

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DANA-FARBER CANCER INSTITUTE, INC.,
Petitioner

v.

Bristol-Myers Squibb Company,
Patent Owner

Case IPR2023-00252

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

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

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

TABLE OF CONTENTS

I.	Introduction	1
II.	Qualifications and Expertise	1
III.	Summary of Opinions	6
IV.	Relevant Legal Standards.....	7
A.	Person of Ordinary Skill in the Art	7
B.	Claim Construction.....	9
C.	Priority.....	12
D.	Obviousness.....	12
V.	Technical Background & State of the Art.....	16
A.	PD-L1	16
B.	Blocking PD-1/PD-L1 Interactions in Cancer Therapy	18
C.	Bladder Cancer	19
VI.	Secondary Considerations	20
VII.	Scope and Content of the Prior Art References	21
A.	WO874	21
B.	NCT664	24
C.	Brahmer	29
D.	Inman.....	32
E.	Irving	34
F.	Nakanishi 2006.....	38
VIII.	Unpatentability of the '299 Patent	39
A.	Claims 1-24 Are Obvious Over WO874 In View of NCT664, Brahmer, and Inman.....	39
1.	The POSA would have been motivated to treat bladder tumors with an anti-PD-L1 antibody	40
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	42

3. The POSA would have been motivated to treat tumors with an anti-PD-L1 antibody where the tumor was refractory to platinum-based chemotherapy	45
4. The POSA would have a motivation to combine WO874, NCT664, Brahmer, and Inman.....	46
5. The POSA would have a reasonable expectation of success in treating bladder tumors using the dosing regimen of WO874 and NCT664 with the infusion rate of Brahmer	48
6. Independent claim 1	52
7. Claims 2 and 3	58
8. Claim 4	59
9. Claim 5	59
10. Claim 6	60
11. Claim 7	61
12. Claims 8 and 9.....	61
13. Claims 10 and 11.....	62
14. Claims 12-15	65
15. Claims 16-21	66
16. Claims 22 and 23.....	67
17. Claim 24	69
B. Claims 1-5, 10-11, and 22-24 Are Obvious Over NCT664 In View of Brahmer and Inman.....	69
1. The POSA would have been motivated to combine the prior art	70
2. The POSA would have a reasonable expectation of success.....	71
3. Independent claim 1	72
4. Claims 2 and 3	77
5. Claim 4	78
6. Claim 5	79
7. Claims 10 and 11	80
8. Claims 22-23	82

9. Claim 24	83
C. Claims 6-9 and 12-21 are obvious over NCT664 in view of Brahmer, Inman, and Irving.....	84
1. Claims 6 & 7	85
2. Claims 8 and 9.....	87
3. Claims 12-15	87
4. Claims 16-21	89
D. Claims 10 and 11 are obvious over WO874 in view of NCT664, Brahmer, and Nakanishi.....	89
IX. Conclusion.....	93

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. 10,138,299 B2 (EX1001, “the ’299 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 ’299 patent (“the Petition”) and will request that the United States Patent and Trademark Office cancel claims 1-24 (the “Challenged Claims”) of the ’299 patent as unpatentable.

3. My opinions in this expert declaration support Dana-Farber’s request for *inter partes* review of the ’299 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, I often handle patients with a variety of cancers. My specialty includes treating patients with gastrointestinal and lung cancer, and other solid tumors, including individuals with bladder cancer.

14. I care for patients receiving radiation for other types of cancers that are treated palliatively. I commonly treat patients in situations where combined chemoradiation therapy is curative such as bladder cancer or other pelvic cancers.

15. 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.

16. I also have significant experience with clinical trials and research regarding non-small cell lung cancer (“NSCLC”) and other solid tumors. 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 lead the efforts at the

Rutgers Cancer Institute for early phase Phase I/II clinical trials with novel cancer agents. My research interests include immunotherapy and lung cancers, including NSCLC, small cell lung cancer, and the use of novel agents. I have authored or co-authored over 200 publications, including numerous publications regarding NSCLC.

17. 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.

18. 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.

19. 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.

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

III. SUMMARY OF OPINIONS

21. 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 '299 patent at the time of the earliest priority application, May 15, 2012.

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

(a) the '299 patent and prosecution history of the '299 patent; (b) all priority

applications leading to the issuance of the '299 patent; and (c) all other documents and exhibits cited herein and as listed in EX1006.

23. First, it is my opinion that claims 1-24 are rendered obvious by WO874 in view of NCT664, Brahmer, and Inman.

24. Second, it is my opinion that claims 1-5, 10-11, and 22-24 are rendered obvious by BMS's clinical trial disclosure, NCT664, in view of Brahmer and Inman.

25. Third, it is my opinion that claims 6-9 and 12-21 are rendered obvious by NCT664 in view of Brahmer, Inman, and Irving.

26. Finally, it is my opinion that claims 10 and 11 are rendered obvious WO874 in view of NCT664, Brahmer, and Nakanishi.

IV. RELEVANT LEGAL STANDARDS

27. 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

28. I have been asked to review the '299 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.

29. It is my opinion that as of the filing date of May 15, 2012, the POSA relevant to the '299 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 also 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.

30. Under this definition, I am qualified to offer opinions regarding the claims of the '299 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 bladder cancer and other solid tumors, 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

31. 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 ’299 patent are being challenged in the present IPR proceeding.

32. 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.

33. 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.

34. Claim 1 of the '299 patent recites a “method of treating a tumor in a human subject in need thereof.” EX1001, cl. 1. I understand that this is referred to as the preamble of the patent claim.

35. The '299 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, 10:8-15. 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 administration of an active agent to, the 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.

The '299 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.” *Id.*, 11:16-29.

36. Given the express definition in the '299 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 a bladder 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, 10:13-14. It does not require proof of clinical efficacy such as what is required for FDA approval.

37. This further aligns with how POSAs thought about the treatment of bladder tumors as of May 2012. Bladder cancer is very difficult to treat, so POSAs prior to May 2012 were generally looking for any form of treatment which would provide even a minimal benefit. EX1062, 244 (“Of newly diagnosed bladder cancer cases, approximately 70%-80% will present with nonmuscle-invasive disease, and despite endoscopic and intravesical treatments, 50%-70% will recur and 10%-30% will progress to muscle-invasive disease.”).

38. 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 '299 patent. Indeed, it is my understanding

that BMS has obtained other patents related to the '299 patent which claim a “therapeutically effective amount” of an anti-PD-L1 antibody. EX1049, cl. 1; EX1050, cl. 1. The absence of this term from the claims of the '299 patent further supports my opinion.

39. However, even if the preamble 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* §§VIII.A-D.

C. Priority

40. I understand that the '299 patent claims priority to a number of patent applications. I have been informed that the '299 patent issued from U.S. Application No. 16/006,473 (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

41. I understand that Dana-Farber bears the burden of proving that the Challenged Claims of the '299 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.

42. I have been asked to consider the question of whether the claims of the '299 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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.

49. 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.

50. 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.

51. 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

52. The '299 patent is directed to a method of treating bladder cancer in a human subject by administering an anti-programmed cell death-ligand 1 (“PD-L1”) antibody.

A. PD-L1

53. 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, expressed on normal cells, binds to PD-1 expressed on activated T-cells, T-cell activity is inhibited. *Id.*

The PD-1/PD-L1 interaction prevents T cells from launching an immune response against an individual's normal cells. *Id.* Overexpression of PD-L1 in 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.*

54. PD-L1 expression has been found in a broad range of cancers including in lung, 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.*

55. 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 bladder cancer. Honjo '048 teaches that its anti-PD-L1 antibody "inhibit[s] . . . PD-L1 function" and results in "suppression of cancer proliferation." EX1009, 10:34-39.

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

56. 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. Accordingly, anti-PD-1 and anti-PD-L1 antibodies were thought to be promising treatments for cancer in human patients.

57. As of the critical date of the '299 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. At least one of these trials 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 and NSCLC showed significant tumor regression. EX1019.

58. 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.

59. 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. EX1021. 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.

C. Bladder Cancer

60. Bladder cancer is a leading cause of cancer mortality in men and women. EX1062. More than half of bladder cancer cases recur after the initial frontline treatment and 10-30% of cases will progress to muscle-invasive disease. *Id.*, 244. Platinum-based chemotherapy, e.g., cisplatin, is a standard of care for

bladder cancer. However, patients with bladder cancer commonly become refractory to platinum-based therapies and in locally advanced and metastatic bladder cancers, the 5-year survival rate is 20% or lower. EX1063.

61. An analysis of PD-L1 expression in human bladder cancer samples demonstrated that PD-L1 is expressed in 28% of bladder cancers and is expressed more in higher stage and more aggressive bladder cancers. EX1065, Table 1. Thus, increased PD-L1 expression was thought to contribute to these advanced bladder cancers' ability to evade the body's anti-tumor immune response. These findings suggested that patients with bladder cancer would likely benefit from treatment with an anti-PD-L1 antibody.

VI. SECONDARY CONSIDERATIONS

62. 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.

63. 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. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. WO874

64. 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 BMS, 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 ’299 patent.

65. WO874 teaches the administration of human monoclonal anti-PD-L1 antibodies for the treatment of 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.

66. 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.” EX1027, 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 a skilled artisan in 2007 to generate anti-PD-L1 antibodies in light of routine and conventional monoclonal antibodies.

67. The POSA would have also understood by March 2010, before the priority date of the '299 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.”).

68. WO874 also teaches that its methods of treatment using its anti-PD-L1 antibodies can be used to treat bladder cancer, in particular. WO874 states that “[e]xamples of other cancers that may be treated using the methods of the invention include . . . cancer of the bladder.” EX1027, 80:21-81:9.

69. WO874 provides *in vitro* experimental data which show that its anti-PD-L1 antibodies “bind to human cell surface PD-L1.” EX1027, 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. EX1027, 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.*, 103:22-104:27. 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.” EX1027, 107:1-2. A person of skill would understand this reported data, in sum, to reflect that human anti-PD-L1 antibodies bind to cancer cells and that anti-PD-L1 antibodies could reasonably be expected to treat tumors.

70. 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. EX1027, 105:9-31. 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.*

B. NCT664

71. Clinical Trial Study NCT00729664 (“NCT664”) is a 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.* 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 also describes an “i.v. infusion” of “MDX-1105” at a 10 mg/kg dose “every 14 days.” *Id.*, 4.

72. The earliest version of NCT664 was submitted on August 4, 2008 and was publicly available to POSAs on August 7, 2008. EX1044. 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 '299 patent.

73. For example, on January 19, 2011, an update to NCT664 was submitted and was publicly available on January 19, 2011. *See* EX1048. This update stated 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.*

74. 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. I, myself, as a POSA, frequently referred to the ClinicalTrials.gov database to keep myself aware of ongoing and upcoming clinical trials. 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.

75. 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.

76. For example, Dr. Hwu published an article on June 25, 2010 entitled “[t]argeted therapy for metastatic melanoma: From bench to bedside.” EX1022 (“Hwu 2010”). 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.*, 3. 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.*, 3. 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.

77. 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 bladder tumors expressed PD-L1. *See infra* §VII.D. As a result, POSAs would be motivated to also treat bladder tumors with MDX-1105, as disclosed by Hwu 2010, with an expectation of success in treating bladder tumors.

78. 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”). 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.

79. 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). 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.” EX1026, 210.

80. 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 intravenous infusion, achieved anti-tumor

activity against various tumors which expressed PD-L1 and showed evidence of clinical activity.

81. 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.

82. 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 bladder tumors as well as other types of cancer. 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.

83. 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”

84. The POSA interested in clinical trials regarding treatment of bladder tumors in May 2012 would have searched for and identified NCT664, particularly in light of the disclosure of Hwu 2010, discussed above. *See supra* §VII.B.¶76. 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.

C. Brahmer

85. 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 '299 patent.

86. 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.*

87. 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.

88. 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.

89. 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.

90. 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.

91. 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.

D. Inman

92. Inman is a peer-reviewed journal article, published online by the American Cancer Society in March 2007. *See* EX1065. This is a recurring publication. Inman describes immunohistochemistry experiments to evaluate PD-L1 expression in a cohort of 280 high-risk urothelial carcinomas of the bladder. *Id.*, 1499. I understand from counsel that Inman is prior art to the '299 patent.

93. Table 1 of Inman reports that 28% of the subjects' tumors expressed PD-L1:

TABLE 1
Baseline Characteristics of the Patient Cohort

	Frequency no. (%)
Age, mean [IQR*]	66.4 [60.3–67.0]
Sex	
Women	53 (19)
Men	227 (81)
Pathologic stage	
pT0	11 (4)
pT1	19 (7)
pT2	52 (19)
pT3/4	184 (66)
Cis	14 (5)
Tumor grade	
Low	74 (26)
High	206 (74)
Lymphocytic infiltration	
None	28 (10)
Focal	90 (32)
Diffuse	162 (58)
PD-L1 IHC staining	
Negative	203 (73)
Positive	77 (28)

* Interquartile range.

Id., 1501.

94. As the authors of Inman note, “host immunity appears to modulate bladder cancer pathogenesis” and it was “clear that T-cell-inhibitory PD—L1 is aberrantly expressed in many forms of cancer and, in this context, has been implicated as a mechanism for tumors acquiring the ability to evade the host immune system.” *Id.*, 1502. Inman reports that “PD-L1” acts by “neutralizing T

cells that normally guard against cancer invasion from the epithelium not the bladder musculature.” *Id.*, 1499.

95. Inman also reports that “the amounts of PD-L1 expressed by urothelial tumor cells increase steadily with advancing local tumor stage,” and that “increasing levels of PD-L1 expression by urothelial tumor cells more than double the risk of advancing from one stage category to the next, independent of tumor grade, age, gender, and lymphocytic infiltration.” *Id.*, 1503. As Inman teaches, this suggests that the “presence of the PD-L1 glycoprotein . . . may affect malignant stage progression . . . and implies that the host’s immune response is a factor as well.” *Id.* Ultimately, Inman shows that “increasing levels of PD-L1 expression within the bladder tumor microenvironment correlates with increased local aggressiveness of this cancer.” *Id.*, 1504.

96. Given the results reported by Inman, the authors conclude that PD-L1 “acts as a predictive marker for local tumor stage progression” for bladder cancer. *Id.*, 1505. Thus, Inman teaches that PD-L1 is a “viable prognostic marker” and a “rational immunotherapeutic target for the treatment of urothelial bladder carcinoma.” *Id.*

E. Irving

97. 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. I understand from counsel that Irving is prior art to the ’299 patent. *Id.*

98. 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).” EX1058, [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.*

99. 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].

100. 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

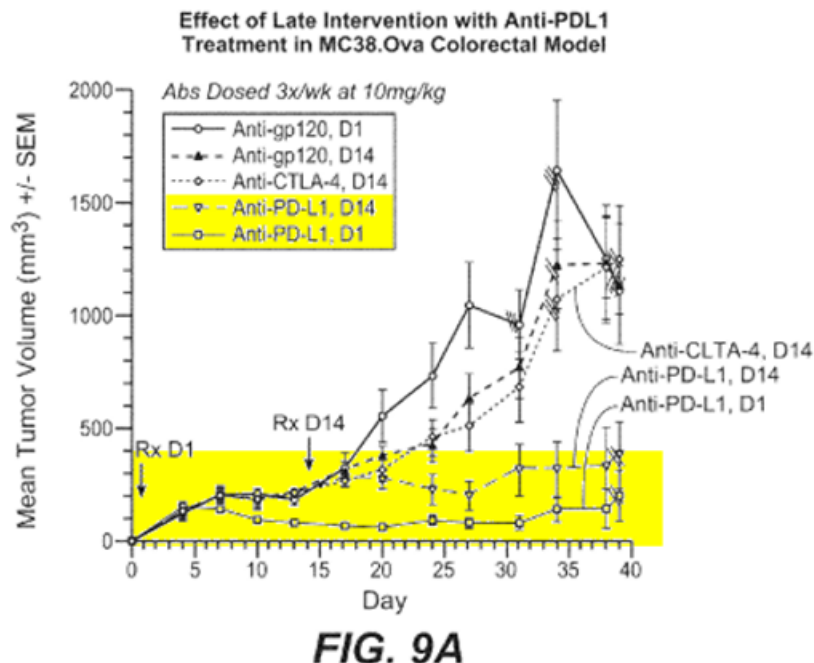
regulates T-cell receptor signaling. PD-L1 expression has been shown in situ on a wide variety [sic] of solid tumors, including breast, lung, colon, ovarian, melanoma, bladder, liver, salivary, stomach, gliomas, thyroid, thymic, epithelial, head and neck cancers. Brown et al., J. Immunol. 170: 1257-66 (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).

EX1058, [0419].

101. 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. EX1058, [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].

102. Specifically, Irving inoculated mice with MC38Ova colon carcinoma cells and treated the animals with 10 mg/kg anti-PD-L1 antibodies. EX1058, Example 9. 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). EX1058, [0049].



EX1058, Figure 9A (annotated).

103. Irving also discloses that PD-L1 expression has been shown on a variety of tumors, including bladder tumors. EX1058, [0419]. Irving claims, *inter alia*, methods of treating bladder 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.

EX1058, cls. 81, 84, and 95.

104. 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].

F. Nakanishi 2006

105. Nakanishi 2006 is a peer-reviewed journal article, published online by the journal Cancer Immunology, Immunotherapy in December 2006. EX1066. This is a recurring publication. It is my understanding from counsel that Nakanishi 2006 is prior art to the ’299 patent.

106. Nakanishi 2006 “analyzed the relationship between [PD-L1] expression and various clinicopathological features and postoperative prognosis” in patients with urothelial cancer, a form of bladder cancer. EX1066, 1173.

Specifically, Nakanishi 2006 examined 65 urothelial cancer cases and evaluated PD-L1 expression in tumors, and the numbers and phenotypes of tumor-infiltrating lymphocytes, by immunohistochemistry and flow cytometry. *Id.*

107. Nakanishi 2006 demonstrated that “aberrant expression of [PD-L1] in urothelial cancer is associated with aggressive tumors, suggesting a regulatory role of tumor-associated [PD-L1] in antitumor immunity.” *Id.*

108. Nakanishi 2006 also showed that in the “65 surgically resected specimens of urothelial cancer, the expression of [PD-L1] was demonstrated on the plasma membrane and in the cytoplasm of cancer cells in a focal pattern (Fig. 1). The mean percentage of [PD-L1]-positive cells among the cancer cells was $21.1 \pm 11.0\%$ (mean $\pm$ SD; median, 20.0%; range, 2.1–47.1%).” *Id.*, 1175.

VIII. UNPATENTABILITY OF THE '299 PATENT

A. Claims 1-24 Are Obvious Over WO874 In View of NCT664, Brahmer, and Inman

109. Claims 1-24 of the '299 patent are obvious over WO874 in view of NCT664, Brahmer, and Inman. The claims of the '299 patent are directed to a “method of treating a 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 “tumor is derived from a bladder cancer” and wherein “the tumor is refractory to a platinum based chemotherapy.” EX1001, cl.

1. In my opinion, the POSA would have been motivated to treat a bladder tumor with 10 mg/kg of anti-PD-L1 antibody every 2 weeks by 60-minute intravenous infusion, where the tumor is refractory to a platinum based chemotherapy.

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

110. The POSA would have been motivated to administer anti-PD-L1 antibodies to treat bladder tumors based on the disclosure of WO874, NCT664, Brahmer, and Inman. As of the priority date of the '299 patent, the POSA was already interested in exploring alternative treatments for cancer, including bladder tumors, such as immunotherapy. This is because traditional first-line treatments, such as platinum-based chemotherapy, were often clinically ineffective against bladder tumors. Thus, the POSA would have been interested in other potential forms of immunotherapy, including anti-PD-L1 antibody therapy.

111. WO874 teaches the use of anti-PD-L1 antibodies to treat various forms of cancer, including bladder cancer. *See supra* §VII.A. Given these teachings, the POSA reviewing WO874 would have thus been motivated to administer anti-PD-L1 antibody treatment for bladder tumors.

112. And 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 measurable advanced or recurrent solid tumors (renal cell

carcinoma, NSCLC, malignant melanoma, or epithelial ovarian cancer). EX1021,

3. And the POSA, as explained above, already knew before the priority date that the clinical trial had shown clinical responses in subjects. *See supra* §VII.B.

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 bladder cancer, which POSAs knew could express PD-L1.

113. The POSA would have also been motivated to pursue anti-PD-L1 antibody treatments for bladder tumors in light of Brahmer and Inman. 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 bladder tumors, which were known to express PD-L1, given Brahmer's reported success with an anti-PD-1 antibody. Similarly, Inman disclosed that PD-L1 expression on bladder tumors was associated with tumor immune evasion and suggested PD-L1 as an immunotherapeutic target and predictive marker for tumor progression. EX1065.

Thus, given Inman's teaching, the POSA would have understood that PD-L1 expression by bladder tumors likely played a role in tumor resistance and immune evasion and would have further been motivated to pursue anti-PD-L1 antibody treatment for bladder tumors.

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

114. As explained above, see *supra* §VII.B, NCT664 disclosed a Phase I clinical trial that administered an anti-PD-L1 antibody at 10 mg/kg once every two weeks. 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 an anti-PD-L1 antibody that was reportedly efficacious before the priority date of the '299 patent—in other words, a 10 mg/kg dose once every 2 weeks.

115. This is confirmed by the disclosure of WO874, which also teaches that a 10 mg/kg dose every 2 weeks by intravenous infusion could be used to administer its anti-PD-L1 antibodies for the treatment of various tumors, including bladder cancer. See *supra* §VII.A.

116. The POSA also would have been aware from Brahmer that BMS' 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* §VII.C. 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.

117. 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. Other research on other monoclonal antibodies reflect that this is precisely what POSAs did as of the priority date.

118. 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 intravenous 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.

119. 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 tumors with an anti-PD-L1 antibody where the tumor was refractory to platinum-based chemotherapy

120. The POSA would have also been motivated to treat bladder tumors which were a refractory to platinum-based chemotherapy with an anti-PD-L1 antibody.

121. First, the POSA would have known in light of Inman's disclosures that bladder tumors can express PD-L1, and the POSA would have understood PD-L1's role in tumor evasion. *See supra* §VII.D. 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 bladder tumors that express PD-L1, regardless of whether or not they were refractory to platinum-based chemotherapy.

122. Moreover, in 2012, treatment options for bladder tumors were limited and POSAs were well aware of this issue. Other than surgical resection, which is not always possible for bladder tumors, platinum-based chemotherapy was a common form of treatment for bladder tumors. Even today, POSAs consider the application of platinum-based chemotherapy 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, as reflected by Inman, for bladder tumors as an alternative treatment in the event that platinum-based chemotherapy was therapeutically ineffective. It was also known as of the priority date that many patients had refractory bladder tumors which were unresponsive to platinum-based chemotherapy. Thus, the POSA would have a motivation to pursue immunotherapy for patients who were refractory to platinum-based chemotherapy as the POSA would be motivated to pursue alternative forms of treatment for such tumors.

4. The POSA would have a motivation to combine WO874, NCT664, Brahmer, and Inman

123. It is also my opinion that the POSA would have been motivated to combine the teachings of WO874, NCT664, Brahmer, and Inman.

124. The POSA looking at the teachings of WO874 would have also looked to the teachings of NCT664, Brahmer, and Inman. The POSA reviewing WO874 would look for disclosed clinical trials testing anti-PD-L1 antibodies in human cancers and would quickly identify NCT664 as one of the only clinical trials which tested anti-PD-L1 antibodies for the treatment of cancer. The POSA would also recognize that MDX-1105 in NCT664 was administered as the same dosing regimen disclosed in WO874 and would have known that there had been

reported clinical responses, as reported by Hwu 2010, Topalian 2011, and Topalian 2012. *See supra* §VII.B.

125. Given the POSA's knowledge of PD-L1 and its role in tumor evasion, the expression of PD-L1 on bladder cancer, and the success of anti-PD-1 and anti-PD-L1 treatment as reported in Brahmer, WO874, and NCT664, the POSA would have also looked to Inman to determine PD-L1 expression patterns on bladder tumors specifically. Inman would provide further motivation to use the dosing regimen of WO874 and NCT664 (10 mg/kg once every 2 weeks by intravenous infusion) to treat bladder tumors based on its teaching that PD-L1 is a predictive marker for tumor progression for bladder tumors, and the reported clinical responses in the NCT664 trial. EX1065.

126. The POSA would have also been motivated to use the infusion rate of Brahmer, combined with the dosing regimen of WO874 and NCT664. Brahmer, WO874, and NCT664 are all directed towards the administration of monoclonal antibodies to cancer patients targeting the PD-1/PD-L1 pathway, one describing an anti-PD-1 antibody and two describing anti-PD-L1 antibodies. 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 bladder tumors using the dosing regimen of WO874 and NCT664 with the infusion rate of Brahmer

127. It is also my opinion that the POSA would have reasonably expected success using an anti-PD-L1 antibody with WO874 and NCT664’s dosing regimen with Brahmer’s infusion rate to treat bladder 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 bladder tumors. However, regardless of whether or not my position is correct, it is my opinion that the POSA would have a reasonable expectation of success.

128. WO874 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* §VII.A. 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.” EX1027, 77:6-8. WO874 also teaches the use of anti-PD-L1

antibodies to treat bladder cancer, as discussed above. *See supra* §VII.A; EX1027, 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.

129. This is consistent with the teaching of the '299 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.

130. The POSA would have also been aware of the anti-PD-1 clinical trials that had been described in Brahmer. The POSA was aware that MDX-1106, i.e., nivolumab, had achieved anti-tumor clinical activity in patients in a variety of cancers. 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.

131. 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 aggression 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.” EX1019, 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.

132. 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.

133. BMS’ 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. 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 ’299 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 bladder 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.

134. In addition, the POSA also knew that the specific methods of treatment disclosed by NCT664 were already successful. As described above, Huw 2010, Topalian 2011, and Topalian 2012, *see supra* §VII.B, all disclosed that the 10 mg/kg dose of anti-PD-L1 antibody in NCT664 had achieved clinical responses against tumors in the trial. Thus, even if Brahmer itself could not provide a reasonable expectation of success because it is an anti-PD-1 antibody, NCT664 would because describes the use of an anti-PD-L1 antibody, just like the claims of the ’299 patent.

135. 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 various types of cancer. EX1069, 2464.

6. Independent claim 1

136. Claim 1 is obvious in light of the combined teachings of WO874, NCT664, Brahmer, and Inman.

137. Even assuming the preamble phrase “[a] method of treating a tumor in a human subject,” is limiting, this limitation is disclosed by WO874 and NCT664. WO874 discloses the use of anti-PD-L1 antibodies to treat a variety of tumors, including bladder tumors. EX1027, 80:21-81:9. NCT664 discloses a Phase I clinical trial administering an anti-PD-L1 antibody (MDX-1105) to subjects with various advanced or recurrent tumors. EX1021. NCT664 therefore discloses the treatment of tumors in human subjects.

138. 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* §VII.B. The

POSA would thus know that the disclosed treatment regimen of NCT664 could be used to treat tumors and achieve antitumor activity before the critical date.

139. Both WO874 and NCT664 disclose the administration of an anti-PD-L1 antibody “to the subject about 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.

140. 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* §VII.A; EX1030, [0177]. 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.

141. 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.

142. 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.

143. Moreover, as explained above, the POSA would have also determined, through routine experimentation, that a 60-minute infusion of an anti-PD-L1 antibody to be effective. *See supra* §VIII.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 WO874 and 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* §VIII.A.2.

144. 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 intravenous 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.

145. The claim limitation which states that “the tumor is derived from a bladder cancer” is also disclosed by WO874. WO874 discloses the use of anti-PD-L1 antibodies to treat a variety of tumors, including bladder tumors. EX1027, 80:21-81:9.

146. The “bladder cancer” claim limitation is also obvious in light of the known clinical responses disclosed by Brahmer regarding its anti-PD-1 antibody and the known clinical responses achieved in the NCT664 trial, as disclosed by Hwu 2010, Topalian 2011, and Topalian 2011. *See supra* §VII.B. The POSA would have understood that an anti-PD-L1 antibody could be used to treat a variety of tumors which express PD-L1, including bladder tumors, based on the known role of PD-L1 in tumor evasion and its expression on a variety of cancers, including bladder cancer (as reported by Inman).

147. The claim limitation that states “wherein the tumor is refractory to a platinum-based chemotherapy” is disclosed by NCT664 or is obvious in light of WO847, NCT664, Brahmer, and the general knowledge of the POSA. The inclusion criteria NCT664 state that the treated malignancies include “*refractory*” cancers, including patients who previously failed chemotherapy or radiotherapy. EX1021, 5. The POSA would understand relapsed and/or refractory cancers to include subjects who were unresponsive to standard of care platinum-based chemotherapy. EX1021, 5 (noting that subjects who failed “prior systemic platinum-based therapy” were included in trial). Indeed, as of May 2012, platinum-based chemotherapy was considered the standard first-line treatment for patients with bladder cancer. EX1067, 2432 (noting that “[c]isplatin-based combination chemotherapy is considered standard first-line treatment for patients with metastatic urothelial carcinoma”).

148. It would have been obvious to the POSA to administer immunotherapy, including anti-PD-L1 antibodies, to patients who were unsuccessfully treated with platinum-based chemotherapy as immunotherapy provides an alternative mechanism to treat refractory cancers. POSAs would have thus been motivated to use anti-PD-L1 antibody treatments for cancers that express PD-L1, including bladder cancer, where standard treatments such as platinum-

based chemotherapy failed. Indeed, bladder cancer that could not be surgically resected and was unresponsive to platinum-based chemotherapy was—and remains—notoriously difficult to treat. The POSA would have been motivated to use any form of treatment that had reported clinical responses and anti-tumor activity, including anti-PD-L1 antibodies, to treat difficult-to-treat bladder cancer that expressed PD-L1. And the POSA knew, based on the disclosure of Inman, that many bladder cancers expressed PD-L1.

149. Additionally, Brahmer also discloses 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. It further identifies that numerous patients had previously been treated with chemotherapy. *Id.*, 3169. The POSA reading Brahmer would understand relapsed and/or refractory cancers to include cancers which were unresponsive to pretreatment with platinum-based chemotherapy as this was a first-line treatment for patients with various types of cancer.

150. For these reasons, WO874 in combination with NCT664, Brahmer, and Inman 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 bladder tumors given the reported efficacy of the anti-PD-L1 and anti-PD-1 antibodies in WO874, NCT664, and Brahmer. *See supra* §VII.A-C.

7. Claims 2 and 3

151. Claim 2 depends from claim 1 and further requires that the “tumor is advanced.” EX1001, cl. 2.

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

153. It is my opinion that these claim limitations are obvious in light of WO874 in view of NCT664, Brahmer, and Inman.

154. Brahmer’s phase I clinical trial reported that its an anti-PD-1 antibody achieved reduction of tumor activity in patients “with advanced treatment-refractory solid tumors.” EX1019, 3168. NCT664 also discloses subjects “with selected advanced or recurrent solid tumors.” EX1021, 2. The POSA would understand both disclosures to refer to “advanced” tumors, including tumors which are locally advanced.

155. The POSA would have been motivated to pursue treatment for advanced and locally advanced tumors with anti-PD-L1 antibodies given the teachings of WO874 and NCT664 regarding methods of treating cancer with anti-

PD-L1 antibodies, as POSAs knew each had achieved anti-tumor activity. The POSA would have also had a reasonable expectation of success, as explained above, *see supra* §VIII.A.5, given the data in WO874 and the disclosed clinical responses of other monoclonal antibodies targeting the PD-1/PD-L1 pathway.

8. Claim 4

156. 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 Inman.

157. WO874 discloses that its anti-PD-L1 antibodies are “also useful for treatment of metastatic cancers, especially metastatic cancers that express PD-L1.” EX10207, 81:7-9. And, as explained above, NCT664 and Brahmer further describe the treatment of metastatic tumors. *See supra* §VII.B-C.

9. Claim 5

158. Claim 5 also depends from claim 1 and requires that the “treatment lasts more than 12 weeks.” EX1001, cl. 5. It is my opinion that Claim 5 is obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

159. This limitation is disclosed by NCT664 or is obvious in light of the general knowledge of the POSA. NCT664 discloses that “[t]he maximum duration of study drug treatment for a subject is 2 years.” EX1021, 3. This describes treatment that lasts more than 12 weeks.

160. More generally, the POSA would understand that immunotherapy treatment for cancer should generally be sustained. The POSA would not believe treatment under 12 weeks—a short period of treatment—to be sufficient to achieve the needed clinical progress for patients, particularly where such treatment is effective. The POSA would want such treatment to be sustained to ensure that the tumor either continues to shrink in response to treatment or, alternatively, does not spread any further in response to treatment. It would be obvious to the POSA to continue treatment for more than 12 weeks when administering such an anti-PD-L1 antibody to bladder cancer patients.

10. Claim 6

161. Claim 6 depends from claim 1 and requires that “the anti-PD-L1 antibody is formulated in a pharmaceutical composition.” EX1001, cl. 6. It is my opinion that Claim 6 is obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

162. This limitation is disclosed by WO874. WO874 describes “pharmaceutical compositions containing the [anti-PD-L1] antibodies.” EX1027, 20:31. It further states that its anti-PD-11 antibody invention “provides 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.*, 72:9-15.

11. Claim 7

163. Claim 7, which depends from claim 6, 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. 7. It is my opinion that Claim 7 is obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

164. This claim limitation is disclosed by WO874. WO874 states that the “pharmaceutical compounds of the invention may include one or more pharmaceutically acceptable salts.” EX1027, 72:30-31. Its compositions “also may include a pharmaceutically acceptable anti-oxidant.” EX1027, 73:11-12. WO874 also states that there are “suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention.” EX1027, 73:19-20.

165. The POSA would understand WO874 to disclose that the pharmaceutical composition can further comprise a pharmaceutically acceptable salt, an antioxidant, an aqueous carrier, and/or a non-aqueous carrier in light of these statements.

12. Claims 8 and 9

166. Claim 8, which depends from claim 7, further requires that the pharmaceutically acceptable “salt comprises a sodium salt.” EX1001, cl. 8.

167. Claim 9, which also depends from claim 7, requires that the pharmaceutically acceptable “salt comprises sodium chloride.” EX1001, cl. 9.

168. It is my opinion that both claims 8 and 9 are obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

169. WO874 discloses these additional limitations. It provides that “[e]xamples” of pharmaceutically acceptable salts include “base addition salts,” (EX1027, 72:30-73:2), and that one such base addition salt is “sodium” and “the like.” EX1027, 72:30-73:10. The POSA would understand that sodium chloride is a salt containing sodium. WO874 also notes that it may “be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions.” EX1027, 73:30-31. Thus, WO874 discloses the additional limitations of claims 8 and 9.

13. Claims 10 and 11

170. Claim 10 depends from claim 1 and additionally requires that “at least 1% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 10.

171. Claim 11 also depends from claim 1 and requires that “at least 5% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 11.

172. It is my opinion that these additional claim limitations in claims 9 and 10 would be obvious to the POSA as it would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

173. WO874 teaches that “PD-L1 expression” has been found in several cancers” and that its methods of treatment using anti-PD-L1 antibodies could be used to treat bladder cancer. EX1027, 1:19-21. Examples 7 and 8 of WO874 disclose experiments showing that anti-PD-L1 human monoclonal antibodies promote T-cell proliferation and reverse the suppression of T-cell proliferation. EX1027, 101-103. Inman confirms that PD-L1 is in fact expressed on bladder tumors. EX1065, 1505.

174. Based on these teachings, it is my opinion that the POSA would have found it obvious to administer anti-PD-L1 antibody treatment to treat bladder tumors where at least 1% or 5% of tumor cells exhibit membrane PD-L1 expression, which are both relatively low levels of PD-L1 expression. If there was no membrane PD-L1 expression or insignificant expression in the tumor, the tumor would not be a practical target for treatment with an anti-PD-L1 antibody. In fact, the claims’ requirement effectively covers a range of patients whose tumors have anywhere from 1% (or 5%) to 100% of tumor cells that express PD-L1.

175. The POSA would have been motivated to treat tumors where at least 1% or 5% of tumor cells in the treated tumor exhibit membrane PD-L1 expression. 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. Brahmer teaches that “[PD-L1] expression on tumors may affect the ability to respond” to PD-1/PD-L1 blockade and that “tumor cell surface expression of [PD-L1] may be a predictor of responsiveness.” EX1019, 3169, 3172. This alone would have provided a motivation to pursue treatment of bladder tumors where at least 1% or 5% of tumor cells express PD-L1.

176. Furthermore, in 2012, treatment options for bladder tumors that were not surgically resectable were extremely limited and P OSAs 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% or 5%. Thus, the limited nature of treatment at the time would further provide the POSA with significant motivation to treat a tumor with 1% or 5% PD-L1 expression on tumor cells with an anti-PD-L1 antibody.

177. Moreover, as of the priority date, it was known by the POSA that platinum-based chemotherapy was a first-line therapy against bladder tumors. EX1067. As of the priority date, POSAs were interested in pursuing alternative treatment regimens, including monoclonal antibody treatments, for bladder tumors

as an alternative treatment in the event that platinum-based chemotherapy was ineffective. Thus, the POSA would have a motivation to pursue immunotherapy for patients who were refractory to platinum-based chemotherapy. This would include pursuing treatment for PD-L1 positive tumors even if the tumor expressed PD-L1 as low as 1%.

14. Claims 12-15

178. Claims 12-15 depend from claims 1-4 and each of claims 12-15 further require that the claimed methods also comprise “administering an anti-cancer agent.” EX1001, cls. 12-15. It is my opinion that Claims 12-15 are obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

179. I understand the claim limitation “administering 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 1-4. If the anti-cancer agent could be the anti-PD-L1 antibody of claims 1-4, then claims 12-15 would be redundant of those claims. Were that the case, claims 12-15 would be obvious over WO874, NCT664, Brahmer, and Inman, as explained above.

180. This limitation is disclosed by WO874. WO874 states 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 how the

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. It also states that 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. WO874 thus discloses methods of administering anti-PD-L1 antibodies which further comprise a step of administering an anti-cancer agent.

15. Claims 16-21

181. Claims 16-21 respectively depend from claims 12-15 and add the same limitations to each claim.

182. Claims 16, 18, and 20 each require that the additionally administered “anti-cancer agent” of claims 12-14 “is a chemotherapy.” EX1001, cls. 16, 18, 20.

183. Claims 17, 19, and 21 each require that the additionally administered “anti-cancer agent” of claims 12-14 “is a radiotherapy.” EX1001, cls. 17, 19, 21.

184. It is my opinion that Claims 16-21 are obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

185. Both of the additional “chemotherapy” and “radiotherapy” limitations are disclosed by WO874. WO874 discloses that “PD-L1 blockade may also be combined with standard cancer treatments.” EX1027, 82:32. The POSA would

understand standard cancer treatments to encompass traditional treatments, including both chemotherapy and radiotherapy. WO874 goes on to disclose that “PD-L1 blockade may be effectively combined with chemotherapeutic regimes.” *Id.*, 82:32-33; *see also id.*, 88:12-18.

186. With respect to “radiotherapy,” WO874 states that “[o]ther combination therapies that may result in synergy with PD-L1 blockade through cell death are radiation, surgery, and hormone deprivation.” *Id.*, 83:9-10; *see also id.*, 88:1-3 (stating that “human anti-PD-L1 antibodies of the invention can be co-administered with one or more therapeutic agents, e.g., a cytotoxic agent, a radiotoxic agent or an immunosuppressive agent”), 88:5-8 (describing co-administration with “an anti-cancer therapy, e.g., radiation”). WO874 discloses both the additional limitations of claims 16-21.

16. Claims 22 and 23

187. Claim 22 depends from the method of claim 1 and further requires that the “platinum-based chemotherapy is a platinum-based doublet chemotherapy.” EX1001, cl. 22.

188. Claim 23 also depends from the method of claim 1 and further requires that the “platinum-based chemotherapy comprises cisplatin, carboplatin, or both.” EX1001, cl. 23.

189. These additional limitations would have also been obvious in light of NCT664 and the general knowledge of the POSA.

190. The inclusion criteria for the clinical trial disclosed in NCT664 state that the treated malignancies include “refractory” cancers. EX1021, 5. The POSA would understand relapsed and/or refractory cancers to include subjects who were unresponsive to standard of care platinum-based chemotherapy, which would include cisplatin or carboplatin-based chemotherapy. As of the priority date, platinum-based chemotherapy and platinum-based doublet chemotherapy were considered the standard first-line and second-line treatment for patients with bladder cancer, respectively, and patients were treated with both cisplatin and carboplatin. For patients that do not respond to cisplatin or carboplatin, they were treated with platinum-based doublet chemotherapy, which consists of combinations of cisplatin or carboplatin with vinorelbine, gemcitabine or taxanes.

191. The POSA would have had a motivation to administer immunotherapy, including anti-PD-L1 antibodies, to patients who were unsuccessfully treated with platinum-based chemotherapy, including cisplatin or carboplatin, as immunotherapy provides an alternative mechanism to treat refractory cancers. And the POSA would have a reasonable expectation of success

in doing so as many bladder cancers express PD-L1, as taught by Inman. Thus, it is my opinion that claims 22-23 of the '299 patent are obvious.

17. Claim 24

192. Claim 24 depends from claim 1 and requires “wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody.” EX1001, cl. 25.

193. Administering antihistamine prior to the anti-PD-L1 antibody would have also been obvious in light of WO874 and the general knowledge of the POSA. It is routine to pre-administer antihistamine before chemotherapy and immunotherapy. Antihistamines are administered to prevent hypersensitivity reactions in platinum-based chemotherapy. Likewise, antihistamines are administered to prevent infusion reactions in the context of immunotherapy (i.e., administration of monoclonal antibodies). *See, e.g.*, EX1068, Tables 3 and 4 (Table 3 lists platinum-based compounds where hypersensitivity reactions are managed via antihistamines. Table 4 lists monoclonals where infusion reactions are managed via antihistamines).

B. Claims 1-5, 10-11, and 22-24 Are Obvious Over NCT664 In View of Brahmer and Inman

194. It is also my opinion that claims 1-5, 10-11, and 22-24 of the '299 patent are obvious over NCT664, Brahmer, and Inman. In my opinion, in view of these prior art references, the POSA would have been motivated to treat a bladder

tumor with 10 mg/kg of anti-PD-L1 antibody every 2 weeks by 60-minute intravenous infusion, where the subject was refractory to platinum-based chemotherapy.

1. The POSA would have been motivated to combine the prior art

195. As explained above, *see supra* §§VII.B and VIII.A, the POSA reviewing NCT664 would have been motivated to administer an anti-PD-L1 antibody treatment for a bladder tumor and combine its teachings with the disclosure of Inman and Brahmer.

196. POSAs were interested in exploring alternative forms of treatment for cancer, including for bladder cancer at the time of the invention because traditional treatments, such as platinum-based therapy were often not therapeutically effective. This alone would provide a motivation to pursue immunotherapy, including anti-PD-L1 immunotherapy.

197. In addition, the POSA would have had a motivation to combine these references as NCT664 disclosed a Phase I clinical trial administering an anti-PD-L1 antibody at 10 mg/kg once every two weeks, and it was known by the POSA that the clinical trial had achieved clinical responses in treating a variety of cancers. This also would have provided a motivation to the POSA to pursue anti-

PD-L1 antibody treatment for bladder cancer, and to identify whether bladder cancers express PD-L1.

198. The POSA would have identified that Inman discloses that bladder cancers also express PD-L1, further providing a motivation to pursue anti-PD-L1 antibody treatment for bladder cancer. As the purpose of an anti-PD-L1 antibody is to treat tumors that express PD-L1, the POSA would have been motivated to treat tumors which are PD-L1 positive and express PD-L1.

199. 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* §§VII.B-C and VIII.A.2. 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. 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.

2. The POSA would have a reasonable expectation of success

200. As explained above, *see supra* §VIII.A.6, in light of the disclosed clinical responses and anti-tumor activity achieved by NCT664 and the Phase I trial of Brahmer, the POSA would have reasonably expected that the claimed methods would treat bladder tumors. That is particularly true where the POSA

understood the role of PD-L1 in assisting tumor evasion and PD-L1's expression on bladder tumors, as taught by Inman. *See supra* §VII.D.

3. Independent claim 1

201. Claim 1 is obvious in light of the combined teachings of WO874, NCT664, Brahmer, and Inman.

202. NCT664 discloses a Phase I clinical trial administering an anti-PD-L1 antibody (MDX-1105) to subjects with various advanced or recurrent tumors. EX1021. NCT664 therefore discloses the treatment of tumors in human subjects.

203. 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* §VII.B. The POSA would thus know that the disclosed treatment regimen of NCT664 could be used to treat tumors and achieve antitumor activity before the critical date.

204. NCT664 discloses the administration of an anti-PD-L1 antibody “to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks.” 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, 4. And, as explained above, the antibody MDX-1105 was known in the art before the critical date. *See supra* §VII.A; EX1030, [0177]. 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.

205. 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.

206. 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.

207. Moreover, as explained above, the POSA would have also determined, through routine experimentation, that a 60-minute infusion of an anti-PD-L1 antibody to be effective. *See supra* §VII.C. 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 WO874 and 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* §VIII.A.2.

208. 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 intravenous 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 the 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.

209. The claim limitation which states that “the tumor is derived from a bladder cancer” is also disclosed by WO874. WO874 discloses the use of anti-PD-L1 antibodies to treat a variety of tumors, including bladder tumors. EX1027, 80:21-81:9.

210. The “bladder cancer” claim limitation is also obvious in light of the known clinical responses disclosed by Brahmer regarding its anti-PD-1 antibody and the known clinical responses achieved in the NCT664 trial, as disclosed by Hwu 2010, Topalian 2011, and Topalian 2011. *See supra* §VII.B. The POSA would have understood that an anti-PD-L1 antibody could be used to treat a variety of tumors which express PD-L1, including bladder tumors, based on the known role of PD-L1 in tumor evasion and its expression on a variety of cancers, including bladder cancer (as reported by Inman).

211. The claim limitation that states “wherein the tumor is refractory to a platinum based chemotherapy” is disclosed by NCT664 or is obvious in light of WO874, NCT664, Brahmer, and the general knowledge of the POSA. The inclusion criteria NCT664 state that the treated malignancies include “**refractory**” cancers, including patients who previously failed chemotherapy or radiotherapy. EX1021, 4-5. The POSA would understand relapsed and/or refractory cancers to include subjects who were unresponsive to standard of care platinum-based chemotherapy. EX1021, 5 (noting that subjects who failed “prior systemic platinum-based therapy” were included in trial). Indeed, as of May 2012, platinum-based chemotherapy was considered the standard first-line treatment for patients with bladder cancer. EX1067, 2432 (noting that “[c]isplatin-based

combination chemotherapy is considered standard first-line treatment for patients with metastatic urothelial carcinoma”).

212. It would have been obvious to the POSA to administer immunotherapy, including anti-PD-L1 antibodies, to patients who were unsuccessfully treated with platinum-based chemotherapy as immunotherapy provides an alternative mechanism to treat refractory cancers. POSAs would have thus been motivated to use anti-PD-L1 antibody treatments for cancers that express PD-L1, including bladder cancer, where standard treatments such as platinum-based chemotherapy failed. Indeed, bladder cancer that could not be surgically resected and was unresponsive to platinum-based chemotherapy was—and remains—notoriously difficult to treat. The POSA would have been motivated to use any form of treatment that had reported clinical responses and anti-tumor activity, including anti-PD-L1 antibodies, to treat difficult-to-treat bladder cancer that expressed PD-L1. And the POSA knew, based on the disclosure of Inman, that many bladder cancers expressed PD-L1.

213. Additionally, Brahmer also discloses 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. It further identifies that numerous patients had previously been treated with chemotherapy. EX1019, 3169. The

POSA reading Brahmer would understand relapsed and/or refractory cancers to include cancers which were unresponsive to pretreatment with platinum-based chemotherapy as this was a first-line treatment for patients with various types of cancer.

214. For these reasons, NCT664 in combination with Brahmer and Inman 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 bladder tumors given the reported efficacy of the anti-PD-L1 and anti-PD-1 antibodies in WO874, NCT664, and Brahmer. *See supra* §VIII.A.5.

4. Claims 2 and 3

215. Claim 2 depends from claim 1 and further requires that the “tumor is advanced.” EX1001, cl. 2.

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

217. It is my opinion that these claim limitations are obvious in light of NCT664 in view of Brahmer and Inman.

218. Brahmer’s phase I clinical trial reported that its an anti-PD-1 antibody achieved reduction of tumor activity in patients “with advanced treatment-

refractory solid tumors.” EX1019, 3168. NCT664 also discloses subjects “with selected advanced or recurrent solid tumors.” EX1021, 2. The POSA would understand both disclosures to refer to “advanced” tumors, including tumors which are locally advanced.

219. The POSA would have been motivated to pursue treatment for advanced and locally advanced tumors with anti-PD-L1 antibodies given the teachings of NCT664 regarding methods of treating cancer with anti-PD-L1 antibodies, as POSAs knew it had achieved anti-tumor activity. The POSA would have also had a reasonable expectation of success, as explained above, *see supra* §VIII.B.2, given the disclosed clinical responses of other monoclonal antibodies targeting the PD-1/PD-L1 pathway.

5. Claim 4

220. 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 Inman.

221. NCT664 and Brahmer describe the treatment of metastatic tumors. *See supra* §§VII.B-C and VIII.A.8. NCT 664 states that it treated advanced/metastatic epithelial ovarian cancer. Additionally, Brahmer discloses that nivolumab was effective in treatment-refractory metastatic solid tumors. EX1019, 3167, 3172. The POSA would have been well aware that an anti-PD-L1

antibody affects the same PD-1/PD-L1 interaction impacted by nivolumab and consequently would have reasonably expected an anti-PD-L1 antibody to also treat metastatic cancers.

6. Claim 5

222. Claim 5 also depends from claim 1 and requires that the “treatment lasts more than 12 weeks.” EX1001, cl. 5. It is my opinion that Claim 5 is obvious based on the combination of NCT664, Brahmer, and Inman.

223. This limitation is disclosed by NCT664 or is obvious in light of the general knowledge of the POSA. NCT664 discloses that “[t]he maximum duration of study drug treatment for a subject is 2 years.” EX1021, 3. This describes treatment that lasts more than 12 weeks. *Id.*

224. More generally, the POSA would understand that immunotherapy treatment for cancer should generally be sustained. The POSA would not believe that treatment under 12 weeks—a short period of treatment—to be sufficient to achieve the needed clinical progress for patients, particularly where such treatment is effective. The POSA would want such treatment to be sustained to ensure that the tumor either continues to shrink in response to treatment or, alternatively, does not spread any further in response to treatment. It would be obvious to the POSA to continue treatment for more than 12 weeks when administering such an anti-PD-L1 antibody to bladder cancer patients.

7. Claims 10 and 11

225. Claim 10 depends from claim 1 and additionally requires that “at least 1% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 10.

226. Claim 11 also depends from claim 1 and requires that “at least 5% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 11.

227. It is my opinion that these additional claim limitations in claims 10 and 11 would be obvious to the POSA as it would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

228. It was known by the POSA in May 2012 that PD-L1 was expressed in a variety of cancers. Inman teaches that PD-L1 is in fact expressed on bladder tumors. EX1065, 1499, 1505. Inman also discusses who PD-L1 would be a viable target for future immunotherapeutic treatments.

229. Based on these teachings, it is my opinion that the POSA would have found it obvious to administer anti-PD-L1 antibody treatment to treat bladder tumors where at least 1% or 5% of tumor cells exhibit membrane PD-L1 expression, which are both relatively low levels of PD-L1 expression. If there was no membrane PD-L1 expression or insignificant expression in the tumor, the tumor would not be a practical target for treatment with an anti-PD-L1 antibody.

230. The POSA would have been motivated to treat tumors where at least 1% or 5% of tumor cells in the treated tumor exhibit membrane PD-L1 expression.

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. Brahmer teaches that “[PD-L1] expression on tumors may affect the ability to respond” to PD-1/PD-L1 blockade and that “tumor cell surface expression of [PD-L1] may be a predictor of responsiveness.” EX1019, 3172. This alone would have provided a motivation to pursue treatment of bladder tumors where at least 1% or 5% of tumor cells express PD-L1.

231. Furthermore, in 2012, treatment options for bladder tumors that were not surgically resectable 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% or 5%. Thus, the limited nature of treatment at the time would further provide the POSA with significant motivation to treat a tumor with 1% or 5% PD-L1 expression on tumor cells with an anti-PD-L1 antibody.

232. Moreover, as of the priority date, it was known by the POSA that platinum-based chemotherapy was a first-line therapy against bladder tumors.

EX1067, 2432. As of the priority date, POSAs were interested in pursuing alternative treatment regimens, including monoclonal antibody treatments, for bladder tumors as an alternative treatment in the event that platinum-based chemotherapy was ineffective. Thus, the POSA would have a motivation to pursue immunotherapy for patients who were refractory to platinum-based chemotherapy. This would include pursuing treatment for PD-L1 positive tumors even if the tumor expressed PD-L1 as low as 1%.

8. Claims 22-23

233. Claim 22 depends from the method of claim 1 and further requires that the “platinum-based chemotherapy is a platinum-based doublet chemotherapy.” EX1001, cl. 22.

234. Claim 23 also depends from the method of claim 1 and further requires that the “platinum-based chemotherapy comprises cisplatin, carboplatin, or both.” EX1001, cl. 23.

235. These additional limitations would have also been obvious in light of NCT664 and the general knowledge of the POSA.

236. The inclusion criteria for the clinical trial disclosed in NCT664 state that the treated malignancies include “refractory” cancers. EX1021, 5. The POSA would understand relapsed and/or refractory cancers to include subjects who were unresponsive to standard of care platinum-based chemotherapy, which would

include cisplatin or carboplatin-based chemotherapy. As of the priority date, platinum-based chemotherapy and platinum-based doublet chemotherapy were considered the standard first-line and second-line treatment for patients with bladder cancer, respectively, and patients were treated with both cisplatin and carboplatin. For patients that do not respond to cisplatin or carboplatin, they were treated with platinum-based doublet chemotherapy, which consists of combinations of cisplatin or carboplatin with vinorelbine, gemcitabine or taxanes.

237. The POSA would have had a motivation to administer immunotherapy, including anti-PD-L1 antibodies, to patients who were unsuccessfully treated with platinum-based chemotherapy, including cisplatin or carboplatin, as immunotherapy provides an alternative mechanism to treat refractory cancers. And the POSA would have a reasonable expectation of success in doing so as many bladder cancers express PD-L1, as taught by Inman. Thus, it is my opinion that claims 22-23 of the '299 patent are obvious.

9. Claim 24

238. Claim 24 depends from claim 1 and requires “wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody.” EX1001, cl. 24.

239. Administering antihistamine prior to the anti-PD-L1 antibody would have also been obvious in light of NCT664 and the general knowledge of the POSA. It is routine to pre-administer antihistamine before chemotherapy and

immunotherapy. Antihistamines are administered to prevent hypersensitivity reactions in platinum-based chemotherapy. Likewise, antihistamines are administered to prevent infusion reactions in the context of immunotherapy (i.e., administration of monoclonal antibodies). *See, e.g.*, EX1068, Tables 3 and 4 (Table 3 lists platinum-based compounds where hypersensitivity reactions are managed via antihistamines. Table 4 lists monoclonals where infusion reactions are managed via antihistamines).

C. Claims 6-9 and 12-21 are obvious over NCT664 in view of Brahmer, Inman, and Irving

240. Claims 6-9 and 12-21 of the '299 patent are obvious over NCT664 in view of Brahmer, Inman, and Irving. As explained above, *see supra* §VIII.B it is my opinion that claims 1-5, 10-11, and 22-24 are obvious in light of the combination of NCT664, Brahmer, and Inman. 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 6-9 and 12-21 of the '299 patent obvious.

241. As I already opined above, the POSA would have a motivation to combine the teachings of NCT664, Brahmer, and Inman. *See supra* §VIII.B. 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.

242. 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 Inman, *see supra* §VIII.B.2, 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* §VII.E. Irving would thus further support the POSA's expectation of success.

1. Claims 6 & 7

243. Claim 6, which depends from claim 1, requires that “the anti-PD-L1 antibody is formulated in a pharmaceutical composition.” EX1001, cl. 6.

244. Claim 7, which depends from claim 6, 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. 7.

245. It is my opinion that each of these claims is obvious in view of the combination of NCT664, Brahmer, Inman, and Irving. Specifically, Irving teaches these additional limitations.

246. 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.”).

247. 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 6 and 7. It is thus my opinion that claims 7-9 are also obvious given the additional teachings of Irving.

2. Claims 8 and 9

248. Claim 8, which depends from claim 7, further requires that the pharmaceutically acceptable “salt comprises a sodium salt.” EX1001, cl. 8. Claim 9, which also depends from claim 7, requires that the pharmaceutically acceptable “salt comprises sodium chloride.” EX1001, cl. 9. It is also my opinion that these claims are obvious from the combination of NCT664, Inman, Brahmer, and Irving.

249. 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.*, [0625] (emphasis added). Sodium chloride is one type of sodium salt and thus satisfies both claims 8 and 9. Given this teaching, my opinion is that claims 8 and 9 are also obvious given the additional teachings of Irving.

3. Claims 12-15

250. Claims 12-15 depend from claims 1-4 and each of claims 12-15 further require that the claimed methods also comprise “administering an anti-cancer agent.” EX1001, cls. 12-17. It is my opinion that Claims 12-15 are obvious based on the combination of NCT664, Brahmer, Inman, and Irving.

251. I understand the claim limitation “administering 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 1-4. If the anti-cancer agent could be the anti-PD-L1 antibody of claims 1-4, then claims 12-15 would be redundant of those claims. Were that the case, claims 12-15 would be obvious over NCT664, Brahmer, and Inman, as explained above.

252. 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, [0492]. 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 12-15 are also obvious given the additional teachings of Irving.

4. Claims 16-21

253. Claims 16-21 respectively depend from claims 12-15 and add the same limitations to each claim.

254. Claims 16, 18, and 20 each require that the additionally administered “anti-cancer agent” of claims 12-14 “is a chemotherapy.” EX1001, cls. 16, 18, 20.

255. Claims 17, 19, and 21 each require that the additionally administered “anti-cancer agent” of claims 12-14 “is a radiotherapy.” EX1001, cls. 17, 19, 21.

256. It is my opinion that Claims 16-21 are obvious based on the combination of WO874, NCT664, Brahmer, and Inman.

257. Both of the additional “chemotherapy” and “radiotherapy” limitations are disclosed by Irving. Irving discloses the administration of an anti-PD-L1 antibody “in combination with a chemotherapeutic agent.” EX1058, [0032]. It also refers to “[t]raditional therapies for cancer,” such as “radiation therapy” and teaches that such “conventional treatments for the treatment of cancer immunity may be conducted . . . simultaneous with the administration the anti-PD-L1 antibodies of the invention.” EX1058, [0428-0429].

D. Claims 10 and 11 are obvious over WO874 in view of NCT664, Brahmer, and Nakanishi

258. Claims 10-11 of the '299 patent are obvious over WO874 in view of Brahmer, NCT664, and Nakanishi.

259. As I already opined above, the POSA would have a motivation to combine the teachings of WO874, NCT664, and Brahmer. *See supra* §§VIII.A.1-4. It is also my opinion that the POSA would be motivated to combine those teachings with that Nakanishi. Nakanishi teaches that PD-L1 expression on bladder cancer is very high. EX1066. The mean percentage of PD-L1 positive cells in 65 surgically resected specimens was approximately 20%. *See supra* §VII.F. The POSA who is interested in pursuing methods of treating bladder cancer would be interested in Nakanishi's teaching regarding PD-L1 expression by bladder cancer. Thus, in view of the POSA's knowledge of PD-L1, its role in tumor evasion, and the success of anti-PD-1 treatment (i.e., MDX-1106/nivolumab), the POSA would have looked to Nakanishi to determine PD-L1 expression patterns on bladder cancers.

260. Nakanishi itself provides the motivation to use the dosing regimen of WO874 and NCT664 to treat bladder cancer. Nakanishi reports that "the aberrant expression of [PD-L1] in urothelial cancer is associated with aggressive tumors, suggesting a regulatory role of tumor-associated [PD-L1] in antitumor immunity. Therefore, the manipulation of tumor-associated [PD-L1] may become a beneficial target for immunotherapy in human urothelial cancer." EX1066, 1173. Nakanishi

itself teaches POSAs that anti-PD-L1 antibodies may be a useful means of treating human urothelial cancer.

261. For the same reasons stated above, the POSA would have a reasonable expectation of success in using the claimed dosing regimens with an anti-PD-L1 antibody in light of NCT664, Brahmer, and Inman, *see supra* §VIII.B.2. Even if the preambles required clinical efficacy, which, in my opinion, they do not, the POSA would reasonably expect the combination to be clinically efficacious.

262. Claim 10 depends from claim 1 and additionally requires that “at least 1% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 10.

263. Claim 11 also depends from claim 1 and requires that “at least 5% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 11.

264. In addition to the reasons discussed above for why the POSA would have found it obvious to treat bladder tumors that express PD-L1 at least 1% or 5% with anti-PD-L1 antibodies, *see supra* §§VII.F and VIII.A.13 and VIII. B.7, it is also my opinion that these additional claim limitations in claims 10 and 11 would be obvious to the POSA in view of Nakanishi. As discussed above, *see supra* §VII.F, Nakanishi teaches that PD-L1 expression in 65 surgically resected bladder cancer specimens is above both 1% and 5%. EX1066, 1175. The POSA would have been motivated to treat bladder cancer tumors which expressed PD-L1 at the

rate disclosed in Nakanishi, *see supra* §§VII.F, VIII.A.13 and VIII. B.7, which falls within the range of claims 10 and 11.

IX. CONCLUSION

265. 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.