

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 IPR2023-00249

U.S. Patent No. 10,323,092 B2
Filed: June 12, 2018
Issued: June 18, 2019
Inventors: John P. Cogswell et al.

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

EXPERT DECLARATION OF DR. SALMA JABBOUR, M.D.

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I, Dr. Salma Jabbour, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Dana-Farber Cancer Institute, Inc. (“Dana-Farber” or “Petitioner”) as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials that I have reviewed in relation to U.S. Patent No. 10,323,092 B2 (EX1001, “the ’092 patent”), which I understand is assigned to Bristol-Myers Squibb Company (“BMS” or “Patent Owner”).

2. I understand that Dana-Farber intends to petition for *inter partes* review of the ’092 patent (“the Petition”) and will request that the United States Patent and Trademark Office cancel claims 1-25 (the “Challenged Claims”) of the ’092 patent as unpatentable.

3. My opinions in this expert declaration support Dana-Farber’s request for *inter partes* review of the ’092 patent and the cancellation of the Challenged Claims.

4. 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

5. I graduated from the University of Virginia with my B.A. in Biology, with Distinction, in 1996, where I was also an Echols Scholar for being in the top

10% of undergraduates for high academic achievement and activities. I then went on to obtain my M.D. from the University of Maryland School of medicine in 2001, where I graduated Cum Laude.

6. After graduation, from 2001-2006, I completed my Internship with the Department of Medicine at the University of Maryland and went on to be an Assistant and eventual Chief Resident in the Department of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins University School of Medicine.

7. In 2006, after completing my residency, I joined the Department of Radiation Oncology at the Cancer Institute of New Jersey, Robert Wood Johnson Medical School, the University of Medicine and Dentistry of New Jersey as an Assistant Professor. In 2013, I earned the rank of Associate Professor at the Rutgers Cancer Institute of New Jersey in the Department of Radiation Oncology, Rutgers Robert Wood Johnson Medical School.

8. I am currently a radiation oncologist at the Rutgers Cancer Institute of New Jersey and was previously the Clinical Chief of the Radiation Oncology Clinic at Robert Wood Johnson University Hospital, a RWJBarnabas Health facility. I am also a Professor at the Robert Wood Johnson Medical School and Vice Chair of Clinical Research and Faculty Development at the Rutgers Cancer

Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, Rutgers University.

9. I have received various honors and awards as an oncologist. I have been named a Fellow of the American Society of Radiation Oncology. This distinction honors individuals who have made significant contributions to the society and to the field of radiation oncology through research, education, patient care and service to the field. The American Society for Radiation Oncology is the largest radiation oncology society in the world. Of over 10,000 members worldwide, only a few hundred have been awarded the honor of being named a Fellow of the American Society of Radiation Oncology. I have been a member of the society since 2006 and am currently a member of the Lung Track Selection Committee.

10. In December 2021, I was designated as an Expertscape Expert in Lung Cancer. Expertscape is a service which assists patients identify doctors and hospitals that have expertise in particular medical disorders or conditions.

11. I also recently received the Inaugural Cancer Center Director's Award, which is a Research Grant for \$50,000 that is awarded for leadership, innovation, collaboration, and dedication to the Rutgers Cancer Institute of New Jersey.

12. I was also a Co-Editor of a Special Issue for Translational Lung Cancer Research where the Topic was “Combining Radiation Therapy and Immunotherapy for Thoracic Malignancies.”

13. In my role as a radiation oncologist, often handle patients with a variety of cancers. My specialty includes treating patients with gastrointestinal and lung cancer, including individuals with non-small cell lung cancer as well as other cancers. I estimate that I have treated over 1700-2000 cases of patients with non-small cell lung cancer.

14. I am currently Deputy Editor on the Editorial Board for the International Journal of Radiation Oncology, Biology, Physics and a reviewer for Clinical Cancer Research and JAMA Oncology. From 2007-2013, I was on the Editorial Board for the Journal of Clinical Oncology.

15. I also have significant experience with clinical trials and research regarding non-small cell lung cancer. I am a member of the Rutgers Cancer Institute of NJ’s Clinical Trials Steering Committee, and I have also been a Phase I Developmental Therapeutics Team Member. I am the contact Principal Investigator for our National Cancer Institute UM1 Clinical Trials Evaluation Program Grant in which I led the efforts at the Rutgers Cancer Institute for early Phase I/Phase II clinical trials with novel cancer agents. My research interests

include immunotherapy and lung cancers, including non-small cell lung cancer, small cell lung cancer, and the use of novel agents. I have authored or co-authored over 200 publications, including numerous publications regarding non-small cell lung cancer.

16. I am and have been the Principal Investigator for multiple Investigator-Initiated Clinical Trials. I am currently the Principal Investigator on a soon to be initiated Phase I trial of AN0025 with Chemoradiation Therapy in Stage III NSCLC. I have also participated as a Principal Investigator in Phase I and Phase II trials regarding Pembrolizumab in the treatment of gastric cancer and NSCLC.

17. I am currently a lead investigator in ongoing Phase II clinical trials regarding the use of pembrolizumab in combination with platinum doublet chemotherapy and radiotherapy for the treatment of unresectable, locally advanced Stage III NSCLC. I have also been an investigator in Phase II and III trials regarding the use of atezolizumab to treat limited stage small cell lung cancer and a Phase I trial of atezolizumab and varlilumab in patients with metastatic NSCLC.

18. I have been an investigator on other early phase studies including: NCI/CTEP #10021: A Phase 2 Study of MEDI4736 (durvalumab) and Tremelimumab Alone or in Combination with High or Low-Dose Radiation in

Metastatic Colorectal and NSCLC; NCI/CTEP #10276: A Phase I/II Study of M3814 and Avelumab in Combination with Hypofractionated Radiation in Patients with Advanced/Metastatic Solid Tumors and Hepatobiliary Malignancies; R2810-ONC-1423: A First-In-Human Study of Repeat Dosing with REGN2810, A Monoclonal, Fully Human Antibody to Programmed Death-1 (PD-1), As Single Therapy and In Combination with Other Anti-Cancer Therapies, In Patients with Advanced Malignancies; and a subinvestigator on ECOG E6508: A Phase II Study of L-BLP25 and Bevacizumab in Unresectable Stage IIIA and IIIB Non-Squamous Non-Small Cell Lung Cancer after Definitive Chemoradiation.

19. A current copy of my curriculum vitae is included at EX1004.

III. SUMMARY OF OPINIONS

20. My opinions and views set forth in this declaration are based on my education, training, and research regarding the use of PD-1/PD-L1 antibodies to treat cancer, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '092 patent at the time of the earliest priority application, May 15, 2012.

21. In forming my opinions, I have reviewed the following materials:

(a) the '092 patent and prosecution history of the '092 patent; (b) all priority applications leading to the issuance of the '092 patent; and (c) all other documents and exhibits cited herein and as listed in EX1006 .

22. First, it is my opinion that claims 1-6 and 24-25 are rendered obvious by BMS's clinical trial disclosure, NCT664 in view of Brahmer and Mu.

23. Second, it is my opinion that claims 7-23 are rendered obvious in view NCT664 in view of Brahmer, Mu, and Irving.

24. Finally, it is my opinion that claims 1-25 are rendered obvious by WO874 in view of Mu, NCT664 and Brahmer.

IV. RELEVANT LEGAL STANDARDS

25. 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. Person of Ordinary Skill in the Art

26. I have been asked to review the '092 patent from the perspective of the person of ordinary skill in the art ("POSA") as of the earliest claimed priority date for the patent, 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.

27. It is my opinion that as of the filing date of May 15, 2012, the POSA relevant to the '092 patent would have been a practicing oncologist, who conducts or is familiar with clinical research, 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 experience in designing clinical trials and have 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.

28. Under this definition, I am qualified to offer opinions regarding the claims of the '092 patent. I have an M.D., and I am an oncologist with over 16 years of experience post-residency, and 20 years including my residency training, in treating cancer, including non-small cell lung cancer ("NSCLC"), including 16 years spent researching and employing monoclonal antibodies for the treatment of cancer as part of a care team for patients.

B. Claim Construction

29. It is my further understanding that the numbered paragraphs at the end of the disclosure of a U.S. Patent are the patent "claims" that define the scope of the alleged invention. I understand that the validity of these claims of the '092 patent is being challenged in the present IPR proceeding.

30. I have been informed that, in this proceeding, the Board must determine the scope of the claims by giving the claims their ordinary and customary meaning in light of the specification, as the claims would be interpreted by one of ordinary skill in the art. I also understand that the Board interprets claims at the time of the “effective filing date,” or “priority date,” which is (1) the actual filing date of the patent or the application containing a claim to the invention; or (2) the filing date of the earliest priority application that describes the subject matter of the claim.

31. I understand that patent claims generally include a “transitional” term or phrase, such as “consisting” or “comprising,” which may connect the preamble of the claim to the body of the claim. I have been informed that if a claim uses the term “consisting” as a transition term, that means that the claim is a “closed” claim, which means that the claim is limited to the claim features that follow the transition term and nothing else. On the other hand, I understand that the transition term “comprising” denotes an “open” claim, which means that the claim is not limited to only the features recited in the claim and could encompass the listed elements as well as other unrecited elements.

32. Claim 1 of the '092 patent recites a “method of treating late-stage non-small cell lung cancer (NSCLC) tumor in a human subject.” EX1001, cl. 1. I understand that this is referred to as the preamble of the patent claim.

33. The '092 patent's specification defines “[t]reatment” of a subject to refer to an intervention or process performed on a subject “with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease.”

EX1001 at 10:10-16. This definition is shown below:

10 response. “Treatment” or “therapy” of a subject refers to any
type of intervention or process performed on, or the admin-
istration of an active agent to, the subject with the objective
of reversing, alleviating, ameliorating, inhibiting, slowing
down or preventing the onset, progression, development,
15 severity or recurrence of a symptom, complication, condi-
tion or biochemical indicia associated with a disease.

The '092 patent separately defines a “therapeutically effective amount,” which does not appear in the claims, to encompass an antibody which “protects a subject against the onset of a disease or promotes disease regression.”

34. Given the express definition in the '092 patent of “treatment,” it is my opinion that the POSA would have understood, at most, that the preamble of claim 1 would require that an anti-PD-L1 antibody be administered with the intent of

treating an NSCLC tumor. Furthermore, the POSA would understand that a method of treatment does not require that the method be efficacious—it only requires that the anti-PD-L1 antibody be given with the intent to achieve some degree of anti-tumor activity, such as the amelioration of “a symptom . . . associated with a disease.” EX1001 at 10:10-16. It does not require proof of clinical efficacy such as what is required for FDA approval.

35. This further aligns with how POSAs thought about the treatment of NSCLC as of May 2012. NSCLC is very difficult to treat, so POSAs as of May 2012 were generally looking for any form of treatment which would provide even a minimal benefit.

36. The POSA would understand that the specification’s definition of a “therapeutically effective amount” would require efficacy, but that this claim term is absent from all of the claims of the ’092 patent. Indeed, it is my understanding that BMS has obtained other patents related to the ’092 patent which claim a “therapeutically effective amount” of an anti-PD-L1 antibody. *See* EX1049 (U.S. Patent No. 10,308,714); EX1050 (U.S. Patent No. 10,266,594). The absence of this term from the claims of the ’092 patent further supports my opinion.

37. However, even if the preamble was limiting and required proof of clinical efficacy for a “method of treatment,” it is still my opinion that the claims would be obvious for the reasons discussed below. *See infra* §IX.

C. Priority

38. I understand that the '092 patent claims priority to a number of patent applications. I have been informed that the '092 patent issued from U.S. Application No. 16/006,493 (EX1010), which claims priority to various applications, the earliest being: No. 61/647,442 (filed May 15, 2012; EX1011); and No. 61/790,747 (filed Mar. 15, 2013; EX1012).

D. Obviousness

39. I understand that Dana-Farber bears the burden of proving that the Challenged Claims of the '092 patent are invalid and it must prove this by a preponderance of the evidence, which means that invalidity must be shown to be more likely than not.

40. I have been asked to consider the question of whether the claims of the '092 patent would have been obvious as of the effective filing date. I understand that this analysis must be conducted from the perspective of the POSA, and whether the skilled artisan would consider any differences between the prior art and what is claimed to have been obvious.

41. To make this assessment, I have been informed that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

42. I have been instructed that one must not engage in hindsight. Rather, I understand that one should instead consider what the POSA would have reason to pursue further, and steps that were routinely done, such as in response to known problems, steps, or obstacles.

43. It is my understanding that the following is a non-exhaustive list of rationales that may support the obviousness of an invention: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; use of a known technique to improve a similar device (method, or product) in the same way; applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led the

POSA to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention with a reasonable expectation of success.

44. It is my understanding that the motivation to combine prior art references may be implicit and may be found in the knowledge of the POSA, or in the nature of the problem to be solved. Specifically, it is my understanding that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but also when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is more effective, safer, cheaper, or cleaner. In assessing implicit motivation, the question is whether the POSA possesses knowledge and skills rendering him capable of combining the prior art references. It is my further understanding that the motivation to combine references may be found in the nature of the problem to be solved where prior art references are directed to precisely the same problem.

45. I also understand that prior art may be relied on for its express disclosure and teachings. I also understand that the prior art may be relied upon for a teaching of features that are necessarily present in the prior art reference even if that specific feature is not expressly or explicitly disclosed.

46. I also understand that the reasonable expectation of success does not require certainty, absolute predictability of success, or conclusive proof of efficacy. All that is required is a reasonable expectation of success by the POSA in light of the prior art as of the effective filing date.

47. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of nonobviousness, if any such indicia are offered.

48. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome by the prior art to the claims at issue. I understand that these objective indicia are also known as “secondary considerations of nonobviousness,” and may include long-felt but unmet need, unexpected results, commercial success, among others.

49. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be comparable with the scope of the challenged claims. This means that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand the proponent of that evidence must establish a “nexus” or a sufficient connection or tie between that evidence and the merits of the claimed invention. I understand

that there is a presumption that there is a nexus between the merits of the claimed invention only when the patentee shows that the offered evidence of secondary considerations is tied to a specific product and that product is the invention disclosed and claimed in the patent. If the secondary consideration evidence offered results from something other than the merits of the claim, such as features known in the prior art, then I understand that there is no nexus or tie to the claimed invention. I also understand it is the Patent Owner who has the burden of proving that a nexus exists, and I understand that secondary considerations will not overcome a strong showing of obviousness.

V. TECHNICAL BACKGROUND & STATE OF THE ART

1. PD-L1

50. PD-L1 is a transmembrane glycoprotein and a ligand of the immune checkpoint receptor programmed cell death protein 1 (“PD-1”), which is a member of the CD28 family of receptors. EX1013. When PD-L1 binds to PD-1 expressed on activated T-cells, T-cell activity is inhibited. *Id.* When PD-L1 is expressed by normal cells, the PD-1/PD-L1 interaction prevents T-cells from launching an immune response against those cells. *Id.* Overexpression of PD-L1 by tumor cells, however, suppresses the proliferation, cytokine production, and cytotoxic activity of T-cells, effectively inhibiting the body’s immune response to malignant

tumor cells. EX1014. Inhibiting the binding of PD-L1 to PD-1 impairs the growth of tumors via T-cell activation. *Id.*

51. PD-L1 expression has been found in a broad range of cancers including in lung (e.g., NSCLC), stomach, colon, breast, cervix, ovary, renal cell, and bladder. EX1015; EX1023. Thus, it was known in the art that various tumors may evade anti-tumor immunity by expressing PD-L1 and that targeting the interaction of PD-L1/PD-1 is a promising approach to activate anti-tumor immunity. *Id.*

52. The Honjo-Freeman '048 patent is an early description of the discovery of Dr. Gordon Freeman of the Dana-Farber Cancer Institute, and others, in decoding the relationship between PD-1, PD-L1, and cancer. EX1009. Honjo-Freeman '048 describes “compositions for cancer or infection treatment” which “inhibit[] immunosuppressive signals induced by PD-1, PD-L1 or PD-L2.” EX1009, 1:7-10. Honjo '048 discloses methods of treating cancers in human subjects using anti-PD-L1 antibodies. EX1009,10:37-38 (noting that inventors “invented” an “anti-PD-L1 antibody”), 11:13-23 (“[c]ancer or tumour of which the therapeutic potential could be expected by administration of the composition for cancer treatment of the present invention include . . . squamous carcinoma (for example, cervical canal, eyelid, tunica conjunctiva, vagina, lung, oral cavity, skin,

urinary bladder, tongue, larynx, and gullet)”). These teachings include the use of an anti-PD-L1 antibody to treat NSCLC. Honjo ’048 teaches that its anti-PD-L1 antibody “inhibit[s] . . . PD-L1 function” and results in “suppression of cancer proliferation.” *Id.* at 10:34-39.

2. Blocking PD-1/PD-L1 Interactions in Cancer Therapy

53. As early as 2002, it was known that administration of an anti-PD-L1 antibody inhibited growth of cancer cells in mouse models. EX1014. It was also known that administration of an anti-PD-1 antibody prevented metastasis of melanoma and colon cancer in mice. EX1016. And it was known that a range of human solid tumors highly express PD-L1. EX1017. Accordingly, anti-PD-1 and anti-PD-L1 antibodies were thought to be promising treatments for cancer in human patients.

54. As of the critical date of the ’092 patent, there were at least four ongoing or completed human clinical trials studying the safety and efficacy of an anti-PD-1 antibody in patients with advanced or recurrent solid tumors or refractory or relapsed malignancies. EX1018, Table 2.

55. BMS’s own anti-PD-1 antibody clinical trial, NCT00441337, led to promising efficacy results in human patients. In this study, one patient with colon cancer showed a durable complete response (ongoing for 21 months at the time it was reported), two patients with melanoma and renal cell carcinoma showed

partial responses, and two patients with melanoma NSCLC showed significant tumor regression. EX1019.

56. In addition to the anti-PD-1 antibody clinical trials, there were also at least two ongoing human clinical trials studying the safety and efficacy of an anti-PD-L1 antibody in patients with locally advanced, metastatic, or recurrent solid tumors. EX1020; EX1021.

57. As explained further below, *see infra* §VIII.A, NCT00729664 (“NCT664”), a BMS sponsored trial, studied the safety and efficacy of administering the anti-PD-L1 antibody, MDX-1105, at various doses, including 10 mg/kg, every two weeks in patients with advanced or recurrent solid tumors, including renal cell carcinoma, NSCLC, malignant melanoma, and epithelial ovarian cancer. Early reported NCT664 trial results were successful: patients with melanoma who were treated with MDX-1105 had partial responses and stable disease and did not show any significant adverse events. EX1022.

3. NSCLC

58. NSCLC is a leading cause of cancer mortality in men and women. EX1051. NSCLC is often diagnosed at a late stage resulting in a poor prognosis, with a 5-year survival rate after diagnosis of only 10-15%. EX1052, 5094.

59. By 2004, it was reported that most NSCLC tumors express PD-L1. EX1052, 5096. It was also known that higher expression of PD-L1 in NSCLC

tumors correlated with a poor prognosis in these patients. EX1023, Abstract. These findings, together with the results from the anti-PD-1 antibody clinical trial reported in Brahmer, suggested that patients with NSCLC would benefit from treatment with an anti-PD-L1 and/or anti-PD-1 antibody.

VI. SECONDARY CONSIDERATIONS

60. I understand that Patent Owner has the burden of establishing secondary considerations of nonobviousness to overcome Petitioner's strong *prima facie* showing of obviousness above. I further understand that although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.

61. I am not aware of any secondary considerations that support the nonobviousness of the Challenged Claims. To the extent that Patent Owner identifies any alleged objective evidence of non-obvious, I reserve my right to respond to such evidence.

VII. THE PRIOR ART CITED IN THE GROUNDS IS NOT CUMULATIVE OF THE PRIOR ART CONSIDERED DURING PROSECUTION

62. I have been asked to review the file history of the '092 patent and the prior art cited by the examiner during prosecution, namely:

- Korman et al. (US 2009/0055944) (EX1053);
- Smith (US 2011/0250201) (EX1054);

- Hansen et al. (US 2011/0244546) (EX1055).

63. I was asked to determine if the prior art cited in the Grounds of Petitioner's petition were cumulative of Korman, Smith, and Hansen. It is my opinion that the prior art cited in the Grounds in Petitioner's Petition is not cumulative of the prior art considered during prosecution.

64. During prosecution of the '092 patent, the Examiner rejected all pending claims based on indefiniteness and obviousness grounds. EX1024, 218-225. Regarding obviousness, the Examiner found that the method of treating NSCLC claims were obvious over Korman, Smith, and Hansen in view of American Cancer Society, "What is Non-Small Cell Lung Cancer?" 2016 ("ACS") (EX1056), and Auperin et al. J. Clin. Oncol., 2010, 28:2181-2190 ("Auperin") (EX1057). *Id.*, 221-225. The Examiner determined that the Korman publication taught a method of treating NSCLC using a PD-L1 antibody at a dose of 10 mg/kg every two weeks. *Id.*, 221-222. The Examiner also found that the 60-minute infusion time was typical in the art for the administration of therapeutic monoclonal antibodies as taught by Smith and Hansen. *Id.*, 222-223.

65. BMS responded to the Examiner's rejection by amending the base claim to add a single limitation—"and wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression." *Id.*, 250. BMS contended that this

newly introduced limitation was not explicitly taught by Korman and thus rendered the claims non-obvious:

references cited. The Examiner has failed to show that the combination of the alleged disclosures of the cited references teaches or suggests treating a NSCLC using an anti-PD-L1 antibody, wherein at least 1% of tumor cells exhibit membranous PD-L1 expression. In particular, The Examiner has pointed to no part of Korman that allegedly discloses membranous PD-L1 expression by at least 1% of tumor cells, and none of Smith, Hansen, and Auperin discloses PD-L1 expression at all, let alone membranous PD-L1 expression by at least 1% of tumor cells.

Id. at 258. The Examiner then allowed the claims to issue without any explanation.

Id. at 280-285.

66. In contrast to the art relied upon by the Examiner, it is my opinion that the Grounds presented in the petition are not cumulative and do not present the same or substantially the same prior art or arguments made during prosecution. This is for numerous reasons, discussed below.

67. First, all three Grounds rely on NCT664, Brahmer, and Mu. NCT664, the primary reference for Ground 1 and 2, and a significant reference for Ground 3, describes the Phase I clinical trial of an anti-PD-L1 antibody, MDX-1105. *See* EX1021. I have reviewed the prosecution history of the '092 patent and I have determined that BMS did not disclose NCT664 during prosecution. Similarly, BMS did not disclose Mu which, as explained below, *see infra* §VIII.C, discloses

the association between PD-L1 expression and NSCLC. This reference as well was not addressed during prosecution. Finally, while BMS did disclose Brahmer, see EX1024, 200, Brahmer was not discussed by the Examiner or referenced in the Examiner's sole rejection.

68. Second, the only clinical trial disclosure made by BMS to the Examiner was the disclosure of an anti-PD-1 antibody trial. EX1024, 205. BMS did not disclose NCT664, which was BMS's own clinical trial directed at an anti-PD-L1 antibody, to the Examiner. Moreover, none of the references cited or relied upon by the Examiner in its non-final rejection discuss the clinical trial. EX1024, 218-225.

69. Third, none of the references relied upon by the Examiner—Korman, Hansen, and Smith—provide any human clinical trial data with either an anti-PD-1 antibody like Brahmer, or an anti-PD-L1 antibody like NCT664.

70. Even though the Korman reference considered by the Examiner is the U.S. publication of its corresponding PCT application, WO874, and thus contains the same disclosure as WO874, the Examiner did not consider its teachings in conjunction with the NCT664, Brahmer, or Mu references as stated in Ground 3.

71. These references—NCT664, Brahmer, and Mu—are not cumulative of and are materially different from the Smith and Hansen references relied upon

by the Examiner. The Examiner relied upon Smith and Hansen for the disclosure of a one-hour IV infusion, but neither Smith nor Hansen relate to PD-1 or PD-L1 technology. Brahmer, by contrast, provides multiple teachings regarding the use of anti-PD-1 antibodies to treat NSCLC and the association between PD-L1 expression and treatment, *see infra* §VIII.B. These teachings are not contained anywhere in Smith or Hansen. Similarly, NCT664 describes an anti-PD-L1 antibody trial that showed antitumor activity, and Mu also teaches that PD-L1 expression by NSCLC tumors is associated with poor outcomes. *See infra* §VIII.A and §VIII.C.

72. I also understand from Counsel that, even if a petition raises Grounds which are cumulative of prior art addressed during prosecution, the Board will consider institution where there has been a material error by the Office during prosecution. Here, with respect to Ground 3 and its inclusion of WO874, it is my opinion that the Examiner made a material error in allowing the claims.

73. During prosecution, the Examiner correctly determined that the disclosure of Korman—the same as WO874—taught virtually every element of the claims. The Examiner found that it taught a method of treating lung cancer by administering an anti-PD-L1 antibody. EX1024, 221-222. The Examiner also found that it disclosed the administration of the antibody at a 10 mg/kg dose once

every two weeks by intravenous infusion. *Id.* The Examiner also found that it would have been obvious to apply anti-PD-L1 antibody treatment to “NSCLC patients previously treated with chemotherapy and radiotherapy.” *Id.*, 222.

Finally, the Examiner also noted, consistent with this petition, that it was “typical in the art at the time of the invention . . . to administer therapeutic antibodies by 60 minutes-long intravenous infusion.” *Id.*

74. BMS did not challenge any of these findings by the Examiner. BMS overcame the Examiner’s rejection by adding the limitation which required that “at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression.” BMS then told the Examiner that the claims should be allowed because Korman did not teach or suggest treating NSCLC with an anti-PD-L1 antibody wherein at least 1% of tumor cells exhibit membranous PD-L1 expression. EX1024, 258. Presumably, the Examiner allowed these claims because of this additional limitation.

75. In my opinion, it was clearly incorrect for the Examiner to allow these claims in light of this obvious limitation. Numerous prior art references, including NCT664, Brahmer, and Mu, disclosed the association between PD-L1 expression on tumors, including NSCLC tumors, with tumor evasion and poor outcomes for patients. *See infra* §§VIII.A-C. Additionally, anti-PD-L1 antibodies are designed to work on tumors that express PD-L1 on the membrane of tumor cells. The

POSA understood this as of the May 2012 priority date and the POSA would have known that it would not make sense to treat a tumor that did not express a minimal level of PD-L1. Thus, even though Korman, and WO874, do not expressly teach this limitation, the Examiner erred by not finding this limitation to be plainly obvious to the POSA.

VIII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. NCT664

76. Clinical Trial Study NCT00729664 (“NCT664”) is the clinical trial publication publicly available through clinicaltrials.gov. It describes a “Phase 1 study of a fully human monoclonal IgG4 antibody targeting the Programmed Death-Ligand 1 (PD-L1).” EX1021, 3. This anti-PD-L1 antibody was called “MDX-1105.” *Id.* The study describes enrolling subjects with “measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer.” *Id.* The “Inclusion Criteria” of the study indicates that subjects with NSCLC were required to have “refractory or recurrent histologically or cytologically confirmed advanced NSCLC.” *Id.*, 5. Each subject must also have failed “at least 1 prior systemic taxane-based therapy.” *Id.* Each subject could also have been treated with up to 3 systemic therapies for advanced/recurrent disease or have become intolerant to a

systemic therapy. *Id.* It further describes administering “MDX-1105” via “i.v. infusion” in various cohorts, including a 10 mg/kg dose “every 14 days.” *Id.*, 3.

77. With respect to NSCLC cancer subjects, the inclusion criteria state that subjects had to have had “refractory or recurrent histologically or cytologically confirmed advanced NSCLC,” which would include late-stage NSCLC tumors. EX1021, 5. It further specifies that the malignancy must be deemed “unresectable.” *Id.*

78. The earliest version of NCT664 was submitted on August 4, 2008 and was publicly available to POSAs on August 7, 2008. EX1045. Since then, numerous other updates regarding NCT664 were submitted and were publicly available to POSAs on ClinicalTrials.gov prior to May 15, 2011. I understand from counsel that NCT664 is prior art to the '092 patent.

79. For example, on January 19, 2011, an update to NCT664 was submitted and was publicly available on January 19, 2011. *See* EX1048. This update reiterated that one arm of the study administered an “[a]nti-PDL-1 antibody” known as “BMS-936559 (MDX-1105)” at a “10 mg/kg” dose by an “[i]ntravenous” solution every “14 days.” *Id.*

80. While NCT664 states that it was designed, in part, to evaluate “preliminary efficacy” in solid tumors, the POSA already knew before the priority

date that the study was reporting efficacy with MDX-1105 as a form of treating cancer.

81. For example, Dr. Hwu published an article on June 25, 2010 entitled “[t]argeted therapy for metastatic melanoma: From bench to bedside.” EX1022, 3. This article was publicly available prior to May 15, 2011 and is thus prior art. Hwu 2010 describes Dr. Hwu’s team participated “in a phase 1 study of anti-PD-L1 monoclonal antibody (MDX-1105, Medarex) in refractory metastatic melanoma.” *Id.* The POSA would have known that this clinical trial was NCT664 as it was the only Phase I clinical trial testing MDX-1105 at the time of this publication. Hwu 2010 notes that in their cohort, “MDX-1105 has been tolerated by all patients” and that “[m]ost adverse events were mild.” *Id.* In terms of efficacy, Hwu 2010 discloses that “[c]linical responses were observed at all dose levels,” including the 10 mg/kg dose every 2 weeks, and that “[d]urable partial responses and stable disease were noted in patients whose disease had progressed after at least one, and as many as five, prior systemic therapies.” *Id.* Thus, the POSA would have understood that the 10 mg/kg arm of NCT664 had already obtained clinical responses and had shown anti-tumor activity indicative of clinical efficacy.

82. While Hwu 2010 is in the context of metastatic melanoma, its clinical results would certainly provide a motivation for a POSA to treat any tumor which expresses PD-L1, as that is the purpose of an anti-PD-L1 antibody. As discussed below, POSAs knew that NSCLC tumors expressed PD-L1. *See infra* §VIII.C. As a result, POSAs would be motivated to also treat NSCLC tumors with MDX-1105, as disclosed by Hwu 2010, with an expectation of success in treating NSCLC.

83. Other publications before the earliest priority date reported the same. For example, Topalian et al. published an article “Cancer Immunotherapy Comes of Age” in the Journal of Clinical Oncology and was published online on October 31, 2011. EX1025. Topalian 2011 discloses that a “blocking antibody against the major ligand for PD-1—B7-H1/PD-L1 (MDX-1105/BMS936559)—is also in phase I clinical testing in patients with advanced solid tumors, and preliminary evidence of clinical activity against melanoma, RCC, and non-small-cell lung cancer has been shown.” *Id.*, 4833.

84. Some of the same authors of Topalian 2011 published another piece, entitled “Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity”, which published in Current Opinion in Immunology in 2012 and was available online on January 9, 2012. *See* EX1026. Topalian 2012 also reports that MDX-1105 showed “preliminary evidence of activity against melanoma, kidney

cancer and NSCLC. These complementary results further validate the PD-1 pathway as a target for immunotherapy.” *Id.*, 210.

85. Thus, in light of the teachings of Hwu 2010, Topalian 2011, and Topalian 2012, the POSA would have known that the 10 mg/kg arm of NCT664, administered once every two weeks by IV infusion, achieved anti-tumor activity against NSCLC and showed evidence of clinical activity.

86. The POSA as of May 2012 would have frequently referred to the ClinicalTrials.gov database to evaluate and keep themselves aware of ongoing and upcoming clinical trials. POSAs knew that this is where information regarding new clinical trials are published. I, myself, as a POSA, frequently referred to the ClinicalTrials.gov database to keep myself aware of ongoing and upcoming clinical trials. I would often go to ClinicalTrials.gov to identify more information on a drug or to evaluate treatment options for particular types of cancer. I was aware of BMS’s NCT664 Phase I trial prior to May 2012 and would expect other POSAs to have been aware of the trial as well.

87. Today, and prior to May 2012, I often search for and review clinical trial disclosures related to my area of clinical practice, including therapies related to treatment of NSCLC. In searching for clinical trial disclosures, I search using

various fields, including keyword searches, drug names, drug targets, NCT clinical trial disclosure numbers, sponsors, or authors.

88. For example, when I search clinicaltrials.gov using the following search terms, I am able to easily locate NCT664:

- “PDL1” or “PD-L1” or “anti-PDL-1 antibody”
- “MDX-1105”
- NCT00729664
- “Bristol-Myers Squibb”
- BMS-936559

89. The POSA interested in clinical trials regarding NSCLC in May 2012 would have searched for and identified NCT664, particularly in light of the disclosure of Hwu 2010, discussed above. *See supra* §VIII.A.¶81. That same POSA would have reviewed the “History of Changes” and all the various “Study Record Versions” posted before May 2012 regarding NCT664 on ClinicalTrials.gov. EX1021. In fact, in my experience, I often refer to both the current version of a clinical trial protocol posted to ClinicalTrials.gov and prior versions which may contain additional information regarding the clinical trial. In my opinion, the POSA would have reviewed and relied upon all of the various

disclosures made before May 2012 in the “History of Changes” regarding NCT664. EX1021.

B. Brahmer

90. Brahmer is a peer-reviewed journal article published in the Journal of Clinical Oncology in 2010. *See* EX1019. This is a reoccurring publication.

Brahmer describes the results of a Phase I study regarding MDX-1106, which is an anti-PD-1 antibody. It later became known that MDX-1106 was nivolumab, which is now marketed and sold by BMS as an anti-PD-1 antibody therapy for certain cancers. I understand from counsel that Brahmer is prior art to the '092 patent.

91. Brahmer describes a Phase I study that studied the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid tumors. EX1019, 3167. The study also evaluated antitumor activity, pharmacodynamics, and immunologic correlates. *Id.* Brahmer discloses that the Phase I study administered an anti-PD-1 antibody, MDX-1106, to patients having advanced metastatic melanoma, colorectal cancer, castrate-resistant prostate cancer, NSCLC, or renal cell carcinoma. *Id.*

92. Brahmer discloses that the patients in its Phase I study “received a 60-minute intravenous infusion of MDX-1106 at 0.3, 1, 3, or 10 mg/kg.” EX1019, 3168. The study organizers “found evidence of antitumor activity, with one [complete response] (ongoing at 21 months) and two [partial responses] (ongoing

at 3 and 16 months) in patients with CRC, melanoma, and RCC; significant lesional regressions were seen in two additional patients with melanoma and NSCLC.” *Id.*, 3172. Moreover, Brahmer teaches that the “observed clinical activity of MDX-1106 is most likely exerted through immunologic mechanisms rather than direct tumoricidal effects, since nonhematologic tumors do not express PD-1.” *Id.* Thus, Brahmer teaches that the anti-PD-1 antibody’s clinical activity was likely due to its immunologic mechanism, i.e., its ability to inhibit the PD-1/PD-L1 pathway.

93. Brahmer also teaches that an “important factor in determining outcomes may be intratumoral expression of [PD-L1], either by tumor cells or by nontransformed cells in the tumor microenvironment. As suggested by our preliminary biopsy analysis, tumor cell surface expression of [PD-L1] may be a predictor of responsiveness to PD-1 blockade.” EX1019, 3172. Further in support of this factor, Brahmer teaches that patients with tumors that expressed PD-L1 showed tumor regression with treatment with MDX-1106. *Id.* Brahmer refers to “B7-H1”, a synonym for PD-L1.

94. Brahmer speculates on two possible scenarios for T-cell inhibition:

Two possible scenarios for T cell inhibition via PD-1:[PD-L1] ligation have been proposed in the context of cancer.^{16,17} First, lymphocytes may encounter [PD-L1] expressed on activated antigen-presenting

cells during priming or reactivation in lymphoid organs. In addition, tumor-specific effector lymphocytes may be inhibited on contact with [PD-L1]–positive tumor cells. In the latter case, direct tumor assessment for [PD-L1] expression may provide a powerful predictive biomarker for responsiveness to anti–PD-1.

Id.

95. Given Brahmer’s teaching both mechanisms involve the PD-L1 ligand, and its teachings that tumor cell expression of PD-L1 is a likely predictor of responsiveness to PD-1 blockade, the POSA would understand that MDX-1106’s mechanism of action involves blocking the interaction between PD-1 and PD-L1. The POSA would also understand that an antibody which targets the PD-L1 ligand would also be likely to achieve anti-tumor activity for the same reason than an anti-PD-1 antibody would.

96. Thus, the POSA would understand in light of Brahmer’s disclosures regarding the anti-PD-1 antibody, MDX-1106, that an anti-PD-L1 antibody was likely to achieve anti-tumor activity in patients. The POSA would have been motivated to pursue such anti-PD-L1 antibodies because they would similarly block the PD-1/PD-L1 interaction by targeting PD-L1.

C. Mu

97. Mu is a peer-reviewed journal article which was published online in the Journal of Medical Oncology in April 2010. This is a reoccurring publication. EX1023. I understand from counsel that Mu is prior art to the '092 patent.

98. Mu describes an immunohistochemical analysis which was used to evaluate the expression of PD-L1 in 109 NSCLC tissues and para-tumor issues. EX1023, 683. The authors then evaluated “[a]ssociations between expressed PD-L1 and tumor histological types, degree of differentiation, and lymph node metastasis [sic].” *Id.*, 682.

99. Mu teaches that “[PD-L1] has been shown to be involved in negative regulation of immune responses through PD-1 receptor on activated T and B cells and has been thought to be an important strategy by which cancer cells evade host immune surveillance. Cancer cells expressing PD-L1 have been shown to increase apoptosis of antigen-specific human T-cell clones and to inhibit CD4 and CD8 T-cell activation in vitro.” *Id.*

100. The authors of Mu report that they found the “expression rate of PD-L1 in NSCLC was associated with histological types and overall survival” and that patients with “either adenocarcinoma or survival time after surgery less than 3 years showed higher expression rate of PD-L1.” *Id.*, Abstract. The authors also

report that a Cox model analysis indicated “that PD-L1 might be regarded as a poor prognostic factor.” *Id.*

101. As shown in Figure 2 of Mu, a multivariate analysis showed that “PD-L1 positive lung cancer cells were significantly related to a poor prognosis”:

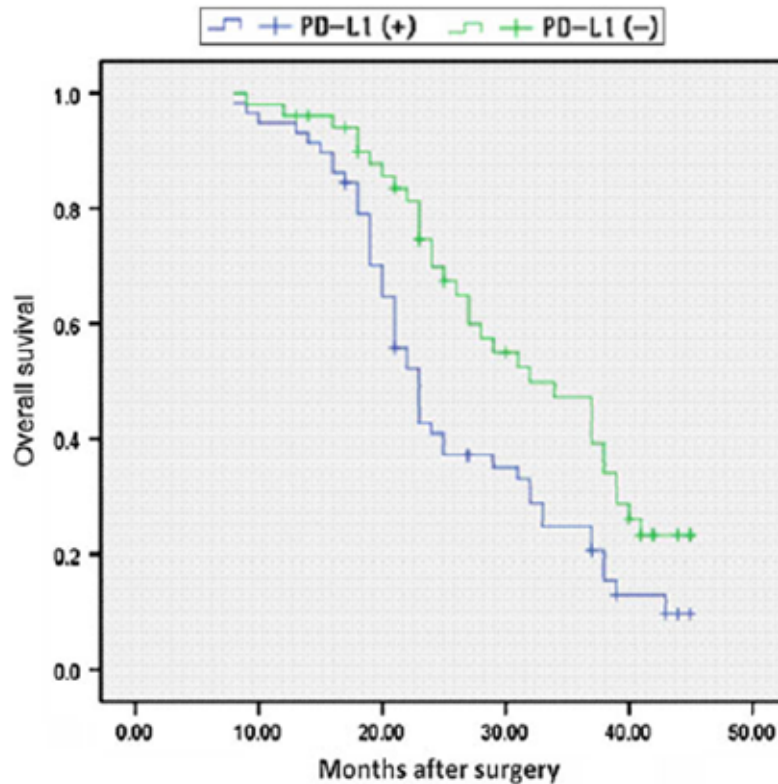


Fig. 2 Kaplan–Meier survival curves of patients with lung cancer according to the presence of PD-L1-positive lung cancer cells

102. Mu further reports that its study and others have found that the blockade of PD-L1 “has been shown to increase antitumoral T-cell responses directed against PD-L1-positive tumors in vitro and in vivo.” *Id.*, 685. Mu also reports that they “have demonstrated the expression of PD-L1 in surgically

resected specimens of non-small cell lung cancer, and expression of these molecules is found in both the plasma membrane and cytoplasm of cancer cells.”

Id. Specifically, 53.2% of the 109 subjects had PD-L1 positive tumors. *Id.*, 684.EX In contrast, the paratumor tissues failed to express PD-L1. *Id.*, 685.

103. Mu thus teaches that NSCLC tumors are significantly more likely to be positive for PD-L1 expression. Consistent with the above, Mu concludes by stating that their experiments “indicate PD-L1 expression had contributed to DC maturation within tumor cell area and correlated with the survival of patients with lung cancer.” *Id.*, 687.

104. Mu also provides a Table (Table 2), which illustrates the percentage of PD-L1 expression in the tumor regions of NSCLC tumor specimens it studied:

Table 2 The percentage of PD-L1 on CD1 α - and CD83-positive TIDC in tumor regions			
Tumor specimen	CD83/CD1 α %	PD-L1/CD1 α %	PD-L1/CD83%
1	40.0	62.2	27.8
2	51.2	56.1	42.9
3	69.2	69.2	40.7
4	47.5	77.5	47.4
5	37.1	74.3	30.8
6	52.4	61.9	54.5
7	68.9	57.8	51.6
8	34.0	74.0	41.2
9	51.4	70.3	42.1
10	54.2	41.7	15.4
11	116.7	50.0	28.6
12	66.1	58.9	40.5
13	35.3	55.9	25.0
14	28.3	87.0	30.8
15	45.9	78.4	35.3
16	31.6	81.6	33.3
17	51.2	65.9	42.9
18	66.7	70.6	44.1
19	76.7	76.7	30.4
20	126.1	43.5	37.9
Mean \pm SD	58.23 \pm 26.14	65.68 \pm 12.50	37.16 \pm 9.52
rs		-0.532	0.537
P		0.016*	0.015*
* $P < 0.05$			

Id., 687.

105. Thus, the POSA would understand from Mu that NSCLC cells are significantly more likely to be positive for PD-L1 expression and that PD-L1 expression in tumor cells likely played a role in resisting an immune response and

promoting tumor progression. The POSA would also understand, in light of Mu, that an anti-PD-L1 antibody which could inhibit PD-L1 signaling would increase antitumoral T-cell responses and could improve outcomes in patients with PD-L1 positive NSCLC tumors. The POSA would have been motivated to pursue anti-PD-L1 antibodies as a form of treatment for NSCLC tumors in light of Mu's teachings.

106. While Mu analyzed tumor specimens which were Stage I, Stage II, or Stage III tumors, *Id.*, 683, the POSA would have expected, based on Mu's teachings, that NSCLC tumor cells can express PD-L1 and that this would be expected at all stages, including for Stage IV tumors. The POSA would understand that Stage IV NSCLC tumors would be just as likely to express PD-L1 given that Stages I-III do as well.

D. Irving

107. U.S. Patent Application App. No. 12/633,339 published on August 12, 2010 with the Publication No. US 2010/0203056 A1 (hereafter referred to as "Irving"). EX1058. Irving is entitled "Anti-PD-L1 Antibodies and Their Use to Enhance T-Cell Function" and would have been publicly available to the POSA on August 12, 2010. *Id.* I understand from counsel that Irving is prior art to the '092 patent.

108. Irving teaches that by at least 2010 it was well-known that “T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1).” *Id.*, [0005]. As a result, as Irving explained, there was “intense interest” in inhibiting PD-L1 signaling to “enhance T cell immunity for the treatment of cancer (e.g., tumor immunity) and infection, including both acute and chronic (e.g., persistent) infection.” *Id.*

109. Irving teaches “anti-PD-L1 antibodies, including nucleic acid encoding and compositions containing such antibodies, and for their use to enhance T-cell function to upregulate cell-mediated immune responses and for the treatment of T cell dysfunctional disorders, including infection (e.g., acute [sic] and chronic) and tumor immunity.” *Id.*, [0006].

110. As Irving explains, it was known by the POSA in 2010 that tumor cells which express PD-L1 were tied to immune evasion:

PD-L1 expression on many tumors is a component to this suppression and may act in concert with other immunosuppressive signals. PD-L1 negatively regulates T-cell receptor signaling. PD-L1 expression has been shown in situ on a wide variety [sic] of solid tumors, including breast, lung, colon, ovarian, melanoma, bladder, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers. Brown et al., J. Immunol. 170: 1257-66 (2003); Dong et al., Nat. Med. 8: 793-800 (2002); Hamanishi et al., PNAS

104: 3360-65 (2007); Strome et al., Cancer Res. 63: 6501-5 (2003); Inman et al., Cancer 109: 1499-505 (2007); Konishi et al., Clin. Cancer Res. 10: 5094-100 (2004); Nakanishi et al., Cancer Immunol. Immunother. 56: 1173-82 (2007); Nomi et al., Clin. Cancer Res. 13: 2151-57 (2004); Thompson et al., PNAS 101: 17174-79 (2004); Wu et al., Acta Histochem. 108: 19-24 (2006).

Id., [0419].

111. To solve the issue of tumor immune evasion by expression of PD-L1, Irving developed antibodies to PD-L1 and tested them in the treatment of tumors. Irving discloses the treatment of tumors in an animal model using anti-PD-L1 antibodies. *Id.*, [0594]-[0602] (Examples 8 and 9), Figures 9 and 10. Example 8 discloses treatment with anti-PD-L1 antibodies at a 10 mg/kg dose and that the “[b]lockade of PD-L1 either early or in late intervention is highly effective as a single agent therapy at preventing tumor growth.” *Id.*, [0595].

112. Specifically, Irving inoculated mice with MC38Ova colon carcinoma cells and treated the animals with 10 mg/kg anti-PD-L1 antibodies. *Id.*, Example 8. Figure 9A shows “a significant reduction in MC38Ova colon carcinoma tumor growth as a result of application of anti-PD-L1 antibody following therapeutic treatment of established tumors (treatment begun at Day 14, when tumor is 250 mm³). *Id.*, [0049].

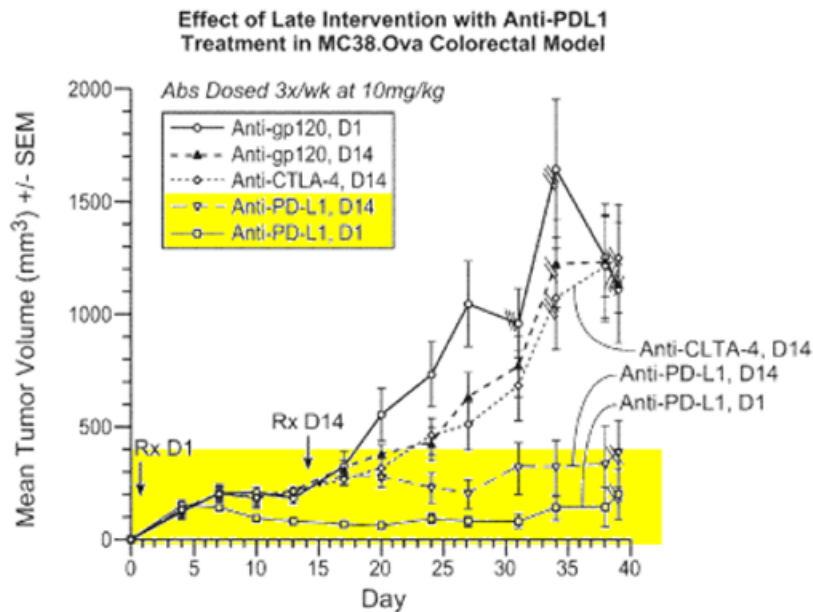


FIG. 9A

Id., Figure 9A (annotated).

113. Irving also discloses that PD-L1 expression has been shown on a variety of tumors, including lung tumors. *Id.*, [0419]. Irving claims, *inter alia*, methods of treating lung cancer:

81. A method of treating a T-cell dysfunctional disorder comprising administering a therapeutically effective amount of the composition of claim 48 to a patient suffering from a T-cell dysfunctional disorder.

84. The method of claim 81, wherein the T-cell dysfunctional disorder is tumor immunity.

95. The method of claim 84, wherein the tumor immunity results from a cancer selected from the group consisting of: breast, lung, colon, ovarian,

melanoma, bladder, kidney, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers, gastric and pancreatic cancer.

Id., cls. 81, 84, and 95.

114. Irving also discloses the various components of pharmaceutical formulations incorporating anti-PD-L1 antibodies. In a section entitled “Pharmaceutical Formulations,” Irving describes how “[t]herapeutic formulations” can be prepared. *Id.*, [0389]. These include the use of salts, antioxidants, and carriers. *Id.*, [0389]-[0397]. Irving also teaches the use of preservatives and wetting agents. *Id.*, [0217], [0395].

115. Irving also states that:

Studies relating to . . . PD-L1 expression on tumors to disease outcome show that PD-L1 expression strongly correlates with unfavorable prognosis in kidney, ovarian, bladder, breast, gastric, and pancreatic cancer, but perhaps not small cell lung cancer.

Id., [0422].

116. The POSA, as of the publication of Irving, would understand this statement to apply to *small cell* lung cancer, not non-small cell lung cancer.

117. Moreover, even to the extent the POSA would understand the above statement in Irving to apply to NSCLC, Irving does not teach away. The POSA would understand that Irving is the publication of an application which was filed on December 8, 2009. *Id.*, 1. The POSA would understand that the authors of

Irving did not have the benefit of later art, such as Mu, which clarified that NSCLC tumors did in fact express PD-L1 and its expression was correlated with negative survival outcomes. The POSA would not have credited this statement by Irving as of the priority date of the '092 patent.

118. Indeed, the only reference addressing NSCLC which is cited in that paragraph of Irving is Konishi 2004, a much older publication. *Id.*, [0422], EX1052. Konishi 2004 was published in the Journal of Clinical Cancer Research in 2004, which is a reoccurring publication. EX1052. Konishi 2004, like Mu, investigated the expression of PD-L1 in tumor specimens of non-small cell lung cancer. The authors of Konishi 2004 found that PD-L1 was expressed in *all* non-small cell lung cancer tumor specimens they evaluated. *Id.*, 5094. Moreover, Konishi 2004 taught that the percentage of tumor-infiltrating lymphocytes (TILs) significantly decreased in PD-L1 positive tumor regions as compared to PD-L1 negative tumor regions. *Id.* Thus, rather than teach away, Konishi 2004 further supports what the POSA already knew as of May 2012—that PD-L1 was expressed on NSCLC tumors and that it reduced tumor-infiltrating lymphocytes on PD-L1 positive tumors and thus played a role in tumor immune evasion. While Konishi 2004 did not find a “statistically significant relationship” between the expression of PD-L1 and the prognosis of patients, Mu, a more recent publication

which studied tumor specimens from twice as many subjects, did find such a relationship. *Id.*, 5097; EX1023, 682. Thus, the POSA would not have credited this statement from Irving and would have understood PD-L1 expression in NSCLC tumors to assist with immune response evasion and to be associated with negative outcomes in patients.

E. WO874

119. International Publication No. WO 2007/005874 A2 (“WO874”) is a PCT application which published and was publicly available on January 11, 2007. EX1027, 1. WO874 is entitled “Human Monoclonal Antibodies to Programmed Death Ligand 1 (PD-L1).” *Id.* Two other anti-PD-L1 antibody patents assigned to U.S. Patent Nos. 9,580,505 and 9,580,507 claim priority to WO874 and are similarly directed towards anti-PD-L1 antibodies and methods of treatment. EXS1059 and 1060. I understand from counsel that WO874 is prior art to the ’092 patent.

120. WO874 teaches the administration of human monoclonal anti-PD-L1 antibodies for the treatment of tumors, including lung tumors. It begins by disclosing that “PD-L1 expression has been found in several murine and human cancers, including human lung, ovarian and colon carcinoma and various myelomas.” EX1027, 1:19-21. It describes its invention as providing “isolated

monoclonal antibodies, in particular human monoclonal antibodies that bind to PD-L1 and exhibit numerous desirable properties.” *Id.*, 1-2.

121. Specifically, WO874 “pertains to methods of inhibiting growth of tumor cells in a subject using anti-PD-L1 antibodies . . . as well as to treat diseases such as cancer.” *Id.*, 21:1-6. It further discloses the sequences for numerous anti-PD-L1 antibodies, including human monoclonal antibodies 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7, and 13G4. *Id.*, 26:6-14. WO874 also teaches methods of identifying and preparing additional anti-PD-L1 antibodies for evaluation. *Id.*, 40:1-8, 51:18-52:4. Such antibodies can be prepared using “conventional monoclonal antibody methodology,” as disclosed by WO874. *Id.*, 55:10-15. It would have been routine for the skilled artisan in 2007 to generate anti-PD-L1 antibodies in light of routine and conventional monoclonal antibodies.

122. The POSA would have also understood by March 2010, before the priority date of the ’092 patent, that “MDX-1105,” as used in NCT664, was specifically disclosed in WO874. EX1030, [0177] (“A specific example of an anti-B7-H1 antibody useful in the methods of the invention is MDX-1105 (WO/2007/005874, published 11 Jan. 2007)), a human anti-B7-H1 anti body.”).

123. WO874 also teaches that its methods of treatment using its anti-PD-L1 antibodies can be used to treat lung cancer, in particular. WO874 lists

“[p]referred cancers whose growth may be inhibited by the antibodies of the invention” and identified “lung cancer” as one such example of a preferred cancer. EX1027, 80:21-82:9; 1:19-20.

124. WO874 provides *in vitro* experimental data which show that its anti-PD-L1 antibodies “bind to human cell surface PD-L1.” *Id.*, 100:1-31 (Examples 5 and 6), Figures 37A-C. Example 7 discusses experimental results regarding numerous anti-PD-L1 human monoclonal antibodies, including data presented in Figure 40 which shows that such antibodies promote T-cell proliferation and IFN- γ secretion in a concentration-dependent manner, in contrast to control antibodies. *Id.*, Example 7. Example 10 and 11 (Figures 45 and 46) show that various anti-PD-L1 monoclonal antibodies block binding of PD-L1 with human PD-1. *Id.*, Example 10 and 11. As WO874 reports, this “demonstrates that the anti-PD-L1 HuMAbs block binding of PD-L1 ligand to cell surface PD-1” in *in vitro* experiments. *Id.*, 103:22-104:27. Example 14 further discloses data evaluating the binding profiles of multiple human anti-PD-L1 antibodies with lung carcinoma tissues. *Id.*, 106:1-107:18. WO874 reports that “[w]eak to moderate staining was observed . . . in tumor cells of lung carcinoma tissues.” *Id.*, 107:1-2. A person of skill would understand this reported data, in sum, to reflect that human anti-PD-L1

antibodies bind to lung cancer cells and that anti-PD-L1 antibodies could reasonably be expected to treat lung tumors.

125. WO874 also discloses the treatment of tumors in an animal model with its anti-PD-L1 antibodies. Example 13 of WO874 discloses experiments performed in mice which were implanted with MC38 colorectal cancer cells. The mice were then selected for treatment once the tumors reached a size of 100-200 mm³. EX1027, Example 13. The mice were then treated with anti-PD-L1 antibodies at a 10 mg/kg dose. The results of the study indicate that the anti-PD-L1 antibody had a “modest effect on tumor growth resulting in a delay of tumor growth.” *Id.*

IX. UNPATENTABILITY OF THE '092 PATENT

A. Claims 1-6 and 24-25 of the '092 Patent are Unpatentable as Obvious Over NCT664 In View of Brahmer and Mu

126. Claims 1-6 and 24-25 of the '092 patent are obvious over NCT664 in view of Brahmer and Mu. The claims of the '092 patent are directed to a “method of treating a late stage non-small cell lung cancer (NSCLC) tumor in a human subject by administering “about 10 mg/kg” of an anti-PD-L1 antibody “every 2 weeks” by intravenous infusion “over 60 minutes,” and wherein the subject was pretreated for a chemotherapy and radiotherapy and wherein “at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression.” EX1001, cl. 1. In my

opinion, the POSA would have been motivated to treat NSCLC with 10 mg/kg of anti-PD-L1 antibody every 2 weeks by 60-minute intravenous infusion, where the subject was pretreated for chemotherapy and radiotherapy and where at least 1% of tumor cells express PD-L1 on the membrane.

1. The POSA would have been motivated to treat late-stage NSCLC tumors with an anti-PD-L1 antibody.

127. The POSA would have been motivated to administer anti-PD-L1 antibodies to treat late-stage NSCLC tumors based on the disclosure of NCT664, Mu, and Brahmer. As of the priority date of the '092 patent, the POSA was already interested in exploring alternative treatments for cancer, including NSCLC tumors, such as immunotherapy. This is because traditional first-line treatments, such as chemotherapy and radiotherapy, were often clinically ineffective against various NSCLC tumors. Thus, given the problems with traditional treatments, the POSA would have been interested in other potential forms of immunotherapy, including anti-PD-L1 antibody therapy.

128. Indeed, NCT664 disclosed a Phase I clinical trial that administered an anti-PD-L1 antibody at 10 mg/kg once every two weeks to treat a variety of cancers, including late-stage NSCLC. EX1021. And the POSA, as explained above, already knew before the priority date that the clinical trial had shown clinical responses in subjects. *See supra* §VIII.A. Given that the trial was already

reporting clinical responses in subjects, the POSA would certainly have been motivated to pursue anti-PD-L1 antibody treatments for lung cancer.

129. The POSA would have also been motivated to pursue anti-PD-L1 antibody treatments for NSCLC tumors in light of Brahmer and Mu. Brahmer discloses that a prior Phase I study conducted by BMS with an anti-PD-1 antibody had shown preliminary evidence of antitumor activity. EX1019. It further teaches that a response to treatment appeared to be associated with PD-L1 tumor expression. *Id.* The POSA would understand that an anti-PD-1 antibody is directed towards the same PD-1/PD-L1 pathway that an anti-PD-L1 antibody would be targeted at. Hence, the POSA would have been motivated to also pursue anti-PD-L1 antibodies as treatment for NSCLC tumors given Brahmer's reported success with an anti-PD-1 antibody. Similarly, Mu disclosed that PD-L1 expression on NSCLC tumors was associated with poor prognosis. EX1023. Thus, given Mu's teaching, the POSA would have understood that PD-L1 expression by tumors likely played a role in tumor resistance and immune evasion and would have further been motivated to pursue anti-PD-L1 antibody treatment.

2. The POSA would have been motivated to use the claimed dosing regimen of 10 mg/kg every 2 weeks by 60-minute intravenous infusion.

130. As explained above, see *supra* §VIII.A, NCT664 disclosed a Phase I clinical trial that administered an anti-PD-L1 antibody at 10 mg/kg once every two

weeks to treat NSCLC. EX1021. The POSA already knew before the priority date that the clinical trial, including the 10 mg/kg dose, had shown clinical responses in subjects. Thus, the POSA would be motivated to pursue the specific dose of anti-PD-L1 antibody that was reportedly efficacious before the priority date of the '092 patent—in other words, a 10 mg/kg dose once every 2 weeks.

131. The POSA also would have been aware from Brahmer that BMS's prior Phase I study with an anti-PD-1 antibody, which targets the same PD-1/PD-L1 pathway, was infused using a 60-minute intravenous infusion, and that Brahmer taught that this dosing regimen was associated with preliminary evidence of antitumor activity. *See supra* §VIII.B. Thus, the POSA would have been further motivated to pursue a 60-minute intravenous infusion for an anti-PD-L1 antibody in light of Brahmer.

132. In addition, the POSA would have been motivated to investigate a 60-minute intravenous infusion even apart from Brahmer's disclosure. Longer administration times require considerable healthcare resources and are inconvenient for patients. This is why the POSA would have investigated a one-hour infusion time. Research on other monoclonal antibodies reflect that this is precisely what POSAs did as of the priority date.

133. For example, a publication in the European Journal of Haematology in 2009 entitled “Rapid infusion of rituximab over 60 min,” authored by Mark Tuthill and other authors (“Tuthill 2009”) investigated the safety and effectiveness of administering rituximab at 60-minute intravenous infusions. EX1028. The authors did so because administration “over 2 to 3 h requires considerable healthcare resources and is inconvenient for patients.” *Id.*, 322. Consistent with the rationale for why the POSA would have investigated a 60-minute IV infusion time through routine experimentation, Tuthill 2009 notes the “interest” in “reduc[ing] the burden on healthcare resources and patient inconvenience.” *Id.* Similarly, a publication in Alimentary Pharmacology and Therapeutics, published online on May 25, 2011, investigated the safety and tolerability of a 60-minute infusion of infliximab, noting that the longer “time interval has substantial impact on healthcare resources and is costly in terms of patient’s time away from work.” EX1040, 181. Thus, even apart from Brahmer’s teaching, the POSA would have been motivated to pursue a shorter 60-minute intravenous infusion for an anti-PD-L1 antibody to reduce the impact on healthcare costs and patients. That is especially so here as a 60-minute infusion is a common infusion time. For example, most chemotherapies are also administered over this time period.

134. A 60-minute intravenous infusion time period for an anti-PD-L1 antibody would also have been determined through routine experimentation. POSAs routinely adjust doses in evaluating the administration of antibodies, and would do the same with an anti-PD-L1 antibody. The POSA, in evaluating the 10 mg/kg dosage of NCT664 would have evaluated shorter and longer time intervals, such as 30 minutes or 90 minutes, in determining an appropriate administration time.

3. The POSA would have been motivated to treat NSCLC tumors where at least 1% of tumor cells express PD-L1 and where the subject had previously been treated with chemotherapy and radiotherapy.

135. The POSA would have also been motivated to treat NSCLC tumors which had previously been pretreated with chemotherapy and radiotherapy with an anti-PD-L1 antibody and where at least 1% of the tumor cells express PD-L1.

136. First, the POSA would have known in light of Mu's disclosures that NSCLC tumors can express PD-L1, and the POSA would have understood PD-L1's role in tumor evasion. *See supra* §VIII.C. Mu itself teaches that PD-L1 positive NSCLC cancer cells were "significantly related to a poor prognosis." EX1023, 686. Thus, the POSA would have known that the expression of PD-L1 on tumor cells assists with tumor evasion and that the administration of an effective anti-PD-L1 antibody could bind PD-L1 expressed on tumors, thereby

preventing the tumor from evading tumor infiltrating lymphocytes. This alone would have provided a motivation to pursue treatment of NSCLC tumors where at least 1% of tumor cells express PD-L1.

137. Furthermore, in 2012, treatment options for NSCLC tumors were extremely limited and POSAs were well aware of this issue. Because treatment options were so few, the POSA would have been motivated to administer an anti-PD-L1 antibody as long as the tumor expressed PD-L1, even if such expression was as low as 1%. Thus, the limited nature of treatment at the time would further provide the POSA with significant motivation to treat a tumor with at least 1% PD-L1 expression on tumor cells with an anti-PD-L1 antibody. In fact, the claims' requirement of "at least 1%" effectively covers a range of patients whose tumors have anywhere from 1% to 100% of tumor cells that express PD-L1. The POSA would have been motivated to treat those patients with an anti-PD-L1 antibody.

138. Second, as of the priority date, it was known by the POSA that chemotherapy and radiotherapy were first-line modes of treatment for NSCLC tumors. Even today, these are the first methods of treating NSCLC tumors before the POSA considers the application of immunotherapy. As of the priority date, POSAs were interested in pursuing alternative treatment regimens, including monoclonal antibody treatments, for NSCLC tumors as an alternative treatment in

the even that chemotherapy and radiotherapy were therapeutically ineffective. It was also known as of the priority date that many patients had refractory NSCLC, *i.e.*, NSCLC tumors which were unresponsive to multiple prior treatments, including radiotherapy and chemotherapy. Thus, the POSA would have a motivation to pursue immunotherapy for patients who were refractory to both chemotherapy and radiotherapy.

4. The POSA would have a motivation to combine NCT664, Brahmer, and Mu.

139. It is also my opinion that the POSA would have been motivated to combine the teachings of NCT664, Brahmer, and Mu.

140. The POSA looking at the teachings of the NCT664 reference would have looked to the teachings of Mu and Brahmer. Given the POSA's knowledge of PD-L1 and its role in tumor evasion, the expression of PD-L1 on lung cancer, and the success of anti-PD-1 treatment, the POSA would have looked to Mu to determine PD-L1 expression patterns on NSCLC tumors specifically. Mu would provide further motivation to use the dosing regimen of NCT664 to treat NSCLC tumors based on its teaching that "PD-L1 positive lung cancer cells was significantly related to a poor prognosis," and that it "plays a role in disease progression." EX1023, 686-87.

141. The POSA would have been motivated to use the infusion rate of Brahmer, combined with the dosing regimen of NCT664. Both Brahmer and NCT664 are directed towards the administration of monoclonal antibodies to NSCLC patients, one describing an anti-PD-1 antibody and one describing an anti-PD-L1 antibody. Thus, the POSA would have looked to Brahmer's infusion rate to apply to the administration of MDX-1105. By targeting the PD-1-axis pathway with antibody therapy, the POSA would understand that Brahmer's infusion method would be an obvious choice for the infusion rate of an anti-PD-L1 antibody.

5. The POSA would have a reasonable expectation of success in treating late-stage NSCLC using the dosing regimen of NCT664 with the infusion rate of Brahmer

142. It is also my opinion that the POSA would have reasonably expected success using NCT664's dosing regimen with Brahmer's infusion rate to treat late-stage NSCLC tumors in a human subject. As explained above, *see supra* §IV.B, it is my opinion that the preambles do not require clinical efficacy but only require an intent to achieve some degree of antitumor activity against NSCLC. However, regardless of whether or not my position is correct, it is my opinion that the POSA would have a reasonable expectation of success.

143. The POSA would have also been aware of the anti-PD-1 clinical trials described in Brahmer. The POSA was aware that MDX-1106, i.e., nivolumab, had

achieved anti-tumor clinical activity in patients, including those with NSCLC. EX1019, 3169; *see also* EX1029. The POSA would understand that these successful clinical results of nivolumab, an anti-PD-1 immunotherapy, taught that other monoclonal antibodies that disrupt the interaction of PD-1 with PD-L1 would likely be successful in treating tumors that express PD-L1.

144. The POSA also already knew that tumor cells that express PD-L1 would be responsive to treatment with anti-PD-L1 antibodies. Brahmer described a correlation between membranous PD-L1 expression on tumor cells and the likelihood of tumor regression with treatment by an anti-PD-1 antibody. EX1019, 3170. Brahmer thus taught that “tumor cell surface expression of [PD-L1] may be a predictor of responsiveness to PD-1 blockade.” *Id.*, 3172. The POSA would have thus reasonably expected an anti-PD-L1 antibody to successfully treat tumors expressing PD-L1 in light of the MDX-1106 Phase I clinical trials. The POSA would have expected an anti-PD-L1 antibody to attack the same pathway as the anti-PD-1 antibody and disrupt the PD-1/PD-L1 interaction that gives rise to tumor evasion. Thus, Brahmer teaches the POSA that an anti-PD-L1 antibody which also blocks the interaction of PD-1/PD-L1 is reasonably likely to achieve a clinical response.

145. This is further supported by the clinical trial protocol which supported NCT664:

1.4. Rationale for MDX-1105

1.4.1. Dose Selection

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

EX1038, 26.

146. BMS's own clinical trial protocol used the results of data from MDX-1106 to justify the "[r]ationale for MDX-1105," including its dose selection. Indeed, BMS stated that "efficacy is expected to manifest at a dose between 1 and 15 mg/kg," based on the anti-PD-1 studies. *Id.* While I understand that this protocol is not prior art as it was not publicly available, it is dated June 17, 2008 and reflects how POSAs would have understood the results of Brahmer to inform anti-PD-L1 treatment moving forward. This protocol thus confirms that the POSA, at the time of the alleged invention of the '092 patent, would have looked to PD-1 (nivolumab/MDX-1106) clinical trials to gauge the likelihood of success of a method of treatment using a PD-L1 antibody. The POSA would thus have had a reasonable expectation that anti-PD-L1 monoclonal antibodies would be expected to treat NSCLC tumors in light of these prior art disclosures as it was known that

monoclonal antibodies targeting the PD-1/PD-L1 pathway would achieve successful clinical outcomes.

147. In addition, the POSA also knew that the specific methods of treatment disclosed by NCT664 were already successful. As described above, Hwu 2010, Topalian 2011, and Topalian 2012, *see supra* §VIII.A, all disclosed the clinical success of the 10 mg/kg dose of anti-PD-L1 antibody in NCT664.

148. Even if the POSA did not know that the specific methods of treatment were already successful (which they did), the disclosed treatment regimen of NCT664 did in fact achieve successful treatment, as disclosed by Brahmer 2012. Brahmer 2012 published the results of the NCT664 trial and concluded that its treatment regimen “induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rate of 12 to 41% at 24 weeks) in patients with select advanced cancer, including non–small-cell lung cancer.” EX1069, 2464.

6. Independent claim 1

149. Claim 1 is obvious in light of the combined teachings of NCT664, Brahmer, and Mu.

150. NCT664 discloses a Phase I clinical trial administering an anti-PD-L1 antibody (MDX-1105) to subjects with advanced or recurrent NSCLC. EX1021. The inclusion criterion includes subjects with “non-small cell lung cancer.” *Id.*, 5.

While the '092 patent does not provide a definition of what constitutes “late stage” NSCLC, the ordinary meaning of “late stage NSCLC” to a POSA would include Stage III or Stage IV tumors, i.e., advanced tumors, as well as tumors which were unresectable. This is confirmed by claim 2, which depends from claim 1, and requires that the tumor be “Stage IV NSCLC.” EX1001, cl. 2. NCT’ 664 discloses the treatment of advanced NSCLC tumors, which would include Stage III and Stage IV tumors. *Id.* NCT664 therefore discloses the treatment of late-stage NSCLC tumors in human subjects.

151. As explained above, the POSA also knew, in light of the disclosures of Hwu 2010, Topalian 2011, and Topalian 2012, that NCT664 had shown clinical responses in patients at all doses in the NCT664 trial. *See supra* §VIII.A. The POSA would thus know that the disclosed treatment regimen of NCT664 could be used to treat NSCLC tumors and achieve antitumor activity before the critical date.

152. NCT664 also discloses the administration of MDX-1105 by “i.v. infusion” at a 10 mg/kg dose “every 14 days,” i.e., every two weeks. EX1021, 3, 4. And, as explained above, the antibody MDX-1105 was known in the art before the critical date. *See supra* §IX.A.5. NCT664 thus discloses “administering to the subjects about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks” by intravenous infusion. EX1001, cl. 1.

153. It further would have been obvious to the POSA to administer the anti-PD-L1 antibody “over 60 minutes infusion” in light of NCT664, Brahmer, and the general knowledge of the POSA as of the critical date. EX1001, cl. 1.

154. Brahmer discloses that its anti-PD-1 antibody was administered by intravenous infusion for 60 minutes at a 10 mg/kg dose. EX1019, 3168. In light of Brahmer, which used this infusion rate for an anti-PD-1 antibody successfully, the POSA would have been motivated to use the 60-minute intravenous infusion rate for an anti-PD-L1 antibody.

155. Moreover, as explained above, the POSA would have also determined, through routine experimentation, that a 60-minute infusion of an anti-PD-L1 antibody would be effective. *See supra* §IX.A.2. The POSA would routinely adjust the dose in evaluating the administration of an anti-PD-L1 antibody. The POSA, in evaluating the 10 mg/kg dosage of NCT664 would have evaluated shorter and longer time intervals, such as 30 minutes or 90 minutes, in determining an appropriate administration time. Ultimately, the POSA would be motivated to investigate shorter administration times, such as 60-minutes, as longer administration times require considerable healthcare resources and are inconvenient for patients, as explained above. *See supra* §IX.A.2.

156. The POSA would also have a reasonable expectation that the 60-minute intravenous infusion time would be successful. The POSA would have been aware that various other prior art monoclonal antibodies had been administered over 60-minute intravenous infusions as approved by the FDA. *See* EX1031 (cetuximab approved by the FDA with weekly 60-minute infusions); EX1032 (panitumumab approved by the FDA for administration every 14 days as an intravenous infusion over 60 minutes or 90 minutes); EX1033 (natalizumab approved by the FDA for IV infusion over “approximately one hour.”); EX1009, 13:2-3 (teaching an intravenous administration can occur for “1 to 24 hours,” which encompasses a 60-minute time). As there were multiple approved monoclonal antibodies approved by FDA with 60-minute infusion times, the POSA would have had further reason to test it and would have had a reasonable expectation that the infusion time would succeed.

157. The claim limitation that states “wherein the subject is pretreated for a chemotherapy and a radiotherapy” is disclosed by NCT664 or is obvious from NCT664 and Mu. NCT664’s inclusion criteria states that the “[s]ubjects must have *refractory* or recurrent histologically or cytologically confirmed advanced NSCLC.” EX1021, 5. As of the priority date, the POSA knew that chemotherapy and radiotherapy were first line treatments for NSCLC. *See supra* §IX.A.1. Thus,

the POSA would understand NCT664's disclosure of refractory non-small cell lung cancer to include patients that would have been pretreated with both chemotherapy and radiotherapy.

158. Similarly, Brahmer disclosed the treatment of patients with an anti-PD-1 antibody, targeting the same PD-1/PD-L1 pathway, for "treatment-refractory solid tumors." EX1019, 3167. Numerous patients in Brahmer were previously treated with chemotherapy and radiation therapy. *Id.*, 3169. The POSA would understand treatment-refractory tumors to include tumors that were unresponsive to pretreatment with chemotherapy and radiotherapy, as taught by Brahmer.

159. Consistent with what the POSA already understood as of the priority date, Mu teaches that "chemotherapy and radiotherapy have low efficacy" against lung cancer. EX1023, 682. It would have thus been obvious to the POSA to administer forms of immunotherapy, including anti-PD-L1 antibodies, to patients who were pretreated with chemotherapy and radiotherapy and whose treatment was ineffective.

160. It further would have been obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must have at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression. Mu teaches the POSA that NSCLC cells are significantly more likely to be positive for PD-L1 expression, and,

consistent with what the POSA already knew, that PD-L1 expression in tumors assists tumors to resist immune response and promotes tumor progression. Mu notes that the “[t]he percentage of PD-L1-positive cells in non-small cell lung cancer was 53.2% (58/109).” EX1023, 684. Thus, the POSA would understand that NCT664 disclosed treating NSCLC “wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression.”

161. Moreover, this limitation would be obvious to the POSA because a tumor must have at least a minimal amount of tumor cells exhibit PD-L1 for that subject to be a potential target of treatment with an anti-PD-L1 antibody. Indeed, if a tumor did not even have a minimal amount, *i.e.*, 1%, of its cells express PD-L1, there would be no purpose in administering an anti-PD-L1 antibody to treat that tumor.

162. For these reasons, NCT664 in combination with Brahmer and Mu render independent claim 1 obvious. The POSA would be motivated to combine this art to achieve the particular limitations of the claim, including the claimed dosing regimen. Moreover, even assuming that the preamble is a claim limitation, the POSA would also have a reasonable expectation that the combination could treat NSCLC tumors. *See supra* §IX.A.5.

7. Claims 2 and 3

163. Claim 2 depends from claim 1 and further requires that the “tumor is Stage IV NSCLC.” EX1001, cl. 2.

164. Claim 3 also depends from claim 1 and further requires that the “tumor is advanced or recurrent.” EX1001, cl. 3.

165. These additional limitations are disclosed by Brahmer and Mu.

166. Brahmer teaches that its anti-PD-1 antibody achieved reduction of tumor activity in patients “with advanced treatment-refractory solid tumors.” EX1019, 3168. The same is true for NCT664 which states that its subjects had “advanced or recurrent solid tumors.” EX1021.

167. Furthermore, Mu involved an analysis of Stage I, II, or III NSCLC tumor specimens which had been surgically removed. Stage IV tumors are routinely needle biopsied, rather than surgically removed due to their nature. Figure 2 of Mu, illustrated above, *see supra* §VIII.C, shows that PD-L1 expression was related to poor prognosis following surgical resection. EX1023, 685. Thus, the POSA would have found it obvious to treat NSCLC tumors that are PD-L1 positive and that recurred after the subject previously had their Stage I or II tumor removed.

168. More generally, the POSA would have understood that PD-L1 positive NSCLC tumors should be responsive to anti-PD-L1 antibody therapy

regardless of stage as the anti-PD-L1 antibody targets the same PD-1/PD-L1 pathway, which the POSA would not expect to be different depending on the stage.

8. Claim 4

169. Claim 4 depends from claim 1 and requires that the “tumor is metastatic.” EX1001, cl. 4. It is my opinion that Claim 4 is obvious based on the combination of NCT664, Brahmer, and Mu.

170. This additional limitation is disclosed by NCT664 and Brahmer. NCT664 describes the treatment of metastatic tumors. EX1021. Brahmer also discloses that nivolumab effectively treated treatment-refractory metastatic solid tumors. EX1019, 3169. As explained above, the POSA would have known that an anti-PD-L1 antibody affects the same PD-1/PD-L1 interaction that is affected by an anti-PD-1 antibody. Thus, the POSA would have reasonably expected that an anti-PD-L1 antibody could also treat metastatic cancers in light of Brahmer.

9. Claim 5

171. Claim 5 depends from claim 1 and requires that the “subject has previously had a stage I and/or II tumor that has surgically been removed.” EX1001, cl. 5. It is my opinion that Claim 5 is obvious based on the combination of NCT664, Brahmer, and Mu.

172. Mu describes a study where the subjects each had either stage I, II, or III NSCLC tumors surgically removed. EX1023, 683. The authors then analyzed

the survival time of each patient afterwards. Figure 2 of Mu, depicted above, *see supra* §VIII.C, shows that PD-L1 positive lung cancer cells were related to a poor diagnosis following the surgical resection of stage I, II, or III tumors. *Id.*, 685. As Mu teaches that a stage I, II, or III PD-L1 positive NSCLC tumors are much more likely to have a poor prognosis following surgical resection, it would have been obvious to the POSA to further treat NSCLC tumors with further therapy, including anti-PD-L1 antibodies, following surgical resection.

10. Claim 6

173. Claim 6 depends from claim 1 and requires that the “treating lasts more than 12 weeks.” EX1001, cl. 6. It is my opinion that Claim 6 is obvious based on the combination of NCT664, Brahmer, and Mu.

174. This limitation is disclosed by NCT664. NCT664 states that 10 mg/kg of anti-PDL-1 antibody was administered “[e]very 14 days” for cycles of “42 days,” i.e., a 6-week cycle. EX1021, 3. NCT664 describes that “[t]he maximum duration of study drug treatment for a subject is 2 years.” *Id.* NCT664 therefore describes treatment that lasts more than 12 weeks.

175. Moreover, this limitation would be obvious as the POSA would understand that immunotherapy treatment should generally be sustained for late-stage tumors and that treatment under 12 weeks would be unlikely to achieve

the necessary clinical progress for patients, as with other antibody therapies or chemotherapy.

11. Claims 24 & 25

176. Claim 24 depends from claim 1 and further requires “measuring membranous PD-L1 expression on tumor cells prior to administering the anti-PD-L1 antibody.” EX1001, cl. 24. Claim 25 depends from claim 24 and further requires that “the measuring comprises an immunohistochemistry.” *Id.*, cl. 25. It is my opinion that both of these claims are also obvious based on the combination of NCT664, Brahmer, and Mu.

177. As Mu teaches, *see supra* §VIII.C, certain NSCLC tumors are PD-L1 positive but not all NSCLC tumors are necessarily PD-L1 positive. The POSA would understand that, if an NSCLC tumor is not PD-L1 positive, it would not make sense to treat that subject with an anti-PD-L1 antibody. It would therefore have been obvious to the POSA to use standard techniques, including immunohistochemistry, to measure membranous PD-L1 expression on NSCLC tumor cells before administering the anti-PD-L1 antibody. This would confirm whether or not the tumor cells are PD-L1 positive before proceeding with treatment.

178. Mu itself teaches that “immunohistochemistry” was performed to detect the expression of PD-L1. EX1023, 683. Immunohistochemistry (“IHC”) is

a common technique well-known to POSAs by May 2012. IHC is routinely used to detect a variety of antigens and was known as a technique that could be used to detect the membranous expression of PD-L1 on tumor cells. The POSA who would have been motivated to measure membranous PD-L1 expression on tumor cells would have been motivated to use immunohistochemistry techniques to detect the presence of PD-L1, particularly in light of Mu.

B. Claims 7-23 of the '092 Patent are Obvious Over NCT664 In View of Brahmer, Mu, and Irving

179. Claims 7-23 of the '092 patent are obvious over NCT664 in view of Brahmer, Mu, and Irving. As explained above, *see supra* §IX.A, it is my opinion that claims 1-6 and 24-25 are obvious in light of the combination of NCT664, Brahmer, and Mu. It is also my opinion, as further explained below, that the same combination with the additional teachings of Irving regarding the use of anti-PD-L1 antibodies in pharmaceutical compositions also render claims 7-23 of the '092 patent obvious.

180. As I already opined above, the POSA would have a motivation to combine the teachings of NCT664, Brahmer, and Mu. *See supra* §IX.A.4. It is also my opinion that the POSA would be motivated to combine those teachings with that of Irving. Irving is also directed to the use of anti-PD-L1 antibodies to treat tumors, which is precisely the same type of disclosure that the POSA would

be interested in. Moreover, the POSA who is interested in pursuing further methods of treatment with anti-PD-L1 antibodies would be interested in pursuing pharmaceutical compositions incorporating the anti-PD-L1 antibody. Irving provides various teachings regarding the use of anti-PD-L1 antibodies in pharmaceutical compositions and is a reference that the POSA would have looked to in developing a method of treating tumors with anti-PD-L1 antibodies.

181. In addition to the reasonable expectation of success with an anti-PD-L1 antibody that a POSA would have in light of NCT664, Brahmer, and Mu, *see supra* §IX.A.5, Irving further provides support for the use of anti-PD-L1 antibodies for treating cancer. As explained above, Irving teaches the effectiveness of anti-PD-L1 antibodies in achieving anti-tumor activity. *See supra* §VIII.D. Irving would thus further support the POSA's expectation of success.

1. Claims 7-9

182. Claim 7 depends from claim 1 and requires that “the anti-PD-L1 antibody is formulated in a pharmaceutical composition.” EX1001, cl. 7. Claim 8, which depends from claim 7, requires that the “pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, or any combination thereof.” EX1001, cl. 8. Claim 9, which also depends from claim 7, requires that “the pharmaceutical composition comprises a preservative, a wetting agent, an emulsifying agent, a dispersing agent,

or any combination thereof.” EX1001, cl. 9. It is my opinion that each of these claims is obvious in view of the combination of NCT664, Brahmer, Mu, and Irving.

183. Specifically, Irving teaches these additional limitations.

184. Irving discloses “anti-PD-L1 antibodies, nucleic acid encoding the same, therapeutic compositions thereof.” EX1058, Abstract. Irving discloses an embodiment where the invention “provides for compositions comprising any of the above described anti-PD-L1 antibodies in combination with at least one pharmaceutically-acceptable carrier.” *Id.*, [0022]; *see also* [0029] (“the invention provides for a composition comprising an anti-PD-L1 antibody or antigen binding fragment . . . and at least one pharmaceutically acceptable carrier.”).

185. Irving goes on to describe various “Pharmaceutical Formulations” that can be prepared using “pharmaceutically acceptable carriers, excipients, or stabilizers.” *Id.*, [0389]. It describes how “salts” can be used in such a formulation. *Id.*, [0391]. It further describes how “wetting agents” can be used to “help solubilize the therapeutic agent,” *Id.*, [0395], and how preservatives can be added to the formulations to reduce bacterial activity, providing multiple examples of each for use in pharmaceutical compositions. *Id.*, [0217]. Irving thus teaches

the additional elements of claims 7-9. It is thus my opinion that claims 7-9 are also obvious given the additional teachings of Irving.

2. Claims 10 and 11

186. Claim 10, which depends from claim 8, further requires that the pharmaceutically acceptable “salt comprises a sodium salt.” EX1001, cl. 10. Claim 11, which also depends from claim 8, requires that the pharmaceutically acceptable “salt comprises sodium chloride.” EX1001, cl. 11. It is also my opinion that these claims are obvious from the combination of NCT664, Mu, Brahmer, and Irving.

187. Irving teaches a pharmaceutical composition with a pharmaceutically acceptable salt where the salt comprises a “sodium salt” or “sodium chloride.” Example 11 of Irving discusses the preparation of anti-PD-L1 antibodies. EX1058, Example 11. Example 11 describes formulations with anti-PD-L1 antibodies which were “formulated into 20 mM Hepes, pH 6.8 with *0.14 M sodium chloride* and 4% mannitol” *Id.* at [0625] (emphasis added). Sodium chloride is one type of sodium salt and thus satisfies both claims 10 and 11. It is thus my opinion that claims 10 and 11 are also obvious given the additional teachings of Irving.

3. Claims 12-17

188. Claims 12-17 depend from claims 1-6 and each of claims 12-17 further require that the claimed method also comprise “administering an

anti-cancer agent.” EX1001, cls. 12-17. It is my opinion that these claims are obvious given the combination of NCT664, Brahmer, Mu, and Irving.

189. The POSA would understand these claims’ requirement that the method of treatment also administer “an anti-cancer agent,” to require the administration of an additional anti-cancer agent other than the anti-PD-L1 antibody administered intravenously by the methods of claims 1-6. This is because, if the anti-cancer agent could be the anti-PD-L1 antibody, then claims 12-17 would be redundant of claim 1 and would add nothing to claim 1. Were that the case, claims 12-17 would be obvious over NCT664, Mu, and Brahmer, as explained above.

190. Irving teaches the administration of an additional anti-cancer agent with the administration of an anti-PD-L1 antibody for the treatment of cancer. Irving states that “[i]n the treatment of cancer, any of the previously described conventional treatments for the treatment of cancer immunity may be conducted, prior, subsequent or simultaneous with the administration of the anti-PD-L1 antibodies of the invention. Additionally, the anti-PD-L1 antibodies of the invention may be adminstrered [sic] prior, subsequent or simultaneous with conventional cancer treatments, such as the administration of tumor-binding antibodies (e.g., monoclonal antibodies, toxin-conjugated monoclonal antibodies)

and/or the administration of chemotherapeutic agents.” EX1058, [0429]. This discloses the use of additional anti-cancer agents along with the administration of an anti-PD-L1 antibody to treat tumors. It is thus my opinion that claims 12-17 are also obvious given the additional teachings of Irving.

4. Claims 18-23

191. Claims 18-23 respectively depend from claims 12-17 and each of claims 18-23 further require that the additionally administered “anti-cancer agent” of claims 12-17 “is an anti-CTLA-4 antibody.” EX1001, cls. 18-23. It is my opinion that these claims are obvious given the combination of NCT664, Brahmer, Mu, and Irving.

192. Irving teaches the administration of an additional anti-cancer that is an anti-CTLA-4 antibody. Irving states that its invention includes “an article of manufacture comprising any of the above described anti-PD-L1 compositions in combination with at least one BNCA molecules. In one aspect, the BNCA molecules is an antibody, antigen binding antibody fragment, BNCA oligopeptide, BNCA RNAi or BNCA small molecule. In another aspect, the B7 negative costimulatory molecule is selected from the group consisting of: CTLA-4, PD-1, PD-L1, PD-L2, B7.1, B7-H3 and B7-H4.” EX1058, [0031]. Irving further teaches that “the antagonism of CTLA-4 (e.g., antagonist anti-CTLA antibodies) . . . may be useful to enhance immune response in the treatment of infection (e.g., acute and

chronic) and tumor immunity.” *Id.*, [0074]. It is thus my opinion that claims 18-23 are also obvious given the additional teachings of Irving.

C. Claims 1-25 of the '092 Patent Are Obvious Over WO874 in View of NCT664, Mu, and Brahmer

193. It is also my opinion that claims 1-25 of the '092 patent are obvious over WO874 in view of NCT664, Brahmer, and Mu. In my opinion, in view of these prior art references, the POSA would have been motivated to treat NSCLC with 10 mg/kg of anti-PD-L1 antibody every 2 weeks by 60-minute intravenous infusion, where the subject was pretreated for chemotherapy and radiotherapy and where at least 1% of tumor cells express PD-L1 on the membrane.

1. The POSA would have been motivated to combine WO874 with NCT664, Mu, and Brahmer.

194. As explained above, *see supra* §IX.A, the POSA would have been motivated to (1) treat NSCLC tumors with an anti-PD-L1 antibody; (2) to use the claimed dosing regimen of 10 mg/kg every 2 weeks by 60 minute intravenous infusion; and (3) to treat NSCLC tumors where at least 1% of tumor cells express PD-L1 and where the subject had previously been treated with chemotherapy and radiotherapy in view of the NCT664, Brahmer, and Mu references.

195. WO874 teaches the use of anti-PD-L1 antibodies to treat various forms of cancer, including lung cancer. *See supra* §VIII.E. The POSA reviewing

WO874 would have thus been motivated to administer anti-PD-L1 antibody treatment for NSCLC tumors.

196. The POSA would also be motivated to combine the teachings of WO874 with the disclosures of Mu, NCT664, and Brahmer. As stated above, *see supra* §IX.A.2, the POSA was interested in exploring alternative forms of treatment for NSCLC as traditional treatments, such as radiotherapy and chemotherapy, were often not therapeutically effective for NSCLC tumors. There would have been a motivation to pursue other forms of treatment, such as immunotherapy.

197. The POSA would have known PD-L1 and its role in tumor evasion, and would have been motivated to use the anti-PD-L1 antibodies disclosed in WO874 to treat lung tumors, including NSCLC tumors.

198. The POSA would have been aware of Mu's teaching that NSCLC tumors could be PD-L1 positive, *see supra* §VIII.C, and the ongoing NCT664 clinical trial that disclosed a 10 mg/kg once every 2-week dosing regimen that achieved anti-tumor activity in subjects with NSCLC. *See supra* §VIII.A. The POSA would have also been aware of Brahmer's disclosure of an anti-PD-1 antibody that was successfully infused intravenously for 60 minutes.

199. The POSA would have also been motivated to combine WO874 with these references. Because the POSA would have knowledge of PD-L1 and its role in tumor evasion, the POSA would have looked to references, such as Mu, which evaluated the expression of PD-L1 on NSCLC tumors. The POSA would have thus been motivated to look to the teachings of Mu.

200. The POSA would also have been motivated to look to the infusion rate of Brahmer along with the dosing regimen of NCT664, for the reasons discussed above. *See supra* §IX.A.4. In addition, given the reported success of anti-PD-L1 and anti-PD-1 antibodies in Brahmer, Hwu 2010, and Topalian 2011, the POSA would be motivated to look at ongoing successful clinical trials in human patients, including the trial of NCT664 and Brahmer. The POSA would have noted that the dosage of an anti-PD-L1 antibody disclosed in NCT664 for the treatment of NSCLC tumors is the same dosage as what was disclosed in WO874, i.e., 10 mg/kg once every two weeks.

201. Moreover, as disclosed by WO874, techniques for generating and testing human monoclonal antibodies were well-known by persons of skill and conventional. EX1027, 56:1-58:16. It would have been routine for a skilled artisan to create anti-PD-L1 antibodies based on the teachings of WO874, including those specifically disclosed by WO874. As discussed above, one of the

antibodies disclosed by WO874, antibody 12A4, is the same antibody, MDX-1105, that was the subject of the NCT664 study. The POSA would have been motivated to evaluate 12A4 as its sequence was specifically disclosed in WO874 as an anti-PD-L1 antibody that could be used in a method of treatment.

2. The POSA would have had a reasonable expectation of success in combining these references.

202. The POSA would also have a reasonable expectation of success in using an anti-PD-L1 antibody to treat NSCLC in a human subject in light of WO874, NCT664, Brahmer, and Mu. As explained above, the teachings of NCT664, Brahmer, and Mu would provide a reasonable expectation of success to treat an NSCLC tumor in a human subject. *See supra* §IX.A.5.

203. WO874 further discloses *in vitro* experimental data and *in vivo* experiments that disclose the treatment of tumors in an animal model using anti-PD-L1 antibodies. *See supra* §VIII.E. It further teaches that such models can be “predictive of efficacy in human tumors.” EX1027, 77:4-5. WO874 also notes that *in vitro* assays can be used to evaluate compounds: “[a]lternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner.” *Id.*, 77:6-8. WO874 also teaches the use of anti-PD-L1 antibodies to treat lung cancer, as discussed above. *See supra* §VIII.E; *Id.*, 80:21-82:9. Thus,

the POSA reviewing WO874 would understand that *in vitro* and *in vivo* experimental data would support the treatment of human subjects using anti-PD-L1 antibodies.

204. This is consistent with the teaching of the '092 patent which states that therapeutic agents can be evaluated “in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.” EX1001, 11:18-31.

3. Independent Claim 1

205. Claim 1 is obvious in light of the combined teachings of NCT664, Brahmer, and Mu.

206. Even assuming the preamble phrase “[a] method of treating a late stage non-small cell lung cancer (NSCLC) tumor in a human subject,” is limiting, WO874 discloses this limitation. WO874 discloses methods of treating cancer with anti-PD-L1 antibodies, including lung cancer. *See* EX1027, 1:19-20; 80:21-81:9 (“Preferred cancers whose growth may be inhibited by the antibodies of the invention include cancers typically responsive to immunotherapy . . . Non-limiting examples . . . include . . . lung cancer”).

207. While WO874 does not expressly list NSCLC, it teaches the treatment of lung cancer with anti-PD-L1 antibodies. The POSA would have known that there are only two types of lung cancer—small cell lung cancer and non-small cell

lung cancer. It was also well-known that the vast majority of lung cancer (approximately 85%) presents itself as NSCLC. The POSA reviewing WO874 would understand its reference to “lung cancer” to encompass both types of lung cancer and certainly NSCLC as WO874 does not limit its teaching regarding its anti-PD-L1 antibodies to only small cell lung cancer.

208. Furthermore, as discussed above, this limitation is disclosed by NCT664. *See supra* §VIII.A. In short, NCT664 discloses a Phase I clinical trial administering anti-PD-L1 antibodies (MDX-1105) to subjects with advanced or recurrent NSCLC. EX1021. NCT664 therefore discloses the treatment of late-stage NSCLC in human subjects. Moreover, based on Hwu, Topalian 2011, and Topalian 2012, the POSA knew that NCT664 had shown clinical responses in patients at all doses in the trial, indicating that the disclosed dosing regimens could be used to treat NSCLC tumors and achieve antitumor activity. And, as explained above, *see supra* §VIII.B, Brahmer reported that an anti-PD-1 antibody, targeting the same PD-1/PD-L1 pathway, showed evidence of anti-tumor activity and that membranous expression of PD-L1 was associated with tumor suppression. Thus, the POSA would understand from WO874, NCT664, and Brahmer that an anti-PD-L1 antibody could also achieve anti-tumor activity.

209. Both WO874 and NCT664 disclose the administration of 10 mg/kg of an anti-PD-L1 antibody every 2 weeks. WO874 teaches that “[f]or administration of the antibody,” dosages can be “10 mg/kg body weight” and that “[a]n exemplary treatment regime entails administration . . . once every two weeks.” EX1027, 75:20-25.

210. As discussed above, *see supra* §VIII.A, NCT664 also discloses the administration of 10 mg/kg of an anti-PD-L1 antibody once every two weeks. And, it was also known by March 2010, that “MDX-1105” in NCT664 was a disclosed anti-PD-L1 antibody in WO874. *See* EX1023, [0177] (“A specific example of an anti-B7-H1 antibody useful in the methods of the invention is MDX-1105 (WO/2007/ 005874, published 11 Jan. 2007)), a human anti-B7-H1 anti body.”). Therefore, the POSA would understand that the antibody used in NCT664 and that received clinical responses was disclosed by WO874.

211. It further would have been obvious to the POSA to administer the anti-PD-L1 antibody “over 60 minutes infusion” in light of WO874, Brahmer, and the general knowledge of the POSA as of the critical date. EX1001, cl. 1. WO874 discloses that its claimed composition can “be administered via one or more routes of administration using one or more of a variety of methods known in the art . . . Preferred routes of administration for antibodies of the invention include

intravenous . . . , for example by injection or infusion.” EX1027, 77:13-24; 87:26-32 (“For example, the antibody compositions can be administered by injection (e.g., intravenous or subcutaneous”). As discussed above, the POSA would have determined, through routine experimentation, that a 60-minute infusion would be effective. *See supra* §IX.A.2.

212. Brahmer also discloses that its anti-PD-1 antibody was administered by intravenous infusion for 60 minutes at a 10 mg/kg dose. EX1019, 3168. In light of Brahmer, which used this infusion rate for an anti-PD-1 antibody successfully, the POSA would have been motivated to use the 60-minute intravenous infusion rate for an anti-PD-L1 antibody.

213. The claim limitation that states “wherein the subject is pretreated for a chemotherapy and a radiotherapy” is disclosed by NCT664 or is obvious from NCT664 and Mu. As discussed above, *see supra* §IX.A, NCT664 discloses this limitation, or it would be obvious in light of the additional teachings of Brahmer and Mu.

214. Finally, the claim limitation that “wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression” would be obvious given WO874, Mu, and Brahmer. WO874 teaches that “PD-L1 expression” has been found in several cancers, including human lung cancer and that PD-L1 may play a

role in “tumor immunity.” EX1027, 1:19-23. As explained above, *see supra* §V.3, the POSA would know that NSCLC is the most common type of human lung cancer and that it often expresses PD-L1 on the membrane of tumor cells.

WO874’s Examples 7 and 8 further describe experiments which demonstrates that its anti-PD-L1 human monoclonal antibodies promote T-cell proliferation and, importantly, reverse the suppression of T-cell proliferation. *Id.*, 101-103. It would have been obvious to the POSA in light of this disclosure that an anti-PD-L1 antibody should be used to treat tumors where at least 1% of the tumor cells exhibit membrane PD-L1 expression.

215. Furthermore, as explained above, Brahmer and Mu taught that NSCLC cells can be PD-L1 positive and PD-L1 expression was a predictor of responsiveness to PD-1/PD-L1 blockade. *See supra* §§VIII B,C. It would have thus been obvious to the POSA to only treat those tumors that exhibited at least some level of expression of PD-L1.

216. For these reasons, WO874 in combination with NCT664, Brahmer, and Mu render independent claim 1 obvious. The POSA would be motivated to combine this art to achieve the particular limitations of the claim, including the claimed dosing regimen. Moreover, even assuming that the preamble is a claim

limitation, the POSA would also have a reasonable expectation that the combination could treat NSCLC tumors. *See supra* §IX.C.2.

4. Claims 2-3

217. Claim 2 depends from claim 1 and further requires that the “tumor is Stage IV NSCLC.” EX1001, cl. 2.

218. Claim 3 also depends from claim 1 and further requires that the “tumor is advanced or recurrent.” EX1001, cl. 3.

219. These additional limitations are disclosed by Brahmer and Mu.

220. Brahmer teaches that its anti-PD-1 antibody achieved reduction of tumor activity in patients “with advanced treatment-refractory solid tumors.” EX1019, 3168. The same is true for NCT664 which states that its subjects had “advanced or recurrent solid tumors.” EX1021.

221. Furthermore, Mu involved an analysis of Stage I, II, and III NSCLC tumor specimens which had been surgically removed. Figure 2 of Mu, illustrated above, *see supra* §VIII.C, shows that PD-L1 expression was related to poor prognosis following surgical resection. EX1023, 685. Thus, the POSA would have found it obvious to treat NSCLC tumors that are PD-L1 positive and that recurred after the subject previously had their Stage I, II, or III tumor removed.

5. Claim 4

222. Claim 4 depends from claim 1 and requires that the “tumor is metastatic.” EX1001, cl. 4. It is my opinion that Claim 4 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

223. WO874 discloses that its anti-PD-L1 antibodies “also useful for treatment of metastatic cancers, especially metastatic cancers that express PD-L1.” EX1027, 81:7-9. And, as explained above, NCT664 and Brahmer further describe the treatment of metastatic tumors. *See supra* §§VIII.A,B.

6. Claim 5

224. Claim 5 depends from claim 1 and requires that the “subject has previously had a stage I and/or II tumor that has surgically been removed.” EX1001, cl. 5. It is my opinion that Claim 5 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

225. Mu describes a study where the subjects each had either Stage I, II, or III NSCLC tumors surgically removed. EX1023, 683. The authors then analyzed the survival time of each patient afterwards. Figure 2 of Mu, depicted above, *see supra* §VIII.C, shows that PD-L1 positive lung cancer cells were related to a poor diagnosis following the surgical resection of stage I or stage II tumors. *Id.*, 685. As Mu teaches that a stage I or II PD-L1 positive NSCLC tumors are much more likely to have a poor prognosis following surgical resection, it would have been

obvious to the POSA to further treat NSCLC tumors with further therapy, including anti-PD-L1 antibodies, following surgical resection.

7. Claim 6

226. Claim 6 depends from claim 1 and requires that the “treating lasts more than 12 weeks.” EX1001, cl. 6. It is my opinion that Claim 6 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

227. This limitation is disclosed by NCT664. NCT664 states that 10 mg/kg of anti-PDL-1 antibody was administered “[e]very 14 days” for cycles of “42 days,” i.e., a 6-week cycle. EX1021, 3. NCT664 describes that “[t]he maximum duration of study drug treatment for a subject is 2 years.” *Id.* NCT664 therefore describes treatment that lasts more than 12 weeks.

228. Moreover, this limitation would be obvious as the POSA would understand that immunotherapy treatment should generally be sustained for late-stage tumors and that treatment under 12 weeks would be unlikely to achieve the necessary clinical progress for patients.

8. Claim 7

229. Claim 7 depends from claim 1 and requires that “the anti-PD-L1 antibody is formulated in a pharmaceutical composition.” EX1001, cl. 7. It is my opinion that Claim 7 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

230. WO874 teaches this additional limitation. WO874 describes “pharmaceutical compositions containing the [anti-PD-L1] antibodies.” EX1027, 20:31. It teaches formulating its anti-PD-L1 antibodies in “a composition, e.g., a pharmaceutical composition, containing one or a combination of monoclonal antibodies . . . of the present invention, formulated together with a pharmaceutically acceptable carrier.” *Id.* at 72:7-11. Thus, my opinion is that claim 7 is also obvious given the additional teachings of WO874.

9. Claim 8

231. Claim 8, which depends from claim 7, requires that the “pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, or any combination thereof.” EX1001, cl. 8. It is my opinion that Claim 8 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

232. WO874 teaches this additional limitation. WO874 teaches that “the “pharmaceutical compounds of the invention may include one or more pharmaceutically acceptable salts.” EX1027, 72:30-31. It further discloses that its compositions “also may include a pharmaceutically acceptable anti-oxidant.” *Id.*, 73:11-12. It further states that there are “suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention.” *Id.*,

73:19-20. Thus, my opinion is that claim 8 is also obvious given the additional teachings of WO874.

10. Claim 9

233. Claim 9, which also depends from claim 7, requires that “the pharmaceutical composition comprises a preservative, a wetting agent, an emulsifying agent, a dispersing agent, or any combination thereof.” EX1001, cl. 9. It is my opinion that Claim 9 is obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

234. WO874 teaches this limitation. WO874 states that its pharmaceutical compositions “may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents.” EX1027, 73:26-27. Thus, my opinion is that claim 9 is also obvious given the additional teachings of WO874.

11. Claims 10 and 11

235. Claim 10, which depends from claim 8, further requires that the pharmaceutically acceptable “salt comprises a sodium salt.” EX1001, cl. 10. Claim 11, which also depends from claim 8, requires that the pharmaceutically acceptable “salt comprises sodium chloride.” EX1001, cl. 11. It is also my opinion that these claims are obvious from the combination of WO874, NCT664, Brahmer, and Mu.

236. WO874 teaches these additional limitations. WO874 states that “[e]xamples of pharmaceutically acceptable salts include . . . base addition salts.” EX1027, 73:2. It further discloses that one such base addition salt is “sodium” and “the like.” *Id.*, 72:30-73:10. The POSA would know that sodium chloride is a salt containing sodium. WO874 also states that it may “be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions.” *Id.*, 73:30-31. Given this teaching, my opinion is that claims 10 and 11 are also obvious given the additional teachings of WO874.

12. Claims 12-17

237. Claims 12-17 depend from claims 1-6 and each of claims 12-17 further require that the claimed method also comprise “administering an anti-cancer agent.” EX1001, cls. 12-17. It is my opinion that these claims are obvious given the combination of WO874, NCT664, Brahmer, and Mu.

238. The POSA would understand these claims’ requirement that the method of treatment also administer “an anti-cancer agent,” to require the administration of an additional anti-cancer agent other than the anti-PD-L1 antibody administered intravenously by the methods of claims 1-6. This is because, if the anti-cancer agent could be the anti-PD-L1 antibody, then claims 12-17 would be redundant of claim 1 and would add nothing to claim 1.

239. WO874 teaches this additional limitation. It teaches that the “human anti-PD-L1 antibodies of the invention can be coadministered with one or other more therapeutic agents, e.g., a cytotoxic agent, a radiotoxic agent or an immunosuppressive agent.” EX1027, 88:1-3. It further discusses notes that the anti-PD-L1 antibody “can be administered before, after or concurrently with the agent or can be co-administered with other known therapies, e.g., an anti-cancer therapy, e.g., radiation.” *Id.*, 88:5-7. WO874 further describes how the “[c]o-administration of the human anti-PD-L1 antibodies, or antigen binding fragments thereof, of the present invention with chemotherapeutic agents provides two *anti-cancer agents* which operate via different mechanisms.” *Id.*, 88:12-14. Given these additional teachings, my opinion is that claims 12-17 are also obvious.

13. Claims 18-23

240. Claims 18-23 respectively depend from claims 12-17 and each of claims 18-23 further require that the additionally administered “anti-cancer agent” of claims 12-17 “is an anti-CTLA-4 antibody.” EX1001, cls. 18-23. It is my opinion that these claims are obvious given the combination of WO874, NCT664, Brahmer, and Mu.

241. WO874 teaches the administration of an additional anti-cancer agent that is an anti-CTLA-4 antibody. WO874 teaches that “[o]ther antibodies which may be used to activate host immune responsiveness can be used in combination

with anti-PD-L1” antibodies. EX1027, 83:31-33. WO874 then identifies such antibodies, including “antibodies which block the activity of negative costimulatory molecules such as CTLA-4,” i.e., anti-CTLA-4 antibodies. *Id.*, 84:3-10. WO874 states that antibodies which block such negative costimulatory molecules such as CTLA-4 “[p]rovide for increased levels of T cell activation.” *Id.*, 84:4-10.

242. Example 13 of WO874 describes the *in vivo* efficacy of a combination therapy utilizing both anti-PD-L1 antibodies and anti-CTLA-4 antibodies. *Id.*, 105:11-31. After mice were injected with 10 mg/kg anti-CTLA-4 antibody 9D9 as well as 10 mg/kg anti-PD-L1 antibody MIH5, WO874 reported that the “combination treatment of CTLA-4 antibody and PD-L1 antibody has a significantly greater effect on tumor growth and results in tumor free mice.” *Id.*, 105:27-31. It is thus my opinion that claims 18-23 are also obvious given the additional teachings of WO874.

14. Claims 24 & 25

243. Claim 24 depends from claim 1 and further requires “measuring membranous PD-L1 expression on tumor cells prior to administering the anti-PD-L1 antibody.” EX1001, cl. 24. Claim 25 depends from claim 24 and further requires that “the measuring comprises an immunohistochemistry.” *Id.*, cl.

25. It is my opinion that both of these claims are also obvious based on the combination of WO874, NCT664, Brahmer, and Mu.

244. As Mu teaches, *see supra* §VIII.C, certain NSCLC tumors are PD-L1 positive but not all NSCLC tumors are necessarily PD-L1 positive. The POSA would understand that, if an NSCLC tumor is not PD-L1 positive, it would not make sense to treat that subject with an anti-PD-L1 antibody. It would therefore have been obvious to the POSA to use standard techniques, including immunohistochemistry, to measure membranous PD-L1 expression on NSCLC tumor cells before administering the anti-PD-L1 antibody. This would confirm whether or not the tumor cells are PD-L1 positive before proceeding with treatment.

245. Mu itself teaches that “immunohistochemistry” was performed to detect the expression of PD-L1. EX1023, 683. Immunohistochemistry (“IHC”) is a common technique well-known to POSAs by May 2012. IHC is routinely used to detect a variety of antigens and was known as a technique that could be used to detect the membranous expression of PD-L1 on tumor cells. The POSA who would have been motivated to measure membranous PD-L1 expression on tumor cells would have been motivated to use immunohistochemistry techniques to detect the presence of PD-L1, particularly in light of Mu.

X. CONCLUSION

246. 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: 02 December 2022

Salma Jabbour, M.D.

Salma Jabbour, M.D.