Protocol

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

Protocol for: Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20. DOI: 10.1056/NEJMoa1500596

MERCK EX1117
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00625

This supplement contains the following items:

1. Original protocol (version 1.1), final protocol (version 7), summary of changes

TITLE: Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors

Johns Hopkins Protocol #:	J1365, NA_00085756
Merck Protocol #:	MK-3475-016
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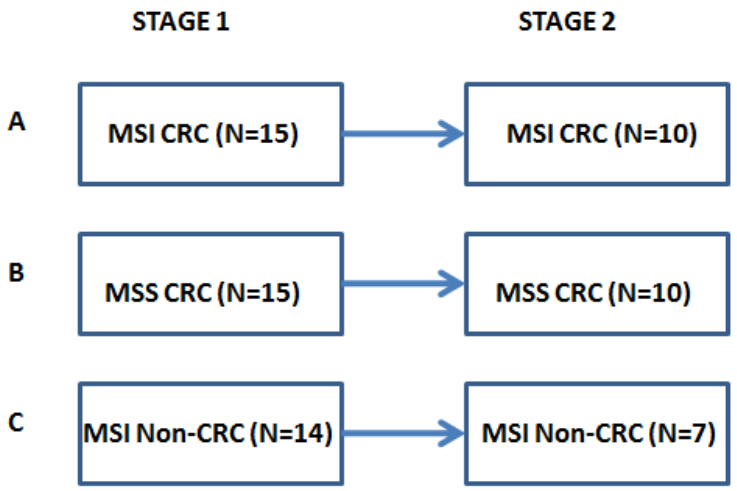
Protocol Type / Version # / Version Date: Original/ Version 1/ May 1, 2013
Original/ Version 1.1/ May 30, 2013

SCHEMA



MSI = Microsatellite Instability; MSS = Microsatellite Stability; CRC = Colorectal Carcinoma

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1. OBJECTIVES

1.1. Primary Objectives

1.1.1 To determine the immune-related progression free survival (irPFS) rate at 20 weeks and objective response rate (irORR) in patients with MSI positive and negative colorectal adenocarcinoma treated with MK-3475 using immune related response criteria (irRC).

1.1.2 To determine the immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma treated with MK-3475 using immune related response criteria (irRC) at 20 weeks.

1.2. Secondary Objectives

1.2.1 To determine the overall survival of patients with MSI positive and negative tumors treated with MK-3475.

1.2.2 To estimate irPFS and PFS in patients with MSI positive and negative tumors treated with MK-3475 at 28 weeks using irRC and RECIST 1.1.

1.2.3 To estimate best overall response rate and disease control rate in patients with MSI positive and negative tumors treated with MK-3475.

1.2.4 To assess safety and characterize toxicities of MK-3475 in patients with MSI positive and negative tumors.

1.2.5 To evaluate MSI as a marker to predict treatment response.

1.3 Exploratory Objectives

1.3.1 To explore the association of MSI positive, PD-L1 positivity, and tumor infiltrating lymphocyte characteristics with clinical responses. Archived tumor tissue (when available) and tumor tissue obtained at baseline and during treatment will be compared. In addition, we will compare differences in PD-L1 expression between the primary and secondary sites of cancer.

1.3.2 To assess tumor tissue for molecular determinants of response, progression and disease stability using next generation sequencing technology.

1.3.3 To assess tumor burden dynamics using both standard protein biomarkers such as CEA, CA19-9, C-reactive protein, and other exploratory circulating biomarkers in serial collections of sera and plasma at baseline and throughout treatment.

1.3.4 To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and

toxicity. DNA will be extracted from whole blood and used to evaluate for any germline mutations which may correlate with response or toxicity.

1.3.5 To collect peripheral blood lymphocytes to explore the association of MSI positive, PD-1 positivity, and lymphocyte activation markers with clinical responses.

1.4 Study Design

This is a multi-center, open label, two-stage, phase 2 study to evaluate the clinical activity of MK-3475 in MSI positive and MSI negative solid tumors. We will enroll three cohorts of patients to receive MK-3475: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumors but not colorectal adenocarcinoma (Cohort C). MK-3475 will be administered at 10 mg/kg every 14 days. Archived tumor samples or newly obtained biopsies will be used for determining MSI. MSI positive tumors will be defined using standard clinical criteria and require at least two loci to be evaluable [1, 2].

The primary endpoints for Cohorts A and B are immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC); irPFS is defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC; and irORR is the proportion of subjects whose best overall response is a CR or PR. Each cohort will be assessed separately.

The primary endpoint for Cohort C is immune-related progression-free survival (irPFS) rate assessed using immune related response criteria (irRC) at 20 weeks, defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC.

This design aims to evaluate treatment benefit and evaluate MSI as a predictive biomarker for treatment with MK-3475 simultaneously.

For Cohorts A and B, MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_{10}) or less or irORR is 5% (p_{20}) or less, and considered active if the irPFS rate at 20 weeks is 25% or greater (p_{11}) and irORR is 21% or greater (p_{21}). The endpoints will be tested in the hierarchical order first with irPFS at 20 weeks. If the null hypothesis of 20-week irPFS being 5% is rejected (i.e. the result reaches statistical significance), we will proceed to test for irORR. If irPFS is not significant at the 0.05 level (one-sided test), the statistical testing for irORR will not occur.

A two-stage Green-Dahlberg design is used for Cohort A and B. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 15 patients. Based on Green-Dahlberg design, if 0 irPFS are observed, enrollment in that cohort will be terminated. If at least one patient is free of disease

progression at 20 weeks per irRC, an additional 10 subjects will be enrolled into that cohort. If 3 or fewer patients are progression free at 20 weeks in the total of 25 patients enrolled in that cohort, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we proceed to test for the endpoint of irORR in that cohort. If 4 or more responders (CR or PR) are observed, we conclude the regimen is promising with that cohort and warrants further study for that cohort.

For Cohort C, MK-3457 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_0) or less and considered active if the irPFS rate at 20 weeks is 25% or greater (p_1).

A two-stage Green-Dahlberg design is used for Cohort C. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 14 patients. If 0 irPFS are observed, enrollment in Cohort C will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 7 subjects will be enrolled into Cohort C. If 3 or fewer patients are progression free at 20 weeks in the total of 21 patients enrolled in Cohort C, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we conclude the regimen is promising and warrants further study for this patient population.

No intra-subject dose escalation or reduction is allowed. Patients who do not receive at least 1 dose of MK-3475 will be replaced.

Patient immune and clinical responses will be evaluated through the following methods at baseline and during treatment: 1. tumor biopsies, 2. peripheral blood lymphocytes, 3. serum and plasma, and 4. CT scans will be obtained for assessment of activity and correlative studies.

Patients who have a confirmed complete response by two scans ≥ 4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. MK-3475 may be resumed upon disease recurrence in these patients. If a patient with a CR has discontinued treatment but then resumes treatment upon disease recurrence, the procedures will be followed as described in the Study Calendar (**section 10.0**).

Patients with tumor progression by RECIST imaging or laboratory parameters prior to their 7 month evaluation but without rapid clinical deterioration or significant change in performance status who do not require additional immediate therapy, may continue to be treated with MK-3475 and clinically observed following the assigned imaging schedule to allow detection of a subsequent tumor response. Tumor assessments will be made using RECIST 1.1 and immune-related response criteria (irRC). Subjects that meet the above criteria and continue on study therapy must discontinue MK-3475 upon confirmed documentation of PD at 7 months using irRC unless there are signs of delayed stabilization (disease progression at week 20, but

disease is stable at week 28 in comparison to week 20).

All patients will be followed for at least 30 days after their last dose of study drug (serious adverse events will be collected for 90 days after the end of treatment) or until initiation of a new anti-cancer treatment, whichever occurs first.

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first. Information of the new cancer therapy will be collected.

Patients who discontinued study therapy without documented disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) for approximately two years after the last dose of study drug, 2) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 3) documented disease progression, or 4) until death, whichever occurs first.

Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

2. BACKGROUND

2.1 Study Disease

Microsatellite instability (MSI) is the accumulation of sequencing errors in microsatellites. This occurs in tumors with deficiency in DNA mismatch repair. MSI is present in Lynch Syndrome which is an inherited cancer syndrome that predisposes patients to colon, endometrial, gastric cancer, ovarian, small intestine, liver, hepatobiliary, upper urinary tract, brain, and prostate cancer. MSI is also present in 10-20% of sporadic colorectal [3], gastric [4], prostate [5], lung [6, 7], ampullary [8], and endometrial cancers [9]. Between 0.3% and 13% of pancreatic cancers are reported to be MSI as well [10]. The study is designed to test an immunotherapy in MSI colorectal adenocarcinomas with an additional exploratory cohort in other MSI disease types.

2.2 MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [11]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [12-47]. In particular, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma,

malignant MEL and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma [48; 49].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [11]. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors [12-15]. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [50]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) [16], pancreatic carcinoma [17], hepatocellular carcinoma [18], ovarian carcinoma [19] and non-small cell lung cancer (NSCLC) [28]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant MEL [20]. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. MK-3475 also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells.

Amongst 132 subjects with MEL treated with MK-3475 at 10 mg/kg Q2W (n=57), 10 mg/kg Q3W (n=54), and 2 mg/kg Q3W (n=21) the most common AEs (>15%) were fatigue, nausea, rash, diarrhea, cough, and pruritus. The most common drug-related AEs (>10%) included: fatigue, rash, diarrhea, pruritus and arthralgia. The incidence of Grade 3-5 AEs was 27%. Twenty-one potentially immune-related AEs were reported and included: rash (6 subjects, 4.5%), influenza (4 subjects, 3.0%), pruritis (3 subjects, 2.2%), eczema (3 subjects, 2.2%), vitiligo (3 subjects, 2.2%),

hypothyroidism (3 subjects, 2.2%), pyrexia (2 subjects, 1.5%), arthralgia (2 subjects, 1.5%), myositis (2 subjects, 1.5%), and cough (2 subjects, 1.5%).

2.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure [IB] for Preclinical and Clinical Data

2.4 Rationale

Blockade of immune checkpoints such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) is showing promise in patients with cancer. CTLA-4 and PD-1 are upregulated on activated T cells and provide inhibitory signals to T cells undergoing activation. Inhibitory antibodies directed at these receptors have been shown to break immune tolerance and promote anti-tumor immunity. MK-3475 is a humanized monoclonal IgG4 antibody against PD-1 and is showing activity in multiple tumor types including melanoma and non-small cell lung cancer (NSCLC). Previously, activity of a different PD-1 blocking antibody, BMS-936558, a fully humanized monoclonal IgG4 antibody, also showed activity in melanoma, NSCLC, and a complete response in a single patient with colorectal cancer [28, 51].

As with all targeted therapies, we expect a subset of patients will respond to immunotherapy and there may be genetic determinants that define an 'immune responsive' phenotype. A cancer genomics perspective may provide insight as to why patients with melanoma and NSCLC, and perhaps other tumor types, respond to these therapies. The average number of somatic mutations in human cancer varies widely (**Table 1**) [52]. Three factors are known to be associated with high somatic mutation burdens: exposure to environmental carcinogens (e.g. UV radiation and tobacco) [53, 54]; repair defects (e.g., mismatch repair gene inactivation) [55]; or exposures to mutagenic therapies (e.g., alkylating agents) [56]. Melanomas and NSCLC are known to have high burdens of somatic mutations. We therefore hypothesize that there will be a correlation between the number of somatic mutations in individual tumors and the response to immune checkpoint inhibitors since each protein-coding mutation has the potential to serve as a novel antigen for an immune response. If this hypothesis is correct, it would suggest that immune checkpoint inhibitors might work best in tumors with high mutation burdens. Furthermore, tumors deficient in mismatch repair may be particularly susceptible to immunotherapy as this phenotype results in ongoing accumulation of mutations at a high frequency.

Table 1. The average number of somatic mutations in a representative group of human cancers	
Tumor	**Average # of mutations per case**
Tumors exposed to mutagenic therapies	>1000
Sun exposed melanomas	>1000
Mismatch repair deficient tumors	>600
Non-small cell lung cancers	540
Colorectal cancers	77
Pancreatic cancers	48
Glioblastomas	36
Meduloblastomas	8

MSI tumors are deficient in DNA mismatch repair which leads to a high rate of spontaneous mutations and the potential for the expression of neo-antigens. Furthermore, similar to melanoma, MSI positive colon cancers, there is often prominent lymphocyte infiltration [3, 4]. This is another clue that this subset of tumors may have baseline tumor infiltrating lymphocytes that can be harnessed with immune checkpoint blockade. Interestingly, the colorectal patient with the complete response is known to have an MSI positive tumor [57]. This study aims to evaluate MSI as a predictor of response to anti-PD-1 blockade with MK-3475.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Cohort A: Patients with histologically proven metastatic or locally advanced MSI colorectal adenocarcinoma.

3.1.2 Cohort B: Patients with histologically proven metastatic or locally advanced microsatellite stable (MSS) colorectal adenocarcinoma.

3.1.3 Cohort C: Patients with histologically proven metastatic or locally advanced non-colorectal MSI adenocarcinoma.

3.1.4 Patients with the presence of at least one lesion with measurable disease as defined by 10mm in longest diameter for a soft tissue lesions or 15mm in short axis for a lymph node by RECIST 1.1 and irRC criteria for response assessment.

3.1.5 Patients must agree to have a biopsy at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.6 Patients with colon cancer must have received or refused at least 2 prior cancer therapy regimens. Patients with other cancer types must have received

or refused at least 1 prior cancer therapy regimen. Patients should have progressed on the most recent regimen.

3.1.7 Age ≥18 years.

3.1.8 ECOG performance status 0-1 (**Appendix A**).

3.1.9 Life expectancy of greater than 3 months.

3.1.10 Patients must have normal organ and marrow function as defined below:

– Leukocytes	≥3,000/mcL
– Absolute neutrophil count	≥1,500/mcL
– Platelets	≥90 x 10^3/uL
– Hemoglobin	≥9.0 g/dL
– Total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤1.5x ULN
– Creatinine	≤1.5 x ULN

3.1.11 Female patient of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

3.1.12 Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception.

Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients with >50 percent involvement of the liver with tumor as determined by the Principal Investigator.

3.2.2 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

3.2.3 Patient who has had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study drug.

3.2.4 Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 28 days of the first dose of study drug.

3.2.5 Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.

3.2.6 Patients who have had surgery within 4 weeks of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, etc), celiac plexus block, and biliary stent placement.

3.2.7 Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies.

3.2.8 Patients who have received any of the following concomitant therapy: IL-2, interferon or other non-study immunotherapy regimens; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses) within 1 week prior to first dose.

3.2.9 Patients who have received any non-oncology vaccine therapy used for prevention of infectious diseases including seasonal vaccinations for up to 28 days prior to or after any dose of MK-3475. Examples include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

3.2.10 Patients receiving growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), erythropoietin, etc. within 14 days of study drug administration. Use of such agents while on study is also prohibited. Prior use of growth factors should be documented in the patient's medical history.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would

limit compliance with study requirements.

3.2.12 History of any autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with Graves Disease will be allowed.

3.2.13 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), hepatitis B, or hepatitis C infection.

3.2.14 Patients with clinical or radiographic ascites (only minimal/small radiographic fluid stable over a 6 week period will be allowed).

3.2.15 Patients with clinical or radiographic pleural fluid (only minimal/small radiographic fluid stable over a 6 week period will be allowed).

3.2.16 Patients with evidence of interstitial lung disease.

3.2.17 Patients with a pulse oximetry of <92% on room air.

3.2.18 Patients on supplemental home oxygen.

3.2.19 Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

3.2.20 Women who are pregnant or breastfeeding.

3.2.21 Women with a positive pregnancy test on enrollment or prior to investigational product administration.

3.2.22 Sexually active fertile men not using effective birth control if their partners are WOCBP.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 MSI Testing

MSI testing is already standardized and performed in CLIA-certified laboratories without need for assay development. Archived tumor samples or newly obtained biopsies will be used for determining MSI. MSI status will be performed locally by

CLIA certified immunohistochemistry (IHC) or PCR based tests for eligibility.

Evaluable patients will be confirmed using the MSI Analysis System from Promega at Johns Hopkins. This test will determine MSI status through the insertion or deletion of repeating units in the five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24). At least 2 MSI loci are required to be evaluable in Cohorts A and C. Patients may be assigned to a new cohort and/or replaced based on the Promega test results.

The MSI Analysis System (Promega), Version 1.2, is a fluorescent multiplex PCR-based method used to detect microsatellite instability (MSI), a form of genomic instability. This instability is due to insertion or deletion of repeating units during DNA replication and failure of the mismatch repair system (MMR) to correct these errors. MSI analysis typically involves comparing allelic profiles of microsatellite markers generated by amplification from matching pairs of test samples, which may be MMR-deficient, and normal tissue samples. New alleles in the abnormal sample not found in the corresponding normal sample indicate the presence of MSI.

The MSI Analysis System, Version 1.2, includes fluorescently labeled primers (marker panel) for co-amplification of seven markers for analysis of the MSI-high (MSI-H) phenotype, including five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24) and two highly polymorphic pentanucleotide repeat markers (Penta C and Penta D). Amplified fragments are detected using an ABI PRISM® 310, 3100, 3100-Avant, 3130 or 3130xl Genetic Analyzer after spectral calibration. GeneMapper® 4.0 software will be used for data analysis and assignment of genotype.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should call the Lead Study Coordinator at XXX-XXX-XXXX or e-mail to verify drug availabilities. The fax cover sheet, Registration Form, and Eligibility Worksheet will be supplied to each participating site.

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with Dr. Le or Dr. Diaz. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and faxed 410-502-2730 or e-mailed juram1@jhmi.edu to the Lead Study Coordinator:

- Fax cover sheet
- Registration Form
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Checklist
- Copy of required screening tests and scans

The Research Nurse or Study Coordinator at the participating site will then call 410-502-3038 or e-mail the Lead Study Coordinator to verify eligibility. To complete the registration process, the Lead Study Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
MK-3475	No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient per **section 5.2.1**.	10 mg/kg	IV over 30 minutes	Day 1	14 days

MK-3475 will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The pharmacists will prepare the MK-3475 medication for administration. The Procedures Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration. This document is available for reference by the pharmacist and study personnel.

5.2 General Concomitant Medication and Supportive Care Guidelines

MK-3475 is a humanized monoclonal Ab. Subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study.

5.2.1 Infusion Reactions

MK-3475 infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with MK-3475 are shown below.

Guidance on Infusion and Hypersensitivity Reactions:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 3 or 4 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 stop the infusion.** Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. Additional appropriate medical therapy may include but is not limited to: • Epinephrine • IV fluids, • Bronchodilators • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (e.g., 1-2 mg/kg/day of prednisone or equivalent), Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.** **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE).		

5.2.2 Immune-Related Adverse Events (IRAEs)

Blocking PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritis, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events, now termed IRAEs, noted in previous BMS 936558 studies.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE CRF. Identification and treatment of IRAEs can be found in **Appendix B**.

Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz immediately. In addition, any Grade 3, 4 or 5 irAE must be reported as an Event of Clinical Interest (ECI) within 24 hours even if no Serious Adverse Event Criteria are met.

5.3 Dosing Criteria

Dosing will be delayed for the following laboratory criteria:

- AST, ALT > 2.5 x ULN (AST, ALT >5 x ULN for patient with liver metastases)
- Total bilirubin >1.5 x ULN
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 x 10^3/uL

5.4 Definition of an Overdose for this Protocol

Overdose is defined as:
The patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to the Sponsor and within two (2) business days to Merck Global Safety. Merck Global Safety (GS) contact information can be found in Section 7.5.1.

5.5 Contraception, Use in Pregnancy, Use in Nursing

5.5.1 Contraception

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also required for the female partners of male patients). The

2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1through 120 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.5.2 Use in Pregnancy

MK-3475 may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck Global Safety without delay. The outcome must be reported to the Sponsor within 24 hours and to Merck Global Safety within two (2) business days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the Sponsor and to Merck Global Safety as described in Section 7.5.1. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor and to Merck Global Safety.

5.5.3 Use in Nursing Women

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

5.6 Duration of Therapy

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- No sign of disease stabilization by 7 months,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see **section 5.9.2**),
- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines (see **section 6.2**)
- Patient withdraws consent,
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The Sponsor and Merck should be included in this decision,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up, or
- Patient becomes pregnant.

Patients who have a confirmed complete response by two scans ≥ 4 weeks apart and who have been on MK-3475 treatment for at least 24 weeks -may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. MK-3475 may be resumed upon disease recurrence in these patients. If a patient with a CR has discontinued treatment but then resumes treatment upon disease recurrence, the procedures will be followed as described in the Study Calendar (**section 10.0**). Subjects who restart treatment after relapse from CR should resume at the same dose and cycle interval which they were receiving prior to discontinuation.

For scheduling reasons or patient's personal reason unrelated to toxicity, patients who have been on MK-3475 study therapy for at least 24 weeks may have a treatment-free interval of up to 9 weeks if considered in a patient's best interest by the Investigator. Any longer interval requires discussion with and approval by the Sponsor on an individual basis.

5.7 Off Study/Safety Follow-up Visit

After a patient is discontinued from MK-3475, a mandatory Off Study/Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **sections 5.7 and 10.0** as appropriate. The patient will be monitored for adverse events up to the mandatory Off Study/Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

5.8 Duration of Follow Up

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

Patients, who discontinued study therapy without documented disease progression, should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) for approximately two years after the last dose of study drug, 2) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 3) documented disease progression, or 4) until death, whichever occurs first.

Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

5.9 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 5.6** applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.9.1 Disease Progression

MK-3475 is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of MK-3475 dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory

parameter increases during the first 2-4 months of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor progression by RECIST imaging or laboratory parameters prior to their 7 month evaluation but without rapid clinical deterioration or change in PS who do not require additional immediate therapy, may continue to be treated with MK-3475 and clinically observed following the assigned imaging schedule to allow detection of a subsequent tumor response. Tumor assessments will be made using RECIST 1.1 and immune-related RECIST criteria (irRC). Subjects that meet the above criteria and continue on study therapy must discontinue MK-3475 if there are no signs of disease stabilization by 7 months using irRC.

5.9.2 IRAEs

Permanent discontinuation of MK-3475 should be considered for any of the following:

1. Severe or life-threatening related adverse reactions, including, but not limited to, any of the following (Sponsor and Merck must be notified in the event of these AEs, and final decision regarding treatment will be made after a discussion):

    - Grade 3-4 toxicity (non-hematologic or hematologic). Grade 3 toxicities may be able to be re-dosed on a case by case basis after approval of the Sponsor and Merck.

    - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal

    - Total serum bilirubin >3 times upper limit of normal

    - Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations

    - Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy

    - Any grade Guillain-Barré syndrome, or myasthenia gravis or other neurologic symptoms that impact activity of daily living

    - Severe immune-mediated reactions involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)

- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
- Grade 4 infusion reaction

2. Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤10 mg prednisone or equivalent per day

   If any of the above events occur, the investigator should discuss with Sponsor and Merck to make a decision on discontinuation of MK-3475 study treatment.

In case toxicity does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of MK-3475 study drug, study therapy discontinuation should be considered after discussion with the Sponsor and Merck. With Sponsor and Merck agreement, patients still at Grade 2 may continue in the study only if asymptomatic and controlled. Two dosing delays due to the same toxicity will be permitted. In the event of a third occurrence of the same toxicity which would require dosing delay, study therapy will be discontinued permanently.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications

Dose reduction or dose increase of MK-3475 will not be permitted in individual patients.

6.2 Dosing Delays

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per the table below:

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicity	1	No	N/A	N/A	N/A

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Appendix B.	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Appendix B for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	Toxicity resolved to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Severe or life-threatening AEs	Any	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Subject should be discontinued if toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Sponsor and Merck agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 30 days unless related to the investigational agent. All Serious adverse events will be collected for 90 days after the end of treatment.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz. In addition, any Grade 3, 4 or 5 irAE must be reported as an Event of Clinical Interest (ECI) within 24 hours even if no Serious Adverse Event Criteria are met.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

7.1 Definitions

7.1.1 Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

7.1.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- 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 for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
- 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 [eg, 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.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Events **not** considered to be serious adverse events are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a 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).

7.1.3 Adverse Events of Clinical Interest (ECI) for MK-3475

These selected non-serious related adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Experience Case Report Forms/Worksheets.

Events of clinical interest for this trial include:

- an overdose of Merck's product, as defined in **Section 5.4**, that is not associated with clinical symptoms or abnormal laboratory results.

- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

- Events that are CTCAE Grade 2 and higher and considered by the Investigator to be irAEs should be reported as events of clinical interest. Examples are included in the table below:

Skin: • Rash • Pruritus • Dermatitis • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Erythema multiforme • Psoriasis • Vitiligo • Urticaria • Alopecia • Hypopigmentation	**Gastrointestinal:** • Diarrhea • Enterocolitis • Pancreatitis	**Respiratory:** • Pneumonitis/pneumonia • Allergic rhinitis Infusion-related reaction or hypersensitivity
Endocrine: • Hypopituitarism/hypophysitis • Adrenal insufficiency • Hypogonadism • Hypothyroidism • Hyperthyroidism • Thyroiditis	**Ocular:** • Uveitis • Iritis • Conjunctivitis • Episcleritis • Scleritis • Blepharitis	**Cardiovascular:** • Pericarditis • Myocarditis • Angiopathy • Temporal arteritis • Vasculitis
Neurologic: • Neuropathy • Guillain-Barré syndrome • Myasthenia gravis • Meningitis	**Muscular-Joint:** • Polymyalgia rheumatic • Arthritis	**Laboratory investigations:** Increase of • Alanine aminotransferase • Aspartate aminotransferase • Thyroid stimulating hormone
Kidney: • Nephritis	**Liver:** • Hepatitis	**Hematologic:** • Hemolytic anemia

7.2 Relationship

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

7.4 Handling of Expedited Safety Reports

In accordance with local regulations, the Sponsor (Dr. Diaz) will notify investigators of all SAEs that are unexpected (ie, not previously described in the Investigator Brochure), and definitely, probably, or possibly related to MK-3475. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators within 48 hours. Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of ESRs by the investigator to Health Authorities should be handled according to local regulations.

7.5 Reporting

7.5.1 General

All adverse events (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs).

In addition, all serious adverse events, regardless of causality to study drug and/or administration device, will be reported promptly to Dr. Luis Diaz (fax: 410-955-0548, e-mail: Ldiaz1@jhmi.edu) within 24 hours of recognition of the adverse event using the form found in **Appendix C**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

All serious adverse events, regardless of causality to study drug and/or administration will be forwarded to Merck's Global Safety ("Merck GS") group within two (2) business days of learning of the event.

Non-serious Events of Interest will be forwarded to Merck GS and will be handled in the same manner as SAEs.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, that occurs during the trial or within 120 days of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to Merck GS.

SAE reports and any other relevant safety information are to be forwarded to Merck GS facsimile number: +1-215-993-1220.

7.5.2 Institutional Review Board (IRB)

Participating sites will be responsible for reporting to their IRB. All serious adverse events will be reported to the IRB per institutional standards within 3 business days of recognition of the adverse event if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product. If the serious adverse event is unrelated to administration of the investigational agents, then it will be reported to the IRB within 15 days of recognition of the serious adverse event. Upon receipt of the report of the serious adverse event by IRB, follow-up information will be given to the IRB within 15 days.

7.5.3 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the Sponsor (Dr. Diaz).

7.5.3.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-827-9796) to the FDA within 7 calendar days of first learning of the event.

15 Calendar-Day Written Report:
The Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event.

7.5.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the Sponsor-Investigator.

8. PHARMACEUTICALINFORMATION (MK-3475)

8.1 Agent Accountability

The sponsor/investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

8.2 Mode of Action

MK-3475 is a highly selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

8.3 Description

Clinical Supplies will be provided by Merck as summarized in the table below:

Product Name & Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Injection

8.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open label kits will be provided for patient dosing.

8.5 Preparation

Refer to Procedures Manual for preparation instructions.

8.6 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Refer to Procedures Manual for Storage conditions.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.7 Stability

Refer to Procedures Manual for Stability information.

8.8 Route of Administration

The reconstituted product is intended for IV administration.

8.9 Patient Care Implications

Based on results from the nonclinical studies, there are currently no specific safety considerations. MK-3475 is a humanized monoclonal Ab. Thus far, serious infusion reactions have been infrequent and manageable. However, subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study. In the event that a subject experiences an allergic reaction to MK-3475, treatment (i.e., vasopressors, H2-blockers, antihistamines, H1-blockers, steroids) should be administered, as appropriate, and prophylaxis should be considered. Surveillance for the appearance of HAH is included in all protocols.

MK-3475 has the same mechanism of action as BMS 936558. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK. Accordingly, the adverse events observed with BMS 936558 may serve as in indicator for the adverse events to expect for MK-3475 in cancer patients. Immune-related AEs (irAEs) are of special interest because of the mechanism of action of anti-PD-1 and prior experience with anti–CTLA-4 mAbs. Up to the cut-off date for this IB, the only possibly irAEs included pneumonitis (Grade 2), arthralgia and myalgia. One case of intestinal perforation was not considered immune related.

Overall, MK-3475 has been safe and well tolerated. However, prompt identification of irAEs and appropriate treatment (e.g. withdrawal of study medication and treatment with corticosteroids) will be critical to optimizing the therapeutic index. Individual protocols and the Guidance for Identification and Treatment of IRAEs **(Appendix B)** outline specific guidance for prompt identification and treatment of irAEs. Timely discussions of how to manage irAEs is also encouraged.

8.10 Agent Ordering

Requests for MK-3475 should be sent via email to:

Amy Meister
Merck Sharp & Dohme Corp.
351 North Sumneytown Pike
North Wales, PA 19454
Mailstop: UG-4D72
phone: 267-305-3268
email: amy.meister@merck.com

8.11 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9. CORRELATIVE/SPECIAL STUDIES

Sample collection, storage, and shipment instructions will be provided in the Procedures Manual.

9.1 Tumor Tissue Studies

Tumor biopsies will be collected (if a patient's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at the 20 week timepoint (4-6 cores per timepoint). Additional optional biopsies may be obtained later in the course of therapy. Archival tumor samples will also be collected for every patient. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the procedures manual.

9.1.1 To explore the association of MSI positive, PD-L1 positivity, and tumor infiltrating lymphocyte characteristics with clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment (20 weeks) will be compared. PD-L1 expression may predict response to anti-PD-1 [28, 51]. However, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre and post-treatment tumor biopsies will also be analyzed for PD-1 expression as well as infiltration of immune cells (effector T cells, Tregs, B cells, dendritic cells, etc). Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches. Preliminary data from a pancreatic cancer immunotherapy study suggests that induction of a $T_h1$and T_h17 phenotype at the tumor itself predicts response. Furthermore, upregulation of other inhibitory molecules such as IL-10 and TGF-β may identify other targets for combinatorial strategies.

Slides (20 are requested, but a minimum of 10 will be accepted) from a newly obtained biopsy sample of at least one tumor lesion at baseline will be submitted for PD-L1 staining. For patients with non-biopsiable disease, slides from an archival tumor tissue sample can be submitted. Biopsy or archival tissue samples should have proper size to enable IHC analysis of PD-L1.

9.1.2 The Ludwig Center for Cancer Genetics will perform whole-exome sequencing using next-generation sequencing on DNA from tumors and matched normal tissue. As with all targeted therapies, we expect a subset of patients will respond to immunotherapy and there may be genetic determinants that define this response. These studies will define the genetic landscape of these tumors and may determine an 'immune responsive' phenotype. Furthermore, since each mutation is a potential neo-antigen that may drive an immune response, we will evaluate each mutation for antigenic potential in our model [58].

9.2 Peripheral Blood Lymphocytes (PBLs)

Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS and MSI positivity. PBL will be collected at baseline and with each treatment. PBL are isolated and stored frozen until use.

9.3 Serum and Plasma Marker Studies

Pre and post-treatment sera and plasma will be collected to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. Whole blood will be collected in a 10 milliliter Serum Separator Tube (SST tube) at the designated time points and processed using standard laboratory procedures. Using a pipette, aliquots of 1 mL of serum should be transferred to cryogenic vials and stored at -80°C.

We will also collect whole blood in a 10 mL plasma preparation tubes with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) and gently swirl tubes to mix blood with EDTA. Within two hours of collection, the sample will be processed using standard procedures for plasma separation. Plasma will be divided into 1 mL aliquots and stored at -80°C. Pellets from this separation procedure will be washed in PBS and then divided into aliquots and also stored at -80°C.

9.4 Normal tissue based studies

To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA will be extracted from whole blood (collection and processing described in 9.3) and used to evaluate for any germline mutations that may correlate with response or toxicity. A SNP array may be performed on each case using the Affymetrix Genome-wide Human SNP Array 6.0 (Santa Clara, CA).

10. STUDY CALENDAR

	Pre-Study[19]	Cycle (14 days) [19]	20 Weeks	Off Study[20]
Visit Windows (days)[1]	-28 to -1	+7	+/- 14	+/- 7
MK-3475		X		
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographics	X			
MSI Testing	X			
Medical history	X			
Cancer History[2]	X			
Concurrent meds	X	X	X	X
Physical exam[3]	X	X	X	X
Vital signs[4]	X	X	X	X
Height	X			
Weight	X	X	X	X
Performance status (PS)	X	X	X	X
Hematology profile[5, 11]	X	X	X	X
Chemistry profile[6, 11]	X	X	X	X
Autoimmune and Endocrine Panel[7, 11]	X	X	X	X
Urinalysis & Microscopic Exam[8, 11]	X	X	X	X
B-HCG[9, 11]	X			
Serum Tumor Markers[10, 11]	X	X	X	X
Adverse event evaluation		X	X	X
ECG[12]	X	X		X
Radiologic evaluation[13]	X	X	X	X
Tumor measurements[13]	X	X	X	X
Peripheral blood (30cc)	X	X	X	X
Serum (10cc)	X	X	X	X
Whole Blood Sample for Plasma (10cc)	X	X	X	X
PK Samples [14]		X		
AHA Sample[15]		X		
Lactoferrin[16]	X			
Archival Tissue[17]	X			
Tumor Biopsies[18]	X		X	

1: Longer delays to be approved by the Sponsor and Merck.
2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens.
3: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter.
4: Temperature, respiration rate, blood pressure, and pulse should be taken prior to MK-3475, at the end of the infusion, and 1 hour post- infusion.
5: Albumin, amylase, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
6: CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
7: Anti-nuclear antibody (ANA), Total T3, Free T4, and TSH.
8: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
9: Serum or urine pregnancy test (women of childbearing potential).
10: C-reactive protein for all patients. Disease specific tumor markers where appropriate.
11: Labs may be collected within a window of up to 3 days prior to dosing.
12: ECG should be performed at baseline, 30 minutes post-cycle 1 infusion, pre-cycle 8 infusion, and at the off study visit.
13: Radiologic evaluations and tumor measurements will be performed at baseline (within 14 days prior to the first dose of MK-3475), 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter.
14: PK samples will be collected (3cc each) at the following timepoints: pre-dose trough and post-dose peak during Cycles 1 and 2, pre-dose trough samples only will be collected every 4 cycles starting with Cycle 5 and again 30 days after discontinuation of study drug. All trough samples should be drawn within 24 hours before infusion of MK-3475. All peak samples should be drawn within 30 minutes after the end of the infusion. An additional single PK sample should be drawn between 24 to 96 hours after Cycle 1 dosing.
15: Anti-MK-3475 antibodies should be drawn (10cc each) with all pre-dose trough PK samples and 6 months post-discontinuation (where possible). Refer to the Procedures Manual for further details.
16: Values at baseline and when a patient is diagnosed with colitis will be collected when available.
17: Archival tumor samples will be collected for every patient. For patients with non-biopsiable disease, the tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspirates will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
18: Tumor biopsies to be taken (if a patient's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at the 20 week timepoint (4-6 cores per timepoint). Additional optional biopsies may be obtained later in the course of therapy. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
19: Patients that will be retreated after progressing from a CR must undergo the following evaluations: physical exam, vitals, weight, PS, hematology and chemistry profile, autoimmune and endocrine panel, urinalysis, H-HCG, serum tumor markers, radiographic evaluations, and tumor measurements. The following samples will be collected at baseline and while on study: interval medical and cancer history, peripheral blood, serum, whole blood for plasma, and biopsy. Subjects who restart treatment after relapse from CR should resume at the same dose and cycle interval which they were receiving prior to discontinuation.
20: 30 days after their last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response at the 12 week timepoint and then every 8 weeks thereafter. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [**Appendix D**] and the immune related Response criteria (irRC) [**Appendix E**]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. RECIST and irRC response assessments will be performed locally for the trial and centrally at Johns Hopkins for publication.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MK-3475.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on

CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: A PET-CT can be used to obtain the images as long as the CT is of diagnostic quality.

11.1.3 Duration of Response as per RECIST 1.1 and irRC

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. In order to be considered durable, Stable Disease must be maintained for at least 6 weeks (this will be attained by the 9 week time point).

11.1.4 Progression-Free Survival (PFS) as per RECIST 1.1 and irRC

PFS is defined as the duration of time from start of treatment to time of first documented progression or death, whichever occurs first.

11.1.5 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines and instructions for AE reporting can be found in **Section 7.0 (Adverse Events: List and Reporting Requirements)**.

12.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

Protocol Chair
The Protocol Chair is responsible for performing the following tasks:
- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

Coordinating Center
The Coordinating Center is responsible for performing the following tasks:
- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites
Participating sites are responsible for performing the following tasks:
- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.

- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

12.2 Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled to include the Investigator and Merck representatives. During these meetings, the Investigator shall provide Merck with study progress updates. The Investigator will provide a summary of key points from the weekly meetings with a focus on safety of the protocol participants, enrollment status, and progress of data for objectives. In addition, Merck will provide safety and applicable program updates to the Sponsor.

12.3 Monitoring

This is a DSMP Level II study under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan (DSMP, 12/6/2012, **Appendix F**). Eligibility for all sites will be monitored by the JHU SKCCC CRO. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP). The protocol will be monitored internally by the Principal Investigator at each site. External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating site(s): The protocol will be monitored by the internal CRO at each site. A report of the reviews will be submitted to the Johns Hopkins principal investigator and SKCCC CRO.

Authorized representatives of the Coordinating Center may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and

data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Dr. Diaz will be holding the IND for this study. He will comply with all regulated reporting requirements to the FDA.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a multicenter, open-label, two-stage, phase 2 study to evaluate the clinical activity of MK-3475 in MSI positive and MSI negative solid tumors. We will enroll three cohorts of patients: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumors but not colorectal adenocarcinoma (Cohort C); all cohorts will receive MK-3475. Each cohort will be assessed separately. This design aims to evaluate MSI as a biomarker and evaluate treatment benefit simultaneously.

The primary endpoints for Cohorts A and B are immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC); irPFS is defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC; and irORR is the proportion of subjects whose best overall response is a CR or PR.

The primary endpoint for Cohort C is immune-related progression-free survival (irPFS) rate assessed using immune related response criteria (irRC) at 20 weeks, defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC. Each cohort will be assessed separately.

The secondary efficacy endpoints include overall survival, progression-free survival according to RECIST 1.1 (PFS), best overall response (BOR), duration of objective response (DOOR), time to objective response (TDOR), and disease control rate (DCR) per RECIST 1.1, and irPFS, irBOR, irDOOR, irTDOR, irDCR per irRC.

We will also evaluate safety and toxicity of MK-3475. We will evaluate exploratory endpoints of pharmacogenomics and predictive biomarkers for responses.

13.2 Sample Size/Accrual Rate

For Cohort A and B, a total of 25 patients are planned.

MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_{10}) or less or irORR is 5% (p_{20}) or less, and considered active if the irPFS rate at 20 weeks is 25% or greater (p_{11}) and irORR is 21% or greater (p_{21}). We will apply a step-down gatekeeping procedure to preserve a study-wise type I error rate at 0.05 when evaluating co-primary endpoints of irPFS

and irORR for Cohort A and B. Specifically, the endpoints will be tested in the hierarchical order first with irPFS at 20 weeks. If the null hypothesis of 20-week irPFS being 5% is rejected (i.e. the result reaches statistical significance), we will proceed to test for irORR. If irPFS is not significant at the 0.05 level (one-sided test), the statistical testing for irORR will not occur. Twenty-five patients in Cohort A and B would provide 90% power to detect an improved irPFS rate at 20 weeks from 5% to 25%, a 20% increase, at significance level of 0.05 based on a one-sided test. For an improved irORR from 5% to 21%, a total of 25 patients would provide 80% power to detect an of 16% increase using a one-sided exact binomial test at a 0.05 significance level.

For Cohort A and B, there will be 1 interim and 1 final analysis for irPFS, and 1 final analysis of irORR. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 15 patients. According to Green-Dahlberg design, if 0 irPFS are observed, enrollment in that cohort will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 10 subjects will be enrolled into that cohort. If 3 or fewer patients are progression free at 20 weeks in the total of 25 patients enrolled in that cohort, then the regimen will be considered inactive. If 4 or more patients are progression free at 20 weeks, we proceed to test for the endpoint of irORR for that cohort. If 4 or more responders (CR or PR) are observed, we conclude the regimen is promising with that cohort and warrants further study.

There is a 1.3% probability of stopping for futility under the alternative hypothesis p_{11} (i.e. incorrectly stopping at the interim when the drug is efficacious) and a 46% probability of stopping for futility under the null hypothesis p_{10} (i.e. correctly stopping at the interim when the drug is not efficacious).

For Cohort C, a total of 21 patients are planned, respectively. MK-3457 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_0) or less and considered active if the irPFS rate at 20 weeks is 25% or greater (p_1).

A two-stage Green-Dahlberg design is used for Cohort C. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 14 patients. If 0 irPFS are observed, enrollment in Cohort C will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 7 subjects will be enrolled into Cohort C. If 3 or fewer patients are progression free at 20 weeks in the total of 21 patients enrolled in Cohort C, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we conclude the regimen is promising and warrants further study this patient population.

This design provides 81% power to detect an improved irPFS rate at 20 weeks from 5% to 25% in Cohort C respectively, a 20% increase, with a type I error of 0.05. There is a 1.8% probability of stopping for futility under the alternative hypothesis p_1 (i.e. incorrectly stopping at the interim when the drug is efficacious) and a 49%

probability of stopping for futility under the null hypothesis p_0 (i.e. correctly stopping at the interim when the drug is not efficacious).

13.3 Stratification Factors

We will enroll three cohorts of patients based on disease and MSI status: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumors but not colorectal adenocarcinoma (Cohort C);

13.4 Analysis of Primary Endpoints

For Cohort A and B, immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC) are co-primary endpoints. irPFS rate at 20 weeks will be estimated as the proportion of patients alive and free of disease progression at 20 weeks per irRC, along with its 95% confidence interval (CI); irORR will be estimated as the proportion of subjects whose best overall response is either a CR or PR with corresponding 95% CI. The patients who drop out of the study due to toxicity and do not have a follow-up scan will be considered non-responders. The formal statistical testing for irORR will take place only if 20-week irPFS is statistically significant. For Cohort C, irPFS will be the primary endpoint. The evaluable population includes all subjects who receive at least one dose of MK-3475.

13.5 Analysis of Secondary Endpoints

Overall survival (OS) is the time from the first day of study treatment with MK-3475 to the date of death due to any cause. A subject who has not died will be censored at last known date alive. Kaplan-Meier curves will be used to summarize OS.

The analyses described below will be conducted on the basis of responses as assessed by both RECIST v1.1 and irRC. Summary statistics will be provided for each cohort as well as for each tumor type for Cohort C. The analysis will also be conducted in PD-L1+ versus PD-L1- protein expression subgroups.

PFS is defined as the time from the first day of study treatment to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Kaplan-Meier curves will be used to summarize PFS.

ORR is defined as the proportion of subjects whose best overall response (BOR) from baseline is either a CR or PR. BOR is determined by the best response designation recorded between the date of the first study treatment and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue MK-3475 beyond progression, the BOR should be

determined based on response designations recorded at the time of the initial progression. DCR is the proportion of patients with CR, PR, or SD.

Among patients with an objective response, DOOR is defined as the time between the date of initial complete or partial response to the date of the first documented tumor progression or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTOR is defined as the time from the first day of study treatment to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

13.6 Safety Analysis

The safety analysis will be performed in all treated subjects. Toxicity will be tabulated by type and grade.

13.7 Biomarker Analysis

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond toMK-3475 and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily- as outlined in the exploratory objectives- on germline mutations and SNPs, and on MSI positive, PD-L1positivity, and tumor infiltrating lymphocyte in tumor specimens. Similar analyses will be completed with peripheral blood samples. We will also explore standard protein biomarkers such as CEA, CA19-9, C-reactive protein, and other exploratory circulating biomarkers.

Associations between biomarkers and efficacy measures will be analyzed on all subjects with available biomarker data. Efficacy measures will include OS and standard and immune criteria of response and PFS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made. Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. The relationships between binary measures (e.g. response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Guidance for Identification and Treatment of IRAEs

Merck has developed the following guidelines regarding how to identify, evaluate and manage irAEs that may occur in patients receiving MK-3475. It is possible that irAEs other than those listed in this document may be observed in patients receiving MK- 3475, therefore all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune related. This document is meant to be a general guidance; therefore, recommendations in the current document might not be all inclusive. As such Investigators are encouraged to contact Dr. Le or Dr. Diaz as needed to discuss cases that warrant separate discussion outside of the scope of current guidelines. Permanent discontinuation of MK-3475 due to irAE may be subject of discussion between the Sponsor and treating Investigator. Unless specified later in this document, the general approach to handling irAEs is as follows:

- Mild (Grade 1) irAEs – provide symptomatic treatment.
- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated.
- Clinically significant or severe (≥Grade 3) irAEs –discontinue MK-3475 and treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg prednisone or equivalent per day within 12 weeks.

All AEs are to be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (http://ctep.cancer.gov).

If an irAE does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of MK-3475, study therapy discontinuation should be considered after discussion with Dr. Le or Dr. Diaz. With Investigator and sponsor agreement, patients still at Grade 2 may continue in the study only if asymptomatic and the event is under control. Two dosing delays due to toxicity will be permitted. If a third dosing delay is required study therapy will be discontinued permanently.

These guidelines will be periodically updated as new information becomes available.

Note: Steroid tapers should be gradual. Rapid reductions in steroid dose after an initial pulse which is often used in the standard treatment of autoimmunity should be avoided. An example of how a steroid taper could be carried out after initial high dose steroids is as follows: **i**f the patient's status is clinically improving, the steroids can be tapered every 3 days or so, cutting the dose by a third to a half each time, until he gets down to the equivalent of 60-80 mg/day of prednisone. At that point, the taper should be slowed down, cutting by 10-20 mg each time. The duration of the entire steroid course should be at least 3 weeks.

However, patients with lower grade toxicity may have been able to be tapered from lower doses of steroids i.e. 60mg/day using a 4 week taper.

Skin

Relevant Clinical Experience

Ipilimumab - skin irAEs (rash, pruritus) of any grade were reported in 47 to 68% of patients, with 4% being Grade 3 or 4. While most dermatologic irAEs are successfully managed with symptomatic treatments, rare cases (<1%) of life-threatening irAEs (toxic epidermal necrolysis and Stevens-Johnson syndrome) were reported for patients treated with ipilimumab. As such early identification of skin irAEs and dermatology consult is recommended.

BMS-936558 (MDX-1106) – the most common skin irAEs of any grade were rash (16%) and pruritus (9%). The only severe skin irAE was pruritus reported in one patient.

BMS-936559 (MDX-1105) – the most common skin irAEs of any grade were rash (7%) and pruritus (6%), no events were Grade 3 or 4.

Symptoms

Symptoms may include (but not limited to):

– Rash

– Pruritus

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

Course of Action

Grade 1-2 events:

– Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl).

– Withhold MK-3475 if Grade 2 symptoms persist for > 1 week despite above treatment. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3 events:

– Discontinue MK-3475.

– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 4 events:

– Discontinue MK-3475 and initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Pneumonitis

Relevant Clinical Experience
Ipilimumab – pneumonitis of any grade was reported in less than 1% of patients.
BMS-936558 (MDX-1106) – pneumonitis of any grade was reported in 3% of patients, with 1% of the events being Grade 3 or 4. There were 3 drug related deaths due to pneumonitis.
BMS-936559 (MDX-1105) – pneumonitis of any grade has not been reported.

Symptoms
Symptoms may include (but not limited to):
– Dyspnea*
– Dry cough
– Hemoptysis
– Fever
– Chest pain and/or tightness*
– Abnormal breath sounds
– Fatigue

*If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Course of Action
Grade 1 events – (asymptomatic with radiographic findings only):
– MK-3475 may be continued only if the radiographic findings are subtle and has been documented to be stable over a 2 week period on CT imaging.
– Radiologic findings should be followed on serial imaging studies.
– Consider pulmonary consultation and/or bronchoscopy if clinically indicated.

Grade 2 events -
– DiscontinueMK-3475.
– Consider pulmonary consultation.
– Consider pulmonary function tests.
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3-4 events:
– Discontinue MK-3475
Consider pulmonary function tests with pulmonary consult.
– Bronchoscopy with biopsy and/or BAL is recommended.
– Treat with intravenous steroids (methylprednisolone 500 mg over 24 hours). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or

dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.

– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.

Gastrointestinal (Diarrhea/Colitis)

Relevant Clinical Experience

Ipilimumab - diarrhea of any grade was reported in 44% of patients with 18% being Grade 3 or 4. Diarrhea can also be associated with signs and symptoms of colitis, and result in bowel obstruction and perforation, potentially requiring colostomy. The rate of bowel perforation after treatment with ipilimumab was reported as less than 1%. Early implementation of the below diarrhea treatment guidelines (DTGs) has been shown to reduce bowel perforation and colectomy rates, drug-related diarrhea and serious gastrointestinal irAEs by up to 50% in patients treated with ipilimumab. Prophylactic use of budesonide to prevent ipilimumab induced diarrhea/colitis is not recommended based on the results of a Double-Blind Phase II study conducted to determine if prophylactic budesonide reduced the rate of Grade ≥2 diarrhea in ipilimumab-treated patients. Even though budesonide was not shown to prevent diarrhea/colitis, it has been successfully used to treat these events when they do occur as described below.
BMS-936558 (MDX-1106) – diarrhea of any grade was reported in 11% of patients, with 1% of the events being a Grade 3 or 4.
BMS-936559 (MDX-1105) – diarrhea of any grade was reported in 9% of the patients, no events were Grade 3 or 4.

Ipilimumab induced diarrhea and/or colitis has been reported to progress from mild to severe within 24 hours. Although this has not been reported in any patients receiving an anti-PD-1 mAb (BMS-936558 [MDX-1106] or MK-3475), patients should be advised to contact the site as soon as initial symptoms appear.

Symptoms

Symptoms may include (but not limited to):
– Diarrhea
– Constipation
– Abdominal pain, cramping and/or bloating
– Nausea and/or vomiting
– Blood and/or mucus in stool with or without fever
– Rectal bleeding
– Peritoneal signs consistent with bowel perforation
– Ileus

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.

Course of Action

Grade 1 diarrhea:
– Treat symptomatically.
– Endoscopy is recommended if symptoms persist

Grade 2 diarrhea:
– Withhold MK-3475.

– Endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).
– Grade 1 events that persist for >1 week or Grade 2 events should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.
– Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation.
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3-4 diarrhea (or Grade 2 diarrhea that persist after initial steroid treatment):
– Discontinue MK-3475.
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Treat with intravenous steroids (methylprednisolone 500 mg over 24 hours) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis.
– If symptoms persist despite the above treatment a surgical consult should be obtained.

Hepatic

Relevant Clinical Experience

Ipilimumab – hepatic irAEs were reported in 3% to 9% of patients. Most patients had an asymptomatic increase of transaminases and bilirubin, however some patients also had fevers and malaise.

BMS-936558 (MDX-1106) – the most common hepatic irAEs were alanine aminotransferase increased (4% overall with 1% being either Grade 3 or 4) and aspartate aminotransferase increased (3% overall with 1% being either Grade 3 or 4).

BMS-936559 (MDX-1105) – alanine aminotransferase increased was reported in 1% of patients, no events were Grade 3 or 4.

Symptoms

Symptoms may include (but not limited to):

– Elevations in:
  - o AST >2.5 times upper limit of normal (ULN)
  - o ALT >2.5 times ULN
  - o Total bilirubin >1.5 times ULN

– Fever

– Malaise

– Upper quadrant abdominal pain

Differential Diagnosis

All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.

Course of Action

Grade 1 Events:

– Monitor liver function tests more frequently until returned to baseline values.

Grade 2 Events:

– Monitor liver function tests more frequently until returned to baseline values.

– Withhold MK-3475

Grade 3-4 Events:

– Discontinue MK-3475 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.

– Treat with high-dose intravenous glucocortico steroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.

– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolatemofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

– Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Endocrine

Relevant Clinical Experience
Ipilimumab – hypophysitis was reported in 1% to 6% of patients.
BMS-936558 (MDX-1106) – hypothyroidism of any grade was reported in 3% of patients, with <1% being either Grade 3 or 4.
BMS-936559 (MDX-1105) – hypothyroidism of any grade was reported in 2% of patients, no events were Grade 3 or 4.

Symptoms
Symptoms may include (but not limited to):
– Fatigue, weakness
– Headache
– Mental status and/or behavior changes
– Fever
– Vision disturbances
– Cold intolerance
– Abdominal pain
– Unusual bowel habits
– Loss of appetite
– Nausea and/or vomiting
– Hypotension*
– Arrhythmias*
– Abnormal thyroid function tests and/or serum chemistries

*If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential Diagnosis
All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. An endocrinology consultation is recommended.

Course of Action
Grade 1-2 events:
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).

Grade 3-4 events:
– Discontinue MK-3475
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

– Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and intravenous methylprednisolone should be initiated.

Neurologic

Relevant Clinical Experience
Ipilimumab – transient sensory and motor peripheral neuropathies have been reported in less than 1% of patients.
BMS-936558 (MDX-1106) – neuropathy of any grade has not been reported.
BMS-936559 (MDX-1105) – neuropathy of any grade has not been reported, however one patient was reported to have Grade 3-4 myasthenia gravis.

Symptoms
Symptoms may include (but not limited to):
– Unilateral or bilateral weakness
– Sensory alterations
– Paresthesia

Differential Diagnosis
All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection.

Course of Action
Grade 1events:
– Treat and monitor symptoms as indicated.

Grade 2 events:
-Treat and monitor symptoms as indicated.
-Withhold MK-3475. It is up to the discretion of the Investigator, after consultation with a the sponsor to determine whether or not treatment with MK-3475 should continue.

Grade 3-4 events:
– Discontinue MK-3475
– Treat with systemic corticosteroid of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Note: Cases of Myasthenia Gravis and Guillain Barre Syndrome have responded to steroids and standard therapies such as pheresis and IVIG. A neurologist should be consulted in these cases.

Eye

Relevant Clinical Experience
Ipilimumab– episcleritis and uveitis occur in less than 1% of patients.
BMS-936558 (MDX-1106) – one patient who received BMS-936558 (MDX-1106) in combination with a peptide vaccine experienced a dose-limiting optic neuritis.
BMS-936559 (MDX-1105) – Grade 1 or 2 dry eye was reported as an irAE for 1% of the patients. Grade 3-4 endophthalmitis was reported in one patient.

Symptoms
Symptoms may include (but not limited to):
– Photophobia
– Pain
– Dryness of the eyes
– Blurred vision
– Diffuse erythema and a prominent blush on the sclerae.

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts).

Course of Action
Grade 1-2 events
– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue MK-3475 if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3-4 events
– Discontinue MK-3475.
– Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

APPENDIX C: SAE Reporting Form

Serious Adverse Event Reporting Form

Please notify Dr. Diaz within 24 hour

Protocol Title:	**Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors**		
Protocol Number (MK-3475-016):	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐**Initial** ☐**Follow-up** ☐**Final Follow-up** ☐**Death** ☐**Addendum to:**	**Serious Criteria (check all that apply):** ☐Death ☐Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital Anomoly ☐ Other Important Medical Event ☐ Cancer ☐ Overdose	**Hospital Admission Date:**	**Date Event Discovered:**

Section A: Subject Information		
Subject ID:	**Subject Initial:**	**Subject Gender:** ☐**Male** ☐**Female**

Section B: Event Information		
Event diagnosis or symptoms:	**Date of First Dose (MK-3475):**	**Action taken with the study drug (MK-3475):** ☐**None** ☐**Interrupted** ☐**Discontinued**
	Date of Last Dose (MK-3475) prior to Event:	
	Number of Total Doses (MK-3475):	

Event Onset Date:	Event End Date:

Relationship to:	MK-3475	Underlying Disease
Unrelated	☐	☐
Probably Unrelated	☐	☐
Possible Related	☐	☐
Probably Related	☐	☐
Definitely Related	☐	☐

Section C: Brief Description of the Event:

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

APPENDIX D: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until

disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX E: Immune Related Response Criteria

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden.**

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.

- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Investigators Imaging Operations Manual (IIOM) for more details.

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

APPENDIX F: Data Safety Monitoring Plan (DSMP)

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

DATA AND SAFETY MONITORING PLAN

Version 5.0: 12/6/2012
NCI Approval Date: 12/11/2012

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1. Background

NIH policy requires that grantees have in place procedures for the data and safety monitoring of clinical trials.[1] This is to ensure the safety of participants, validity and integrity of the data, and the appropriate termination of trials for which significant benefits or risks have been uncovered or for which it appears that the trial cannot be concluded successfully. The Sidney Kimmel Comprehensive Cancer Center (SKCCC) Institutional Data and Safety Monitoring Plan (DSMP) was developed to comply with the NIH policies, the NCI's *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* guidance document,[2] and FDA regulations for monitoring IND trials.

1.1. NIH Principles of Monitoring Data and Safety

- All clinical trials require monitoring. Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III), etc.
- Monitoring should be commensurate with risks and the method and degree of monitoring needed is related to the degree of risk involved. [3] A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.
- Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

1.2. National Cancer Institute's Definition of a Clinical Trial

- The NCI operational definition of a clinical trial is a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.
- In the area of molecular or imaging diagnostics, the NCI considers a study to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way, the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not

clinical trials and are not covered by this DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects.

- Behavioral clinical trials include interventions whose goals are to increase behaviors (e.g., cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials and are not covered under this plan.

2. Monitoring the Progress of Trials and the Safety of Participants

2.1. Oversight and Responsibilities for Monitoring of Clinical Trials

The Associate Director for Clinical Research (ADCR) has overall responsibility for data and safety monitoring of clinical trials conducted at the SKCCC. The ADCR appoints the Chairperson and all members of both Clinical Research Review Committee (CRC) and the Safety Monitoring Committee (SMC). See Appendix A for the relationship of the oversight committees and groups.

- **Institutional Review Board**

The Johns Hopkins Medicine Institutional Review Boards (JHM IRBs) are responsible for protecting the rights and welfare of the human subjects of research conducted by faculty and staff at Johns Hopkins Institutions. The JHM IRBs review all human subject research projects conducted by Hopkins faculty and staff. For cancer related studies, the JHM IRB does not begin the review process until the CRC has approved the trial. The IRB reviews and approves monitoring plans for each study.

- **Committee on Outside Interests (COI)**

The institution addresses conflicts through the Organization Policy on Committee on Outside Interests (COI) and the JHM IRB (Policy No. 103.11 - July 2007).[4] The Organization policy on Conflict of Interest includes specific management requirements applicable to conflict of interest associated with conduct of human subject's research protocols. The OHSR will work with the Office of Policy Coordination (OPC) to ensure that conflicts associated with research protocols are identified and reviewed by the Committee on Outside Interests (COI) before JHM IRB review is completed. The OPC staffs the COI, which is the Committee charged with review of conflict of interest associated with research projects. Effective June 2007, all disclosures of outside interests to the OPC occur through the electronic system known as eOPC. OHSR staff members have access to eOPC for purposes of obtaining management plans and the COI meeting schedule. When feasible, a member of the OHSR Compliance Team attends meetings of the COI to facilitate communications between the two offices. The JHM IRBs may not take final action on new applications until COI review is complete and management recommendations are finalized. An OHSR staff member attends JHM IRB meetings and presents the COI management terms to the IRB. The JHM IRB may accept COI management terms or may impose additional restrictions. The JHM IRB may not approve a study with a level of conflict of management that is less than that recommended by the COI. More information on how the institution handles conflicts of interests can be found at their Office of Policy Coordination.[5]

- **Clinical Research Committee - Sub Committee (CRC-SC)**

The adequacy of each study protocol's data and safety monitoring plan is first reviewed at the CRC-SC and then forwarded to the CRC for approval. This evaluation is based on the criteria detailed in this SKCCC Data and Safety Monitoring Plan. While all interventional trials are required to have a Data and Safety Monitoring section in the protocol, Institutional and Externally Peer Review trials are required to have language regarding the oversight under the auspices of SKCCC DSMP. The Level of oversight is also stated in this section. The Quality Assurance reviewer notifies the study team if the DSMP section or oversight level is not included in the protocol.

- **Clinical Research Review Committee (CRC)**

The Clinical Research Review Committee is charged with ensuring that protocols meet the Center's standards for Scientific Merit, Scientific Priority, and Adequate Scientific Progress as well as ensuring the inclusion of women and minorities and children in research. The CRC in concurrence with the PI determines the risk level then reviews and approves the study specific data and safety monitoring plan. Once a study is approved by the CRC, it is forwarded to the IRB for review.

- **Safety Monitoring Committee**

The SMC is responsible for ensuring the safety of participants and the validity and integrity of the data. It is also charged with appropriate closure or termination of studies for which significant benefits or risks have been uncovered. The committee is also tasked with suspending or closing a study because of inadequate data quality or validity. In Section 2.3, there is a more detailed description of the SMC.

- **Internal Data Monitoring**

The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance, and identification, grading, coding, and required reporting of all anticipated and unanticipated adverse events and protocol problems. Although this responsibility is usually shared among the PI, research nurse, and data manager, the PI is ultimately responsible for grading and attribution of all events.

- **External Data Monitoring and Auditing**

The SKCCC CRO Quality Assurance Group (CRO QA group) is responsible for auditing and monitoring all interventional clinical trials. However, if a Sponsor/PI has their own external data monitors then the CRO QA group is not responsible for auditing or monitoring. An example of this is an Industrial study where the sponsor contracts with a CRO or uses their in-house monitors.

An exception: while NCI-CTEP utilizes Theradex for its Phase I study monitoring, the CRO QA group may perform periodic audits due to the higher risk of these particular studies. In addition, the CRO QA group will only audit consortium-sponsored externally peer-reviewed trials (monitored by the applicable consortium) on an as-needed basis.

- **Investigational Drug Pharmacy**

The Johns Hopkins Oncology Investigational Drug Pharmacy is the only entity that has access to the study drug assignment of blinded trials. The investigator must follow the trial's randomization procedures, and should ensure that the code is broken only in accordance with the protocol. The investigator must promptly document and explain to the sponsor and

institution any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

2.2. SKCCC Data and Safety Monitoring Plan (DSMP)

This DSMP plan outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to assure and document data integrity and protocol compliance. This plan is comprised of leveled-oversight-mechanisms and complies with NIH/NCI[6] and FDA standards. [7]

- All clinical trials at SKCCC are required to have Data and Safety Monitoring and Adverse Event /Problem sections in the protocol. The CRC in concurrence with the PI determines the risk level of the trial during the initial CRC review of the Protocol. The DSMP Oversight Level must be specified in the protocol for review and subsequent approval by the SKCCC Clinical Research Committee (CRC), the Institutional Review Board (IRB) and, if applicable, the SKCCC Safety Monitoring Committee (SMC) or the National Cancer Institute (NCI).

- Oversight Levels are based on risk assessment (see Appendix B), complexity, and external monitoring in place by the sponsor, e.g.: CTEP studies are monitored through CTMS and even though they may be high risk, could be assigned to Level 1 oversight.

- The SKCCC Clinical Research Office (CRO) conducts two types of data and safety inspections: monitoring and auditing. Guidelines detailing the auditing and monitoring processes are found in Appendix C.

  - Auditing is a periodic review of a random selection of trial-related activities and documents to determine whether the study is being conducted properly. Reviews determine if data are recorded and reported accurately according to the protocol, standard operating procedures (SOPs), good clinical practice (GCP), and regulatory requirement(s).[5]

  - Monitoring a clinical trial is an ongoing review of the conduct of the trial, throughout the duration of the study. It includes adherence to study design, data integrity and validity, and appropriate reporting of protocol problems and adverse events.

- At SKCCC, the Associate Director for Clinical Research, Clinical Research Review Committee (CRC), SKCCC Safety Monitoring Committee (SMC), CRO Quality Assurance Group, and the PI share monitoring responsibilities. It is important to note that the PI has primary responsibility for continuous internal monitoring.

- The SKCCC DSMP utilizes a four-level oversight system as described below.

  - **Level 1** is designed for institutional and externally peer reviewed Phase I and II trials where a JH investigator does not sponsor the IND/IDE. All medium and high risk studies receive an early audit as soon as possible after the first subject is enrolled, and then periodically, as long as subjects are actively receiving the protocol intervention. Risk levels for these trials may vary from low to high.

    - High-risk trials are audited at least annually.

    - Medium-risk trials are audited at least every two years.

- Low-risk trials do not receive an early audit, but are audited at year-one, and at least every three years thereafter.
- Examples of Level 1 studies include investigator-initiated trials and NIH funded trials that are externally monitored by CTMS or CDUS.

- **Levels 2, 3, and 4** utilize an external monitoring process. If a Johns Hopkins investigator sponsors an IND or IDE, Level 2 or 3 external monitoring is required. Such monitoring may be performed either by the SKCCC CRO QA group or contracted through an external Clinical Research Organization.
  - **Level 2** monitoring is for low to medium risk studies; monitoring frequency is every 6 months and covers at least 30% of subjects. If major issues are discovered, the rate of monitoring may be increased at the discretion of the Quality Assurance Supervisor or the SMC. An example of a Level 2 trial is use of an FDA drug or device approved for another use.
  - **Level 3** is for higher risk studies. 100% of the subjects on these studies are monitored at least quarterly, or as defined by an external data and safety monitoring committee or board. Examples of Level 3 studies are gene-transfer, vaccine, and first in human use.
  - **Level 4** is meets the NIH requirement for all Phase III studies to have a Data and Safety Monitoring Board (DSMB – see Appendix E). 100% of the subjects on these studies their data monitored at least quarterly.

2.3. Safety Monitoring Committee (SMC)

The SMC is charged with ensuring the safety of participants and the validity and integrity of the data and the appropriate closure of studies for which significant benefits or risks have been uncovered. The Committee is responsible for continuous, ongoing review of the conduct of the trial, including adherence to study design, documentation of appropriate monitoring, and proper reporting of protocol problems and events. Inherent in this process is the goal of enhancing the quality of the research by providing the investigator with constructive criticism. The SMC membership includes physicians and other representatives from various Center Programs, biostatistics, data management, nursing, and quality assurance. See Appendix D for the current SMC members.

- The SMC meets monthly to review interventional studies that are either open to accrual or closed to accrual but have subjects in active treatment. The review process is outlined in section 2.4. Cooperative Group and Industrial trials are exempt from SMC review as long as they have an external review process detailed in the protocol or the IRB application.

- A meeting quorum is reached once 50% + 1 of SMC voting members are present.

- SMC members may not have a conflict of interest with any aspect of the trials they monitor. Before the committee initiates discussion on a study, the SMC Chair instructs all SMC voting members (including the Chair) who function as a member of the study under discussion to exit the meeting room until discussion and voting on that study has concluded. All conflicted members are noted on the SMC voting form.

- At the conclusion of each study's discussion, each member makes a data quality, safety, and overall assessment recommendation via selecting one or more of the below categories on the SMC study voting form.

Safety Assessment

For safety, the oncologist assigned to review the study prior to the meeting presents his/her findings at the meeting and then concludes by offering a safety assessment recommendation. The full committee then discusses this and votes per the following outcomes:

- Abstain (Insufficient Info)
- Acceptable
- Acceptable-with-Actions - Require a written response for SMC chair review
- Acceptable-with-Actions - Require a written response for SMC review
- Unacceptable - Place trial on hold pending further SMC review
- Unacceptable - Recommend closure of the trial with required reporting to appropriate regulatory agencies

Data Quality Assessment

For data quality, a QA Specialist group compiles and presents a data quality summary to the Committee and offers a data quality recommendation to the SMC. The full committee discusses these data quality findings and the CRO QA group's data quality recommendation during the meeting and votes per the following outcomes:

- Acceptable
- Acceptable-with-Actions - Require a written response for QA review
- Acceptable-with-Actions - Require a written response for SMC review
- Unacceptable - Place trial on hold pending further QA/SMC review
- Unacceptable - Recommend closure of the trial with required reporting to appropriate regulatory agencies

Overall Assessment

Each committee member's overall study assessment is made by taking into consideration a study's safety profile and its data quality (and is instructed to weigh any safety-related concerns more heavily). After study-related discussion has concluded, each member makes their final determination on a study via selecting only one of the below Overall Assessment categories on the SMC study voting form:

- Acceptable
- Acceptable-with-Actions
- Unacceptable

Reporting

Votes are tabulated as above and the PI and study team are sent an outcome letter within 1-3 days of the meeting. The letter states the overall outcome and the safety and data quality outcomes. If actions or questions are noted in any category, the PI is informed via the letter

and is required to send a written response to the SMC at least a week prior to the next scheduled SMC meeting.

When an SMC assessment requires an action, the PI is responsible for submitting a copy of the report, along with any responses, to the IRB within 60 days (or earlier, depending on the severity of the issue). When an SMC assessment is acceptable, the study team can submit a copy of the report to the IRB with their study's next IRB continuing review application (or with the study termination report, if applicable).

Ensuring Data Confidentiality during the SMC Review Process

In order to ensure the confidentiality of blinded randomization assignments throughout the conduct and review of a trial, the Johns Hopkins Oncology Investigational Drug Pharmacy is the only entity that has access to the study drug assignment of blinded studies. Nonetheless, if the SMC has significant concerns about the safety of study participants on a blinded study, it can compel the Investigational Drug Pharmacy to break the blind for SMC-review purposes only. In any case, clinical investigators must promptly document and explain to the trial sponsor, institution, and regulatory authorities (if applicable) any unintended unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event, etc.) of a study's investigational product(s).

Research participant confidentiality is maintained throughout the SMC review process by including only subject ID numbers in documentation provided to the committee (as opposed to including identifiable data such as subject name, initials, etc.).

2.4. Safety Monitoring Committee Review Guidelines

The SMC provides thorough and ongoing review and monitoring of patient risks, study progress, safety, data accuracy and integrity, and overall protocol compliance.

The full SMC meets once per month to ensure that all DSMP Levels I, III, and IV studies are reviewed at least annually, and that all DSMP Level II studies are reviewed at least semi-annually. A full SMC study review includes an evaluation of the following items:

- an updated data quality summary and trending analysis of all audits/monitoring visits (to evaluate the accuracy and integrity of data),
- an updated study master protocol deviation log (to evaluate protocol compliance),
- an updated study master adverse event log (to evaluate patient safety) and the current study consent document (used to compare the risk section in the current consent doc against the observed adverse events),
- an updated progress summary (to evaluate study progress), and
- any outcomes from external study Medical Expert Committee or DSMB reviews (if applicable).

Study accrual is evaluated annually by the Clinical Research Review Committee (refer to Appendix A).

The SMC Chair or designee reviews all serious adverse events, protocol problems, and amendments that pertain to safety-related issues, on a weekly basis. Submissions that affect participant safety or change risk are referred to the full committee for review at the monthly meeting.

At any point along this ongoing SMC review process the SMC can suspend, recommend closure, or terminate a study. When any of these actions occur, the PI and/or IRB must report them to appropriate regulatory authorities (e.g., NIH, FDA, DHHS, etc.).

A complete itemized description of the SMC's monthly review process - categorized by study type and study DSMP Level - is presented below.

INSTITUTIONAL AND EXTERNALLY PEER REVIEWED STUDIES

Level 1

- The SMC reviews the following **annually:**
  - Continuing review reports
    - Study summary
    - Adverse events
    - Deviation log
  - Audits – internal and external reports
    - Summary and trend analysis
  - Other external reports

- The SMC reviews the following **monthly:**
  - Major issues that affect patient safety or change risk
    - Protocol amendments
    - FDA alerts
    - NCI Action Letters
    - Major protocol violations
  - All Deaths on study
    - Within 30 days of last treatment, **and**
    - Possibly related to study agent or procedure
  - Serious Adverse Events that may cause a study to be placed on hold

Level 2

- The SMC is the designated trial monitor for these studies.

- The SMC reviews the following **every 6 months** unless otherwise specified:
  - Study summary
  - Adverse events
  - Response data
  - Deviation logs
  - Audit reports – internal and external
  - Monitoring reports summary and trends analysis
  - IND/IDE summary report, if applicable

- The SMC reviews the following **monthly:**
  - Major issues that affect patient safety or change risk

        - Protocol amendments
        - FDA alerts
        - NCI Action Letters
        - Major protocol violations
    - All Deaths on study
        - Within 30 days of last treatment and
        - Possibly related to study agent or procedure
    - Serious Adverse Events that may cause a study to be placed on hold

Levels 3 & 4

- A DSMB, Medical Expert Committee, or other external safety review mechanism is the designated trial monitor for these studies.

- The SMC reviews the following **annually:**
    - Continuing review reports
        - Study summary
        - Adverse events
        - Deviation log
    - Audit reports – internal and external
    - Monitoring Report summary and trends analysis
    - IND/IDE summary report, if applicable
    - External safety monitoring board or committee minutes

- The SMC reviews the following **monthly:**
    - Major issues that affect patient safety or change risk
        - Protocol Amendments
        - FDA alerts
        - NCI Action Letters
        - Major protocol violations
    - All Deaths on study
        - Within 30 days of last treatment, **and**
        - Possibly related to study agent or procedure
    - Serious Adverse Events that may cause a study to be placed on hold

NATIONAL AND INDUSTRIAL STUDIES

- The SMC reviews the following **annually:**
    - The QA specialist for the disease group reviews sponsors monitoring and auditing reports. Reports with concerns are forwarded to the SMC for their review and comment.

- The SMC reviews the following **monthly:**
    - All Deaths on study

  - Within 30 days of last treatment, **and**
  - Possibly related to study agent or procedure
- Serious Adverse Events that may cause a study to be placed on hold
- Cooperative Group Audits
- 483s issued by the FDA
- Sponsor complaints – repeated

ADDRESSING MINOR AND MAJOR AUDIT OR MONITORING DEFICIENCIES/DISCREPANCIES

Per JHU SKCCC policies, minor deficiencies or discrepancies (i.e. items that do not affect the outcome or interpretation of the study and do not put the patient at risk) must be addressed by the study team within 10 days of an audit report or within 30 days of a monitoring report. A JHU SKCCC CRO QA Specialist will verify resolution of a study's minor audit or monitoring visit deficiencies at the study's next scheduled audit/monitoring visit. The SMC is notified of prolonged unresolved minor deficiencies as needed (i.e. immediately if necessary, or at the study's next scheduled annual or semi-annual (if applicable) SMC review).

Per JHU SKCCC policies, major deficiencies or discrepancies (i.e. items that yield questionable data, affect patient safety or research ethics, etc.) observed by an auditor or monitor must be addressed by the study team per applicable institutional policy (and no later than 10 days (audit) or 30 days (monitoring visit) per JHU SKCCC policies). Depending on the severity, major deficiencies may be submitted to the SMC Chair for immediate review and study team follow-up. Major deficiencies may also be reportable to the IRB, sponsor, and/or FDA, as applicable (depending on the SMC's assessment, the institution's policies, and sponsor/protocol's requirements).

In order to ensure appropriate team responsiveness to audit or monitoring deficiencies/discrepancies, the SMC reserves the right to issue the following study actions:

- produce a Corrective Action Preventive Action (CAPA) plan for repeated minor observations, or major observations not sufficiently addressed by the study team;
- halt enrollment, if warranted;
- close the study, if warranted;
- terminate the study, if warranted.

If the SMC or institution halts enrollment, closes, or terminates a study then the team must inform the IRB, protocol sponsor, and/or FDA (as applicable).

2.5. Data and Safety Monitoring Board for Institutional Phase III Studies

Phase III studies are required to have a DSMB. If the study does not have an external DSMB, the investigator may obtain assistance from the CRO or the Johns Hopkins School of Medicine to assemble a DSMB. A template DSMB charter is shown in Appendix E. The DSMB is charged with monitoring and evaluating three aspects of clinical trials. These include:

- Safety: By reviewing interim toxicity data for a trial in order to assure the continuing safety of subjects.

- Efficacy: By reviewing interim analyses of outcome data, prepared by the study statisticians to assure that the data are consistent with identifying an important clinical efficacy.

- Study Progress: By reviewing outcome data, to assure that the study can be completed in a reasonable period to be of significant clinical relevance.

3. Compliance with Problem/Adverse Event Reporting Requirements

Problems and adverse events include on-site and off-site adverse events, injuries, side effects, breaches of confidentiality, or other problems that may occur any time during or after the research study

Reporting of problems/events involving risk to participants or others in all clinical trials at SKCCC is conducted in accordance with federal regulations and guidelines as well as Institutional policies and guidelines. In addition, problem/event reporting procedures are specified in detail in each protocol.

Multi- Site trials where the Johns Hopkins Investigator is responsible for the coordinating center, the JH PI must communicate timely all Serious Adverse Events and Protocol Problems to each site with instructions to report to their local IRB per local IRB guidelines.

Reporting Guidelines followed at SKCCC:

- NCI
  CTEP, NCI Guidelines: Adverse Event Reporting Requirements[8]
  NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs[9]
  NCI Data and Safety Monitoring Guidelines[10]

- FDA
  Information for FDA-Regulated Industry[11]
  21 CFR 312.32 IND Safety Reports[12]
  21 CFR 812.150 IDE Safety Reports[13]

- Johns Hopkins Institutional Review Board (JHM IRB)
  Protocol Event and Protocol Deviation Reporting Requirements[14]

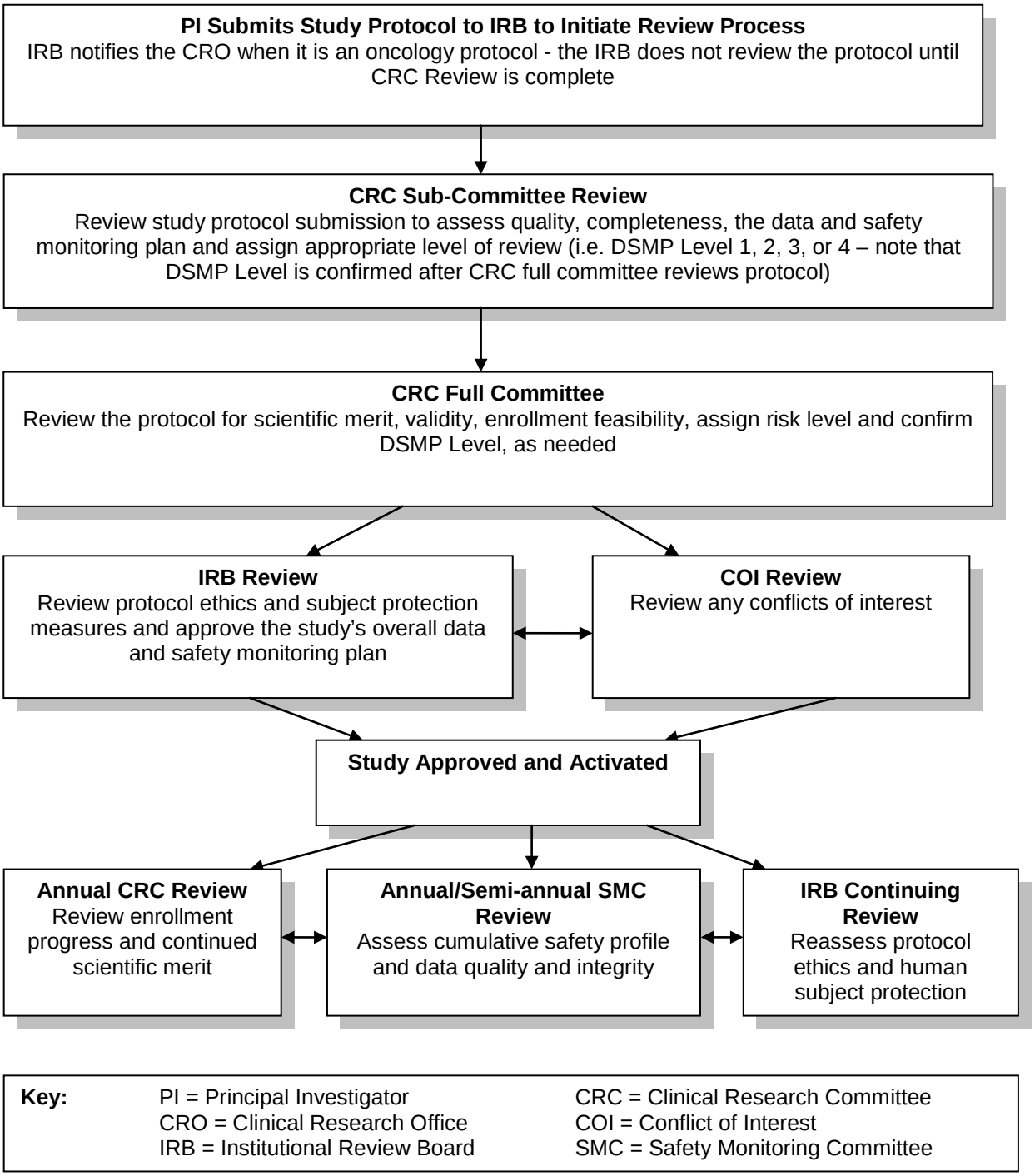
- Western Institutional Review Board (WIRB)
  WIRB Protocol Deviations & Violations / Unanticipated Problems Reporting System[15]

4. Multi-Site Clinical Trials

Principal Investigators from the SKCCC may invite Investigators from other institutions to participate in a clinical trial. In these cases, the Principal Investigator is ultimately responsible for the conduct of the trials at all participating sites, and is required to establish a Coordinating Center to manage all trial related documents and data. SKCCC Coordinating Center SOPs, Operations Manual, and IRB Approved protocol exist to assist an investigator when they are responsible for the coordinating center of a clinical.

The SKCCC Coordinating Center Protocol is available in Appendix F. The protocol describes the processes and oversight that SKCCC coordinating centers have in place for collecting and reporting AEs to all necessary regulatory agencies and co-investigators at participating institutions.

Appendix A: Schema Review Committees Interaction



The CRC, IRB, or SMC can suspend, recommend closure, or terminate a study at any point. When any of these actions occur, the PI and/or IRB must report this to appropriate regulatory authorities (e.g., the NIH, FDA, DHHS, etc.).

Appendix B: Assessment of Risk

Participant risk, along with, the size and complexity of the trial must be considered when assessing the level of risk to an investigator-initiated or NIH-sponsored trial to ensure data and safety monitoring activities are adequate. The CRC in concurrence with the PI determine the risk level of the trial.

The PI of the trial is responsible for determining the level of monitoring based on participant risk, number of participants, and complexity of the trial. Any trial with a high risk to participants is considered high risk; however, a medium risk trial with a complex design could also be considered high risk.

After reviewing the risk, size, and complexity of the trial, the CRC determines if they agree with the adequacy of the monitoring plan in the protocol. If the plan is not adequate, it must be revised by the PI.

In general, the committee uses the following guidelines to determine risk but considers the uniqueness of each trial to ensure the appropriate risk level is assigned. In addition, risk levels can be adjusted during the conduct of the trial by the IRB, CRC, or SMC if the plan is determined to be inadequate or excessive. Trials designated as high risk by the NIH must remain in the High Risk category.

Risk Level	Example of Trial
High	• Phase 1 trials • Trials using gene transfer therapy • First in human use • Any trial designated by the NIH as high risk • Trials using large numbers of participants (Phase III trials) • IDE or IND sponsor is a Johns Hopkins Investigator with any of the above noted attributes
Medium	• Trials using commercially approved agents or devices • All other trials involving therapeutic interventions, e.g., drugs, biologics, devices • IDE or IND sponsor is a Johns Hopkins Investigator with any of the above noted attributes
Low	• Trials involving non-therapeutic interventions, e.g., nutritional, behavioral
Exempt	• Non-Interventional trials, e.g., blood draws, imaging, survey

Appendix C: Quality Assurance Auditing and Monitoring Guidelines

Level 1

- Auditing only (no monitoring required)

  - Early audits of interventional studies are scheduled after the first subject is enrolled. The focus is protocol compliance. Findings are reviewed with the PI and study staff.

  - Routine audits as described below are scheduled periodically on interventional studies that are either open to new accrual or closed to accrual but have subjects in active treatment. Both an administrative/regulatory and subject reviews are performed. A random selection of at least 10% (maximum of six) of subjects' research records and corresponding source documents are reviewed.

  - Areas of concentration for audits are:
    - Valid signed consent forms
    - Eligibility
    - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
    - Treatment administration
    - Response / outcome assessment
    - Timely submission of continuing review reports and amendments
    - Data quality and overall protocol compliance
    - Accrual

  - Audit findings are reviewed with the PI and study staff and a summary report is sent to the SMC and/or DSMB for review.

  - The intensity of each audit is determined by taking into account the experience of the research team, the protocol's complexity, the rate of enrollment, and previous audit results; this facilitates appropriate prioritization of QA resources according to study risk and cumulative study circumstances.

Level 2

- Auditing – None

- Data monitoring visits occur at least every 6 months. Consents and eligibility are monitored for 100% of all subjects. Full monitoring as described below occurs for at least 30% of subjects enrolled on the trial.

- During routine monitoring visits, the following are reviewed:
  - Valid signed consent forms
  - Eligibility
  - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
  - Treatment administration

- Response / outcome assessment
- Timely submission of continuing review reports and amendments
- Data quality and overall protocol compliance
- Accrual

- An Administrative/regulatory review is performed at least annually

- A pharmacy review or device accountability will be performed during every third monitoring visit or at least once per year

- Following a monitoring visit, a summary report is prepared and sent to the PI, study staff, and SMC for review.

- The intensity of each Level II monitoring visit is determined by taking into account the experience of the research team, the protocol's complexity, the rate of enrollment, and previous monitoring results; this facilitates appropriate prioritization of QA resources according to study risk and cumulative study circumstances.

Levels 3 & 4

- Auditing – None

- 100% of the subjects on these studies are monitored at least quarterly, or as defined by external sponsor data and safety monitoring mechanism criteria. 100% of all subjects receive full monitoring as described below.

- During routine monitoring visits, the following are generally reviewed:
  - Valid signed consent forms
  - Eligibility
  - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
  - Treatment administration
  - Response / outcome assessment
  - Timely submission of continuing review reports and amendments
  - Data quality and overall protocol compliance
  - Accrual

- An Administrative/regulatory review is performed at least annually.

- Drug or device accountability is performed during every third monitoring visit or at least once per year.

- Following a monitoring visit, a summary report is prepared and sent to the PI, study staff, and SMC for review.

DSMP Level Schema for Institutional and Externally-Funded Peer Reviewed Studies				
	Level 1	**Level 2**	**Level 3**	**Level 4**
Study Category	Phase I or phase II interventional studies (level depends on study risk)			Phase III studies
	N/A	JHU investigator-sponsored IND/IDE studies (level depends on study risk)		
General Oversight				
Institutional Oversight	All levels: Institutional Review Board			
Cancer Center Oversight	All levels: Clinical Research Review Committee (CRC) for scientific merit, priority and progress			
Internal Monitoring Oversight	PI and study staff			
Safety Monitoring Oversight	SMC		External Safety Monitoring and SMC*	Independent DSMB and SMC**
Study-Specific Monitoring/Auditing				
Study monitoring	N/A	SKCCC CRO or external		
CRO auditing	Required	Not required		
Frequency of CRO monitoring/auditing	After 1st subject and then periodically	At least semi-annually	At least quarterly, or as defined by external DSMB	
Intensity of CRO monitoring/auditing	Random selection of 10% of subjects (max of 6)	Random selection of 30% of subjects	100% of all subjects	
* Medical Expert Committee, DSMB, or other SMC-approved monitoring mechanism ** Johns Hopkins Institutional DSMB, or other SMC-approved DSMB				

Johns Hopkins Investigator Sponsored IDE or IND Trials

- Before the Cancer Center activates an IRB-approved IND/IDE JHU sponsor-investigator study a pre-enrollment review is performed, and includes the following steps:
  - A thorough review of all relevant regulatory submissions to the relevant government agencies;
  - A comprehensive review of the study regulatory binder;
  - Ascertainment of who the IND/IDE regulatory submissions manager will be for the given IND/IDE;
  - CRO issuance of a preliminary report to the study team summarizing any review observations and a request that they be addressed by the study team.
  - Once the above four tasks are complete, a review exit meeting is held to discuss the results of the pre-enrollment review report. During this exit meeting, a summary of the regulatory responsibilities of IND/IDE sponsor/sponsor-

investigator is presented and discussed with the study team. Once the sponsor/sponsor-investigator has acknowledged his /her responsibilities and all outstanding issues have been resolved, a final report is sent to the study team and IRB. Only after this process has completed may the Cancer Center activate the study. In addition, all audit/monitoring visits are documented via an audit/monitoring report and recorded entry in the site visit log (found in the study regulatory binder).

Appendix D: Current SKCCC Safety Monitoring Committee

2013 Safety Monitoring Committee

Member	Research Program	Title	Voting Member
Julie Brahmer, MD, Chair	Upper Aerodigestive	Assistant Professor of Oncology	Yes
Javier Bolanos-Meade, MD, Co-Chair	Hematologic Malignancies and BMT	Assistant Professor of Oncology	Yes
Emanuel Antonarakis, MD	Prostate	Assistant Professor of Oncology	Yes
Jaishri Blakeley, MD	Brain	Assistant Professor of Oncology	Yes
Dung Le, MD	Gastrointestinal	Assistant Professor of Oncology	Yes
Amy Goodrich, CRNP	Clinical Research Office	Heme Nurse Practitioner and Research Nurse Manager for Center (faculty)	Yes
Patricia Rennie, MS, CCRP	Hematologic Malignancies and BMT	Assistant Program Manager, Hematologic Malignancies and BMT Program	Yes
Christian Meyer, MD	Sarcoma	Assistant Professor of Oncology	Yes
Keith Pratz, MD	Hematologic Malignancies and BMT	Assistant Professor of Oncology	Yes
Roisin Connolly, MBBS	Breast	Assistant Professor of Oncology	Yes
Hao Wang, PhD	Biostatistics Core	Assistant Professor, Department of Biostatistics	Yes
Travis Ché Jarrell, MPIA, RAC	Clinical Research Office	Quality Assurance Supervisor	No

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Appendix E: DSMB Template Charter

1. The DSMB Membership will include voting and nonvoting members. The core DSMB must include five members. These should include at least one experienced oncologist, a statistician and a lay representative. Members should be selected based upon their expertise, experience, reputation for objectivity, knowledge of clinical trial methodology and absence of a significant conflict of interest. Members may not have a conflict of interest with any aspect of the trials they monitor. Conflict of interest is defined by the Johns Hopkins University Conflict of Interest Policy. The DSMB will meet at least twice annually or more frequently as dictated by the requirements of clinical trials under its supervision. Data review dates should be selected so that the committee can prepare a report for the continuing review of supervised trials.

2. The formal meeting of the DSMB for each trial shall consist of three parts. The first part is an open session in which members of the clinical team, including the principal investigator and trial statisticians are available to review data with the DSMB. Outcome results must not be discussed during this open session. Following the open session, the DSMB may hold a closed session including members of the board and appropriate members of the coordinating center and the statistician handling the trial. The third phase of each meeting is an executive session involving only voting DSMB members and may be held to allow the DSMB to discuss general conduct of the trial and all outcome results, including toxicities, adverse events, and other protocol events/problems, to develop recommendations, and to take votes as necessary. The DSMB recommendation and the SKCCC action plan, if any, will be forwarded together to the IRB, NIH, FDA, and sponsor as appropriate, providing the opportunity for their opinions and recommendations. In no cases will the DSMB recommendations be taken as binding, provided reasons for an alternative course of action are endorsed by the CRC and investigator.

3. Following each study review, the DSMB will recommend either:

   3.1. Continuation of the trial as is using the current protocol and statistical plan.

   3.2. Continuation of the project with modifications as outlined by the board

   3.3. Immediate suspension of the trial for safety reasons with a recommended plan of follow-up to minimize subject harm.

   3.4. Place the study on a clinical hold. Subjects may continue on their assigned treatments until clarifications requested by the board are resolved.

   3.5. Termination of the trial because of 1) treatment effectiveness demonstrated earlier than expected (“early stopping”), 2) futility of further accrual to meet the trials goal, 3) discovery of new information that precludes completion of the trial, or 4) structural problems in trial execution that are not amenable to correction.

Appendix F: SKCCC Multi-Center Guidelines

SKCCC Coordinating Center Protocol

Coordinating Centers are required when a principal investigator invites other sites to participate in a clinical trial based at The Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins.

Coordinating Centers provide administrative, data management, regulatory, and organizational support in the conduct of a multi-center trial. Coordinating Centers also function as the central location for multi-center trial documents and patient registration. Coordinating Centers monitor the conduct and progress of a clinical trial at all participating sites.

Coordinating Centers must:

- Verify that each participating institution has a Federal Wide Assurance (FWA) number.
- Confirm that IRB approval has been obtained at each participating site prior to their first patient registration.
- Maintain copies of IRB approvals from each site.
- Implement central patient registration.
- Prepare appropriate data as required for review by the Protocol Chair.
- Establish procedures for documentation, reporting, and submitting of adverse events to the Protocol Chair and all regulatory bodies.
- Facilitate audits by securing selected source documents and research records from participating sites for audit or by conducting audits at participating sites.

Document Distribution and Tracking

The SKCCC Coordinating Center ensures the following documents are available to the participating sites via email at the time a new protocol is activated:

- Johns Hopkins IRB approved protocol
- Johns Hopkins IRB approved model consent form
- Other pertinent documents

The SKCCC Coordinating Center is responsible for the coordination, development, submission, and approval of all protocol amendments. The protocol will not be modified by any site other than the Coordinating Center. There will be only one version of the protocol and each participating institution will use that document. All amendments and other pertinent protocol information are sent to participating sites via email, as a PDF document, after approval by a Johns Hopkins IRB. The Coordinating Center ensures that all participating

institutions are using the correct version of the protocol. The Coordinating Center maintains a Regulatory Database that records the protocol and informed consent version, Johns Hopkins IRB approval and expiration date, participating site distribution date, and participating site confirmation for receiving such documents.

Collection and Review of Regulatory Documents

The SKCCC Coordinating Center maintains a regulatory file for each participating site. The following documents must be received by the Coordinating Center prior to a participating site being authorized to enroll patients:

- Letter of Understanding
- IRB protocol approval letter: the letter must include the protocol name, version, and dates of protocol approval and expiration
- IRB approved consent form: the entire consent form must be submitted and must include the protocol name and date of approval
- OHRP Federal Wide Assurance number
- IRB membership list, if available
- FDA Form 1572, if appropriate
- Curriculum vitae, signed and dated within the last two years, of all investigators and sub-investigators
- Medical license for all investigators and sub-investigators
- Financial disclosure forms, if appropriate
- Human Subjects Training certification for all study personnel
- Laboratory certification and normal ranges

The SKCCC Coordinating Center reviews the documents received for completeness and accuracy and will file accordingly. The participating site's IRB approval and expiration dates will be logged into the Regulatory Database. This database also maintains the version, approval / expiration information for all participating site's IRB renewal and amendments with corresponding revised consent forms. Hence, the database will also track that sites are using the most recently approved protocol and consent. The system will NOT allow patient registration unless the current version is approved.

Quality Assurance

The Coordinating Center is responsible for auditing and/or monitoring the progress of the study at participating sites. The schedule is based on the complexity and risk level of the trial.

Audits must occur at least every three years and may occur in one of two ways: (1) source documents and research records are brought from the participating site to the Coordinating Center or (2) selected patient records may be reviewed on site by a Coordinating Center

representative. The Coordinating Center may also monitor participating sites by telephone between visits. Site monitoring logs must be kept to document frequency of visit or contact.

Study data will be monitored by the Coordinating Center at the time of case report forms are submitted as defined by the protocol and/or the letter of understanding.

On a typical monitoring visit to a site, the Coordinating Center representative should inspect the following:

- **Original, signed consent forms to ensure that one is available for each subject.**
- **Case report forms and source documentation for validity and consistency in the completed entries, as well as, accuracy, legibility, signatures and dates.**
- **Treatment administration records to ensure concurrence between dispensing records and CRFs as to subject identity, and dosage of study drug administered.**
- **Compliance with the protocol will also be checked.**
- **Pharmacy drug accountability records for accuracy and completeness, and study drug storage to ensure proper maintenance and supply levels.**

Adverse Event Reporting

The SKCCC Coordinating Center is the central location for the collection and maintenance of adverse event documentation and must submit adverse event reports to the Protocol Chair for review. All serious adverse events must be submitted within 24 hours. All adverse events must be reported as outlined in the protocol. The Protocol Chair is ultimately responsible for the required reporting of all adverse events to the appropriate regulatory agencies and participating institutions.

The Coordinating Center provides serious adverse event forms to be used by all participating sites. Information to be provided must include:

- **Subject ID number, and initials**
- **Date of the event**
- **Description of the event**
- **Description of site's response to the event**
- **Outcome of event**
- **Subject's status on the study (on-study, off-study, etc)**
- **Attribution of event to study drug**

The Coordinating Center maintains documentation of all adverse events for the entire study. Each site will maintain its own documentation as required.

The Principal Investigator at each site must report events per the protocol. Participating sites must also report adverse events to their local IRB according to their specific requirements and to the SKCCC Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined by the protocol must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events that may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within three (3) working days of the participating site Principal Investigator's learning of the event.

Adverse Events, which result in no change to protocol, informed consent, or risk to subjects, must be reported to the Coordinating Center on a monthly basis.

Protocol Deviation Reporting

All deviations from the currently approved protocol must be documented on the protocol deviation log provided by the Coordinating Center.

Protocol deviations that place one or more study subjects at increased risk must be reported to the Coordinating Center within 10 days of the site Principal Investigators learning of the event. Protocol deviations that do not present an increased risk to study subjects must be reported to the Coordinating Center at the time of protocol continuing review. Participating sites must also report all protocol deviations to their local IRB according to their specific requirements.

Data Submission

A detailed plan for collection and management of data from participating sites will be outlined in the study protocol and/or the letter of understanding. In addition, the Coordinating Center will issue a data submission calendar to the participating site at the time of each patient registration.

End Notes

[1] http://grants.nih.gov/grants/guide/notice-files/not98-084.html, and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

[2] http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

[4] http://irb.jhmi.edu/Policies/103_11.html

[5] http://www.hopkinsmedicine.org/Research/OPC/index.html

[6] http://cancertrials.nci.nih.gov/clinicaltrials/patientsafety/dsm-guidelines

[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

[8] NCI Reporting Guidelines at http://ctep.gov/reporting

[9] NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs

[10] http://cancertrials.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines/page5

[11] http://www.fda.gov/oc/industry/default.htm

[12] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

[13] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.150

[14] http://irb.jhmi.edu/Guidelines/reportingrequirements.html

[15] http://www.wirb.com/Pages/default.aspx

TITLE: Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors

Johns Hopkins Protocol #: J1365, NA_00085756

Merck Protocol #: MK-3475-016

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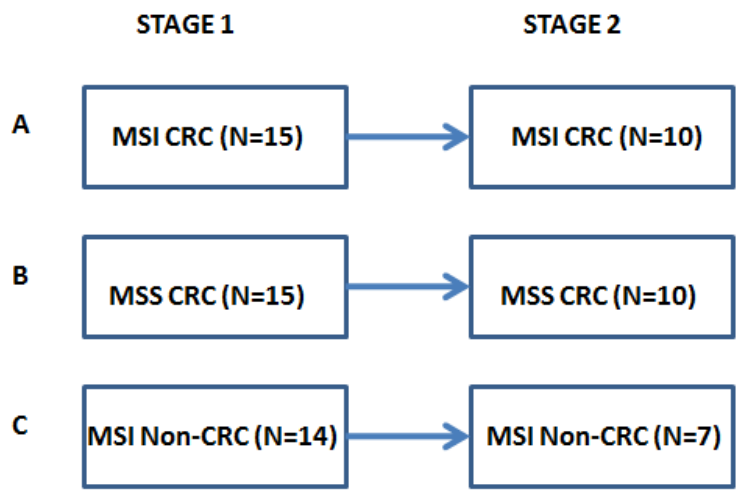
Protocol Type / Version # / Version Date: Original/ Version 1/ May 1, 2013
Original/ Version 1.1/ May 30, 2013
Amendment 1/ Version 2/ July 18, 2013
Amendment 2/ Version 3/ September 19, 2013
Amendment 3/ Version 4/ January 13, 2014
Amendment 4/ Version 5/ March 18, 2014
Amendment 5/ Version 6/ May 5, 2014
Amendment 6/ Version 7/ November 19, 2014

SCHEMA



MSI = Microsatellite Instability; MSS = Microsatellite Stability; CRC = Colorectal Carcinoma

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1. OBJECTIVES

1.1. Primary Objectives

1.1.1 To determine the immune-related progression free survival (irPFS) rate at 20 weeks and objective response rate (irORR) in patients with MSI positive and negative colorectal adenocarcinoma treated with MK-3475 using immune related response criteria (irRC).

1.1.2 To determine the immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal solid tumor malignancies treated with MK-3475 using immune related response criteria (irRC) at 20 weeks.

1.2. Secondary Objectives

1.2.1 To determine the overall survival of patients with MSI positive and negative tumors treated with MK-3475.

1.2.2 To estimate irPFS and PFS in patients with MSI positive and negative tumors treated with MK-3475 at 28 weeks using irRC and RECIST 1.1.

1.2.3 To estimate best overall response rate and disease control rate in patients with MSI positive and negative tumors treated with MK-3475.

1.2.4 To assess safety and characterize toxicities of MK-3475 in patients with MSI positive and negative tumors.

1.2.5 To evaluate MSI as a marker to predict treatment response.

1.3 Exploratory Objectives

1.3.1 To explore the association of MSI positive, PD-L1 positivity, and tumor infiltrating lymphocyte characteristics with clinical responses. Archived tumor tissue (when available) and tumor tissue obtained at baseline and during treatment will be compared. In addition, we will compare differences in PD-L1 expression between the primary and secondary sites of cancer.

1.3.2 To assess tumor tissue for molecular determinants of response, progression and disease stability using next generation sequencing technology.

1.3.3 To assess tumor burden dynamics using both standard protein biomarkers such as CEA, CA19-9, C-reactive protein, and other exploratory circulating biomarkers in serial collections of sera and plasma at baseline and throughout treatment.

1.3.4 To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and

toxicity. DNA will be extracted from whole blood and used to evaluate for any germline mutations which may correlate with response or toxicity.

1.3.5 To collect peripheral blood lymphocytes to explore the association of MSI positive, PD-1 positivity, and lymphocyte activation markers with clinical responses.

1.3.6 To determine alternative markers of MSI status. This includes but is not limited to MLH 1, MSH 2, MSH 6, PMS2, BRAF pV600E, and TGFBR2.

1.4 Study Design

This is a multi-center, open label, two-stage, phase 2 study to evaluate the clinical activity of MK-3475 in MSI positive and MSI negative solid tumors. We will enroll three cohorts of patients to receive MK-3475: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumor malignancies but not colorectal adenocarcinoma (Cohort C). MK-3475 will be administered at 10 mg/kg every 14 days. Archived tumor samples or newly obtained biopsies will be used for determining MSI. MSI positive tumors will be defined using standard clinical criteria and require at least two affected loci[1, 2]. Patients will be evaluable if they receive one dose of MK-3475 and if MSI results are confirmed using the MSI Analysis System from Promega (**section 3.4**).

The primary endpoints for Cohorts A and B are immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC); irPFS is defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC; and irORR is the proportion of subjects whose best overall response is a CR or PR. Each cohort will be assessed separately.

The primary endpoint for Cohort C is immune-related progression-free survival (irPFS) rate assessed using immune related response criteria (irRC) at 20 weeks, defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC.

This design aims to evaluate treatment benefit and evaluate MSI as a predictive biomarker for treatment with MK-3475 simultaneously.

For Cohorts A and B, MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_{10}) or less or irORR is 5% (p_{20}) or less, and considered active if the irPFS rate at 20 weeks is 25% or greater (p_{11}) and irORR is 21% or greater (p_{21}). The endpoints will be tested in the hierarchical order first with irPFS at 20 weeks. If the null hypothesis of 20-week irPFS being 5% is rejected (i.e. the result reaches statistical significance), we will proceed to test for irORR. If irPFS is not significant at the 0.05 level (one-sided test), the statistical testing for irORR will not occur.

A two-stage Green-Dahlberg design is used for Cohort A and B. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 15 evaluable patients. Based on Green-Dahlberg design, if 0 irPFS are observed, enrollment in that cohort will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 10 evaluable subjects will be enrolled into that cohort. If 3 or fewer patients are progression free at 20 weeks in the total of 25 evaluable patients enrolled in that cohort, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we proceed to test for the endpoint of irORR in that cohort. If 4 or more responders (CR or PR) are observed, we conclude the regimen is promising with that cohort and warrants further study for that cohort.

For Cohort C, MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_0) or less and considered active if the irPFS rate at 20 weeks is 25% or greater (p_1).

A two-stage Green-Dahlberg design is used for Cohort C. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 14 evaluable patients. If 0 irPFS are observed, enrollment in Cohort C will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 7 evaluable subjects will be enrolled into Cohort C. If 3 or fewer patients are progression free at 20 weeks in the total of 21 evaluable patients enrolled in Cohort C, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we conclude the regimen is promising and warrants further study for this patient population.

No intra-subject dose escalation or reduction is allowed. Patients who do not receive at least 1 dose of MK-3475 will be replaced.

Patient immune and clinical responses will be evaluated through the following methods at baseline and during treatment: 1. tumor biopsies, 2. peripheral blood lymphocytes, 3. serum and plasma, and 4. CT/MRI scans will be obtained for assessment of activity and correlative studies.

Patients who have a confirmed complete response by two scans ≥ 4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. MK-3475 may be resumed upon disease recurrence in these patients. Treatment may also be resumed in patients with SD, PR or CR who stopped MK-3475 treatment after 24 months of study therapy for reasons other than disease progression or intolerability. Criteria and procedures for retreatment are described in **Section 5.6** and **10.0**.

Patients with tumor progression by RECIST imaging or laboratory parameters prior to their 7 month evaluation but without rapid clinical deterioration or significant change in performance status who do not require additional immediate therapy, may

continue to be treated with MK-3475 and clinically observed following the assigned imaging schedule to allow detection of a subsequent tumor response. Tumor assessments will be made using RECIST 1.1 and immune-related response criteria (irRC). Subjects that meet the above criteria and continue on study therapy must discontinue MK-3475 upon confirmed documentation of PD at 7 months using irRC (or by the radiologist if irRC is still pending) unless there are signs of delayed stabilization (disease progression at week 20, but disease is stable at week 28 in comparison to week 20).

All patients will be followed for at least 30 days after their last dose of study drug (serious adverse events will be collected for 90 days after the end of treatment) or until initiation of a new anti-cancer treatment, whichever occurs first.

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first. Information of the new cancer therapy will be collected.

Patients who discontinued study therapy without documented disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) for approximately two years after the last dose of study drug, 2) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 3) documented disease progression, or 4) until death, whichever occurs first.

Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

2. BACKGROUND

2.1 Study Disease

Microsatellite instability (MSI) is the accumulation of sequencing errors in microsatellites. This occurs in tumors with deficiency in DNA mismatch repair. MSI is present in Lynch Syndrome which is an inherited cancer syndrome that predisposes patients to colon, endometrial, gastric cancer, ovarian, small intestine, liver, hepatobiliary, upper urinary tract, brain, and prostate cancer. MSI is also present in 10-20% of sporadic colorectal [3], gastric [4], prostate [5], lung [6, 7], ampullary [8], and endometrial cancers [9]. Between 0.3% and 13% of pancreatic cancers are reported to be MSI as well [10]. The study is designed to test an immunotherapy in MSI colorectal adenocarcinomas with an additional exploratory cohort in other MSI disease types.

2.2 MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [11]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [12-47]. In particular, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant MEL and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma [48; 49].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [11]. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors [12-15]. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [50]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) [16], pancreatic carcinoma [17], hepatocellular carcinoma [18], ovarian carcinoma [19] and non-small cell lung cancer (NSCLC) [28]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant MEL [20]. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. MK-3475 also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells.

Amongst 132 subjects with MEL treated with MK-3475 at 10 mg/kg Q2W (n=57), 10 mg/kg Q3W (n=54), and 2 mg/kg Q3W (n=21) the most common AEs (>15%) were fatigue, nausea, rash, diarrhea, cough, and pruritus. The most common drug-related AEs (>10%) included: fatigue, rash, diarrhea, pruritus and arthralgia. The incidence of Grade 3-5 AEs was 27%. Twenty-one potentially immune-related AEs were reported and included: rash (6 subjects, 4.5%), influenza (4 subjects, 3.0%), pruritis (3 subjects, 2.2%), eczema (3 subjects, 2.2%), vitiligo (3 subjects, 2.2%), hypothyroidism (3 subjects, 2.2%), pyrexia (2 subjects, 1.5%), arthralgia (2 subjects, 1.5%), myositis (2 subjects, 1.5%), and cough (2 subjects, 1.5%).

2.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure [IB] for Preclinical and Clinical Data

2.4 Rationale

Blockade of immune checkpoints such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) is showing promise in patients with cancer. CTLA-4 and PD-1 are upregulated on activated T cells and provide inhibitory signals to T cells undergoing activation. Inhibitory antibodies directed at these receptors have been shown to break immune tolerance and promote anti-tumor immunity. MK-3475 is a humanized monoclonal IgG4 antibody against PD-1 and is showing activity in multiple tumor types including melanoma and non-small cell lung cancer (NSCLC). Previously, activity of a different PD-1 blocking antibody, BMS-936558, a fully humanized monoclonal IgG4 antibody, also showed activity in melanoma, NSCLC, and a complete response in a single patient with colorectal cancer [28, 51].

As with all targeted therapies, we expect a subset of patients will respond to immunotherapy and there may be genetic determinants that define an 'immune responsive' phenotype. A cancer genomics perspective may provide insight as to why patients with melanoma and NSCLC, and perhaps other tumor types, respond to these therapies. The average number of somatic mutations in human cancer varies widely (**Table 1**) [52]. Three factors are known to be associated with high somatic mutation burdens: exposure to environmental carcinogens (e.g. UV radiation and tobacco) [53, 54]; repair defects (e.g., mismatch repair gene inactivation) [55]; or exposures to mutagenic therapies (e.g., alkylating agents) [56]. Melanomas and NSCLC are known to have high burdens of somatic mutations. We therefore hypothesize that there will be a correlation between the number of somatic mutations in individual tumors and the response to immune checkpoint inhibitors since each protein-coding mutation has the potential to serve as a novel antigen for an immune response. If this hypothesis is correct, it would suggest that immune checkpoint inhibitors might work best in tumors with high mutation burdens. Furthermore, tumors deficient in mismatch repair may be particularly susceptible to immunotherapy as this phenotype results in ongoing accumulation of mutations at a high frequency.

Table 1. The average number of somatic mutations in a representative group of human cancers	
Tumor	**Average # of mutations per case**
Tumors exposed to mutagenic therapies	>1000
Sun exposed melanomas	>1000
Mismatch repair deficient tumors	>600
Non-small cell lung cancers	540
Colorectal cancers	77
Pancreatic cancers	48
Glioblastomas	36
Meduloblastomas	8

MSI tumors are deficient in DNA mismatch repair which leads to a high rate of spontaneous mutations and the potential for the expression of neo-antigens. Furthermore, similar to melanoma, MSI positive colon cancers, there is often prominent lymphocyte infiltration [3, 4]. This is another clue that this subset of tumors may have baseline tumor infiltrating lymphocytes that can be harnessed with immune checkpoint blockade. Interestingly, the colorectal patient with the complete response is known to have an MSI positive tumor [57]. This study aims to evaluate MSI as a predictor of response to anti-PD-1 blockade with MK-3475.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Cohort A: Patients with histologically proven metastatic or locally advanced MSI colorectal adenocarcinoma.

3.1.2 Cohort B: Patients with histologically proven metastatic or locally advanced microsatellite stable (MSS) colorectal adenocarcinoma.

3.1.3 Cohort C: Patients with histologically proven metastatic or locally advanced non-colorectal MSI solid tumor malignancies.

3.1.4 Patients with the presence of at least one lesion with measurable disease as defined by 10mm in longest diameter for a soft tissue lesions or 15mm in short axis for a lymph node by RECIST 1.1 and irRC criteria for response assessment.

3.1.5 Patients must agree to have a biopsy at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.6 Patients with colon cancer must have received at least 2 prior cancer therapy

regimens. Patients with other cancer types must have received at least 1 prior cancer therapy regimen. Patients must have progressive disease on study entry.

3.1.7 Age ≥18 years.

3.1.8 ECOG performance status 0-1 (**Appendix A**).

3.1.9 Life expectancy of greater than 3 months.

3.1.10 Patients must have normal organ and marrow function as defined below:

– Absolute neutrophil count	≥1,000/mcL
– Platelets	≥90 x 10^3/uL
– Hemoglobin	≥9.0 g/dL
– Total bilirubin	≤1.5x ULN (patients with diagnosed Gilbert's Syndrome will not be excluded if their direct bilirubin is within normal institutional limits)
– AST(SGOT)/ALT(SGPT)	≤2.5x ULN or ≤5x ULN for subjects with liver metastases
– Creatinine	≤1.5 x ULN

3.1.11 Female patient of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

3.1.12 Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception.

Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 1 week prior to trial treatment. This is not applicable to patients with primary brain tumors.

3.2.2 Patient who has had chemotherapy, or biological cancer therapy within 2 weeks prior to the first dose of study drug. Patient who has had radiation within 4 weeks prior to the first dose of study drug.

3.2.3 Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of study drug.

3.2.4 Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.

3.2.5 Patients who have had surgery within 4 weeks of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, etc), celiac plexus block, and biliary stent placement.

3.2.6 Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies.

3.2.7 Patients who have received any of the following concomitant therapy: IL-2, interferon or other non-study immunotherapy regimens; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses) within 1 week prior to first dose. Note: Systemic steroid therapy allowed for subjects with primary brain tumors as long as ≤ dexamethasone 4 mg or its steroid equivalent.

3.2.8 Patients who have received a live vaccine within 4 weeks prior to or after any dose of MK-3475.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.2.9 Patients receiving growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), erythropoietin, etc. within 2 weeks of study drug administration. Use of such agents while on study is also prohibited.

Prior use of growth factors should be documented in the patient's medical history.

3.2.10 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 History of any autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with thyroid disease will be allowed. Autoimmune diagnoses not listed here must be approved by the protocol chair.

3.2.13 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), hepatitis B, or hepatitis C infection.

3.2.14 Patients with evidence of interstitial lung disease.

3.2.15 Patients with a pulse oximetry of <92% on room air.

3.2.16 Patients on supplemental home oxygen.

3.2.17 Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

3.2.18 Women who are pregnant or breastfeeding.

3.2.19 Women with a positive pregnancy test on enrollment or prior to investigational product administration.

3.2.20 Sexually active fertile men not using effective birth control if their partners are WOCBP.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 MSI Testing

MSI testing is already standardized and performed in CLIA-certified laboratories without need for assay development. Archived tumor samples or newly obtained

biopsies will be used for determining MSI. For patients who do not have sufficient normal tissue for MSI testing purposes, a buccal swab or purple top blood tube will be obtained. MSI testing in colorectal cancer is already clinically indicated. For other non-colorectal cancers where MSI testing is not currently clinically indicated, a pre-screening consent will be obtained to collect tissue for MSI testing. The prescreening consent can be obtained over the phone. A copy of the consent will be faxed to the site and the original will be mailed. MSI status will be performed locally by CLIA certified immunohistochemistry (IHC) or PCR based tests for eligibility.

Evaluable patients will be confirmed using the MSI Analysis System from Promega. This test will determine MSI status through the insertion or deletion of repeating units in the five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24). At least 2 MSI loci are required to be evaluable in Cohorts A and C. Patients may be assigned to a new cohort and/or replaced based on the Promega test results.

The MSI Analysis System (Promega), Version 1.2, is a fluorescent multiplex PCR-based method used to detect microsatellite instability (MSI), a form of genomic instability. This instability is due to insertion or deletion of repeating units during DNA replication and failure of the mismatch repair system (MMR) to correct these errors. MSI analysis typically involves comparing allelic profiles of microsatellite markers generated by amplification from matching pairs of test samples, which may be MMR-deficient, and normal tissue samples. New alleles in the abnormal sample not found in the corresponding normal sample indicate the presence of MSI.

The MSI Analysis System, Version 1.2, includes fluorescently labeled primers (marker panel) for co-amplification of seven markers for analysis of the MSI-high (MSI-H) phenotype, including five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24) and two highly polymorphic pentanucleotide repeat markers (Penta C and Penta D). Amplified fragments are detected using an ABI PRISM® 310, 3100, 3100-Avant, 3130 or 3130xl Genetic Analyzer after spectral calibration. GeneMapper® 4.0 software will be used for data analysis and assignment of genotype.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should call the Lead Study Coordinator at 443-287-7846 or aeyring1@jhmi.edu to verify drug availabilities. The fax cover sheet, Registration Form, and Eligibility Worksheet will be supplied to each participating site.

Following registration, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with Dr. Le or Dr. Diaz. If a patient does not receive protocol therapy following registration, the

patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and faxed 410-502-5860 or e-mailed aeyring1@jhmi.edu to the Lead Study Coordinator:

- Fax cover sheet
- Registration Form
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Checklist
- Copy of required screening tests and scans

The Research Nurse or Study Coordinator at the participating site will then call 443-287-7846 or e-mail the Lead Study Coordinator to verify eligibility. To complete the registration process, the Lead Study Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
MK-3475	No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient per **section 5.2.1**.	10 mg/kg	IV over 30 minutes	Day 1	14 days

MK-3475 will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However,

given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The pharmacists will prepare the MK-3475 medication for administration. The Procedures Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration. This document is available for reference by the pharmacist and study personnel.

5.2 General Concomitant Medication and Supportive Care Guidelines

MK-3475 is a humanized monoclonal Ab. Subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study.

5.2.1 Infusion Reactions

MK-3475 infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with MK-3475 are shown below.

Guidance on Infusion and Hypersensitivity Reactions:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 3 or 4 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 stop the infusion.** Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. Additional appropriate medical therapy may include but is not limited to: • Epinephrine • IV fluids, • Bronchodilators • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (e.g., 1-2 mg/kg/day of prednisone or equivalent), Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.** **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE).		

5.2.2 Immune-Related Adverse Events (IRAEs)

Blocking PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritis, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events, now termed IRAEs, noted in previous BMS 936558 studies.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE CRF. Identification and treatment of IRAEs can be found in **Appendix B**.

Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz immediately. In addition, irAEs listed in **Section 7.1.3** must be reported as an Event of Clinical Interest (ECI) within 24 hours to the Sponsor and Merck Global Safety even if no Serious Adverse Event Criteria are met.

5.3 Dosing Criteria

Dosing will be delayed for the following laboratory criteria:

- AST, ALT > 2.5 x ULN (AST, ALT >5 x ULN for patient with liver metastases)
- Total bilirubin >1.5 x ULN (patients with diagnosed Gilbert's Syndrome, direct bilirubin should be within normal institutional limits)
- Hemoglobin < 8 g/dL
- ANC < 1000/uL
- Platelets < 80 x 10^3/uL

5.4 Definition of an Overdose for this Protocol

Overdose is defined as:
The patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to the Sponsor and Merck Global Safety. Merck Global Safety (GS) contact information can be found in Section 7.5.1.

5.5 Contraception, Use in Pregnancy, Use in Nursing

5.5.1 Contraception

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also required for the female partners of male patients). The 2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1through 120 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1

through 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.5.2 Use in Pregnancy

MK-3475 may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck Global Safety without delay. The outcome must be reported to the Sponsor within 24 hours and to Merck Global Safety if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the Sponsor and to Merck Global Safety as described in Section 7.5.1. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor and to Merck Global Safety.

5.5.3 Use in Nursing Women

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

5.6 Duration of Therapy

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- No sign of disease stabilization by 7 months,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see **section 5.9.2**),
- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines (see **section 6.2**)
- Patient withdraws consent,
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The Sponsor and Merck should be included in this decision,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up, or
- Patient becomes pregnant.
- Completed 24 months of treatment with MK-3475

Note: 24 months of study medication is calculated from the date of first dose.

Patients who stop MK-3475 with SD or better may be eligible for up to one year of additional MK-3475 therapy if they progress after stopping MK-3745 and they meet the following criteria:

EITHER

- Stopped initial treatment with MK-3475 after attaining an investigator determined confirmed CR according to RECIST 1.1
  - Was treated for at least 24 weeks with MK-3475 before discontinuing therapy
  - Received at least two treatments with MK-3475 beyond the date when the initial CR was declared

OR

- Subject had SD, PR or CR and stopped MK-3475 treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475
- Did not receive any anti-cancer treatment since the last dose of MK-3475
- Have a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in **Section 5.3**
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (**Section 5.5.1**).
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation. Study visit requirements are outlined in the Study Calendar (**section 10.0**).

5.7 Off Study/Safety Follow-up Visit

After a patient is discontinued from MK-3475, a mandatory Off Study/Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **sections 5.7 and 10.0** as appropriate. The patient will be monitored for adverse events up to the mandatory Off Study/Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

5.8 Duration of Follow Up

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

Patients, who discontinued study therapy without documented disease progression, should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every 12 weeks until, 1) for approximately

two years after the last dose of study drug, 2) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 3) documented disease progression, or 4) until death, whichever occurs first.

Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

5.9 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 5.6** applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.9.1 Disease Progression

MK-3475 is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of MK-3475 dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor progression by RECIST imaging or laboratory parameters prior to their 7 month evaluation but without rapid clinical deterioration or change in PS who do not require additional immediate therapy, may continue to be treated with MK-3475 and clinically observed following the assigned imaging schedule to allow detection of a subsequent tumor response. Tumor assessments will be made using RECIST 1.1 and immune-related RECIST criteria (irRC). Subjects that meet the above criteria and continue on study therapy must discontinue MK-3475 if there are no signs of disease stabilization by 7 months using irRC (or by the radiologist if irRC is still pending).

5.9.2 IRAEs

Permanent discontinuation of MK-3475 should be considered for any of the following:

1. Severe or life-threatening related adverse reactions, including, but not limited to, any of the following (Sponsor and Merck must be notified in the event of these AEs, and final decision regarding treatment will be made after a discussion):

   - Grade 3-4 toxicity (non-hematologic or hematologic). Grade 3 toxicities may be able to be re-dosed on a case by case basis after approval of the Sponsor and Merck.

   - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal

   - Total serum bilirubin >3 times upper limit of normal

   - Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations

   - Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy

   - Any grade Guillain-Barré syndrome, or myasthenia gravis or other neurologic symptoms that impact activity of daily living

   - Severe immune-mediated reactions involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)

   - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

   - Grade 4 infusion reaction

2. Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤10 mg prednisone or equivalent per day

   If any of the above events occur, the investigator should discuss with Sponsor and Merck to make a decision on discontinuation of MK-3475 study treatment.

In case toxicity does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of MK-3475 study drug, study therapy discontinuation should be considered after discussion with the Sponsor and Merck. With Sponsor and Merck agreement, patients still at Grade 2 may continue in the study only if asymptomatic and controlled. Two dosing delays due to the same toxicity will be permitted. In the event of a third occurrence of the same toxicity which would require dosing delay, study therapy will be discontinued permanently.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications

Dose reduction or dose increase of MK-3475 will not be permitted in individual patients.

6.2 Dosing Delays

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per the table below:

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, ~~3~~	No	N/A	N/A	N/A
	3[a]	**Yes**	**Toxicity resolves to Grade 0-1 or baseline**	**May increase the dosing interval by 1 week for each occurrence**	**Toxicity does not resolve within 12 weeks of last infusion** ***Permanent discontinuation should be considered for any severe or life-threatening event***
	4	Yes	Toxicity resolves to Grade 0-1 or baseline**, only after discussion with Principal Investigator**	May increase the dosing interval by 1 week	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity · Grade 2 alopecia · Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1 and 5.6.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

	4	Yes	Toxicity resolves to Grade 0-1 or baseline, only after discussion with Principal Investigator	Increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion. *Permanent discontinuation should be considered.*

[a]Excluding Grade 3 neutropenia, anemia, and thrombocytopenia from the dose modification instructions.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With Sponsor and Merck agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will only be followed for 30 days unless related to the investigational agent. All Serious adverse events will be collected for 90 days after the end of treatment.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz. In addition, irAEs listed in **Section 7.1.3** must be reported as an Event of Clinical Interest (ECI) within 24 hours to the Sponsor and to Merck Global Safety even if no Serious Adverse Event Criteria are met.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

7.1 Definitions

7.1.1 Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

7.1.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- 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 for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
- 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 [eg, 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.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Events **not** considered to be serious adverse events are hospitalizations for the:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a 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).

7.1.3 Adverse Events of Clinical Interest (ECI) for MK-3475

These selected non-serious related adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event of Clinical Interest Case Report Form found in **Appendix C**.

Events of clinical interest for this trial include:

- an overdose of Merck's product, as defined in **Section 5.4**, that is not associated with clinical symptoms or abnormal laboratory results.

- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal <u>and</u> an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal <u>and</u>, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *<u>Note</u>: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

- Events that are CTCAE Grade 2 and higher and considered by the Investigator to be irAEs should be discussed with Dr. Le or Dr. Diaz immediately. In addition, irAEs listed in the table below must be reported as events of clinical interest within 24 hours to the Sponsor and to Merck Global Safety.

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

7.2 Relationship

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

7.4 Handling of Expedited Safety Reports

In accordance with local regulations, the Sponsor (Dr. Diaz) will notify investigators of all SAEs that are unexpected (ie, not previously described in the Investigator Brochure), and definitely, probably, or possibly related to MK-3475. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators within 48 hours. Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of ESRs by the investigator to Health Authorities should be handled according to local regulations.

7.5 Reporting

7.5.1 General

All adverse events (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs).

In addition, all serious adverse events, regardless of causality to study drug and/or administration device, will be reported promptly to Dr. Luis Diaz (fax: 443-873-5067, e-mail: Ldiaz1@jhmi.edu) within 24 hours of recognition of the adverse event using the form found in **Appendix D**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

All serious adverse events, regardless of causality to study drug and/or administration will be forwarded to Merck's Global Safety ("Merck GS") group within 24 hours of learning of the event.

Non-serious Events of Interest will be forwarded to Merck GS and will be handled in the same manner as SAEs.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, that occurs during the trial or within 120 days of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to Merck GS.

SAE reports and any other relevant safety information are to be forwarded to Merck GS facsimile number: +1-215-993-1220.

7.5.2 Institutional Review Board (IRB)

Participating sites will be responsible for reporting to their IRB. All serious adverse events will be reported to the IRB per institutional standards within 3 business days of recognition of the adverse event if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product. If the serious adverse event is unrelated to administration of the investigational agents, then it will be reported to the IRB within 15 days of recognition of the serious adverse event. Upon receipt of the report of the serious adverse event by IRB, follow-up information will be given to the IRB within 15 days.

7.5.3 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the Sponsor (Dr. Diaz).

7.5.3.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-827-9796) to the FDA within 7 calendar days of first learning of the event.

15 Calendar-Day Written Report:
The Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event.

7.5.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the Sponsor-Investigator.

8. PHARMACEUTICALINFORMATION (MK-3475)

8.1 Agent Accountability

The sponsor/investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

8.2 Mode of Action

MK-3475 is a highly selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

8.3 Description

Clinical Supplies will be provided by Merck as summarized in the table below:

Product Name & Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Injection

8.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open label kits will be provided for patient dosing.

8.5 Preparation

Refer to Procedures Manual for preparation instructions.

8.6 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Refer to Procedures Manual for Storage conditions.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.7 Stability

Refer to Procedures Manual for Stability information.

8.8 Route of Administration

The reconstituted product is intended for IV administration.

8.9 Patient Care Implications

Based on results from the nonclinical studies, there are currently no specific safety considerations. MK-3475 is a humanized monoclonal Ab. Thus far, serious infusion reactions have been infrequent and manageable. However, subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study. In the event that a subject experiences an allergic reaction to MK-3475, treatment (i.e., vasopressors, H2-blockers, antihistamines, H1-blockers, steroids) should be administered, as appropriate, and prophylaxis should be considered. Surveillance for the appearance of HAH is included in all protocols.

MK-3475 has the same mechanism of action as BMS 936558. Preclinical studies have suggested similar potency, and PK modeling has suggested similar human PK. Accordingly, the adverse events observed with BMS 936558 may serve as in indicator for the adverse events to expect for MK-3475 in cancer patients. Immune-related AEs (irAEs) are of special interest because of the mechanism of action of anti-PD-1 and prior experience with anti–CTLA-4 mAbs. Up to the cut-off date for this IB, the only possibly irAEs included pneumonitis (Grade 2), arthralgia and myalgia. One case of intestinal perforation was not considered immune related.

Overall, MK-3475 has been safe and well tolerated. However, prompt identification of irAEs and appropriate treatment (e.g. withdrawal of study medication and treatment with corticosteroids) will be critical to optimizing the therapeutic index. Individual protocols and the Guidance for Identification and Treatment of IRAEs **(Appendix B)** outline specific guidance for prompt identification and treatment of irAEs. Timely discussions of how to manage irAEs is also encouraged.

8.10 Agent Ordering

Requests for MK-3475 should be sent via email to:

Mark Anthony Lee
Merck Sharp & Dohme Corp.
351 North Sumneytown Pike
North Wales, PA 19454
Mailstop: RY34-A297
phone: 732-594-1138
email: mark_lee@merck.com

8.11 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9. CORRELATIVE/SPECIAL STUDIES

Sample collection, storage, and shipment instructions will be provided in the Procedures Manual.

9.1 Tumor Tissue Studies

Tumor biopsies will be collected (if a patient's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at the 20 week timepoint (4-6 cores per timepoint). Additional optional biopsies may be obtained later in the course of therapy. Archival tumor samples will also be collected for every patient (slides and/or blocks). Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the procedures manual.

9.1.1 To explore the association of MSI positive, PD-L1 positivity, and tumor infiltrating lymphocyte characteristics with clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment (20 weeks) will be compared. PD-L1 expression may predict response to anti-PD-1 [28, 51]. However, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre and post-treatment tumor biopsies will also be analyzed for PD-1 expression as well as infiltration of immune cells (effector T cells, Tregs, B cells, dendritic cells, etc). Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches. Preliminary data from a pancreatic cancer immunotherapy study suggests that induction of a $T_h1$and T_h17 phenotype at the tumor itself predicts response. Furthermore, upregulation of other inhibitory molecules such as IL-10 and TGF-β may identify other targets for combinatorial strategies.

Slides from a newly obtained biopsy sample of at least one tumor lesion at baseline or from archived tissue will be submitted for PD-L1 and biomarker staining. Biopsy or archival tissue samples should have proper size to enable IHC analysis of PD-L1.

9.1.2 The Ludwig Center for Cancer Genetics will perform whole-exome sequencing using next-generation sequencing on DNA from tumors and matched normal tissue. As with all targeted therapies, we expect a subset of patients will respond to immunotherapy and there may be genetic determinants that define this response. These studies will define the genetic landscape of these tumors and may determine an 'immune responsive' phenotype. Furthermore, since each mutation is a potential neo-antigen that may drive an immune response, we will evaluate each mutation for antigenic potential in our model [58].

9.1.3 In cases, where the genes listed are known to be mutated, we will test for MSI status since there is a correlation between MSI status and these mutations.

Deleterious mutations in the following genes:

- MLH 1
- MSH 2
- MSH 6
- PMS2
- BRAF pV600E
- TGFBR2

9.2 Peripheral Blood Lymphocytes (PBLs)

Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS and MSI positivity. PBL will be collected at baseline, 2 weeks, 4 weeks, 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter. PBL are isolated and stored frozen until use.

9.3 Serum and Plasma Marker Studies

Sera and plasma will be collected at baseline, 2 weeks, 4 weeks, 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. In addition, we will look at alternative methods to identify MSI in circulating tumor DNA. Whole blood will be collected in a 10 milliliter Serum Separator Tube (SST tube) at the designated time points and processed using standard laboratory procedures. Using a pipette, aliquots of 1 mL of serum should be transferred to cryogenic vials and stored at -80°C.

We will also collect whole blood in two 10 mL plasma preparation tubes with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) and gently swirl tubes to mix blood with EDTA. Within two hours of collection, the sample will be processed using standard procedures for plasma separation. Plasma will be divided into 1 mL aliquots and stored at -80°C. Pellets from this separation procedure will be washed in PBS and then divided into aliquots and also stored at -80°C.

9.4 Normal tissue based studies

To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA will be extracted from whole blood (collection and processing described in 9.3) and used to evaluate for any germline mutations that may correlate with response or toxicity. A SNP array may be performed on each case using the Affymetrix Genome-wide Human SNP Array 6.0 (Santa Clara, CA).

9.5 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities. Detailed instructions for tissue collection and shipment are provided in the procedures manual.

10. STUDY CALENDAR

Study Procedures	Pre-Study[19]		Cycle (14 days)[20]	20 Weeks[21]	Off Study[22]
Visit Windows (days)[1]	N/A	-28 to -1	+7	**+/- 14**	+/- 14
MK-3475			X		
Pre-screening consent[2]		X			
Informed consent		X			
Inclusion/exclusion criteria		X			
Demographics		X			
MSI Testing	X				
Medical history		X			
Cancer History[3]		X			
Concurrent meds		X	X	**X**	X
Physical exam[4]		X	X	**X**	X
Vital signs[5]		X	X	**X**	X
Height	X				
Weight		X	X	**X**	X
Performance status (PS)		X	X	**X**	X
Hematology profile[6, 12]		X	X	**X**	X
Chemistry profile[7, 12]		X	X	**X**	X
TSH, T3, FT4[8, 12]			X	**X**	X
Urinalysis & Microscopic Exam[9, 12]		X			
B-HCG[10, 12]		X			
Serum Tumor Markers[11, 12]		X	X	**X**	X
Adverse event evaluation			X	**X**	X
Radiologic evaluation[13]		X	X	**X**	X
Tumor measurements[13]		X	X	**X**	X
Whole blood for PBL (approximately 32cc)[14]			X	**X**	
Serum (approximately 10cc)[14]			X	**X**	
Whole Blood Sample for Plasma (approximately 20cc)[14]			X	**X**	
Lactoferrin[15]		X			
Archival Tissue[16]		X	X		
Tumor Biopsies[17]		X		**X**	
Buccal Swab/purple top tube[18]		X	X		

1: Longer delays to be approved by the Sponsor.
2: Pre-screening informed consent for MSI testing (Cohort C only).
3: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens.
4: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion.
5: Temperature, respiration rate, blood pressure, and pulse should be taken at baseline, prior to MK-3475 infusion, and at the end of the infusion. Pulse oximetry should be taken at baseline and prior to each MK-3475 infusion.
6: CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
7: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
8: TSH (Total T3 and Free T4 if TSH is outside the normal range).
9: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
10: Serum or urine pregnancy test (women of childbearing potential).
11: Disease specific tumor markers where appropriate. C-reactive protein for all patients starting with Cycle 1.
12: Labs may be collected within a window of up to 3 days prior to dosing.
13: Radiologic evaluations and tumor measurements will be performed at baseline (within 14 days prior to the first dose of MK-3475), 12 weeks (+/- 2 week), and then every 8 weeks (+/- 2 week) thereafter including the off study evaluation. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.
14: See Correlative Studies I table below for further details.
15: Values at baseline and when a patient is being evaluated for potential colitis will be collected when available.
16: Attempts to obtain archival tumor samples will be made for every patient until the sample is obtained or documentation that the sample cannot be obtained. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspirates will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
17: Tumor biopsies to be taken (if a patient's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at the 20 week timepoint (4-6 cores per timepoint). Additional optional biopsies may be obtained later in the course of therapy. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
18: Buccal swabs and/or purple top tube will be obtained only for those patients who do not have enough normal tissue for MSI testing. This collection can occur any time after consent.
19: Patients who stop MK-3475 with SD or better may be eligible for up to one year of additional MK-3475 therapy if they progress after stopping MK-3745 and they meet the criteria listed in Section 5.6 must undergo the following evaluations: interval medical and cancer history, physical exam, vitals, weight, PS, hematology and chemistry profile, autoimmune and endocrine panel, urinalysis, serum or urine pregnancy test, serum tumor markers, radiographic evaluations, and tumor measurements. The following samples will be collected at baseline and while on study: peripheral blood, serum, whole blood for plasma, and biopsy. Subjects who restart treatment after relapse should resume at the same dose and cycle interval which they were receiving prior to discontinuation.
20: For cycle 1, study procedures do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.
21: Week 20 evaluations (calculated from the date of the first dose), which include additional blood, CT/MRI scans and tumor measurements, may coincide with a cycle visit. All week 20 evaluations must be completed at the Week 20 time point.
22: 30 days after their last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. Patients who discontinue from treatment should be contacted every three months to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.

Correlative Studies I						
	Baseline	**2 Weeks**	**4 Weeks**	**12 Weeks**	**20 Weeks**	**Q 8 Weeks**
Whole blood for PBL (approximately 32cc) [1]	X	X	X	X	X	X
Serum (approximately 10cc) [1]	X	X	X	X	X	X
Whole Blood Sample for Plasma (approximately 20cc) [1]	X	X	X	X	X	X

1: Blood and serum samples will be collected at baseline (Day -28 to Day 1), 2 weeks (+/- 1 week), 4 weeks (+/- 1 week), 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response at the 12 week timepoint and then every 8 weeks thereafter. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [**Appendix E**] and the immune related Response criteria (irRC) [**Appendix F**]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. RECIST and irRC response assessments will be performed locally for the trial and centrally at Johns Hopkins for publication.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MK-3475.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on

CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: A PET-CT can be used to obtain the images as long as the CT is of diagnostic quality.

11.1.3 Duration of Response as per RECIST 1.1 and irRC

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. In order to be considered durable, Stable Disease must be maintained for at least 6 weeks (this will be attained by the 9 week time point).

11.1.4 Progression-Free Survival (PFS) as per RECIST 1.1 and irRC

PFS is defined as the duration of time from start of treatment to time of first documented progression or death, whichever occurs first.

11.1.5 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines and instructions for AE reporting can be found in **Section 7.0 (Adverse Events: List and Reporting Requirements)**.

12.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

Protocol Chair
The Protocol Chair is responsible for performing the following tasks:
- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

Coordinating Center
The Coordinating Center is responsible for performing the following tasks:
- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites
Participating sites are responsible for performing the following tasks:
- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.

- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

12.2 Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled to include the Investigator and Merck representatives. During these meetings, the Investigator shall provide Merck with study progress updates. The Investigator will provide a summary of key points from the weekly meetings with a focus on safety of the protocol participants, enrollment status, and progress of data for objectives. In addition, Merck will provide safety and applicable program updates to the Sponsor.

12.3 Monitoring

This is a DSMP Level II study under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan (DSMP, 12/6/2012, **Appendix G**). Eligibility for all sites will be monitored by the JHU SKCCC CRO. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP). The protocol will be monitored internally by the Principal Investigator at each site. External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating site(s): The protocol will be monitored by the internal CRO at each site. A report of the reviews will be submitted to the Johns Hopkins principal investigator and SKCCC CRO.

Authorized representatives of the Coordinating Center may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and

data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Dr. Diaz will be holding the IND for this study. He will comply with all regulated reporting requirements to the FDA.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a multicenter, open-label, two-stage, phase 2 study to evaluate the clinical activity of MK-3475 in MSI positive and MSI negative solid tumors. We will enroll three cohorts of patients: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumor malignancies but not colorectal adenocarcinoma (Cohort C); all cohorts will receive MK-3475. Each cohort will be assessed separately. This design aims to evaluate MSI as a biomarker and evaluate treatment benefit simultaneously.

The primary endpoints for Cohorts A and B are immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC); irPFS is defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC; and irORR is the proportion of subjects whose best overall response is a CR or PR.

The primary endpoint for Cohort C is immune-related progression-free survival (irPFS) rate assessed using immune related response criteria (irRC) at 20 weeks, defined as the proportion of subjects alive and free of disease progression at 20 weeks per irRC. Each cohort will be assessed separately.

The secondary efficacy endpoints include overall survival, progression-free survival according to RECIST 1.1 (PFS), best overall response (BOR), duration of objective response (DOOR), time to objective response (TDOR), and disease control rate (DCR) per RECIST 1.1, and irPFS, irBOR, irDOOR, irTDOR, irDCR per irRC.

We will also evaluate safety and toxicity of MK-3475. We will evaluate exploratory endpoints of pharmacogenomics and predictive biomarkers for responses.

13.2 Sample Size/Accrual Rate

For Cohort A and B, a total of 25 evaluable patients are planned.

MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_{10}) or less or irORR is 5% (p_{20}) or less, and considered active if the irPFS rate at 20 weeks is 25% or greater (p_{11}) and irORR is 21% or greater (p_{21}). We will apply a step-down gatekeeping procedure to preserve a study-wise type I error rate at 0.05 when evaluating co-primary endpoints of irPFS

and irORR for Cohort A and B. Specifically, the endpoints will be tested in the hierarchical order first with irPFS at 20 weeks. If the null hypothesis of 20-week irPFS being 5% is rejected (i.e. the result reaches statistical significance), we will proceed to test for irORR. If irPFS is not significant at the 0.05 level (one-sided test), the statistical testing for irORR will not occur. Twenty-five patients in Cohort A and B would provide 90% power to detect an improved irPFS rate at 20 weeks from 5% to 25%, a 20% increase, at significance level of 0.05 based on a one-sided test. For an improved irORR from 5% to 21%, a total of 25 patients would provide 80% power to detect an of 16% increase using a one-sided exact binomial test at a 0.05 significance level.

For Cohort A and B, there will be 1 interim and 1 final analysis for irPFS, and 1 final analysis of irORR. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 15 evaluable patients. According to Green-Dahlberg design, if 0 irPFS are observed, enrollment in that cohort will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 10 evaluable subjects will be enrolled into that cohort. If 3 or fewer patients are progression free at 20 weeks in the total of 25 evaluable patients enrolled in that cohort, then the regimen will be considered inactive. If 4 or more patients are progression free at 20 weeks, we proceed to test for the endpoint of irORR for that cohort. If 4 or more responders (CR or PR) are observed, we conclude the regimen is promising with that cohort and warrants further study.

There is a 1.3% probability of stopping for futility under the alternative hypothesis p_{11} (i.e. incorrectly stopping at the interim when the drug is efficacious) and a 46% probability of stopping for futility under the null hypothesis p_{10} (i.e. correctly stopping at the interim when the drug is not efficacious).

For Cohort C, a total of 21 evaluable patients are planned, respectively. MK-3475 will be considered to be inactive and of no interest for further evaluation if the irPFS rate at 20 weeks is 5% (p_0) or less and considered active if the irPFS rate at 20 weeks is 25% or greater (p_1).

A two-stage Green-Dahlberg design is used for Cohort C. An interim analysis will be conducted in order to assess futility after irPFS at 20 weeks are available for the first 14 evaluable patients. If 0 irPFS are observed, enrollment in Cohort C will be terminated. If at least one patient is free of disease progression at 20 weeks per irRC, an additional 7 evaluable subjects will be enrolled into Cohort C. If 3 or fewer patients are progression free at 20 weeks in the total of 21 evaluable patients enrolled in Cohort C, then the regimen will be considered inactive in that cohort. If 4 or more patients are progression free at 20 weeks, we conclude the regimen is promising and warrants further study this patient population.

This design provides 81% power to detect an improved irPFS rate at 20 weeks from 5% to 25% in Cohort C respectively, a 20% increase, with a type I error of 0.05. There is a 1.8% probability of stopping for futility under the alternative hypothesis p_1 (i.e. incorrectly stopping at the interim when the drug is efficacious) and a 49%

probability of stopping for futility under the null hypothesis p_0 (i.e. correctly stopping at the interim when the drug is not efficacious).

13.3 Stratification Factors

We will enroll three cohorts of patients based on disease and MSI status: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumor malignancies but not colorectal adenocarcinoma (Cohort C);

13.4 Analysis of Primary Endpoints

For Cohort A and B, immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate (irORR) assessed using immune related response criteria (irRC) are co-primary endpoints. irPFS rate at 20 weeks will be estimated as the proportion of patients alive and free of disease progression at 20 weeks per irRC, along with its 95% confidence interval (CI); irORR will be estimated as the proportion of subjects whose best overall response is either a CR or PR with corresponding 95% CI. The patients who drop out of the study due to toxicity and do not have a follow-up scan will be considered non-responders. The formal statistical testing for irORR will take place only if 20-week irPFS is statistically significant. For Cohort C, irPFS will be the primary endpoint. The evaluable population includes all subjects who receive at least one dose of MK-3475 and have MSI results confirmed using the MSI Analysis System from Promega (**section 3.4**). This test will determine MSI status through the insertion or deletion of repeating units in the five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24). At least 2 MSI loci are required to be evaluable in Cohorts A and C. Patients may be assigned to a new cohort and/or replaced based on the Promega test results.

13.5 Analysis of Secondary Endpoints

Overall survival (OS) is the time from the first day of study treatment with MK-3475 to the date of death due to any cause. A subject who has not died will be censored at last known date alive. Kaplan-Meier curves will be used to summarize OS.

The analyses described below will be conducted on the basis of responses as assessed by both RECIST v1.1 and irRC. Summary statistics will be provided for each cohort as well as for each tumor type for Cohort C. The analysis will also be conducted in PD-L1+ versus PD-L1- protein expression subgroups.

PFS is defined as the time from the first day of study treatment to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Kaplan-Meier curves will be used to summarize PFS.

ORR is defined as the proportion of subjects whose best overall response (BOR) from baseline is either a CR or PR. BOR is determined by the best response designation recorded between the date of the first study treatment and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue MK-3475 beyond progression, the BOR should be determined based on response designations recorded at the time of the initial progression. DCR is the proportion of patients with CR, PR, or SD.

Among patients with an objective response, DOOR is defined as the time between the date of initial complete or partial response to the date of the first documented tumor progression or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTOR is defined as the time from the first day of study treatment to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

13.6 Safety Analysis

The safety analysis will be performed in all treated subjects. Toxicity will be tabulated by type and grade.

13.7 Biomarker Analysis

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond toMK-3475 and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily- as outlined in the exploratory objectives- on germline mutations and SNPs, and on MSI positive, PD-L1 positivity, and tumor infiltrating lymphocyte in tumor specimens. Similar analyses will be completed with peripheral blood samples. We will also explore standard protein biomarkers such as CEA, CA19-9, C-reactive protein, and other exploratory circulating biomarkers.

Associations between biomarkers and efficacy measures will be analyzed on all subjects with available biomarker data. Efficacy measures will include OS and standard and immune criteria of response and PFS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made. Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. The relationships between binary measures (e.g. response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios,

or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Guidance for Identification and Treatment of IRAEs

Merck has developed the following guidelines regarding how to identify, evaluate and manage irAEs that may occur in patients receiving MK-3475. It is possible that irAEs other than those listed in this document may be observed in patients receiving MK- 3475, therefore all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune related. This document is meant to be a general guidance; therefore, recommendations in the current document might not be all inclusive. As such Investigators are encouraged to contact Dr. Le or Dr. Diaz as needed to discuss cases that warrant separate discussion outside of the scope of current guidelines. Permanent discontinuation of MK-3475 due to irAE may be subject of discussion between the Sponsor and treating Investigator. Unless specified later in this document, the general approach to handling irAEs is as follows:

– Mild (Grade 1) irAEs – provide symptomatic treatment.
– Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated.
– Clinically significant or severe (≥Grade 3) irAEs –discontinue MK-3475 and treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg prednisone or equivalent per day within 12 weeks.

All AEs are to be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (http://ctep.cancer.gov).

If an irAE does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of MK-3475, study therapy discontinuation should be considered after discussion with Dr. Le or Dr. Diaz. With Investigator and sponsor agreement, patients still at Grade 2 may continue in the study only if asymptomatic and the event is under control. Two dosing delays due to toxicity will be permitted. If a third dosing delay is required study therapy will be discontinued permanently.

These guidelines will be periodically updated as new information becomes available.

Note: Steroid tapers should be gradual. Rapid reductions in steroid dose after an initial pulse which is often used in the standard treatment of autoimmunity should be avoided. An example of how a steroid taper could be carried out after initial high dose steroids is as follows: if the patient's status is clinically improving, the steroids can be tapered every 3 days or so, cutting the dose by a third to a half each time, until he gets down to the equivalent of 60-80 mg/day of prednisone. At that point, the taper should be slowed down, cutting by 10-20 mg each time. The duration of the entire steroid course should be at least 3 weeks.

However, patients with lower grade toxicity may have been able to be tapered from lower doses of steroids i.e. 60mg/day using a 4 week taper.

Skin

Relevant Clinical Experience
Ipilimumab - skin irAEs (rash, pruritus) of any grade were reported in 47 to 68% of patients, with 4% being Grade 3 or 4. While most dermatologic irAEs are successfully managed with symptomatic treatments, rare cases (<1%) of life-threatening irAEs (toxic epidermal necrolysis and Stevens-Johnson syndrome) were reported for patients treated with ipilimumab. As such early identification of skin irAEs and dermatology consult is recommended.
BMS-936558 (MDX-1106) – the most common skin irAEs of any grade were rash (16%) and pruritus (9%). The only severe skin irAE was pruritus reported in one patient.
BMS-936559 (MDX-1105) – the most common skin irAEs of any grade were rash (7%) and pruritus (6%), no events were Grade 3 or 4.

Symptoms
Symptoms may include (but not limited to):
– Rash
– Pruritus

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

Course of Action
Grade 1-2 events:
– Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl).
– Withhold MK-3475 if Grade 2 symptoms persist for > 1 week despite above treatment. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3 events:
– Discontinue MK-3475.
– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 4 events:
– Discontinue MK-3475 and initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Pneumonitis

Relevant Clinical Experience
Ipilimumab – pneumonitis of any grade was reported in less than 1% of patients.
BMS-936558 (MDX-1106) – pneumonitis of any grade was reported in 3% of patients, with 1% of the events being Grade 3 or 4. There were 3 drug related deaths due to pneumonitis.
BMS-936559 (MDX-1105) – pneumonitis of any grade has not been reported.

Symptoms
Symptoms may include (but not limited to):
– Dyspnea*
– Dry cough
– Hemoptysis
– Fever
– Chest pain and/or tightness*
– Abnormal breath sounds
– Fatigue

*If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Course of Action
Grade 1 events – (asymptomatic with radiographic findings only):
– MK-3475 may be continued only if the radiographic findings are subtle and has been documented to be stable over a 2 week period on CT imaging.
– Radiologic findings should be followed on serial imaging studies.
– Consider pulmonary consultation and/or bronchoscopy if clinically indicated.

Grade 2 events -
– DiscontinueMK-3475.
– Consider pulmonary consultation.
– Consider pulmonary function tests.
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3-4 events:
– Discontinue MK-3475
Consider pulmonary function tests with pulmonary consult.
– Bronchoscopy with biopsy and/or BAL is recommended.
– Treat with intravenous steroids (methylprednisolone 500 mg over 24 hours). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or

dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.

– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.

Gastrointestinal (Diarrhea/Colitis)

Relevant Clinical Experience
Ipilimumab - diarrhea of any grade was reported in 44% of patients with 18% being Grade 3 or 4. Diarrhea can also be associated with signs and symptoms of colitis, and result in bowel obstruction and perforation, potentially requiring colostomy. The rate of bowel perforation after treatment with ipilimumab was reported as less than 1%. Early implementation of the below diarrhea treatment guidelines (DTGs) has been shown to reduce bowel perforation and colectomy rates, drug-related diarrhea and serious gastrointestinal irAEs by up to 50% in patients treated with ipilimumab. Prophylactic use of budesonide to prevent ipilimumab induced diarrhea/colitis is not recommended based on the results of a Double-Blind Phase II study conducted to determine if prophylactic budesonide reduced the rate of Grade ≥2 diarrhea in ipilimumab-treated patients. Even though budesonide was not shown to prevent diarrhea/colitis, it has been successfully used to treat these events when they do occur as described below.
BMS-936558 (MDX-1106) – diarrhea of any grade was reported in 11% of patients, with 1% of the events being a Grade 3 or 4.
BMS-936559 (MDX-1105) – diarrhea of any grade was reported in 9% of the patients, no events were Grade 3 or 4.

Ipilimumab induced diarrhea and/or colitis has been reported to progress from mild to severe within 24 hours. Although this has not been reported in any patients receiving an anti-PD-1 mAb (BMS-936558 [MDX-1106] or MK-3475), patients should be advised to contact the site as soon as initial symptoms appear.

Symptoms
Symptoms may include (but not limited to):
– Diarrhea
– Constipation
– Abdominal pain, cramping and/or bloating
– Nausea and/or vomiting
– Blood and/or mucus in stool with or without fever
– Rectal bleeding
– Peritoneal signs consistent with bowel perforation
– Ileus

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.

Course of Action
Grade 1 diarrhea:
– Treat symptomatically.
– Endoscopy is recommended if symptoms persist

Grade 2 diarrhea:
– Withhold MK-3475.

– Endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).
– Grade 1 events that persist for >1 week or Grade 2 events should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.
– Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation.
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Grade 3-4 diarrhea (or Grade 2 diarrhea that persist after initial steroid treatment):
– Discontinue MK-3475.
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Treat with intravenous steroids (methylprednisolone 500 mg over 24 hours) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis.
– If symptoms persist despite the above treatment a surgical consult should be obtained.

Hepatic

Relevant Clinical Experience
Ipilimumab – hepatic irAEs were reported in 3% to 9% of patients. Most patients had an asymptomatic increase of transaminases and bilirubin, however some patients also had fevers and malaise.
BMS-936558 (MDX-1106) – the most common hepatic irAEs were alanine aminotransferase increased (4% overall with 1% being either Grade 3 or 4) and aspartate aminotransferase increased (3% overall with 1% being either Grade 3 or 4).
BMS-936559 (MDX-1105) – alanine aminotransferase increased was reported in 1% of patients, no events were Grade 3 or 4.

Symptoms
Symptoms may include (but not limited to):
– Elevations in:
  - o AST >2.5 times upper limit of normal (ULN)
  - o ALT >2.5 times ULN
  - o Total bilirubin >1.5 times ULN

– Fever
– Malaise
– Upper quadrant abdominal pain

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.

Course of Action
Grade 1 Events:
– Monitor liver function tests more frequently until returned to baseline values.

Grade 2 Events:
– Monitor liver function tests more frequently until returned to baseline values.
– Withhold MK-3475

Grade 3-4 Events:
– Discontinue MK-3475 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
– Treat with high-dose intravenous glucocortico steroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolatemofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
– Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Endocrine

Relevant Clinical Experience
Ipilimumab – hypophysitis was reported in 1% to 6% of patients.
BMS-936558 (MDX-1106) – hypothyroidism of any grade was reported in 3% of patients, with <1% being either Grade 3 or 4.
BMS-936559 (MDX-1105) – hypothyroidism of any grade was reported in 2% of patients, no events were Grade 3 or 4.

Symptoms
Symptoms may include (but not limited to):
– Fatigue, weakness
– Headache
– Mental status and/or behavior changes
– Fever
– Vision disturbances
– Cold intolerance
– Abdominal pain
– Unusual bowel habits
– Loss of appetite
– Nausea and/or vomiting
– Hypotension*
– Arrhythmias*
– Abnormal thyroid function tests and/or serum chemistries

*If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential Diagnosis
All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. An endocrinology consultation is recommended.

Course of Action
Grade 1-2 events:
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).

Grade 3-4 events:
– Discontinue MK-3475
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

– Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and intravenous methylprednisolone should be initiated.

Neurologic

Relevant Clinical Experience
Ipilimumab – transient sensory and motor peripheral neuropathies have been reported in less than 1% of patients.
BMS-936558 (MDX-1106) – neuropathy of any grade has not been reported.
BMS-936559 (MDX-1105) – neuropathy of any grade has not been reported, however one patient was reported to have Grade 3-4 myasthenia gravis.

Symptoms
Symptoms may include (but not limited to):
– Unilateral or bilateral weakness
– Sensory alterations
– Paresthesia

Differential Diagnosis
All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection.

Course of Action
Grade 1events:
– Treat and monitor symptoms as indicated.

Grade 2 events:
-Treat and monitor symptoms as indicated.
-Withhold MK-3475. It is up to the discretion of the Investigator, after consultation with a the sponsor to determine whether or not treatment with MK-3475 should continue.

Grade 3-4 events:
– Discontinue MK-3475
– Treat with systemic corticosteroid of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Note: Cases of Myasthenia Gravis and Guillain Barre Syndrome have responded to steroids and standard therapies such as pheresis and IVIG. A neurologist should be consulted in these cases.

Eye

Relevant Clinical Experience
Ipilimumab– episcleritis and uveitis occur in less than 1% of patients.
BMS-936558 (MDX-1106) – one patient who received BMS-936558 (MDX-1106) in combination with a peptide vaccine experienced a dose-limiting optic neuritis.
BMS-936559 (MDX-1105) – Grade 1 or 2 dry eye was reported as an irAE for 1% of the patients. Grade 3-4 endophthalmitis was reported in one patient.

Symptoms
Symptoms may include (but not limited to):
– Photophobia
– Pain
– Dryness of the eyes
– Blurred vision
– Diffuse erythema and a prominent blush on the sclerae.

Differential Diagnosis
All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts).

Course of Action
Grade 1-2 events
– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue MK-3475 if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3-4 events
– Discontinue MK-3475.
– Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

APPENDIX C: Adverse Event of Clinical Interest (ECI) Reporting Form

Adverse Event of Clinical Interest (ECI) Reporting Form

Please notify: Dr. Diaz within 24 hours (Fax: 443-873-5067) email: ldiaz1@jhmi.edu
Merck within 24 hours (Fax: +1-215-993-1220)

Protocol Title:	**Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors**		
Protocol Number (MK-3475-016):	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐**Initial** ☐**Follow-up** ☐**Final Follow-up** ☐**Addendum to:**			

Section A: Subject Information		
Subject ID:	**Subject Initial:**	**Subject Gender:** ☐**Male** ☐**Female**

Section B: Event Information		
Event diagnosis or symptoms:	**Date of First Dose (MK-3475):**	**Action taken with the study drug (MK-3475):** ☐**None** ☐**Interrupted** ☐**Discontinued** ☐**Delayed**
	Date of Last Dose (MK-3475) prior to Event:	
	Number of Total Doses (MK-3475):	
Event Onset Date:	**Event End Date:**	**Date Event Discovered:**

Relationship to:	**MK-3475**	**Underlying Disease**
Unrelated	☐	☐
Probably Unrelated	☐	☐
Possible Related	☐	☐
Probably Related	☐	☐
Definitely Related	☐	☐

Section C: Brief Description of the Event: (please include relevant procedures and laboratory values)

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to ECI)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

APPENDIX D: SAE Reporting Form

Serious Adverse Event Reporting Form

Please notify: Dr. Diaz within 24 hours (Fax: 443-873-5067) email: ldiaz1@jhmi.edu
Merck within 24 hours (Fax: +1-215-993-1220)

Protocol Title:	**Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors**		
Protocol Number (MK-3475-016):	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐ **Initial** ☐ **Follow-up** ☐ **Final Follow-up** ☐ **Death** ☐ **Addendum to:**	**Serious Criteria (check all that apply):** ☐ Death ☐ Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital Anomoly ☐ Other Important Medical Event ☐ Cancer ☐ Overdose	**Hospital Admission Date:** **Hospital Discharge Date:**	**Date Event Discovered:**

Section A: Subject Information		
Subject ID:	**Subject Initial:**	**Subject Gender:** ☐ **Male** ☐ **Female**

Section B: Event Information		
Event diagnosis or symptoms:	**Date of First Dose (MK-3475):**	**Action taken with the study drug (MK-3475):** ☐ **None** ☐ **Interrupted** ☐ **Discontinued** ☐ **Delayed**
	Date of Last Dose (MK-3475) prior to Event:	
	Number of Total Doses (MK-3475):	

Event Onset Date:	Event End Date:

Relationship to:	MK-3475	Underlying Disease
Unrelated	☐	☐
Probably Unrelated	☐	☐
Possible Related	☐	☐
Probably Related	☐	☐
Definitely Related	☐	☐

Section C: Brief Description of the Event:

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

APPENDIX E: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until

disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX F: Immune Related Response Criteria

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden.**

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.

- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Investigators Imaging Operations Manual (IIOM) for more details.

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

APPENDIX G: Data Safety Monitoring Plan (DSMP)

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

DATA AND SAFETY MONITORING PLAN

Version 5.0: 12/6/2012
NCI Approval Date: 12/11/2012

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1. Background

NIH policy requires that grantees have in place procedures for the data and safety monitoring of clinical trials.[1] This is to ensure the safety of participants, validity and integrity of the data, and the appropriate termination of trials for which significant benefits or risks have been uncovered or for which it appears that the trial cannot be concluded successfully. The Sidney Kimmel Comprehensive Cancer Center (SKCCC) Institutional Data and Safety Monitoring Plan (DSMP) was developed to comply with the NIH policies, the NCI's *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* guidance document,[2] and FDA regulations for monitoring IND trials.

1.1. NIH Principles of Monitoring Data and Safety

- All clinical trials require monitoring. Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III), etc.
- Monitoring should be commensurate with risks and the method and degree of monitoring needed is related to the degree of risk involved. [3] A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.
- Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

1.2. National Cancer Institute's Definition of a Clinical Trial

- The NCI operational definition of a clinical trial is a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.
- In the area of molecular or imaging diagnostics, the NCI considers a study to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way, the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not

clinical trials and are not covered by this DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects.

- Behavioral clinical trials include interventions whose goals are to increase behaviors (e.g., cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials and are not covered under this plan.

2. Monitoring the Progress of Trials and the Safety of Participants

2.1. Oversight and Responsibilities for Monitoring of Clinical Trials

The Associate Director for Clinical Research (ADCR) has overall responsibility for data and safety monitoring of clinical trials conducted at the SKCCC. The ADCR appoints the Chairperson and all members of both Clinical Research Review Committee (CRC) and the Safety Monitoring Committee (SMC). See Appendix A for the relationship of the oversight committees and groups.

- **Institutional Review Board**

The Johns Hopkins Medicine Institutional Review Boards (JHM IRBs) are responsible for protecting the rights and welfare of the human subjects of research conducted by faculty and staff at Johns Hopkins Institutions. The JHM IRBs review all human subject research projects conducted by Hopkins faculty and staff. For cancer related studies, the JHM IRB does not begin the review process until the CRC has approved the trial. The IRB reviews and approves monitoring plans for each study.

- **Committee on Outside Interests (COI)**

The institution addresses conflicts through the Organization Policy on Committee on Outside Interests (COI) and the JHM IRB (Policy No. 103.11 - July 2007).[4] The Organization policy on Conflict of Interest includes specific management requirements applicable to conflict of interest associated with conduct of human subject's research protocols. The OHSR will work with the Office of Policy Coordination (OPC) to ensure that conflicts associated with research protocols are identified and reviewed by the Committee on Outside Interests (COI) before JHM IRB review is completed. The OPC staffs the COI, which is the Committee charged with review of conflict of interest associated with research projects. Effective June 2007, all disclosures of outside interests to the OPC occur through the electronic system known as eOPC. OHSR staff members have access to eOPC for purposes of obtaining management plans and the COI meeting schedule. When feasible, a member of the OHSR Compliance Team attends meetings of the COI to facilitate communications between the two offices. The JHM IRBs may not take final action on new applications until COI review is complete and management recommendations are finalized. An OHSR staff member attends JHM IRB meetings and presents the COI management terms to the IRB. The JHM IRB may accept COI management terms or may impose additional restrictions. The JHM IRB may not approve a study with a level of conflict of management that is less than that recommended by the COI. More information on how the institution handles conflicts of interests can be found at their Office of Policy Coordination.[5]

- **Clinical Research Committee - Sub Committee (CRC-SC)**

The adequacy of each study protocol's data and safety monitoring plan is first reviewed at the CRC-SC and then forwarded to the CRC for approval. This evaluation is based on the criteria detailed in this SKCCC Data and Safety Monitoring Plan. While all interventional trials are required to have a Data and Safety Monitoring section in the protocol, Institutional and Externally Peer Review trials are required to have language regarding the oversight under the auspices of SKCCC DSMP. The Level of oversight is also stated in this section. The Quality Assurance reviewer notifies the study team if the DSMP section or oversight level is not included in the protocol.

- **Clinical Research Review Committee (CRC)**

The Clinical Research Review Committee is charged with ensuring that protocols meet the Center's standards for Scientific Merit, Scientific Priority, and Adequate Scientific Progress as well as ensuring the inclusion of women and minorities and children in research. The CRC in concurrence with the PI determines the risk level then reviews and approves the study specific data and safety monitoring plan. Once a study is approved by the CRC, it is forwarded to the IRB for review.

- **Safety Monitoring Committee**

The SMC is responsible for ensuring the safety of participants and the validity and integrity of the data. It is also charged with appropriate closure or termination of studies for which significant benefits or risks have been uncovered. The committee is also tasked with suspending or closing a study because of inadequate data quality or validity. In Section 2.3, there is a more detailed description of the SMC.

- **Internal Data Monitoring**

The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance, and identification, grading, coding, and required reporting of all anticipated and unanticipated adverse events and protocol problems. Although this responsibility is usually shared among the PI, research nurse, and data manager, the PI is ultimately responsible for grading and attribution of all events.

- **External Data Monitoring and Auditing**

The SKCCC CRO Quality Assurance Group (CRO QA group) is responsible for auditing and monitoring all interventional clinical trials. However, if a Sponsor/PI has their own external data monitors then the CRO QA group is not responsible for auditing or monitoring. An example of this is an Industrial study where the sponsor contracts with a CRO or uses their in-house monitors.

An exception: while NCI-CTEP utilizes Theradex for its Phase I study monitoring, the CRO QA group may perform periodic audits due to the higher risk of these particular studies. In addition, the CRO QA group will only audit consortium-sponsored externally peer-reviewed trials (monitored by the applicable consortium) on an as-needed basis.

- **Investigational Drug Pharmacy**

The Johns Hopkins Oncology Investigational Drug Pharmacy is the only entity that has access to the study drug assignment of blinded trials. The investigator must follow the trial's randomization procedures, and should ensure that the code is broken only in accordance with the protocol. The investigator must promptly document and explain to the sponsor and

institution any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

2.2. SKCCC Data and Safety Monitoring Plan (DSMP)

This DSMP plan outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to assure and document data integrity and protocol compliance. This plan is comprised of leveled-oversight-mechanisms and complies with NIH/NCI[6] and FDA standards. [7]

- All clinical trials at SKCCC are required to have Data and Safety Monitoring and Adverse Event /Problem sections in the protocol. The CRC in concurrence with the PI determines the risk level of the trial during the initial CRC review of the Protocol. The DSMP Oversight Level must be specified in the protocol for review and subsequent approval by the SKCCC Clinical Research Committee (CRC), the Institutional Review Board (IRB) and, if applicable, the SKCCC Safety Monitoring Committee (SMC) or the National Cancer Institute (NCI).

- Oversight Levels are based on risk assessment (see Appendix B), complexity, and external monitoring in place by the sponsor, e.g.: CTEP studies are monitored through CTMS and even though they may be high risk, could be assigned to Level 1 oversight.

- The SKCCC Clinical Research Office (CRO) conducts two types of data and safety inspections: monitoring and auditing. Guidelines detailing the auditing and monitoring processes are found in Appendix C.

  - Auditing is a periodic review of a random selection of trial-related activities and documents to determine whether the study is being conducted properly. Reviews determine if data are recorded and reported accurately according to the protocol, standard operating procedures (SOPs), good clinical practice (GCP), and regulatory requirement(s).[5]

  - Monitoring a clinical trial is an ongoing review of the conduct of the trial, throughout the duration of the study. It includes adherence to study design, data integrity and validity, and appropriate reporting of protocol problems and adverse events.

- At SKCCC, the Associate Director for Clinical Research, Clinical Research Review Committee (CRC), SKCCC Safety Monitoring Committee (SMC), CRO Quality Assurance Group, and the PI share monitoring responsibilities. It is important to note that the PI has primary responsibility for continuous internal monitoring.

- The SKCCC DSMP utilizes a four-level oversight system as described below.

  - **Level 1** is designed for institutional and externally peer reviewed Phase I and II trials where a JH investigator does not sponsor the IND/IDE. All medium and high risk studies receive an early audit as soon as possible after the first subject is enrolled, and then periodically, as long as subjects are actively receiving the protocol intervention. Risk levels for these trials may vary from low to high.

    - High-risk trials are audited at least annually.

    - Medium-risk trials are audited at least every two years.

- Low-risk trials do not receive an early audit, but are audited at year-one, and at least every three years thereafter.
- Examples of Level 1 studies include investigator-initiated trials and NIH funded trials that are externally monitored by CTMS or CDUS.

- **Levels 2, 3, and 4** utilize an external monitoring process. If a Johns Hopkins investigator sponsors an IND or IDE, Level 2 or 3 external monitoring is required. Such monitoring may be performed either by the SKCCC CRO QA group or contracted through an external Clinical Research Organization.
  - **Level 2** monitoring is for low to medium risk studies; monitoring frequency is every 6 months and covers at least 30% of subjects. If major issues are discovered, the rate of monitoring may be increased at the discretion of the Quality Assurance Supervisor or the SMC. An example of a Level 2 trial is use of an FDA drug or device approved for another use.
  - **Level 3** is for higher risk studies. 100% of the subjects on these studies are monitored at least quarterly, or as defined by an external data and safety monitoring committee or board. Examples of Level 3 studies are gene-transfer, vaccine, and first in human use.
  - **Level 4** is meets the NIH requirement for all Phase III studies to have a Data and Safety Monitoring Board (DSMB – see Appendix E). 100% of the subjects on these studies their data monitored at least quarterly.

2.3. Safety Monitoring Committee (SMC)

The SMC is charged with ensuring the safety of participants and the validity and integrity of the data and the appropriate closure of studies for which significant benefits or risks have been uncovered. The Committee is responsible for continuous, ongoing review of the conduct of the trial, including adherence to study design, documentation of appropriate monitoring, and proper reporting of protocol problems and events. Inherent in this process is the goal of enhancing the quality of the research by providing the investigator with constructive criticism. The SMC membership includes physicians and other representatives from various Center Programs, biostatistics, data management, nursing, and quality assurance. See Appendix D for the current SMC members.

- The SMC meets monthly to review interventional studies that are either open to accrual or closed to accrual but have subjects in active treatment. The review process is outlined in section 2.4. Cooperative Group and Industrial trials are exempt from SMC review as long as they have an external review process detailed in the protocol or the IRB application.

- A meeting quorum is reached once 50% + 1 of SMC voting members are present.

- SMC members may not have a conflict of interest with any aspect of the trials they monitor. Before the committee initiates discussion on a study, the SMC Chair instructs all SMC voting members (including the Chair) who function as a member of the study under discussion to exit the meeting room until discussion and voting on that study has concluded. All conflicted members are noted on the SMC voting form.

- At the conclusion of each study's discussion, each member makes a data quality, safety, and overall assessment recommendation via selecting one or more of the below categories on the SMC study voting form.

Safety Assessment

For safety, the oncologist assigned to review the study prior to the meeting presents his/her findings at the meeting and then concludes by offering a safety assessment recommendation. The full committee then discusses this and votes per the following outcomes:

- Abstain (Insufficient Info)
- Acceptable
- Acceptable-with-Actions - Require a written response for SMC chair review
- Acceptable-with-Actions - Require a written response for SMC review
- Unacceptable - Place trial on hold pending further SMC review
- Unacceptable - Recommend closure of the trial with required reporting to appropriate regulatory agencies

Data Quality Assessment

For data quality, a QA Specialist group compiles and presents a data quality summary to the Committee and offers a data quality recommendation to the SMC. The full committee discusses these data quality findings and the CRO QA group's data quality recommendation during the meeting and votes per the following outcomes:

- Acceptable
- Acceptable-with-Actions - Require a written response for QA review
- Acceptable-with-Actions - Require a written response for SMC review
- Unacceptable - Place trial on hold pending further QA/SMC review
- Unacceptable - Recommend closure of the trial with required reporting to appropriate regulatory agencies

Overall Assessment

Each committee member's overall study assessment is made by taking into consideration a study's safety profile and its data quality (and is instructed to weigh any safety-related concerns more heavily). After study-related discussion has concluded, each member makes their final determination on a study via selecting only one of the below Overall Assessment categories on the SMC study voting form:

- Acceptable
- Acceptable-with-Actions
- Unacceptable

Reporting

Votes are tabulated as above and the PI and study team are sent an outcome letter within 1-3 days of the meeting. The letter states the overall outcome and the safety and data quality outcomes. If actions or questions are noted in any category, the PI is informed via the letter

and is required to send a written response to the SMC at least a week prior to the next scheduled SMC meeting.

When an SMC assessment requires an action, the PI is responsible for submitting a copy of the report, along with any responses, to the IRB within 60 days (or earlier, depending on the severity of the issue). When an SMC assessment is acceptable, the study team can submit a copy of the report to the IRB with their study's next IRB continuing review application (or with the study termination report, if applicable).

Ensuring Data Confidentiality during the SMC Review Process

In order to ensure the confidentiality of blinded randomization assignments throughout the conduct and review of a trial, the Johns Hopkins Oncology Investigational Drug Pharmacy is the only entity that has access to the study drug assignment of blinded studies. Nonetheless, if the SMC has significant concerns about the safety of study participants on a blinded study, it can compel the Investigational Drug Pharmacy to break the blind for SMC-review purposes only. In any case, clinical investigators must promptly document and explain to the trial sponsor, institution, and regulatory authorities (if applicable) any unintended unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event, etc.) of a study's investigational product(s).

Research participant confidentiality is maintained throughout the SMC review process by including only subject ID numbers in documentation provided to the committee (as opposed to including identifiable data such as subject name, initials, etc.).

2.4. Safety Monitoring Committee Review Guidelines

The SMC provides thorough and ongoing review and monitoring of patient risks, study progress, safety, data accuracy and integrity, and overall protocol compliance.

The full SMC meets once per month to ensure that all DSMP Levels I, III, and IV studies are reviewed at least annually, and that all DSMP Level II studies are reviewed at least semi-annually. A full SMC study review includes an evaluation of the following items:

- an updated data quality summary and trending analysis of all audits/monitoring visits (to evaluate the accuracy and integrity of data),
- an updated study master protocol deviation log (to evaluate protocol compliance),
- an updated study master adverse event log (to evaluate patient safety) and the current study consent document (used to compare the risk section in the current consent doc against the observed adverse events),
- an updated progress summary (to evaluate study progress), and
- any outcomes from external study Medical Expert Committee or DSMB reviews (if applicable).

Study accrual is evaluated annually by the Clinical Research Review Committee (refer to Appendix A).

The SMC Chair or designee reviews all serious adverse events, protocol problems, and amendments that pertain to safety-related issues, on a weekly basis. Submissions that affect participant safety or change risk are referred to the full committee for review at the monthly meeting.

At any point along this ongoing SMC review process the SMC can suspend, recommend closure, or terminate a study. When any of these actions occur, the PI and/or IRB must report them to appropriate regulatory authorities (e.g., NIH, FDA, DHHS, etc.).

A complete itemized description of the SMC's monthly review process - categorized by study type and study DSMP Level - is presented below.

INSTITUTIONAL AND EXTERNALLY PEER REVIEWED STUDIES

Level 1

- The SMC reviews the following **annually:**
  - Continuing review reports
    - Study summary
    - Adverse events
    - Deviation log
  - Audits – internal and external reports
    - Summary and trend analysis
  - Other external reports

- The SMC reviews the following **monthly:**
  - Major issues that affect patient safety or change risk
    - Protocol amendments
    - FDA alerts
    - NCI Action Letters
    - Major protocol violations
  - All Deaths on study
    - Within 30 days of last treatment, **and**
    - Possibly related to study agent or procedure
  - Serious Adverse Events that may cause a study to be placed on hold

Level 2

- The SMC is the designated trial monitor for these studies.

- The SMC reviews the following **every 6 months** unless otherwise specified:
  - Study summary
  - Adverse events
  - Response data
  - Deviation logs
  - Audit reports – internal and external
  - Monitoring reports summary and trends analysis
  - IND/IDE summary report, if applicable

- The SMC reviews the following **monthly:**
  - Major issues that affect patient safety or change risk

        - Protocol amendments
        - FDA alerts
        - NCI Action Letters
        - Major protocol violations
    - All Deaths on study
        - Within 30 days of last treatment and
        - Possibly related to study agent or procedure
    - Serious Adverse Events that may cause a study to be placed on hold

Levels 3 & 4

- A DSMB, Medical Expert Committee, or other external safety review mechanism is the designated trial monitor for these studies.

- The SMC reviews the following **annually:**
    - Continuing review reports
        - Study summary
        - Adverse events
        - Deviation log
    - Audit reports – internal and external
    - Monitoring Report summary and trends analysis
    - IND/IDE summary report, if applicable
    - External safety monitoring board or committee minutes

- The SMC reviews the following **monthly:**
    - Major issues that affect patient safety or change risk
        - Protocol Amendments
        - FDA alerts
        - NCI Action Letters
        - Major protocol violations
    - All Deaths on study
        - Within 30 days of last treatment, **and**
        - Possibly related to study agent or procedure
    - Serious Adverse Events that may cause a study to be placed on hold

NATIONAL AND INDUSTRIAL STUDIES

- The SMC reviews the following **annually:**
    - The QA specialist for the disease group reviews sponsors monitoring and auditing reports. Reports with concerns are forwarded to the SMC for their review and comment.

- The SMC reviews the following **monthly:**
    - All Deaths on study

  - Within 30 days of last treatment, **and**
  - Possibly related to study agent or procedure
- Serious Adverse Events that may cause a study to be placed on hold
- Cooperative Group Audits
- 483s issued by the FDA
- Sponsor complaints – repeated

ADDRESSING MINOR AND MAJOR AUDIT OR MONITORING DEFICIENCIES/DISCREPANCIES

Per JHU SKCCC policies, minor deficiencies or discrepancies (i.e. items that do not affect the outcome or interpretation of the study and do not put the patient at risk) must be addressed by the study team within 10 days of an audit report or within 30 days of a monitoring report. A JHU SKCCC CRO QA Specialist will verify resolution of a study's minor audit or monitoring visit deficiencies at the study's next scheduled audit/monitoring visit. The SMC is notified of prolonged unresolved minor deficiencies as needed (i.e. immediately if necessary, or at the study's next scheduled annual or semi-annual (if applicable) SMC review).

Per JHU SKCCC policies, major deficiencies or discrepancies (i.e. items that yield questionable data, affect patient safety or research ethics, etc.) observed by an auditor or monitor must be addressed by the study team per applicable institutional policy (and no later than 10 days (audit) or 30 days (monitoring visit) per JHU SKCCC policies). Depending on the severity, major deficiencies may be submitted to the SMC Chair for immediate review and study team follow-up. Major deficiencies may also be reportable to the IRB, sponsor, and/or FDA, as applicable (depending on the SMC's assessment, the institution's policies, and sponsor/protocol's requirements).

In order to ensure appropriate team responsiveness to audit or monitoring deficiencies/discrepancies, the SMC reserves the right to issue the following study actions:

- produce a Corrective Action Preventive Action (CAPA) plan for repeated minor observations, or major observations not sufficiently addressed by the study team;
- halt enrollment, if warranted;
- close the study, if warranted;
- terminate the study, if warranted.

If the SMC or institution halts enrollment, closes, or terminates a study then the team must inform the IRB, protocol sponsor, and/or FDA (as applicable).

2.5. Data and Safety Monitoring Board for Institutional Phase III Studies

Phase III studies are required to have a DSMB. If the study does not have an external DSMB, the investigator may obtain assistance from the CRO or the Johns Hopkins School of Medicine to assemble a DSMB. A template DSMB charter is shown in Appendix E. The DSMB is charged with monitoring and evaluating three aspects of clinical trials. These include:

- Safety: By reviewing interim toxicity data for a trial in order to assure the continuing safety of subjects.

- Efficacy: By reviewing interim analyses of outcome data, prepared by the study statisticians to assure that the data are consistent with identifying an important clinical efficacy.

- Study Progress: By reviewing outcome data, to assure that the study can be completed in a reasonable period to be of significant clinical relevance.

3. Compliance with Problem/Adverse Event Reporting Requirements

Problems and adverse events include on-site and off-site adverse events, injuries, side effects, breaches of confidentiality, or other problems that may occur any time during or after the research study

Reporting of problems/events involving risk to participants or others in all clinical trials at SKCCC is conducted in accordance with federal regulations and guidelines as well as Institutional policies and guidelines. In addition, problem/event reporting procedures are specified in detail in each protocol.

Multi- Site trials where the Johns Hopkins Investigator is responsible for the coordinating center, the JH PI must communicate timely all Serious Adverse Events and Protocol Problems to each site with instructions to report to their local IRB per local IRB guidelines.

Reporting Guidelines followed at SKCCC:

- NCI
  CTEP, NCI Guidelines: Adverse Event Reporting Requirements[8]
  NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs[9]
  NCI Data and Safety Monitoring Guidelines[10]

- FDA
  Information for FDA-Regulated Industry[11]
  21 CFR 312.32 IND Safety Reports[12]
  21 CFR 812.150 IDE Safety Reports[13]

- Johns Hopkins Institutional Review Board (JHM IRB)
  Protocol Event and Protocol Deviation Reporting Requirements[14]

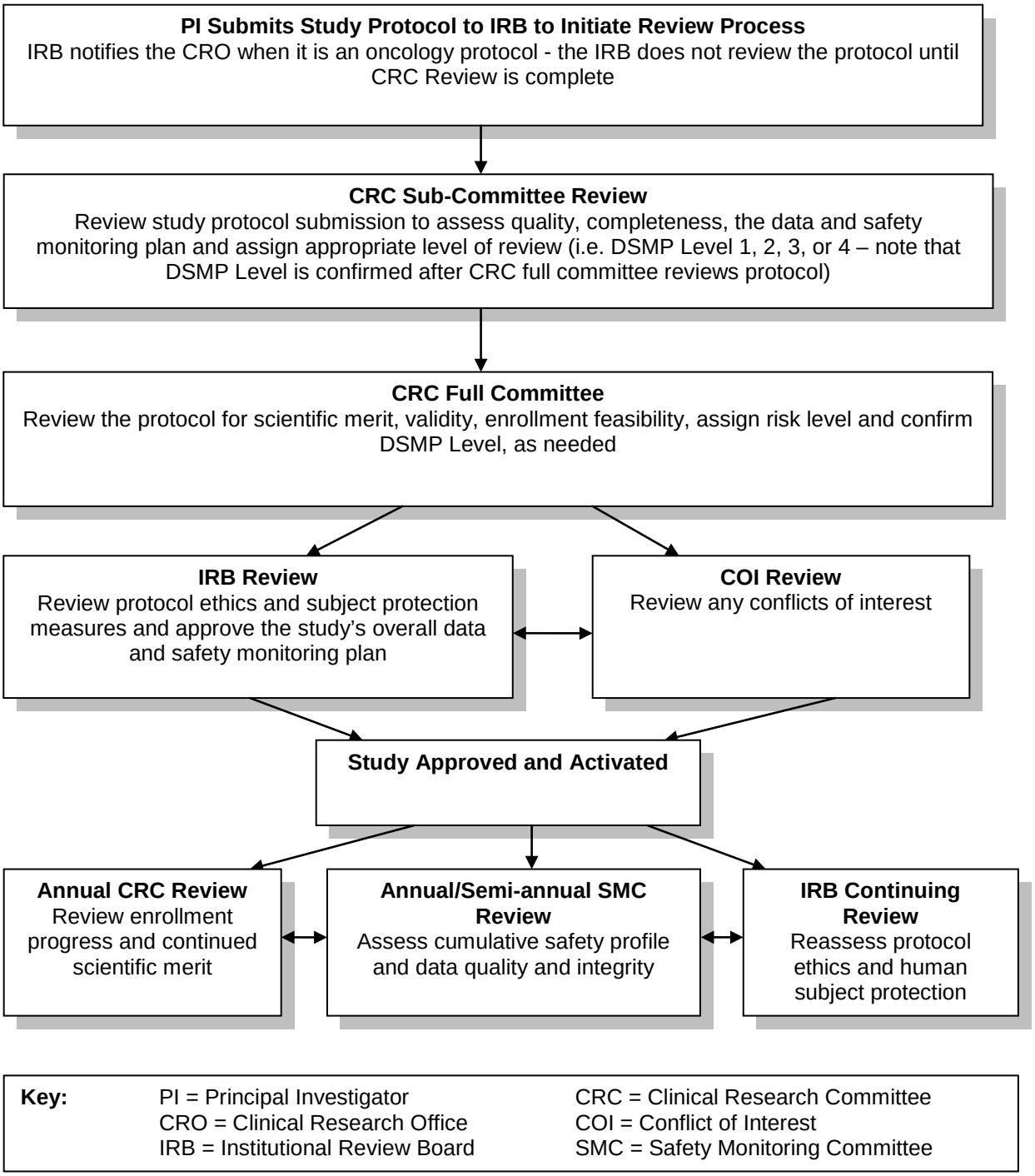
- Western Institutional Review Board (WIRB)
  WIRB Protocol Deviations & Violations / Unanticipated Problems Reporting System[15]

4. Multi-Site Clinical Trials

Principal Investigators from the SKCCC may invite Investigators from other institutions to participate in a clinical trial. In these cases, the Principal Investigator is ultimately responsible for the conduct of the trials at all participating sites, and is required to establish a Coordinating Center to manage all trial related documents and data. SKCCC Coordinating Center SOPs, Operations Manual, and IRB Approved protocol exist to assist an investigator when they are responsible for the coordinating center of a clinical.

The SKCCC Coordinating Center Protocol is available in Appendix F. The protocol describes the processes and oversight that SKCCC coordinating centers have in place for collecting and reporting AEs to all necessary regulatory agencies and co-investigators at participating institutions.

Appendix A: Schema Review Committees Interaction



The CRC, IRB, or SMC can suspend, recommend closure, or terminate a study at any point. When any of these actions occur, the PI and/or IRB must report this to appropriate regulatory authorities (e.g., the NIH, FDA, DHHS, etc.).

Appendix B: Assessment of Risk

Participant risk, along with, the size and complexity of the trial must be considered when assessing the level of risk to an investigator-initiated or NIH-sponsored trial to ensure data and safety monitoring activities are adequate. The CRC in concurrence with the PI determine the risk level of the trial.

The PI of the trial is responsible for determining the level of monitoring based on participant risk, number of participants, and complexity of the trial. Any trial with a high risk to participants is considered high risk; however, a medium risk trial with a complex design could also be considered high risk.

After reviewing the risk, size, and complexity of the trial, the CRC determines if they agree with the adequacy of the monitoring plan in the protocol. If the plan is not adequate, it must be revised by the PI.

In general, the committee uses the following guidelines to determine risk but considers the uniqueness of each trial to ensure the appropriate risk level is assigned. In addition, risk levels can be adjusted during the conduct of the trial by the IRB, CRC, or SMC if the plan is determined to be inadequate or excessive. Trials designated as high risk by the NIH must remain in the High Risk category.

Risk Level	Example of Trial
High	• Phase 1 trials • Trials using gene transfer therapy • First in human use • Any trial designated by the NIH as high risk • Trials using large numbers of participants (Phase III trials) • IDE or IND sponsor is a Johns Hopkins Investigator with any of the above noted attributes
Medium	• Trials using commercially approved agents or devices • All other trials involving therapeutic interventions, e.g., drugs, biologics, devices • IDE or IND sponsor is a Johns Hopkins Investigator with any of the above noted attributes
Low	• Trials involving non-therapeutic interventions, e.g., nutritional, behavioral
Exempt	• Non-Interventional trials, e.g., blood draws, imaging, survey

Appendix C: Quality Assurance Auditing and Monitoring Guidelines

Level 1

- Auditing only (no monitoring required)

  - Early audits of interventional studies are scheduled after the first subject is enrolled. The focus is protocol compliance. Findings are reviewed with the PI and study staff.

  - Routine audits as described below are scheduled periodically on interventional studies that are either open to new accrual or closed to accrual but have subjects in active treatment. Both an administrative/regulatory and subject reviews are performed. A random selection of at least 10% (maximum of six) of subjects' research records and corresponding source documents are reviewed.

  - Areas of concentration for audits are:
    - Valid signed consent forms
    - Eligibility
    - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
    - Treatment administration
    - Response / outcome assessment
    - Timely submission of continuing review reports and amendments
    - Data quality and overall protocol compliance
    - Accrual

  - Audit findings are reviewed with the PI and study staff and a summary report is sent to the SMC and/or DSMB for review.

  - The intensity of each audit is determined by taking into account the experience of the research team, the protocol's complexity, the rate of enrollment, and previous audit results; this facilitates appropriate prioritization of QA resources according to study risk and cumulative study circumstances.

Level 2

- Auditing – None

- Data monitoring visits occur at least every 6 months. Consents and eligibility are monitored for 100% of all subjects. Full monitoring as described below occurs for at least 30% of subjects enrolled on the trial.

- During routine monitoring visits, the following are reviewed:
  - Valid signed consent forms
  - Eligibility
  - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
  - Treatment administration

- Response / outcome assessment
- Timely submission of continuing review reports and amendments
- Data quality and overall protocol compliance
- Accrual

- An Administrative/regulatory review is performed at least annually

- A pharmacy review or device accountability will be performed during every third monitoring visit or at least once per year

- Following a monitoring visit, a summary report is prepared and sent to the PI, study staff, and SMC for review.

- The intensity of each Level II monitoring visit is determined by taking into account the experience of the research team, the protocol's complexity, the rate of enrollment, and previous monitoring results; this facilitates appropriate prioritization of QA resources according to study risk and cumulative study circumstances.

Levels 3 & 4

- Auditing – None

- 100% of the subjects on these studies are monitored at least quarterly, or as defined by external sponsor data and safety monitoring mechanism criteria. 100% of all subjects receive full monitoring as described below.

- During routine monitoring visits, the following are generally reviewed:
  - Valid signed consent forms
  - Eligibility
  - Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
  - Treatment administration
  - Response / outcome assessment
  - Timely submission of continuing review reports and amendments
  - Data quality and overall protocol compliance
  - Accrual

- An Administrative/regulatory review is performed at least annually.

- Drug or device accountability is performed during every third monitoring visit or at least once per year.

- Following a monitoring visit, a summary report is prepared and sent to the PI, study staff, and SMC for review.

DSMP Level Schema for Institutional and Externally-Funded Peer Reviewed Studies				
	Level 1	**Level 2**	**Level 3**	**Level 4**
Study Category	Phase I or phase II interventional studies (level depends on study risk)			Phase III studies
	N/A	JHU investigator-sponsored IND/IDE studies (level depends on study risk)		
General Oversight				
Institutional Oversight	All levels: Institutional Review Board			
Cancer Center Oversight	All levels: Clinical Research Review Committee (CRC) for scientific merit, priority and progress			
Internal Monitoring Oversight	PI and study staff			
Safety Monitoring Oversight	SMC		External Safety Monitoring and SMC*	Independent DSMB and SMC**
Study-Specific Monitoring/Auditing				
Study monitoring	N/A	SKCCC CRO or external		
CRO auditing	Required	Not required		
Frequency of CRO monitoring/auditing	After 1st subject and then periodically	At least semi-annually	At least quarterly, or as defined by external DSMB	
Intensity of CRO monitoring/auditing	Random selection of 10% of subjects (max of 6)	Random selection of 30% of subjects	100% of all subjects	
* Medical Expert Committee, DSMB, or other SMC-approved monitoring mechanism ** Johns Hopkins Institutional DSMB, or other SMC-approved DSMB				

Johns Hopkins Investigator Sponsored IDE or IND Trials

- Before the Cancer Center activates an IRB-approved IND/IDE JHU sponsor-investigator study a pre-enrollment review is performed, and includes the following steps:
  - A thorough review of all relevant regulatory submissions to the relevant government agencies;
  - A comprehensive review of the study regulatory binder;
  - Ascertainment of who the IND/IDE regulatory submissions manager will be for the given IND/IDE;
  - CRO issuance of a preliminary report to the study team summarizing any review observations and a request that they be addressed by the study team.
  - Once the above four tasks are complete, a review exit meeting is held to discuss the results of the pre-enrollment review report. During this exit meeting, a summary of the regulatory responsibilities of IND/IDE sponsor/sponsor-

investigator is presented and discussed with the study team. Once the sponsor/sponsor-investigator has acknowledged his /her responsibilities and all outstanding issues have been resolved, a final report is sent to the study team and IRB. Only after this process has completed may the Cancer Center activate the study. In addition, all audit/monitoring visits are documented via an audit/monitoring report and recorded entry in the site visit log (found in the study regulatory binder).

Appendix D: Current SKCCC Safety Monitoring Committee

2013 Safety Monitoring Committee

Member	Research Program	Title	Voting Member
Julie Brahmer, MD, Chair	Upper Aerodigestive	Assistant Professor of Oncology	Yes
Javier Bolanos-Meade, MD, Co-Chair	Hematologic Malignancies and BMT	Assistant Professor of Oncology	Yes
Emanuel Antonarakis, MD	Prostate	Assistant Professor of Oncology	Yes
Jaishri Blakeley, MD	Brain	Assistant Professor of Oncology	Yes
Dung Le, MD	Gastrointestinal	Assistant Professor of Oncology	Yes
Amy Goodrich, CRNP	Clinical Research Office	Heme Nurse Practitioner and Research Nurse Manager for Center (faculty)	Yes
Patricia Rennie, MS, CCRP	Hematologic Malignancies and BMT	Assistant Program Manager, Hematologic Malignancies and BMT Program	Yes
Christian Meyer, MD	Sarcoma	Assistant Professor of Oncology	Yes
Keith Pratz, MD	Hematologic Malignancies and BMT	Assistant Professor of Oncology	Yes
Roisin Connolly, MBBS	Breast	Assistant Professor of Oncology	Yes
Hao Wang, PhD	Biostatistics Core	Assistant Professor, Department of Biostatistics	Yes
Travis Ché Jarrell, MPIA, RAC	Clinical Research Office	Quality Assurance Supervisor	No

<u>SMC Contact Information:</u>
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Phone: 410.955.4429
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Appendix E: DSMB Template Charter

1. The DSMB Membership will include voting and nonvoting members. The core DSMB must include five members. These should include at least one experienced oncologist, a statistician and a lay representative. Members should be selected based upon their expertise, experience, reputation for objectivity, knowledge of clinical trial methodology and absence of a significant conflict of interest. Members may not have a conflict of interest with any aspect of the trials they monitor. Conflict of interest is defined by the Johns Hopkins University Conflict of Interest Policy. The DSMB will meet at least twice annually or more frequently as dictated by the requirements of clinical trials under its supervision. Data review dates should be selected so that the committee can prepare a report for the continuing review of supervised trials.

2. The formal meeting of the DSMB for each trial shall consist of three parts. The first part is an open session in which members of the clinical team, including the principal investigator and trial statisticians are available to review data with the DSMB. Outcome results must not be discussed during this open session. Following the open session, the DSMB may hold a closed session including members of the board and appropriate members of the coordinating center and the statistician handling the trial. The third phase of each meeting is an executive session involving only voting DSMB members and may be held to allow the DSMB to discuss general conduct of the trial and all outcome results, including toxicities, adverse events, and other protocol events/problems, to develop recommendations, and to take votes as necessary. The DSMB recommendation and the SKCCC action plan, if any, will be forwarded together to the IRB, NIH, FDA, and sponsor as appropriate, providing the opportunity for their opinions and recommendations. In no cases will the DSMB recommendations be taken as binding, provided reasons for an alternative course of action are endorsed by the CRC and investigator.

3. Following each study review, the DSMB will recommend either:

   3.1. Continuation of the trial as is using the current protocol and statistical plan.

   3.2. Continuation of the project with modifications as outlined by the board

   3.3. Immediate suspension of the trial for safety reasons with a recommended plan of follow-up to minimize subject harm.

   3.4. Place the study on a clinical hold. Subjects may continue on their assigned treatments until clarifications requested by the board are resolved.

   3.5. Termination of the trial because of 1) treatment effectiveness demonstrated earlier than expected (“early stopping”), 2) futility of further accrual to meet the trials goal, 3) discovery of new information that precludes completion of the trial, or 4) structural problems in trial execution that are not amenable to correction.

Appendix F: SKCCC Multi-Center Guidelines

SKCCC Coordinating Center Protocol

Coordinating Centers are required when a principal investigator invites other sites to participate in a clinical trial based at The Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins.

Coordinating Centers provide administrative, data management, regulatory, and organizational support in the conduct of a multi-center trial. Coordinating Centers also function as the central location for multi-center trial documents and patient registration. Coordinating Centers monitor the conduct and progress of a clinical trial at all participating sites.

Coordinating Centers must:

- Verify that each participating institution has a Federal Wide Assurance (FWA) number.
- Confirm that IRB approval has been obtained at each participating site prior to their first patient registration.
- Maintain copies of IRB approvals from each site.
- Implement central patient registration.
- Prepare appropriate data as required for review by the Protocol Chair.
- Establish procedures for documentation, reporting, and submitting of adverse events to the Protocol Chair and all regulatory bodies.
- Facilitate audits by securing selected source documents and research records from participating sites for audit or by conducting audits at participating sites.

Document Distribution and Tracking

The SKCCC Coordinating Center ensures the following documents are available to the participating sites via email at the time a new protocol is activated:

- Johns Hopkins IRB approved protocol
- Johns Hopkins IRB approved model consent form
- Other pertinent documents

The SKCCC Coordinating Center is responsible for the coordination, development, submission, and approval of all protocol amendments. The protocol will not be modified by any site other than the Coordinating Center. There will be only one version of the protocol and each participating institution will use that document. All amendments and other pertinent protocol information are sent to participating sites via email, as a PDF document, after approval by a Johns Hopkins IRB. The Coordinating Center ensures that all participating

institutions are using the correct version of the protocol. The Coordinating Center maintains a Regulatory Database that records the protocol and informed consent version, Johns Hopkins IRB approval and expiration date, participating site distribution date, and participating site confirmation for receiving such documents.

Collection and Review of Regulatory Documents

The SKCCC Coordinating Center maintains a regulatory file for each participating site. The following documents must be received by the Coordinating Center prior to a participating site being authorized to enroll patients:

- Letter of Understanding
- IRB protocol approval letter: the letter must include the protocol name, version, and dates of protocol approval and expiration
- IRB approved consent form: the entire consent form must be submitted and must include the protocol name and date of approval
- OHRP Federal Wide Assurance number
- IRB membership list, if available
- FDA Form 1572, if appropriate
- Curriculum vitae, signed and dated within the last two years, of all investigators and sub-investigators
- Medical license for all investigators and sub-investigators
- Financial disclosure forms, if appropriate
- Human Subjects Training certification for all study personnel
- Laboratory certification and normal ranges

The SKCCC Coordinating Center reviews the documents received for completeness and accuracy and will file accordingly. The participating site's IRB approval and expiration dates will be logged into the Regulatory Database. This database also maintains the version, approval / expiration information for all participating site's IRB renewal and amendments with corresponding revised consent forms. Hence, the database will also track that sites are using the most recently approved protocol and consent. The system will NOT allow patient registration unless the current version is approved.

Quality Assurance

The Coordinating Center is responsible for auditing and/or monitoring the progress of the study at participating sites. The schedule is based on the complexity and risk level of the trial.

Audits must occur at least every three years and may occur in one of two ways: (1) source documents and research records are brought from the participating site to the Coordinating Center or (2) selected patient records may be reviewed on site by a Coordinating Center

representative. The Coordinating Center may also monitor participating sites by telephone between visits. Site monitoring logs must be kept to document frequency of visit or contact.

Study data will be monitored by the Coordinating Center at the time of case report forms are submitted as defined by the protocol and/or the letter of understanding.

On a typical monitoring visit to a site, the Coordinating Center representative should inspect the following:

- **Original, signed consent forms to ensure that one is available for each subject.**
- **Case report forms and source documentation for validity and consistency in the completed entries, as well as, accuracy, legibility, signatures and dates.**
- **Treatment administration records to ensure concurrence between dispensing records and CRFs as to subject identity, and dosage of study drug administered.**
- **Compliance with the protocol will also be checked.**
- **Pharmacy drug accountability records for accuracy and completeness, and study drug storage to ensure proper maintenance and supply levels.**

Adverse Event Reporting

The SKCCC Coordinating Center is the central location for the collection and maintenance of adverse event documentation and must submit adverse event reports to the Protocol Chair for review. All serious adverse events must be submitted within 24 hours. All adverse events must be reported as outlined in the protocol. The Protocol Chair is ultimately responsible for the required reporting of all adverse events to the appropriate regulatory agencies and participating institutions.

The Coordinating Center provides serious adverse event forms to be used by all participating sites. Information to be provided must include:

- **Subject ID number, and initials**
- **Date of the event**
- **Description of the event**
- **Description of site's response to the event**
- **Outcome of event**
- **Subject's status on the study (on-study, off-study, etc)**
- **Attribution of event to study drug**

The Coordinating Center maintains documentation of all adverse events for the entire study. Each site will maintain its own documentation as required.

The Principal Investigator at each site must report events per the protocol. Participating sites must also report adverse events to their local IRB according to their specific requirements and to the SKCCC Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined by the protocol must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events that may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within three (3) working days of the participating site Principal Investigator's learning of the event.

Adverse Events, which result in no change to protocol, informed consent, or risk to subjects, must be reported to the Coordinating Center on a monthly basis.

Protocol Deviation Reporting

All deviations from the currently approved protocol must be documented on the protocol deviation log provided by the Coordinating Center.

Protocol deviations that place one or more study subjects at increased risk must be reported to the Coordinating Center within 10 days of the site Principal Investigators learning of the event. Protocol deviations that do not present an increased risk to study subjects must be reported to the Coordinating Center at the time of protocol continuing review. Participating sites must also report all protocol deviations to their local IRB according to their specific requirements.

Data Submission

A detailed plan for collection and management of data from participating sites will be outlined in the study protocol and/or the letter of understanding. In addition, the Coordinating Center will issue a data submission calendar to the participating site at the time of each patient registration.

End Notes

[1] http://grants.nih.gov/grants/guide/notice-files/not98-084.html, and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

[2] http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

[4] http://irb.jhmi.edu/Policies/103_11.html

[5] http://www.hopkinsmedicine.org/Research/OPC/index.html

[6] http://cancertrials.nci.nih.gov/clinicaltrials/patientsafety/dsm-guidelines

[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

[8] NCI Reporting Guidelines at http://ctep.gov/reporting

[9] NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs

[10] http://cancertrials.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines/page5

[11] http://www.fda.gov/oc/industry/default.htm

[12] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

[13] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.150

[14] http://irb.jhmi.edu/Guidelines/reportingrequirements.html

[15] http://www.wirb.com/Pages/default.aspx

Summary of Changes to the Protocol entitled: Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors

Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added study team members Deborah Armstrong, Ronan Kelly, and Atif Zaheer to update the title page from a previous change in research • Added: **Amendment 1/ Version 2/ July 18, 2013**	1-2	N/A
2	Eligibility criteria	• Eligibility criteria for bilirubin were updated to include: (patients with diagnosed Gilbert's Syndrome will not be excluded if their direct bilirubin is within normal institutional limits)	14	3.1.10
3	MSI Testing	• Added: MSI testing in colorectal cancer is already clinically indicated. For other non-colorectal cancers where MSI testing is not currently clinically indicated, a pre-screening consent will be obtained to collect tissue for MSI testing.	16-17	3.4
4	General Guidelines	• Added study coordinator phone number and e-mail address	17	4.1
5	Dosing Criteria	• Dosing criteria for bilirubin were updated to: Total bilirubin >1.5 x ULN (patients with diagnosed Gilbert's Syndrome, direct bilirubin should be within normal institutional limits)	21	5.3
6	Tumor Tissue Studies	• Updated the number of slides required for PD-L1 staining: Slides (10 are requested, but a minimum of 5 will be accepted) from a newly obtained biopsy sample of at least one tumor lesion at baseline will be submitted for PD-L1 staining.	36	9.1

7	Correlative/Special Studies	• Clarified the collection of PBLs: PBL will be collected at baseline, 2 weeks, 4 weeks, 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter including the off study evaluation. • Clarified the collection of sera and plasma: Sera and plasma will be collected at baseline, 2 weeks, 4 weeks, 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter including the off study evaluation to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches.	36	9.0
8	Study Calendar	• Added a pre-screening consent for MSI testing of patients in Cohort C • Clarified that radiologic evaluations will also be done during the off study evaluation in the calendar footnote. • Clarified blood and serum collection times to: Blood and serum samples will be collected at baseline, 2 weeks, 4 weeks, 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter including the off study evaluation.	38-39	10.0

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Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added study team members Maryann Moreland as the lead study coordinator to update the title page from a previous change in research • Added Study Team Members: Mark Lazarev and Nicolas Llosa • Updated Jennifer Uram's address • Added: **Amendment 2/ Version 3/ September 19, 2013**	1-2	N/A
2	Table of Contents	• Updated appendices	6	N/A
3	Study Design	• Added "affected" to describe loci: MSI positive tumors will be defined using standard clinical criteria and require at least two affected loci[1, 2]. • Added "evaluable" to reflect that only patients with evaluable specimens will be included in the analysis. • Added sentence to clarify which patients will be evaluated for determining MSI: Patients will be evaluable if they receive one dose of MK-3475 and if MSI results are confirmed using the MSI Analysis System from Promega at Johns Hopkins (section 3.4).	8-9	1.4
4	Registration Procedures	• Updated the contact information for Lead Study Coordinator, Maryann Moreland. • Increased the timeframe between registration and treatment start: Following registration, patients should begin protocol treatment within 7 business days.	17-18	4.0

5	Adverse Events	• Added reference to Adverse Event of Clinical Interest Case Report Form found in Appendix **C**. • Changed Appendix C to Appendix D	29-31	7.0
6	Correlative/Special Studies	• Increased number of tumor tissue slides for PD-L1 staining and added biomarker staining: Slides (28 are requested if possible) from a newly obtained biopsy sample of at least one tumor lesion at baseline will be submitted for PD-L1 and biomarker staining. • Increased the number of EDTA tubes for the whole blood collection: We will also collect whole blood in two 10 mL plasma preparation tubes with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) and gently swirl tubes to mix blood with EDTA. • Added sub section 9.5 Diagnostic Tissue Samples: Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities. Detailed instructions for tissue collection and shipment are provided in the procedures manual.	36-37	9.0

7	Study calendar	• Added new column heading “Study Procedures”. • Added column to Pre study to clarify there is no time frame limit to collect MSI testing results and height. • Clarified peripheral blood as Whole Blood for PBL. • Added “approximately” to blood draw amounts. • Deleted Whole Blood for PBL, Serum and Whole Blood for Plasma from baseline evaluations. • Amended footnote 5: Temperature, respiration rate, blood pressure, and pulse should be taken at baseline, prior to MK-3475 infusion, at the end of the infusion, and 1 hour post-infusion. Pulse oximetry should be taken at baseline and prior to each MK-3475 infusion. • Reversed footnotes 6 and 7. • Amended footnote 11 to clarify time point collection of C-reactive protein: Disease specific tumor markers where appropriate. C-reactive protein for all patients starting with Cycle 1. • Amended footnote 14: Radiologic evaluations and tumor measurements will be performed at baseline (within 14 days prior to the first dose of MK-3475), 12 weeks (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter including the off study evaluation. Weeks are in reference to calendar week and should not be adjusted due to dosing delays • Amended footnote 15: See Correlative Studies I table below for further details.	38-40	10.0

7 cont	Study Calendar	• Deleted footnote 16: We are no longer collecting PK samples per Merck • Amended footnote 17: We are no longer collecting AHA samples per Merck • Amended footnote 18 (now 16): Values at baseline and when a patient is being evaluated for potential colitis will be collected when available • Amended footnote 19 (now 17): Attempts to obtain archival tumor samples will be made for every patient until the sample is obtained or documentation that the sample cannot be obtained. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspirates will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual • Footnote 20 is now 18 • Footnote 21 is now 19 • Added footnote 20 to clarify week 20 evaluations: Week 20 evaluations, (calculated from the date of the first dose), which include additional blood, CT scans and tumor measurements, may coincide with a cycle visit. All week 20 evaluations must be completed at the Week 20 time point. • Updated original footnote 22 to 21. • Added Correlative Studies I table to clarify time points of whole blood and serum collection		

8	Measurement of Effect	• Updated Appendix D and Appendix E to E and F respectively.	41	11.0
9	Monitoring	• Updated Appendix F to Appendix G	44	12.0
10	Statistical Considerations	• Added "evaluable" to reflect that only patients with evaluable specimens will be included in the analysis • Clarified evaluable population and described MSI testing: The evaluable population includes all subjects who receive at least one dose of MK-3475 and have MSI results confirmed using the MSI Analysis System from Promega at Johns Hopkins (section 3.4). This test will determine MSI status through the insertion or deletion of repeating units in the five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24). At least 2 MSI loci are required to be evaluable in Cohorts A and C. Patients may be assigned to a new cohort and/or replaced based on the Promega test results.	46-47	13.0
11	NA	• Inserted new Appendix C Adverse Event of Clinical Interest (ECI) Reporting Form	66-67	NA
12	NA	• Updated Data Safety Monitoring Plan (DSMP) to Appendix G	77	NA
13	Study Design and Statistical Considerations	• Corrected compound name typo to MK-3475.	9 and 46	

Summary of Changes to the Protocol entitled: Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors

Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added: Amendment 3/ Version 4/ January 13, 2014	2	N/A
2	Eligibility Criteria	• Updated criteria 3.1.6 to read: "Patients with colon cancer must have received at least 2 prior cancer therapy regimens. Patients with other cancer types must have received at least 1 prior cancer therapy regimen. Patients must have progressive disease on study entry." • Updated criteria 3.2.3 to read: "Patient who has had chemotherapy, or biological cancer therapy within 2 weeks prior to the first dose of study drug. Patient who has had radiation within 4 weeks prior to the first dose of study drug. " • Updated exclusion criteria so all times were listed in weeks (and not days)	13-15	3.1
3	MSI Testing	• Added: "For patients who do not have sufficient normal tissue for MSI testing purposes, a buccal swab or purple top blood tube will be obtained." • Added: "The prescreening consent can be obtained over the phone. A copy of the consent will be faxed to the site and the original will be mailed." • Removed that the Promega testing must take place at Johns Hopkins	17	3.4
4	General Concomitant Medication and Supportive Care Guidelines	• Clarified that events of clinical interest will be reported to the sponsor and Merck within 2 business days.	21	5.2
5	Adverse Events: List and Reporting Requirements	• Clarified that events of clinical interest will be reported to the sponsor and Merck within 2 business days.	28	7
6	Correlative studies	• Clarified that off study serum and whole blood samples are no longer required	37	9
7	Study Calendar	• Clarified that off study serum and whole blood samples are no longer required	39-41	10

		• Added buccal swabs for MSI testing. "Buccal swabs and/or purple top tube will be obtained only for those patients who do not have enough normal tissue for MSI testing. This collection can occur any time after consent." • Clarified that "Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion." • Clarified that "For cycle 1, study procedures do not need to be repeated if they were conducted within 3 days of the pre-study evaluations."		

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Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added: Amendment 4/ Version 5/ March 18, 2014 • Removed co-investigator Emily Petito and added Tammy Beckman to match previous amendments • Added co-investigator Ilene Browner • Updated the lead study coordinator to Aleksandra Eyring and updated the contact information	2	N/A
2	Study Design	• Removed "at Johns Hopkins" from the promega testing to be consistent with the last IRB approved amendment	8, 47	1.4, 13.4
3	Eligibility Criteria	• Changed the organ and marrow function to match the criteria that we use for dosing (section 5.3). We have updated these criteria because we have seen early signs of activity from MK-3475 and we do not want to unnecessarily exclude patients who might benefit.	14	3.1
4	Exclusion Criteria	• Removed "Patients with >50 percent involvement of the liver with tumor as determined by the Principal Investigator." • Updated "History of any autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with thyroid disease will be allowed. Autoimmune diagnoses not listed here must be approved by the protocol chair." • Updated "Patients with clinically relevant ascites (tense abdomen or ascites requiring paracentesis)" We have updated these criteria because we have seen early signs of activity from MK-3475 and we do not want to unnecessarily exclude patients who might benefit.	15-16	3.2

5	Registration Procedures	• Updated the lead study coordinator's contact information	17-18	4
6	Dosing Delays	• An amended table regarding Dose Modification Guidelines for Drug-Related Adverse Events has been included from Merck	26-27	6.2
7	Calendar	• 1 hour post-infusion vitals were removed since they are no longer required by Merck.	39	10

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Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added: Amendment 5/ Version 6/ May 5, 2014 • Added co-investigator Robert Anders to match previous amendment • Updated Dr. Diaz's fax number	1-2	N/A
2	Objectives	• Cohort C will now be defined as "MSI positive non-colorectal solid tumor malignancies" • Added exploratory objective: "1.3.6 To determine alternative markers of MSI status. This includes but is not limited to MLH 1, MSH 2, MSH 6, PMS2, BRAF pV600E, and TGFBR2."	7-8	1.0
3	Study Design	• Cohort C will now be defined as "MSI positive solid tumors malignancies but not colorectal adenocarcinoma" • Clarification: "CT/MRI scans will be obtained for assessment of activity and correlative studies"	8-9	1.4
4	Eligibility Criteria	• Cohort C: Patients with histologically proven metastatic or locally advanced non-colorectal MSI solid tumor malignancies • Updated 3.2.1 to include that this exclusion criteria is not applicable to patients with primary brain tumors. • Clarified 3.2.7 that "Note: Systemic steroid therapy allowed for subjects with GBM as long as ≤ dexamethasone 4 mg or its steroid equivalent." • Updated 3.2.15: Patients with clinical significant pleural fluid (symptomatic or fluid requiring thoracentesis).	13-16	3.1, 3.2
5	Reporting	• Updated Dr. Diaz's fax number	31	7.5

Change Number	Section	Change Description	Page Number	Section Number

6	Correlative Studies	• Updated: "Archival tumor samples will also be collected for every patient (slides and/or blocks)."
		• Updated: "Slides from a newly obtained biopsy sample of at least one tumor lesion at baseline or from archived tissue will be submitted for PD-L1 and biomarker staining."
		• Added: 9.1.3 In cases, where the genes listed are known to be mutated, we will test for MSI status since there is a correlation between MSI status and these mutations. Deleterious mutations in the following genes:
		  • MLH 1
		  • MSH 2
		  • MSH 6
		  • PMS2
		  • BRAF pV600E
		  • TGFBR2
		• Added to 9.3 "In addition, we will look at alternative methods to identify MSI in circulating tumor DNA."
			35-36	9.0

7	Study Calendar	• Removed the requirement for ECGs on this study as Merck has confirmed that the FDA no longer requires ECG for cardiac monitoring above which is required for standard clinical practice	38-39	10.0
8	Statistical Considerations	• Cohort C will now be defined as "MSI positive solid tumors malignancies but not colorectal adenocarcinoma"	45, 47	13.0
9	Appendix C and D	• Updated Dr. Diaz's fax number • Updated action taken by adding a "delayed" check box	68, 71	Appendi ces

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Change Number	Section	Change Description	Page Number	Section Number
1	Title Page	• Added: Amendment 6/ Version 7/ November 19, 2014 • Added co-investigator Ana Angarita Africano, Nafi Aygun, Karen Bleich, Karen Horton, Pamela Johnson, Siva Raman, Stefan Zimmerman. • Added Principal Investigators from the Other clinical trial sites: Todd Crocenzi, M.D., Providence Medical Center George Fischer, M.D., Ph.D., Stanford University Tim Greten, M.D., National Cancer Institute Richard M. Goldberg, M.D., The Ohio State University James Lee, M.D., Ph.D., University of Pittsburgh	1-2	N/A

Change Number	Section	Change Description	Page Number	Section Number
2	Eligibility Criteria	• Removed leukocyte inclusion criteria in 3.1.10 to be consistent with Merck's program. • Updated AST/ALT criteria in 3.1.10 to be consistent with Merck's program: "≤2.5x ULN or ≤5x ULN for subjects with liver metastases" • Updated exclusion criteria 3.2.8 to be consistent with Merck's program: "Patients who have received a live vaccine within 4 weeks prior to or after any dose of MK-3475. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed." • Removed the following exclusion criteria to be more consistent with the Merck program: 3.2.14 Patients with clinically relevant ascites (tense abdomen or ascites requiring paracentesis). 3.2.15 Patients with clinical significant pleural fluid (symptomatic or fluid requiring thoracentesis).	15	3.2

Change Number	Section	Change Description	Page Number	Section Number
3	Treatment Plan	• Updated ECI reporting requirements per Merck's guidance document: "Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz immediately. In addition, irAEs listed in **Section 7.1.3** must be reported as an Event of Clinical Interest (ECI) within 24 hours to the Sponsor and Merck Global Safety even if no Serious Adverse Event Criteria are met." • Updated overdose reporting to Merck as 24 hours • Updated pregnancy reporting to Merck as 24 hours • Updated discontinuation criteria to include patients who "Completed 24 months of treatment with MK-3475" • Updated criteria for retreatment with MK-3475 for "Patients who stop MK-3475 with SD or better may be eligible for up to one year of additional MK-3475 therapy if they progress after stopping MK-3745 and they meet the following criteria": **EITHER** o Stopped initial treatment with MK-3475 after attaining an investigator determined confirmed CR according to RECIST 1.1 ▪ Was treated for at least 24 weeks with MK-3475 before discontinuing therapy ▪ Received at least two treatments with MK-3475 beyond the date when the initial CR was declared **OR** o Subject had SD, PR or CR and stopped MK-3475 treatment after 24 months of study therapy for reasons other than disease progression or intolerability **AND** • Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475 • Did not receive any anti-cancer treatment since the last dose of MK-3475	21-24	5.2.2, 5.4, 5.5.2, 5.6

Change Number	Section	Change Description	Page Number	Section Number
		• Have a performance status of 0 or 1 on the ECOG Performance Scale • Demonstrate adequate organ function as detailed in **Section 5.3** • Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication. • Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (**Section 5.5.1**). • Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. • Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator. Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation. Study visit requirements are outlined in the Study Calendar (**section 10.0**).	21-24	5.2.2, 5.4, 5.5.2, 5.6

Change Number	Section	Change Description	Page Number	Section Number
4	Adverse Events	• Updated: "Patients who experience a Grade 2 or higher irAE should be discussed with Dr. Le or Dr. Diaz. In addition, irAEs listed in **Section 7.1.3** must be reported as an Event of Clinical Interest (ECI) within 24 hours to the Sponsor and to Merck Global Safety even if no Serious Adverse Event Criteria are met." • Updated: "Events that are CTCAE Grade 2 and higher and considered by the Investigator to be irAEs should be discussed with Dr. Le or Dr. Diaz immediately. In addition, irAEs listed in the table below must be reported as events of clinical interest within 24 hours to the Sponsor and to Merck Global Safety." • Added table with irAEs that must be reported as ECIs. • Updated SAE reporting to Merck as 24 hours	29, 31-32	7.0, 7.1.3
5	Agent Ordering	• Updated the contact information to: Mark Anthony Lee Merck Sharp & Dohme Corp. 351 North Sumneytown Pike North Wales, PA 19454 Mailstop: RY34-A297 phone: 732-594-1138 email: mark_lee@merck.com	37	8.10

Change Number	Section	Change Description	Page Number	Section Number
6	Study Calendar	• Updated window for off study visit to +/-14 days • Removed requirement for on study and off study urinalysis (patients will do baseline only) • Removed amylase from the chemistry panel • Updated TSH, T3, FT4 to the following: TSH (Total T3 and Free T4 if TSH is outside the normal range). • Removed autoimmune panel (ANA) • Updated window for scans to be +/- 2 weeks • Clarified Study visit requirements for patients restarting treatment: "Patients who stop MK-3475 with SD or better may be eligible for up to one year of additional MK-3475 therapy if they progress after stopping MK-3745 and they meet the criteria listed in Section 5.6 must undergo the following evaluations: interval medical and cancer history, physical exam, vitals, weight, PS, hematology and chemistry profile, autoimmune and endocrine panel, urinalysis, serum or urine pregnancy test, serum tumor markers, radiographic evaluations, and tumor measurements. The following samples will be collected at baseline and while on study: peripheral blood, serum, whole blood for plasma, and biopsy. Subjects who restart treatment after relapse should resume at the same dose and cycle interval which they were receiving prior to discontinuation."	40-41	10.0
7	Appendix C	• Updated SAE reporting to Merck as 24 hours	70	App C
8	Appendix D	• Updated SAE reporting to Merck as 24 hours • Added hospital discharge date to SAE form	73	App D