			•[17]	•	•[17]	•		•	•	•
Serum chemistry	•	•[17]			•[17]	•	•[17]	•		•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Flow cytometry		•								•		
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity		•								•	•	
MDX-1105 infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

(continued)

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Table 1 Footnotes:

1. Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.
4. To include collection of prior medication and prior/concurrent medical conditions.
5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).
6. Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.

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8. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

9. ECOG Performance Status to be assessed before each infusion.

10. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

11. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

12. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

13. Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

14. To be performed if clinically indicated and if not done within the preceding 28 days.

15. If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

16. To be performed pre- and postinfusion.

(continued)

[17] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.

[18] Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]	•	
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•[15]	•[15]		•	•	•
Serum chemistry	•[15]	•[15]	•[15]		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[16]	•				•	•	•
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

continued

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•				•	•	
MDX-1105 infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

1. Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days (and no later than 28 ± 2 days) after the last dose of the prior treatment cycle.

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Table 2 Footnotes *(continued)*

3. The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
4. Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
5. Pharmacokinetic sampling to be performed according to Table 3.
6. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.
7. ECOG Performance Status to be assessed before each infusion.
8. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note:** Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).
9. The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.
10. To be performed if clinically indicated and if not done within the preceding 28 days.
11. Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.
12. If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.
13. At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation.
14. To be performed pre- and postinfusion.

(continued)

Table 2 Footnotes *(continued)*

15. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
16. CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.
17. Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.
18. Sample collected for Cycles 2 and 3 only.

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Table 3: Pharmacokinetic Sampling Schedule

Sample collection time points	Cycle 1[1]					Cycle 2-16[2]	Follow-up Visits 1 and 2[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
Any time during the visit		•	•				•
-30 to 0 minutes before infusion	•			•	•	•	
At the end of infusion	•			•	•	•	
30 minutes after the infusion							
60 minutes after the infusion	•						
120 minutes after the infusion	•						
240 minutes after the infusion	•						

1. Blood samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.
2. For Cycles 2-16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX-1105 and at the end of each infusion.
3. A single sample will be taken at Follow-up Visits 1 and 2.

1. INTRODUCTION AND RATIONALE

1.1. Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

MDX-1105 is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with

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advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006.[2] The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

1.2. PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative

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regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,4,5,6,7,8,9,10] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[7] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both PD-L1^{+} and PD-L1^{-} tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co-stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models

of autoimmunity.[14] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[32] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. [32] Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[33] In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[6] Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD-1 blockade.[33,34] Using a murinized anti-mouse PD-1 antibody, Medarex showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD-L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, MDX-1105 represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3. Summary of MDX-1105 Preclinical Studies

MDX-1105 is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. MDX-1105 was selected to inhibit the interaction of PD-L1 with its receptor PD-1. MDX-1105-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated

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with melanoma antigen peptide vaccines. Blocking of PD-L1 using MDX-1105 can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of MDX-1105 shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of MDX-1105 at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. MDX-1105 was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4. Rationale for MDX-1105

1.4.1. Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol MDX1105-01 will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where MDX-1105 doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2. Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 14 April 2008, there were no DLTs reported after single dose administration of 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer (Protocol MDX-1106-01). A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg of MDX-1106 over 32 weeks. Twenty-one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with MDX-1105 will be closely monitored in Protocol MDX1105-01.

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Seventeen subjects (17/88, 19.3%) with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

2.2. Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) the immunogenicity of MDX-1105; 3) the preliminary multidose pharmacokinetic profile of MDX-1105, and 4) histologic, serologic, and cellular immune correlates of toxicity and/or clinical activity.

3. OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1. Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or

decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2. Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.

b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1. Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication

3.2.2. Initiation of the Additional Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to

accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.2.3. Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.3. Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to MDX-1105 that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive MDX-1105 therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters

(SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

– PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the Medarex Medical Monitor as described in Section 8.7.

– PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.

  - If, at each subsequent imaging evaluation (Cycle 3 or later)**, there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to MDX-1105 that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

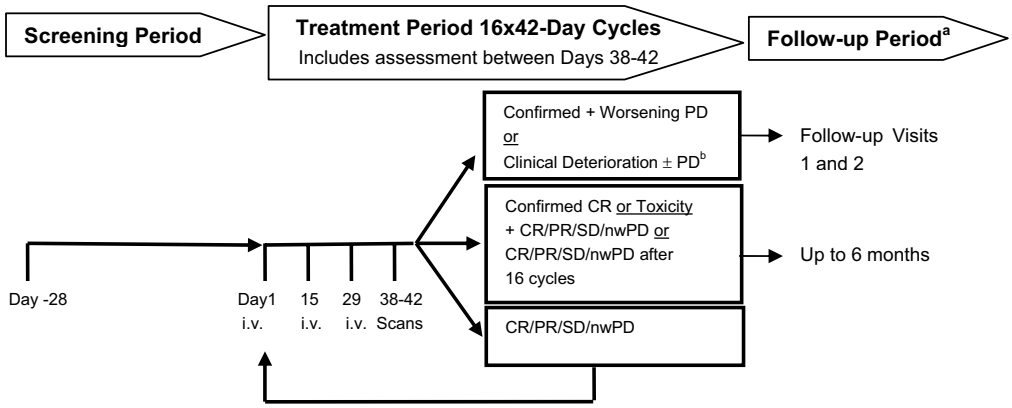
3.4. Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent Follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

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The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

4. STUDY POPULATION

Up to 130 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

4.1. Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period

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(no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;
2. Life expectancy ≥ 12 weeks;
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1);
4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy.

   For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

   For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.
5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;
6. May have been treated with up to 5 previous systemic therapies for advanced/recurrent disease or have become intolerant to a systemic therapy;

7. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast – preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;
8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;
9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
10. At least 28 days since the last chemotherapy, immunotherapy, biological or investigational therapy, or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of MDX-1105 and have recovered from any toxicity associated with such treatment;
11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;
12. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;
13. Screening laboratory values must meet the following criteria:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 X ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 X ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

14. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral

oophorectomy); or utilizing a reliable form of contraception. Women of child bearing potential must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug; and

15. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2. Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);
3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;
4. Active infection (viral, bacterial, or fungal):
   a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of MDX-1105;
   b. Known history of infection with Human Immunodeficiency Virus
   c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)
5. Evidence of bleeding diathesis or coagulopathy;
6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;
7. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;
8. Known current drug or alcohol abuse;
9. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;

10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
11. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses >10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;
12. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;
13. Psychiatric illness or social situation that would preclude study compliance; or
14. Pregnant or nursing.

5. RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6. ASSIGNMENT TO STUDY

The investigative site will contact Medarex for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by Medarex. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7. DOSAGE AND ADMINISTRATION

7.1. Physical Description of Study Drug

MDX-1105 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of MDX-1105 (10 mg/mL).

7.2. Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.3. Storage

MDX-1105 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1105 include laboratory coats and gloves. Note: once MDX-1105 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for MDX-1105 supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between MDX-1105 and polyolefin bags have been observed.

7.4. Study Drug Preparation and Administration

MDX-1105 (0.3, 1, 3, and 10 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). The following steps outline the procedures to be followed for the preparation and infusion of MDX-1105.

1. Allow the appropriate number of vials of MDX-1105 to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the MDX-1105 solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of MDX-1105 solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)
4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary.
5. Prepare the MDX-1105 solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX-1105 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX-1105

10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted MDX-1105 is needed. In this case, all drug should be infused in 60 minutes.

6. Mix by GENTLY inverting several times. DO NOT shake.
7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
8. Record the time MDX-1105 was prepared on the i.v. bag label.
9. Attach the i.v. bag containing the MDX-1105 solution to the infusion set, 0.2 μm in-line filter, and infusion pump.
10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Please note the following:

- **Do not** enter into each vial more than once.
- **Do not** prepare MDX-1105 for infusion in glass syringes.
- **Do not** administer study drug as an i.v. push or bolus injection.

7.5. Drug Accountability

Medarex, Inc. is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by Medarex or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Medarex at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs) or at a central depot.

7.6. Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for MDX-1105 except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1. A subject will be considered to have discontinued study drug if they miss 2 consecutive doses within a cycle.

8. TOXICITY AND MANAGEMENT

8.1. Dose Escalation

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced. A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be treated at the MTD or at the highest dose studied if the MTD is not identified.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2. Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis.

All adverse events that meet DLT criteria**,** as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to Medarex, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3. Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a ≥ Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

8.4. Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the

dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

8.5. Infusion Reactions

Since MDX-1105 contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-L1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and must be reported to Medarex within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

Prophylactic premedication (e.g., acetaminophen or diphenhydramine) may be given before infusions, if indicated by a prior infusion reaction, anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional MDX-1105 administrations.

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For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the MDX-1105 infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further MDX-1105 will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional MDX-1105 administrations. If necessary (persistent mild or moderate infusion reactions), corticosteroids (up to 25 mg of SoluCortef or equivalent) may be added. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of MDX-1105. Begin an i.v. infusion of normal saline, and treat the subject as follows: bronchodilator, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. MDX-1105 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.6. Possible Toxicities

There is no clinical experience with MDX-1105 to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm:** Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with MDX-1105, and has not been seen in preclinical testing.
- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs):** Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and

colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of irAEs is currently hypothetical, as no subjects have been treated with MDX-1105 to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, limited experience with human subjects treated with anti-PD-1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). A management algorithm for high-grade irAEs in this current study is provided in the Investigator Brochure. **All irAEs should be managed according to this algorithm.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105 program.

8.7. Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the Medarex Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

9. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10. CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.

b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.

c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.

d. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.

e. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of MDX-1105 and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11. STUDY EVALUATIONS

11.1. Study Procedures by Visit

11.1.1. Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1105 need not be repeated**.**

11.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)

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- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG

- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
  - Hepatitis B and C testing;
- Concomitant medications

11.1.3. Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start MDX-1105 treatment within 28 days of Screening. Subjects will receive 1 dose of MDX-1105 every 14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1105 will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses,

see Section 7.6 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1. Cycle 1

Cycle 1 will begin with the first i.v. infusion of MDX-1105 (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).
- Serum samples for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).

- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.3.2. Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of MDX-1105 (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further

cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry

- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.4. Follow-up

There are 3 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity
- Serum samples for pharmacokinetic evaluation of MDX-1105
- Vital sign measurements

- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Optional biopsies and/or cryopreserved PBMC as outlined in Sections 11.1.2 and 11.1.3.1.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5. Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 3 doses of MDX-1105 in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6. Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up

- Death
- Other

11.2. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1105: vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1. Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of MDX-1105-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the MDX-1105 drug itself, and is characterized by antibodies that the subject may develop that react with MDX-1105. These may result in more rapid clearance of MDX-1105 from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with MDX-1105 at a later date.

11.2.3. Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and

tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3. Efficacy Evaluations

11.3.1. Efficacy Parameter

The primary efficacy parameter is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of Medarex.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of MDX-1105 and more likely capture its true potential to induce clinical responses.

11.4. Pharmacokinetic Evaluations

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

Blood samples for the analysis of serum concentrations of MDX-1105 will be drawn in all subjects according to the schedule listed below and in Table 3. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1. Cycle 1

- **Day 1:** pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, and 8:** single serum samples will be taken on each day.
- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and immediately at the end of each MDX-1105 infusion.

11.4.2. Cycles 2-16

- **Days 1, 15, and 29:** serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3. Follow-up Visits

- **Follow-up Visits 1 and 2:** single serum samples to be taken.

12. ADVERSE EVENT REPORTING

Clinical events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, version 3.0.[37] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE

version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug – related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

- **Not related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

- **Related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted

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12.1.1. Safety Reporting For Adverse Events

All adverse events occurring within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.
- Only treatment-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects 70 days after the administration of the last dose of study drug.

12.2. Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; hospitalization to facilitate the work up of a $\leq$ Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3. Rapid Notification of Serious Adverse Events

12.3.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she provided informed consent and HIPAA authorization, while receiving study treatment or during the 70 days following study drug administration must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring greater than 70 days from the last dose of MDX-1105 must be reported if deemed related to study drug. The report must include the event term, subject identifier, attribution, description, concomitant medication used to treat the event, and any other relevant information. Follow-up information about previously reported serious adverse events must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to Medarex or its designee. The field monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and fax confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.3.3. Contact Persons and Numbers

The Medarex Central Emergency Contact telephone and serious adverse event fax numbers are listed on the cover page of the protocol.

12.4. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, Medarex considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5. Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1105 and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1. Reporting of Pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Medarex and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Medarex according to Serious Adverse Event reporting procedures described in Section 12.3.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate

pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.6. Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105

program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

12.7. Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

13. STATISTICAL METHODS

13.1. Sample Size Determination

A total of up to 130 subjects are to be enrolled in this study based on the study design for dose escalation, safety evaluation and anti-tumor activity evaluation requirements

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that BORR for subjects in the expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

13.2. Study Populations

13.2.1. Safety Population

The safety population includes all subjects who receive at least 1 dose or any partial dose of MDX-1105.

13.2.2. Per-protocol Population

The per-protocol population includes all subjects dosed at the MTD (or the highest dose studied if the MTD is not identified) in the safety population who have the correct disease diagnosis, valid baseline tumor assessment showing measurable disease, and at least 1 valid postbaseline tumor assessment. Any subject who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the per-protocol population.

A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population with the exception of those withdrawn for rapid progression after receiving only 2 or 3 doses.

13.2.3. Pharmacokinetic Population

The pharmacokinetic population includes all subjects in the safety population who complete all 3 infusions in Cycle 1 and have completed the pharmacokinetic assessments of that cycle.

13.3. Statistical Considerations

The Biostatistics group at Medarex, Inc. or its designees will analyze the data collected in this study.

All data will be listed individually by subject. Continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency and percentage.

The baseline value for an analysis variable is the last measurement before study drug administration.

Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05.

13.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.3.2. Extent of Exposure

The total dosage (mg), total number of doses, and total number of treatment cycles will be summarized by dose level using descriptive statistics.

13.3.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications will be summarized by dose level using descriptive statistics. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study.

13.3.4. Safety

The safety analysis will be conducted on the safety population. The following safety parameters will be evaluated:

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

An immune-related adverse event (irAE), a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a preferred term and a system organ class for each adverse event. The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, treatment-related serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE version 3.0), and additional grouping by severity and relationship to study drug.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Physical Examinations

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history and will be included in the respective summaries.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level using descriptive statistics.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE 3.0 Grade will be assigned to some of the laboratory parameters, which are included in "CTCAE version 3.0". Central laboratory values will be listed. Laboratory values which are outside normal range will be flagged as H (above high normal limit), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE 3.0 Grade will also be flagged in the listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

Diagnostic Tests

Diagnostic tests results will be summarized by dose level using descriptive statistics.

Immune Safety Evaluations

Immune safety tests results will be summarized by dose level using descriptive statistics.

Immunogenicity

Immunogenicity measurement for human anti-human antibodies (HAHA) will be summarized appropriately.

13.3.5. Efficacy

The primary efficacy endpoint is the BORR during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of Medarex. In each expansion cohort, a one-sample exact Binomial test will be performed for the BORR and the 95% confidence intervals will be determined.

The secondary efficacy endpoints include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), progression-free survival, and the time to response and duration of response for those subjects with confirmed responses. All the secondary efficacy parameters will be summarized using

descriptive statistics for each expansion cohort. Progression-free survival will be summarized using Kaplan-Meier survival methods. Time to response and duration of response will be summarized for those subjects with confirmed responses.

For the expansion cohorts, efficacy analyses will only be applied to the cohorts that enroll at least 16 subjects.

13.3.6. Pharmacokinetic

Plasma concentrations of MDX-1105 will be determined by a validated method at the times listed in the time and events schedule tables.

Definition and Calculation of Pharmacokinetic Parameters

The following pharmacokinetic parameters will be estimated and reported:

$AUC_{0\rightarrow t}$ Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).

$AUC_{0\rightarrow \infty}$ Area under the curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z).

λ_z Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of $\log_e$ (concentration) vs time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time and (iii) the correlation coefficient r of regression must be ≥ 0.95.

C_{max} Maximum plasma concentration observed postdose.

t_{max} Time at which the C_{max} occurs.

$t_{½}$ Elimination half-life, determined as $0.693/\lambda_z$.

The pharmacokinetic parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

13.3.7. Exploratory Immune Function Studies

Flow Cytometry

Flow cytometry results will be summarized using descriptive statistics or as otherwise appropriate.

Exploratory Immune Function

The effects of MDX-1105 on humoral and cellular immune responses to tumor antigens (when available) and a panel of recall nontumor antigens will be assessed. Parameters to be examined will include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment will be assessed. These parameters will be summarized by dose level using descriptive statistics, and may be reported as part of a separate document.

13.4. Missing-Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

13.5. Statistical Software

The estimation of pharmacokinetic parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher.

14. ETHICAL ASPECTS

14.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Medarex SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

14.2. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and

other study documents submitted to Medarex or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Medarex, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC must be given to Medarex before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to Medarex or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

14.4. Informed Consent

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Medarex supplies a proposed ICF that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Medarex or its designee before submission to the IRB/IEC and a copy of the approved version must be provided to the Medarex monitor after IRB/IEC approval.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Medarex before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Medarex monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Medarex in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, Medarex should be notified and the IRB/IEC for the center should be informed within 1 working day.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization [CRO]); and
2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Medarex representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Medarex monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the

protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Medarex or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Medarex will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.4. Auditing Procedures

In addition to the routine monitoring procedures, Medarex, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Medarex, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Medarex immediately that this request has been made.

15.5. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Medarex. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Medarex statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Medarex.

Medarex must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Medarex personnel.

15.6. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Medarex or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Medarex (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Medarex, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7. Discontinuation of Study

Medarex reserves the right to discontinue any study for any reason at any time.

15.8. Data Management

15.8.1. Data Collection

Investigators must enter the information required by the protocol onto the Medarex CRFs that are printed on "no carbon required" paper. Medarex monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to Medarex, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.8.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following Medarex, or its designee, data management procedures. Obvious errors will be corrected by Medarex personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Medarex study team.

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17. APPENDICES

Appendix 1: ECOG Performance Status

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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Appendix 2: RECIST With Modification

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having "symptomatic deterioration."

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.

continued

Definitions *(continued)*

Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not "selected" images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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MEDAREX

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Clinical Protocol MDX1105-01 Amendment 3

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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Replace all previous version(s) of the protocol with this revised Protocol Amendment No. 3

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SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

MDX1105-01

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) immunogenicity of MDX-1105; 3) preliminary multidose pharmacokinetic profile of MDX-1105; and 4) histologic, serologic, and cellular immune correlates of toxicity and/or clinical activity.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.

b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansions

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Melanoma Expansions

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once

enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.

- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1105 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at

the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

The maximum duration of a subject's participation in this study is approximately 2.5 years.

STUDY POPULATION

Up to 130 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

MDX-1105 will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, and 10 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of Medarex.

The secondary efficacy parameters include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with confirmed responses.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with MDX-1105; Tumor response status will be assessed using RECIST with modifications, as well as by tumor-specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9).

EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

For Cycle 1, Day 1, blood samples for assessment of the serum concentration of MDX-1105 will be drawn within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-up Visits 1 and 2.

STATISTICAL METHODS

A total of up to 130 subjects are to be enrolled in this study based on the study design for dose escalation, safety evaluation, and anti-tumor activity evaluation requirements.

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that BORR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.

Efficacy and safety parameters will be summarized by dose and by indication using descriptive statistics. For BORR in each expansion cohort, a one-sided exact Bionomial text will be performed and the 95% confidence intervals will be determined. Time to response and duration of response will be summarized for those subjects with confirmed responses. For the expansion cohorts, efficacy analyses will only be applicable to cohorts that enroll at least 16 subjects. The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests, immune safety assays, ECOG, physical examination, vital signs, ECGs, and immunogenicity results will be summarized using descriptive statistics.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BORR	Best overall response rate
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1

Abbreviation	Term
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•	•	•	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[11]	•[12]								•	•[14]	•	•
Brain CT scan/MRI[11,13]	•								•[14]	•	•	•
Bone scan (if clinically indicated)[15]	•								•	•[15]	•[15]	•[15]
Response assessment									•			
ECG (12-lead)	•	•[16]								•		
Hematology	•	•[17]		•	•	•	•	•		•	•	•
Serum chemistry	•	•		•	•	•	•	•		•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Flow cytometry		•								•		
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity		•								•	•	
MDX-1105 infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

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Table 1 Footnotes:

1. Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.
2. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
3. Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.
4. To include collection of prior medication and prior/concurrent medical conditions.
5. Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).
6. Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
7. Pharmacokinetic sampling to be performed according to Table 3.

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8. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

9. ECOG Performance Status to be assessed before each infusion.

10. Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

11. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

12. Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of MDX-1105 need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

13. Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

14. To be performed if clinically indicated and if not done within the preceding 28 days.

15. If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

16. To be performed pre- and postinfusion.

(continued)

[17] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.

[18] Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•	•		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•	•	
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•	•		•	•	•
Serum chemistry	•	•	•		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[16]	•				•	•	•
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

continued

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1**[2]	**15**	**29**	**42**[3]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•				•	•	
MDX-1105 infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

1. Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2. End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days (and no later than 28 ± 2 days) after the last dose of the prior treatment cycle.

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Table 2 Footnotes *(continued)*

3. The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.
4. Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.
5. Pharmacokinetic sampling to be performed according to Table 3.
6. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.
7. ECOG Performance Status to be assessed before each infusion.
8. Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note:** Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).
9. The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.
10. To be performed if clinically indicated and if not done within the preceding 28 days.
11. Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.
12. If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.
13. At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on the tumor response evaluation.
14. To be performed pre- and postinfusion.

(continued)

Table 2 Footnotes *(continued)*

15. During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
16. CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.
17. Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.
18. Sample collected for Cycles 2 and 3 only.

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Table 3: Pharmacokinetic Sampling Schedule

Sample collection time points	Cycle 1[1]					Cycle 2-16[2]	Follow-up Visits 1 and 2[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
Any time during the visit		•	•				•
-30 to 0 minutes before infusion	•			•	•	•	
At the end of infusion	•			•	•	•	
30 minutes after the infusion	•						
60 minutes after the infusion	•						
120 minutes after the infusion	•						
240 minutes after the infusion	•						

1. Blood samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.
2. For Cycles 2-16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX-1105 and at the end of each infusion.
3. A single sample will be taken at Follow-up Visits 1 and 2.

1. INTRODUCTION AND RATIONALE

1.1. Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

MDX-1105 is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with

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advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006. The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006. The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006. The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006. The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

1.2. PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative

regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,4,5,6,7,8,9,10] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness. Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both PD-L1^{+} and PD-L1^{-} tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co-stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models

of autoimmunity. PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody. Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. [32] Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice. In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition. Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD-1 blockade.[33,34] Using a murinized anti-mouse PD-1 antibody, Medarex showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD-L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, MDX-1105 represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3. Summary of MDX-1105 Preclinical Studies

MDX-1105 is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. MDX-1105 was selected to inhibit the interaction of PD-L1 with its receptor PD-1. MDX-1105-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated

with melanoma antigen peptide vaccines. Blocking of PD-L1 using MDX-1105 can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of MDX-1105 shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of MDX-1105 at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. MDX-1105 was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4. Rationale for MDX-1105

1.4.1. Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol MDX1105-01 will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where MDX-1105 doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2. Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 14 April 2008, there were no DLTs reported after single dose administration of 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer (Protocol MDX-1106-01). A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg of MDX-1106 over 32 weeks. Twenty-one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with MDX-1105 will be closely monitored in Protocol MDX1105-01.

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Seventeen subjects (17/88, 19.3%) with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of MDX-1105 when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

2.2. Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with MDX-1105; 2) the immunogenicity of MDX-1105; 3) the preliminary multidose pharmacokinetic profile of MDX-1105, and 4) histologic, serologic, and cellular immune correlates of toxicity and/or clinical activity.

3. OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of MDX-1105 a fully human monoclonal IgG4 antibody targeting the Programmed Death – Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1. Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or

decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2. Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.

b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1. Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication

3.2.2. Initiation of the Additional Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to

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accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.2.3. Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.3. Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of MDX-1105 will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to MDX-1105 that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive MDX-1105 therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters

(SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

– PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the Medarex Medical Monitor as described in Section 8.7.

– PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.

  - If, at each subsequent imaging evaluation (Cycle 3 or later)**, there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

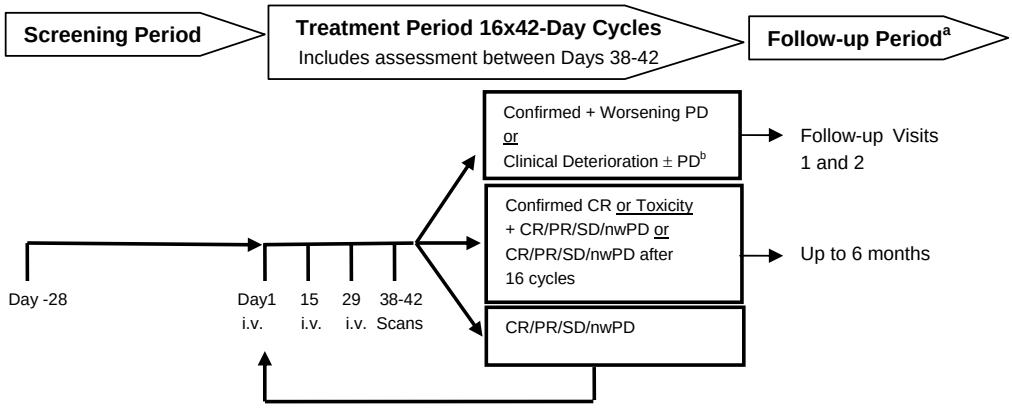
- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to MDX-1105 that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

3.4. Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent Follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

4. STUDY POPULATION

Up to 130 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

4.1. Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period

(no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;
2. Life expectancy ≥ 12 weeks;
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1);
4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy.

   For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

   For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.
5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;
6. May have been treated with up to 5 previous systemic therapies for advanced/recurrent disease or have become intolerant to a systemic therapy;

7. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast – preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;
8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;
9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
10. At least 28 days since the last chemotherapy, immunotherapy, biological or investigational therapy, or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of MDX-1105 and have recovered from any toxicity associated with such treatment;
11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;
12. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;
13. Screening laboratory values must meet the following criteria:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 X ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 X ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

14. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral

oophorectomy); or utilizing a reliable form of contraception. Women of child bearing potential must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug; and

15. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2. Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);
3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;-
4. Active infection (viral, bacterial, or fungal):
   a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of MDX-1105;
   b. Known history of infection with Human Immunodeficiency Virus
   c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)
5. Evidence of bleeding diathesis or coagulopathy;
6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;
7. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;
8. Known current drug or alcohol abuse;
9. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;

10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
11. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses >10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;
12. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;
13. Psychiatric illness or social situation that would preclude study compliance; or
14. Pregnant or nursing.

5. RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6. ASSIGNMENT TO STUDY

The investigative site will contact Medarex for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by Medarex. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7. DOSAGE AND ADMINISTRATION

7.1. Physical Description of Study Drug

MDX-1105 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of MDX-1105 (10 mg/mL).

7.2. Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.3. Storage

MDX-1105 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1105 include laboratory coats and gloves. Note: once MDX-1105 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for MDX-1105 supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between MDX-1105 and polyolefin bags have been observed.

7.4. Study Drug Preparation and Administration

MDX-1105 (0.3, 1, 3, and 10 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). The following steps outline the procedures to be followed for the preparation and infusion of MDX-1105.

1. Allow the appropriate number of vials of MDX-1105 to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the MDX-1105 solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of MDX-1105 solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)
4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary.
5. Prepare the MDX-1105 solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX-1105 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX-1105

10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted MDX-1105 is needed. In this case, all drug should be infused in 60 minutes.

6. Mix by GENTLY inverting several times. DO NOT shake.
7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
8. Record the time MDX-1105 was prepared on the i.v. bag label.
9. Attach the i.v. bag containing the MDX-1105 solution to the infusion set, 0.2 μm in-line filter, and infusion pump.
10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Please note the following:

- **Do not** enter into each vial more than once.
- **Do not** prepare MDX-1105 for infusion in glass syringes.
- **Do not** administer study drug as an i.v. push or bolus injection.

7.5. Drug Accountability

Medarex, Inc. is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by Medarex or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Medarex at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs) or at a central depot.

7.6. Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for MDX-1105 except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1. A subject will be considered to have discontinued study drug if they miss 2 consecutive doses within a cycle.

8. TOXICITY AND MANAGEMENT

8.1. Dose Escalation

The first cohort of 1 subject will receive MDX-1105 at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced. A total of 16 subjects (6 in the dose-escalation cohort + 10 in the expansion cohort) will be treated at the MTD or at the highest dose studied if the MTD is not identified.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2. Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and Medarex on an ongoing basis.

All adverse events that meet DLT criteria**,** as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to Medarex, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3. Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a ≥ Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and Medarex approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

8.4. Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the

dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

8.5. Infusion Reactions

Since MDX-1105 contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-L1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and must be reported to Medarex within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

Prophylactic premedication (e.g., acetaminophen or diphenhydramine) may be given before infusions, if indicated by a prior infusion reaction, anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional MDX-1105 administrations.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the MDX-1105 infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further MDX-1105 will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional MDX-1105 administrations. If necessary (persistent mild or moderate infusion reactions), corticosteroids (up to 25 mg of SoluCortef or equivalent) may be added. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of MDX-1105. Begin an i.v. infusion of normal saline, and treat the subject as follows: bronchodilator, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. MDX-1105 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.6. Possible Toxicities

There is no clinical experience with MDX-1105 to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm:** Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with MDX-1105, and has not been seen in preclinical testing.
- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs):** Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and

colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of irAEs is currently hypothetical, as no subjects have been treated with MDX-1105 to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, limited experience with human subjects treated with anti-PD-1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). A management algorithm for high-grade irAEs in this current study is provided in the Investigator Brochure. **All irAEs should be managed according to this algorithm.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105 program.

8.7. Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the Medarex Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

9. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10. CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.

b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.

c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.

d. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.

e. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of MDX-1105 and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11. STUDY EVALUATIONS

11.1. Study Procedures by Visit

11.1.1. Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1105 need not be repeated**.**

11.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)

- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG

- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
  - Hepatitis B and C testing;
- Concomitant medications

11.1.3. Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start MDX-1105 treatment within 28 days of Screening. Subjects will receive 1 dose of MDX-1105 every 14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1105 will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses,

see Section 7.6 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1. Cycle 1

Cycle 1 will begin with the first i.v. infusion of MDX-1105 (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).
- Serum samples for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B-cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).

- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.3.2. Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of MDX-1105 (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further

cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of MDX-1105 as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry

- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- MDX-1105 infusions
- Concomitant medications
- Adverse event assessment

11.1.4. Follow-up

There are 3 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity
- Serum samples for pharmacokinetic evaluation of MDX-1105
- Vital sign measurements

- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Optional biopsies and/or cryopreserved PBMC as outlined in Sections 11.1.2 and 11.1.3.1.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5. Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 3 doses of MDX-1105 in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6. Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up

- Death
- Other

11.2. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1105: vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of MDX-1105, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1. Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of MDX-1105-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the MDX-1105 drug itself, and is characterized by antibodies that the subject may develop that react with MDX-1105. These may result in more rapid clearance of MDX-1105 from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with MDX-1105 at a later date.

11.2.3. Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and

tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3. Efficacy Evaluations

11.3.1. Efficacy Parameter

The primary efficacy parameter is the best overall response rate (BORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of Medarex.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of MDX-1105 and more likely capture its true potential to induce clinical responses.

11.4. Pharmacokinetic Evaluations

Pharmacokinetic parameters include $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, λ_z, C_{max}, t_{max}, and $t_{½}$.

Blood samples for the analysis of serum concentrations of MDX-1105 will be drawn in all subjects according to the schedule listed below and in Table 3. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1. Cycle 1

- **Day 1:** pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, and 8:** single serum samples will be taken on each day.
- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and immediately at the end of each MDX-1105 infusion.

11.4.2. Cycles 2-16

- **Days 1, 15, and 29:** serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3. Follow-up Visits

- **Follow-up Visits 1 and 2:** single serum samples to be taken.

12. ADVERSE EVENT REPORTING

Clinical events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, version 3.0.[37] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE

version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug – related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

- **Not related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

- **Related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted

12.1.1. Safety Reporting For Adverse Events

All adverse events occurring within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.
- Only treatment-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects 70 days after the administration of the last dose of study drug.

12.2. Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; hospitalization to facilitate the work up of a $\leq$ Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3. Rapid Notification of Serious Adverse Events

12.3.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she provided informed consent and HIPAA authorization, while receiving study treatment or during the 70 days following study drug administration must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring greater than 70 days from the last dose of MDX-1105 must be reported if deemed related to study drug. The report must include the event term, subject identifier, attribution, description, concomitant medication used to treat the event, and any other relevant information. Follow-up information about previously reported serious adverse events must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to Medarex or its designee. The field monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and fax confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.3.3. Contact Persons and Numbers

The Medarex Central Emergency Contact telephone and serious adverse event fax numbers are listed on the cover page of the protocol.

12.4. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, Medarex considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5. Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1105 and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1. Reporting of Pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Medarex and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Medarex according to Serious Adverse Event reporting procedures described in Section 12.3.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate

pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.6. Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the expected mechanism of action of MDX-1105, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1105

program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

12.7. Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

13. STATISTICAL METHODS

13.1. Sample Size Determination

A total of up to 130 subjects are to be enrolled in this study based on the study design for dose escalation, safety evaluation and anti-tumor activity evaluation requirements

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that BORR for subjects in the expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

13.2. Study Populations

13.2.1. Safety Population

The safety population includes all subjects who receive at least 1 dose or any partial dose of MDX-1105.

13.2.2. Per-protocol Population

The per-protocol population includes all subjects dosed at the MTD (or the highest dose studied if the MTD is not identified) in the safety population who have the correct disease diagnosis, valid baseline tumor assessment showing measurable disease, and at least 1 valid postbaseline tumor assessment. Any subject who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the per-protocol population.

A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population with the exception of those withdrawn for rapid progression after receiving only 2 or 3 doses.

13.2.3. Pharmacokinetic Population

The pharmacokinetic population includes all subjects in the safety population who complete all 3 infusions in Cycle 1 and have completed the pharmacokinetic assessments of that cycle.

13.3. Statistical Considerations

The Biostatistics group at Medarex, Inc. or its designees will analyze the data collected in this study.

All data will be listed individually by subject. Continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency and percentage.

The baseline value for an analysis variable is the last measurement before study drug administration.

Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05.

13.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.3.2. Extent of Exposure

The total dosage (mg), total number of doses, and total number of treatment cycles will be summarized by dose level using descriptive statistics.

13.3.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications will be summarized by dose level using descriptive statistics. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study.

13.3.4. Safety

The safety analysis will be conducted on the safety population. The following safety parameters will be evaluated:

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

An immune-related adverse event (irAE), a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a preferred term and a system organ class for each adverse event. The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, treatment-related serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE version 3.0), and additional grouping by severity and relationship to study drug.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Physical Examinations

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history and will be included in the respective summaries.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level using descriptive statistics.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE 3.0 Grade will be assigned to some of the laboratory parameters, which are included in "CTCAE version 3.0". Central laboratory values will be listed. Laboratory values which are outside normal range will be flagged as H (above high normal limit), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE 3.0 Grade will also be flagged in the listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

Diagnostic Tests

Diagnostic tests results will be summarized by dose level using descriptive statistics.

Immune Safety Evaluations

Immune safety tests results will be summarized by dose level using descriptive statistics.

Immunogenicity

Immunogenicity measurement for human anti-human antibodies (HAHA) will be summarized appropriately.

13.3.5. Efficacy

The primary efficacy endpoint is the BORR during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of Medarex. In each expansion cohort, a one-sample exact Binomial test will be performed for the BORR and the 95% confidence intervals will be determined.

The secondary efficacy endpoints include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), progression-free survival, and the time to response and duration of response for those subjects with confirmed responses. All the secondary efficacy parameters will be summarized using

descriptive statistics for each expansion cohort. Progression-free survival will be summarized using Kaplan-Meier survival methods. Time to response and duration of response will be summarized for those subjects with confirmed responses.

For the expansion cohorts, efficacy analyses will only be applied to the cohorts that enroll at least 16 subjects.

13.3.6. Pharmacokinetic

Plasma concentrations of MDX-1105 will be determined by a validated method at the times listed in the time and events schedule tables.

Definition and Calculation of Pharmacokinetic Parameters

The following pharmacokinetic parameters will be estimated and reported:

$AUC_{0\rightarrow t}$ Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).

$AUC_{0\rightarrow \infty}$ Area under the curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z).

λ_z Terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of $\log_e$ (concentration) vs time with the following constraints: (i) there must be at least 3 consecutive measurable concentrations, (ii) all concentrations must be declining with time and (iii) the correlation coefficient r of regression must be ≥ 0.95.

C_{max} Maximum plasma concentration observed postdose.

t_{max} Time at which the C_{max} occurs.

$t_{½}$ Elimination half-life, determined as $0.693/\lambda_z$.

The pharmacokinetic parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

13.3.7. Exploratory Immune Function Studies

Flow Cytometry

Flow cytometry results will be summarized using descriptive statistics or as otherwise appropriate.

Exploratory Immune Function

The effects of MDX-1105 on humoral and cellular immune responses to tumor antigens (when available) and a panel of recall nontumor antigens will be assessed. Parameters to be examined will include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment will be assessed. These parameters will be summarized by dose level using descriptive statistics, and may be reported as part of a separate document.

13.4. Missing-Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

13.5. Statistical Software

The estimation of pharmacokinetic parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher.

14. ETHICAL ASPECTS

14.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Medarex SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

14.2. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and

other study documents submitted to Medarex or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Medarex, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC must be given to Medarex before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to Medarex or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

14.4. Informed Consent

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Medarex supplies a proposed ICF that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Medarex or its designee before submission to the IRB/IEC and a copy of the approved version must be provided to the Medarex monitor after IRB/IEC approval.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Medarex before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Medarex monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Medarex in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, Medarex should be notified and the IRB/IEC for the center should be informed within 1 working day.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization [CRO]); and
2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Medarex representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Medarex monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the

protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Medarex or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Medarex will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.4. Auditing Procedures

In addition to the routine monitoring procedures, Medarex, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Medarex, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Medarex immediately that this request has been made.

15.5. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Medarex. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Medarex statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Medarex.

Medarex must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Medarex personnel.

15.6. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Medarex or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Medarex (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Medarex, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7. Discontinuation of Study

Medarex reserves the right to discontinue any study for any reason at any time.

15.8. Data Management

15.8.1. Data Collection

Investigators must enter the information required by the protocol onto the Medarex CRFs that are printed on "no carbon required" paper. Medarex monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to Medarex, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.8.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following Medarex, or its designee, data management procedures. Obvious errors will be corrected by Medarex personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Medarex study team.

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17. APPENDICES

Appendix 1: ECOG Performance Status

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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Appendix 2: RECIST With Modification

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having "symptomatic deterioration."

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.

continued

Definitions *(continued)*

Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not "selected" images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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Protocol Number:	CA210001 (MDX1105-01)
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EUDRACT Number	NA
Date:	17-Jun-2008
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Clinical Protocol CA210001 (MDX1105-01)

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

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Incorporates amendment(s) 01, 02, 03, 04

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

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SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

CA210001 (MDX1105-01)

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105).

Exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs).

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

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If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Bristol-Myers Squibb Co. (BMS) approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.
c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansions

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Melanoma Expansions

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.

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- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

The maximum duration of a subject's participation in this study is approximately 2.5 years.

STUDY POPULATION

Up to 130 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

BMS-936559 (MDX-1105) will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, and 10 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other

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irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the objective response rate (ORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of BMS.

In addition to ORR at 4 cycles, the ORR across the entire study (regardless of time of response) will be calculated for each subject. Time to response, duration or response will also be calculated and estimated within each indication and across indications. Disease control (BOR outcome of CR, PR or SD) rate (DCR), duration of disease control and Progression Free Survival (PFS) are additional endpoints.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with BMS-936559 (MDX-1105).

EXPLORATORY IMMUNE FUNCTION AND OTHER BIOMARKER EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include AUC(0-T), AUC(INF), Cmax, Tmax, T-HALF, Vss, and CLT.

For Cycle 1, Day 1, blood samples for assessment of the serum concentration of BMS-936559 (MDX-1105)will be drawn within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-up Visits 1 and 2.

STATISTICAL METHODS

Sample Size Determination:

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level. Up to seven

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expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts. A total of up to 130 subjects are to be enrolled in this study.

In order to perform preliminary evaluation of anti-tumor activity, the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that RR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Statistical Analysis:

All recorded adverse events will be listed and tabulated by system organ class, preferred term and dose. Vital signs and clinical laboratory test results (including immune safety test results) will be listed and summarized by dose. Any significant physical examination findings, ECG results, and clinical laboratory results will be listed. Selected safety summaries may also be tabulated by indication.

Efficacy parameters (ORR at 4 cycles and ORR from the entire study, Time to response, Duration of response, Disease control rate, Duration of Disease Control and PFS) will be summarized by dose and by indication using descriptive statistics for expansion cohorts. For ORR during first 4 cycles in each expansion cohort, 90% confidence intervals will be calculated. Median time to response and duration of response for those subjects with confirmed responses, duration of disease control and PFS will be summarized, using Kaplan-Meier methodology, at each expansion cohort.

Immunogenicity measurements for human anti-human antibodies (HAHA) will be listed. A listing for subjects with at least one positive HAHA assessment will be provided. HAHA responses will also be tabulated by frequency distribution. Associations with safety and or PK exposure will be explored.

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1Day1 by dose. Geometric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T) and AUC(INF). Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided. Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose. Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model.

Summary statistics for immune function and other biomarker measures, including but not limited to results from flow cytometry and humoral/cellular immune responses will be tabulated by dose level and study day. Associations of such measures with clinical outcome or safety events of interest (e.g. irAE) may be explored graphically based on data availability.

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ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BOR	Best overall response
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HAHA	Human anti-human antibodies
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous

Abbreviation	Term
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]		•	•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/abdomen/pelvis)[11]	•[12]								•	•[14]	•	
Brain CT scan/MRI[11,13]	•[12]								•[14]	•[14]	•[14]	•[14]
Bone scan (if clinically indicated)[15]	•[12]								•[15]	•[15]	•[15]	•[15]
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Response assessment									•			
ECG (12-lead)	•[12]	•[16]								•		
Hematology	•	•[17]		•	•[17]	•	•[17]		•	•	•	•
Serum chemistry	•	•[17]		•	•[17]	•	•[17]		•	•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry		•								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity		•								•	•	
BMS-936559 (MDX-1105) infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

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Table 1 Footnotes:

1 Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3 Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

4 To include collection of prior medication and prior/concurrent medical conditions.

5 Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).

6 Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.

7 Pharmacokinetic sampling to be performed according to Table 3.

8 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

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Table 1 Footnotes *(continued)*

9 ECOG Performance Status to be assessed before each infusion.

10 Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a10% or greater change in weight [increase or decrease] since the previous cycle).

11 The same technique (CT/MRI) used at baseline should be utilized throughout the study.

12 Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of BMS-936559 (MDX-1105) need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

13 Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

14 To be performed if clinically indicated and if not done within the preceding 28 days.

15 If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

16 To be performed pre- and postinfusion.

17 During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

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Table 1 Footnotes *(continued)*

[18] Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]		
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•[15]	•[15]		•	•	•
Serum chemistry	•[15]	•[15]	•[15]		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[16]	•				•	•	•
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•				•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
BMS-936559 (MDX-1105) infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

[1] Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

[2] End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days (and no later than 28 ± 2 days) after the last dose of the prior treatment cycle.

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Table 2 Footnotes *(continued)*

3 The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

4 Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.

5 Pharmacokinetic sampling to be performed according to Table 3.

6 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

7 ECOG Performance Status to be assessed before each infusion.

8 Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note**: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

9 The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.

10 To be performed if clinically indicated and if not done within the preceding 28 days.

11 Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

12 If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.

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Table 2 Footnotes *(continued)*

[13] At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation.

[14] To be performed pre- and postinfusion.

[15] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[16] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

[17] Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

[18] Sample collected for Cycles 2 and 3 only.

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Table 3: Pharmacokinetic Sampling Schedule

Sample collection time points	Cycle 1[1]					Cycle 2-16[2]	Follow-up Visits 1 and 2[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
Any time during the visit		•	•				•
-30 to 0 minutes before infusion	•			•	•	•	
At the end of infusion	•			•	•	•	
30 minutes after the infusion	•						
60 minutes after the infusion	•						
120 minutes after the infusion	•						
240 minutes after the infusion	•						

[1] Blood samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.

[2] For Cycles 2-16, samples will be drawn every 14 days, within 30 minutes before the administration of BMS-936559 (MDX-1105) and at the end of each infusion.

[3] A single sample will be taken at Follow-up Visits 1 and 2.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

BMS-936559 (MDX-1105) is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

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An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

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An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006.[2] The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

1.2 PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[34,5,6,7,8,9,10] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[7] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both $PD\text{-}L1^{+}$ and $PD\text{-}L1^{-}$ tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid

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cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity.[14] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[32] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. 32 Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[33] In a

pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[6] Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD 1 blockade.33,34 Using a murinized anti-mouse PD 1 antibody, Medarex (now BMS) showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD -L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, BMS-936559 (MDX-1105) represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3 Summary of BMS-936559 (MDX-1105) Preclinical Studies

BMS-936559 (MDX-1105) is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. BMS-936559 (MDX-1105) was selected to inhibit the interaction of PD-L1 with its receptor PD-1. BMS-936559 (MDX-1105)-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using BMS-936559 (MDX-1105) can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of BMS-936559 (MDX-1105) shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of BMS-936559 (MDX-1105) at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. BMS-936559 (MDX-1105) was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4 Rationale for BMS-936559 (MDX-1105)

1.4.1 Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol CA210001 (MDX1105-01) will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where BMS-936559 (MDX-1105) doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed

to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2 Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 14 April 2008, there were no DLTs reported after single dose administration of 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer (Protocol MDX-1106-01). A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg of MDX-1106 over 32 weeks. Twenty one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with BMS-936559 (MDX-1105) will be closely monitored in Protocol CA210001 (MDX1105-01).

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Seventeen subjects (17/88, 19.3%) with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) the immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105).

2.3 Exploratory Objective

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs).

3 OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1 Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2 Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.
c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1 Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication.

3.2.2 Initiation of the Additional Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.3 Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject

develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to BMS-936559 (MDX-1105) that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive BMS-936559 (MDX-1105) therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the BMS Medical Monitor as described in Section 8.7.
- PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.
  - If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

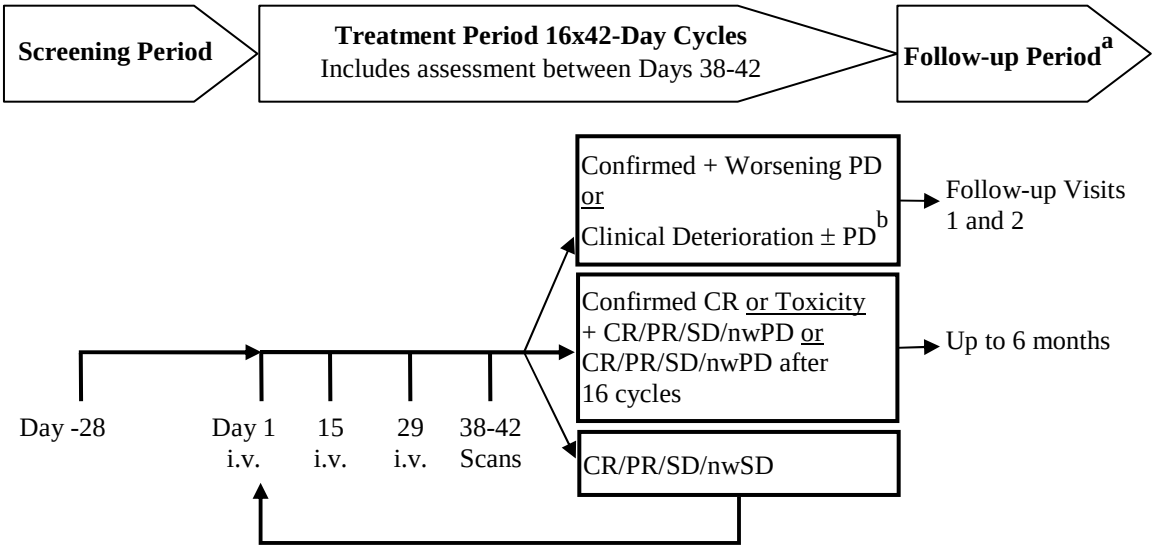
- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to BMS-936559 (MDX-1105) that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

3.4 Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent Follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

3.5 Stopping Rules

3.5.1 Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a greater than or equal to Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

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3.5.2 Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.5.3 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator’s opinion, is attributable to disease progression, is unlikely to reverse with

continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression

- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

3.6 Post Study Access to Therapy

At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study, or to establishe a separate long term follow up/treatment study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study should no additional study drug be available.

4 STUDY POPULATION

Up to 130 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor's Medical Monitor, or designee, before enrolling the subject into the study.

For entry into the study, the following criteria MUST be met.

4.1 Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;

2. Life expectancy ≥ 12 weeks;

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1);

4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least

1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy.

For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;

6. Not applicable as of revised protocol number 04;

7. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast - preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;

8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;

9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;

10. At least 14 days or 5 half-lives (whichever is longer) since the last chemotherapy, immunotherapy, biological therapy, or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of BMS-936559 (MDX-1105) and have recovered from any clinically significant toxicity associated with such treatment;

11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

12. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

13. Screening laboratory values must meet the following criteria:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 x ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

14. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a

hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women of child bearing potential (WOCBP) must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug.

15. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;

2. Prior therapy with an anti-PD 1, anti-PD L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);

3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;

4. Active infection (viral, bacterial, or fungal):

    a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of BMS-936559 (MDX-1105);
    b. Known history of infection with Human Immunodeficiency Virus
    c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)

5. Evidence of bleeding diathesis or coagulopathy;

6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;

7. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;

8. Known current drug or alcohol abuse;

9. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;

10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;

11. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses > 10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;

12. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;

13. Psychiatric illness or social situation that would preclude study compliance; or

14. Pregnant or nursing.

15. Prisoners or subjects who are involuntarily incarcerated, or

16. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg infectious disease) illness

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5 RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6 ASSIGNMENT TO STUDY

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by BMS. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7 DOSAGE AND ADMINISTRATION

All protocol-specified investigational and noninvestigational products are considered study drug.

7.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product is BMS-936559 (MDX-1105).

7.2 Physical Description of Study Drug

BMS-936559 (MDX-1105) is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of BMS-936559 (MDX-1105) (10 mg/mL).

7.3 Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.4 Storage

BMS-936559 (MDX-1105) vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of BMS-936559 (MDX-1105) include laboratory coats and gloves. Note: once BMS-936559 (MDX-1105) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for BMS-936559 (MDX-1105) supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936559 (MDX-1105) and polyolefin bags have been observed.

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.5 Study Drug Preparation and Administration

BMS-936559 (MDX-1105) (0.3, 1, 3, and 10 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). The following steps outline the procedures to be followed for the preparation and infusion of BMS-936559 (MDX-1105).

1. Allow the appropriate number of vials of BMS-936559 (MDX-1105) to stand at room temperature for approximately 5 minutes before preparation.

2. Ensure that the BMS-936559 (MDX-1105) solution is clear, colorless and essentially free from particulate matter on visual inspection.

3. Aseptically withdraw the required volume of BMS-936559 (MDX-1105) solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary.

5. Prepare the BMS-936559 (MDX-1105) solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of BMS-936559 (MDX-1105) (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of BMS-936559 (MDX-1105) 10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted BMS-936559 (MDX-1105) is needed. In this case, all drug should be infused in 60 minutes.

6. Mix by GENTLY inverting several times. DO NOT shake.

7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.

8. Record the time BMS-936559 (MDX-1105) was prepared on the i.v. bag label.

9. Attach the i.v. bag containing the BMS-936559 (MDX-1105) solution to the infusion set, 0.2 μm in-line filter, and infusion pump.

10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.

11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Please note the following:

- **Do not** enter into each vial more than once.
- **Do not** prepare BMS-936559 (MDX-1105) for infusion in glass syringes.
- **Do not** administer study drug as an i.v. push or bolus injection.

7.6 Drug Accountability

BMS is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by BMS or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given

to BMS at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.7 Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1.

7.8 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

7.9 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 TOXICITY AND MANAGEMENT

8.1 Dose Escalation

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2 Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

All adverse events that meet DLT criteria, as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to BMS, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3 Infusion Reactions

Since BMS-936559 (MDX-1105) contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-L1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and must be reported to BMS within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

Prophylactic premedication (e.g., acetaminophen or diphenhydramine) may be given before infusions, if indicated by a prior infusion reaction, anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional BMS-936559 (MDX-1105) administrations.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the BMS-936559 (MDX-1105) infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further BMS-936559 (MDX-1105) will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg administered at least 30 minutes before additional BMS-936559 (MDX-1105) administrations. If necessary (persistent mild or moderate infusion reactions), corticosteroids (up to 25 mg of SoluCortef or equivalent) may be added. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for

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other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of BMS-936559 (MDX-1105). Begin an i.v. infusion of normal saline, and treat the subject as follows: bronchodilator, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. BMS-936559 (MDX-1105) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.4 Possible Toxicities

There is no clinical experience with BMS-936559 (MDX-1105) to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity**: Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm**: Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with BMS-936559 (MDX-1105), and has not been seen in preclinical testing.

- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system**: Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression**: Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood**: A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin**: The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs)**: Given the expected mechanism of action of BMS-936559 (MDX-1105), namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of irAEs is currently hypothetical, as no subjects have been treated with BMS-936559 (MDX-1105) to date, and are based upon preclinical studies in mice deficient in PD-1 and PD-L1, treatment of mice with anti-PD-1 and anti-PD-L1 antibodies, limited experience with human subjects treated with anti-PD-1 antibodies, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time or may require institution of counteracting immunosuppressive therapies.

  BMS has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). A management algorithm for high-grade irAEs in this current study is provided in the Investigator Brochure. **All irAEs should be managed according to this algorithm.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program.

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9 COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10 CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.
b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.
c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
d. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.
e. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of BMS-936559 (MDX-1105) and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11 STUDY EVALUATIONS

11.1 Study Procedures by Visit

11.1.1 Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936559 (MDX-1105) need not be repeated.

11.1.2 Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)
- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.

- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG
- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid

- Electrolytes (sodium, potassium, chloride, and bicarbonate)
- Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.

  Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
- Hepatitis B and C testing;

- Concomitant medications

11.1.3 Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start BMS-936559 (MDX-1105) treatment within 28 days of Screening. Subjects will receive 1 dose of BMS-936559 (MDX-1105) every 14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses, see Section 7.6 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1 Cycle 1

Cycle 1 will begin with the first i.v. infusion of BMS-936559 (MDX-1105) (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples

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should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:

- Hematology with differential (as outlined in Section 11.1.2)
- Chemistry (as outlined in Section 11.1.2)
- Urinalysis (as outlined in Section 11.1.2)

- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.3.2 Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of BMS-936559 (MDX-1105) (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status

- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)

- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.4 Follow-up

There are 3 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105)
- Vital sign measurements
- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Optional biopsies and/or cryopreserved PBMC as outlined in Sections 11.1.2 and 11.1.3.1.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5 Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they have:

- Completed 3 doses of BMS-936559 (MDX-1105) in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6 Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up
- Death
- Other

11.1.7 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with the protocol
- Disease progression as defined in Section 3.3
- Significant clinical deterioration

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

11.2 Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of BMS-936559 (MDX-1105): vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1 Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a

consequence of BMS-936559 (MDX-1105)-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2 Immunogenicity

Immunogenicity refers to the development of an immune response to the BMS-936559 (MDX-1105) drug itself, and is characterized by antibodies that the subject may develop that react with BMS-936559 (MDX-1105). These may result in more rapid clearance of BMS-936559 (MDX-1105) from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with BMS-936559 (MDX-1105) at a later date.

11.2.3 Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3 Efficacy Evaluations

11.3.1 Efficacy Parameter

The primary efficacy parameter is the objective response rate (ORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be

assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of BMS.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of BMS-936559 (MDX-1105) and more likely capture its true potential to induce clinical responses.

11.4 Pharmacokinetic Evaluations

Pharmacokinetic parameters include AUC(0-T), AUC(INF), Cmax, Tmax, T-HALF, Vss, and CLT.

Blood samples for the analysis of serum concentrations of BMS-936559 (MDX-1105) will be drawn in all subjects according to the schedule listed below and in Table 3. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1 Cycle 1

- **Day 1**: pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, and 8**: single serum samples will be taken on each day.
- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

11.4.2 Cycles 2-16

- **Days 1, 15, and 29**: serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3 Follow-up Visits

- **Follow-up Visits 1 and** 2: single serum samples to be taken.

12 ADVERSE EVENT REPORTING

12.1 Definitions

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, version 3.0.[37] If

CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate.

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug - related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as “not related” or “related”. The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

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- **Not related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

- **Related**

  The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted

12.1.1 Safety Reporting For Nonserious Adverse Events

A *nonserious adverse event* is an AE not classified as serious (see Section 12.2 for the definition of serious AE).

Nonserious AE occurred after the initiation of study drug and within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only treatment-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects beyond 70 days after the administration of the last dose of study drug.

All identified nonserious AEs must be recorded and described on the AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page.

12.2 Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.6.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

12.3 Rapid Notification of Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.4 Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. Although overdose is not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner. (see Section 12.3, Serious Adverse Events for reporting details).

12.5 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page and/or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

12.6 Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive BMS-936559 (MDX-1105) and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.6.1 Reporting of Pregnancy

The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.7 Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the expected mechanism of action of BMS-936559 (MDX-1105), namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical

experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

BMS has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

12.8 Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size Determination

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level. Up to seven expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts. A total of up to 130 subjects are to be enrolled in this study.

In order to perform preliminary evaluation of anti-tumor activity, the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that RR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

13.2 Populations for Analyses

13.2.1 Safety Population

The safety population includes all subjects who receive BMS-936559 (MDX-1105).

13.2.2 Efficacy Population

All subjects who receive BMS-936559 (MDX-1105) and with required baseline and at least one post-treatment radiologic tumor assessment.

13.2.3 Pharmacokinetic Population

All available concentration-time data from subjects who receive BMS-936559 (MDX-1105) will be reported. All available derived pharmacokinetic parameter values will be included in the pharmacokinetic dataset and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

13.2.4 Immunogenicity Population

All available data from subjects who receive BMS-936559 (MDX-1105) and have a baseline and additional post-treatment measurement samples collected will be included in the immunogenicity dataset.

13.3 Endpoint Definitions

13.3.1 Safety Endpoints

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurement, physical examinations, clinical laboratory tests, ECG, immune safety laboratory tests, ECOG performance status, diagnostics test and immunogenicity measurement for human anti-human antibodies (HAHA). Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

13.3.2 Efficacy Endpoints

Primary efficacy endpoint: ORR (objective response rate) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of investigator evaluations.

Secondary efficacy endpoint: ORR during the entire study, Disease Control (BOR outcome of CR, PR or SD) rate, Progression-free survival (PFS), Time to response, Duration of response, and Duration of disease control.

13.3.3 Pharmacokinetic Endpoints

Pharmacokinetic of BMS-936559 (MDX-1105) will be derived from plasma concentration versus time. The following pharmacokinetic parameters will be estimated and reported:

AUC(0-T)	Area under the plasma/serum drug concentration-time curve from t=0 to last measurable sampling time.
AUC(INF)	Area under the plasma/serum concentration-time curve from t=0, extrapolated to infinity.
Cmax	Maximum observed concentration in plasma.
Tmax	Time to reach Cmax in plasma.
T-HALF	Terminal-phase elimination half-life in plasma.
Vss	Volume of distribution at steady state
CLT	Total body clearance of drug from plasma.

Individual subject pharmacokinetic parameter values will be derived by non-compartmental method by a validated pharmacokinetic program.

13.4 Analyses

13.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.4.2 Safety Analyses

The safety analysis will be conducted on the safety population.

All recorded adverse events will be listed and tabulated by system organ class, preferred term and dose. Vital signs and clinical laboratory test results (including immune safety test results) will be listed and summarized by dose. Any significant physical examination findings, ECG results and clinical laboratory results will be listed. Safety summaries may also be tabulated by indication.

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13.4.3 Efficacy Analyses

Individual tumor response as defined by RECIST with modifications will be listed by dose and indication.

Primary analyses:

For the expanded cohorts, best overall tumor response during the first 4 cycles will be tabulated by dose and indication. In each expansion cohort, for the ORR during the first 4 cycles, point estimate and 2-sided exact 90% confidence intervals will be calculated.

Secondary analyses:

For the expanded cohorts, Time to response and Duration of response will be computed for all treated subjects with confirmed response (CR or PR), and summarized by dose and indication. Best overall tumor response during entire study will be tabulated by dose and indication. Point estimate and 2-sided exact 90% confidence intervals for the ORR during the entire study will be provided. Disease control rate will be similarly estimated by dose and indication. Median time to response and duration of response for those subjects with confirmed responses, duration of disease control and PFS will be summarized by 95% confidence-intervals using Kaplan-Meier methodology, at each expansion cohort.

13.4.4 Immunogenicity Analyses

Individual immunogenicity measurement for human anti-human antibodies (HAHA) will be listed. A listing for subjects with at least one positive HAHA assessment will be provided. HAHA responses will also be tabulated by frequency distribution. Associations with safety and or PK exposure may be explored.

13.4.5 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1Day1 by dose. Geomeric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T) and AUC(INF). Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and

Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided.

Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose.

Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameters (slope of the linear regression) will be calculated.

Data describing the plasma concentration versus time from this study may be used for future population pharmacokinetic evaluations of the drug which may be reported separately.

13.4.6 Exploratory Analyses

Flow Cytometry

Summary statistics for immune function and other biomarker measures, including but not limited to results from flow cytometry will be tabulated by dose level and study day. Associations of such measures with clinical outcome or safety events of interest (e.g. irAE) may be explored graphically based on data availability.

Exploratory Immune Function

The effects of BMS-936559 (MDX-1105) on humoral and cellular immune responses to tumor antigens (e.g. CA-125 and CEA or CA19-9) and a panel of recall nontumor antigens will be assessed based on data availability. Parameters to be examined may include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment. Summary statistics for these parameters will be tabulated by dose level and study day. Associations between these measures and clinical endpoints will be explored graphically.

14 ETHICAL ASPECTS

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with BMS SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to BMS or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of BMS, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

14.4 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

15 ADMINISTRATIVE REQUIREMENTS

15.1 Protocol Amendments

The study shall be conducted as described in this approved protocol. Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in

the CRF. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the BMS monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;

2. Significant change in the study design (e.g., addition or deletion of a control group);

3. Increase in the number of procedures to which subjects are exposed; or

4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., BMS staff versus a contract research organization [CRO]); and

2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2 Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a BMS representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the BMS monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. BMS monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

15.4 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to BMS or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the electronic CRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique

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user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) and the following noninvestigational product(s): #?# is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

15.5 Auditing Procedures

In addition to the routine monitoring procedures, BMS, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. BMS, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS immediately that this request has been made.

15.6 Publication of Results

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

15.7 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by BMS or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by BMS (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.8 Discontinuation of Study

BMS reserves the right to discontinue any study for any reason at any time.

15.9 Data Management

15.9.1 Data Collection

Investigators must enter the information required by the protocol onto the BMS CRFs that are printed on "no carbon required" paper. BMS monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to BMS, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.9.2 Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following BMS, or its designee, data management procedures. Obvious errors will be corrected by BMS personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the BMS study team.

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APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	ead

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APPENDIX 2 RECIST WITH MODIFICATIONS

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target

lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.”

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.
Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not “selected” images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.

continued

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Definitions *(continued)*

Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

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APPENDIX 3 PRE-EXISTING AUTOIMMUNE DISEASES

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	17-Jun-2008
Revised Date	16-Jun-2010

Clinical Protocol CA210001 (MDX1105-01)

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Revised Protocol Number: 05

Incorporates amendment(s) 01, 02, 03, 04, 05

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

CA210001 (MDX1105-01)

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105).

Exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs).

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

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If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Bristol-Myers Squibb Co. (BMS) approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.
c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansions

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Melanoma Expansions

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.

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- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) development of a ≥ Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

The maximum duration of a subject's participation in this study is approximately 2.5 years.

STUDY POPULATION

Up to 130 subjects may be enrolled. Subjects will have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

DOSAGE AND ADMINISTRATION

BMS-936559 (MDX-1105) will be administered as a 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). Cohorts will include escalating dose levels of 0.3, 1, 3, and 10 mg/kg/dose.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other

irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the objective response rate (ORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of BMS.

In addition to ORR at 4 cycles, the ORR across the entire study (regardless of time of response) will be calculated for each subject. Time to response, duration or response will also be calculated and estimated within each indication and across indications. Disease control (BOR outcome of CR, PR or SD) rate (DCR), duration of disease control and Progression Free Survival (PFS) are additional endpoints.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with BMS-936559 (MDX-1105).

EXPLORATORY IMMUNE FUNCTION AND OTHER BIOMARKER EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include AUC(0-T), AUC(INF), Cmax, Tmax, T-HALF, Vss, and CLT.

For Cycle 1, Day 1, blood samples for assessment of the serum concentration of BMS-936559 (MDX-1105)will be drawn within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before each infusion and immediately after the infusion is completed.

For Cycles 2 to 16, samples will be drawn every 14 days, within 30 minutes before the administration of MDX 1105, and immediately after the infusion is completed.

Single samples will also be collected at Follow-up Visits 1 and 2.

STATISTICAL METHODS

Sample Size Determination:

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level. Up to seven

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expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts. A total of up to 130 subjects are to be enrolled in this study.

In order to perform preliminary evaluation of anti-tumor activity, the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that RR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Statistical Analysis:

All recorded adverse events will be listed and tabulated by system organ class, preferred term and dose. Vital signs and clinical laboratory test results (including immune safety test results) will be listed and summarized by dose. Any significant physical examination findings, ECG results, and clinical laboratory results will be listed. Selected safety summaries may also be tabulated by indication.

Efficacy parameters (ORR at 4 cycles and ORR from the entire study, Time to response, Duration of response, Disease control rate, Duration of Disease Control and PFS) will be summarized by dose and by indication using descriptive statistics for expansion cohorts. For ORR during first 4 cycles in each expansion cohort, 90% confidence intervals will be calculated. Median time to response and duration of response for those subjects with confirmed responses, duration of disease control and PFS will be summarized, using Kaplan-Meier methodology, at each expansion cohort.

Immunogenicity measurements for human anti-human antibodies (HAHA) will be listed. A listing for subjects with at least one positive HAHA assessment will be provided. HAHA responses will also be tabulated by frequency distribution. Associations with safety and or PK exposure will be explored.

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1Day1 by dose. Geometric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T) and AUC(INF). Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided. Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose. Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model.

Summary statistics for immune function and other biomarker measures, including but not limited to results from flow cytometry and humoral/cellular immune responses will be tabulated by dose level and study day. Associations of such measures with clinical outcome or safety events of interest (e.g. irAE) may be explored graphically based on data availability.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BOR	Best overall response
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HAHA	Human anti-human antibodies
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous

Abbreviation	Term
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
RT	Radiation therapy
SD	Stable disease
SLD	Sum of the longest diameter
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for pharmacokinetics[7]		•	•	•	•		•			•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/abdomen/pelvis)[11]	•[12]								•	•[14]	•	•
Brain CT scan/MRI[11,13]	•[12]								•[14]	•[14]	•[14]	•[14]
Bone scan (if clinically indicated)[15]	•[12]								•[15]	•[15]	•[15]	•[15]
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Response assessment									•			
ECG (12-lead)	•[12]	•[16]								•		
Hematology	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Serum chemistry	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry		•								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity		•								•	•	
BMS-936559 (MDX-1105) infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

continued

Footnotes can be found on the following page.

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Table 1 Footnotes:

1 Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3 Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

4 To include collection of prior medication and prior/concurrent medical conditions.

5 Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).

6 Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.

7 Pharmacokinetic sampling to be performed according to Table 3.

8 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

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Table 1 Footnotes *(continued)*

[9] ECOG Performance Status to be assessed before each infusion.

[10] Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a10% or greater change in weight [increase or decrease] since the previous cycle).

[11] The same technique (CT/MRI) used at baseline should be utilized throughout the study.

[12] Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of BMS-936559 (MDX-1105) need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

[13] Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

[14] To be performed if clinically indicated and if not done within the preceding 28 days.

[15] If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

[16] To be performed pre- and postinfusion.

[17] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

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Table 1 Footnotes *(continued)*

[18] Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Immunohistochemistry (IHC) for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	•	•	•		•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]		
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•[15]	•[15]		•	•	•
Serum chemistry	•[15]	•[15]	•[15]		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[16]	•				•	•	•
Optional tumor or other biopsy[17]							
Urinalysis	•	•	•		•	•	•
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[18]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•				•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up-2**	**Follow-up-3**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
BMS-936559 (MDX-1105) infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

[1] Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 6 months follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

[2] End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days (and no later than 28 ± 2 days) after the last dose of the prior treatment cycle.

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Table 2 Footnotes *(continued)*

3 The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

4 Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated timepoints must be performed and found to be negative before infusion for women of childbearing potential.

5 Pharmacokinetic sampling to be performed according to Table 3.

6 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

7 ECOG Performance Status to be assessed before each infusion.

8 Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note**: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

9 The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.

10 To be performed if clinically indicated and if not done within the preceding 28 days.

11 Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 and 3.

12 If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.

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Table 2 Footnotes *(continued)*

13 At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation.

14 To be performed pre- and postinfusion.

15 During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

16 CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

17 Biopsies at screening are required if no previous tumor biopsy report available. Consent to request previous tumor biopsy specimens is required. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. IHC for PD-L1 expression or other markers may be done on tumor samples collected during or before this study.

18 Sample collected for Cycles 2 and 3 only.

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Table 3: Pharmacokinetic Sampling Schedule

Sample collection time points	Cycle 1[1]					Cycle 2-16[2]	Follow-up Visits 1 and 2[3]
	Day 1	Days 2-4	Day 8	Day 15	Day 29	Days 1, 15, 29	
Any time during the visit		•	•				•
-30 to 0 minutes before infusion	•			•	•	•	
At the end of infusion	•			•	•	•	
30 minutes after the infusion	•						
60 minutes after the infusion	•						
120 minutes after the infusion	•						
240 minutes after the infusion	•						

[1] Blood samples will be drawn on Day 1 (Cycle 1 only) within 30 minutes before infusion, at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. For Days 2, 3, 4, and 8, a single sample will be collected. On Days 15 and 29, samples will be collected within 30 minutes before infusion and immediately after infusion is completed. Samples are to be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion.

[2] For Cycles 2-16, samples will be drawn every 14 days, within 30 minutes before the administration of BMS-936559 (MDX-1105) and at the end of each infusion.

[3] A single sample will be taken at Follow-up Visits 1 and 2.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

BMS-936559 (MDX-1105) is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006.[2] The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

1.2 PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[34,5,6,7,8,9,10] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[7] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[4,5,6,9] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both $PD\text{-}L1^{+}$ and $PD\text{-}L1^{-}$ tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[11,12,13,14,15] PD-1 is primarily expressed on activated T cells, B cells, and myeloid

cells.[16] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[17,18,19,20,21,22,23] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[22,24] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[25,26,27] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity.[14] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[21,25,28,29]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[30,31,32,33,34] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[32] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. 32 Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[33] In a

pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[6] Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[35] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD 1 blockade.33,34 Using a murinized anti-mouse PD 1 antibody, Medarex (now BMS) showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[36] This suggests that PD-1/PD -L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, BMS-936559 (MDX-1105) represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3 Summary of BMS-936559 (MDX-1105) Preclinical Studies

BMS-936559 (MDX-1105) is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. BMS-936559 (MDX-1105) was selected to inhibit the interaction of PD-L1 with its receptor PD-1. BMS-936559 (MDX-1105)-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using BMS-936559 (MDX-1105) can also reverse the suppressive activity of T regulatory cells in in vitro assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of BMS-936559 (MDX-1105) shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of BMS-936559 (MDX-1105) at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. BMS-936559 (MDX-1105) was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4 Rationale for BMS-936559 (MDX-1105)

1.4.1 Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol CA210001 (MDX1105-01) will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where BMS-936559 (MDX-1105) doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases are designed

to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2 Safety Considerations

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 14 April 2008, there were no DLTs reported after single dose administration of 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg of MDX-1106 (an anti-PD-1 antibody) to subjects with cancer (Protocol MDX-1106-01). A related serious adverse event (colitis) has been reported in a subject who received 5 doses of 1 mg/kg of MDX-1106 over 32 weeks. Twenty one subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for colitis to emerge with repeated dosing with BMS-936559 (MDX-1105) will be closely monitored in Protocol CA210001 (MDX1105-01).

Adverse events of uveitis and other inflammatory eye conditions were reported after ipilimumab treatment (an anti-CTLA monoclonal antibody) in a Phase 3 study in subjects with melanoma who had received previous treatment. Of the 144 subjects who had ophthalmologic assessments at both baseline and week 12 on study, 56 (38.9%) exhibited an abnormality at baseline and 56 (38.9%) continued to have an abnormality at week 12. Seventeen subjects (17/88, 19.3%) with a normal baseline were abnormal at week 12. Subjects' baseline ophthalmologic examinations did not assist the Investigator in the diagnosis of clear-cut cases of uveitis and other inflammatory eye conditions confirmed by symptomatic ophthalmologic evaluations. On the basis of these observations, ophthalmologic examinations will not be performed in this study unless clinically indicated for signs or symptoms.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and epithelial ovarian cancer (epOC).

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) the immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105).

2.3 Exploratory Objective

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs).

3 OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 6 months). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1 Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2 Expansion Cohorts

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Additional cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.
c. In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1 Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication.

3.2.2 Initiation of the Additional Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.3 Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor response evaluation. The response

assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to BMS-936559 (MDX-1105) that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive BMS-936559 (MDX-1105) therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the BMS Medical Monitor as described in Section 8.7.
- PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.
  - If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

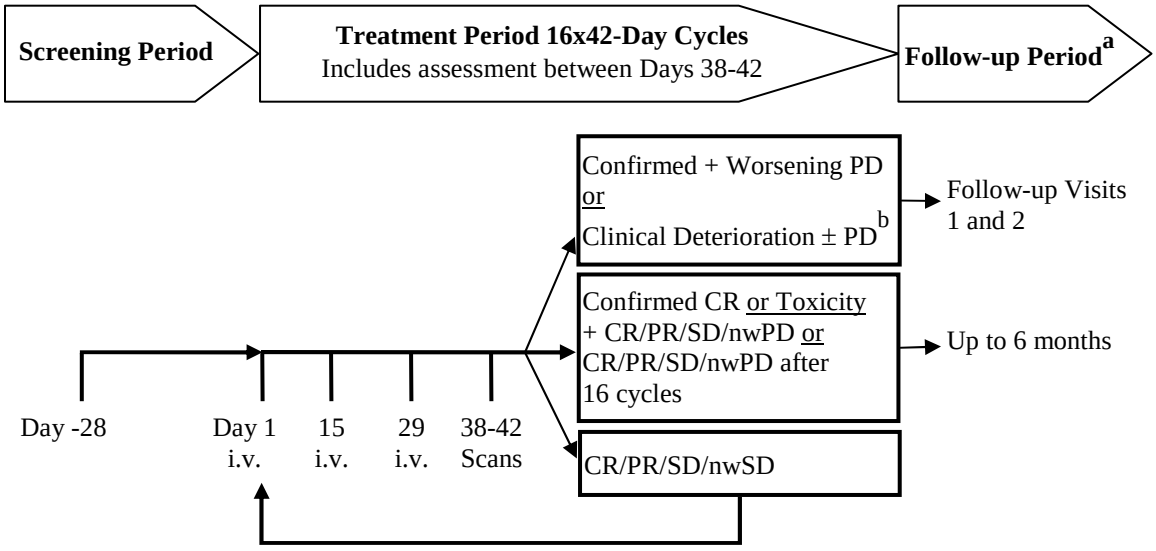
- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to BMS-936559 (MDX-1105) that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

3.4 Follow-up Period

The maximum duration of follow up will be approximately 6 months. All subjects should complete Follow-up Visit 1. Completion of subsequent Follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 1: Individual Subject Flow (Up to 2 Years Treatment, Up to 6 Months Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

3.5 Stopping Rules

3.5.1 Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a greater than or equal to Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

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3.5.2 Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.5.3 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator’s opinion, is attributable to disease progression, is unlikely to reverse with

continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression

- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

3.6 Post Study Access to Therapy

At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study, or to establishe a separate long term follow up/treatment study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study should no additional study drug be available.

4 STUDY POPULATION

Up to 130 subjects are to be enrolled in this study. Subjects must have advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, or epOC.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor's Medical Monitor, or designee, before enrolling the subject into the study.

For entry into the study, the following criteria MUST be met.

4.1 Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;

2. Life expectancy ≥ 12 weeks;

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1);

4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least

1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy.

For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;

6. Not applicable as of revised protocol number 04;

7. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast - preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;

8. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;

9. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;

10. At least 14 days or 5 half-lives (whichever is longer) since the last chemotherapy, immunotherapy, biological therapy, or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of BMS-936559 (MDX-1105) and have recovered from any clinically significant toxicity associated with such treatment;

11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

12. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

13. Screening laboratory values must meet the following criteria:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 x ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

14. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a

hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women of child bearing potential (WOCBP) must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug.

15. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;

2. Prior therapy with an anti-PD 1, anti-PD L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);

3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;

4. Active infection (viral, bacterial, or fungal):

    a. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of BMS-936559 (MDX-1105);
    b. Known history of infection with Human Immunodeficiency Virus
    c. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)

5. Evidence of bleeding diathesis or coagulopathy;

6. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;

7. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;

8. Known current drug or alcohol abuse;

9. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;

10. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;

11. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses > 10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;

12. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;

13. Psychiatric illness or social situation that would preclude study compliance; or

14. Pregnant or nursing.

15. Prisoners or subjects who are involuntarily incarcerated, or

16. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg infectious disease) illness

5 RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6 ASSIGNMENT TO STUDY

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by BMS. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7 DOSAGE AND ADMINISTRATION

All protocol-specified investigational and noninvestigational products are considered study drug.

7.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product is BMS-936559 (MDX-1105).

7.2 Physical Description of Study Drug

BMS-936559 (MDX-1105) is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of BMS-936559 (MDX-1105) (10 mg/mL).

7.3 Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.4 Storage

BMS-936559 (MDX-1105) vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of BMS-936559 (MDX-1105) include laboratory coats and gloves. Note: once BMS-936559 (MDX-1105) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for BMS-936559 (MDX-1105) supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936559 (MDX-1105) and polyolefin bags have been observed.

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.5 Study Drug Preparation and Administration

BMS-936559 (MDX-1105) (0.3, 1, 3, and 10 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 3 infusions in each cycle (up to 16 cycles). The following steps outline the procedures to be followed for the preparation and infusion of BMS-936559 (MDX-1105).

All subjects receiving the 10 mg/kg dose to be pre-medicated with both 650 mg of acetaminophen and 50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to the start of infusion of BMS-936559 (MDX-1105).

1. Allow the appropriate number of vials of BMS-936559 (MDX-1105) to stand at room temperature for approximately 5 minutes before preparation.

2. Ensure that the BMS-936559 (MDX-1105) solution is clear, colorless and essentially free from particulate matter on visual inspection.

3. Aseptically withdraw the required volume of BMS-936559 (MDX-1105) solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary.

5. Prepare the BMS-936559 (MDX-1105) solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of BMS-936559 (MDX-1105) (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of

BMS-936559 (MDX-1105) 10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted BMS-936559 (MDX-1105) is needed. In this case, all drug should be infused in 60 minutes.

6. Mix by GENTLY inverting several times. DO NOT shake.

7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.

8. Record the time BMS-936559 (MDX-1105) was prepared on the i.v. bag label.

9. Attach the i.v. bag containing the BMS-936559 (MDX-1105) solution to the infusion set, 0.2 μm in-line filter, and infusion pump.

10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.

11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Please note the following:

- **Do not** enter into each vial more than once.
- **Do not** prepare BMS-936559 (MDX-1105) for infusion in glass syringes.
- **Do not** administer study drug as an i.v. push or bolus injection.

7.6 Drug Accountability

BMS is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by BMS or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to BMS at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.7 Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose). Subsequent visits should follow the regular schedule relative to Day 1.

7.8 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

7.9 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

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8 TOXICITY AND MANAGEMENT

8.1 Dose Escalation

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2 Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

All adverse events that meet DLT criteria, as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to BMS, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3 Infusion Reactions

As of the date of this protocol revision, it has been observed that of the 44 subjects having received at least one dose of BMS-936559 (MDX-1105) at the 10 mg/kg dose level, 8 subjects have experienced infusion reactions (3 Grade 1, 4 Grade 2, and 1 Grade 3). All of the subjects recovered with symptomatic treatment and 7 of the 8 were able to tolerate completion of infusion without further reaction. One subject discontinued due to recurrence of symptoms upon resuming infusion. One subject of 19 at the 3 mg/kg dose level also experienced a Grade 2 infusion reaction. This subject also responded to treatment and tolerated completion of infusion without incident.

Based on these observations, **all subjects on this study receiving the 10 mg/kg dose must be pre-medicated with both 650 mg of acetaminophen and 50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to the start of infusion of BMS-936559 (MDX-1105).** The pre-medication will be required for each infusion

regardless of whether the subject has been treated or has experienced infusion reactions previously.

Infusion reactions should be graded according to CTCAE Version 3.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include but are not limited to fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be readily available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

In each case of an infusion reaction, the Investigator should institute treatment measures according to the best available medical practice. The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C)

Treatment: Decrease the study drug infusion rate by 50% and monitor closely for any worsening. Any worsening or recurrence of these symptoms at the reduced rate would be considered a second event and management should follow the guidelines under the “Re-treatment with BMS-936559 (MDX-1105) Following Infusion Reactions” section below.

CTCAE Grade 2 Allergic reaction/hypersensitivity (Rash, flushing urticaria, dyspnea, drug fever > 38°C)

Treatment: Stop study drug infusion. Administer bronchodilators, oxygen, etc as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening. Any worsening or recurrence of these symptoms at the reduced rate would be considered a second event and management should follow the guidelines under the “Re-treatment with BMS-936559 (MDX-1105) Following Infusion Reactions” section below.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity

A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

Treatment of Grade 3 or 4 Infusion Reaction:

Stop the study drug infusion immediately and disconnect infusion tubing from the subject.

Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact the Medical Monitor and document as a serious adverse event.

No further study drug treatment is to be administered.

8.3.1 Re-treatment with BMS-936559 (MDX-1105) Following Infusion Reactions

Once the study drug infusion rate has been decreased due to an infusion reaction (i.e., the subject has experienced a Grade 1 or 2 infusion reaction) the rate will remain decreased (i.e., a 2 hour infusion rather than a 1 hour infusion) for all subsequent infusions.

If the subject has not been receiving any pre-medication, subsequent doses should be pre-medicated with 650 mg acetaminophen and 50 mg of diphenhydramine (po or IV) at least 30 minutes prior to infusion. If the subject is in the 10 mg/kg dose cohort and has, therefore, already been receiving acetaminophen/diphenhydramine pre-medication, consideration should be made to pre-medicate subsequent infusions with corticosteroid.

If the subject experiences a second allergic/infusion reaction at the reduced rate (regardless of Grade) despite pre-medication with acetaminophen, diphenhydramine, and corticosteroid, the infusion should be stopped and the subject should be discontinued from treatment.

If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from treatment. If there is any question as to whether an observed

reaction is an allergic/infusion reaction of Grades 1 - 4, the medical monitor should be contacted immediately to discuss.

8.4 Possible Toxicities

There is no clinical experience with BMS-936559 (MDX-1105) to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity**: Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm**: Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with BMS-936559 (MDX-1105), and has not been seen in preclinical testing.
- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system**: Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression**: Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood**: A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin**: The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs)**: Given the expected immunostimulatory mechanism of action of BMS-936559 (MDX-1105), immune-related Adverse Events

(irAEs) may be anticipated. Examples of irAEs could include: persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

- BMS had reported irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).
- Among the 80 subjects already treated with BMS-936559 (MDX-1105), there has been a report of a Grade 4 pan-endophthalmitis (occurring in a subject receiving the 3 mg/kg dose) and Grade 3 Myasthenia Gravis (occurring in a subject receiving the 10 mg/kg dose). Each of these subjects responded to corticosteroid treatment (the Myasthenia Gravis subject also received plasmaphersis), but irAEs do have the potential to be life-theratening. **All irAEs should, therefore, be managed according to the algorithm provided in the Investigator Brochure.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to better define the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program, but our current experience suggests that, like ipilimumab, early intervention with immunosuppressive agents such as corticosteroids are beneficial for managing irAEs with BMS-936559 (MDX-1105).

9 COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10 CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.
b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.
c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
d. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.
e. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of BMS-936559 (MDX-1105) and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

11 STUDY EVALUATIONS

11.1 Study Procedures by Visit

11.1.1 Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be

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asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936559 (MDX-1105) need not be repeated.

11.1.2 Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)
- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

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- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG
- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
  - Hepatitis B and C testing;

- Concomitant medications

11.1.3 Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start BMS-936559 (MDX-1105) treatment within 28 days of Screening. Subjects will receive 1 dose of BMS-936559 (MDX-1105) every 14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a

subject with additional cycles of BMS-936559 (MDX-1105) will be determined by the response assessment (described below). Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle. The maximum duration of study treatment for a subject is 2 years. Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses, see Section 7.6 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1 Cycle 1

Cycle 1 will begin with the first i.v. infusion of BMS-936559 (MDX-1105) (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).

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- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)

- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.3.2 Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of BMS-936559 (MDX-1105) (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study drug treatment is 2 years.

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry

- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)

- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.4 Follow-up

There are 3 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 6 months. All subjects should complete Follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 and 3) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 6 months until relapse, initiation of a new therapy, or a total of 6 months follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity

- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105)
- Vital sign measurements
- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Optional biopsies and/or cryopreserved PBMC as outlined in Sections 11.1.2 and 11.1.3.1.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5 Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they have:

- Completed 3 doses of BMS-936559 (MDX-1105) in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6 Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up
- Death
- Other

11.1.7 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with the protocol
- Disease progression as defined in Section 3.3
- Significant clinical deterioration

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

11.2 Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of BMS-936559 (MDX-1105): vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1 Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of BMS-936559 (MDX-1105)-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.2.2 Immunogenicity

Immunogenicity refers to the development of an immune response to the BMS-936559 (MDX-1105) drug itself, and is characterized by antibodies that the subject may develop that react with BMS-936559 (MDX-1105). These may result in more rapid clearance of BMS-936559 (MDX-1105) from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with BMS-936559 (MDX-1105) at a later date.

11.2.3 Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3 Efficacy Evaluations

11.3.1 Efficacy Parameter

The primary efficacy parameter is the objective response rate (ORR) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of BMS.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable

or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of BMS-936559 (MDX-1105) and more likely capture its true potential to induce clinical responses.

11.4 Pharmacokinetic Evaluations

Pharmacokinetic parameters include AUC(0-T), AUC(INF), Cmax, Tmax, T-HALF, Vss, and CLT.

Blood samples for the analysis of serum concentrations of BMS-936559 (MDX-1105) will be drawn in all subjects according to the schedule listed below and in Table 3. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1 Cycle 1

- **Day 1**: pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
- **Days 2, 3, 4, and 8**: single serum samples will be taken on each day.
- **Days 15 and 29**: single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

11.4.2 Cycles 2-16

- **Days 1, 15, and 29**: serum samples will be drawn within 30 minutes before infusion and at the end of each infusion on infusion days.

11.4.3 Follow-up Visits

- **Follow-up Visits 1 and** 2: single serum samples to be taken.

12 ADVERSE EVENT REPORTING

12.1 Definitions

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, version 3.0.[37] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate.

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug - related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

- **Not related**
  The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
- **Related**
  The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted

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12.1.1 Safety Reporting For Nonserious Adverse Events

A *nonserious adverse event* is an AE not classified as serious (see Section 12.2 for the definition of serious AE).

Nonserious AE occurred after the initiation of study drug and within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only treatment-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects beyond 70 days after the administration of the last dose of study drug.

All identified nonserious AEs must be recorded and described on the AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page.

12.2 Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.6.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure

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- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

12.3 Rapid Notification of Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event.

12.4 Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. Although overdose is not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner. (see Section 12.3, Serious Adverse Events for reporting details).

12.5 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page and/or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

12.6 Pregnancy

Pregnancy testing must also be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule tables, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive BMS-936559 (MDX-1105) and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.6.1 Reporting of Pregnancy

The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male subjects, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported when possible.

12.7 Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the expected mechanism of action of BMS-936559 (MDX-1105), namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical as this is the first-in-human trial, and these events are considered based upon preclinical studies in mice deficient in PD-1 or PD-L1, limited clinical experience with an anti-PD-1 antibody (MDX-1106), as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

BMS has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

12.8 Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 3 unexpected toxicity (regardless of attribution)

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size Determination

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level. Up to seven expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts. A total of up to 130 subjects are to be enrolled in this study.

In order to perform preliminary evaluation of anti-tumor activity, the sample size of each expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that RR for subjects in an expansion cohort would be 10%. Based on this assumption, a sample size of 16 subjects in an expansion cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

13.2 Populations for Analyses

13.2.1 Safety Population

The safety population includes all subjects who receive BMS-936559 (MDX-1105).

13.2.2 Efficacy Population

All subjects who receive BMS-936559 (MDX-1105) and with required baseline and at least one post-treatment radiologic tumor assessment.

13.2.3 Pharmacokinetic Population

All available concentration-time data from subjects who receive BMS-936559 (MDX-1105) will be reported. All available derived pharmacokinetic parameter values will be included in the pharmacokinetic dataset and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

13.2.4 Immunogenicity Population

All available data from subjects who receive BMS-936559 (MDX-1105) and have a baseline and additional post-treatment measurement samples collected will be included in the immunogenicity dataset.

13.3 Endpoint Definitions

13.3.1 Safety Endpoints

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurement, physical examinations, clinical laboratory tests, ECG,

immune safety laboratory tests, ECOG performance status, diagnostics test and immunogenicity measurement for human anti-human antibodies (HAHA). Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

13.3.2 Efficacy Endpoints

Primary efficacy endpoint: ORR (objective response rate) during the first 4 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of investigator evaluations.

Secondary efficacy endpoint: ORR during the entire study, Disease Control (BOR outcome of CR, PR or SD) rate, Progression-free survival (PFS), Time to response, Duration of response, and Duration of disease control.

13.3.3 Pharmacokinetic Endpoints

Pharmacokinetic of BMS-936559 (MDX-1105) will be derived from plasma concentration versus time. The following pharmacokinetic parameters will be estimated and reported:

AUC(0-T)	Area under the plasma/serum drug concentration-time curve from t=0 to last measurable sampling time.
AUC(INF)	Area under the plasma/serum concentration-time curve from t=0, extrapolated to infinity.
Cmax	Maximum observed concentration in plasma.
Tmax	Time to reach Cmax in plasma.
T-HALF	Terminal-phase elimination half-life in plasma.
Vss	Volume of distribution at steady state
CLT	Total body clearance of drug from plasma.

Individual subject pharmacokinetic parameter values will be derived by non-compartmental method by a validated pharmacokinetic program.

13.4 Analyses

13.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, disease information, and medical conditions will be summarized by dose cohort using descriptive statistics.

13.4.2 Safety Analyses

The safety analysis will be conducted on the safety population.

All recorded adverse events will be listed and tabulated by system organ class, preferred term and dose. Vital signs and clinical laboratory test results (including immune safety test results) will be listed and summarized by dose. Any significant physical examination findings, ECG results and clinical laboratory results will be listed. Safety summaries may also be tabulated by indication.

13.4.3 Efficacy Analyses

Individual tumor response as defined by RECIST with modifications will be listed by dose and indication.

Primary analyses:

For the expanded cohorts, best overall tumor response during the first 4 cycles will be tabulated by dose and indication. In each expansion cohort, for the ORR during the first 4 cycles, point estimate and 2-sided exact 90% confidence intervals will be calculated.

Secondary analyses:

For the expanded cohorts, Time to response and Duration of response will be computed for all treated subjects with confirmed response (CR or PR), and summarized by dose and indication. Best overall tumor response during entire study will be tabulated by dose and

indication. Point estimate and 2-sided exact 90% confidence intervals for the ORR during the entire study will be provided. Disease control rate will be similarly estimated by dose and indication. Median time to response and duration of response for those subjects with confirmed responses, duration of disease control and PFS will be summarized by 95% confidence-intervals using Kaplan-Meier methodology, at each expansion cohort.

13.4.4 Immunogenicity Analyses

Individual immunogenicity measurement for human anti-human antibodies (HAHA) will be listed. A listing for subjects with at least one positive HAHA assessment will be provided. HAHA responses will also be tabulated by frequency distribution. Associations with safety and or PK exposure may be explored.

13.4.5 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1Day1 by dose. Geomeric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T) and AUC(INF). Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided.

Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose.

Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameters (slope of the linear regression) will be calculated.

Data describing the plasma concentration versus time from this study may be used for future population pharmacokinetic evaluations of the drug which may be reported separately.

13.4.6 Exploratory Analyses

Flow Cytometry

Summary statistics for immune function and other biomarker measures, including but not limited to results from flow cytometry will be tabulated by dose level and study day. Associations of such measures with clinical outcome or safety events of interest (e.g. irAE) may be explored graphically based on data availability.

Exploratory Immune Function

The effects of BMS-936559 (MDX-1105) on humoral and cellular immune responses to tumor antigens (e.g. CA-125 and CEA or CA19-9) and a panel of recall nontumor antigens will be assessed based on data availability. Parameters to be examined may include lymphocyte phenotype, activation and response to antigens, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment. Summary statistics for these parameters will be tabulated by dose level and study day. Associations between these measures and clinical endpoints will be explored graphically.

14 ETHICAL ASPECTS

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with BMS SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel

where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to BMS or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of BMS, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

14.4 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

15 ADMINISTRATIVE REQUIREMENTS

15.1 Protocol Amendments

The study shall be conducted as described in this approved protocol. Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the BMS monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;

2. Significant change in the study design (e.g., addition or deletion of a control group);

3. Increase in the number of procedures to which subjects are exposed; or

4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., BMS staff versus a contract research organization [CRO]); and

2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2 Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a BMS representative will review the protocol, CRFs, and other study documents with the

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Investigators and their staff. During the study, the BMS monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. BMS monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

15.4 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to BMS or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated

by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the electronic CRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) and the following noninvestigational product(s): #?# is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

15.5 Auditing Procedures

In addition to the routine monitoring procedures, BMS, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. BMS, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS immediately that this request has been made.

15.6 Publication of Results

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to

publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

15.7 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by BMS or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by BMS (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.8 Discontinuation of Study

BMS reserves the right to discontinue any study for any reason at any time.

15.9 Data Management

15.9.1 Data Collection

Investigators must enter the information required by the protocol onto the BMS CRFs that are printed on "no carbon required" paper. BMS monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to BMS, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.9.2 Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following BMS, or its designee, data management procedures. Obvious errors will be corrected by BMS personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the BMS study team.

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APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	ead

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APPENDIX 2 RECIST WITH MODIFICATIONS

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target

lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.”

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.
Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not “selected” images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.

continued

Definitions *(continued)*

Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

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APPENDIX 3 PRE-EXISTING AUTOIMMUNE DISEASES

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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Protocol Number:	CA210001 (MDX1105-01)
IND Number:	101,850
EUDRACT Number	NA
Date:	17-Jun-2008
Revised Date	20-Oct-2010

Clinical Protocol CA210001 (MDX1105-01)

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Revised Protocol Number: 06

Incorporates amendment(s) 01, 02, 03, 04, 05, 06

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This protocol contains information that is confidential and proprietary to Bristol-Myers Squibb

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

CA210001 (MDX1105-01)

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), epithelial ovarian cancer (epOC), gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105), and 4) the dose response relationship in melanoma and in NSCLC.

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs). The exploratory biomarker analysis will explore the hypothesis that immune activation correlates with efficacy and clinical response in subjects after PD-L1 blockade.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 1 year). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The investigator tumor response assessment (by RECIST criteria v1.0) must be completed before the first dose in the next cycle.

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression (PD) after discussion and agreement with the BMS Medical Monitor.

Dose Escalation

An accelerated titration design (ATD) will be utilized for the dose escalation part of this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels were included as part of Amendment 6 to the protocol and did not impact the dose escalation plan or schedule that has been completed prior to Amendment 6). Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a

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≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Bristol-Myers Squibb Co. (BMS) approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment, with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts added with Amendment 6 who will be permitted to dose escalate under circumstances described in section 3.2; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 15 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has been completed prior to Amendment 6: an additional 8 expansion cohorts as described below will be enrolled under Amendment 6. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has been completed as noted in Table 1

a. Primary MTD expansion cohorts (5 cohorts): 1 cohort in each of the 5 disease indications (MEL, RCC, epOC, CRC and NSCLC) at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Non-MTD melanoma expansion cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

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Table: Expansion Cohorts Completed Prior to Amendment 6

Tumor Type	Dose level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Epithelial Ovarian cancer	10 mg/kg
Colorectal adenocarcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg

Under Amendment 6 the following 8 additional cohorts will be enrolled (Figure 1)

c. Additional MEL expansion Cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL will be enrolled. 1 cohort each at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed PD and in consultation and agreement by the BMS Medical Monitor.

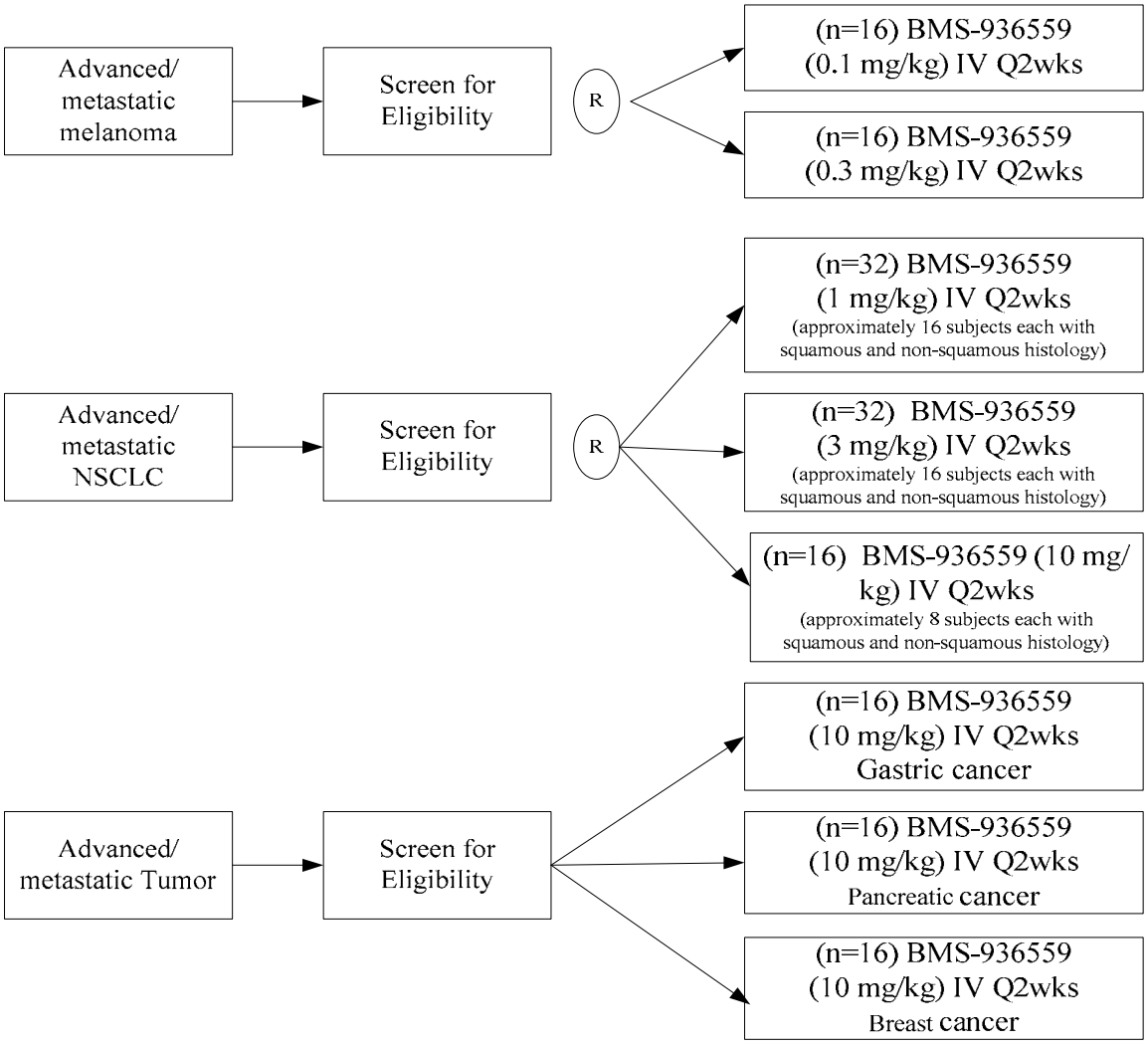
d. NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg and 10 mg/kg dose levels respectively.

e. Additional MTD expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC) will be enrolled; dosed at 10 mg/kg dose level.

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Figure 1: Expansion Cohorts Added Under Protocol Amendment 6



In order to avoid allocation bias, subjects enrolled in the added Melanoma and NSCLC expansion cohorts by Amendment 6 meeting all eligibility criteria will be randomly assigned to one of the two, and one of the three dose levels respectively, according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development.

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Initiation of Additional Expansion Cohorts

In order to gain additional safety and tolerability data on additional dose levels in MEL and NSCLC and preliminary assessment of efficacy in GC, PC and BC, 8 additional expansion cohorts will be enrolled.

- Additional MEL expansion cohorts (n=32): in order to explore safety, tolerability, and activity at alternate dose levels, an additional 2 cohorts of approximately 16 subjects each with metastatic malignant MEL will be enrolled and administered BMS-936559 at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level will have the opportunity to dose escalate to the 1 mg/kg dose level upon confirmed PD on a case-by-case basis and after consultation with the BMS Medical Monitor.
- NSCLC expansion cohorts (N=80): in order to further explore the safety, tolerability, and activity of BMS-936559 in NSCLC; a total of 3 additional cohorts in subjects with NSCLC will be

enrolled; 1 cohort of approximately 32 subjects each will be enrolled and administered BMS-936559 at the 1 mg/kg, 3 mg/kg dose levels, respectively and 16 subjects will be enrolled at 10 mg/kg dose level. Cohorts at each dose level will be comprised of approximately 16 subjects with squamous cell, and 16 subjects with non-squamous cell histologies. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types. With 2 responses out of 16 subjects, the 80% C.I. for the response rate will be (3.4%, 29%), i.e. 2 responses are needed to exclude a lower limit of no responses.

- Additional MTD expansion cohorts (3 cohorts, N= 48): in order to gain additional safety, tolerability data and preliminary assessment of efficacy an additional 3 cohorts of 16 subjects of each in with GC, PC and BC will be enrolled; BMS 936559 will administered at the 10 mg/kg dose level.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of a DLT in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5). Following each treatment cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor assessment (evaluation performed at the end of each of the first 4 cycles and then at the end of every even-numbered cycle). No subject will be permitted dose escalations or de escalations with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who meet the criteria for dose escalation as outlined in section 3.1; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as outline in sections 8.2

(Dose Limiting Toxicity) and 11.1.7 (Discontinuation of Subjects from Treatment); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.

- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 1 year. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

Reinitiation of Study Therapy For Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 3 years.

The maximum duration of a subject's participation in this study is approximately 4 years.

STUDY POPULATION

Up to 290 subjects may be enrolled (if no subjects require replacement). One hundred fifteen (115) subjects have been enrolled prior to Amendment 6. Under Amendment 6 approximately 160 additional subjects with MEL, NSCLC, GC, PC or BC will be enrolled. Subjects with advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, epOC, GC, PC or BC, will be eligible to enroll in the study.

DOSAGE AND ADMINISTRATION

BMS-936559 is to be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an i.v. push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

At doses 1, 3, 10 mg/kg, the total dose needed will be diluted to a total volume of 60 mL in 0.9% sodium chloride. In cases where the total dose volume exceeds 60 mL, no dilution is required. At doses of 1, 3, 10 mg/kg, BMS-936559 should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.

For subjects receiving doses at 0.1 mg/kg and 0.3 mg/kg, BMS-936559 will be diluted to a concentration as close as possible to but not lower than 0.35 mg/mL and infused at a rate of 1 mL/minute.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

Immune-related Adverse Events

An immune-related adverse event (irAE) is a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the objective response rate (ORR) during the entire treatment period (proportion of subjects with confirmed responses of CR or PR) for each indication. Tumor response status will be assessed primarily using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of BMS.

In addition to ORR during the first 4 cycles will be calculated for each subject. Best overall response (BOR), time to response, duration or response will also be calculated and estimated within each indication and across indications. Disease control (BOR outcome of CR, PR or SD) rate (DCR), duration of disease control and Progression Free Survival (PFS) are additional endpoints.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with BMS-936559 (MDX-1105).

Exploratory efficacy evaluations will include the application of an immune-related response criteria based on modifications to the RECIST (v1.0) which will be referred to as irRECIST and include the following parameters: irBOR during the first 4 cycles and the entire study; response categories (irCR, irPR, irSD, and irPD), irORR during the entire treatment period (and in first 4 cycles) and duration of ir-response for those subjects with ir-responses. An outline of the irRECIST criteria is provided in Appendix 3.

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Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

EXPLORATORY IMMUNE FUNCTION AND OTHER BIOMARKER EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Samples for measurement of single nucleotide polymorphisms (SNP) of genes will be collected to evaluate potential associations of genes involved in the immune response with clinical outcome and/or safety.

Peripheral blood samples will be collected to evaluate pharmacodynamic effects using gene expression profiling of mRNA and/or qPCR, and potential associations with clinical outcome.

Blood samples will be collected to evaluate the pharmacodynamic effects on serum cytokines/chemokines such as, but not limited to, IL-1a, IL-2, IFN-g, IL-10, CXCL-9, and CXCL-10 and potential associations of these markers with clinical outcome after treatment with BMS-936559 (MDX-1105).

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include AUC(0-T), AUC(INF), AUC(TAU), AI, Cmax, Cmin, Tmax, T-HALF, Vss, and CLT.

Blood samples will be collected for pharmacokinetic evaluation of BMS-936559 (MDX-1105) in Cycle 1, 2 and 3 beginning Amendment 6. Single samples will also be collected to evaluate serum concentrations of BMS-936559 at the Follow-up Visits 1 and 2. Intense sampling will be collected in first 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and first 3 subjects in each of the 4 cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg) under Amendment 6. Sparse PK samples will be collected from rest of subjects enrolled in each cohort under Amendment 6.

STATISTICAL METHODS

Sample Size Determination:

This is a phase 1 dose-escalation study. The sample size during dose escalation cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level.

Up to 15 expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts subjects (32 subjects each will be enrolled at 1mg/kg and 3 mg/kg and 16 subjects in the 10 mg/kg new NSCLC cohorts). With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 80% confidence interval for an objective response rate would be (3.4%, 30%) if 2 (12.5%) subjects had a response, (7.1% to 37%) if 3 (19%) subjects had a response, (11.4% to 44%) if 4 (25%) subjects had a response and (16.1% to 50%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 80% confidence interval for an objective response rate would be (3.5% to 19.7%) if 3 (9.4%) subjects had a response, (5.6% to 23.4%) if 4 (12.5%) subjects had a response, and (7.8%, 27.1%) if 5 (16%) subjects had a response.

If the true ORR in NSCLC is 15% then with 16 NSCLC patients in each cohort of specific histology and dose, there is 71.5% chance of observing at least 2 responses, and 44% chance of observing at least 3 responses, and there is 28.4% chance of observing 0 or 1 responses (false negative rate). If the true ORR in NSCLC is 5% rather than 15%, then there is 19% and 4.4% chance respectively that there will be at least 2 or at least 3 responses in 16 subjects (false positive rate).

A total of up to 290 subjects are to be enrolled in this study, including dose escalation and dose expansion.

Statistical Analysis:

Safety Analysis: All recorded adverse events will be listed and tabulated by based on worst grade, system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECGs will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided.

Efficacy Analysis: In order to perform preliminary evaluation of anti-tumor activity, BOR outcomes, objective response (ORR), and disease control rate (DCR) will be tabulated by frequency distribution overall, and in the first 4 cycles. For ORR in each expansion cohort, an exact Binomial 90% confidence interval will be determined by Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier method; PFS will be similarly summarized; PFS rate at 24 weeks will also be summarized by frequency distribution tabulated by dose and overall for each tumor type. Individual tumor measurements, tumor burden and %changes in tumor burden will be listed. Changes in tumor burden will be presented graphically for each disease type. Exploratory efficacy analyses will include a frequency of irBOR outcomes and irORR, and a summary of duration of ir-responses. Summary statistics and plots of measures of tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9), may be provided for specific tumor types, based on data availability. The primary efficacy analyses will include all subjects from the first treatment period and followup period until disease progression. Efficacy results on subjects who re-initiate study therapy during the follow-up period will be presented separately for the second treatment period.

In order to characterize the dose response in melanoma cohorts, modeling of tumor response (or AE of interest) as a function of dose will be performed, based on parametric or non-parametric model. For NSCLC cohorts, tumor response measures (e.g. ORR) will also be modeled as a function of dose using some parametric or no-parametric (possibly Bayesian) approach.

Immunogenicity Analysis: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any timepoint will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, and frequency of subjects who develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

Pharmacokinetic Analysis: Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1 Day1 and Cycle 2 Day 1 by dose. Geometric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T), AUC(TAU), AUC(INF), and AI. Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided. Summary statistics will be tabulated for the trough (Cmin) concentration and end of

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infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose. Dose proportionality will be assessed by estimating in Cycle 2 Day 1 the slope of linear regression of BMS-936559 (MDX-1105) log (Cmax) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model.

Biomarkers (immune Function and others): Summary statistics for immune function and other exploratory markers, such as but not limited to cytokines/chemokines, flow cytometry, and mRNA profiling, and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored. Possible associations of cytokines, mRNA, SNP and other potential biomarkers measures (baseline value or change from baseline) with clinical outcome (eg, tumor response) may be explored based on data availability, using response-evaluable subjects, to explore potential predictive markers. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability. Associations of such measures with safety events of interest (e.g. irAE) may also be explored graphically based on data availability.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BOR	Best overall response
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HAHA	Human anti-human antibodies
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous

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Abbreviation	Term
irBOR	Immune-related Best Overall Response
irORR	Immune-related Objective Response Rate
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irSD	Immune-related Stable Disease
irRECIST	Immune-related RECIST
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
RT	Radiation therapy
SD	Stable disease

Abbreviation	Term
SLD	Sum of the longest diameter
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum sample for pharmacokinetics[7]		Serum for PK will be collected according to schedule in Table 3								•	•	
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/abdomen/pelvis)[11]	•[12]								•	•[14]	•	•
Brain CT scan/MRI[11,13]	•[12]								•[14]	•[14]	•[14]	•[14]
Bone scan (if clinically indicated)[15]	•[12]								•[15]	•[15]	•[15]	•[15]
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Response assessment									•			
ECG (12-lead)	•[12]	•[16]								•		
Hematology	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Serum chemistry	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry		•								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity		•								•	•	
Blood Sample for SNP analysis[20]		•										
Serum for cytokine panel[20]		•										
Blood Sample for quantitative PCR or gene expression profiling [20]		•										
BMS-936559 (MDX-1105) infusion		•			•		•					

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

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Table 1 Footnote:

1 Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 1 year follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3 Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

4 To include collection of prior medication and prior/concurrent medical conditions.

5 Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).

6 Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated time points must be performed and found to be negative before infusion for women of childbearing potential.

7 Pharmacokinetic sampling to be performed according to Table 3.

8 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

9 ECOG Performance Status to be assessed before each infusion.

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[10] Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a10% or greater change in weight [increase or decrease] since the previous cycle).

[11] The same technique (CT/MRI) used at baseline should be utilized throughout the study.

[12] Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of BMS-936559 (MDX-1105) need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

[13] Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 -5.

[14] To be performed if clinically indicated and if not done within the preceding 28 days.

[15] If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

[16] To be performed pre- and post infusion.

[17] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[18] A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. **Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or 15 unstained slides) by study personnel for performance of correlative tissue studies.** Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.

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[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

[20] Samples will not be collected on subjects enrolled prior to Amendment 6.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Serum sample for pharmacokinetics[5]	Serum for PK will be collected according to schedule in Table 3				•	•	
Vital signs[6]	•	•	•		•	•	•
ECOG performance status	•[7]	•[7]	•[7]		•	•	•
Physical examination[8]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[9]				•	•[10]	•	•
Brain CT scan/MRI[9,11]				•	•[10]		
Bone scan (if clinically indicated)[12]				•	•[10]		
Response assessment				•[13]			
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
ECG (12-lead)	•[14]				•		
Hematology	•[15]	•[15]	•[15]		•	•	•
Serum chemistry	•[15]	•[15]	•[15]		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[16]	•				•	•	•
Urinalysis	•	•	•		•	•	•
Optional tumor or other biopsy[20]							
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[17]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity	•[19]				•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum for cytokine panel[18]	•[19]						
Blood Sample for quantitative PCR or gene expression profiling[18]	•[19]						
BMS-936559 (MDX-1105) infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2 Footnote:

1 Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 1 year follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days after the last dose of the prior treatment cycle. If treatment is delayed more than 28 days due to resolving toxicity then no more study therapy should be given.

3 The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

4 Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated time points must be performed and found to be negative before infusion for women of childbearing potential.

5 Pharmacokinetic sampling to be performed according to Table 3.

6 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

7 ECOG Performance Status to be assessed before each infusion.

8 Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note**: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

[9] The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.

[10] To be performed if clinically indicated and if not done within the preceding 28 days.

[11] Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2-5.

[12] If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.

[13] At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation.

[14] To be performed pre- and postinfusion.

[15] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[16] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

[17] Sample collected for Cycles 2 and 3 only.

[18] Samples will not be collected on subjects enrolled prior to Amendment 6.

[19] Sample collected for Cycle 2 only.

[20] Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or 15 unstained slides) by study personnel for performance of correlative tissue studies.

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Table 3: Pharmacokinetic Sampling Schedule

Study Day[a]	Time (Relative To Dosing)[a b]	Time (Relative To Dosing) Hour: Min	PK Blood Sample From First 10 Subjects at Each Dose Level[e]	PK Blood Sample From Rest of the Subjects[f]
Cycle 1 Day 1	0 (Predose)	00:00	X	X
	1.0 (EOI)[c]	01:00	X	X
	EOI + 30 min	01:30	X	
	EOI + 60 min	02:00	X	
	EOI + 120 min	03:00	X	
	EOI + 240 min	05:00	X	
Cycle 1 Day 2	24 h	24:00	X	
Cycle 1 Day 3	48 h	48:00	X	X
Cycle 1 Day 4	72 h	72:00	X	
Cycle 1 Day 8	168 h	168:00	X	X
Cycle 1 Day 15	0 (Predose)	336:00	X	X
	1.0 (EOI)[c]	1:00	X	X
Cycle 1 Day 29	0 (Predose)	672:00	X	
	1.0 (EOI)[c]	1:00	X	
Cycle 2 Day 1	0 (Predose)	00:00	X	X
	1.0 (EOI)[c]	01:00	X	X
	EOI + 30 min	01:30	X	
	EOI + 60 min	02:00	X	
	EOI + 120 min	03:00	X	
	EOI + 240 min	05:00	X	
Cycle 2 Day 3	48 h	24:00		
Cycle 2 Day 8	168 h	168:00		
Cycle 2 Day 15	0 (Predose)	336:00	X	
Cycle 3 Day 1	0 (Predose)	00:00	X	X
	1.0 (EOI)[c]	01:00	X	X

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Table 3: Pharmacokinetic Sampling Schedule

Study Day[a]	Time (Relative To Dosing)[a b]	Time (Relative To Dosing) Hour: Min	PK Blood Sample From First 10 Subjects at Each Dose Level[e]	PK Blood Sample From Rest of the Subjects[f]
Follow-up 1[d]	0	00:00	X	X
Follow-up 2[d]	0	00:00	X	X

[a] Predose samples will be drawn within 30 minutes before infusion.

[b] If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit either due to an AE or due to the alternate dose schedule, a single pharmacokinetic sample will be taken at that visit.

[c] EOI: End of Infusion. These samples should be taken immediately prior to stopping the infusion. In the event of a delay beyond 1 h, the sample should be taken at the END of the infusion.

[d] A single sample will be taken at Follow-up Visits 1 and 2.

[e] Intense sampling will be collected in first 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and first 3 subjects in each of the 4 cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg) under Amendment 6.

[f] Sparse PK samples will be collected from rest of subjects enrolled in each cohort under Amendment 6.

Samples are to be drawn from a site other than the infusion site (i.e., contra lateral arm) on days of infusion.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

BMS-936559 (MDX-1105) is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and epithelial ovarian cancer [epOC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006.[2] The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

It is estimated that 207,090 women will be diagnosed with and 39,840 women will die of cancer of the breast in the United States in 2006.[4] About a third of these cases will have regional spread with a 5-year survival of 83.6% and another 5% will have distant metastases with a 5-year survival of 23.4%. Breast cancer is the most common malignancy in the United States and second only to lung cancer as a cause of cancer death in women. The systemic treatment of metastatic breast cancer is dependent on hormone receptor and Her-2 status with cytotoxic/ trastuzumab combinations used for the Her-2 positive patients, hormone therapy for ER/PR positive patients followed by cytotoxics for refractory or resistant cases, and cytotoxics for the triple- negative patients. The treatments available, however, can prolong survival, but tend not to be curative so in spite of the treatments available, this population still represents a large unmet need.[5]

Carcinomas of the upper gastrointestinal tract (esophagus, gastroesophageal junction, and stomach) are a global health problem, and represent the second most common cause of cancer death worldwide.[6] It is estimated that 21,000 men and women (12,730 men and 8,270 women) will be diagnosed with and 10,570 men and women will die of cancer of the stomach in 2010. Gastric carcinoma is often diagnosed at an advanced stage. Advanced upper GI cancer patients are incurable and have a poor prognosis, with a median survival, if untreated, of 3-5 months for gastric cancer;[7] treatment options include DCF (Docetaxel, Cisplatin, 5 FU), ECF (Epirubicin, cisplatin, 5-FU), and other platinum and paclitaxel based regimens.[8] However, a globally accepted standard of care is still not available, and although first-line chemotherapy certainly extends overall survival by several months compared with basic supportive care (9-13 vs. 3-5 months), median survival for patients treated with a second-line regimen remains a dismal 6-8 months. [9,10]

It is estimated that 43,140 men and women (21,370 men and 21,770 women) will be diagnosed with and 36,800 men and women will die of cancer of the pancreas in 2010. Metastatic disease may be treated with gemcitabine-containing regimens, but with little added benefit such that clinical trial is still considered the preferred treatment for metastatic disease according to current NCCN guidelines.[11]

1.2 PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,12,13,14,15,16,17,18] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[15] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[12,13,14,17] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both $PD\text{-}L1^{+}$ and $PD\text{-}L1^{-}$ tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[19,20,21,22,23] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[24] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and

PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[25,26,27,28,29,30,31] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[30,32] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[33,34,35] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity.[22] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[29,33,36,37]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[38,39,40,41,42] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[40] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. 32 Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[41] In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1

antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[14] Anti-PD-L1 monoclonal antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[43] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD 1 blockade.33,34 Using a murinized anti-mouse PD 1 antibody, Medarex (now BMS) showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[44] This suggests that PD-1/PD -L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, BMS-936559 (MDX-1105) represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3 Summary of BMS-936559 (MDX-1105) Preclinical Studies

BMS-936559 (MDX-1105) is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. BMS-936559 (MDX-1105) was selected to inhibit the interaction of PD-L1 with its receptor PD-1. BMS-936559 (MDX-1105)-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using BMS-936559 (MDX-1105) can also reverse the suppressive activity of T regulatory cells *in vitro* assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of BMS-936559 (MDX-1105) shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of BMS-936559 (MDX-1105) at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. BMS-936559 (MDX-1105) was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4 Rationale for BMS-936559 (MDX-1105)

1.4.1 Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol CA210001 (MDX1105-01) will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where BMS-936559 (MDX-1105) doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases as well as the two additional lower dose cohorts of 0.1 mg/kg and 0.3 mg/kg are designed to achieve an

adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2 Summary of Safety

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 29-July-2010, 88 subjects with selected advanced or recurrent solid tumors were treated in a single Phase 1 study (MDX1105-01/CA210001). Safety, tolerability and efficacy of multiple doses of BMS-936559 were assessed at 0.3,1,3 and 10 mg/kg (49 subjects treated at the highest 10 mg/kg dose level). The most frequent AEs were fatigue (37.5 %), diarrhea (28.4 %), nausea (26.1 %), arthralgia (19.3 %), hyperglycemia (18.2 %), decreased appetite (15.9 %), abdominal pain (14.8 %), infusion related reaction (10.2 %) and anemia (14.8 %). There was no pattern in the incidence, severity, or relationship of adverse events to BMS-936559 dose level in CA210001 (MDX1105-01). Of the 88 subjects treated in this study 1 or more irAEs were reported in 28 (31.8 %) subjects. The most common irAEs were diarrhea (13.6 %), pruritis (5.7 %) and rash (4.5 %). Three additional irAEs were reported (myasthenia gravis, endophthalmitis and elevated transaminases), and all the irAEs were Grade 1or 2 in severity; with the exception of the events of Grade 3 myasthenia gravis and grade 3 elevated transaminases, reported for two subjects in the 10 mg/kg arm, and the event of Grade 4 endophthalmitis reported for one subject in the 3 mg/kg treatment arm. Of the 88 subjects who had received at least one dose of BMS-936559, 12 subjects had infusion related reactions. In subjects treated at 10 mg/kg, 10 subjects had infusion related reactions. All infusion related reactions were Grade 1 or 2 with exception of a single Grade 3 event. In subjects treated with 3 mg/kg BMS-936559, 2 subjects had infusion related reactions (both Grade 2). All reported infusion reactions were considered related to BMS-936559 and resolved rapidly with supportive therapy (e.g., diphenhydramine, acetaminophen, corticosteroid and morphine). Of the 88 subjects treated in this study, 21 (14.4 %) SAEs have been reported in 13 subjects. Nine SAEs considered by the investigator, related to study therapy and were reported in 6 subjects (6.7 %) in the 3.0 and 10.0 mg/kg treatment arms.

Updated clinical safety data is available in the Investigator's Brochure for BMS-936559.[45]

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), epithelial ovarian cancer (epOC), gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC).

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) the immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105) and 4) the dose response relationship in melanoma and in NSCLC cohorts.

2.3 Exploratory Objective

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity (irAEs). The exploratory biomarker analysis will explore the hypothesis that immune activation correlates with efficacy and clinical response in patients after PD-L1 blockade.

3 OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and follow-up (up to 1 year). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1 Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels included in the current Amendment 6 did not impact the prior dose escalation plan or schedule as described below). Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment, with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who will be permitted to dose escalate under circumstances described in section 3.2; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2 Expansion Cohorts

To further characterize safety and efficacy, up to 15 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has been completed: an additional 8 expansion cohorts as described below will be enrolled under Amendment 6. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has been completed as noted in Table 4):

a. Primary MTD expansion cohorts (5 cohorts): 1cohort in each of the 5 disease indications (MEL, RCC, epOC, CRC and NSCLC) at a tolerated dose chosen by the sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Non-MTD melanoma expansion cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

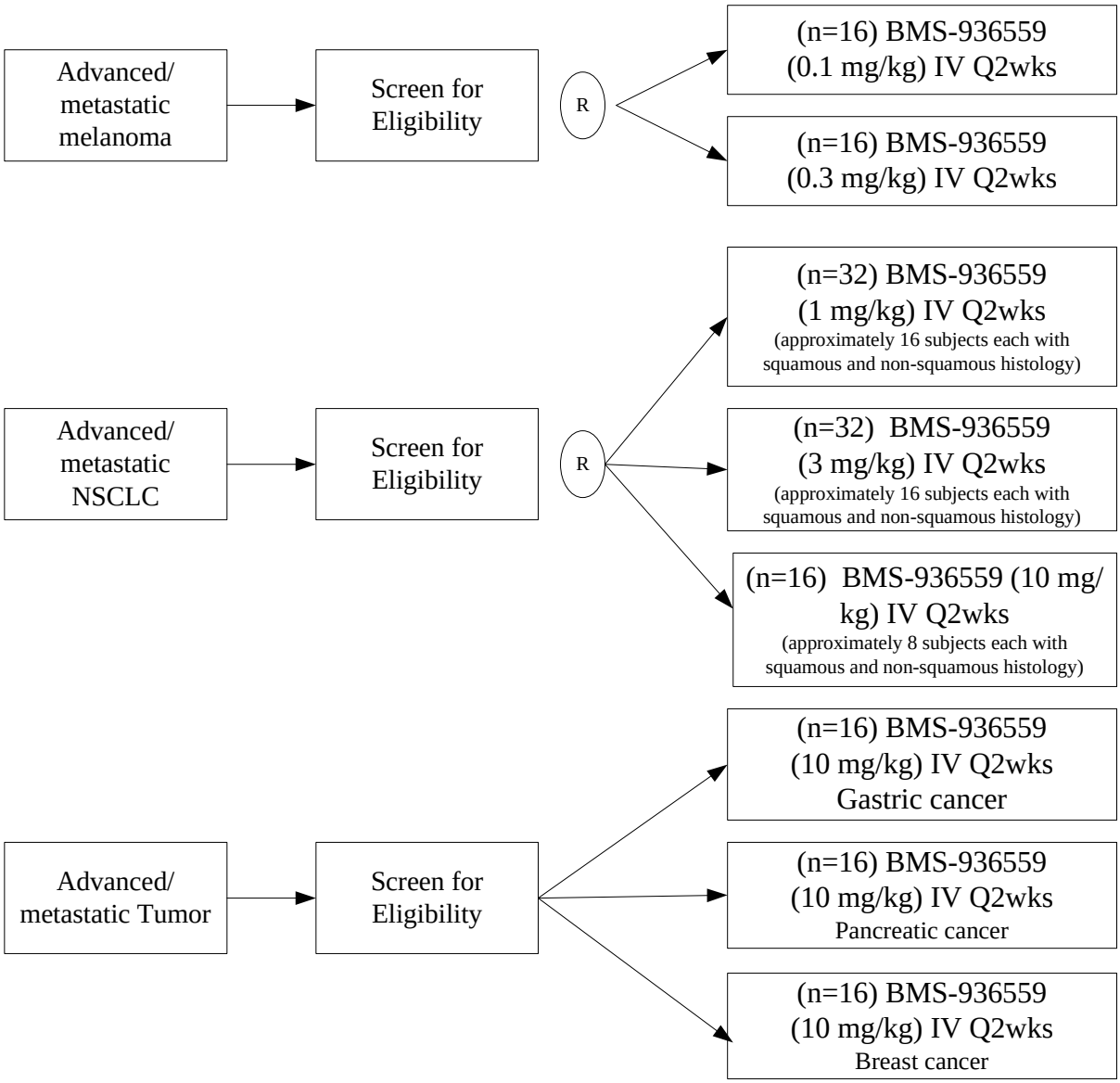
Table 4: Expansion Cohorts Completed Prior to Amendment 6

Tumor Type	Dose level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Epithelial Ovarian cancer	10 mg/kg
Colorectal adenocarcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg

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Figure 1: Expansion Cohorts Added Under Protocol Amendment 6



c. Additional MEL expansion Cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL will be enrolled. 1 cohort each at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed and worsening PD and in consultation and agreement by the BMS Medical Monitor.
d. NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg and 10 mg/kg dose levels respectively.

In order to avoid allocation bias, subjects enrolled in the Melanoma and NSCLC expansion cohorts identified above meeting all eligibility criteria will be randomly assigned to one of the two and one of the three doses, respectively, according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development

e. Additional MTD expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC) will be enrolled; dosed at 10 mg/kg dose level.

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1 Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication.

3.2.1.1 Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.2.1.2 Initiation of the Additional Expansion Cohorts

In order to gain additional safety and tolerability data on additional dose levels in MEL and NSCLC and preliminary assessment of efficacy in GC, PC and BC, 8 additional expansion cohorts will be enrolled.

- Additional MEL expansion cohorts (n=32): in order to explore safety, tolerability, and activity at alternate dose levels, an additional 2 cohorts of approximately 16 subjects each with metastatic malignant MEL will be enrolled and administered BMS-936559 at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level will have the opportunity to dose escalate to the 1 mg/kg dose level upon

confirmed and worsening PD on a case-by-case basis and after consultation with the BMS Medical Monitor.

- NSCLC expansion cohorts (N=80): in order to further explore the safety, tolerability, and activity of BMS-936559 in NSCLC; a total of 3 additional cohorts in subjects with NSCLC will be enrolled; 2 cohorts of approximately 32 subjects each will be enrolled and administered BMS-936559 at the 1 mg/kg and 3 mg/kg dose levels respectively and 16 subjects will be enrolled at 10 mg/kg dose level. Cohorts at each dose level will be comprised of approximately 16 subjects with squamous cell, and 16 subjects with non-squamous cell histologies. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types. With 2 responses out of 16 planned subjects per cohort, the 80% C.I. for the response rate will be (3.4%, 29%), i.e. 2 responses would exclude a lower limit of no response.
- Additional MTD expansion cohorts (3 cohorts, N= 48): in order to gain additional safety, tolerability data and preliminary assessment of efficacy an additional 3 cohorts of 16 subjects of each in with GC, PC and BC will be enrolled; BMS 936559 will administered at 10 mg/kg dose level.

3.3 Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications (Appendix 2. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to BMS-936559 (MDX-1105) that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days after the last dose of the prior treatment cycle to maximize dose intensity. If treatment is delayed more than 28 days due to resolving toxicity then no more study

therapy should be given. No subject will be permitted dose escalations or de-escalations with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as outline in sections 8.2 (Dose Limiting Toxicity) and 11.1.7 (Discontinuation of Subjects from Treatment); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive BMS-936559 (MDX-1105) therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the BMS Medical Monitor as described in Section 8.7.
- PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.
  - If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

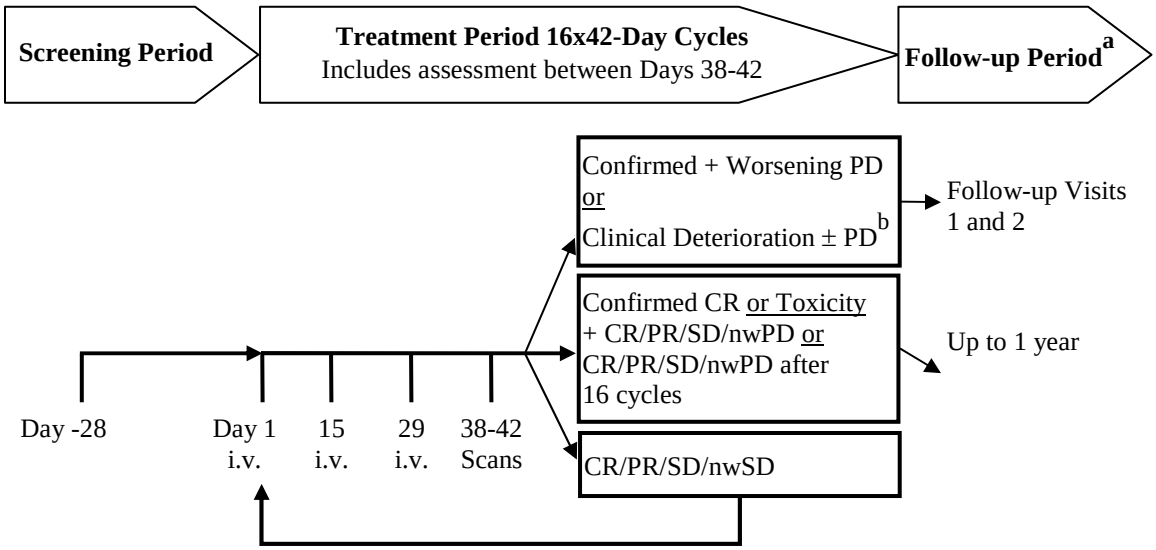
- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to BMS-936559 (MDX-1105) that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

3.4 Follow-up Period

The maximum duration of follow-up will be approximately 1 year. All subjects should complete follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 2: Individual Subject Flow (Up to 3 Years Treatment, Up to 1 Year Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

Re-initiation of Study Therapy for Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in

this setting may receive study therapy for a total of 3 years (including the initial treatment period). Re-initiation of study therapy will only be permitted once for any given subject.

Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy.

Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

3.5 Stopping Rules

3.5.1 Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a greater than or equal to Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

3.5.2 Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review.

After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.5.3 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction

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- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

3.6 Post Study Access to Therapy

Subjects who complete the study and continue to demonstrate clinical benefit may be eligible to receive study drug via an extension of the study, or through another mechanism at the discretion of the sponsor. The sponsor reserve the right to terminate access to study drugs if any of the following occurs: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

4 STUDY POPULATION

Up to 290 subjects may be enrolled (if no subjects require replacement). As of 29-Oct-2010, one hundred fifteen (115) subjects have been enrolled thus far. Under Amendment 6 approximately 160 additional subjects with MEL, NSCLC, GC, PC or BC will be enrolled. Subjects with advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, epOC, GC, PC or BC available, will be eligible to enroll in the study.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor's Medical Monitor, or designee, before enrolling the subject into the study.

For entry into the study, the following criteria MUST be met.

4.1 Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;

2. Life expectancy ≥ 12 weeks;

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 1);

4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy and no more than 4 prior lines of therapy for recurrent or metastatic NSCLC.

For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.

For GC: Subjects must have histologically confirmed advanced, unresectable gastric cancer that is refractory or progressive after front-line therapy. Subjects must have received no more than 1 prior line of therapy for advanced/metastatic gastric cancer.

For PC: Subjects must have histologically confirmed advanced pancreatic cancer with either locally advanced or advanced metastatic disease. The malignancy must be deemed unresectable, and subjects must have received no more than 2 prior lines of therapy.

For BC: Subjects must have histologically confirmed locally advanced or metastatic breast cancer and have tumor that is refractory to or progressive after standard of care therapy. Subjects must have received no more than 3 prior lines of cytotoxic therapy for metastatic disease.

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;

6. Tumor tissue (archival or recent acquisition) must be available for correlative studies for MEL, NSCLC and BC subjects. It is strongly encouraged to make tumor tissue available in GC and PC subjects whenever possible. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. This inclusion criteria will only apply to subjects enrolled under Amendment 6;

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7. Not applicable as of revised protocol number 04;

8. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast - preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;

9. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;

10. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;

11. At least 28 days since the last chemotherapy, immunotherapy, biological therapy (tumor vaccine, cytokine, or growth factor given to control the cancer), or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of BMS-936559 (MDX-1105) and have recovered from any clinically significant toxicity associated with such treatment;

12. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

13. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

14. Screening laboratory values must meet the following criteria:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL

Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 x ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

15. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women of child bearing potential (WOCBP) must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug.

16. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;

2. Prior therapy with an anti-PD 1, anti-PD L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);

3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;

4. Active infection (viral, bacterial, or fungal):

5. Requiring systemic anti-microbial therapeutic treatment within 28 days before the first dose of BMS-936559 (MDX-1105);

6. Known history of infection with Human Immunodeficiency Virus

7. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)

8. Evidence of bleeding diathesis or coagulopathy;

9. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;

10. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;

11. Known current drug or alcohol abuse;

12. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;

13. Underlying medical conditions that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;

14. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses > 10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;

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15. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;

16. Use of any vaccines against infectious diseases (e.g., influenza, varicella, etc.) within 4 weeks (28 days) of initiation of study therapy;

17. Psychiatric illness or social situation that would preclude study compliance; or

18. Pregnant or nursing.

19. Prisoners or subjects who are involuntarily incarcerated, or

20. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg infectious disease) illness

5 RANDOMIZATION AND BLINDING

Blinding is not applicable as this is an open-label study.

The dose escalation part of the study and the primary MTD expansion cohorts and 1 mg/kg and 3 mg/kg non-MTD melanoma expansion cohorts were not randomized.

Under Amendment 6, subjects with NSCLC enrolled under the additional NSCLC expansion cohorts (see sections 3.2 and 3.2.1.2) will be randomly assigned to one of the 3 dose levels (1, 3, or 10 mg/kg) in order to avoid allocation bias in subject dose assignment. Randomization in these cohorts will be stratified by histology cell type (squamous vs. non-squamous).

Similarly, subjects with MEL enrolled under the additional MEL expansion cohorts (see first bullet under section 3.2.1.2) will be randomly assigned to one of 2 dose levels (0.1 or 0.3 mg/kg) in order to avoid allocation bias in subject dose assignment.

Subjects enrolled in the expansion cohorts identified above meeting all eligibility criteria will be randomly assigned to one of the three doses according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply

Management Department of BMS Research and Development. Randomization numbers will be assigned in the order of enrollment within the MEL added expansion cohorts and within the NSCLC added expansion cohorts. Subjects in these cohorts who need to be replaced will be randomized to receive the same dose as the original subject.

6 ASSIGNMENT TO STUDY

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to a treatment cohort, as determined by BMS. Information concerning subjects who are screened and do not meet all entry criteria will be entered into a screening log; data collected on screening failures will not be entered in the clinical database.

7 DOSAGE AND ADMINISTRATION

All protocol-specified investigational and noninvestigational products are considered study drug.

7.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product is BMS-936559 (MDX-1105).

7.2 Non-investigational Product

Non-investigational products are defined as other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

7.3 Physical Description of Study Drug

BMS-936559 (MDX-1105) is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of BMS-936559 (MDX-1105) (10 mg/mL).

7.4 Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.5 Ordering Study Drug

Clinical supplies may be requested by completing a Request Form and faxing it or sending an e-mail it to the Drug Supply Coordinator at BMS.

7.6 Storage

BMS-936559 (MDX-1105) vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of BMS-936559 (MDX-1105) include laboratory coats and gloves. Note: once BMS-936559 (MDX-1105) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for BMS-936559 (MDX-1105) supports 12 hours at room temperature/under room light and 12 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936559 (MDX-1105) and polyolefin bags have been observed.

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.7 Study Drug Preparation and Administration

BMS-936559 (MDX-1105) is to be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an i.v. push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

At doses of (1, 3, and 10 mg/kg, the total dose needed will be diluted to a total volume of 60 mL in 0.9% sodium chloride. In cases where the total dose volume exceeds 60 mL, no dilution is required. At doses of 1, 3, 10 mg/kg, BMS-936559 (MDX-1105) should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.

For subjects receiving doses at 0.1 mg/kg and 0.3 mg/kg, BMS-936559 (MDX-1105) will be diluted to a concentration that is as close as possible to but **no lower than** 0.35 mg/mL and infused at a rate of 1 mL/minute. Rounding during dose preparation should be performed only when absolutely necessary and should only be done in a manner that will allow the minimum concentration of 0.35 mg/mL to be maintained.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936559 (MDX-1105) and polyolefin bags have been observed.

All subjects receiving the 10 mg/kg dose to be pre-medicated with both 650 mg of acetaminophen and 25-50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to the start of infusion of BMS-936559 (MDX-1105).

1. Allow the appropriate number of vials of BMS-936559 (MDX-1105) to stand at room temperature for approximately 5 minutes before preparation.

2. Ensure that the BMS-936559 (MDX-1105) solution is clear, colorless and essentially free from particulate matter on visual inspection.

3. Aseptically withdraw the required volume of BMS-936559 (MDX-1105) solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume of dose is more than 60 mL, no additional dilution is necessary. For subjects receiving doses of 1, 3, and 10 mg/kg, please use the following example to guide study drug preparation:

5. Prepare the BMS-936559 (MDX-1105) solution for infusion per the example provided below:

   Total dose should be calculated as follows:

   Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

   For example, a subject with a body weight of 70 kg would be administered 210 mg of BMS-936559 (MDX-1105) (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of BMS-936559 (MDX-1105) 10 mg/mL and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

   If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted BMS-936559 (MDX-1105) is needed. In this case, all drug should be infused in 60 minutes.

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6. For subjects receiving doses at 0.1 or 0.3 mg/kg, please see the following example for guidance on how to calculate the required volume for infusion

   For 0.3 mg/kg dose and assume subject body weight of 70 kg (other body weights can be calculated similarly):

Total drug to be administered:	0.3 mg/kg x 70 kg = 21 mg
Total prepared dose volume:	21 mg / 0.35 mg/ml = 60 ml
Drug needed for dose preparation:	21 mg / 10 mg/ml = 2.1 ml
0.9% sodium chloride needed for dilution:	60 ml – 2.1 ml = 57.9 ml

   For 0.1 mg/kg dose and assume subject body weight of 70 kg (other body weights can be calculated similarly):

Total drug to be administered:	0.1 mg/kg x 70 kg = 7 mg
Total prepared dose volume:	7 mg / 0.35 mg/ml = 20 ml
Drug needed for dose preparation:	7 mg / 10 mg/ml = 0.7 ml
0.9% sodium chloride needed for dilution:	20 ml – 0.7 ml = 19.3 ml

7. Mix by GENTLY inverting several times. DO NOT shake.

8. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.

9. Record the time BMS-936559 (MDX-1105) was prepared on the i.v. bag label.

10. Attach the i.v. bag containing the BMS-936559 (MDX-1105) solution to the infusion set, 0.2 μm in-line filter, and infusion pump.

11. For subjects at the 1, 3, and 10 mg/kg dose levels, the infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes. For subjects at the 0.1 mg/kg and 0.3 mg/kg, the infusion rate of the infusion pump should be adjusted to allow for an infusion rate of 1 mL/minute.

12. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

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Please note the following:

- **Do not** enter into each vial more than once.
- **Do not** prepare BMS-936559 (MDX-1105) for infusion in glass syringes.
- **Do not** administer study drug as an i.v. push or bolus injection.

7.8 Drug Accountability

BMS is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by BMS or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to BMS at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.9 Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle and for MEL subjects enrolled in 0.1 and 0.3 mg/kg dose cohorts who meet criteria for intra-subject dose escalation as outlined in section 3.2. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days after the last dose of the prior treatment cycle. If treatment is delayed more than 28 days due to non resolving toxicity then no more study therapy should be given. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is more than 2 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose).

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7.10 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

7.11 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 TOXICITY AND MANAGEMENT

8.1 Dose Escalation

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be

enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations or dose adjustments are allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) at the beginning of each cycle and for MEL subjects enrolled in 0.1 and 0.3 mg/kg dose cohorts who meet criteria for intra-subject dose escalation as outlined in section 3.2. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2 Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

All adverse events that meet DLT criteria, as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to BMS, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3 Infusion Reactions

As of the date of this protocol revision (using Amendment 6), it has been observed that of the 74 subjects having received at least one dose of BMS-936559 (MDX-1105) at the 10 mg/kg dose level, 13 subjects have experienced infusion reactions (5 Grade 1, 7 Grade 2, and 1 Grade 3). All of the subjects recovered with symptomatic treatment and 11 of the 13 were able to tolerate completion of infusion without further reaction. Two subjects discontinued due to recurrence of symptoms upon resuming infusion. Two subjects of 19 at the 3 mg/kg dose level also experienced a Grade 2 infusion reaction. These subjects also responded to treatment and tolerated completion of infusion without incident. Since the standard premedication for the 10 mg/kg cohort was instituted, 2 subjects experienced infusion reactions (Grade 2) after premedication. Both subjects responded and recovered with symptomatic treatment.

Based on these observations, **all subjects on this study receiving the 10 mg/kg dose must be pre-medicated with both 650 mg of acetaminophen and 25-50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to the start of infusion of BMS-936559 (MDX-1105).** The pre-medication will be required for each infusion regardless of whether the subject has been treated or has experienced infusion reactions previously.

Infusion reactions should be graded according to CTCAE Version 3.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include but are not limited to fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be readily available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

In each case of an infusion reaction, the Investigator should institute treatment measures according to the best available medical practice. The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C)

Treatment: Decrease the study drug infusion rate by 50% and monitor closely for any worsening. A worsening at this lower infusion rate would constitute a 2nd infusion reaction.

CTCAE Grade 2 Allergic reaction/hypersensitivity (Rash, flushing urticaria, dyspnea, drug fever > 38°C)

Treatment: Stop study drug infusion. Administer epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and/or oxygen as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening. A worsening at this lower infusion rate would constitute a 2nd infusion reaction.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity

A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

Treatment of Grade 3 or 4 Infusion Reaction:

Stop the study drug infusion immediately and disconnect infusion tubing from the subject.

Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact the Medical Monitor and document as a serious adverse event.

No further study drug treatment is to be administered.

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Re-treatment with BMS-936559 (MDX-1105) Following Infusion Reactions

Once the study drug infusion rate has been decreased due to an infusion reaction (i.e., the subject has experienced a Grade 1 or 2 infusion reaction) the rate will remain decreased (i.e., a 2 hour infusion rather than a 1 hour infusion) for all subsequent infusions.

If the subject has not been receiving any pre-medication, subsequent doses should be pre-medicated with 650 mg acetaminophen and 25-50 mg of diphenhydramine (po or IV) at least 30 minutes prior to infusion. If the subject is in the 10 mg/kg dose cohort and has, therefore, already been receiving acetaminophen/diphenhydramine pre-medication, consideration should be made to pre-medicate subsequent infusions with corticosteroid.

If the subject experiences a second allergic/infusion reaction at the reduced rate (regardless of Grade) despite pre-medication with acetaminophen, diphenhydramine, and corticosteroid, the infusion should be stopped and the subject should be discontinued from treatment.

If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from treatment. If there is any question as to whether an observed reaction is an allergic/infusion reaction of Grades 1 - 4, the medical monitor should be contacted immediately to discuss.

8.4 Possible Toxicities

There is no clinical experience with BMS-936559 (MDX-1105) to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity**: Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.
- **Widespread immune activation/cytokine storm**: Cytokine storm events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release

of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with BMS-936559 (MDX-1105), and has not been seen in preclinical testing.

- **Tumor lysis syndrome**: Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Gastrointestinal (GI) system**: Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding.
- **Immune suppression**: Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Blood**: A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin**: The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.
- **Immune-related adverse events (irAEs)**: Given the expected immunostimulatory mechanism of action of BMS-936559 (MDX-1105), immune-related Adverse Events (irAEs) may be anticipated. Examples of irAEs could include: persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.
- BMS had reported irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low-grade and self-limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rash), eye (uveitis and other inflammatory eye conditions), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).
- Among the 115 subjects already treated with BMS-936559 (MDX-1105), there has been a report of a Grade 4 pan-endophthalmitis (occurring in a subject receiving the 3 mg/kg dose) and Grade 3 Myasthenia Gravis (occurring in a subject receiving the 10 mg/kg dose). Each of these subjects responded to corticosteroid treatment (the Myasthenia Gravis subject also received plasmaphersis), but irAEs do have the potential to be life-theratening. **All irAEs should, therefore, be managed according to the algorithm provided in the Investigator Brochure.** Timely application of defined immunosuppressive regimens in the ipilimumab experience appears effective in limiting morbidity and mortality from such events without compromising therapeutic efficacy. Additional clinical experience will be required to better define

the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program, but our current experience suggests that, like ipilimumab, early intervention with immunosuppressive agents such as corticosteroids are beneficial for managing irAEs with BMS-936559 (MDX-1105).

9 COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10 CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.
b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.
c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
d. New Chemotherapy or immunotherapy other than study drug is not permitted.
e. Palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered after consultation with the Medical Monitor.
f. The use of live vaccines while on study is prohibited. The use of any killed or attenuated vaccines for the prevention of influenza is permitted at any time without a study drug washout interval. The use of other killed or attenuated vaccines for the

prevention of infectious diseases may be permitted on a case-by-case basis and must be discussed with the medical monitor prior to its use. A washout interval prior to and post vaccination may be required in these instances. Any vaccinations administered while on study must be documented in the subject's medical records and recorded in the Case Report Form.

g. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of BMS-936559 (MDX-1105) and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

10.1 Treatment of Isolated Lesions

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2. All interventions should be discussed in advance with the BMS Medical Monitor.

11 STUDY EVALUATIONS

11.1 Study Procedures by Visit

11.1.1 Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936559 (MDX-1105) need not be repeated.

11.1.2 Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)
- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at

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the same institution/facility which will be used to measure response during the subject's participation in the study.

- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG
- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
  - Hepatitis B and C testing;
- Concomitant medications

11.1.3 Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start BMS-936559 (MDX-1105) treatment within 28 days of Screening. Subjects will receive 1 dose of BMS-936559 (MDX-1105) every

14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be determined as summarized in Section 3.3. Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) at the beginning of each cycle or subjects in the 0.1 mg/kg or 0.3 mg/kg expansion cohorts as stipulated in section 3.2. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.4). Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses, see Section 7.7 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1 Cycle 1

Cycle 1 will begin with the first i.v. infusion of BMS-936559 (MDX-1105) (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.

- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity
- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be performed and reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Blood sample for SNP analyses (These samples will be collected only for subjects enrolled under Amendment 6)

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- Serum for subsequent cytokine panel assays: may include: IL-1, 2, 4, 5, 6, 10, 13, IFN gamma, TNF alpha, TGF beta, CXCL-9, and CXCL-10 (These samples will be collected only for subjects enrolled under Amendment 6)
- Serum for quantitative PCR: Samples will be analyzed for gene expression profiling (These samples will be collected only for subjects enrolled under Amendment 6)
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Response assessment and documentation
- Adverse event assessment including specific elicitation of symptoms (see Appendix 3) that may be indicative of irAEs.

11.1.3.2 Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of BMS-936559 (MDX-1105) (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.4).

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)

- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry
- Serum for subsequent cytokine panel assays: may include: IL-1, 2, 4, 5, 6, 10, 13, IFN gamma, TNF alpha, TGF beta, CXCL-9, and CXCL-10 (These samples will be collected only for subjects enrolled under Amendment 6 and for cycle 2 only)
- Quantitative PCR: Blood samples will be analyzed for gene expression profiling (These samples will be collected only for subjects enrolled under Amendment 6 and for cycle 2 only)
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.4 Follow-up

There are 5 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 1 year. All subjects should complete follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2-5 will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 1 year until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3
- Vital sign measurements
- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5 Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they have:

- Completed 3 doses of BMS-936559 (MDX-1105) in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6 Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up
- Death
- Other

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should complete Follow-up Visits 1 and 2 to be monitored for 70 days following the last dose of BMS-936559 (MDX-1105) for the occurrence of study drug-related adverse events or other clinically significant adverse event. Subjects who are unable to complete the follow-up visits should be contacted at least once within 70 days following the last dose

of BMS-936559 (MDX-1105). Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.

11.1.7 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with the protocol
- Disease progression as defined in Section 3.3
- Significant clinical deterioration

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

11.2 Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of BMS-936559 (MDX-1105): vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given

the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1 Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of BMS-936559 (MDX-1105)-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol. Blood samples for immunogenicity analysis will be collected from all subjects at predose on Day 1, predose on Cycle 2 Day 1 and all follow-up Visits. Samples will be evaluated for development of Human Anti-Human Antibody (HAHA) in subjects.

11.2.2 Immunogenicity

Immunogenicity refers to the development of an immune response to the BMS-936559 (MDX-1105) drug itself, and is characterized by antibodies that the subject may develop that react with BMS-936559 (MDX-1105). These may result in more rapid clearance of BMS-936559 (MDX-1105) from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with BMS-936559 (MDX-1105) at a later date.

11.2.3 Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Samples for measurement of single nucleotide polymorphisms (SNP) of genes will be collected to evaluate potential associations of genes involved in the immune response with clinical outcome and/or safety.

Peripheral blood samples will be collected to evaluate pharmacodynamic effects using gene expression profiling of mRNA and/or qPCR, and potential associations with clinical outcome.

Blood samples will be collected to evaluate the pharmacodynamic effects on serum cytokines/chemokines such as, but not limited to, IL-1a, IL-2, IFN-g, IL-10, CXCL-9, and CXCL-10 and potential associations of these markers with clinical outcome after treatment with MDX-1105.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3 Efficacy Evaluations

The primary efficacy parameter is the objective response rate (ORR) overall (number of subjects with confirmed responses of CR or PR divided by the total number of treated subjects with measurable disease at baseline) for each indication. Tumor response status will be assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of BMS. The ORR overall during the first 4 cycles will also be similarly calculated. Additional efficacy parameters include the Best Overall Response (BOR) with response categories (CR, PR, SD, PD), disease control rate (number of subjects with CR, PR, or SD divided by the total number of treated subjects with measurable disease at baseline), progression free survival (PFS) and the time to response and duration of response for those subjects with a confirmed response, based on RECIST with modification.

Exploratory efficacy evaluations for statistical analysis will include an immune-related response criteria (irRC) (Appendix 3) based on modifications to the RECIST (v1.0) (denoted as irRECIST) with the following parameters: irBOR with response categories (irCR, irPR, irSD, and irPD), immune-related Objective Response Rate (irORR) during the entire study, and duration of ir-responses for those subjects with ir-responses. The irORR based on the irBOR outcomes in the first 4 cycles may also be derived.

Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of BMS-936559 (MDX-1105) and more likely capture its true potential to induce clinical responses.

11.4 Pharmacokinetic Evaluations

Pharmacokinetic parameters include AUC(0-T), AUC(INF), AUC(TAU), AI, Cmax, Cmin, Tmax, T-HALF, Vss, and CLT.

Blood samples for the analysis of serum concentrations of BMS-936559 (MDX-1105) will be drawn in all subjects according to the schedule listed below and in Table 3. Serum

samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

11.4.1 Cycle 1- 3

Intense sampling will be collected in 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and 3 subjects in each of the cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg) under Amendment 6.

- **Cycle 1**
  - **Day 1:** pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
  - **Days 2, 3, 4 and 8:** Single serum samples will be taken on each day.
  - **Days 15 and 29:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
- **Cycle 2**
  - **Day 1:** pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion.
  - **Days 2, 3, 4, and 8:** single serum samples will be taken on each day.
  - **Day 15:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
- **Cycle 3**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion

Sparse PK sampling: All other subjects in each cohort

- **Cycle 1**
  - **Days 1 and 15:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
  - **Days 3 and 8:** single serum samples will be taken on each day.
- **Cycle 2**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

- **Cycle 3**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

- **Days 1 and 15:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

11.4.2 Cycles 4-16

- **Days 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion on Day 1 for each cycle 4-16.

11.4.3 Follow-up Visits

- **Follow-up Visits 1 and 2:** single serum samples to be taken.

12 ADVERSE EVENT REPORTING

Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1 Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be study drug-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 3.0.[46] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate.

Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 3 and reported in the study report.

A laboratory abnormality is considered an adverse event if it results in

- discontinuation from study drug,
- necessitates therapeutic medical intervention,
- if the Investigator assesses the abnormality as an adverse event, or
- any laboratory test that is clinically significant or meets the definition of an SAE

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value). These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug - related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

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Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken with study drug in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted
7 Study drug dosage adjusted

12.1.1 Safety Reporting For Adverse Events

All adverse events or other clinically significant adverse events occurring up to 70 days after administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Study drug-related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only study drug-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects > 70 days after the administration of the last dose of study drug

A *nonserious adverse event* is an AE not classified as serious.

The collection of nonserious AE information should begin at initiation of study drug and should conclude 70 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 12.3). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

12.2 Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. is fatal or life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);

2. requires or prolongs hospitalization;

3. is significantly or permanently disabling or incapacitating;

4. constitutes a congenital anomaly or a birth defect; or

5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.5.1 or reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient

basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; or hospitalization to facilitate the work up of a Grade 1 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3 Rapid Notification of Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures.

12.3.1 Reporting Responsibility

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment; or during the 70 days following study drug administration; or within 30 days of the last visit for screen failures must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Each serious adverse event must be reported by the Investigator to the BMS Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring after 70 days from the last dose of BMS-936559 (MDX-1105) must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to BMS within 24 hours of receiving the information. BMS, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2 Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to BMS or its designee. The study monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. BMS or designee will

communicate serious adverse events to the study sites as required by regulatory authorities.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

12.3.3 Contact Persons and Numbers

The BMS Central Emergency Contact telephone and SAE telefax numbers are listed on the cover page of the protocol.

12.4 Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5 Pregnancy

Pregnancy testing must be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive BMS-936559 (MDX-1105) and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the study Treatment Period part of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the study Treatment Period part of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.5.1.

Follow-up information regarding the course of the pregnancy, including prenatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

12.6 Immune-Related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of BMS-936559 (MDX-1105), namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical, as very few human subjects have been treated to date, and are based upon preclinical studies in mice deficient in PD-1, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

BMS has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). In addition, the known animal and human toxicity profiles of anti-CTLA-4 antibodies such as ipilimumab include colitis as an expected adverse event. Based on these considerations, BMS-936559 (MDX-1105) may also cause immune-mediated colitis.

Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding. Events of Grade 3 or Grade 4 diarrhea as

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well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. All adverse events of colitis ≥ Grade 2 are deemed to be Events of Special Interest (ESIs), and should be reported using the reporting procedures described in Section 12.7, even if the adverse event itself is not deemed as serious.

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the BMS-936559 (MDX-1105) program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

In all cases, study drug-related ≥ Grade 2 diarrhea/colitis will be managed with regular communication between the Investigator and the BMS Medical Monitor, and with a minimum of at least 1 in-person visit per week until the diarrhea/colitis is < Grade 2. Any Grade 2 adverse event of colitis (per CTCAE) that also results in additional medical requirements, such as more than 2 weeks of immunosuppressive doses of steroids (> 10 mg/day of prednisone or equivalent), blood transfusion, or i.v. hyperalimentation, will be defined as a Grade 3 adverse event. Subjects are to be carefully monitored until recovery of the colitis to ≤ Grade 1.

12.7 Rapid Notification of Adverse Events of Special Interest (EOSI)

In addition to serious adverse events, the following adverse events will be reported to the BMS clinical team within 24 hours even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- ≥ Grade 2 diarrhea/colitis
- ≥ Grade 3 irAE other than diarrhea/colitis
- Any potential Hy's Law case (> 3 x ULN of either ALT/AST with concurrent >2 x ULN of Total Bilirubin and lack of alternate etiology)

12.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size Determination

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level during dose escalation.

Up to 15 expansion cohorts will be enrolled and a total of 16 subjects (32 subjects each will be enrolled at 1mg/kg and 3 mg/kg and 16 subjects in the 10 mg/kg new NSCLC cohorts) will be enrolled for each expansion cohorts. With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 80% confidence interval for an objective response rate would be (3.4%, 30%) if 2 (12.5%) subjects had a response, (7.1% to 37%) if 3 (19%) subjects had a response, (11.4% to 44%) if 4 (25%) subjects had a response and (16.1% to 50%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 80% confidence interval for an objective response rate would be (3.5% to 19.7%) if 3 (9.4%) subjects had a response, (5.6% to 23.4%) if 4 (12.5%) subjects had a response, and (7.8%, 27.1%) if 5 (16%) subjects had a response.

If the true ORR in NSCLC is 15% then with 16 NSCLC patients in each cohort of specific histology and dose, there is 71.5% chance of observing at least 2 responses, and 44% chance of observing at least 3 responses, and there is 28.4% chance of observing 0 or 1 responses (false negative rate). If the true ORR in NSCLC is 5% rather than 15%, then there is 19% and 4.4% chance that there will be at least 2 or at least 3 responses respectively in 16 subjects (false positive rate).

13.2 Populations for Analyses

13.2.1 All Enrolled Population

All subjects who sign informed consent form will be included. Subject disposition will be tabulated using this data set.

13.2.2 All Treated Population

All subjects who receive at least one dose or a partial dose of BMS-936559 (MDX-1105). This population will be used for safety analyses and primary efficacy analyses.

13.2.3 Response Evaluable Population

All subjects who receive BMS-936559 (MDX-1105), have measurable disease at baseline and at least one tumor assessment post-dose.

13.2.4 Pharmacokinetic Population

All available concentration-time data from subjects who receive BMS-936559 (MDX-1105) will be reported. All available derived pharmacokinetic parameter values will be included in the pharmacokinetic dataset and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

13.2.5 Exploratory Biomarker Population

All available data from subjects who receive BMS-936559 and have a baseline measurement (for predictive analysis) and those with baseline and at least one post-

treatment measurement (for pharmacodynamic analyses) will be included in the biomarker dataset.

13.2.6 Immunogenicity Population

All available data from subjects who receive BMS-936559 (MDX-1105) and have a baseline and additional post-treatment measurement samples collected will be included in the immunogenicity dataset. However subjects in the lower doses who were dose escalated will be presented separately in summaries of immunogenicity analyses.

13.3 Endpoint Definitions

13.3.1 Safety Endpoints

Safety assessments will be based on medical review of adverse events and lab abnormality reports. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

13.3.2 Efficacy Endpoints

The primary efficacy endpoint is the objective response rate (ORR) (as defined in Section 11.3) for each indication.

13.3.3 Pharmacokinetic Endpoints

Pharmacokinetic of BMS-936559 (MDX-1105) will be derived from plasma concentration versus time. The following pharmacokinetic parameters will be estimated and reported:

AUC(0-T) Area under the plasma/serum drug concentration-time curve from t=0 to last measurable sampling time.

AUC(INF) Area under the plasma/serum concentration-time curve from t=0, extrapolated to infinity.

AUC(TAU) Area under the concentration-time curve in one dosing interval

AI	Accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose.
Cmax	Maximum observed concentration in plasma.
Tmax	Time to reach Cmax in plasma.
T-HALF	Terminal-phase elimination half-life in plasma.
Vss	Volume of distribution at steady state
CLT	Total body clearance of drug from plasma.

Individual subject pharmacokinetic parameter values will be derived by non-compartmental method by a validated pharmacokinetic program.

13.4 Analyses

13.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, and ECOG status will be summarized by dose using descriptive statistics.

13.4.2 Safety Analyses

All recorded adverse events will be listed and tabulated for the worst CTC grade by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided.

13.4.3 Efficacy Analyses

In order to perform preliminary evaluation of anti-tumor activity, BOR outcomes, objective response (ORR), and disease control rate (DCR) will be tabulated by frequency distribution overall, and in the first 4 cycles. For ORR in each expansion cohort~~,~~ an exact Binomial 90% confidence interval will be determined by Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using the Kaplan-Meier method; PFS will be similarly summarized; PFS rate at 24 weeks will also be summarized by frequency distribution tabulated by dose for each tumor type. Individual tumor measurements, tumor burden and %changes in tumor burden will be listed. Changes in tumor burden will be presented graphically for each disease type. Exploratory efficacy analyses will include a frequency of irBOR outcomes and irORR, and a summary of duration of ir-responses. Summary statistics and plots of measures of tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9), may be provided for specific tumor types, based on data availability.

The primary efficacy analyses will include all subjects from the first treatment period and follow-up period until disease progression. In addition, PFS will be summarized separately for the follow-up period. All primary efficacy analyses will be based on the all treated population; the response evaluable population may also be used for sensitivity analyses.

In order to characterize the dose response in melanoma cohorts, modeling of tumor response (or AE of interest) as a function of dose will be performed, based on parametric or non-parameteric model. For NSCLC cohorts, tumor response measures (e.g. ORR) will also be modeled as a function of dose using some parametric or non-parametric (possibly Bayesian) approach.

13.4.4 Immunogenicity Analyses

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any timepoint will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, and frequency of subjects who

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develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

13.4.5 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1 Day1 and Cycle 2 Day 1 by dose. Geomeric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T), AUC(INF), AUC(TAU), and AI. Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided.

Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose.

Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameters (slope of the linear regression) will be calculated.

Data describing the plasma concentration versus time from this study may be used for future population pharmacokinetic evaluations of the drug which may be reported separately.

13.4.6 Exploratory Biomarkers Analyses

Summary statistics for immune function and other exploratory markers, such as but not limited to serum cytokines/chemokines, flow cytometry, and mRNA profiling, and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored.

Possible associations of various measures (baseline value or change from baseline) of biomarkers including serum cytokines/chemokines, SNP, mRNA profiling with clinical outcome (eg, tumor response) may be explored based on data availability, using response-evaluable subjects, to explore potential predictive markers. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability. Associations of such measures with safety events of interest (e.g. irAE) may also be explored graphically based on data availability.

14 ETHICAL ASPECTS

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with BMS SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to BMS or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of BMS, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

14.4 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion

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and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

15 ADMINISTRATIVE REQUIREMENTS

15.1 Protocol Amendments

The study shall be conducted as described in this approved protocol. Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the BMS monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;

2. Significant change in the study design (e.g., addition or deletion of a control group);

3. Increase in the number of procedures to which subjects are exposed; or

4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., BMS staff versus a contract research organization [CRO]); and

2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2 Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a BMS representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the BMS monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. BMS monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

15.4 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to BMS or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the electronic CRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number

- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

15.5 Auditing Procedures

In addition to the routine monitoring procedures, BMS, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. BMS, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS immediately that this request has been made.

15.6 Publication of Results

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

15.7 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by BMS or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by BMS (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.8 Discontinuation of Study

BMS reserves the right to discontinue any study for any reason at any time.

15.9 Data Management

15.9.1 Data Collection

Investigators must enter the information required by the protocol onto the BMS CRFs that are printed on "no carbon required" paper. BMS monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to BMS, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.9.2 Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following BMS, or its designee, data management procedures.

Obvious errors will be corrected by BMS personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the BMS study team.

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APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	dead

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APPENDIX 2 RECIST WITH MODIFICATIONS

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target

lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.”

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.
Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not “selected” images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.

continued

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Definitions *(continued)*

Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

APPENDIX 3 IMMUNE-RELATED RECIST

Immune-related RECIST (irRECIST) is derived from modified RECIST conventions.

Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at Screening and at the defined tumor assessment time points (see Table 1). Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRECIST.

Measurable Lesions

Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques, or as ≥10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.

Non-Measurable Lesions

Non-target lesions not classified as measurable lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.

Definitions of Index/non-Index Lesions

Index Lesions

Measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Longest Diameters (SLD) for all index lesions will be

calculated and considered the baseline SLD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment.

Non Index Lesions

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.

Calculation of Sum of Longest Diameters (SLD)

Sum of Longest Diameters is an estimate of tumor burden. The greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SLD is calculated as the sum of the longest diameters for index tumor lesions. Several variations of the SLD are identified for the purpose of classification of tumor responses.

SLD at Baseline: The sum of the longest diameters for all index lesions identified at baseline prior to treatment on Day 1.

SLD at tumor assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the SLD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SLD at tumor assessment (irSLD).

SLD at NADIR: For tumors that are assessed more than 1 time after baseline, the lowest value of the SLD (SLD Baseline or SLD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SLD at tumor assessment using the irRECIST for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRECIST accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the ir-response as defined by the Investigator will serve as the basis of exploratory efficacy analyses and guide clinical care.

Definition of Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), which is defined as a decrease, relative to baseline, of 30% or greater in the sum of the longest perpendicular diameters of all index and all new measurable lesions (ie, Percentage Change in Tumor Burden), in the absence of irCR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SLD increases by ≥ 20% when compared to SLD at nadir

Immune-related Stable Disease (irSD), which is defined as not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD)

Immune-related Progressive Disease (irPD), which is defined as at least a 20% increase in Tumor Burden (ie, taking sum of the products of all index lesions and any new measurable lesions) when compared to SLD at nadir.

Definition of Non-Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all non-index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), non-index lesion(s) are not considered in the definition of PR, this term does not apply.

Immune-related Stable Disease (irSD), non-index lesion(s) are not considered in the definition of SD, this term does not apply.

Immune-related Progressive Disease (irPD), increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until Tumor Burden increases by

20% (ie, the SLD at nadir of index lesions and any new measurable lesions increases by the required amount).

Impact of New Lesions on irRECIST

New lesions alone do not qualify as progressive disease. However their contribution to total tumor burden is included in the SLD which in turn feeds into the irRECIST for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRECIST Will Be Based on the Following Criteria:

- **Immune-related Complete Response (irCR):** Complete disappearance of all tumor lesions (index and non-index), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.
- **Immune-related Partial Response (irPR):** The sum of the longest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the longest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Longest Diameters (irSLD). A decrease, relative to baseline of the irSLD of 30% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first irPR.
- **Immune-related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-related Progressive Disease (irPD):** It is recommended in difficult cases (eg, increase in SLD or irSLD accompanied with significant individual lesion regression, "mixed response", or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
  - At least 20% increase in the SLD of all index lesions over nadir SLD calculated for these lesions.
  - At least a 20% increase in the SLD of all index lesions and new measurable lesions (irSLD) over the nadir SLD calculated for the index lesions.

irRC Definitions

Index Lesion Definition	Non Index Lesion Definition	New Measureable Lesions	New Unmeasureable Lesions	% Change in irSLD Tumor Burdon (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≤ -30%	irPR
				> -30% to < +20%	irSD
				≥ +20%	irPD
Stable Disease	Any	Any	Any	> -30% to < +20%	irSD
				≥ +20%	irPD
Progressive Disease	Any	Any	Any	≥ +20%	irPD

Best Overall Response and Date of Progression Using irRECIST (irBOR)

The Investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the Investigators.

APPENDIX 4 PRE-EXISTING AUTOIMMUNE DISEASES

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

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Protocol Number:	CA210001 (MDX1105-01)
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EUDRACT Number	NA
Date:	17-Jun-2008
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Clinical Protocol CA210001 (MDX1105-01)

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

Revised Protocol Number: 07

Incorporates amendment(s) 01, 02, 03, 04, 05, 06, 07

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This protocol contains information that is confidential and proprietary to Bristol-Myers Squibb

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

TITLE

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL NUMBER

CA210001 (MDX1105-01)

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), epithelial ovarian cancer (epOC), gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC).

The secondary objectives are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105), and 4) the dose response relationship in melanoma and in NSCLC.

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity . The exploratory biomarker analysis will explore the hypothesis that immune activation correlates with efficacy and clinical response in subjects after PD-L1 blockade.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and Follow-up (up to 1 year). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The investigator tumor response assessment (by RECIST criteria v1.0) must be completed before the first dose in the next cycle.

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression (PD) after discussion and agreement with the BMS Medical Monitor.

Dose Escalation

An accelerated titration design (ATD) will be utilized for the dose escalation part of this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels were included as part of Amendment 6 to the protocol and did not impact the dose escalation plan or schedule that has been completed prior to Amendment 6). Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a

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≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of dose-limiting toxicities (DLTs).

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose (MTD, the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and Bristol-Myers Squibb Co. (BMS) approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment, with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who will be permitted to dose escalate under circumstances described in section 3.2; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous dose. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 15 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has been completed: an additional 8 expansion cohorts as described below will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has been completed as noted in Table 1

1) Primary MTD expansion cohorts (5 cohorts): 1 cohort in each of the 5 disease indications (MEL, RCC, epOC, CRC and NSCLC) at a tolerated dose chosen by the Sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
2) Non-MTD melanoma expansion cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

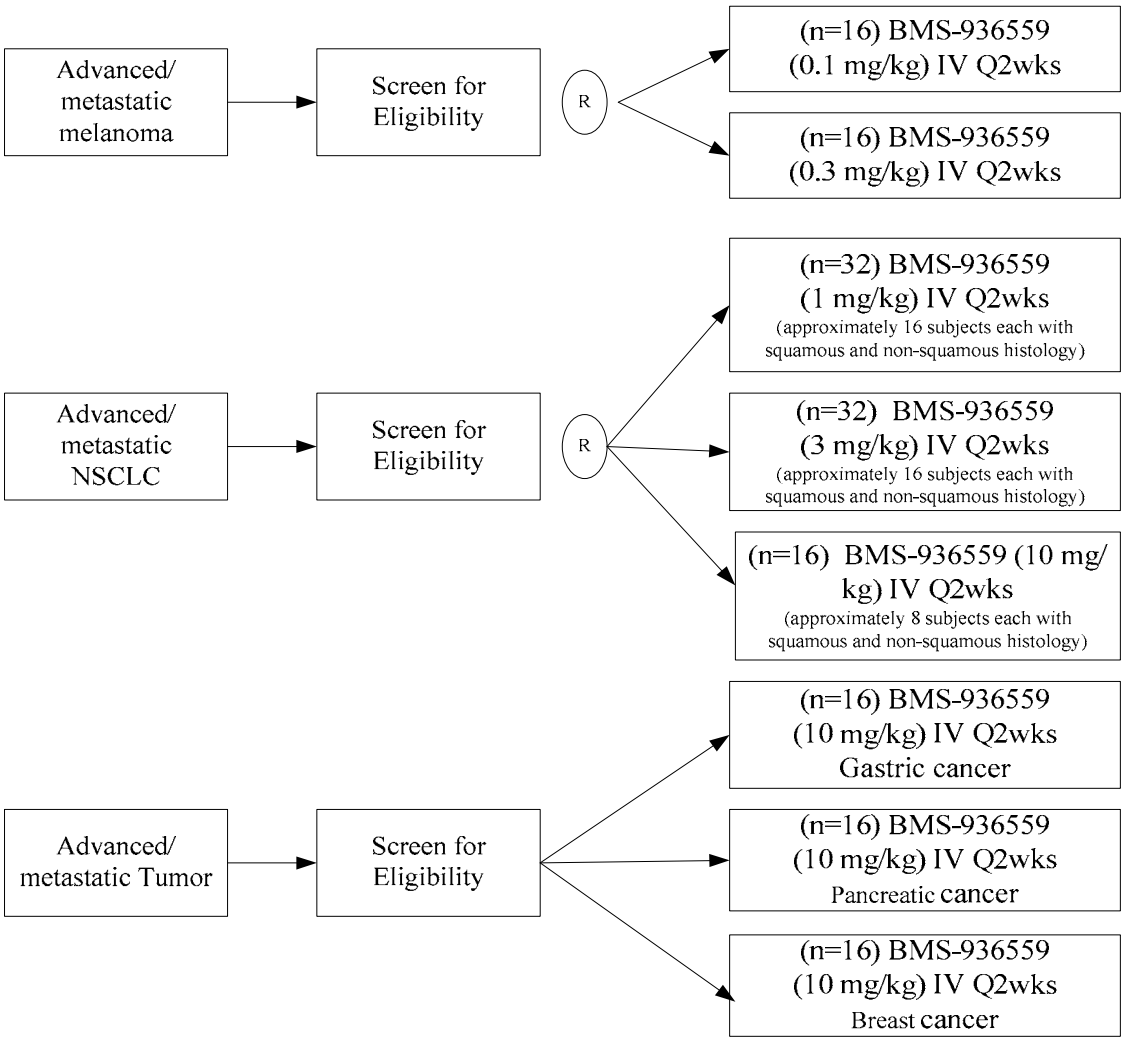
Table: Expansion Cohorts Completed

Tumor Type	Dose level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Epithelial Ovarian cancer	10 mg/kg
Colorectal adenocarcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg

The following 8 additional cohorts will be enrolled (Figure 1)

3) Additional MEL expansion Cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL will be enrolled. 1 cohort each at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed PD and in consultation and agreement by the BMS Medical Monitor.
4) NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg and 10 mg/kg dose levels respectively.
5) Additional MTD expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC) will be enrolled; dosed at 10 mg/kg dose level.

Figure 1: Expansion Cohorts



In order to avoid allocation bias, subjects enrolled in the added Melanoma and NSCLC expansion cohorts by Amendment 6 and 7 meeting all eligibility criteria will be randomly assigned to one of the two, and one of the three dose levels respectively, according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development.

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose escalation plus primary expansion) will be enrolled for each indication.

Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose-escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose-escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

Initiation of Additional Expansion Cohorts

In order to gain additional safety and tolerability data on additional dose levels in MEL and NSCLC and preliminary assessment of efficacy in GC, PC and BC, 8 additional expansion cohorts will be enrolled.

- Additional MEL expansion cohorts (n=32): in order to explore safety, tolerability, and activity at alternate dose levels, an additional 2 cohorts of approximately 16 subjects each with metastatic malignant MEL will be enrolled and administered BMS-936559 at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level will have the opportunity to dose escalate to the 1 mg/kg dose level upon confirmed PD on a case-by-case basis and after consultation with the BMS Medical Monitor.
- NSCLC expansion cohorts (N=80): in order to further explore the safety, tolerability, and activity of BMS-936559 in NSCLC; a total of 3 additional cohorts in subjects with NSCLC will be

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enrolled; 1 cohort of approximately 32 subjects each will be enrolled and administered BMS-936559 at the 1 mg/kg, 3 mg/kg dose levels, respectively and 16 subjects will be enrolled at 10 mg/kg dose level. Cohorts at each dose level will be comprised of approximately 16 subjects with squamous cell, and 16 subjects with non-squamous cell histologies. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types. With 2 responses out of 16 subjects, the 80% C.I. for the response rate will be (3.4%, 29%), i.e. 2 responses are needed to exclude a lower limit of no responses.

- Additional MTD expansion cohorts (3 cohorts, N= 48): in order to gain additional safety, tolerability data and preliminary assessment of efficacy an additional 3 cohorts of 16 subjects of each in with GC, PC and BC will be enrolled; BMS 936559 will administered at the 10 mg/kg dose level.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of a DLT in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5). Following each treatment cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor assessment (evaluation performed at the end of each of the first 4 cycles and then at the end of every even-numbered cycle). No subject will be permitted dose escalations or de escalations with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who meet the criteria for dose escalation as outlined in section 3.1; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as outline in sections 8.2

(Dose Limiting Toxicity) and 11.1.7 (Discontinuation of Subjects from Treatment); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.

- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be approximately 1 year. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection.

Reinitiation of Study Therapy For Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 3 years.

The maximum duration of a subject's participation in this study is approximately 5 years.

STUDY POPULATION

Up to 290 subjects may be enrolled (if no subjects require replacement). One hundred eighty (180) subjects have been enrolled prior to Amendment 7. Approximately 110 additional subjects with MEL, NSCLC, GC, PC or BC will be enrolled. Subjects with advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, epOC, GC, PC or BC, will be eligible to enroll in the study.

DOSAGE AND ADMINISTRATION

BMS-936559 is to be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an i.v. push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

At doses 1, 3, 10 mg/kg, the total dose needed will be diluted to a total volume of 60 mL in 0.9% sodium chloride. In cases where the total dose volume exceeds 60 mL, no dilution is required. At doses of 1, 3, 10 mg/kg, BMS-936559 should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.

For subjects receiving doses at 0.1 mg/kg and 0.3 mg/kg, the drug product BMS-936559 (MDX-1105) will be diluted with BOTH the supplied vehicle for BMS-936559 AND with Normal Saline to a final drug concentration of 0.1 mg/mL and 0.3 mg/mL, respectively.

SAFETY EVALUATIONS

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) performance status evaluations, diagnostic imaging, physical examinations, electrocardiograms, and the incidence and severity of adverse events. Safety will also include tests for autoimmune sera and immunogenicity.

Dose-Limiting Toxicity

A DLT is defined as a study drug-related, Grade 3 or higher adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset] Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

EFFICACY EVALUATIONS

Safety assessments will be based on medical review of adverse events and lab abnormality reports. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle as scheduled in the time and events table. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with BMS-936559 (MDX-1105).

Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

EXPLORATORY IMMUNE FUNCTION AND OTHER BIOMARKER EVALUATIONS

Samples will be collected, and evaluated for lymphocyte phenotype, and cryopreserved lymphocytes and plasma will be stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Samples for measurement of single nucleotide polymorphisms (SNP) of genes will be collected to evaluate potential associations of genes involved in the immune response with clinical outcome and/or safety.

Peripheral blood samples will be collected to evaluate pharmacodynamic effects using gene expression profiling of mRNA and/or qPCR, and potential associations with clinical outcome.

Blood samples will be collected to evaluate the pharmacodynamic effects on serum cytokines/chemokines such as, but not limited to, IL-1a, IL-2, IFN-g, IL-10, CXCL-9, and CXCL-10 and potential associations of these markers with clinical outcome after treatment with BMS-936559 (MDX-1105).

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters include AUC(0-T), AUC(INF), AUC(TAU), AI, Cmax, Cmin, Tmax, T-HALF, Vss, and CLT.

Blood samples will be collected for pharmacokinetic evaluation of BMS-936559 (MDX-1105) in Cycle 1, 2 and 3. Single samples will also be collected to evaluate serum concentrations of BMS-936559 at the Follow-up Visits 1 and 2. Intense sampling will be collected in first 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and first 3 subjects in each of the 4 cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg). Sparse PK samples will be collected from rest of subjects enrolled in each cohort.

STATISTICAL METHODS

Sample Size Determination:

This is a phase 1 dose-escalation study. The sample size during dose escalation cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level.

Up to 15 expansion cohorts will be enrolled and a total of 16 subjects will be enrolled for each expansion cohorts subjects (32 subjects each will be enrolled at 1mg/kg and 3 mg/kg and 16 subjects in the 10 mg/kg new NSCLC cohorts). With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 80% confidence interval for an objective response rate would be (3.4%, 30%) if 2 (12.5%) subjects had a response, (7.1% to 37%) if 3 (19%) subjects had a response, (11.4% to 44%) if 4 (25%) subjects had a response and (16.1% to 50%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 80% confidence interval for an objective response rate would be (3.5% to 19.7%) if 3 (9.4%) subjects had a response, (5.6% to 23.4%) if 4 (12.5%) subjects had a response, and (7.8%, 27.1%) if 5 (16%) subjects had a response.

If the true objective response rate (ORR) in NSCLC is 15% then with 16 NSCLC patients in each cohort of specific histology and dose, there is 71.5% chance of observing at least 2 responses, and 44% chance of observing at least 3 responses, and there is 28.4% chance of observing 0 or 1 responses (false negative rate). If the true ORR in NSCLC is 5% rather than 15%, then there is 19% and 4.4% chance respectively that there will be at least 2 or at least 3 responses in 16 subjects (false positive rate).

A total of up to 290 subjects are to be enrolled in this study, including dose escalation and dose expansion.

Statistical Analysis:

Safety Analysis: All recorded adverse events will be listed and tabulated by based on worst grade, system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECGs will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy Analysis: All available tumor measurement data will be listed. Individual best overall response (BOR) will be listed and tabulated by tumor type and dose cohort for all treated subjects with measurable disease at baseline. Changes in tumor burden will be presented graphically for each tumor type. The objective response rate (ORR), disease control rate (DCR) and corresponding 90% confidence intervals will be reported by tumor type and dose cohort. The ORR is defined as the number of subjects with a BOR

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of PR or CR divided by the number of treated subjects. The DCR is defined as the number of subjects with a BOR of CR, PR, or SD ≥ 12 weeks divided by the number of treated subjects.

Duration of response, defined as the time between the date of first response and the date of disease progression or death, whichever occurs first, will be computed for subjects with a BOR of CR or PR. Time to response, defined as the time between the date of first dose of study therapy and date of first objective response, will be computed for all subjects with a BOR of CR or PR. PFS, defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first, will be computed for all treated subjects with measurable disease at baseline. Medians and corresponding two-sided 95% confidence intervals will be reported for duration of response, time to response and PFS by tumor type and dose and analyzed using Kaplan-Meier methods.

Summary statistics and plots of measures of tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9), may be provided for specific tumor types according to data availability.

Immunogenicity Analysis: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive anti-drug antibody (ADA) at any timepoint will be provided by tumor type and by dose. The frequency of subjects with at least one positive ADA assessment, and frequency of subjects with an increase in ADA levels from baseline will be provided by tumor type and by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status Associations between concentrations of BMS-936559 and ADA assessments may be explored.

Pharmacokinetic Analysis: Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1 Day1 and Cycle 2 Day 1 by dose. Geometric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T), AUC(TAU), AUC(INF), and AI. Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided. Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose. Dose proportionality will be assessed by estimating in Cycle 2 Day 1 the slope of linear regression of BMS-936559 (MDX-1105) log (Cmax) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model.

Biomarkers (immune Function and others): Summary statistics for immune function and other exploratory markers, such as but not limited to cytokines/chemokines, flow cytometry, and mRNA profiling, and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored. Possible associations of cytokines, mRNA, SNP and other potential biomarkers measures (baseline value or change from baseline) with clinical outcome (eg, tumor response) may be explored based on data availability, using response-evaluable subjects, to explore potential predictive markers. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability. Associations of such measures with safety events of interest may also be explored graphically based on data availability.

ABBREVIATIONS

Abbreviation	Term
ATD	Accelerated titration design
BOR	Best overall response
CA-19-9	Carbohydrate antigen-19-9
CA-125	Carbohydrate antigen-125
CEA	Carcinoembryonic antigen
CMV	Cytomegalovirus
CR	Confirmed response
CRC	Colorectal adenocarcinoma
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Form
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
epOC	Epithelial ovarian cancer
GCP	Good Clinical Practice
GI	Gastrointestinal
HAHA	Human anti-human antibodies
HIPAA	Health Information Portability and Accountability Act
HPF	High-powered field
ICF	Informed consent form
irAEs	Immune-related adverse events
i.v.	Intravenous

Abbreviation	Term
irBOR	Immune-related Best Overall Response
irORR	Immune-related Objective Response Rate
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irSD	Immune-related Stable Disease
irRECIST	Immune-related RECIST
IRB/IEC	Institutional review board/independent ethics committee
MEL	Malignant melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PPD	Purified protein derivative
PR	Partial response
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
RT	Radiation therapy
SD	Stable disease

Abbreviation	Term
SLD	Sum of the longest diameter
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

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TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Informed Consent/HIPAA[3]	•											
Inclusion/exclusion criteria	•											
Demographics/medical history[4,5]	•											
Diagnosis confirmation and stage	•											
Tumor-specific therapy history	•											
Pregnancy test[6]	•	•			•		•			•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Vital signs[8]	•	•		•	•	•	•	•		•	•	•
ECOG performance status	•	•[9]		•	•[9]	•	•[9]	•		•	•	•
Physical examination[10]	•	•		•	•	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/abdomen/pelvis)[11]	•[7]								•	•[9]	•	•
Brain CT scan/MRI[11,8]	•[7]								•[9]	•[9]	•[9]	•[9]
Bone scan (if clinically indicated)[10]	•[7]								•[10]	•[10]	•[10]	•[10]
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Response assessment									•			
ECG (12-lead)	•	•[16]								•		
Hematology	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Serum chemistry	•	•[17]		•	•[17]	•	•[17]	•		•	•	•
Immune safety assays		•								•	•	
Optional tumor or other biopsy	•[18]											
Tumor-specific blood tests[19]		•								•	•	•
Hepatitis B and C testing	•											
Urinalysis	•	•		•	•	•	•	•		•	•	•
Flow cytometry		•								•		
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Cryopreserved PBMC (research samples for exploratory immune function evaluation)		•								•		
Serum sample for immunogenicity[7]		Serum for immunogenecity will be collected according to schedule in Table 3								•	•	
Serum sample for pharmacokinetic analysis[7]		Serum for PK will be collected according to schedule in Table 3								•	•	
Blood Sample for SNP analysis[20]		•										
Serum for cytokine panel[20]		•										
Blood Sample for quantitative PCR or gene expression profiling[20]		•										

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Table 1: Time and Events Schedule for Cycle 1

Examination	Screening	Treatment Period								Follow-up Period[1]		
		Cycle 1 (± 1 Day)								Follow-up		
Visit Name	**Screening**	**C1:D1**	**C1:D2-4**	**C1:D8**	**C1:D15**	**C1:D22**	**C1:D29**	**C1:D36**	**C1:D42**	**1**	**2**	**3-5**
Timepoint (Day)	**-28 to -1**	**1**	**2, 3, 4**	**8**	**15**	**22**	**29**	**36**	**42[2]**	**Last Visit + 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
BMS-936559 (MDX-1105) infusion		•			•		•					
Concomitant medications	•	•	•	•	•	•	•	•		•	•	
Adverse events		•	•	•	•	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.												

Footnotes can be found on the following page.

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Table 1 Footnote:

1 Follow-up Visit 1 is to be completed in lieu of the Cycle 2 Day 1 Visit when a subject will not proceed to the second cycle of treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 1 year follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

3 Informed consent/Health Information Portability and Accountability Act (HIPAA) must be signed before the initiation of any study drug administration or procedures. May be signed before Day -28.

4 To include collection of prior medication and prior/concurrent medical conditions.

5 Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions Case Report Form (CRF).

6 Serum β-HCG pregnancy test at Screening and at Follow-Up 2 visits and urine pregnancy test at all other indicated time points must be performed and found to be negative before infusion for women of childbearing potential.

7 Pharmacokinetic sampling to be performed according to Table 3.

8 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. In addition, for Cycle 1 (Day 1), vital signs will be obtained at 120 and 240 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

9 ECOG Performance Status to be assessed before each infusion.

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[10] Physical examination to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Height will be measured at Screening only. Weight to be taken at the Screening Visit and before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (Note: Dose adjustments will only be made if there has been a10% or greater change in weight [increase or decrease] since the previous cycle).

[11] The same technique (CT/MRI) used at baseline should be utilized throughout the study.

[12] Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days (56 days for brain scans) before the administration of BMS-936559 (MDX-1105) need not be repeated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.

[13] Brain CT scan/MRI (MRI preferred) required at Screening if not performed within the previous 56 days (and NOT required for subjects with epOC unless clinically indicated). Brain scans during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm complete response (CR) or partial response (PR), or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated at every cycle during Cycles 1-4, and then at every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2 -5.

[14] To be performed if clinically indicated and if not done within the preceding 28 days.

[15] If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated if not done within the preceding 56 days. Bone scan will not be required at the end of Cycle 1 if positive at Screening, unless clinically indicated.

[16] To be performed pre- and post infusion.

[17] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[18] A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. **Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or 15 unstained slides) by study personnel for performance of correlative tissue studies.** Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.

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[19] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

[20] Samples will not be collected on subjects enrolled prior to Amendment 6.

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Pregnancy test[4]	•	•	•		•	•	
Vital signs[5]	•	•	•		•	•	•
ECOG performance status	•[6]	•[6]	•[6]		•	•	•
Physical examination[7]	•	•	•		•	•	•
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[8]				•	•[9]	•	•
Brain CT scan/MRI[8,10]				•	•[9]		
Bone scan (if clinically indicated)[11]				•	•[9]		
Response assessment				•[12]		•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							
ECG (12-lead)	•[13]				•		
Hematology	•[14]	•[14]	•[14]		•	•	•

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum chemistry	•[14]	•[14]	•[14]		•	•	•
Immune safety assays	•				•	•	
Tumor-specific blood tests[15]	•				•	•	•
Urinalysis	•	•	•		•	•	•
Optional tumor or other biopsy[20]							
Cryopreserved PBMC (research samples for exploratory immune function evaluation)	•[17]				•		
Flow cytometry	•				•		
Serum sample for immunogenicity[19]	Serum for immunogenecity will be collected according to schedule in Table 3						
Serum sample for pharmacokinetic analysis[19]	Serum for PK will be collected according to schedule in Table 3						
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

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Table 2: Time and Events Schedule for Cycles 2-16

Examination	Treatment Period				Follow-up Period[1]		
	Cycles 2-16 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3-5**
Timepoint (Day)	**1[2]**	**15**	**29**	**42[3]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	**Previous Follow-up Visit + 84 Days**
Serum for cytokine panel[18]	•						
Blood Sample for quantitative PCR or gene expression profiling[18]	•						
BMS-936559 (MDX-1105) infusion	•	•	•				
Concomitant medications	•	•	•		•	•	•
Adverse events	•	•	•		•	•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

Table 2 Footnote:

[1] Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.** If a subject remains in the study, subsequent

follow-up visits will continue until disease relapse, disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 1 year follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

2 End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days after the last dose of the prior treatment cycle. If treatment is delayed more than 28 days due to resolving toxicity then no more study therapy should be given.

3 The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

4 Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated time points must be performed and found to be negative before infusion for women of childbearing potential.

5 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

6 ECOG Performance Status to be assessed before each infusion.

7 Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note**: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

8 The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 4 cycles and at the end of every even-numbered cycle after Cycle 4.

9 To be performed if clinically indicated and if not done within the preceding 28 days.

10 Brain CT scan/MRI (MRI preferred) during the Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, to confirm CR or PR, or if clinically indicated. If required due to prior history, subsequent brain CT scans/MRI will be repeated after Cycle 1-4, and then after every even-numbered cycle (6, 8, etc.) and at Follow-up Visits 2-5.

11 If the bone scan is positive at Screening, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.) to confirm CR or PR, or if clinically indicated, and not done within the preceding 56 days.

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[12] At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on the tumor response evaluation.

[13] To be performed pre- and postinfusion.

[14] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[15] CA-125 for epOC subjects only, CEA and CA-19-9 for CRC subjects only.

[17] Sample collected for Cycles 2 and 3 only.

[18] Samples will not be collected on subjects enrolled prior to Amendment 6.

[19] Serum samples for immunogenicity and pharmacokinetic analyses will be collected according to schedule 3.

[20] Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the study as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent. Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or 15 unstained slides) by study personnel for performance of correlative tissue studies.

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Table 2 A: Time and Events Schedule for Reinitiation therapy

Examination	Treatment Period				Follow-up Period[16]		
	Cycles R1- R8 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	
Time point (Day)	**1**[17]	**15**	**29**	**42**[18]	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	
Pregnancy test[19]	•	•	•		•	•	
Vital signs[5]	•	•	•		•	•	
ECOG performance status	•[6]	•[6]	•[6]		•	•	
Physical examination[7]	•	•	•		•	•	
Tumor imaging (CT/MRI chest/ abdomen/pelvis)[8]				•		•	
Response assessment				•		•	
ECG (12-lead)	•				•		
Hematology[9]	•	•	•		•	•	
Serum chemistry[9]	•	•	•		•	•	
Immune safety assays	•				•	•	
Urinalysis	•	•	•		•	•	

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Table 2 A: Time and Events Schedule for Reinitiation therapy

Examination	Treatment Period				Follow-up Period[16]		
	Cycles R1- R8 (± 1 Day)						
Visit Name	**Cn:D1**	**Cn:D15**	**Cn:D29**	**Cn:D42**	**Follow-up 1**	**Follow-up 2**	
Time point (Day)	**1[17]**	**15**	**29**	**42[18]**	**Last Visit + 1 to 7 Days**	**Previous Follow-up Visit + 84 Days**	
BMS-936559 (MDX-1105) infusion	•	•	•				
Serum sample for immunogenicity [10]	•[10]				•	•	
Serum sample for pharmacokinetic analysis [10]	•[10]				•	•	
Concomitant medications	•	•	•		•	•	
Adverse events	•	•	•		•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.							

Table 2A Footnote:

[1] Follow-up Visit 1 is to be completed in lieu of the next cycle Day 1 Visit when a subject will permanently discontinue study drug treatment. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. **Subjects who will discontinue the study due to worsening PD or subsequent clinical deterioration after PD confirmation will complete all Follow-up Visit 1 evaluations and will complete only the pharmacokinetic and immunogenic evaluations and collection of adverse events for Follow-up Visit 2.**

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[2] End of cycle evaluations will be used to determine whether to initiate a new cycle of treatment. The first dose of the next cycle should be given no sooner than 14 ± 2 days after the last dose of the prior treatment cycle. If treatment is delayed more than 28 days due to resolving toxicity then no more study therapy should be given.

[3] The purpose of this visit is for imaging and response assessment by the Investigator. Radiologic procedures and response assessments should occur between Days 38 and 42 and **before** administering the first dose of study drug in the next cycle.

[4] Serum β-HCG pregnancy test at Follow-up 2 and urine pregnancy tests at all other indicated time points must be performed and found to be negative before infusion for women of childbearing potential.

[5] Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion period, and at 15, 30, and 60 minutes postinfusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (or as directed by the Investigator) until the infusion is completed and at 15, 30, and 60 minutes postinfusion and longer if necessary until the subject is stabilized.

[6] ECOG Performance Status to be assessed before each infusion.

[7] Physical examination (excluding height) to be conducted and all abnormal findings and any new or worse signs or symptoms are to be recorded. A complete physical exam should be performed before the initial infusion of each cycle. Weight to be taken before the first infusion of each cycle, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose. (**Note**: Dose adjustments will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous cycle).

[8] The same technique (CT/MRI) used at baseline should be utilized throughout the study. Scan will be repeated at the end of each cycle during first 2 cycles and at the end of every even-numbered cycle after Cycle 2.

[9] During the study Treatment Period, hematology and serum chemistry will be evaluated by both local and central laboratories at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.

[10] Predose samples (0h) samples to be collected from reinitaion treatment cycle 1 and 4 only.

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Table 3: Pharmacokinetic and Immunogenicity Sampling Schedule

Study Day[a]	Time (Relative To Dosing)[a b]	Time (Relative To Dosing) Hour: Min	PK Blood Sample From First 10 Subjects at Each Dose Level[e]	PK Blood Sample From Rest of the Subjects[f]	Immunogenicity Blood Sample From all Subjects
Cycle 1 Day 1	0 (Predose)	00:00	X	X	X
	1.0 (EOI)[c]	01:00	X	X	
	EOI + 30 min	01:30	X		
	EOI + 60 min	02:00	X		
	EOI + 120 min	03:00	X		
	EOI + 240 min	05:00	X		
Cycle 1 Day 2	24 h	24:00	X		
Cycle 1 Day 3	48 h	48:00	X	X	
Cycle 1 Day 4	72 h	72:00	X		
Cycle 1 Day 8	168 h	168:00	X	X	
Cycle 1 Day 15	0 (Predose)	336:00	X	X	X
	1.0 (EOI)[c]	1:00	X	X	
Cycle 1 Day 29	0 (Predose)	336:00	X		
	1.0 (EOI)[c]	1:00	X		
Cycle 2 Day 1	0 (Predose)	00:00	X	X	X
	1.0 (EOI)[c]	01:00	X	X	
	EOI + 30 min	01:30	X		
	EOI + 60 min	02:00	X		
	EOI + 120 min	03:00	X		
	EOI + 240 min	05:00	X		
Cycle 2 Day 3	48 h	48:00	X		
Cycle 2 Day 8	168 h	168:00	X		
Cycle 2 Day 15	0 (Predose)	336:00	X		
Cycle 3 Day 1	0 (Predose)	336:00	X	X	
	1.0 (EOI)[c]	01:00	X	X	

Table 3: Pharmacokinetic and Immunogenicity Sampling Schedule

Study Day[a]	Time (Relative To Dosing)[a b]	Time (Relative To Dosing) Hour: Min	PK Blood Sample From First 10 Subjects at Each Dose Level[e]	PK Blood Sample From Rest of the Subjects[f]	Immunogenicity Blood Sample From all Subjects
Cycle 4 Day 1 and every other cycle Day 1 for first year or discontinuation	0 (Predose)	336:00	X	X	X
Every 4 cycles Day 1 for next year or discontinuation	0 (Predose)	336:00	X	X	X
Follow-up 1[d]	0	00:00	X	X	X
Follow-up 2[d]	0	00:00	X	X	X

[a] Predose samples will be drawn within 30 minutes before infusion.

[b] If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit either due to an AE or due to the alternate dose schedule, a single pharmacokinetic sample will be taken at that visit.

[c] EOI: End of Infusion. These samples should be taken immediately prior to stopping the infusion. In the event of a delay beyond 1 h, the sample should be taken at the END of the infusion.

[d] A single sample will be taken at Follow-up Visits 1 and 2.

[e] Intense sampling will be collected in first 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and first 3 subjects in each of the 4 cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg). Subjects who had screening baseline hemoglobin levels less than 10 g/dL will be excluded from collecting intensive PK sampling.

[f] Sparse PK samples will be collected from rest of subjects enrolled in each cohort.

Samples are to be drawn from a site other than the infusion site (i.e., contra lateral arm) on days of infusion.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens and ongoing immune surveillance is believed to abort the progression of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.[1] Immune evasion may occur by exploiting any of the regulatory checkpoints that control the immune response, including the display of antigens and control of co-stimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by co-stimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

BMS-936559 (MDX-1105) is a fully human monoclonal antibody of IgG4 subtype that targets the Programmed Death-Ligand 1 (PD-L1) cell surface molecule on multiple immune system cells. The binding of PD-L1 to the negative regulatory receptor, programmed death-1 (PD-1), results in the inhibition of immune responses. PD-L1 is also widely expressed by cancers. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors.

Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Eight tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], epithelial ovarian cancer [epOC]), gastric cancer [GC], pancreatic cancer [PC] and breast cancer [BC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

An estimated 39,000 new cases of RCC and 13,000 deaths were seen in the United States in 2006.[2] Recent advances in the molecular biology of RCC have led to several novel therapies with higher response rates for advanced RCC than standard therapies. Three new-targeted agents have been approved recently for advanced RCC:[3] 2 multi-tyrosine kinase inhibitors ([TKIs] Sorafenib, Sutent) and a mammalian target of rapamycin inhibitor ([mTOR] Temsirolimus). Subjects with advanced RCC will relapse on these newer agents and therefore other novel agents need to be developed for this subject population.

An estimated 174,470 new cases of lung cancer and approximately 162,460 deaths were seen in the United States in 2006.[2] The majority of new lung cancer cases (87%) are classified clinically as non-small cell. Because the disease has usually spread by the time it is discovered, chemotherapy alone or combined with radiation is the treatment of choice; on this regimen, a large percentage of patients experience remission. However, the 5-year survival rate for all stages of lung cancer combined is only 15%. The survival rate is 50% for cases detected when the disease is localized; however, only 16% of lung cancers are diagnosed at this early stage. Recent clinical studies of an approved targeted agent for advanced NSCLC, gefitinib (Iressa), did not show improved survival. Thus novel therapies are needed for this subject population.

An estimated 63,000 new cases of MEL and approximately 8,000 deaths were seen in the United States in 2006.[2] The majority of new MEL cases (85%) are diagnosed early as localized tumors and curable. However, approximately 15% of cases are diagnosed as more extensive tumors or have recurred with more extensive disease. Many of these cases are refractory to standard therapy and become unresectable or metastatic. Subjects who have advanced disease have a poor prognosis and are in need of additional novel anticancer agents for treatment.

An estimated 25,000 new cases of ovarian cancer and approximately 14,000 deaths were seen in the United States in 2006.[2] The majority of ovarian cancers (90%) were epithelial in origin (epOC) and approximately 70% present with Stage III or IV disease. Approximately 80% of cases will achieve clinical complete remissions after platinum and taxane therapy. However about 50% to 75% of cases will relapse and have a poor prognosis; these subjects need additional options for treatment on relapse.

An estimated 135,000 new cases of colorectal cancer and approximately 51,000 deaths were seen in the United States in 2006.[2] The majority of colorectal cancer had an adenomatous histology in origin and approximately 60% present with stage II or more. Approximately 50% of cases may be cured by surgery, with 80% recurrence rate in the remainder within 2 years. After irinotecan or platinum based first line therapy, second or greater line therapies result in an overall survival of approximately 1 year. The need for additional and novel therapeutic options for this patient population is great.

It is estimated that 207,090 women will be diagnosed with and 39,840 women will die of cancer of the breast in the United States in 2006.[4] About a third of these cases will have regional spread with a 5-year survival of 83.6% and another 5% will have distant metastases with a 5-year survival of 23.4%. Breast cancer is the most common malignancy in the United States and second only to lung cancer as a cause of cancer death in women. The systemic treatment of metastatic breast cancer is dependent on hormone receptor and Her-2 status with cytotoxic/ trastuzumab combinations used for the Her-2 positive patients, hormone therapy for ER/PR positive patients followed by cytotoxics for refractory or resistant cases, and cytotoxics for the triple- negative patients. The treatments available, however, can prolong survival, but tend not to be curative so in spite of the treatments available, this population still represents a large unmet need.[5]

Carcinomas of the upper gastrointestinal tract (esophagus, gastroesophageal junction, and stomach) are a global health problem, and represent the second most common cause of cancer death worldwide.[6] It is estimated that 21,000 men and women (12,730 men and 8,270 women) will be diagnosed with and 10,570 men and women will die of cancer of the stomach in 2010. Gastric carcinoma is often diagnosed at an advanced stage. Advanced upper GI cancer patients are incurable and have a poor prognosis, with a median survival, if untreated, of 3-5 months for gastric cancer;[7] treatment options include DCF (Docetaxel, Cisplatin, 5 FU), ECF (Epirubicin, cisplatin, 5-FU), and other platinum and paclitaxel based regimens.[8] However, a globally accepted standard of care is still not available, and although first-line chemotherapy certainly extends overall survival by several months compared with basic supportive care (9-13 vs. 3-5 months), median survival for patients treated with a second-line regimen remains a dismal 6-8 months. [9,10]

It is estimated that 43,140 men and women (21,370 men and 21,770 women) will be diagnosed with and 36,800 men and women will die of cancer of the pancreas in 2010. Metastatic disease may be treated with gemcitabine-containing regimens, but with little added benefit such that clinical trial is still considered the preferred treatment for metastatic disease according to current NCCN guidelines.[11]

1.2 PD-1/PD-L1 Pathway and Immune Responses

PD-L1 is a B7 family molecule that negatively regulates T cells. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on a number of other cell types as well, including activated T cells. The negative regulatory activity of PD-L1 has been shown to be mediated through interaction with its receptor, PD-1, on T effector cells. Multiple lines of evidence suggest that the PD-1/PD-L1 pathway plays a critical role in limiting immune responses and maintaining tissue tolerance and resulting in the inhibition of T cell reactivity to tumor antigens.

Aberrant expression of PD L1 by tumor cells has been reported in a number of human malignancies and associated with poor prognosis.[3,12,13,14,15,16,17,18] For example, in RCC high intratumoral expression levels of PD-L1 are related to tumor aggressiveness.[15] Subjects with high tumor and/or lymphocyte PD-L1 levels are almost 5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. It has been reported that PD-L1 expression may be a significant prognostic marker in postoperative esophageal cancer subjects and in subjects with ovarian, bladder, and other cancers.[12,13,14,17] Since normal host mechanisms (i.e., PD-L1 inhibition of T-cell responses by antigen-presenting cells and T-cell anergy mediated by PD-L1/PD-1 interaction) as well as tumor expression of PD-L1 may limit the antitumor response, both $PD\text{-}L1^{+}$ and $PD\text{-}L1^{-}$ tumors may be targeted by inhibiting the interaction of PD-L1 with PD-1.

PD-1 is a type I transmembrane protein in the immunoglobulin gene superfamily of T-cell co stimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA.[19,20,21,22,23] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[24] Two ligands for PD-1 have been identified: PD-L1 (also known as B7-H1) and PD-L2 (programmed death ligand 2; also known as B7-DC). PD-L1 and PD-L2 have

been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[25,26,27,28,29,30,31] PD-L1 is the predominant ligand for PD-1 and its engagement of PD-1 on T cells results in the downregulation of T-cell activation, cell cycle progression, and cytokine secretion. Inhibiting the interaction between PD-1 and PD-L1 has been shown to promote T-cell response to tumor and viral antigens. PD-L2 expression is primarily expressed by activated dendritic cells and is infrequently upregulated on tumors. Thus, PD-L2 may play a more limited role in inhibiting T cell responses because of its narrow expression profile as compared to PD-L1.[30,32] Consequently, inhibiting PD-L1 interactions with PD-1 may be sufficient to promote effective antitumor T cell responses.

Further evidence for the negative regulatory role of PD-L1/PD-1 interaction comes from studies of PD-1-deficient mice that develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[33,34,35] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. PD-1-deficient mice show greater disease susceptibility, particularly in a genetic background prone to autoimmunity (e.g., NOD mice) or in antigen-induced models of autoimmunity.[22] PD-L1 deficient mice show similar disease susceptibilities as PD-l deficient mice in autoimmune-prone genetic backgrounds, but show no autoimmune phenotypes in standard genetic backgrounds (b and d haplotypes) as compared to PD-1 deficiency in the same backgrounds.[29,33,36,37]

Several published murine tumor studies using anti-PD-L1 and anti-PD-1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Expression of PD-L1 in several tumor cell lines renders them resistant to tumor rejection[38,39,40,41,42] and, in one case, less sensitive to the antitumor effects of anti-CD137 antibody.[40] Anti-PD-L1 antibody treatment was able to reverse this resistance when combined with anti-CD137. 32 Anti-PD-L1 moderately inhibits the growth of J558 myeloma, and the growth of J558 tumor cells is suppressed in PD-$1^{-/-}$ mice.[41] In a pancreatic adenocarcinoma model (PAN02), anti-PD-L1 antibody, as well as anti PD-1 antibody, was able to slow tumor growth. In addition, anti-PD-L1 combined with gemcitabine resulted in significant tumor growth inhibition.[14] Anti-PD-L1 monoclonal

antibody together with T_{REG} cell depletion and tumor cell immunization also effectively prevented outgrowth of mouse renal cell carcinoma and kidney cell carcinoma.[43] In studies by Iwai et al, B16 and CT26 metastatic tumors were successfully treated with anti-PD 1 blockade.33,34 Using a murinized anti-mouse PD 1 antibody, Medarex (now BMS) showed that anti-PD-1 antibodies are capable of promoting tumor growth inhibition in SA1/N and MC38 models and that antitumor activity was independent of PD-L1 expression on the tumor.[44] This suggests that PD-1/PD -L1 (and/or the alternate receptor PD-L2) interactions at the level of antigen presentation can inhibit antitumor reactive T cell responses, but does not exclude an inhibitory role for PD-L1 expression at the level of the tumor.

In summary, BMS-936559 (MDX-1105) represents a new therapeutic in the class of immune system activators, such as anti-CTLA-4 and anti-PD-1, which is expected to promote anti-tumor activity by augmenting T-cell responses through the inhibition of negative regulatory checkpoints that govern T cell activity.

1.3 Summary of BMS-936559 (MDX-1105) Preclinical Studies

BMS-936559 (MDX-1105) is an IgG4 antibody with a mutated hinge region (S228P) which binds to PD-L1 with nanomolar affinity and shows a high degree of specificity for PD-L1; no binding is observed to PD-L2 or other members of the related B7 family. BMS-936559 (MDX-1105) was selected to inhibit the interaction of PD-L1 with its receptor PD-1. BMS-936559 (MDX-1105)-mediated PD-1/PD-L1 blockade results in the augmentation of T-cell responses in a variety of functional assays such as the proliferative response of T cells to allogeneic dendritic cells in a mixed lymphocyte reaction (DC-MLR), antigen-specific T-cell responses such as a recall response to cytomegalovirus (CMV) antigen in blood samples from CMV-infected donors, and antitumor peptide responses in subjects treated with melanoma antigen peptide vaccines. Blocking of PD-L1 using BMS-936559 (MDX-1105) can also reverse the suppressive activity of T regulatory cells *in vitro* assays.

Preclinical tumor models in murine syngeneic tumors show that treatment with anti-PD-L1 antibody results in inhibition of tumor growth in a variety of experimental models. In the immunogenic SA1N fibrosarcoma model, anti-PD-L1 antibodies have prevented the outgrowth of unstaged tumors and resulted in tumor growth inhibition in

staged tumors. Long-lived antitumor immunity is observed in tumor free mice. In other models, such as MC38 colon adenocarcinoma, anti-PD-L1 is able to slow the growth of tumors when treatment is begun after tumors have been established.

In vitro evaluation of BMS-936559 (MDX-1105) shows that the antibody is not capable of inducing antibody-dependent cytotoxicity or complement-dependent cytotoxicity with PD-L1 positive cells. In addition, incubation of BMS-936559 (MDX-1105) at high concentrations with blood from normal blood donors resulted in no specific secretion of a variety of cytokines and is thus not expected to independently promote T-cell activation. BMS-936559 (MDX-1105) was well tolerated in Cynomolgus monkeys when administered as a single intravenous (i.v.) injection at dose levels of 1 or 10 mg/kg or administered as weekly doses for 5 weeks at dose levels of 1, 10, and 100 mg/kg. There were no adverse effects on body weights, food consumption, cardiovascular parameters, or clinical pathology.

1.4 Rationale for BMS-936559 (MDX-1105)

1.4.1 Dose Selection

The dose levels for the Phase 1 clinical study were selected based on an evaluation of the toxicology data, in vivo efficacy in oncology models, and clinical data in subjects with cancer treated with MDX-1106 (an IgG4 antibody directed to the PD-1 receptor which inhibits its binding to PD-L1 and PD-L2). In general, efficacy is expected to manifest at a dose between 1 and 10 mg/kg. This may vary with repeated or combination treatments.

The initial dose chosen for Protocol CA210001 (MDX1105-01) will be a repeated dose of 0.3 mg/kg. This dose is > 200-fold lower than the suggested dose level by the no observable adverse effect level considerations from preclinical toxicology studies, where BMS-936559 (MDX-1105) doses of up to 100 mg/kg were safely administered to Cynomolgus monkeys weekly for 5 weeks. Subsequent dose level increases as well as the two additional lower dose cohorts of 0.1 mg/kg and 0.3 mg/kg are designed to achieve an adequate pharmacokinetic profile within what is expected to be the dynamic range of efficacy of the antibody.

1.4.2 Summary of Safety

Based on toxicology studies, no dose-limiting toxicities (DLTs) are anticipated at the proposed clinical doses, but the clinical protocol will provide safety monitoring for immune-based adverse events.

As of 02-Jun-2011 (clinical data cutoff date), 150 subjects with selected advanced or recurrent solid tumors were treated in a single Phase 1 study (MDX1105-01/CA210001). Results from Study MDX1105-01(CA210001) are preliminary and are subject to change. Safety, tolerability and efficacy of multiple doses of BMS-936559 were assessed at 0.3,1,3 and 10 mg/kg (96 subjects treated at the highest 10 mg/kg dose level).

Of the 150 subjects treated in the study, 140 (93.3%) experienced at least 1 AE, regardless of causality. A total of 57 subjects (38.0%) experienced AEs that were considered Grade 3 or 4 in severity. The most frequent AEs reported included fatigue (60 subjects, 40.0%), nausea (50 subjects, 33.3), diarrhea (45 subjects, 30.0%), decreased appetite (34 subjects, 22.7%), headache (32 subjects, 21.3%), and constipation (30 subjects, 20%). There was no dose-related pattern with regard to the incidence, severity, or relationship of AEs.

A total of 94 subjects (62.7%) experienced BMS-936559 treatment-related AEs . Of these subjects, 12 (8.0%) experienced BMS-936559 treatment-related AEs that were considered Grade 3 or 4 in severity. The majority of the study drug related adverse events were Grade 1 or 2 in severity. The most common study drug related adverse events were fatigue (14.0 %), diarrhea (9.3 %), infusion related reaction (11 %), rash (7.3 %), pruritus (6.7 %), headache (6.0 %) and arthralgia (7.8 %).

Twelve of the 150 (8 %) subjects reported Grade 3 or 4 study drug related adverse events. The Grade 3/4 drug-related adverse events include: Grade 3 myasthenia gravis, Grade 3 sarcoidosis, Grade 3 elevated transaminases, Grade 3 fatigue, Grade 3 chest pain, Grade 3 infusion reaction, Grade 3 mucosal inflammation, Grade 3 alopecia, Grade 3 hyperuricaemia, Grade 3 rash maculo-papular and Grade 4 endophthalmitis.

Fourteen serious adverse events (SAEs) considered related to BMS-936559 treatment have been reported in 2 subjects in the 3 mg/kg (27) and 5 subjects in the 10 mg/kg (96) treatment arms. Related SAEs included Grade 1 events of lip swelling, abdominal cramping pain, nausea and autoimmune colitis; Grade 2 events of diarrhea, fatigue, fever,

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ALT elevation and Grade 2/3 AST elevation; Grade 3 events of chest pain, vomiting, sarcoidosis, and myasthenia gravis; and a Grade 4 event of pan-endophthalmitis. No subjects at the 1mg/kg (17 total treated) and 0.3 mg/kg (1 subject treated) reported drug-related SAEs.

Adverse events leading to discontinuation were reported in 14 subjects at 10 mg/kg and in 2 subjects at 3 mg/kg. Seven (7) subjects (50%) in the 10 mg/kg treatment group experienced treatment-related AEs that led to discontinuation. In subjects treated with 3 mg/kg BMS-936559, study drug was discontinued in one subject with melanoma due to Grade 4 endophthalmitis, considered related to study drug.

Updated clinical safety data is available in the Investigator's Brochure for BMS-936559.[45]

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), epithelial ovarian cancer (epOC), gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC).

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) the immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105) and 4) the dose response relationship in melanoma and in NSCLC cohorts.

2.3 Exploratory Objective

The exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity.

The exploratory biomarker analysis will explore the hypothesis that immune activation correlates with efficacy and clinical response in patients after PD-L1 blockade.

3 OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, dose-escalation, and multidose study of BMS-936559 (MDX-1105) a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 6-week cycles), and follow-up (up to 1 year). Each cycle is comprised of 3 doses of study drug administered as an intravenous (i.v.) infusion on Days 1, 15, and 29 with a response assessment between Days 38 and 42. The response assessment must be completed before the first dose in the next cycle.

3.1 Dose Escalation

An accelerated titration design (ATD) will be utilized for this Phase 1 study. Four dose levels are planned: 0.3, 1, 3, and 10 mg/kg/dose (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels included in the current Amendment 6 did not impact the prior dose escalation plan or schedule as described below). Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the maximum tolerated dose

(MTD; the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations are permitted within each subject's treatment, with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who will be permitted to dose escalate under circumstances described in section 3.2; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous dose. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2 Expansion Cohorts

To further characterize safety and efficacy, up to 15 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has been completed: an additional 8 expansion cohorts as described below will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

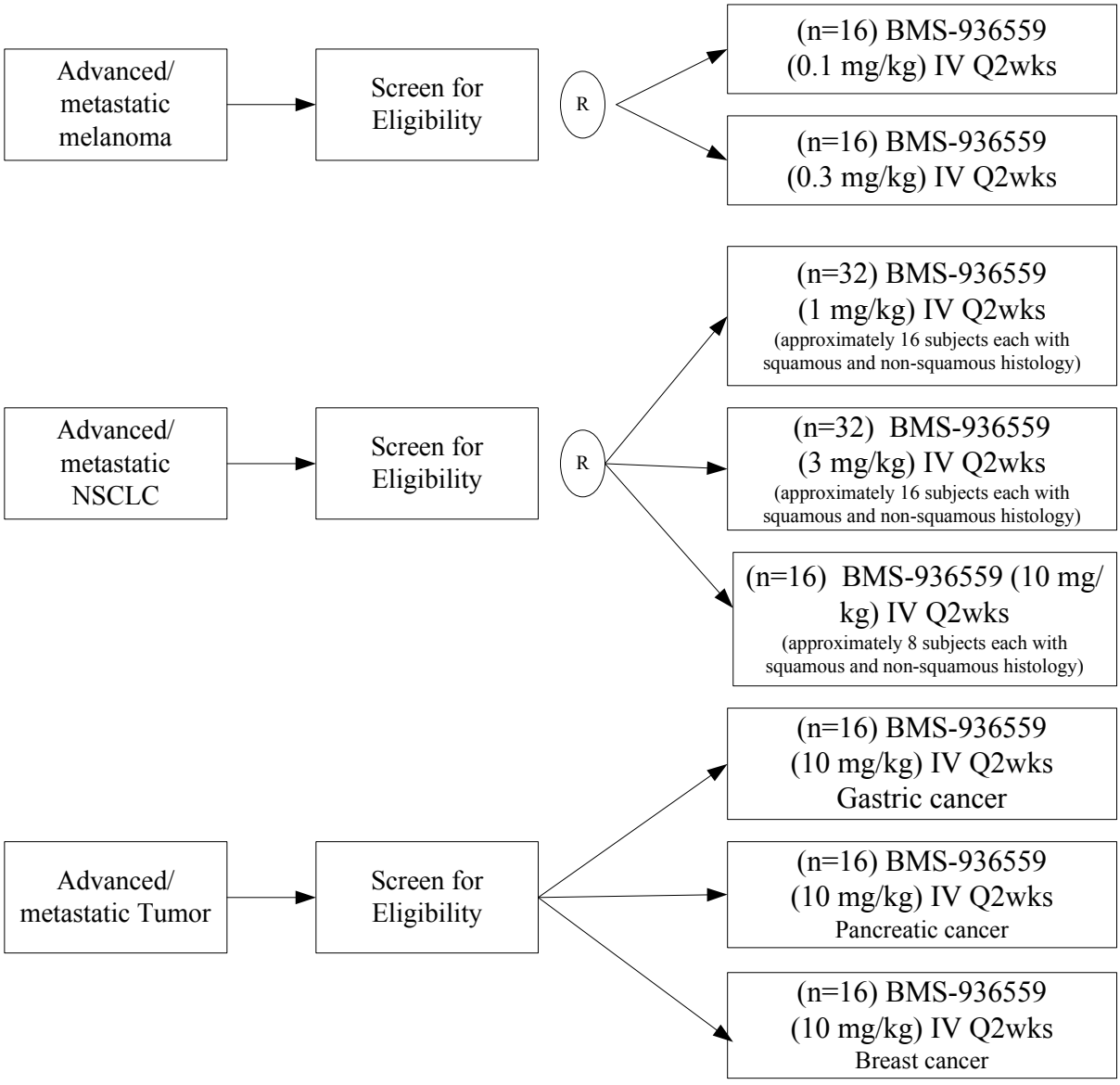
Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has been completed as noted in Table 4):

a. Primary MTD expansion cohorts (5 cohorts): 1cohort in each of the 5 disease indications (MEL, RCC, epOC, CRC and NSCLC) at a tolerated dose chosen by the sponsor that may be up to the highest dose tested that does not exceed the MTD (Primary Expansions). The Sponsor may choose to expand at a dose below the MTD (or the highest dose tested that does not exceed the MTD) if there is evidence for study drug activity at a lower dose.
b. Non-MTD melanoma expansion cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) may also be enrolled.

Table 4: Expansion Cohorts Completed

Tumor Type	Dose level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Epithelial Ovarian cancer	10 mg/kg
Colorectal adenocarcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg

Figure 1: Expansion Cohorts



c. Additional MEL expansion Cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL will be enrolled. 1 cohort each at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed and worsening PD and in consultation and agreement by the BMS Medical Monitor.
d. NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg and 10 mg/kg dose levels respectively.

In order to avoid allocation bias, subjects enrolled in the Melanoma and NSCLC expansion cohorts identified above meeting all eligibility criteria will be randomly assigned to one of the two and one of the three doses, respectively, according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development

e. Additional MTD expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC) will be enrolled; dosed at 10 mg/kg dose level.

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1 Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied) and evaluated at the end of Cycle 1 before any subject is dosed in the primary expansion cohorts. If none of the first 5 subjects in the dose-escalation cohort have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject in the dose-escalation cohort.

The 5 primary expansion cohorts will enroll subjects with MEL, NSCLC, CRC, RCC, and epOC. A total of 16 subjects (dose-escalation plus primary expansion) will be enrolled for each indication.

3.2.1.1 Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL may be enrolled to accrue a total of 16 subjects at doses other than the primary expansion dose (such as 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg) including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level.

- Enrollment into the 1 mg/kg MEL expansion cohort will begin at the same time enrollment into the 3 mg/kg dose-escalation cohort begins.
- If the single subject in the 3 mg/kg dose escalation cohort experiences a ≥ Grade 2 drug-related adverse event or DLT, accrual to the 1 mg/kg MEL expansion cohort will be held until the last subject in 3 mg/kg dose-escalation cohort receives the first dose of study drug successfully.
- If the 1 mg/kg expansion cohort has not been filled by the time the 10 mg/kg dose-escalation cohort is ready to dose, the next subjects will be enrolled into the 10 mg/kg dose escalation cohort. Once enrollment into the 10 mg/kg dose-escalation cohort is complete, subject accrual in the 1 mg/kg MEL expansion cohort may resume.
- Enrollment in the 3 mg/kg MEL expansion cohort will start on completion of enrollment in the 1 mg/kg MEL expansion cohort and enrollment in the 10 mg/kg expansion cohort will start on completion of enrollment in the 3 mg/kg expansion cohort.

3.2.1.2 Initiation of the Additional Expansion Cohorts

In order to gain additional safety and tolerability data on additional dose levels in MEL and NSCLC and preliminary assessment of efficacy in GC, PC and BC, 8 additional expansion cohorts will be enrolled.

- Additional MEL expansion cohorts (n=32): in order to explore safety, tolerability, and activity at alternate dose levels, an additional 2 cohorts of approximately 16 subjects each with metastatic malignant MEL will be enrolled and administered BMS-936559 at the 0.1 mg/kg and 0.3 mg/kg dose levels. Subjects enrolled at either dose level will have the opportunity to dose escalate to the 1 mg/kg dose level upon confirmed and worsening PD on a case-by-case basis and after consultation with the BMS Medical Monitor.

- NSCLC expansion cohorts (N=80): in order to further explore the safety, tolerability, and activity of BMS-936559 in NSCLC; a total of 3 additional cohorts in subjects with NSCLC will be enrolled; 2 cohorts of approximately 32 subjects each will be enrolled and administered BMS-936559 at the 1 mg/kg and 3 mg/kg dose levels respectively and 16 subjects will be enrolled at 10 mg/kg dose level. Cohorts at each dose level will be comprised of approximately 16 subjects with squamous cell, and 16 subjects with non-squamous cell histologies. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types. With 2 responses out of 16 planned subjects per cohort, the 80% C.I. for the response rate will be (3.4%, 29%), i.e. 2 responses would exclude a lower limit of no response.
- Additional MTD expansion cohorts (3 cohorts, N= 48): in order to gain additional safety, tolerability data and preliminary assessment of efficacy an additional 3 cohorts of 16 subjects of each in with GC, PC and BC will be enrolled; BMS 936559 will administered at 10 mg/kg dose level.

3.3 Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications (Appendix 2. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 16 (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a ≥ Grade 3 (CTCAE) adverse event or other adverse conditions related to BMS-936559 (MDX-1105) that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 days after the last dose of the prior treatment cycle to maximize dose intensity. If treatment is delayed more than 28 days due to resolving toxicity then no more study therapy should be given. No subject will be permitted dose escalations or de-escalations with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional

expansion cohorts; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous dose.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936559 (MDX-1105) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as outline in sections 8.2 (Dose Limiting Toxicity) and 11.1.7 (Discontinuation of Subjects from Treatment); 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles.
- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- PR or stable disease (SD): Subjects will continue to receive BMS-936559 (MDX-1105) therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 6 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the BMS Medical Monitor.
- PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.
  - ♦ If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
  - ♦ If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and enter the Follow-up Period.

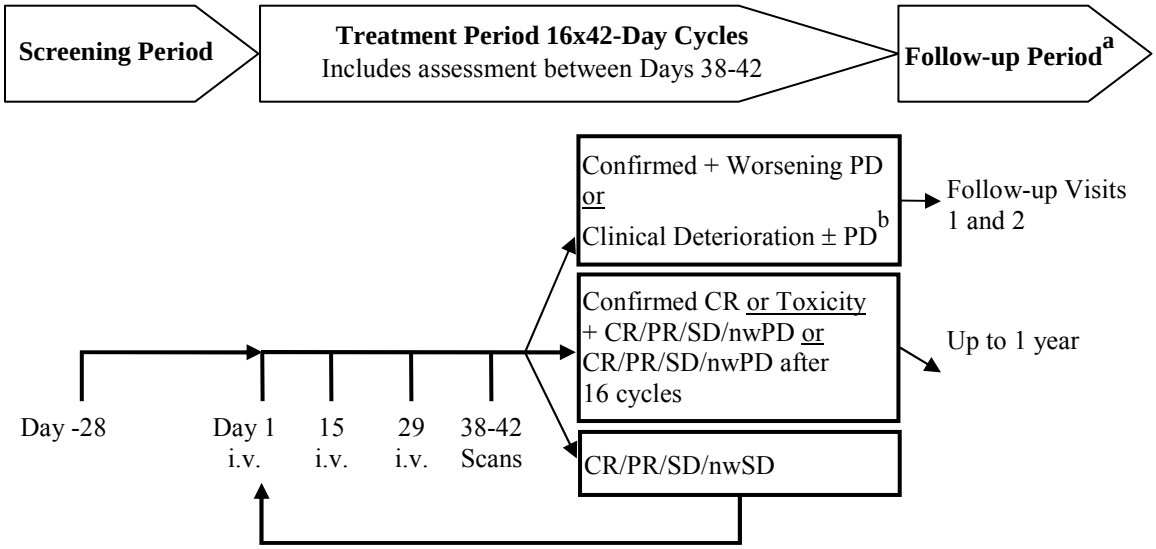
- Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to BMS-936559 (MDX-1105) that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period.

3.4 Follow-up Period

The maximum duration of follow-up will be approximately 1 year. All subjects should complete follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenic evaluations and adverse event collection. Adverse events occurring during the follow-up period should be reported as described in Section 12.1.1.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 2: Individual Subject Flow (Up to 3 Years Treatment, Up to 1 Year Follow- up)



CR = complete response; PR = partial response; SD = stable disease; nwPD = non-worsening progressive disease

[a] For all subjects, all adverse events occurring within 70 days of last dose of study drug should be reported and study drug-related AEs should be followed to resolution or stabilization. After 70 days of last dose of study drug, only treatment-related serious adverse events or late-occurring immune-related adverse events should be reported.

[b] PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up visits should be done unless precluded by disease progression or clinical deterioration.

Re-initiation of Study Therapy for Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Re-initiation of study therapy will only be permitted once for any given subject.

Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy.

Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

3.5 Stopping Rules

3.5.1 Stopping Rules for Dose-Escalation Cohorts

The dose-escalation schema will proceed based upon the occurrence of a greater than or equal to Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (and subsequent IRB and FDA notification).

Considering the anticipated half-life of the molecule, drug-related toxicity is most likely to occur during treatment or within the 10 to 14 days following treatment.

3.5.2 Stopping Rules for Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where DLTs are ≥ 33% and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.5.3 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone
  - spinal cord or nerve root compression
- Bladder outlet or uretheral obstruction
- Development of new central nervous system metastases
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

3.6 Post Study Access to Therapy

Subjects who complete the study and continue to demonstrate clinical benefit may be eligible to receive study drug via an extension of the study, or through another

mechanism at the discretion of the sponsor. The sponsor reserve the right to terminate access to study drugs if any of the following occurs: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

4 STUDY POPULATION

Up to 290 subjects may be enrolled (if no subjects require replacement). As of 20-Sep-2011, one hundred eighty (180) subjects have been enrolled thus far. Approximately 110 additional subjects with MEL, NSCLC, GC, PC or BC will be enrolled. Subjects with advanced or recurrent solid tumors of one of the following histologically documented types: RCC, NSCLC, CRC, MEL, epOC, GC, PC or BC available, will be eligible to enroll in the study.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor's Medical Monitor, or designee, before enrolling the subject into the study.

For entry into the study, the following criteria MUST be met.

4.1 Inclusion Criteria

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria:

1. Adults at least 18 years of age;
2. Life expectancy ≥ 12 weeks;
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 1);
4. Criteria specific to each tumor type:

   For RCC: Subjects must have a histologically confirmed diagnosis of renal cell carcinoma (predominantly clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 previous systemic therapy, such as, but not limited to, treatment with sunitinib, temsirolimus, sorafenib, interleukin-2 (IL-2), and/or chemotherapy.

   For CRC: Subjects must have a histologically or cytologically confirmed recurrent or refractory colorectal carcinoma with tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5-FU or capcitabine), irinotecan, oxaplatin, or cetuximab.

   For NSCLC: Subjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic therapy and no more than 4 prior lines of therapy for recurrent or metastatic NSCLC.

   For MEL: Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after at least 1 prior systemic therapy (may include high-dose IL-2). All melanomas regardless of primary site of disease will be allowed.

   For epOC: Subjects must have a histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with advanced or recurrent disease that is not amendable to cure by surgery or other means and must have failed at least 1 prior systemic therapy.

   For GC: Subjects must have histologically- or cytologically-confirmed gastric carcinoma, including gastric adenocarcinoma or gastro-esophageal junction (GEJ) adenocarcinoma. Patients with adenocarcinoma of the distal esophagus are eligible if

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the primary tumor involves the GEJ. The involvement of the gastroesophageal junction may be documented by endoscopic findings, radiologic imaging, or histology. Subjects must have received no more than 2 prior lines of therapy for advanced/metastatic gastric cancer.

For PC: Subjects must have histologically confirmed advanced pancreatic cancer with either locally advanced or advanced metastatic disease. The malignancy must be deemed unresectable, and subjects must have received no more than 2 prior lines of therapy.

For BC: Subjects must have histologically confirmed locally advanced or metastatic breast cancer and have tumor that is refractory to or progressive after standard of care therapy. Subjects must have received no more than 3 prior lines of cytotoxic therapy for metastatic disease. [Hormone/endocrine therapy for breast cancer and targeted agents such as trastuzumab would not count toward these 3 prior lines of therapy, but would need to be discontinued prior to initiation of study therapy as they would be considered prohibited concomitant anti-cancer therapy. Prior therapy administered in the adjuvant/neoadjuvant setting would not count as therapy for the treatment of metastatic disease].

5. Must have measurable disease with at least 1 unidimensional measurable lesion per RECIST with modifications (see Appendix 2) and evidence of disease progression since the last anti-tumor therapy;
6. Tumor tissue (archival or recent acquisition) must be available for correlative studies for MEL, NSCLC and BC subjects. It is strongly encouraged to make tumor tissue available in GC and PC subjects whenever possible. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. This inclusion criteria will only apply to subjects enrolled after Amendment 5;
7. Not applicable as of revised protocol number 04;
8. Prior treated brain metastases must be without evidence of progression (through magnetic resonance imaging [MRI] with contrast - preferred method or contrast enhanced computed tomography [CT]) for at least 8 weeks and off immunosuppressive doses of systemic medications, such as steroids or absorbed

topical steroids (doses > 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration to be eligible;

9. May have been treated with radiation therapy (RT) provided there are measurable lesions outside the field of RT;

10. Prior systemic RT completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;

11. At least 28 days since the last chemotherapy, immunotherapy, biological therapy (tumor vaccine, cytokine, or growth factor given to control the cancer), or approved TKI therapy (Sunitinib, Sorafenib) before the first dosing of BMS-936559 (MDX-1105) and have recovered from any clinically significant toxicity associated with such treatment;

12. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

13. Prior surgery that required general anesthesia must be completed at least 14 days before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

14. Laboratory values must meet the following criteria at screening and at treatment:

WBC	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ 100,000/μL
Hemoglobin	≥ 9.0 g/dL (may have been transfused)
Creatinine	≤ 2 mg/dL
AST	≤ 2.5 X upper limit of normal (ULN) without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
ALT	≤ 2.5 x ULN without hepatic metastasis ≤ 5 x ULN with hepatic metastasis
Bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

15. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women of child bearing potential (WOCBP) must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug.
16. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other monoclonal antibodies;
2. Prior therapy with an anti-PD 1, anti-PD L1, or anti-CTLA-4 antibody (or any other agents that target T-cell co-stimulation);
3. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast, or localized prostate cancer;
4. Active infection (viral, bacterial, or fungal) requiring intravenous anti-microbial therapeutic treatment within 28 days before the first dose of BMS-936559 (MDX-1105);
5. Known history of infection with Human Immunodeficiency Virus
6. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)
7. Evidence of bleeding diathesis or coagulopathy;
8. Any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or

immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;

9. Recent history of attenuated viral vaccination within 28 days before the first dose of study drug;
10. Known current drug or alcohol abuse;
11. Apparent active or latent tuberculosis infection (purified protein derivative [PPD] test is not required) as indicated by any of the following: PPD recently converted to positive; chest x-ray with evidence of active infectious infiltrate; recent unexplained changes in fever/chill patterns;
12. Underlying medical conditions that, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
13. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic or absorbable topical corticosteroids (doses > 10 mg/day prednisone or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose). Non-absorbed intra-articular steroid injections will be permitted;
14. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;
15. Use of any vaccines against infectious diseases (e.g., influenza, varicella, etc.) within 4 weeks (28 days) of initiation of study therapy;
16. Psychiatric illness or social situation that would preclude study compliance;
17. Pregnant or nursing;
18. Prisoners or subjects who are involuntarily incarcerated;
19. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e., infectious disease) illness;
20. Hospital admission within the past 28 days for and respiratory/pulmonary issue

21. Chronic oxygen supplementation to maintain adequate support at rest.
22. Uncontrolled or significant cardiovascular disease including, but not limited to any of the following:
    a. Myocardial infarction within 6 months
    b. Uncontrolled angina within 3 months
    c. Congestive heart failure within 3 months
    d. Left ventricular ejection fraction (LVEF) ≤ 50%
    e. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes). Controlled atrial fibrillation is not an exclusion criterion.
23. Grade > 1 QTc prolongation at baseline (> 450 msec by Bazett formula) confirmed by a repeat ECG

4.3 Women of child bearing potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT)

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to

prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

5 RANDOMIZATION AND BLINDING

Blinding is not applicable as this is an open-label study.

The dose escalation part of the study and the primary MTD expansion cohorts and 1 mg/kg and 3 mg/kg non-MTD melanoma expansion cohorts were not randomized.

Under Amendment 6, subjects with NSCLC enrolled under the additional NSCLC expansion cohorts (see sections 3.2 and 3.2.1.2) will be randomly assigned to one of the 3 dose levels (1, 3, or 10 mg/kg) in order to avoid allocation bias in subject dose assignment. Randomization in these cohorts will be stratified by histology cell type (squamous vs. non-squamous).

Similarly, subjects with MEL enrolled under the additional MEL expansion cohorts (see first bullet under section 3.2.1.2) will be randomly assigned to one of 2 dose levels (0.1 or 0.3 mg/kg) in order to avoid allocation bias in subject dose assignment.

Subjects enrolled in the expansion cohorts identified above meeting all eligibility criteria will be randomly assigned to one of the three doses according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development. Randomization numbers will be assigned in the order of enrollment within the MEL added expansion cohorts and within the NSCLC added expansion cohorts. Subjects in these cohorts who need to be replaced will be randomized to receive the same dose as the original subject.

6 ASSIGNMENT TO STUDY

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to a treatment cohort, as determined by BMS. Information concerning subjects who are screened and do not meet all entry criteria will be entered into the clinical database.

7 DOSAGE AND ADMINISTRATION

All protocol-specified investigational and noninvestigational products are considered study drug.

7.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational products are BMS-936559 (MDX-1105) drug product and the BMS-936559 vehicle. The vehicle is only for use in the lower dose arms (0.1mg/kg and 0.3mg/kg).

7.2 Non-investigational Product

Non-investigational products are defined as other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

In this protocol, non-investigational product(s) is/are: acetaminophen and diphenhydramine.

7.3 Physical Description of Study Drug

BMS-936559 Injection, (10 mg/mL) **drug product** is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of BMS-

936559 (MDX-1105) (10 mg/mL). The solution is colorless, clear to slightly opalescent solution that is essentially free of particles.

Vehicle for BMS-936559 Injection, (10 mg/mL), 10 mL/Vial, is a sterile clear colorless liquid containing 0.06% polysorbate 80 in water for injection (WFI). This vehicle along with 0.9% sodium chloride injection (normal saline) is used in the dilution of BMS-936559 for the 0.1 mg/kg and 0.3 mg/kg dose levels only.

7.4 Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). The labels for BMS-936559 will bear the sponsor's name and address, the storage conditions, batch number and the standard caution statement, as follows: "Caution: New Drug – Limited". The vials are packaged in boxes (up to 10 vials per container) for storage. The boxes will also contain a label with the information listed.

7.5 Ordering Study Drug

Clinical supplies may be requested by completing a Request Form and faxing it or sending an e-mail it to the Drug Supply Coordinator at BMS.

7.6 Storage

The vials for the BMS-936559 (MDX-1105) drug product must be stored at a temperature of 2°C to 8°C and should be protected from light. The vials for BMS-936559 vehicle must be stored at a temperature of 2°C to 8°C and should be protected from freezing. All vials should be stored in the container in which they are provided (boxes holding up to 10 vials). Recommended safety measures for preparation and handling of BMS-936559 (MDX-1105) include laboratory coats and gloves.

If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Storage and handling guidelines for dosing solutions are provided in section 7.7.

7.7 Study Drug Preparation and Administration

Please read the entire section carefully as preparation instructions will be different depending on the dose.

The following instructions apply to ALL DOSE LEVELS:

- Dose calculations for BMS-936559 will be on the basis of body weight at Day 1 of each cycle
- In all cases, the bag with prepared BMS-936559 should be labeled with the dose level being provided to the subject
- BMS-936559 is to be administered as an IV infusion, using a volumetric pump with a 0.2 micron in-line filter. It is not to be administered as an IV push or bolus injection.
- The infusion should be run over 60 minutes (infusion duration may be extended per guidance in section 8.3 for infusion reactions)
- At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.
- It is recommended that study drug be administered shortly after preparation in order to avoid exposure of the *prepared drug to room temperature* conditions beyond a recommended *4 hour limit*. This 4 hour time limit at room temperature includes time allotted for IV dose administration. In the event that a delay in use of prepared (diluted) study drug is anticipated, it can be refrigerated for a maximum of 12 hours.

Note: The drug preparation method for dose levels of 1, 3 and 10 mg//kg is different from the method for dose levels of 0.1 and 0.3 mg/kg. In addition to drug product vials (BMS-936559 (MDX-1105), (10 mg/mL), vials of BMS-936559 vehicle are needed for preparation of 0.1 and 0.3 mg/kg doses. The vials of BMS-936559 vehicle should NOT to be used for preparation of 1, 3 and 10 mg/kg doses.

7.7.1 Preparation and Administration of BMS-936559 at 0.1 mg/kg and 0.3 mg/kg dose levels

Care must be taken to assure sterility of the prepared solution.

1. At doses levels of 0.1 mg/kg and 0.3 mg/kg, the **drug product BMS-936559 (MDX-1105)** will be **diluted with BOTH** the **supplied vehicle for BMS-936559 AND** with **Normal Saline** to a final drug concentration of 0.1 mg/mL and 0.3 mg/mL, respectively.
2. Calculate the necessary volumes for each: drug product, vehicle, and normal saline as follows:

A = Dose (mg/kg) (either 0.1 or 0.3)

B = Subject Weight (kg)

C = Concentration of the final infusion solution (mg/mL); **C = A**

D = Concentration BMS-936559 drug product in vial = 10 mg/mL

E = Total Drug to be Administered (mg); **E = A x B**

F = **Volume of Drug Product** Needed for Preparation (mL) i.e. E/D; **F = E / D**

G = Volume of Final Infusion Solution (mL); **G = B**

H = **Volume of Vehicle** Needed for Preparation (mL) = **[G - (0.4 x E)] / 6**

I = **Volume of Normal Saline** Needed for Preparation i.e., **I = (G - F) -H**

Example for a 70 kg subject at the 0.3 mg/kg dose

A) Dose = 0.3 mg/kg

B) Subject Weight = 70 kg

C) Concentration of the final infusion solution; **C = A**; **0.3 mg/ml**

D) Drug Product Concentration in the BMS-936559 vial = 10 mg/mL

E) Total Drug to be Administered = A x B = 70 kg x 0.3 mg/kg = 21 mg

F) Volume of Drug Needed for Preparation i.e. E/D= 21 mg/10 mg/mL=2.1 mL Drug Product

G) Volume of Final Infusion Solution; G = B =70 mL

H) **Volume of Vehicle Needed for Preparation** = [70 - (0.4 x 21)]/6 = (70 - 8.4)/6 = 61.6 / 6 = **10.27 ml Vehicle**

I) **Volume of Normal Saline** (G-F) -H=70 mL-2.1 mL-10.27 mL=**57.63 mL Normal Saline**

3. Allow the appropriate number of vials of drug product BMS-936559 (MDX-1105) and vehicle for BMS-936559 to stand at room temperature for approximately 5 minutes before preparation.
4. Ensure that the BMS-936559 (MDX-1105) solution is clear, colorless and essentially free from particulate matter on visual inspection. Ensure that the vehicle for BMS-936559 solution is clear and colorless.
5. Aseptically withdraw required volume of **normal saline** (0.9% sodium chloride) into a syringe and dispense into an empty i.v. bag.
6. Aseptically withdraw required volume of **vehicle** for BMS-936559 into a syringe and dispense into the i.v. bag containing normal saline. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring and repeated friction of plunger against syringe barrel wall)
7. Mix by GENTLY inverting several times.
8. Aseptically withdraw the required volume of BMS-936559 (MDX-1105) **drug product** into a syringe and dispense into the i.v. bag containing the vehicle for BMS-936559 and normal saline. [Do not enter into each vial more than once. Do not prepare BMS-936559 (MDX-1105) for infusion in glass syringes].
9. Mix GENTLY by inverting several times. DO NOT shake.
10. Visually inspect the prepared solution. If it is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.10) and documented on the Drug Accountability Log.
11. Record the time BMS-936559 (MDX-1105) was prepared on the i.v. bag label.
12. Record the dose level of BMS-936559 (MDX-1105) in mg/kg on the i.v. bag label
13. Attach the i.v. bag containing the BMS-936559 (MDX-1105) solution to the infusion set, 0.2 μm in-line filter, and infusion pump.
14. Infuse over 60 minutes as per general guidelines in section 7.7 above. [Do not administer study drug as an i.v. push or bolus injection.]

In the example of the 70 kg subject from above:

The total volume of 70 mL (G) would be infused in 60 minutes and the infusion rate would be adjusted to about 1.17 mL/min.

Please note the following:

- **It is recommended that study drug be administered shortly after preparation in order to avoid exposure of the *prepared drug to room temperature* conditions beyond the recommended *4 hour limit.* This 4 hour time limit at room temperature includes time allotted for IV dose administration. In the event that delayed administration of the prepared (diluted) study drug is anticipated, it can be refrigerated for a maximum of 12 hours.**

7.7.2 Preparation and Administration of BMS-936559 at Dose levels of 1, 3, and 10 mg/kg

Note: All subjects receiving the 10 mg/kg dose are to be pre-medicated with both 650 mg of acetaminophen and 25-50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to starting the infusion of BMS-936559 (MDX-1105).

15. For dose levels of 1, 3 and 10 mg/kg, the total dose to be administered will be diluted to a total volume of 60 mL in sterile **normal saline ONLY [Do Not use vehicle for these doses]**. In cases where the total volume of the dose is more than 60 mL, no additional dilution is necessary.
16. Calculate the necessary volumes for each: **drug product** and **normal saline** as follows:

    A = Dose (mg/kg) (either 1, 3, or 10 mg/kg)

    B = Subject Weight (kg)

    C = Total dose (mg); **C = A x B**

    D = Concentration BMS-936559 drug product in vial = 10 mg/mL

    E = **Volume of Drug Product** Needed for Preparation (mL) i.e. E/D; **E = C / D**

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F = Volume of Final Infusion Solution 60 mL

G = **Volume of Normal Saline** Needed for Preparation (mL); **G = 60 - E**

[If volume of drug product ≥ 60 mL, no additional saline is necessary]

Example for a 70 kg subject at the 3 mg/kg dose

A) Dose = 3 mg/kg

B) Subject Weight = 70 kg

C) Total dose **= A x B = 210 mg**

D) Concentration BMS-936559 drug product in vial = 10 mg/mL

E) **Volume of Drug Product** needed for Preparation (mL); **C/D** = 210 mg/10 mg/ml **= 21 mL Drug Product**

F) Volume of Final Infusion Solution 60 mL

G) **Volume of Normal Saline** Needed for Preparation (mL); 60 - E = 60 mL - 21 mL = **39 mL Normal Saline**

17. Allow the appropriate number of vials of drug product BMS-936559 (MDX-1105) to stand at room temperature for approximately 5 minutes before preparation.
18. Ensure that the BMS-936559 (MDX-1105) drug product solution is clear, colorless and essentially free from particulate matter on visual inspection.
19. Aseptically withdraw required volume of **normal saline** (0.9% sodium chloride) into a syringe and dispense into an empty i.v. bag.
20. Aseptically withdraw the required volume of BMS-936559 (MDX-1105) **drug product** into a syringe and dispense into the i.v. bag containing the normal saline. [Do not enter into each vial more than once. Do not prepare BMS-936559 (MDX-1105) for infusion in glass syringes].
21. Mix GENTLY by inverting several times. DO NOT shake.

22. Visually inspect the prepared solution. If it is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.10) and documented on the Drug Accountability Log.
23. Record the time BMS-936559 (MDX-1105) was prepared on the i.v. bag label.
24. Record the dosage of BMS-936559 (MDX-1105) in mg/kg on the i.v. bag label
25. Attach the i.v. bag containing the BMS-936559 (MDX-1105) solution to the infusion set, 0.2 μm in-line filter, and infusion pump.
26. Infuse over 60 minutes as per general guidelines in section 7.7 above. [Do not administer study drug as an i.v. push or bolus injection.]

In the example of the 70 kg subject at 3mg/kg from above:

The total volume of 60 mL would be infused in 60 minutes and the infusion rate would be 1 mL/min.

Note:

If the total dose calculated from the above formula is more than 600 mg, that means more than 60 mL of undiluted BMS-936559 is needed. In this case, all drug should be infused in 60 minutes at a rate > 1mL/min

Please note the following:

- **It is recommended that study drug be administered shortly after preparation in order to avoid exposure of the *prepared drug to room temperature* conditions beyond a recommended *4 hour limit.* This 4 hour time limit at room temperature includes time allotted for IV dose administration. In the event that a delayed administration of the prepared (diluted) study drug is anticipated, it can be refrigerated for a maximum of 12 hours.**

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7.8 Drug Accountability

BMS is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by BMS or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to BMS at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.9 Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) before any dose for MEL subjects enrolled in 0.1 and 0.3 mg/kg dose cohorts who meet criteria for intra-subject dose escalation as outlined in section 3.2. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 days after the last dose of the prior treatment cycle. If treatment is delayed more than 28 days due to non resolving toxicity then no more study therapy should be given. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is more than 2 days, the procedures at the next visit should be performed (the infusion at the original scheduled visit will be considered a missed dose).

7.10 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

7.11 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 TOXICITY AND MANAGEMENT

8.1 Dose Escalation

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg/dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3+3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. Depending on toxicity, an intermediate dose level may be defined by a protocol amendment. A subject who is withdrawn from the study during Cycle 1 for reasons other than a DLT will be replaced.

If 2 or more delayed DLTs, i.e., DLTs that occur after Cycle 1, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with Investigator and BMS approval (with subsequent IRB and FDA notification).

No dose escalations or de-escalations or dose adjustments are allowed for BMS-936559 (MDX-1105) except for weight changes (a 10% or greater change in weight [increase or decrease]) before any dose and for MEL subjects enrolled in 0.1 and 0.3 mg/kg dose

cohorts who meet criteria for intra-subject dose escalation as outlined in section 3.2. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

8.2 Dose-limiting Toxicity

A DLT is defined as a Grade 3 or higher study drug-related adverse event occurring within the first cycle (42 days) of dosing (excluding tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient [resolving within 6 hours of onset]) Grade 3 infusion adverse event) using National Cancer Institute (NCI) CTCAE version 3.0. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the adverse event.

A ≤ Grade 2 infusion reaction will not be considered a DLT.

Delayed DLTs are adverse events that meet the criteria of DLT and occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and BMS on an ongoing basis.

All adverse events that meet DLT criteria, as well as any ≥ Grade 3 unexpected toxicity (regardless of attribution), must be reported to BMS, within 24 hours using the same rapid notification procedures that are used for serious adverse events (Section 12.3).

8.3 Infusion Reactions

As of June 02 2011, the study team for the multiple ascending dose trial, CA210-001 has observed that fourteen subjects of the 150 subjects who had received at least one dose of BMS-936559 had infusion-related reactions; 1 subject of 27 treated in the 3 mg/kg treatment group and 13 subjects of 96 treated in the 10 mg/kg treatment group. All infusion-related reactions were Grade 1 or Grade 2 with the exception of a single Grade 3 event and all occurred within the first 3 doses of study therapy. A total of 3 subjects were discontinued from study drug treatment for recurrence of symptoms upon resuming the infusion, but the remaining subjects were able to resume and complete infusion after treatment without additional toxicity.

Based on these observations, **all subjects on this study receiving the 10 mg/kg dose must be pre-medicated with both 650 mg of acetaminophen and 25-50 mg of diphenhydramine (oral or IV) at least 30 minutes prior to the start of infusion of BMS-936559.** The pre-medication will be required for each infusion for the first 12

weeks of treatment. Pre-medication will be continued with subsequent treatments at the discretion of the investigator. Since the standard premedication for the 10mg/kg cohort was instituted, 2/62 (3%) subjects experienced infusion reactions (Grade 2) after premedication. All subjects responded and recovered with symptomatic treatment. Infusion reactions that persist for more than 24 hours after completion of the infusion or the need for hospitalization to manage the complications of infusion will be considered dose limiting. Exceptions will be granted only in situations where subjects have contraindications to diphenydramine or acetominophen after discussion with the Medical Monitor.

Infusion reactions should be graded according to CTCAE Version 3.0 allergic reaction/hypersensitivity. These reactions may manifest with signs and symptoms that may include but are not limited to fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be readily available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

In each case of an infusion reaction, the Investigator should institute treatment measures according to the best available medical practice. The following treatment guidelines are suggested:

CTCAE Grade 1

Treatment: Decrease the study drug infusion rate by 50% and monitor closely for any worsening. If infusion reaction recurs at this rate of infusion, the rate may be further reduced. The maximum time of infusion should not exceed 3 hours (180 minutes).

CTCAE Grade 2

Treatment: Stop study drug infusion. Administer epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and/or oxygen as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening. If infusion reaction recurs at this rate of infusion, the rate may be further reduced. The maximum time of infusion should not exceed 3 hours (180 minutes).

CTCAE Grade 3 or Grade 4

Treatment of Grade 3 or 4 Infusion Reaction: Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and/or oxygen as medically indicated. Contact the Medical Monitor and document as a serious adverse event. No further study drug treatment is to be administered.

Re-treatment with BMS-936559 (MDX-1105) Following Infusion Reactions

Once the study drug infusion rate has been decreased due to an infusion reaction (i.e., the subject has experienced a Grade 1 or 2 infusion reaction) the rate will remain decreased (i.e., a 2 hour infusion rather than a 1 hour infusion) for all subsequent infusions. If infusion reaction occurs in subjects treated with a 2 hour infusion, the infusion rate may be further decreased to administer BMS-936559 over 3 hours. Subjects treated with a 3 hour infusion may have subsequent infusions administered over a 2 hour time frame when at least two infusions given over three hours have been tolerated without reaction. Steroids should be used in subjects who continue to experience infusion reactions despite this further decrease in infusion rate.

If the subject has not been receiving any pre-medication, subsequent doses should be pre-medicated with 650 mg acetaminophen and 25-50 mg of diphenhydramine (po or IV) at least 30 minutes prior to infusion. If the subject is in the 10 mg/kg dose cohort and has, therefore, already been receiving acetaminophen/diphenhydramine pre-medication, consideration should be made to pre-medicate subsequent infusions with corticosteroid.

If the subject experiences a second allergic/infusion reaction at the reduced rate (regardless of Grade) despite pre-medication with acetaminophen, diphenhydramine, and corticosteroid, the infusion should be stopped and the subject should be discontinued from treatment.

If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from treatment. If there is any question as to whether an observed reaction is an allergic/infusion reaction of Grades 1 - 4, the medical monitor should be contacted immediately to discuss.

8.4 Possible Toxicities

As of 02-Jun-2011, 150 subjects have been treated in this study. The most frequent AEs reported included fatigue, nausea, diarrhea, decreased appetite, headache, and constipation. While the numbers are small, for most AEs (other than infusion reactions which occurred more frequently at the 10 mg/kg dose), there was no clear dose-related pattern with regard to the incidence, severity, or relationship of AEs. A total of 94 subjects (62.7%) experienced BMS-936559 treatment-related AEs; 12 (8.0%) experienced BMS-936559 that were considered Grade 3 or 4 in severity.

An event of special interest (EOSI) is considered a related AE that is either clinically important because the event requires greater vigilance and special management or because it is a common related AE. Events of special interest (EOSIs) reported in MDX1105-01 (CA210001) included sarcoidosis, infusion-related reactions, diarrhea, hypothyroidism, adrenal insufficiency, increased liver function tests (LFTs), myasthenia gravis, endophthalmitis, rash, and pruritus. There was no clear or consistent pattern in the incidence or severity of the EOSIs related to BMS-936559 dose level. In many of these drug-related events, prompt initiation of immunouppressives, such as corticosteroid should be considered

Infusion reactions/Allergic reaction/hypersensitivity: Fever, chills, shakes, itching,rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 8.5.

9 COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

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10 CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

a. Prophylactic anti-emetics, with the exception of steroids (only allowed to treat infusion reactions), may be administered at the discretion of the treating physician before all doses of study drug anytime after the first dose of Cycle 1.
b. Granulocyte colony-stimulating factor or granulocyte-macrophage colony stimulating factor is not permitted for prophylaxis or to treat Grade 4 neutropenia during Cycle 1.
c. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
d. New Chemotherapy or immunotherapy other than study drug is not permitted.
e. Palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered after consultation with the Medical Monitor.
f. The use of live vaccines while on study is prohibited. The use of any killed or attenuated vaccines for the prevention of influenza is permitted at any time without a study drug washout interval. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis and must be discussed with the medical monitor prior to its use. A washout interval prior to and post vaccination may be required in these instances. Any vaccinations administered while on study must be documented in the subject's medical records and recorded in the Case Report Form.
g. Subjects on immunosuppressive oral or parenteral corticosteroids must be tapered off immunosuppressive doses (> 10 mg/day of prednisone or equivalent) of the medication 2 weeks before the first dose of BMS-936559 (MDX-1105) and must remain off all immunosuppressive doses of oral and parenteral corticosteroids while the subject is on the study (unless required for the treatment of infusion reactions, irAEs, or other adverse events).
h. Denosumab therapy is not permitted, however, bisphosphonates such as zoledronic acid are permitted.

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page.

10.1 Treatment of Isolated Lesions

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2. All interventions should be discussed in advance with the BMS Medical Monitor.

11 STUDY EVALUATIONS

11.1 Study Procedures by Visit

11.1.1 Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points, as described in Sections 11.1.2 through 11.2.3. The Time and Events Schedule (Tables 1 and 2) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 3) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and electrocardiogram (ECG) performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936559 (MDX-1105) need not be repeated.

11.1.2 Screening Period

Subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Demographics and medical history (to include collection of prior medication, medications administered to the subject during the Screening period, and prior and concurrent medical conditions)
- Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- A biopsy to confirm diagnosis if there is no historical documentation available.
- Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires informed consent by the subject
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Inclusion/exclusion criteria
- Serum β-HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Vital sign measurements including temperature, pulse, and resting systolic and diastolic blood pressure
- ECOG performance status
- Physical examination (to include height and weight)
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Brain CT scan/MRI (MRI preferred) not required for subjects with epOC unless clinically indicated. Baseline imaging should be done at the same institution/facility which will be used to measure response during the subject's participation in the study.
- Bone scans (if clinically indicated)
- 12-lead ECG

- Clinical laboratory tests ([central laboratory]:
  - Hematology: Complete blood count with differential (including absolute lymphocyte count) and direct platelet count.
  - Chemistry: Albumin
    SGOT (AST)
    SGPT (ALT)
    Bilirubin (direct and total)
    Calcium
    Creatinine
    Glucose
    Lactate dehydrogenase (LDH)
    Total protein
    Urea nitrogen (BUN)
    Uric acid
  - Electrolytes (sodium, potassium, chloride, and bicarbonate)
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.
    Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
  - Hepatitis B and C testing;

- Concomitant medications

11.1.3 Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Tables 1 and 2). Subjects who meet the selection criteria may start BMS-936559 (MDX-1105) treatment within 28 days of Screening. Subjects will receive 1 dose of BMS-936559 (MDX-1105) every 14 days for a total of 3 doses/cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of BMS-936559 (MDX-1105) will be determined as summarized in Section 3.3. Results of assessments **must** be reviewed and documented before administering the first dose of the next cycle. No subject will be permitted dose escalations or de-escalations except dose adjustment due to 10% or more weight change (increase or decrease) before any dose or subjects in the 0.1 mg/kg or 0.3 mg/kg

expansion cohorts as stipulated in section 3.2. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.4). Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 2 or more days) or missed doses, see Section 7.7 for administration details. A subject who misses a dose during Cycle 1, not due to a DLT, will be replaced.

11.1.3.1 Cycle 1

Cycle 1 will begin with the first i.v. infusion of BMS-936559 (MDX-1105) (Day 1) and will continue through to the Day 42 evaluations. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 3 infusions (Days 1, 15, and 29) with a response assessment between Days 38 and 42.

During Cycle 1, the following evaluations will be performed as indicated in Table 1 and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure will be obtained preinfusion and postinfusion as defined in the Time and Events Schedule (Table 1).
- ECOG performance status (to be conducted before infusion on infusion days)
- Physical examination
- Weight
- Tumor imaging (CT/MRI chest/abdomen/pelvis) at the end of Cycle 1
- Brain CT scan/MRI (MRI preferred) if there is a prior history of lesions present at Screening or as clinically indicated. Brain scan will not be required at the end of Cycle 1 if positive at Screening unless clinically indicated.
- Bone scan (if clinically indicated). Bone scan will not be required at the end of Cycle 1 if positive at baseline unless clinically indicated.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- 12-lead ECG
- Urine pregnancy test to be performed locally (pre-infusion) (for all women of childbearing potential; urine pregnancy test must be negative to continue).
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. (Postinfusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity as outlined in Table 3.

- Flow cytometry: to include but may not be necessarily limited to the analysis of T- and B cell subpopulations. Assays will include but are not limited to phenotypic markers (CD3, CD4, CD8, CD16, CD19, CD14, CD16+56 [NK]).
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma (optional for exploratory immune function evaluation): Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein-Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity and biomarker testing will be governed by type of tumor and availability of test antigens.
- Clinical laboratory tests (local and central laboratories). The results of hematology and chemistry **must be performed and reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site([i.e., contralateral arm) on the days of infusion:
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Urinalysis (as outlined in Section 11.1.2)
- Immune Safety Assays: rheumatoid factor, adrenocorticotropic hormone, thyroid stimulating hormone, free T4 level, C-reactive protein, antinuclear antibody titer and pattern.

  The following tests may also be performed to further characterize immune safety associated with adverse events or from treatment: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50;
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Blood sample for SNP analyses
- Serum for subsequent cytokine panel assays: may include: IL-1, 2, 4, 5, 6, 10, 13, IFN gamma, TNF alpha, TGF beta, CXCL-9, and CXCL-10
- Blood Sample quantitative PCR: Samples will be analyzed for gene expression profiling
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Response assessment and documentation
- Adverse event assessment including specific elicitation of symptoms (see Appendix 3) that may be indicative of irAEs.

11.1.3.2 Cycle 2 to 16

Following Cycle 1, subjects in stable condition will receive additional cycles of BMS-936559 (MDX-1105) (Cycles 2 to 16) until CR, confirmed and worsening PD, development of a ≥ Grade 3 study drug-related CTCAE, intolerability to therapy, or other reason for subject discontinuation from the study. Subjects who achieve a confirmed CR at any time after Cycle 1 will not receive further cycles and will be followed as described in Tables 1 and 2. Visits for Cycles 2 to 16 will occur every 14 days. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.4).

During Cycle 2 and subsequent cycles, the following evaluations will be performed as indicated in Table 2, and the results recorded on the CRF:

- Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure as defined in Table 2.
- ECOG performance status
- Urine pregnancy test (for all women of childbearing potential, to be performed locally; urine pregnancy test must be negative to continue)
- Physical examination
- Weight (Changes to study drug dose will only be made if there has been a 10% or greater change in weight [increase or decrease] since the previous dose.)
- 12-lead ECG
- Tumor imaging (CT/MRI Chest/Abdomen/Pelvis)
- Brain scan CT scan/MRI (MRI preferred) as clinically indicated
- Bone scan, if clinically indicated. If the bone scan is positive at baseline, additional bone scans will be performed every other cycle (end of Cycle 2, 4, 6, etc.), to confirm CR or PR or as clinically indicated and not done within the preceding 28 days.
- Cryopreserved PBMCs for exploratory immune function evaluation (as outlined in Section 11.1.3.1)
- Serum sample for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3. Samples should be drawn from a site other than the infusion site (i.e., contralateral arm).
- Serum sample for immunogenicity as outlined in Table 3.
- Optional tumor or other biopsy (as outlined in Section 11.1.2)
- Flow cytometry

- Serum for subsequent cytokine panel assays: may include: IL-1, 2, 4, 5, 6, 10, 13, IFN gamma, TNF alpha, TGF beta, CXCL-9, and CXCL-10
- Quantitative PCR: Blood samples will be analyzed for gene expression profiling
- Clinical laboratory tests ([local and central laboratories]; the results of hematology and chemistry **must be reviewed before dosing**. Any new ≥ Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples to be drawn from a site other than the infusion site (i.e., contralateral arm):
  - Hematology with differential (as outlined in Section 11.1.2)
  - Chemistry (as outlined in Section 11.1.2)
  - Immune Safety Assays (as outlined in Section 11.1.3.1)
  - Urinalysis (as outlined in Section 11.1.2)

- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- BMS-936559 (MDX-1105) infusions
- Concomitant medications
- Adverse event assessment

11.1.4 Follow-up

There are 5 follow-up visits as indicated in Tables 1 and 2. The maximum duration of follow-up will be approximately 1 year. All subjects should complete follow-up Visit 1 (7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2-5 will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (see Section 3, Overview of Study), all subjects will be followed from the last visit for 1 year until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2), and at Follow-up Visit 2 only pharmacokinetic and immunogenic evaluations will be performed, and adverse events will be collected.

The following evaluations will be performed as indicated above and in Tables 1 and 2, and the results recorded on the CRF:

- Serum β-HCG pregnancy test
- Serum sample for immunogenicity as outlined in Table 3
- Serum samples for pharmacokinetic evaluation of BMS-936559 (MDX-1105) as outlined in Table 3
- Vital sign measurements
- ECOG performance status
- Physical examination
- 12-lead ECG
- Tumor imaging
- Brain scan (MRI preferred) as clinically indicated.
- Bone scan if clinically indicated and not done within the preceding 28 days.
- Clinical laboratory tests as outlined in Section 11.1.2.
- Flow cytometry
- Blood tests of CEA and CA-19-9 for CRC subjects or CA-125 for epOC subjects.
- Concomitant medications
- Adverse event assessment

11.1.5 Cycle 1 Treatment Completion

Subjects will be considered to have completed Cycle 1 treatment if they have:

- Completed 3 doses of BMS-936559 (MDX-1105) in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received.

11.1.6 Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject completion status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject lost to follow-up
- Death
- Other

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should complete Follow-up Visits 1 and 2 to be monitored for 70 days following the last dose of BMS-936559 (MDX-1105) for the occurrence of study drug-related adverse events or other clinically significant adverse event. Subjects who are unable to complete the follow-up visits should be contacted at least once within 70 days following the last dose of BMS-936559 (MDX-1105). Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.

11.1.7 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with the protocol

- Disease progression as defined in Section 3.3
- Significant clinical deterioration

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

11.2 Safety Evaluations

Safety assessments will be based on medical review of adverse events and lab abnormality reports. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

The following evaluations will be performed during the study to measure the safety and tolerability of BMS-936559 (MDX-1105): vital sign measurements, clinical laboratory tests, pregnancy tests, ECOG performance status evaluations, diagnostic imaging, physical examinations, ECGs, and the incidence and severity of adverse events. Given the intended mechanism of action of BMS-936559 (MDX-1105), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, uveitis, or other irAEs. Ophthalmologic examinations should be performed, when clinically indicated, for signs or symptoms of uveitis. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

11.2.1 Immune Safety

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of BMS-936559 (MDX-1105)-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol. Blood samples for immunogenicity analysis will be collected from all subjects at predose

on Day 1, predose on Cycle 2 Day 1 and all follow-up Visits. Samples will be evaluated for development of Anti-Drug Antibody (ADA) in subjects.

11.2.2 Immunogenicity

Immunogenicity refers to the development of an immune response to the BMS-936559 (MDX-1105) drug itself, and is characterized by antibodies that the subject may develop that react with BMS-936559 (MDX-1105). These may result in more rapid clearance of BMS-936559 (MDX-1105) from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with BMS-936559 (MDX-1105) at a later date.

11.2.3 Exploratory Immune Function Evaluations

Samples will be analyzed by flow cytometry, as well as collected for cryopreservation of lymphocytes and plasma and stored for future research (requires specific agreement by the subject in the informed consent), which may include disease-related biomarkers (or antibody responses to selected antigens), and exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Samples for measurement of single nucleotide polymorphisms (SNP) of genes will be collected to evaluate potential associations of genes involved in the immune response with clinical outcome and/or safety.

Peripheral blood samples will be collected to evaluate pharmacodynamic effects using gene expression profiling of mRNA and/or qPCR, and potential associations with clinical outcome.

Blood samples will be collected to evaluate the pharmacodynamic effects on serum cytokines/chemokines such as, but not limited to, IL-1a, IL-2, IFN-g, IL-10, CXCL-9, and CXCL-10 and potential associations of these markers with clinical outcome after treatment with MDX-1105.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia), requiring specific agreement by the subject in the informed consent, may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected

before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

11.3 Efficacy Evaluations

Tumor response will be assessed using RECIST with modifications as detailed in Appendix 2. Independent review of tumor assessments may be requested at the discretion of BMS.

Tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9) will be measured in subjects in the respective expansions cohorts.

The kinetics of objective tumor responses to active immunomodulatory agents appears to be different than that seen with standard chemotherapy or targeted agents. The activation of a potent anti-tumor immune response may require weeks to optimally mature. During this time, some lesions may show enlargement (either due to true tumor growth or to an enhanced inflammatory infiltrate), that would usually be interpreted as true PD, while other lesions may show regression or stability. Yet, with continued treatment, all the lesions may subsequently show regression or stabilization as the full force of the anti-tumor immune response matures. Therefore, subjects with initial tumor volume increase and apparent early progression (during the sixth week of a cycle), but with stable or improved performance and clinical status, will continue to be treated with study drug (as deemed appropriate by the Investigator) for an additional cycle until the next scheduled imaging assessment to confirm progression. In this study, subjects with PD, but without rapid clinical deterioration, will continue to be treated with study drug and clinically observed with an imaging schedule of every 6 weeks to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of BMS-936559 (MDX-1105) and more likely capture its true potential to induce clinical responses.

11.4 Pharmacokinetic Evaluations

Pharmacokinetic parameters include AUC(0-T), AUC(INF), AUC(TAU), AI, Cmax, Cmin, Tmax, T-HALF, Vss, and CLT.

Blood samples for the analysis of serum concentrations of BMS-936559 (MDX-1105) will be drawn in all subjects according to the schedule listed below and in Table 3. Serum samples should be drawn from a site other than the infusion site (i.e., contralateral arm)

on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

Subjects who had screening baseline hemoglobin levels less than 10 g/dL will be excluded from collecting intensive PK sampling.

11.4.1 Cycle 1- 3

Intense sampling will be collected in 10 subjects each at the 0.1, 0.3, 1, and 3 mg/kg dose levels and 3 subjects in each of the 4 cohorts at the 10 mg/kg level (total n=12 @ 10 mg/kg).

- **Cycle 1**
  - **Day 1**: pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.
  - **Days 2, 3, 4 and 8**: Single serum samples will be taken on each day.
  - **Days 15 and 29**: single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
- **Cycle 2**
  - **Day 1:** pre-dose (within 30 minutes before infusion), at the end of infusion, and at 30, 60, 120, and 240 minutes after the infusion.
  - **Days 3 and 8:** single serum samples will be taken on each day.
  - **Day 15:** single serum samples to be taken within 30 minutes before the BMS-936559 (MDX-1105) infusion.
- **Cycle 3**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.

Cycle 4 Day 1 (predose) and every other cycle Day 1 (predose) for first year or discontinuation.

Every 4 cycles Day1 (predose) for next year or discontinuation.

Sparse PK sampling: All other subjects in each cohort

- **Cycle 1**
  - **Days 1 and 15**: single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
  - **Days 3 and 8**: single serum samples will be taken on each day.

- **Cycle 2**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
- **Cycle 3**
  - **Day 1:** single serum samples to be taken within 30 minutes before and immediately at the end of each BMS-936559 (MDX-1105) infusion.
- Cycle 4 Day 1 (predose) and every other cycle Day 1 (predose) for first year or discontinuation.
- Every 4 cycles Day1 (predose) for next year or discontinuation.

11.4.2 Follow-up Visits

- **Follow-up Visits 1 and** 2: single serum samples to be taken.

12 ADVERSE EVENT REPORTING

Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1 Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be study drug-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 3.0.[46] If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 3 and reported in the study report.

A laboratory abnormality is considered an adverse event if it results in

- discontinuation from study drug,
- necessitates therapeutic medical intervention,
- if the Investigator assesses the abnormality as an adverse event, or
- any laboratory test that is clinically significant or meets the definition of an SAE

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value). These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

27. Description

28. Duration (start and end dates)

29. CTCAE Grade 1 through 5 or severity if CTCAE is not available

30. Relationship to the study drug - related or not related

31. Action(s) taken with study drug

32. Whether event was serious

33. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as “not related” or “related”. The Investigator is responsible for determining the study drug relationship for

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each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken with study drug in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

0 No action taken
2 Study drug permanently discontinued due to this adverse event
6 Study drug temporarily interrupted
7 Study drug dosage adjusted

12.1.1 Safety Reporting For Adverse Events

All adverse events or other clinically significant adverse events occurring up to 70 days after administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Study drug-related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only study drug-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects > 70 days after the administration of the last dose of study drug

A *nonserious adverse event* is an AE not classified as serious.

The collection of nonserious AE information should begin at initiation of study drug and should conclude 70 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 12.3). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

12.2 Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. is fatal or life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.5.1 or reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; or hospitalization to facilitate the work up of a Grade 1 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3 Rapid Notification of Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures.

12.3.1 Reporting Responsibility

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment; or during the 70 days following study drug administration; or within 30 days of the last visit for screen failures must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Each serious adverse event must be reported by the Investigator to the BMS Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring after 70 days from the last dose of BMS-936559 (MDX-1105) must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to BMS within 24 hours of receiving the information. BMS, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2 Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to BMS or its designee. The study monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. BMS or designee will communicate serious adverse events to the study sites as required by regulatory authorities.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

12.3.3 Contact Persons and Numbers

The BMS Central Emergency Contact telephone and SAE telefax numbers are listed on the cover page of the protocol.

12.4 Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5 Pregnancy

Pregnancy testing must be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive BMS-936559 (MDX-1105) and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the study Treatment Period part of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the study Treatment Period part of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.5.1.

Follow-up information regarding the course of the pregnancy, including prenatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

12.6 Rapid Notification of Adverse Events of Special Interest (EOSI)

An event of special interest (EOSI) is considered a related AE that is either clinically important because the event requires greater vigilance and special management or because it is a common related AE. Events of special interest (EOSIs) reported in MDX1105-01 (CA210001) included sarcoidosis, infusion-related reactions, diarrhea, hypothyroidism, adrenal insufficiency, increased liver function tests (LFTs), myasthenia gravis, endophthalmitis, rash, and pruritus. There was no clear or consistent pattern in the incidence or severity of the EOSIs related to BMS-936559 dose level.

In addition to serious adverse events, the following adverse events will be reported to the BMS clinical team within 24 hours even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT

- ≥ Grade 2 diarrhea/colitis
- ≥ Grade 3 irAE other than diarrhea/colitis
- Any potential Hy's Law case (> 3 x ULN of either ALT/AST with concurrent >2 x ULN of Total Bilirubin and lack of alternate etiology)

12.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 12.3.2. for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

12.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size Determination

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level during dose escalation.

Up to 15 expansion cohorts will be enrolled and a total of 16 subjects (32 subjects each will be enrolled at 1mg/kg and 3 mg/kg and 16 subjects in the 10 mg/kg new NSCLC cohorts) will be enrolled for each expansion cohorts. With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 80% confidence interval for an objective response rate would be (3.4%, 30%) if 2 (12.5%) subjects had a response, (7.1% to 37%) if 3 (19%) subjects had a response, (11.4% to 44%) if 4 (25%) subjects had a response and (16.1% to 50%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 80% confidence interval for an objective response rate would be (3.5% to 19.7%) if 3 (9.4%) subjects had a response, (5.6% to 23.4%) if 4 (12.5%) subjects had a response, and (7.8%, 27.1%) if 5 (16%) subjects had a response.

If the true ORR in NSCLC is 15% then with 16 NSCLC patients in each cohort of specific histology and dose, there is 71.5% chance of observing at least 2 responses, and 44% chance of observing at least 3 responses, and there is 28.4% chance of observing 0 or 1 responses (false negative rate). If the true ORR in NSCLC is 5% rather than 15%, then there is 19% and 4.4% chance that there will be at least 2 or at least 3 responses respectively in 16 subjects (false positive rate).

13.2 Populations for Analyses

- *All Enrolled Subjects*: All subjects who sign an informed consent form.
- *All Treated Subjects*: All subjects who receive at least one dose of study medication.
- *Pharmacokinetic Subjects*: All subjects who receive at least once dose of study medication and have available serum concentration data.
- *Response-Evaluable Subjects*: All subjects who received at least one dose of study medication and i) have measureable disease at baseline, and ii) have at least one screening (i.e. baseline) and one on-study tumor assessment or documented clinical disease progression/death.

- *Immunogenicity Subjects*: All subjects who receive at least one dose of study medication and have available ADA data
- *Biomarker Subjects*: All subjects who receive at least one dose of study medication and have available biomarker data

13.3 Endpoint Definitions

13.3.1 Safety Endpoints

- Incidence of adverse events: all non-serious adverse events will be collected from Day 1 until 70 days after the subjects last dose of BMS-936559 or until they discontinue the study. [Week 1 - Week 214] All serious adverse events must be collected from the date of the subjects' written consent until 70 days after discontinuation of dosing or until they discontinue the study. [Week -4 - Week 214]
- Incidence of dose limiting toxicities. [Week 1 - Week 7]
- Incidence of clinical laboratory test abnormalities including hematology and serum chemistry abnormalities. [Week 1 - Week 214]
- Mean changes from baseline and standard deviations for scheduled vital sign assessments including blood pressure and heart rate measurements. [Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, and 155]

13.3.2 Efficacy Endpoints

The objective response rate (ORR) and corresponding 90% confidence interval for each tumor type and dose level as assessed during the initial treatment period and follow-up. [Week 1 - Week 153] The ORR is defined as the number of subjects with a BOR of PR or CR divided by the number of treated subjects.

13.3.3 Pharmacokinetic Endpoints

Geometric means and coefficients of variation for the pharmacokinetic parameters of Cmin, Cmax, Ceoinf, and AUC(TAU). [Week 1 - Week 214]

Pharmacokinetic of BMS-936559 (MDX-1105) will be derived from plasma concentration versus time. The following pharmacokinetic parameters will be estimated and reported:

AUC(0-T)	Area under the plasma/serum drug concentration-time curve from t=0 to last measurable sampling time.
AUC(INF)	Area under the plasma/serum concentration-time curve from t=0, extrapolated to infinity.
AUC(TAU)	Area under the concentration-time curve in one dosing interval
AI	Accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose.
Cmax	Maximum observed concentration in plasma.
Tmax	Time to reach Cmax in plasma.
T-HALF	Terminal-phase elimination half-life in plasma.
Vss	Volume of distribution at steady state
CLT	Total body clearance of drug from plasma.

Individual subject pharmacokinetic parameter values will be derived by non-compartmental method by a validated pharmacokinetic program.

13.3.4 Immunogenicity Endpoints

Frequency of subjects who have an increase in the anti-drug antibody levels from baseline. [Week 1 - Week 214]

13.4 Analyses

13.4.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, and ECOG status will be summarized by dose using descriptive statistics.

13.4.2 Safety Analyses

All recorded adverse events will be listed and tabulated for the worst CTC grade by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test

results will be listed and summarized by and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided.

13.4.3 Efficacy Analyses

All available tumor measurement data will be listed. Individual best overall response (BOR) will be listed and tabulated by tumor type and dose cohort for all treated subjects with measurable disease at baseline. Changes in tumor burden will be presented graphically for each tumor type. The objective response rate (ORR), disease control rate (DCR) and corresponding 90% confidence intervals will be reported by tumor type and dose cohort. The ORR is defined as the number of subjects with a BOR of PR or CR divided by the number of treated subjects. The DCR is defined as the number of subjects with a BOR of CR, PR, or SD $\geq$ 12 weeks divided by the number of treated subjects.

Duration of response, defined as the time between the date of first response and the date of disease progression or death, whichever occurs first, will be computed for subjects with a BOR of CR or PR. Time to response, defined as the time between the date of first dose of study therapy and date of first objective response, will be computed for all subjects with a BOR of CR or PR. PFS, defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first, will be computed for all treated subjects with measurable disease at baseline. Medians and corresponding two-sided 95% confidence intervals will be reported for duration of response, time to response and PFS by tumor type and dose and analyzed using Kaplan-Meier methods.

Summary statistics and plots of measures of tumor specific antigen levels for epOC (CA-125) and CRC (CEA and/or CA19-9), may be provided for specific tumor types according to data availability.

Efficacy analyses will be based on RECIST with modifications (see Appendix 2) according to tumor assessment data collected from subjects during the initial treatment period and follow-up period until disease progression. Additional efficacy analyses will be performed based on immune-related response criteria, irRECIST, (see Appendix 3) using immune related efficacy measures, such as immune-related BOR (irBOR), immune-related PFS (irPFS) and immune-related DCR (irDCR). Sensitivity analyses may

be performed on response evaluable subjects and on the population of subjects who enter the retreatment period.

13.4.4 Immunogenicity Analysis

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive anti-drug antibody (ADA) at any timepoint will be provided by tumor type and by dose. The frequency of subjects with at least one positive ADA assessment, and frequency of subjects with an increase in ADA levels from baseline will be provided by tumor type and by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between concentrations of BMS-936559 and ADA assessments may be explored.

13.4.5 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936559 (MDX-1105) on Cycle1 Day1 and Cycle 2 Day 1 by dose. Geomeric means and coefficients of variation will be presented for Cmax, CLT, AUC(0-T), AUC(INF), AUC(TAU), and AI. Median, minima, maxima will be presented for Tmax. Mean and standard deviations will be provided for T-HALF and Vss. To describe the dependency on dose, scatter plots of Cmax, AUC(0-T), and AUC(INF) versus dose will be provided.

Summary statistics will be tabulated for the trough (Cmin) concentration and end of infusion (EOI) concentration of BMS-936559 (MDX-1105) by dose and study day. To assess the attainment of steady state, geometric mean Cmin values will be plotted versus study day by dose.

Dose proportionality will be assessed by estimating the slope of linear regression of BMS-936559 (MDX-1105) log(Cmax) on log(dose) and of log(AUC(INF)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameters (slope of the linear regression) will be calculated.

Data describing the plasma concentration versus time from this study may be used for future population pharmacokinetic evaluations of the drug which may be reported separately.

13.4.6 Exploratory Biomarkers Analyses

Summary statistics for immune function and other exploratory markers, such as but not limited to serum cytokines/chemokines, flow cytometry, and mRNA profiling, and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored.

Possible associations of various measures (baseline value or change from baseline) of biomarkers including serum cytokines/chemokines, SNP, mRNA profiling with clinical outcome (eg, tumor response) may be explored based on data availability, using response-evaluable subjects, to explore potential predictive markers. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability. Associations of such measures with safety events of interest (e.g. irAE) may also be explored graphically based on data availability.

14 ETHICAL ASPECTS

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with BMS SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation/Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

14.2 Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to BMS or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of BMS, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

14.4 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion

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and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

15 ADMINISTRATIVE REQUIREMENTS

15.1 Protocol Amendments

The study shall be conducted as described in this approved protocol. Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the BMS monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., BMS staff versus a contract research organization [CRO]); and
2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2 Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a BMS representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the BMS monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. BMS monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of

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efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

15.4 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to BMS or its designee.

All entries to the CRFs must be made clearly in black ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

If Electronic Data Capture (EDC) system is deployed, the electronic CRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor

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- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

15.5 Auditing Procedures

In addition to the routine monitoring procedures, BMS, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. BMS, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS immediately that this request has been made.

15.6 Publication of Results

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

15.7 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by BMS or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by BMS (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, except to the

extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.8 Discontinuation of Study

BMS reserves the right to discontinue any study for any reason at any time.

15.9 Data Management

15.9.1 Data Collection

Investigators must enter the information required by the protocol onto the BMS CRFs that are printed on "no carbon required" paper. BMS monitors or designees will review the CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to BMS, or its designee, with 1 copy retained at the investigational site.

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.9.2 Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following BMS, or its designee, data management procedures. Obvious errors will be corrected by BMS personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the investigational site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the BMS study team.

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APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	dead

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APPENDIX 2 RECIST WITH MODIFICATIONS

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently (adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). All other lesions (or sites of disease) should be identified as non-target

lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response PR = partial response SD = stable disease and PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.”

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on bone scans, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). • **Longest diameter for target lesions**—The sum of the longest diameter for all target lesions (SLD). • **Complete response**—Disappearance of all target lesions. • **Partial response**—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • **Stable disease**—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • **Progressive disease**—At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since screening (nadir), or the appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA
Nontarget lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. • Complete response—Disappearance of all nontarget lesions. • Incomplete response/stable disease—Persistence of one or more nontarget lesion(s). • Progressive disease—Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. For this study PD must be confirmed unless subject has rapid clinical deterioration. • UE/ND/NA

continued

Definitions *(continued)*

Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.
Computed Tomography and Magnetic Resonance Imaging	CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not “selected” images of the apparent lesion. All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.

continued

Definitions *(continued)*

Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Approved v8.0 930041404 8.0

APPENDIX 3 IMMUNE-RELATED RECIST

Immune-related RECIST (irRECIST) is derived from modified RECIST conventions.

Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at Screening and at the defined tumor assessment time points (see Table 1). Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRECIST.

Measurable Lesions

Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques, or as ≥10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.

Non-Measurable Lesions

Non-target lesions not classified as measurable lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.

Definitions of Index/non-Index Lesions

Index Lesions

Measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Longest Diameters (SLD) for all index lesions will be

calculated and considered the baseline SLD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment.

Non Index Lesions

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.

Calculation of Sum of Longest Diameters (SLD)

Sum of Longest Diameters is an estimate of tumor burden. The greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SLD is calculated as the sum of the longest diameters for index tumor lesions. Several variations of the SLD are identified for the purpose of classification of tumor responses.

SLD at Baseline: The sum of the longest diameters for all index lesions identified at baseline prior to treatment on Day 1.

SLD at tumor assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the SLD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SLD at tumor assessment (irSLD).

SLD at NADIR: For tumors that are assessed more than 1 time after baseline, the lowest value of the SLD (SLD Baseline or SLD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SLD at tumor assessment using the irRECIST for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRECIST accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the ir-response as defined by the Investigator will serve as the basis of exploratory efficacy analyses and guide clinical care.

Definition of Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), which is defined as a decrease, relative to baseline, of 30% or greater in the sum of the longest perpendicular diameters of all index and all new measurable lesions (ie, Percentage Change in Tumor Burden), in the absence of irCR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SLD increases by ≥ 20% when compared to SLD at nadir

Immune-related Stable Disease (irSD), which is defined as not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD)

Immune-related Progressive Disease (irPD), which is defined as at least a 20% increase in Tumor Burden (ie, taking sum of the products of all index lesions and any new measurable lesions) when compared to SLD at nadir.

Definition of Non-Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all non-index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), non-index lesion(s) are not considered in the definition of PR, this term does not apply.

Immune-related Stable Disease (irSD), non-index lesion(s) are not considered in the definition of SD, this term does not apply.

Immune-related Progressive Disease (irPD), increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until Tumor Burden increases by

20% (ie, the SLD at nadir of index lesions and any new measurable lesions increases by the required amount).

Impact of New Lesions on irRECIST

New lesions alone do not qualify as progressive disease. However their contribution to total tumor burden is included in the SLD which in turn feeds into the irRECIST for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRECIST Will Be Based on the Following Criteria:

- **Immune-related Complete Response (irCR):** Complete disappearance of all tumor lesions (index and non-index), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.
- **Immune-related Partial Response (irPR):** The sum of the longest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the longest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Longest Diameters (irSLD). A decrease, relative to baseline of the irSLD of 30% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first irPR.
- **Immune-related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-related Progressive Disease (irPD):** It is recommended in difficult cases (eg, increase in SLD or irSLD accompanied with significant individual lesion regression, "mixed response", or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
  - At least 20% increase in the SLD of all index lesions over nadir SLD calculated for these lesions.
  - At least a 20% increase in the SLD of all index lesions and new measurable lesions (irSLD) over the nadir SLD calculated for the index lesions.

irRC Definitions

Index Lesion Definition	Non Index Lesion Definition	New Measureable Lesions	New Unmeasureable Lesions	% Change in irSLD Tumor Burdon (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≤ -30%	irPR
				> -30% to < +20%	irSD
				≥ +20%	irPD
Stable Disease	Any	Any	Any	> -30% to < +20%	irSD
				≥ +20%	irPD
Progressive Disease	Any	Any	Any	≥ +20%	irPD

Best Overall Response and Date of Progression Using irRECIST (irBOR)

The Investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the Investigators.

APPENDIX 4 PRE-EXISTING AUTOIMMUNE DISEASES

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g. acute Lyme arthritis). Please contact the medical monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

- Acute disseminated encephalomyelitis
- Addison's disease
- Alopecia universalis
- Ankylosing spondylitis
- Antiphospholipid antibody syndrome
- Aplastic anemia
- Asthma
- Autoimmune hemolytic anemia
- Autoimmune hepatitis
- Autoimmune hypoparathyroidism
- Autoimmune hypophysitis
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune thrombocytopenic purpura
- Behcet's disease
- Bullous pemphigold
- Celiac disease
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Chung-Strauss syndrome
- Crohn's disease
- Dermatomyositis
- Diabetes mellitus type 1
- Dysautonomia
- Eczema
- Epidermolysis bullosa acquista
- Gestational pemphigoid
- Giant cell arteritis
- Goodpasture's syndrome
- Graves' disease
- Guillain-Barré syndrome
- Hashimoto's disease
- IgA nephropathy
- Inflammatory bowel disease
- Interstitial cystitis
- Kawasaki's disease
- Lambert-Eaton myasthenia syndrome
- Lupus erythematosus
- Lyme disease - chronic
- Meniere's syndrome
- Mooren's ulcer
- Morphea
- Multiple sclerosis
- Myasthenia gravis
- Neuromyotonia
- Opsoclonus myoclonus syndrome
- Optic neuritis
- Ord's thyroiditis
- Pemphigus
- Pernicious anemia
- Polyarteritis nodusa
- Polyarthritis
- Polyglandular autoimmune syndrome
- Primary biliary cirrhosis
- Psoriasis
- Reiter's syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Stiff-Person syndrome
- Takayasu's arteritis
- Ulcerative colitis
- Vitiligo
- Vogt-Kovanagi-Harada disease
- Vulvodynia
- Wegener's granulomatosis

STATISTICAL ANALYSIS PLAN

A Phase 1, Open-label, Multicenter, Dose-escalation, Multidose Study of BMS-936559 (MDX-1105) Administered Every 14 Days in Subjects with Selected Advanced or Recurrent Solid Tumors

PROTOCOL CA210-001

VERSION 1.1

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1 BACKGROUND AND RATIONALE

CA210-001 is an open-label, multicenter, dose-escalation, and multi-dose study of BMS-936559, a fully human monoclonal IgG4 antibody targeting the Programmed Death - Ligand 1 (PD-L1) membrane receptor on T lymphocytes and other cells of the immune system. Anti-tumor immunotherapy via PD-L1/PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Eight tumor types (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], epithelial ovarian cancer [epOC]), gastric cancer [GC], pancreatic cancer [PC] and breast cancer [BC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1 pathway is important for tumor progression.

Research Hypothesis:

There is no formal research hypothesis to be statistically tested. The purpose of this study is to evaluate the safety and tolerability of BMS-936559 in subjects with selected advanced or recurrent solid tumors. It is also expected that the Maximum Tolerated Dose (MTD) or maximum administered dose will be determined following DLT evaluation.

Schedule of Analyses:

The analyses for top-line results and the clinical study report will be conducted after final database lock. Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

2 STUDY DESCRIPTION

2.1 Study Design

An accelerated titration design (ATD) will be utilized for this Phase 1 study during dose escalation. Four dose escalation levels are planned: 0.3, 1, 3, and 10 mg/kg/dose. Subjects will be assigned to a dose level in the order of study entry.

The first cohort of 1 subject will receive BMS-936559 (MDX-1105) at the 0.3 mg/kg dose level. Enrollment into the next cohort cannot begin until 2 weeks have elapsed since the last subject's third dose in the previous cohort. One subject will be enrolled in each cohort until a subject experiences a ≥ Grade 2 study drug-related adverse event during Cycle 1, whereupon an additional 2 subjects will be enrolled at that dose level. Thereafter, the study will become the traditional 3 + 3 design with 3 or 6 subjects treated at this dose level and at all subsequent dose levels depending upon the incidence of DLTs.

To further characterize safety and efficacy, expansion cohorts as outlined in the table below will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated at the end of Cycle 1 before any subject is dosed in the expansion cohorts. If none of the first 5 subjects has a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following the enrollment of the sixth subject.

Expansion Cohorts		
Tumor Type	Dose level (n)	Note
Melanoma	0.1 mg/kg (n=16)	Added under Amendment 6
	0.3 mg/kg (n=16)	Added under Amendment 6
	1 mg/kg (n=16)	
	3 mg/kg (n=16)	
	10 mg/kg (n=16)	
Non-Small Cell Lung Cancer	1 mg/kg (n=32)	Added under Amendment 6. Approximately 16 subjects each with Squamous and non-Squamous Histology
	3 mg/kg (n=32)	Added under Amendment 6. Approximately 16 subjects each with squamous and non-squamous histology
	10 mg/kg (n=16)	Open histology enrollment.
	10 mg/kg (n=16)	Added under Amendment 6. Approximately 8 subjects each with squamous and non-squamous histology
Renal Cell Carcinoma	10 mg/kg (n= 16)	
Epithelial Ovarian Cancer	10 mg/kg (n= 16)	
Colorectal Adenocarcinoma	10 mg/kg (n= 16)	

Gastric Cancer	10 mg/kg (n= 16)	Added under Amendment 6.
Pancreatic Cancer	10 mg/kg (n= 16)	Added under Amendment 6.
Breast Cancer	10 mg/kg (n= 16)	Added under Amendment 6.

2.2 Treatment Assignment

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to a treatment cohort, as determined by BMS.

In order to avoid allocation bias in the expansion cohorts initiated under Amendment 6, subjects enrolled in the Melanoma (0.1 mg/kg and 0.3 mg/kg) and NSCLC (1 mg/kg, 3 mg/kg, and 10 mg/kg) expansion cohorts identified as meeting all eligibility criteria will be randomly assigned to one of the two and one of the three doses, respectively, according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development.

2.3 Blinding and Unblinding

Blinding is not applicable as this is an open-label study.

2.4 Protocol Amendments

Amendment 1 (September 5, 2008)

The purpose of this amendment was to remove the Off-Study Visit and add (up to) 3 Follow-up Visits. ‘Best observed response rate’ changed to ‘Best overall response rate’.

Amendment 2 (August 18, 2009)

The purpose of this amendment was to add the CRC indication, remove the 15 mg/kg dose level, add permission to collect slides or tissue samples from pre-enrollment tumor biopsies, expand statistical analysis text, add expansion cohorts at the MTD or a lower dose for all 5 indications and add 2 additional expansion cohorts for melanoma at doses other than the primary expansion dose. Reporting period for adverse events was changed

from 90 days following the last dose of study drug to 70 days following the last dose of study drug.

Amendment 3 (October 2, 2009)

The purpose of this amendment is to update the Time and Events Schedule.

Amendment 4 (March 2, 2010)

The purpose of this amendment is to incorporate information and processes resulting from the acquisition of Medarex, Inc. by Bristol-Myers Squibb Co (BMS). Statistical sections are revised to match BMS template and to assure all statistical analyses in the protocol are consistent with BMS statistical principles.

Amendment 5 (June 16, 2010)

The purpose of this amendment is to address potential safety issues.

Amendment 6 (October 20, 2010)

The purpose of this amendment includes the following: 1) to characterize the dose response relationship in melanoma (MEL) and non-small cell lung cancer (NSCLC) cohorts , and 2) evaluation of three new expansion cohorts of 10 mg/kg of BMS-936559 administered every 14 days in subjects with gastric carcinoma (GC), pancreatic carcinoma (PC) and breast cancer (BC).

Amendment 7 (September 21, 2011)

This amendment includes revisions to the dosing solution preparation and storage guidelines.

Amendment 8 (March 14, 2012)

This amendment allows for collection of overall survival data to explore associations with dose and candidate predictive biomarkers.

3 OBJECTIVES

3.1 Primary

The primary objective of this study is to assess the safety and tolerability of BMS-936559 (MDX-1105) when administered every 14 days to subjects with selected advanced or recurrent solid tumors. The malignancies include renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), epithelial ovarian cancer (epOC), gastric cancer (GC), pancreatic cancer (PC) and breast cancer (BC).

3.2 Secondary

The secondary objectives of the study are to evaluate or characterize: 1) preliminary efficacy on the basis of objective responses in subjects treated with BMS-936559 (MDX-1105); 2) the immunogenicity of BMS-936559 (MDX-1105); 3) pharmacokinetics of BMS-936559 (MDX-1105) and 4) the dose response relationship in melanoma and in NSCLC cohorts.

3.3 Exploratory

The first exploratory objective is to explore associations between markers of immune function and other biomarkers and measures of clinical activity and associations with toxicity. The exploratory biomarker analysis will explore the hypothesis that immune activation correlates with efficacy and clinical response in subjects after PD-L1 blockade. The second exploratory objective is to assess the overall survival in subjects receiving BMS-936559. Additional exploratory objectives are to explore potential predictive markers associated with BMS-936559 clinical activity based on levels of expression of PD-L1 in tumor specimens prior to treatment and to characterize the level of PD-L1 receptor occupancy by BMS-936559 in peripheral blood.

4 ENDPOINTS

4.1 Primary

4.1.1 Safety and Tolerability

Occurrence of adverse events (AEs), AEs leading to discontinuation, serious AEs, Grade 3-4 AEs, deaths, graded clinical laboratory test abnormalities per CTCAE 3.0 (hematology and serum chemistry), changes from baseline in vital sign assessments including heart rate and blood pressure measurements.

4.2 Secondary

4.2.1 Preliminary Efficacy

Best overall response (BOR) is the best response designation over the study based on RECIST 1.0 criteria for the individual subject in the study. BOR outcomes are: CR, PR, SD and PD.

Objective response rate (ORR) is defined as the number of subjects with a BOR of complete response (CR) or partial response (PR) divided by the number of subjects in the population of interest.

Duration of Objective Response (DOR), computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the subsequent date of objectively documented disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed, the endpoint will be censored on the date of last tumor assessment.

4.2.2 Immunogenicity

Occurrence of an increase in anti-drug antibody (ADA) levels from baseline

4.2.3 Pharmacokinetics

Pharmacokinetic parameters derived from serum concentration versus time data in subjects with intensive PK sampling enrolled in expansion cohorts post Amendment 6:

AUC(0-T) is defined as the area under the plasma/serum drug concentration-time curve from t=0 to last measurable sampling time.

AUC(TAU) is defined as the area under the concentration-time curve in one dosing interval.

Accumulation index (AI) is defined as the ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose.

Cmax is defined as the maximum observed concentration in plasma.

Tmax is defined as the time to reach Cmax in plasma.

Cmin is defined as the minimum observed drug concentration in serum.

Ceoi is defined as the end of infusion drug concentration in serum.

4.2.4 Dose- response relationship in MEL and NSCLC subjects

The endpoints used to assess this objective will be measures of preliminary efficacy such as occurrence of an OR, %Change on tumor burden, PFS and OS. In addition, potential safety measures such as occurrence of AE of special interest may be used. The totality of the analyses will be evaluated to qualitatively assess dose response.

4.3 Exploratory

Efficacy endpoints based on irRECIST (derived from RECIST 1.0 with modifications) such as immune-related BOR (irBOR), immune-related PFS (irPFS) and immune-related ORR (irORR).

Overall Survival (OS) is defined as the time between the date of first dose of study therapy and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

Biomarker assessments of immune function and other exploratory markers such as PD-L1 expression, PD-L1 receptor occupancy, serum cytokines/chemokines, and mRNA profiling.

5 SAMPLE SIZE AND POWER

This is a phase 1 dose-escalation study. The sample size cannot be precisely determined but depends on the observed toxicity. Cohorts of one or three to six subjects will be treated at each dose level during dose escalation.

Up to 15 expansion cohorts will be enrolled as outlined under Study Design in Section 2.1. Approximately 16 subjects will be enrolled at a given dose cohort for a given tumor type, with the exception of NSCLC where 32 subjects would be enrolled per dose cohort. With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 80% confidence interval for an objective response rate would be (3.4%, 30%) if 2 (12.5%) subjects had a response, (7.1% to 37%) if 3 (19%) subjects had a response, (11.4% to 44%) if 4 (25%) subjects had a response and (16.1% to 50%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 80% confidence interval for an objective response rate would be (3.5% to 19.7%) if 3 (9.4%) subjects had a response, (5.6% to 23.4%) if 4 (12.5%) subjects had a response, and (7.8%, 27.1%) if 5 (16%) subjects had a response.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The study consists of up to five study periods:

Screening Period: Consists of up to 28 days prior to administration of study drug.

Treatment Period: The maximum number of cycles to be administered to an individual subject in this study period is 16 cycles (with up to 3 doses per cycle). At the end of each of the first 4 cycles and then at the end of every even-numbered cycle, the decision to treat a subject with additional cycles of BMS-936559 will be based on tumor response evaluation.

Follow-Up Period: The maximum duration of follow-up will be approximately 1 year.

Retreatment Period: Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS medical monitor.

Retreatment Follow-Up Period: The maximum duration of retreatment follow-up will be approximately 1 year.

6.2 Treatment Regimens

All presentations and analyses will be performed according to the assigned dose at time of study therapy initiation (eg 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg)

6.3 Populations for Analyses

- *All Enrolled Subjects*: All subjects who sign an informed consent form.
- *All Treated Subjects*: All subjects who receive at least one dose of study medication.
- *Pharmacokinetic Subjects*: All subjects who receive at least once dose of study medication and have available serum concentration data.
- *Response-Evaluable Subjects*: All treated subjects with measureable disease at a baseline tumor assessment and one of the following: 1) at least one on-treatment tumor assessment, 2) clinical progression, or 3) death.
- *Immunogenicity Subjects*: All subjects who receive at least one dose of study medication and have available ADA data.

7 STATISTICAL ANALYSES

7.1 General Methods

All statistical analyses will be carries out using SAS software Version 8.2. (SAS Institute, Inc., Cary, NC.), unless otherwise noted.

Continuous variables will be summarized using the mean, standard deviations, median, minimum and maximum values. Discrete variables will be summarized by category using frequencies and percentages. The percentages will be rounded and therefore may not always sum up to 100%.

Time to event variables will be analyzed using Kaplan Meier techniques (K-M). When appropriate, the median along with confidence interval (CI) will be provided using Brookmeyer and Crowley methodology. PFS rates at a fixed time point (e.g. PFS rate at week 24) will be derived from the Kaplan Meier estimate and the corresponding CI will be derived based on Greenwood formula. Since not all subjects adhere to the scheduled

tumor assessment date, a window of 1 week prior to the PFS rate time points will be applied.

Censoring definitions may be updated to reflect initiation of subsequent cancer therapy, according to data availability and clinical adjudication. If results from time to event analyses are non-estimable, these endpoints may be summarized using descriptive statistics.

7.2 Study Conduct

All potential serious breaches of the conditions and principles of Good Clinical Practice (GCP) in connection with the study or protocol will be reported. Additionally, relevant protocol deviations, defined as any significant protocol deviation that could potentially affect the interpretability of the study results, will be reported.

7.3 Study Population

Summaries of study population will be based on all treated subjects except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

Disposition of All Enrolled Subjects (including number of subjects enrolled, treated, response-evaluable, off/on treatment status with reason, off/on study status with reason), by treatment and across treatments for each tumor type and overall across tumor types

Listing of Subject Status for All Treated Subjects

7.3.2 Demographics and Other Baseline Characteristics

Summary of Demographic Characteristics for All Treated Subjects 1) by treatment and across treatments and 2) by tumor type and across tumor types

- Age (summary statistics; <65 yrs, ≥ 65yrs)
- Gender (male, female)
- Race (white, black, asian, other)
- Ethnicity (hispanic/latino, not hispanic/latino)

Summary of Physical Measurements for All Treated Subjects 1) by treatment and across treatments and 2) by tumor type and across tumor types

- Weight (summary statistics)
- Height (summary statistics)
- ECOG performance status (0, 1, 2, 3)

Listing of Demographic Characteristics and Physical Measurements for All Treated Subjects

7.3.3 Medical History

Listing of General Medical History for All Treated Subjects

7.3.4 Disease Characteristics

Summary of Disease Diagnosis for All Treated Subjects by treatment and across treatments [Include histology breakdown for NSCLC]

Summary of Baseline Lesion Type for All Treated Subject by treatment and tumor type [adjudication by clinical; Bone, Liver, Lung, Lymph Node, Other]

Listing of Disease Diagnosis for All Treated Subjects [Include NSCLC histology]

7.3.5 Prior Therapy

Summary of Prior Therapy for All Treated Subjects 1) by treatment and across treatments and 2) by tumor type and across tumor types [Surgery, Immunological or Biologic, Hormonal Radiotherapy, Chemotherapy, Alternative/Herbal, Prior Medications - Other]

Summary of Prior Anti-Angiogenic and Immunotherapy for All Treated RCC Subjects by treatment [adjudication by clinical]

Summary of Prior RAF Inhibitor and Immunotherapy for All Treated MEL Subjects by treatment [adjudication by clinical]

Summary of Prior Platinum Based Therapy and TKI Therapy for All Treated NSCLC Subjects by treatment [adjudication by clinical]

Summary of Prior Nephrectomy Surgery for All Treated RCC Subjects by treatment [adjudication by clinical]

Summary of Prior Therapeutic Surgery for All Treated NSCLC Subjects by treatment [adjudication by clinical]

Summary of Prior Therapeutic Radiotherapy for All Treated NSCLC Subjects by treatment [adjudication by clinical]

Listing of Prior Surgery for All Treated Subjects

Listing of Prior Radiotherapy for All Treated Subjects

Listing of Prior Medication Related to Study Indication for All Treated Subjects

7.4 Extent of Exposure

7.4.1 Definitions:

The duration of therapy is defined at the time between the date of first treatment and the date of last treatment plus 14 days (the intended duration of last dose).

Cumulative dose (mg/kg): Sum over the duration of the study of all delivered doses (mg/kg) per subject where delivered dose in mg/kg is calculated by dividing delivered dose (mg) by body weight (kg), if body weight at time of dosing is not available, previous assessment will be used.

Dose Intensity (mg/kg/dosing interval): Cumulative dose (mg/kg) divided by the duration of therapy in dosing interval units (ie 14 days) defined as follows:

$$\frac{Cumulative\ dose\ of\ study\ therapy\ (mg/kg)}{\left[\left(Date\ of\ last\ dose\ of\ study\ therapy - Date\ of\ \ first\ dose\ of\ study\ therapy + 14\right)/14\right]}$$

Relative Dose Intensity: The dose intensity (mg/kg/dosing interval) divided by the intended dose per interval (eg 3 mg/kg, 10 mg/kg, etc).

7.4.2 Analyses

Summary of Duration of Therapy, Cumulative Dose, Dose Intensity, and Relative Dose Intensity 1) by treatment and across treatments and 2) by tumor type and across tumor types

Summary of the Number of Infusions Received for All Treated Subjects 1) by treatment and across treatments and 2) by tumor type and across tumor types

Listing of Study Drug Administration for All Treated Subjects [with reason for infusion interuption/prolongation]

Listing of Concomitant Medications for All Treated Subjects

7.5 Efficacy

Efficacy populations utilized prior to the final study report may differ from pre-specified populations depending on the purpose and timing of the analysis. For example, to ensure sufficient follow-up time for observing an objective response with robust data to adequately charaterize time to event endpoints, efficacy populations may be restricted to subjects with a minimum follow-up time and/or at least one on-study tumor assessment. All such populations would have a minimum requirement of measurable disease at baseline and at least one dose of study medication. The final study report will utilize only pre-specified populations (eg all treated subjects, response-evaluable subjects).

All efficacy analyses will be based on RECIST 1.0 with modifications according to tumor assessment data collected from subjects during the initial treatment period and follow-up period. Sensitivity analyses may be performed on the population of subjects who enter the retreatment period.

7.5.1 Definitions

Disease control rate (DCR) is defined as the number of subjects with a BOR of CR, PR, or SD >= t, where t = 12 weeks (DCR-12) or 24 weeks (DCR-24), divided by the number of subjects in the population of interest.

Duration of Stable Disease (DSD), computed for all treated subjects with a BOR of SD, is defined as the time between the date of first dose of study therapy and the date of objectively documented disease progression or death, whichever occurs first. For those

subjects who remain alive and have not progressed, the endpoint will be censored on the date of last tumor assessment.

Stable Disease Rate of at least 24 weeks (SDR-24) is defined as the number of subjects with a DSD of at least 24 weeks divided by the number of subjects in the population of interest. Since not all subjects adhere to the scheduled tumor assessment date, a window of 1 week prior to the Week 24 scheduled visit will be applied.

Progression Free Survival (PFS) is defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first. For those subjects who remain alive and have not progressed, the endpoint will be censored on the date of last tumor assessment. For subjects who did not have any on-treatment tumor assessments and remain alive, the endpoint will be censored on the date of first dose of study medication.

Progression free survival rate (PFSR) is defined as the probability of a subject remaining progression free and surviving to time t, where t = 12 weeks (PFSR-12) or 24 weeks (PFSR-24).

Time to response (TTR), computed for all subjects with a BOR of CR or PR, is defined as the time between the date of first dose of study therapy and the first documented objective response.

7.5.2 Analyses

Summary of Best Overall Response 1) by tumor type, 2) by treatment and tumor type, and 3) across treatments and tumor types [Include NSCLC histology]

Summary of Objective Response Rate, Disease Control Rate (DCR-12 and DCR-24) , and Stable Disease Rate (SDR-24) by 1) tumor type, 2) treatment and tumor type, and 3) across treatments and tumor types [Include NSCLC histology and Clopper-Pearson confidence interval for each rate]

Summary Statistics of Time to Response by 1) tumor type and 2) treatment and tumor type [Include NSCLC histology]

Estimated Progression Free Survival Rate at 12 and 24 Weeks by treatment and tumor type [Include NSCLC histology, K-M methodology]

Listing and Summary of Duration of Response by 1) tumor type and 2) treatment and tumor type [Include NSCLC histology, K-M methodology]

Listing and Summary of Duration of Stable Disease by 1) tumor type and 2) treatment and tumor type [Include NSCLC histology, K-M methodology]

Kaplan-Meier Plot of Duration of Response by 1) tumor type and 2) treatment and tumor type [Include median and 95% CI, NSCLC histology]

Kaplan-Meier Plot of Progression Free Survival by 1) tumor type and 2) treatment and tumor type [Include median and 95% CI, NSCLC histology]

Kaplan-Meier Plot of Overall Survival by 1) tumor type and 2) treatment and tumor type [Include median and 95% CI, NSCLC histology]

Individual Subject Plots of Percent Change in Target Lesion Tumor Burden from Baseline by treatment and tumor type [Include NSCLC histology]

Listing of Tumor Measurements for All Lessions

Listing of Tumor Evaluations at Each Assessment

Listing of Subject Best Overall Response and Time to Event Endpoints

7.6 Safety

Summaries of safety will be based on on-treatment events/evaluations observed in all treated subjects except that of serious adverse events and deaths which will be based on all events/evaluations observed in all enrolled subjects while on study. On-Treatment events/evaluations are defined to be those observed between the date of first dose of study drug and 70 days after last dose. Post-Treatment events/evaluations are those occurring more than 70 days after last dose date.

Identification of adverse events of special interest (AEOSI) with potential immune-related etiologies (eg irAEs) is based on ongoing review of safety data. Summaries of AEOSI may be tabulated based on clinical adjudication of existing safety tables, or programmatically generated upon availability of a pre-defined and comprehensive list of AEOSI MedDRA preferred terms.

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Adverse events and laboratory tests results will be graded for severity using NCI CTCAE Version 3.0.

In the AE summary tables, subjects will be counted only once at the worst grade per Preferred Term (PT) and System Organ Class (SOC) levels. The AE tables will list the SOCs (ordered by descending frequency) and the PTs (ordered by descending frequency within each SOC).

7.6.1 Adverse Events

Number (%) of Subjects with On-Treatment Adverse Events by Worst CTC Grade by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Treatment-Related Adverse Events by Worst CTC Grade by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Adverse Events CTC Grades 3-4 by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Treatment-Related Adverse Events CTC Grades 3-4 by treatment and across treatments for All Treated Subjects

Listing of all Adverse Events for All Treated Subjects [includes on-treatment and post-treatment events]

Listing of all On-Treatment Treatment-Related Adverse Events for All Treated Subjects

7.6.2 Serious Adverse Events

Number (%) of Subjects with On-treatment Serious Adverse Events by Worst CTC Grade by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Treatment-Related Serious Adverse Events by Worst CTC Grade by treatment and across treatments for All Treated Subjects

Listing of all Serious Adverse Events for All Enrolled Subjects [includes serious adverse events reported during enrollment, on-treatment, and post-treatment]

Listing of all On-Treatment Treatment-Related Serious Adverse Events for All Treated Subjects

7.6.3 Adverse Events Leading to Discontinuation

Number (%) of Subjects with On-Treatment Adverse Events Leading to Discontinuation by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Treatment-Related Adverse Events Leading to Discontinuation by treatment and across treatments for All Treated Subjects

Listing of all On-Treatment Adverse Events Leading to Discontinuation for All Treated Subjects

7.6.4 Deaths

Summary of Primary Cause of Death for All Treated Subjects

Listing of Deaths for All Enrolled Subjects

7.6.5 Clinical Laboratory Evaluations

Summary of Toxicity Changes from Baseline for Hematology for All Treated Subjects by treatment and across treatments [shift table of worst On-Treatment CTC grade compared to baseline CTC grade]

Summary of Toxicity Changes from Baseline for Serum Chemistry for All Treated Subjects by treatment and across treatments [shift table of worst On-Treatment CTC grade compared to baseline CTC grade]

Summary Statistics and Change from Baseline for Scheduled Laboratory Results for All Treated Subjects by treatment and across treatments

Listing of Laboratory Values for Subjects Meeting Abnormality Criteria

Listing of Laboratory Results for All Treated Subjects

Laboratory Abnormality Criteria

7.6.6 Electrocardiograms

Summary of Scheduled Electrocardiogram Heart Rate and Intervals for All Treated Subjects

Listing of all Electrocardiogram Heart Rates and Intervals for All Treated Subjects

7.6.7 Vital Signs and Physical Findings

Summary of Scheduled Vital Sign Assessments for All Treated Subjects [includes heart rate and blood pressure]

Listing of Vital Sign Assessments for All Treated Subjects

7.7 Pharmacokinetics

Summary Statistics for BMS-936559 Pharmacokinetic Parameters by treatment and study day.

Summary Statistics for BMS-936559 Cmin and Ceoi by treatment and study day.

Scatter plots of Cmax and AUC(0-T) versus dose.

Statistical analysis of dose proportionality [Linear regression of log(Cmax) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model].

Plot of individual and geometric mean Cmin values versus study day by dose.

Plot of individual and geometric mean Ceoi values versus study day by dose.

In addition, concentration data obtained from this study may be combined with other studies for population pharmacokinetic analysis and will be reported separately.

7.8 Dose Response

Initial assessments of the dose response relationship in MEL and NSCLC will be based on review of pre-specified safety and efficacy analyses. If any apparent dose-response associations are observed, additional methods will be applied to characterize the relationship. These will include modeling of efficacy endpoints such as tumor response as

a function of dose based on parametric models, non-parametric, or possibly Bayesian approach.

7.9 Biomarkers

Details of the biomarker analyses are documented in a separate analysis plan.

7.10 Immunogenicity

Summary of Immunogenicity by 1) treatment and across treatments and 2) tumor type and across tumor types [baseline positive, positive any time point, and increase post-baseline]

Listing of Immunogenicity Data for Subjects with at least one Positive ADA assessment

Listing of Immunogenicity Data

8 CONVENTIONS

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to CT SOP 109"). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

9 CONTENT OF REPORTS

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications. Populations utilized in these analyses may differ from pre-specified populations depending on the purpose and timing of the analyses.

10 REFERENCES

Not applicable.