IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DANA-FARBER CANCER INSTITUTE, INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

Case IPR2023-00252

U.S. Patent No. 10,138,299 B2
Filed: June 12, 2018
Issued: November 27, 2018
Inventors: John P. Cogswell et al.

Title: Cancer Immunotherapy By Disrupting PD-1/PD-L1 Signaling

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EXPERT DECLARATION OF MR. ROBERT PAARLBERG

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I, Mr. Robert Paarlberg, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Dana-Farber Cancer Institute, Inc. ("Dana-Farber" or "Petitioner") as an expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the public availability of the information contained in Clinical Study No. NCT00729664 ("NCT664") on ClinicalTrials.gov. This declaration sets forth my analyses and opinions based on my knowledge, experience, and the materials I have considered.

2. It is my opinion that the ClinicalTrials.gov posting for NCT664 was publicly available before May 15, 2012, and as early as August 2008. It is also my opinion that the publicly available records on ClinicalTrials.gov for NCT664, at all times from August 2008 to present, included information identifying the dosing regimens and inclusion criteria involved in that study.

3. I am being paid at an hourly rate for my work on this matter. I have no personal or financial stake in the outcome of the present proceeding.

II. QUALIFICATIONS AND EXPERTISE

4. I am currently a Principal at Paarlberg & Associates, LLC, a consultancy specializing in regulatory policy, regulatory intelligence, and global clinical trial disclosure strategy and operations, which I founded in 2010.

5. I received a B.S. in Chemistry in 1971 and a M.S. in Analytical Chemistry in 1974, both from Purdue University. I have more than forty years of experience working in the regulatory affairs industry, with nearly twenty years of specific experience in ensuring compliance with clinical trial disclosure requirements. Since at least 2005, I have regularly referred to and relied upon the information provided on the ClinicalTrials.gov website for details concerning proposed, ongoing, and completed clinical studies, and as such am familiar with their posting practices.

6. From 1974 to 2002, I was employed at Pharmacia Corporation (formerly The Upjohn Company) during which time I held several regulatory roles, eventually becoming the Senior Director of Global Regulatory Policy & Intelligence.

7. In 2002, I joined UCB, Incorporated. From 2002 to 2004, I held the position of Director of Regulatory Affairs. As Director of Regulatory Affairs, I developed corporate regulatory strategies for the development and approval of new drugs and indications. From 2004 to 2009, I held the position of Director of Global Regulatory Policy & Intelligence. As Director of Global Regulatory Policy & Intelligence, I collaborated on UCB corporate policies, including policies relating to publications on ClinicalTrials.gov. I also organized UCB's first Clinical

Trial Registry and Result Disclosure Process on a global level and was in charge of global oversight of UCB's Clinical Trial Disclosures policies and procedures. In my final role at UCB from 2009 to 2010, I was the Director of Government Affairs & Policy.

8. Upon leaving UCB, I founded the consulting firm, Paarlberg & Associates, LLC, which specializes in, amongst other things, assisting pharmaceutical companies in developing and implementing strategies related to and compliance with clinical trial disclosure requirements both in the United States and in Europe.

9. I have also been active in several professional organizations related to the regulatory affairs industry and clinical trial disclosures throughout my career. For example, I am a member of the Drug Information Association ("DIA") and was the Chair of its Clinical Trial Disclosure Community from 2013 to 2016. I am also a member of the Regulatory Affairs Professional Society ("RAPS"), and a member of the Advisory Board for RegLink Associates which provides customized global regulatory news

10. I have also authored several articles and presented at dozens of conferences on topics related to clinical trial disclosure and registration. I am an

expert in the regulations and requirements governing clinical study disclosures and the public disclosure of clinical studies.

11. Further information concerning my experience can be found in the current copy of my curriculum vitae which is included at EX1004.

III. RELEVANT LEGAL STANDARDS

12. I am not an attorney, and therefore my understanding of patent law and the legal standards set forth in this report is based on explanations provided to me by counsel.

A. Prior Art & Printed Publications

13. It is my understanding that prior art includes patents and printed publications in the relevant art that were publicly available prior to a patent's priority date. I also understand that a printed publication is publicly available if it was disseminated or otherwise accessible to the public interested in the art one year before the effective filing date, which in this case I understand is May 15, 2012. I also understand that whether a reference qualifies as a publicly available printed publication is a legal conclusion based on underlying factual determinations and is decided on a case-by-case inquiry looking into the facts and circumstances surrounding the reference's disclosure to the public.

B. Person of Ordinary Skill in the Art

14. I understand that the prior art should be viewed from the perspective of the person of ordinary skill in the art ("POSA") as of May 15, 2012. I have been informed that the POSA is a hypothetical person who is presumed to have known the relevant art at the priority date of the patent. I have also been informed that the POSA can possess the skills and experience of multiple individuals working together as a team.

15. I understand that Dr. Salma Jabbour has opined that as of the filing date of May 15, 2012, the POSA relevant to this case would have been a practicing physician or an individual with an advanced degree in immunology, molecular biology or a comparable discipline, and several years of post-doctoral and/or work experience. The POSA would have also had familiarity with antibodies, T-cells and other components of the immune system, experimental models used to study immune system functions, the general features of cancer and the progression of the disease of cancer, and the use of immunotherapy to treat cancer. The POSA would have gained such familiarity through study, training, experience, or through consultation with others.

16. While my background and qualifications do not meet this definition of the POSA, I understand from Dr. Jabbour that she and others meeting the

definition of the POSA accessed clinical trial listings on ClinicalTrials.gov before May 15, 2012.

IV. BACKGROUND OF CLINICALTRIALS.GOV

17. ClinicalTrials.gov is a website run by the National Library of Medicine ("NLM") at the National Institutes of Health ("NIH") that provides information concerning not-yet initiated, ongoing, and completed clinical studies. The website was established and continues to be maintained in response to a series of federal laws mandating the NIH to collect and publicly disseminate information concerning clinical studies.

18. In 1997 the FDA Modernization Act ("FDAMA") was enacted. FDAMA Section 113 required the NIH to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions. The information submitted included a description of the purpose of each experimental drug, eligibility criteria, location of trial sites, and a point of contact. FDAMA also mandated that the information in the databank be in a form readily understood by members of the public and imposed a requirement that information be submitted within 21 days of study protocol approval.

19. On February 29, 2000, the NIH launched the first version of ClinicalTrials.gov, "a consumer-friendly database." EX1034 (Feb. 29, 2000 NIH

Press Release)[1] at 1. In its press release announcing the platform, the NIH stated that "ClinicalTrials.gov provides patients, families and members of the public easy access to information about the location of clinical trials, their design and purpose, criteria for participation, and, in many cases, further information about the disease and treatment under study." *Id.* Despite the site's launch, the FDAMA legislation did not provide enforcement provisions and many trials were not registered.

20. In response to this perceived shortcoming, the medical community called for more expansive clinical trial registration in the early-mid 2000s. In 2005, the International Committee of Medical Journal Editors ("ICMJE"), which includes editors from several of the major medical journals, began requiring that trials, regardless of study phase, be registered on a publicly accessible database, such as ClinicalTrials.gov, as a condition for publication, incentivizing study sponsors to register trials or else risk being unable to publish their results. EX1035

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[1] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, Press Release: National Institutes of Health Launches "ClinicalTrials.gov" (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html.

(ClinicalTrials.gov History, Policies, and Laws)[2] at 2. Additionally, in 2006 the World Health Organization drafted guidance stating that all clinical trials should be registered and provided a set of 20 items that should be included in each submission. *Id.* at 2.

21. As a result of the growing requirements for clinical trial registration domestically and abroad, the U.S. Congress enacted the FDA Amendments Act of 2007 ("FDAAA"). Among the many components of the law, Title VIII (Clinical Trials Databases) expanded the required information for Phase II through Phase IV submissions to include (1) a brief title, intended for the lay public; (2) a brief summary, intended for the lay public; (3) the primary purpose; (4) the study design; (5) the study phase, if applicable; (6) the study type; (7) the primary disease or condition being studied, or the focus of the study; (8) the intervention name and intervention types; (9) the study start date; (10) the expected completion

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[2] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *History, Policies, and Laws*, https://clinicaltrials.gov/ct2/about-site/history#InternationalCommittee (last accessed Nov. 23, 2022).

date; (11) the target number of subjects; and (12) outcomes, including primary and secondary outcome measures. 42 U.S.C. § 282(j)(2)(A)(ii).

22. Title VIII of FDAAA also required the submission of clinical trial results and mandated that the site contain searchable categories, allowing the public to search for trials by the disease or condition, name of the intervention, location, age group, study phase, sponsor, recruitment status, or identification number. *Id.* at § 282(j)(2)(B)(i). Per Title VIII of FDAAA, for studies initiated after the act, a party must submit required information within 21 days of the first patient's enrollment. *Id.* at § 282(j)(2)(C)(ii). Additionally, penalties for failing to register an applicable clinical trial included civil monetary penalties up to $10,000 for each day of the violation. 21 U.S.C. § 333(f)(3)(B).

23. The NIH swiftly implemented the changes required by Title VIII of FDAAA such that by October 2008, ClinicalTrials.gov offered "up-to-date information for locating federally and privately supported clinical trials" and contained information on 63,054 clinical trials sponsored by the National Institutes of Health, other federal agencies, and private industry. EX1036 (About

ClinicalTrials.gov)[3], 6. By that time, the site had received over 40 million page views per month and 50,000 visitors daily. *Id.* ClinicalTrials.gov currently lists 434,253 studies with locations in all 50 States and in 221 countries.[4] As of March 2021, ClinicalTrials.gov receives about 4.5 million visitors monthly. *Id.*

24. ClinicalTrials.gov is intended for a wide audience. Patients and their families can look for ongoing trials using experimental treatments for conditions of interest. Physicians can review the site for the current status of studies for drugs that could be relevant to their practice, and researchers regularly use the site to

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[3] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *About ClinicalTrials.gov*, www.clinicaltrials.gov/ct2/info/about (Oct. 13, 2008). EX1036 includes a notarized affidavit (pg. 1-3) from Nathaniel E Frank White, Records Request Processor at the Internet Archive, authenticating that the foregoing is a true and accurate copy of the archived website from October 13, 2008.

[4] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, Clinicaltrials.gov, *Trends*, https://clinicaltrials.gov/ct2/resources/trends (last accessed Nov. 23, 2022).

gather information about clinical study protocols and results. Additionally, the search capabilities were designed to allow interested parties of all experience and education levels, including patients, to find clinical trials of interest. In my experience, ClinicalTrials.gov is considered a reliable, trustworthy and one of the preeminent disclosure sites by the global clinical trial disclosure community.

25. By 2008, ClinicalTrials.gov had advanced search capability that would allow any interested person, including patients, to search the database to find relevant clinical trials. EX1036 (Advanced Search)[5] at 8. For example, one could search using search terms, for example, "lung cancer," to identify any clinical trials that included that term anywhere in the posting. One could also search by sponsor, e.g., "Bristol Myers Squibb" to identify all clinical trials sponsored by that sponsor. *Id.*

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[5] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *ClinicalTrials.gov Advanced Search*, (July 1, 2008). EX1036 includes a notarized affidavit (pg. 1-3) from Nathaniel E Frank White, Records Request Processor at the Internet Archive, authenticating that the foregoing is a true and accurate copy of the archived website from July 1, 2008. .

V. PROCESS FOR SUBMITTING AND POSTING CLINICAL TRIAL INFORMATION

26. Within 21 days of the first patient's enrollment, study sponsors or investigators must register the trial with ClinicalTrials.gov. In addition to other optional criteria, the sponsor or investigator must provide: a brief title (intended for the lay public); a brief summary (intended for lay people); primary purpose; study design; study phase; study type; the primary disease or condition being studied, or the focus of the study; the intervention name and intervention type; study start date; expected completion date; target number of subjects; outcomes, including primary and secondary measures; recruitment information including eligibility criteria; gender; age limits; acceptance of healthy volunteers; recruitment status and individual site status; location and contact information; and administrative data. EX1036 (ClinicalTrials.gov Pages)[6] at 9-17; *id.* at 14; 42 U.S.C. § 282(j)(2)(A)(ii).

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[6] ClinicalTrials.gov, *ClinicalTrials.gov Protocol Data Element Definitions*, http://prsinfo.clinicaltrials.gov/definitions.html (March 6, 2008) (pg. 9-17). EX1036 includes a notarized affidavit (pg. 1-3) from Nathaniel E Frank White,

27. After the record is submitted, a ClinicalTrials.gov staff member reviews the record before releasing the information for publication on the site. EX1036 (Registering Clinical Trials with ClinicalTrials.gov)[7] 25-27. The record is then available, including its unique NCT identifier, on ClinicalTrials.gov within 2-5 business days after it is released. *Id.*

28. Study sponsors are responsible for ensuring that all the information for their record is timely and accurate. EX1039 (ClinicalTrials.gov Pages) at 14. All submissions are reviewed by ClinicalTrials.gov staff and the database is updated daily. *Id.* Updates are required for changes to study start date, recruitment

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Records Request Processor at the Internet Archive, authenticating that the foregoing is a true and accurate copy of the archived website from March 6, 2008.

[7] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, *ClinicalTrials.gov, Registering Clinical Trials with ClinicalTrials.gov*, http://prsinfo.clinicaltrials.gov/registering.pdf (October 1, 2008). EX1036 includes a notarized affidavit (pg. 1-3) from Nathaniel E Frank White, Records Request Processor at the Internet Archive, authenticating that the foregoing is a true and accurate copy of the archived website from October 1, 2008.

status, site status, and completion date. EX1041 (ClinicalTrials.gov, How to Edit Your Study Record)[8] at 1.

29. ClinicalTrials.gov displays the most recent version of the study record, and a history of changes is available on the ClinicalTrials.gov archive site. *Id.* at 2. The archive site provides "[t]he full history of the changes made to a record." EX1042 (ClinicalTrials.gov, Background)[9] at 1. Information from prior submissions is never removed. *Id.*

VI. NCT664 ON CLINICALTRIALS.GOV

A. NCT664 Was Publicly Available Prior to May 2012 and As Early as August 2008

30. I accessed the ClinicalTrials.gov website and located the record for the August 2008 listing of NCT664, entitled "A Phase 1, Open-Label, Dose-

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[8] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *How to Edit Your Study Record*, https://clinicaltrials.gov/ct2/manage-recs/how-edit (last accessed Nov. 23, 2022).

[9] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, *ClinicalTrials.gov, Background*, https://www.clinicaltrials.gov/ct2/about-site/background (last accessed Nov. 23, 2022).

Escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects With Selected Advanced or Recurrent Solid Tumors" EX1021 (August 2008 of NCT664).

31. I was able to locate the record by searching using the keywords "PDL1", "PD-L1", "anti-PDL-1 antibody", "MDX-1105", NCT00729664, "Bristol-Myers Squibb", or "BMS-936559". I understand from Dr. Jabbour that these would have been search terms that the POSA would have used to find clinical trials related to investigations on the use of anti-PD-L1 antibodies. As I explained above, this search functionality was available on ClinicalTrials.gov as early as 2008 and prior to May 2012. By then, any interested person would have been able to easily search on the site using the same search terms, or others, to locate the record for NCT664.

32. NCT664 study record from August 4, 2008 (First Submitted) describes an open-label study to study MDX-1105, an anti-PD-L1 antibody:

> This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.

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

EX1021 (August 2008 of NCT664) at 3.

33. The study record indicates that the study was "First Posted" on August 7, 2008:

ClinicalTrials.gov Identifier: NCT00729664

Recruitment Status : Completed
First Posted : August 7, 2008
Last Update Posted : September 7, 2015

EX1045 at 1.

34. The "First Posted" date is "[t]he date on which the study record was first available on ClinicalTrials.gov." EX1043 (ClinicalTrials.gov, Glossary)[10] at 3-4.

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[10] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *Glossary of Common Site Terms*, https://clinicaltrials.gov/ct2/about-studies/glossary (last accessed Nov. 23, 2022).

35. In view of this "First Posted" date, and based on my experience with ClinicalTrials.gov, it is my opinion that NCT664 was publicly available in 2008.

36. I also accessed the "Key Record Dates" for NCT664. EX1044 (NCT664 Key Record Dates)[11]:

Key Record Dates

ClinicalTrials.gov Identifier:	NCT00729664
Brief Title:	Multiple Ascending Dose (MDX1105-01) (Anti-PDL1)
First Submitted :	August 4, 2008
First Submitted that Met QC Criteria :	August 4, 2008
First Posted :	August 7, 2008 (Estimate)
Last Update Submitted that Met QC Criteria :	September 3, 2015
Last Update Posted :	September 7, 2015 (Estimate)

37. The Key Record Dates for study NCT664 identifies a "first submitted" date of August 4, 2008, and a "first submitted that met QC criteria" date of August 4, 2008. *Id.* These reflect the date that the study sponsor or investigator first submitted the information to ClinicalTrials.gov, and the date that

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[11] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *Key Record Dates – NCT00729664,* https://clinicaltrials.gov/ct2/keydates/NCT00729664 (last accessed Nov. 23, 2022).

the study sponsor or investigator first submitted information consistent with the NLM quality control review criteria, respectively. EX1043 (ClinicalTrials.gov Glossary) at 4.

38. The difference of a few days between August 4 and August 7, 2008 is accounted for as a "delay of a few days between the date the study sponsor or investigator submitted the study record and the first posted date." *Id*. Although the record may have been available shortly before or after August 7, 2008, that date is consistent with the August 4, 2008 "first submitted that met QC criteria date," and in my experience, the estimated posting date is typically accurate to within a few days. In my opinion, the original study record for NCT664 was most likely publicly available by August 7, 2008, and certainly within a few days thereafter.

39. To further confirm the posting date, I also accessed the History of Changes for NCT664. EX1021 (August 2008 of NCT664)[12]. The History of

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[12] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, *History of Changes for Study: NCT00729664* - https://clinicaltrials.gov/ct2/history/NCT00729664 (last accessed Nov. 23, 2022).

Changes shows a first version, with a submission date of August 4, 2008, followed by several updates. *Id.* at 1-2. Between August 4, 2008, and January 2012, there were 13 updates to the clinical study record. *Id.* All of these versions were publicly available to any interested person. As of September 3, 2015 there have been 42 updates to the clinical study record. *Id.*

40. Indeed, the fact that there are multiple versions of the NCT664 study record between August 4, 2008, and January 2012, itself provides further confirmation that the record was publicly available prior to the critical date because the subsequent versions indicate that the preceding versions were themselves publicly available. In other words, ClinicalTrials.gov would only provide an update if the preceding version was itself publicly available on the site.

41. I also searched "Medarex," the listed sponsor of NCT664 when first submitted, at clinicaltrials.gov. I then entered that search URL at Internet Archive (http://clinicaltrials.gov/ct2/results?spons=%22Medarex%22&spons_ex=Y). The January 19, 2009 and May 11, 2009 archived entries for this search lists the MDX-1105 Phase 1 trial at entry 12 on both archived dates:

12	Not yet recruiting	Phase 1 Open Label Study of MDX-1105 in Subjects With Solid Tumors Conditions: Renal Cell Carcinoma; Non-Small Cell Lung Cancer; Malignant Melanoma; Epithelial Ovarian Cancer Intervention: Biological: MDX-1105

EX1036 at 18-23[13]. This further establishes that NCT was publicly available by at least 2009.

42. As further proof that NCT664 was publicly available, Ascierto et al., which published in October 2010 and I understand constitutes prior art under pre-AIA 35 U.S.C. § 102(b), states "the anti-PD–L1 (B7/H1) mAb MDX-1105 has been developed. This is a fully-human mAb that binds PD-L1 and blocks the binding and the activation of its receptor PD1. At present, it is under evaluation in a phase I clinical trial.45" EX1018, 515. In support, Ascierto et al. cites reference 45, which is "ClinicalTrials.gov. Study of MDX-1105 in subjects with selected advanced or recurrent solid tumors (MDX1105– 01). Available from

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[13] U.S. NAT'L LIBRARY OF MED., NAT'L INST. OF HEALTH, ClinicalTrials.gov, search results for "Medarex" (January 19, 2009 and May 11, 2009). EX1036 includes a notarized affidavit (pg. 1-3) from Nathaniel E Frank White, Records Request Processor at the Internet Archive, authenticating that the foregoing is a true and accurate copy of the archived website from January 19, 2009 (pg. 18-20) and May 11, 2009 (pg. 21-23), respectively.

https://clinicaltrials.gov/ct2/show/NCT00729664." *Id.* Citation number 45 in Ascierto et al. references both NCT664 in the provided hyperlink and MDX-1105.

B. Each Version of the NCT664 Clinical Trial Record from 2008 to the Present Includes a Treatment Protocol to Treat Cancer, Including Non-Small Cell Lung Cancer, With MDX-1105

43. The History of Changes shows all the versions of the study record, from the original submission up to the current version, dated September 3, 2015. EX1021 (August 2008 of NCT664). I reviewed each and every version of the study record from August 4, 2008, to September 3, 2015, and each version contains essentially the same relevant disclosures, as I explain below.

44. The information included in the first version of NCT664, dated August 4, 2008 is provided in EX1021 (August 2008 of NCT664). The first two pages of EX1021 provide a History of Changes, listing each version since August 4, 2008. This History of Changes would not have been included in the original posting as it appeared in August 2008, as this is a listing of all subsequent versions. Nevertheless, the remainder of EX1021 identifies the information that was provided in the first version of NCT664 that was publicly accessible in August 2008.

45. Exhibit 1021 states that version 1 (v1) was submitted on August 4, 2008, is titled "A Phase 1, Open-Label, Dose-Escalation, Multidose Study of

MDX-1105 Administered Every 14 Days in Subjects With Selected Advanced or Recurrent Solid Tumors", as shown below:

Study NCT00729664
Submitted Date: August 4, 2008 (v1)

Study Identification

Unique Protocol ID:	MDX 1105-01
Brief Title:	Phase 1 Open Label Study of MDX-1105 in Subjects With Solid Tumors
Official Title:	A Phase 1, Open-Label, Dose-Escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects With Selected Advanced or Recurrent Solid Tumors
Secondary IDs:	

Study Status

Record Verification:	August 2008
Overall Status:	Not yet recruiting
Study Start:	November 2008
Primary Completion:	
Study Completion:	
First Submitted:	August 4, 2008
First Submitted that Met QC Criteria:	August 4, 2008
First Posted:	August 7, 2008 [Estimate]
Last Update Submitted that Met QC Criteria:	August 4, 2008
Last Update Posted:	August 7, 2008 [Estimate]

46. The August 4, 2008 listing included the following disclosures:

- This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). (EX1021 at 3.)
- MDX-1105 will be administered every 14 Days in subjects with selected advanced or recurrent solid tumors. (*Id.* at 2 [Title].)
- Dose levels include 10 mg/kg/dose. (*Id.* at 3.)
- The conditions being tested include Renal Cell Carcinoma; Non-Small Cell Lung Cancer ("NSCLC"), and Malignant Melanoma; Epithelial Ovarian Cancer. (*Id.* at 3.)
- The tumors being treated are advanced or recurrent. (*Id.* at 2 [Title].)

47. Between August 4, 2008, and September 3, 2015, there were 42 revisions to the study record. EX1021 (August 2008 of NCT664). I reviewed each of these versions. None of the updates for any of these versions altered any of the foregoing text which is clearly shown when a comparison is made.

48. For example, on April 17, 2009 a new version was submitted to NCT664. A comparison of the August 4, 2008 and April 17, 2009 records can be viewed in the History of Changes page by checking box "A" for the August 4, 2008, record, and box "B" for the April 17, 2009 record. The merged comparison identifies all of the changes that were made to NCT664 record between the August 4, 2008 and the April 17, 2009 versions. EX1046 (August 2008 and April 2009 comparison).

49. As shown in the comparison, the April 17, 2009 version edited the content in the Detailed Description of the trial (additions are shown in green, and deletions in red):

Study Identification

Unique Protocol ID: MDX 1105-01

Brief Title: Phase 1 Open Label Study of MDX-1105 in Subjects With Solid Tumors

Official Title: A Phase 1, Open-Label, Dose-Escalation, Multidose Study of MDX-1105 Administered Every 14 Days in Subjects With Selected Advanced or Recurrent Solid Tumors

Secondary IDs:

Study Status

Record Verification: ~~August 2008~~ April 2009

Study Description

Brief Summary: The primary purpose of this study is to determine the safety of MDX- ~~1105, including the maximum dose that can be tolerated when administered for 14 days in subjects with solid tumors.~~ 1105. The study will also evaluate the preliminary effectiveness of the study drug in various types of solid tumors. How MDX-1105 is absorbed,distributed,metabolized and eliminated from the body will also be studied.

Detailed Description: This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.

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

The maximum total study participation duration for a subject is 2.5 years.

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

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

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

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

~~Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 38 to 42. Subjects with initial progressive disease (PD) based on sum of the longest diameter (SLD) or development of new lesions at the end of a cycle, but with otherwise stable or improved performance and clinical status, will continue to be treated with study drug for 1 additional cycle. At the next scheduled imaging evaluation, if there is further increase in the SLD, or development of additional new lesions, then PD has been confirmed and the subject will stop treatment and complete the off treatment procedures. If the SLD remains the same or decreased~~

50. As shown above, the key disclosures set forth in paragraph 46 above, remained the same. Namely, that NCT664 is a Phase I study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1) for patients with measurable advanced or recurrent solid tumors including non-small cell lung cancer. *Id.* at 3. MDX-1105 will be administered every 14 Days in subjects with selected advanced or recurrent solid tumors (*id.* at 2, 4 [Title and Assigned Interventions]), and the dose levels included 10 mg/kg/dose. *Id.* at 4.

51. There were also changes to "Arms and Interventions" and "Outcome Measures":

▼ Arms and Interventions

Arms	Assigned Interventions
Experimental: ~~4~~ Study Drug ~~5 cohorts (0.3,1,3,10 and 15mg/kg/dose)~~ Dosing with study drug	Biological: MDX-1105 MDX-1105 i.v.infusion, ~~5~~ 4 cohorts,0.3,1,3,10 ~~,15~~ mg/kg/dose every 14 days for a total of 3 ~~infusions~~ infusions per cycle

▼ Outcome Measures

Primary Outcome Measures:

1. To determine the safety, maximum tolerated dose(MTD and dose-limiting toxicity(DLT)of MDX-1105
   [Time Frame: ~~MDX-1105 administered as an infusion every 14 days for a total of 3 infusions~~ Weekly and bi-weekly]

Secondary Outcome Measures:

1. Evaluate preliminary efficacy in solid tumors on the basis of objective responses
   [Time Frame: ~~Days 1, 15 and 29~~ Day 42]

Id. at 4.

52. Again, in these changes, the details regarding the dosing at 10 mg/kg/dose and frequency (14 days) remained unchanged. *Id.*

53. I also compared the August 4, 2008 and June 24, 2009 versions to identify any differences between these versions. A comparison is shown in Exhibit 1047. The June 24, 2009 version includes the same August 4, 2008 disclosures identified in paragraph 46.

54. Specifically, as shown below by the changes to the Study Description and Arms and Interventions, the nature and details of the disclosures identified in paragraph 46 remain substantively unchanged. It remained clear from the June 24, 2009 version that NCT664 is a Phase I study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1) for patients with measurable advanced or recurrent solid tumors including non-small cell lung cancer. *Id.* at 3. MDX-1105 will be administered every 14 Days in subjects with

selected advanced or recurrent solid tumors (*id.* at 2, 4 [Title and Assigned Interventions]), and the dose levels included 10 mg/kg/dose. *Id.* at 4.

Study Description

Brief Summary: ~~The primary purpose of this study is to determine the safety of MDX-1105, including the maximum dose that can be tolerated when administered for 14 days in subjects with solid tumors. The study will also evaluate the preliminary effectiveness of the study drug in various types of solid tumors. How MDX-1105 is absorbed,distributed,metabolized and eliminated from the body will also be studied.~~ The primary purpose of this study is to determine if MDX-1105 is safe and tolerated when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

Detailed Description: ~~This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.~~ This is an open label, multicenter, dose escalation and multidose study of MDX-11-5, a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1).

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 17, 6 week cycles), and Follow-up (up to 6 months).

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

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

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

~~A DLT is defined as a greater than or equal to Grade 3 drug related adverse event occurring within the first cycle(42 days) of dosing (excluding tumor flare defined as local pain, irritation, or~~

Arms and Interventions

Arms	Assigned Interventions
Experimental: ~~1~~ MDX-1105 ~~5 cohorts (0.3,1,3,10,and 15mg/kg/dose)~~ 5 escalating dose arms	Biological: MDX-1105 ~~MDX-1105 i.v.infusion, 5 cohorts,0.3,1,3,10,15mg/kg/dose every 14 days for a total of 3 infusions~~ Dose levels include .3, 1, 3, 10 and 15 mg/kg/dose, administered IV

55. I also compared the August 4, 2008 and October 27, 2009 versions to identify any differences between these versions. A comparison is shown in Exhibit 1039. The October 27, 2009 version includes the same August 4, 2008 disclosures identified in paragraph 46.

56. As shown below by the changes to the Study Description and Arms and Interventions, the nature of and details of the disclosures identified in paragraph 46 remain substantively unchanged. It remained clear from the October 27, 2009 version that NCT664 is a Phase I study of a fully human monoclonal

IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1) for patients with measurable advanced or recurrent solid tumors including non-small cell lung cancer. *Id.* at 3. MDX-1105 will be administered every 14 Days in subjects with selected advanced or recurrent solid tumors (*id.* at 2, 4 [Title and Assigned Interventions]), and the dose levels included 10 mg/kg/dose. *Id.* at 4.

Study Description

Brief Summary: ~~The primary purpose of this study is to determine the safety of MDX-1105, including the maximum dose that can be tolerated when administered for 14 days in subjects with solid tumors. The study will also evaluate the preliminary effectiveness of the study drug in various types of solid tumors. How MDX-1105 is absorbed,distributed,metabolized and eliminated from the body will also be studied.~~ The primary purpose of this study is to determine if MDX-1105 is safe and tolerated when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

Detailed Description: ~~This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.~~ This is an open label, multicenter, dose escalation and multidose study of MDX-11-5, a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1).

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 six-week cycles), and Follow-up (up to 6 months).

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

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

Arms and Interventions

Arms	Assigned Interventions
Experimental: ~~1~~ MDX-1105 ~~5 cohorts (0.3,1,3,10,and 15mg/kg/dose)~~ 4 escalating dose arms	Biological: MDX-1105 ~~MDX-1105 i.v infusion, 5 cohorts,0.3,1,3,10,15mg/kg/dose every 14 days for a total of 3 infusions~~ Dose levels include .3, 1, 3, and 10mg/kg/dose, administered IV

57. I also compared the August 4, 2008 and January 19, 2011 versions to identify any differences between these versions. A comparison is shown in Exhibit 1048. The January 19, 2011 version includes the same August 4, 2008 disclosures identified in paragraph 46.

58. Again, as shown below by the changes to the Study Description and Arms and Interventions, the nature and details of the disclosures identified in paragraph 46 remain substantively unchanged. It remained clear from the January 19, 2011 version that NCT664 is a Phase I study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1) for patients with measurable advanced or recurrent solid tumors including non-small cell lung cancer. *Id.* at 3. MDX-1105 will be administered every 14 Days in subjects with selected advanced or recurrent solid tumors (*id.* at 2, 4 [Title and Assigned Interventions]), and the dose levels included 10 mg/kg/dose. *Id.* at 4.

Study Description

Brief Summary: ~~The primary purpose of this study is to determine the safety of MDX-1105, including the maximum dose that can be tolerated when administered for 14 days in subjects with solid tumors. The study will also evaluate the preliminary effectiveness of the study drug in various types of solid tumors. How MDX-1105 is absorbed,distributed,metabolized and eliminated from the body will also be studied.~~ The primary purpose of this study is to determine if MDX-1105 is safe and tolerated when administered every 14 days to subjects with selected advanced or recurrent solid tumors.

Detailed Description: ~~This is a Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1). Up to 40 subjects with measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.~~ This is an open label, multicenter, dose escalation and multidose study of MDX-11-5, a fully human monoclonal IgG4 antibody targeting the Programed Death-Ligand 1 (PD-L1).

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 16 six-week cycles), and Follow-up (up to 6 months).

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

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

~~A total of 16 subjects (6 in the dose escalation cohort + 10 in the expansion cohort) will be enrolled at the MTD or the highest dose studied if the MTD is not identified. For the expansion~~

▾ Arms and Interventions

Arms	Assigned Interventions
Experimental: Anti-PDL-1 antibody (Arm 1) ~~5 cohorts (0.3,1,3,10,and 15mg/kg/dose)~~ BMS-936559 (MDX-1105)	~~Biological: MDX-1105~~ Biological: Anti-PDL-1 antibody ~~MDX-1105 i.v.infusion, 5 cohorts,0.3,1,3,10,15mg/kg/dose every 14 days for a total of 3 infusions~~ Solution, Intravenous, 0.1 mg/kg, Every 14 days, 3 doses per each cycle of 42 days, 16 cycles/48 doses depending on response Other Names: • BMS-936559 • MDX 1105
Experimental: Anti-PDL-1 antibody (Arm 2) BMS-936559 (MDX-1105)	Biological: Anti-PDL-1 antibody Solution, Intravenous, 0.3 mg/kg, Every 14 days, 3 doses per each cycle of 42 days, 16 cycles/48 doses depending on response Other Names: • BMS-936559 • MDX 1105
Experimental: Anti-PDL-1 antibody (Arm 3) BMS-936559 (MDX-1105)	Biological: Anti-PDL-1 antibody Solution, Intravenous, 1 mg/kg, Every 14 days, 3 doses per each cycle of 42 days, 16 cycles/48 doses depending on response Other Names: • BMS-936559 • MDX 1105
Experimental: Anti-PDL-1 antibody (Arm 4) BMS-936559 (MDX-1105)	Biological: Anti-PDL-1 antibody Solution, Intravenous, 3 mg/kg, Every 14 days, 3 doses per each cycle of 42 days, 16 cycles/48 doses depending on response Other Names: • BMS-936559 • MDX 1105
Experimental: Anti-PDL-1 antibody (Arm 5) BMS-936559 (MDX-1105)	Biological: Anti-PDL-1 antibody Solution, Intravenous, 10 mg/kg, Every 14 days, 3 doses per each cycle of 42 days, 16 cycles/48 doses depending on response Other Names: • BMS-936559 • MDX 1105

59. I reviewed a comparison between the August 4, 2008 version and each and every subsequent version. In addition to those discussed above, while the revisions made since April 2009 relate to various aspects of NCT664, including Arms and Interventions, Study Design, Study Identification, Study Description, Study Status, Eligibility, Outcome Measures and Conditions, these revisions have no bearing on the disclosures identified in paragraph 46.

VII. CONCLUSION

60. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with knowledge that willful false statements and the like are made punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: 12/2/22

Robert Paarlberg