

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DANA-FARBER CANCER INSTITUTE, INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

Case IPR2023-00252

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

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

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO.
10,138,299 B2**

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1012	U.S. Provisional Application No. 61/790,747 (“the ’747 provisional”)
1013	Okazaki and Honjo, <i>PD-1 and PD-L1 ligands: from discovery to clinical application</i> , 19(7) Int. Immunol. 813 (2007) (“Okazaki 2007”)
1014	Iwai et al., <i>Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade</i> , 99(19) Proc. Nat. Acad. Sci. 12293 (2002) (“Iwai 2002”)
1015	Blank et al., <i>Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy</i> , 54 Cancer Immunol. Immunother. 307 (2005) (“Blank 2005”)
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1017	Brown et al., <i>Blockade of Programmed Death-1 Ligands on Dendritic Cells Enhances T Cell Activation and Cytokine Production</i> , 170 J. Immunol. 1257 (2003) (“Brown 2003”)
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1022	Hwu, <i>Targeted therapy for metastatic melanoma: From bench to bedside</i> , Healio.com (June 25, 2010) (“Hwu 2010”)
1023	Mu et al., <i>High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation</i> , 28 Med. Oncol. 682 (2010) (“Mu”)
1024	File History for U.S. Patent No. 10,138,299 B2 (“the ’299 patent file history”)
1025	Topalian et al., <i>Cancer Immunotherapy Comes of Age</i> , 29(36) J. Clin. Oncol. 4828 (2011) (“Topalian 2011”)
1026	Topalian et al., <i>Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity</i> , 24 Curr. Opin. Immunol. 207 (2012) (“Topalian 2012”)
1027	PCT Publication No. WO 2007/005874 A2 (“WO874”)
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1029	M. Sznol, et al. Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies, <i>Journal of Clinical Oncology</i> 2010 28:15 suppl, 2506-2506(“Sznol 2010”)
1030	U.S. Publication No. US 2010/0055102 A1 (“the ’102 publication”)
1031	U.S. Food & Drug Admin., <i>Erbitux® (cetuximab), Highlights of Prescribing Information</i> (First approved 2004) (“Erbitux Label”)
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1034	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, Press Release: National Institutes of Health Launches “ClinicalTrials.gov” (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html . (“Feb. 29, 2000 NIH Press Release”)
1035	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, ClinicalTrials.gov, History, Policies, and Laws, https://clinicaltrials.gov/ct2/about-site/history#InternationalCommittee (last accessed Nov. 7, 2022). (“ClinicalTrials.gov History, Policies, and Laws”)
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1037	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, Clinicaltrials.gov, Home page, https://clinicaltrials.gov/ (November 2022). (“ClinicalTrials.gov Home Page”)
1038	Protocol for: Brahmer et al., Safety and activity of anti-PD-L1 antibody in patients with advanced cancer, <i>N Engl J Med</i> 2012;366:2455-65 (2012) (“NCT 664 Protocol”)
1039	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, ClinicalTrials.gov, History of Changes for Study: NCT00729664 - https://clinicaltrials.gov/ct2/history/NCT00729664?A=1&B=7&C=merged#StudyPageTop (“August 4, 2008 vs October 27, 2009 comparison”)
1040	Lee et al., <i>A one-hour infusion of infliximab during maintenance therapy is safe and well tolerated: a prospective cohort study</i> , 34 <i>Aliment Pharmacol. Ther.</i> 181 (2011) (“Lee”)
1041	U.S. NAT’L LIBRARY OF MED., NAT’L INST. OF HEALTH, ClinicalTrials.gov, How to Edit Your Study Record, https://clinicaltrials.gov/ct2/manage-recs/how-edit . (“ClinicalTrials.gov, How to Edit Your Study Record”)

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1058	U.S. Publication No. US 2010/0203056 A1 ("Irving")
1059	U.S. Patent No. 9,580,505 ("the '505 patent")
1060	U.S. Patent No. 9,580,507 ("the '507 patent")
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1063	von der Maase et al., <i>Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients With Bladder Cancer</i> , 23(21) J. Clin. Oncol. 4602 (2005) (“von der Maase 2005”)
1064	Drayton and Catto, <i>Molecular mechanisms of cisplatin resistance in bladder cancer</i> , 12(2) Expert Rev. Anticancer Ther. 271 (2012) (“Drayton and Catto 2012”)
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1066	Nakanishi et al., <i>Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers</i> , 56 Cancer Immunol. Immunother. 1173 (2007) (“Nakanishi 2007”)
1067	Galsky et al., <i>Treatment of Patients With Metastatic Urothelial Cancer “Unfit” for Cisplatin-Based Chemotherapy</i> , 29(17) J. Clin. Oncol. 2432 (2011) (“Galsky 2011”)
1068	Lenz, <i>Management and Preparedness for Infusion and Hypersensitivity Reactions</i> , 12 The Oncologist 601 (2007) (“Lenz 2007”)
1069	Brahmer et al., <i>Safety and activity of anti-PD-L1 antibody in patients with advanced cancer</i> , N Engl J Med 2012;366:2455-65 (2012) (“Brahmer 2012”)
1070	December 5, 2022, Letter to Hon. Kathi Vidal from Senators Warren and Jayapal

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Dana-Farber Cancer Institute, Inc. (“Dana-Farber” or “Petitioner”) requests *inter partes* review (“IPR”) of claims 1-24 (the “Challenged Claims”) of U.S. Patent No. 10,138,299 owned by Bristol-Myers Squibb Co. (“BMS” or “Patent Owner”).

I. INTRODUCTION

The discovery of anti-programmed cell death protein 1/ligand 1 (“PD-1/PD-L1”) antibodies to treat cancer, including lung cancer, is disclosed in U.S. Patent No. 7,595,048 and its relatives (now known as the “Honjo-Freeman Patents”), whose inventors include Dr. Gordon Freeman of Dana-Farber, a non-profit research hospital dedicated to advancing the understanding, diagnosis, treatment, cure, and prevention of cancer. This Nobel Prize-winning discovery was groundbreaking; it won industry acclaim for revolutionizing cancer therapeutics¹ and spurred BMS, Merck & Co., Sanofi, Novartis AG, AstraZeneca Pharmaceuticals LP, and others to invest in commercializing antibodies targeting the PD-1/PD-L1 pathway.

The path from invention to commercial therapeutic can sometimes lead to unexpected or surprising findings that are inventive in their own right. While time

¹ Other awards included the 2014 William B. Coley Award and the 2017 Warrant Alpert Foundation Prize, both shared with Dr. Freeman.

consuming, the path can also be routine, where the results are neither surprising, unexpected nor even notable for anything other than following the express teachings of the prior art. The line between the two paths is important; one represents patentable innovation necessary to translate early discoveries to commercial products, whereas the other represents routine testing where additional issued patents impede patient access to biosimilar or generic drugs upon expiry of the patents covering the break-through invention.²

For the Challenged Claims, the path was not only routine but published years earlier, making them plainly invalid. In 2008, nearly four years before the '299 patent's earliest priority date in May 2012, BMS published NCT00729664 ("NCT664"), a clinical trial using the very dosing regimen in the Challenged Claims, including administering an anti-PD-L1 antibody at 10 mg/kg every two weeks to treat solid tumors. BMS' NCT664 disclosure was highly relevant to prosecution of the pending '299 patent claims, but BMS failed to disclose NCT664 to the Examiner.

NCT664 fully anticipates the Challenged Claims but for one limitation: that

² See June 8, 2022, Letter to Hon. Kathi Vidal from Senators Leahy et al.

(EX1008); *see also* December 5, 2022, Letter to Hon. Kathi Vidal from Senators Warren and Jayapal (EX1070).

the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion.

The '299 specification makes clear that this limitation is unremarkable, routine, predictable. The '299 patent mentions infusion time only once without noting anything significant about 60 minutes as compared to other infusion times.

EX1001, 67:57. This is not surprising. An infusion time of 60 minutes is normal and routine in both cancer treatments and clinical practice generally; indeed, it is described abundantly in the art. The '048 patent describes 60 minutes as the lower end of the typical intravenous administration range. *See* EX1009, 12:62-13:3.

Brahmer discloses that its anti-PD-1 antibody, which achieved clinical response, was administered by intravenous infusion for 60 minutes at 10 mg/kg. *See infra* §VII.C.

The '299 patent adds nothing inventive to the seminal teachings of the Honjo-Freeman Patents and the subsequent prior art. In obtaining the Challenged Claims, BMS extends its monopoly on PD-L1 antibodies through a patent not supported by unexpected results or by overcoming technical problems encountered in drug development, but rather, through superficial prosecution amendments that specify dosing parameters devoid of any unexpected result and that are untethered to solving any technical problem and unremarkable to the skilled artisan. The '299

patent, is precisely the type of patent cited by policymakers and consumer groups as an abuse of the patent system, inflating drug prices and stifling competition.³

Dana-Farber seeks cancellation of the Challenged Claims to extinguish the cloud of improperly extended monopoly rights that BMS has layered around the Honjo-Freeman inventions. As a cancer institute, Dana-Farber is interested in ensuring that upon expiration of the Honjo-Freeman Patents, their inventions are free to be widely and extensively practiced.

II. BASIS FOR THE PETITION AND MANDATORY NOTICES

A. Identification of Challenge under 37 C.F.R. §§ 42.104(b)(1) & (2)

Petitioner requests IPR on the following grounds:

Ground	Claims	Basis	Prior Art
1	1-24	§ 103	WO874 in view of NCT664, Brahmer, and Inman
2	1-5, 10-11, and 22-24	§ 103	NCT664 in view of Brahmer and Inman
3	6-9 and 12-21	§ 103	NCT664 in view of Brahmer, Inman, and Irving
4	10 and 11	§ 103	WO874 in view of NCT664, Brahmer, and Nakanishi

³ <https://www.reuters.com/business/healthcare-pharmaceuticals/consumer-group-says-drugmakers-abuse-us-patent-system-keep-prices-high-2022-09-16/>.

These bases are described in greater detail below and in the declarations of Dr. Salma Jabbour, M.D. and Robert Paarlberg. (EX1002 and 1003).

B. Grounds for Standing under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '299 patent is available for IPR, *see* 37 C.F.R. § 42.102(a), and that it is not barred or estopped from requesting an IPR on the grounds identified herein. *See* 37 C.F.R. § 42.101.

C. Fees under 37 C.F.R. §§ 42.15(a) and 42.103

Fees under 37 C.F.R. § 42.15(a) are being paid concurrently herewith. Counsel for Petitioner authorizes the U.S. Patent and Trademark Office to charge Deposit Account No. 502778.

D. Real Party-in-Interest under 37 C.F.R. § 42.8(b)(1)

The Real Party-in-Interest is Dana-Farber Cancer Institute, Inc.

E. Related Matters under 37 C.F.R. § 42.8(b)(2)

Petitioner and Patent Owner are engaged in litigation involving Petitioner's state law claims concerning Patent Owner's licensing of patents co-owned by Petitioner and Patent Owner in *Dana-Farber Cancer Institute, Inc. v. Bristol-Myers Squibb, Co.*, et al., C.A. No. 19-cv-11380-PBS (D. Mass.). This case was filed nine days after judgment was entered in an inventorship litigation, in which Dana-Farber prevailed against BMS and established that Dr. Freeman is a co-inventor of the revolutionary work on administering PD-1 and PD-L1 antibodies to treat cancer claimed in the Honjo-Freeman Patents. *See Dana Farber Cancer*

Institute, Inc. v. Ono Pharm. Co., 379 F. Supp. 3d 53 (D. Mass. 2019), aff'd 964 F.3d 1365 (Fed. Cir. 2020).

Patent Owner has asserted the '299 patent against AstraZeneca Pharmaceuticals LP in *Bristol-Myers Squibb Company et al v. AstraZeneca Pharmaceuticals LP et al.*, C.A. No. 22-cv-00346 (D. Del.). Upon information and belief, that case is ongoing, with the parties engaging in fact discovery. D.I. No. 62 (Nov. 7, 2022 Joint Status Report).

Petitioner also identifies *Dana-Farber Cancer Institute, Inc. v. Bristol-Myers Squibb, Co.*, Case No. IPR2023-00249 (P.T.A.B.) (U.S. Patent No. 10,323,092), filed concurrently herewith.

F. Lead and Backup Counsel and Service Information under 37 C.F.R. §§ 42.8(b)(3) & (4)

Petitioner is contemporaneously filing a power of attorney for the following counsel:

Lead	Back-Up
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III. PERSON OF ORDINARY SKILL IN THE ART (POSA)

The POSA 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 comparable discipline, and several years of post-doctoral and/or work experience. The POSA would have experience in designing clinical trials and familiarity, gained through study, training or experience, or through consultation with others, 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.

IV. STATE OF THE ART AT THE CLAIMED CRITICAL DATE

A. Technical Field

The '299 patent is directed to a method of treating bladder cancer in a human by administering an anti-PD-L1 antibody.

1. PD-L1

PD-L1, a member of the CD28 receptor family, is a transmembrane glycoprotein and a ligand of the immune checkpoint receptor PD-1. EX1013; EX1002, ¶53. PD-L1 binding to PD-1, expressed on activated T-cells, inhibits

T-cell activity. *Id.* PD-L1 overexpression by tumor cells suppresses the proliferation, cytokine production, and T cell cytotoxicity, effectively inhibiting the body's immune response to malignant tumor cells. EX1014; EX1002, ¶53. Inhibiting the binding of PD-L1 to PD-1 impairs the growth of tumors via T cell activation. *Id.*

PD-L1 expression has been found in a broad range of cancers including in lung (*e.g.*, NSCLC), stomach, colon, breast, cervix, ovary, renal cell, and bladder. EX1015; EX1023; EX1002, ¶54. Thus, it was known 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.*

The Honjo-Freeman '048 patent describes the groundbreaking discovery of Dana-Farber 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.” *Id.*, 1:7-10. Honjo-Freeman '048 discloses methods of treating cancers in human subjects using anti-PD-L1 antibodies. *Id.*, 10:37-38 (noting that inventors “invented” an “anti-PD-L1 antibody”), *id.*, 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 anti-PD L1 antibodies to treat bladder cancer. EX1002, ¶55. Honjo-Freeman '048 teaches that its anti-PD-L1 antibodies "inhibit . . . PD-L1 function" and results in "suppression of cancer proliferation." EX1009, 10:34-39.

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

Before the '299 patent, there were at least four ongoing or completed 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; EX1002, ¶57. BMS' own anti-PD-1 antibody clinical trial, NCT00441337, published in Brahmer, led to promising efficacy results in patients. EX1019. In this study, many patients showed complete and partial responses, including one patient with colon cancer showed a durable complete response (ongoing for 21 months at the time it was reported). *Id.*

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; EX1002, ¶58.

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; EX1002, ¶59.

3. Bladder Cancer

Bladder cancer is a leading cause of cancer mortality in men and women. EX1062; EX1002, ¶60. More than half of bladder cancer cases recur after the initial frontline treatment and 10-30% of cases will progress to muscle-invasive disease. EX1062, 244; EX1002, ¶60. Platinum-based chemotherapy, *e.g.*, cisplatin, is a standard of care for bladder cancer. However, patients 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; EX1002, ¶60.

An analysis of PD-L1 expression 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; EX1002, ¶61. Thus, increased PD-L1 expression was thought to contribute to advanced bladder cancer's ability to evade the body's anti-tumor immune response. EX1002, ¶61. These findings confirm the '048 patent's teaching that anti-PD-L1 antibodies would be expected to treat,

inter alia, bladder cancer, and support that patients with bladder cancer would benefit from treatment with an anti-PD-L1 antibody.. EX1002, ¶61.

V. THE '299 PATENT

A. Priority

The '299 patent issued from Application No. 16/006,473 (EX1010), filed on June 12, 2018, and claims priority to: No. 61/647,442, filed on May, 15, 2012 (EX1011) and No. 61/790,747, filed on March 15, 2013 (EX1012).

B. Prosecution History

The '473 application claims as -filed were broadly directed to, *inter alia*, methods of treating cancer by administering “an effective amount of an antibody or an antigen-binding portion thereof that disrupts the interaction between [PD-1] and [PD-L1]” EX1024, 154. The original claims were not limited to any type of cancer; any specific antibody; any dosing regimen; or any PD-L1 expression patterns in tumor cells. *Id.*

BMS filed a Preliminary Amendment on June 14, 2018, amending the claims to specify a method of treating bladder, urethra, ureter, or renal pelvis cancer by administering 10 mg/kg of an anti-PD-L1 antibody every two weeks, intravenously over a period of 60 minutes, wherein the tumor is refractory to platinum-based chemotherapy. *Id.*, 178.

On August 7, 2018, the Examiner issued a non-final office action rejecting all pending claims on indefiniteness and written description grounds. *Id.*, 216-222.

The Examiner concluded that claims did not comply with the written description requirement because the application lacked support for a method of treating a urethra, bladder, ureter, or renal pelvis-derived tumor that is refractory to platinum-based chemotherapy. *Id.*, 220. The Examiner reasoned that these cancers are disclosed in the application but are not described as being refractory to platinum-based chemotherapy. *Id.*

In response, BMS amended the base claim to specify bladder cancer as the only cancer type. *Id.*, 249-251. BMS did not point to or submit any evidence of success in treating bladder cancer with a PD-L1 antibody, instead BMS relied on the disclosure of bladder cancer in the application. *Id.*, 252-259. BMS argued that several passages in the application that refer to treating bladder cancer that is refractory to platinum-based chemotherapy satisfied the written description requirement. *Id.*, 255-258.

A Notice of Allowance issued, without comment, on October 18, 2018. *Id.*, 272-274.

The '299 patent issued on November 27, 2018. *Id.*, 299.

VI. CLAIM CONSTRUCTION

The Challenged Claims must be “construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b),” *i.e.*, the *Phillips* standard. 37 C.F.R. § 42.100(b); 83

Fed. Reg. 197, 51340-51359 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Petitioner and Dr. Jabbour have applied this standard.

A. The Challenged Claims’ Preamble

The preamble of the ’299 patent’s sole independent claim provides, “[a] method of treating a tumor in a human subject in need thereof.” EX1001, cl. 1. The Board should construe this preamble as not requiring clinical efficacy.

B. The Preamble Does Not Contain a Clinical Efficacy Requirement

The preamble does not require clinical efficacy. The ’299 specification defines “[t]reatment” to mean 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, 10:8-14 (emphasis added). In contrast, a “therapeutically effective amount,” which does not appear in the claims, is defined to mean “protect[ing] a subject against the onset of a disease or promotes disease regression.” *Id.*, 11:16-24.

The body of the claim recites each of the steps, including administering 10 mg/kg of an anti-PD-L1 antibody every 2 weeks through a 60-minute intravenous infusion. EX1001, cl. 1. Each of these steps with a specific dose and timing is “performed the same way” regardless of any clinical result. *Bristol-Myers Squibb*

Co. v. Ben Venue Labs. Inc., 246 F.3d 1368, 1375 (Fed. Cir. 2001); *see also In re Copaxone*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble non-limiting where it “does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims”).

The distinction between “treatment” and “therapeutically effective amount” is also aligned with how POSAs viewed treatment of bladder cancer in May 2012. EX1002, ¶¶36-39. As noted by Dr. Jabbour, bladder cancer was notoriously difficult to treat in May 2012, so POSAs were looking for any form of treatment which could be provided with the purpose of achieving even a minimal benefit. *Id.*

Thus, the preamble would require only that an anti-PD-L1 antibody be administered with the *objective or purpose, i.e., intent*, of treating the bladder tumor. Clinical efficacy is not required. *See In re Montgomery*, 677 F.3d, 1375, 1380 (Fed. Cir. 2012) (claims to a method for treating or preventing a stroke do not create “an efficacy requirement”); *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881, Paper 94 at 12-21 (PTAB Nov. 9, 2022)

(finding “[a] method for treating an angiogenic eye disorder in a patient” does not require “any particular level of effectiveness”).⁴

VII. SCOPE AND CONTENT OF PRIOR ART

A. WO874 Teaches the Administration of Anti-PD-L1 Antibodies to Treat Bladder Tumors

International Publication No. WO 2007/005874 A2 discloses the administration of anti-PD-L1 antibodies for the treatment of tumors. It published on January 11, 2007 and is therefore prior art to the '299 patent under 35 U.S.C. § 102(b). EX1027. Several BMS patents claim priority to WO874 and are directed to anti-PD-L1 antibodies and methods of treatment. EX1059; EX1060.

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. WO874 discloses sequences for numerous anti-PD-L1 antibodies (*id.*, 13:10-28, 26:6-14), as well as methods of preparing anti-PD-L1 antibodies for evaluation (*id.*, 40:1-9; 51:18-52:4). It teaches that monoclonal antibodies “can be produced by a variety of techniques, including conventional monoclonal antibody

⁴ Even if the claims required some degree of clinical efficacy, they are obvious as there was already evidence of clinical efficacy before the critical date. *See infra* §VII.B.

methodology.” *Id.*, 55:10-15. WO874 discloses that its methods of treatment with anti-PD-L1 antibodies can apply to bladder cancer. *Id.*, 80:21-82:9 (“Examples of other cancers that may be treated using the methods of the invention include . . . cancer of the bladder.”); EX1002, ¶¶65-68.

WO874 discloses *in vitro* experimental data showing that anti-PD-L1 antibodies “bind to human cell surface PD-L1.” *Id.*, 100:1-31 (Examples 5 and 6), Figures 37A-C. Example 7 of WO874 further discusses the results of experiments regarding numerous anti-PD-L1 human monoclonal antibodies, including data presented in Figure 40 which shows that such antibodies promote T-cell proliferation and IFN- γ secretion in a concentration-dependent manner, in contrast to control antibodies. *Id.*, Example 7. Examples 10 and 11 (Figures 45 and 46) of WO874 further illustrate how various anti-PD-L1 monoclonal antibodies block binding of PD-L1 with human PD-1, “demonstrate[ing] 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. The POSA would understand this to reflect that anti-PD-L1 antibodies would reasonably be expected to treat tumors that express PD-L1. EX1002, ¶69.

In addition to *in vitro* assays, WO874 also discloses the treatment of tumors in an animal model using anti-PD-L1 antibodies. EX1002, ¶70. Example 13 discloses that mice implanted with MC38 colorectal cancer cells and treated with

anti-PD-L1 antibodies at a 10 mg/kg dose experienced a “modest effect on tumor growth resulting in a delay of tumor growth.” EX1027, 105:12-31. WO874 also claims, *inter alia*, a method of treating bladder cancer. *Id.*, cl. 51.

The Examiner did not explicitly consider or issue any rejection over the disclosure of WO874, let alone WO874 in combination with NCT664, Brahmer, or Inman. This combination renders the Challenged Claims obvious. *See infra* §XIII.

B. NCT664 Teaches the Claimed Method of Treatment

NCT664 is a clinical study titled “Phase 1 study of a fully human monoclonal IgG4 antibody targeting the [PD-L1].” EX1021, 3. The clinical trial included subjects with “measurable advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer).” *Id.* The inclusion criteria specified, *inter alia*, patients who previously failed chemotherapy or radiotherapy. NCT664 was designed to include 5 cohorts (0.3, 1, 3, 10, 15mg/kg/dose) of MDX-1105 via intravenous infusion, every 14 days for a total of 3 infusions. *Id.*, 3.

NCT664 is a prior art printed publication, which was publicly available on ClinicalTrials.gov by at least 2008, and constitutes prior art under pre-AIA 35 U.S.C. § 102(b). Despite being BMS’ own study, NCT664 was not disclosed to, or cited by, the Examiner during prosecution.

The NCT664 study record was “First Posted” on August 7, 2008, and therefore was publicly available at least as of that date. EX1003, ¶¶30-59.

Petitioner’s expert, Mr. Paarlberg explains, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials, and NCT664 was publicly accessible more than one year before the earliest claimed priority date. EX1003, ¶¶17-29. The ClinicalTrials.gov database provides key publication dates for each study submitted. According to the NIH, the “First Posted” date is “[t]he date on which the study record was first available on ClinicalTrials.gov.” EX1003, ¶34. While the protocol has since been updated, this petition relies only upon updates which were posted and made publicly available more than one year before the ’299 patent’s earliest priority date. EX1003, ¶43-58.

C. Brahmer Teaches Successful Use of an anti-PD-1 Antibody with a 60-Minute Infusion Time

Brahmer is a peer-reviewed journal article, published in the Journal of Clinical Oncology in 2010, which is a reoccurring publication, and thus, constitutes prior art under pre-AIA 35 U.S.C. § 102(b). EX1019. While Brahmer is listed on the face of the ’299 patent, it was not cited by the Examiner to reject the pending claims or otherwise substantively relied upon.

Brahmer describes a “phase I study sought to determine the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid

tumors and to preliminarily assess antitumor activity, pharmacodynamics, and immunologic correlates.” EX1019, 3167. Brahmer administered an anti-PD-1 antibody (MDX-1106 = nivolumab) to patients having “advanced metastatic melanoma, colorectal cancer (CRC), castrate-resistant prostate cancer, non-small-cell lung cancer (NSCLC), or renal cell carcinoma (RCC).” *Id.*; EX1002, ¶87. The patients “received a 60-minute intravenous infusion of MDX-1106 at 0.3, 1, 3, or 10 mg/kg.” EX1019, 3168.

Brahmer reports that 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.

Brahmer explains that MDX-1106 blocks PD-1’s interaction with PD-L1⁵ and consequently “[a]nother 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.” *Id.* Thus, Brahmer teaches that patients with

⁵ Brahmer refers to “B7-H1”, a synonym for PD-L1. EX1002, ¶88.

tumors expressing PD-L1 showed tumor regression following treatment with MDX-1106. *Id.*, 3167, Fig. 2, Appendix Table 2.

Brahmer teaches a direct role of PD-L1 in the mechanism of action of MDX-1106 in the treatment of cancer:

Two possible scenarios for T cell inhibition via PD-1:[PD-L1] ligation have been proposed in the context of cancer. 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., 3172.

The POSA knowing the successful results of the anti-PD-1 antibody MDX-1106/nivolumab confirmed by Brahmer (EX1019) would have understood, that the PD-1/PD-L1 pathway is a target for successful cancer treatment and been motivated to block PD-1/PD-L1 interaction by targeting PD-L1. EX1002, ¶¶90-91.

D. Inman Teaches That Bladder Tumors Express PD-L1

Inman is a peer-reviewed journal article, published online by the American Cancer Society in March 2007, which is a recurring publication, and thus constitutes prior art under pre-AIA 35 U.S.C. § 102(b). EX1065. Inman was not

cited on the face of the '299 patent, it was not cited by the Examiner or otherwise substantively relied upon.

Inman identifies PD-L1 as a “predictive marker” for tumor stage progression in bladder cancers and that PD-L1 plays a role in “neutralizing T cells that normally guard against cancer invasion.” *Id.*, 1499, 1505; EX1002, ¶¶93-96.

Inman concludes that its studies “suggest that BCG induces strong PD-L1 expression in host tissues that might have important implications for antitumoral tumor immunotherapy.” *Id.*, 1505. Inman confirms that tumor PD-L1 expression plays a significant role in the development of certain bladder cancers and that immunotherapy is one mechanism of treating patients where there is PD-L1 tumor expression. EX1002, ¶¶93-96.

E. Irving teaches Anti-PD-L1 Antibodies and Formulations

Irving is titled “Anti-PD-L1 Antibodies and Their Use To Enhance T-Cell Function” and published on August 12, 2010 and is therefore prior art to the '299 patent under 35 U.S.C. § 102(b). EX1058. Irving is cited on the face of the '299 patent, but was not cited by the Examiner to reject the pending claims, nor otherwise substantively relied upon. EX1001.

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; EX1002, ¶¶98-104. Irving claims methods of treating bladder cancer. *Id.*, cls. 81, 84, and 95.

Irving discloses, in detail, the various components of pharmaceutical formulations of the anti-PD-L1 antibodies, including salts, antioxidants, and carriers. EX1058, [0389]; *see also* [0390]-[0397]. Irving further discloses preservatives ([0217]) and wetting agents ([0395]).

F. Nakanishi Teaches Bladder Cancer Cells Highly Express PD-L1

Nakanishi is a peer-reviewed journal article, published online by Cancer Immunology, Immunotherapy in December 2007, which is a recurring publication, and thus constitutes prior art under pre-AIA 35 U.S.C. § 102(b). EX1066. Nakanishi was not cited on the face of the '299 patent, it was not cited by the Examiner or otherwise substantively relied upon. EX1001.

Nakanishi “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; EX1002, ¶¶106-108. Nakanishi 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.*

Nakanishi showed that in “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. GROUND 1: CLAIMS 1-24 ARE UNPATENTABLE AS OBVIOUS OVER WO874 IN VIEW OF NCT664, BRAHMER, AND INMAN

A. Ground 1 Overview

Claims 1-24 are rendered obvious under 35 U.S.C. § 103 by WO874, NCT664, Inman, and/or Brahmer.

1. The POSA Would Have Been Motivated to Combine WO874, Inman, NCT664, and Brahmer

“Motivation to combine may be found in many different places and forms.” *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *see also Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (the motivation to combine can be supported by expert testimony regarding knowledge of the POSA at the time of invention). A motivation to modify or combine the prior art “may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.” *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006). And a “motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art.” *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006).

POSAs were interested in exploring alternative treatments for bladder cancer at the time of the invention as traditional treatments, such as radiotherapy and

chemotherapy were not always therapeutically effective. EX1002, ¶110. WO874 discloses that anti-PD-L1 antibodies were useful to treat various cancers, including bladder cancer and discloses experimental data that supports the use of anti-PD-L1 antibodies as a form of treatment. *See supra* §VII.A.

WO874 also claims, *inter alia*, a method of treating bladder cancer. EX1027, cl. 50. The POSA would have thus been motivated to use anti-PD-L1 antibody treatments for bladder cancer in light of WO874. EX1002, ¶¶110-112.

Given that 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. EX1002, ¶113. It was known by POSAs that certain bladder tumors express PD-L1, as taught by Inman. *See supra* §VII.D. Thus, the POSA would have had a motivation to treat bladder tumors which expressed PD-L1 with anti-PD-L1 antibodies in light of the teachings of WO874 in view of Inman. EX1002, ¶¶110-113.

WO874 also discloses administration of 10 mg/kg of an anti-PD-L1 antibody once every two weeks to treat various cancers. EX1027, 75:20-25; EX1002, ¶115. The POSA also would have been motivated to use dosing and treatment regimens that showed clinical responses. EX1002, ¶¶114-119. The POSA would have known of ongoing clinical trials regarding anti-PD-L1 antibody

treatments, including NCT664, which disclosed the administration of 10 mg/kg of an anti-PD-L1 antibody once every two weeks to treat various cancers. *Id.*, ¶114.

The POSA would also be aware that BMS had conducted a previous study with an anti-PD-1 antibody, *i.e.*, an antibody that is directed towards the same PD-1/PD-L1 pathway using a 60-minute intravenous infusion, *see infra* §VII.C, which was standard in the art, and Brahmer disclosed that this antibody had shown preliminary evidence of antitumor activity and that a response to treatment was associated with tumor PD-L1 expression. EX1002, ¶116; EX1019; *Custom Accessories, Inc. v. Jeffrey–Allan Indus.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (“[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art”).

The '299 patent does not state that other infusion times would not work, or would be any less effective. EX1001. This is not a case of unexpected results at 60 minutes relative to other infusions times.

The POSA would have thus been motivated to combine the teachings of WO874 with the teachings of NCT664, Inman, and Brahmer. EX1002, ¶¶123-126. In view of WO874, the POSA would have looked to the teachings of NCT664, Inman, and Brahmer. *Id.*

The POSA would have been motivated to combine WO874 specifically with NCT664, Inman, and/or Brahmer. *Id.*

First, 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 Inman to determine PD-L1 expression patterns on bladder cancers. EX1002, ¶125. Inman teaches that bladder cancers express PD-L1. Inman also provides the motivation to use the dosing regimen of WO874 to treat bladder cancer by showing that "our study indicates that T lymphocytes may represent a critical immune barrier against tumor progression in bladder cancer. Given that *in vivo* antibody-mediated blockade has recently been shown to potentiate antitumoral immunity in murine studies, it appears that PD-L1 may serve as a viable prognostic marker to predict UC risk as well as a rational immunotherapeutic target for the treatment of urothelial bladder carcinoma." EX1065, 1505, EX1002, ¶125. The POSA would have been motivated to target the PD-L1 pathway via the dosing regimen of WO874 (specifically 10 mg/kg of an anti-PD-L1 antibody once every two weeks). EX1027, 75:20-25.

Second, the POSA would have been motivated to use Brahmer's infusion rate to arrive at the Challenged Claims. EX1002, ¶126. Both Brahmer and WO874 are directed to administration of antibodies targeting the PD-1/PD-L1 pathway to treat cancer, including bladder cancer: Brahmer describes administration of an anti-PD-1 antibody; and WO874 describes administration of an anti-PD-L1 antibody. *Id.* Thus, the POSA would have been motivated to

specifically look to Brahmer’s infusion rate to apply to administration of MDX-1105. *Id.* The POSA would have expected that by also targeting the PD-1/PD-L1 pathway by antibody therapy, Brahmer’s disclosure would be an obvious choice for the infusion rate for administration of MDX-1105 targeting the same pathway. *Id.*

Third, the successful use of anti-PD-L1 and anti-PD-1 antibodies (*see* EXS1019, 1022, 1025, and 1026), would have motivated the POSA to look to the ongoing successful clinical trial in human patients. EX1002, ¶¶75-80. The POSA would have been specifically motivated to look to NCT664 which disclosed the use of anti-PD-L1 antibodies for the treatment of various cancers using the same dosage as WO874. *Id.*

2. The POSA Would Have Had a Reasonable Expectation of Success

The POSA would have reasonably expected that an anti-PD-L1 antibody would successfully treat bladder tumors. EX1002, ¶¶127-135.

The ’299 patent’s claims do not require clinical efficacy. *See* §VI.B, *supra*. All that is required is that the POSA reasonably expect that the dosing region would be useful in treating cancer by achieving some degree of anti-cancer activity, not necessarily clinical efficacy. *See Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 99 at 24-30 (PTAB Sept. 21, 2017) (claims were not “limited to a clinically effective treatment” and “Petitioner need not establish a

reasonable likelihood of a successful phase III trial or FDA approval to demonstrate obviousness”). Even if the preamble required clinical efficacy, the POSA would have reasonably expected successfully treating bladder cancer patients with the claimed dosing regimen for the reasons discussed below.

WO874 discloses that “[t]he ability of a compound to inhibit tumor growth can be evaluated in an animal model system *predictive of efficacy* in human tumors.” EX1027, 77:4-5; EX1002, ¶128. It goes on to state that “[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; EX1002, ¶128. The ’299 patent specification concedes the same, stating that the “ability of a therapeutic agent to promote disease regression can be evaluated using *a variety of methods* known to the skilled practitioner, such as in human subjects during clinical trials, *in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in in vitro assays*.” EX1001, 11:24-29 (emphases added); EX1002, ¶129.

Consistent with the disclosure of WO874 and the ’299 patent, WO874 provides a reasonable expectation of success regarding the use of an anti-PD-L1 antibody to treat bladder tumors. EX1027, 21:1-6; 1:19-20; 80:21-82:9; EX1002, ¶¶128-129. 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. EX1002, ¶¶128-129. Thus, WO874 in view of Inman provides a reasonable expectation of success for the administration of anti-PD-L1 antibodies to treat bladder tumors. EX1002, ¶¶127-135.

To the extent the POSA would have any remaining doubt, the POSA would have also reasonably expected success in view of the disclosures of Brahmer and NCT664. EX1002, ¶¶130-135. The POSA was aware that PD-1/PD-L1 monoclonal antibodies had achieved clinical activity against tumors.⁶ *Id.* The POSA was aware that MDX-1106 *i.e.*, nivolumab, had undergone clinical trials where anti-tumor clinical activity was observed in patients. EX1019, 3169; *see also* EX1029; EX1002, ¶¶130-135. The POSA would understand that the successful clinical results of nivolumab, BMS' anti-PD-1 immunotherapy, teaches that other monoclonal antibodies that disrupt the interaction of PD-1 with PD-L1 would be successful in treating tumors that express PD-L1. EX1002, ¶¶130-135.

It was also well known that tumor cells that express PD-L1 are responsive to treatment with anti-PD-L1 antibodies. Indeed, Brahmer found a correlation

⁶ In addition to the MDX-1106 anti-PD-1 clinical trial, there were at least three ongoing or completed clinical trials studying the safety and efficacy of an anti-PD-1 antibody, and at least two ongoing clinical trials studying the safety and efficacy of an anti-PD-L1 antibody prior to the '299 patent, discussed *supra*.

between membranous PD-L1 tumor cell expression and the likelihood of tumor regression with treatment by an anti-PD-1 antibody. EX1002, ¶131; EX1019, 3170. It explicitly teaches that “tumor cell surface expression of [PD-L1] may be a predictor of responsiveness to PD-1 blockade.” EX1019, 3712; EX1002, ¶131. The POSA would reasonably expect an anti-PD-L1 antibody to successfully treat PD-L1 positive tumors in light of Brahmer. EX1002, ¶131. The anti-PD-L1 antibody would be expected to attack the same pathway, the PD-1/PD-L1 interaction, that gives rise to tumor evasion. *Id.* Thus, Brahmer teaches the POSA that an anti-PD-L1 antibody is reasonably likely to achieve a clinical response. *Id.*

The fact 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 is established by BMS’ NCT664 clinical trial protocol:

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).

EX1038, 27; EX1002, ¶132.

The POSA would thus have reasonably expected that anti-PD-L1 monoclonal antibodies would treat bladder tumors in light of these prior art

disclosures. EX1002, ¶¶130-135. *See Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (“This court has long rejected a requirement of ‘[c]onclusive proof of efficacy’ for obviousness.”); *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success [A]ll that is required is a reasonable expectation of success.”); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

That knowledge alone establishes a reasonable expectation of success. But, here, the POSA also knew that the specific methods of treatment disclosed by NCT664 using an anti-PD-L1 antibody were successful. EX1002, ¶¶76-80, 134. Numerous pre-priority date publications report on the success that MDX-1105 had in NCT664:

- Hwu 2010 (EX1022) at 3 (emphasis added): “MDX-1105 has been tolerated by all [melanoma] patients. Most adverse events were mild and were related to inflammatory responses in the tumors, not immune-related toxicity. ***Clinical responses were observed at all dose levels (1 mg/kg to 10 mg/kg every 2 weeks). Durable 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.***”
- Topalian 2011 (EX1025) at 4833: “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.”

- Topalian 2012 (EX1026) at 210: “A blocking antibody against the ligand B7-H1/PD-L1 (MDX-1105/BMS-936559) is also currently in phase I clinical testing in patients with advanced solid tumors, and it has shown preliminary evidence of activity against melanoma, kidney cancer and NSCLC. These complementary results further validate the PD-1 pathway as a target for immunotherapy.”

This, the POSA would reasonably expect success in using the WO874 and NCT664 dosing regimens, combined with Brahmer’s infusion rate to achieve anti-tumor activity in human subjects. EX1002, ¶¶125-135. To the extent BMS contends that this does not support a reasonable expectation of success with respect to bladder cancer, that position would directly conflict with BMS’ position during prosecution. *See* EX1024, 219-221; 255-58 (noting that the specification listed “cancer of the bladder” as an example that could be treated based on “indications of a very broad applicability of anti-PD-L1 immunotherapy provided herein.”). WO874 similarly discloses bladder cancer as one of the cancers that could be treated using an anti-PD-L1 antibody and NCT664 and Brahmer also provide the POSA with an indication of the broad applicability of anti-PD-L1 immunotherapy to PD-L1 positive cancers. *See* §VII.A-C; EX1002, ¶¶110-113. Even if the

preambles required clinical efficacy, the POSA would also reasonably expect the combination to be clinically efficacious. *Id.* Even if the preambles required clinical efficacy, it is axiomatic that “inherency may supply a missing claim limitation in an obviousness analysis.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014). The Federal Circuit, in *In re Montgomery*, noted that “even if the claim includes an efficacy requirement,” that “efficacy is inherent in carrying out the claim steps.” 677 F.3d 1375, 1381 (Fed. Cir. 2012). Similarly, as each step of the claim body is obvious over NCT664, Brahmer, and Inman, any efficacy required by the preamble would be inherent in carrying out those claim steps. EX1002, ¶135 (discussing Brahmer 2012 and showing the efficacy is inherent).

B. The Prior Art Discloses Each and Every Limitation of Claims 1-24

1. Claim 1

a) “A method of treating a tumor in a human subject in need thereof . . .”

Claim 1 is directed to a “method of treating a tumor in a human subject in need thereof.” EX1001, cl. 1.

WO874 discloses methods of treating cancers in human subjects using anti-PD-L1 antibodies. EX1027, 21:1-6; EX1002, ¶¶137-138. WO874 also discloses that PD-L1 expression has been found in several murine and human cancers, including bladder and colon cancer. *Id.*, 1:19-20; 80:21-82:9 (“Examples of other

cancers that may be treated using the methods of the invention include . . . cancer of the bladder.”); EX1002, ¶¶137-138. NCT664 discloses a clinical trial administering an anti-PD-L1 antibody (MDX-1105/BMS-936559) to subjects with various cancers. EX1021; EX1002, ¶¶137-138.⁷ Brahmer reports that an anti-PD-1 antibody, nivolumab, showed evidence of anti-tumor activity in humans and that membranous PD-L1 expression was associated with tumor suppression. EX1002, ¶¶86-87. The POSA would thus understand from WO874, NCT664, and Brahmer that an anti-PD-L1 antibody would also achieve anti-tumor activity by targeting the same pathway. EX1002, ¶¶137-142.

WO874 teaches that bladder cancer is treatable with anti-PD-L1 antibodies. It was known that certain bladder tumors express PD-L1, as taught by Inman. Inman teaches that PD-L1 is a “predictive marker” for tumor stage progression in bladder cancers and that PD-L1 plays a role in “neutralizing T cells that normally guard against cancer invasion.” EX1065, 1499, 1505. Inman states that its studies “might have important implications for antitumoral tumor immunotherapy.” *Id.* It would have thus been obvious to apply WO874’s methods of treatment to subjects with bladder cancer, given Inman’s disclosures. EX1002, ¶136-138.

⁷ This is the same clinical trial reported in the ’299 patent’s Examples. EX1001.

b) “comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks”

WO874 discloses 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; EX1002, ¶139. NCT664 discloses “MDX-1105 [intravenous] infusion, 5 cohorts, 0.3,1,3,10,15mg/kg/dose every 14 days for a total of 3 infusions” in its clinical trial. EX1021, 4; EX1002, ¶140.

Techniques for generating human monoclonal antibodies were well-known by skilled artisans (EX1002, ¶66), as also disclosed by WO874. EX1027, 56:1-58:16. Thus, it would have been routine for a skilled artisan to generate anti-PD-L1 antibodies. EX1002, ¶66.

The antibody MDX-1105 was known in the art prior to the critical date. EX1030, [0177] (“A specific example of an anti-[PD-L1] 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.”); EX1002, ¶67.

c) “wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion”

It would have been obvious to administer the anti-PD-L1 antibody intravenously over 60 minutes infusion in light of WO874, the general knowledge of the POSA, and Brahmer as of the critical date. EX1002, ¶¶141-144.

WO874 discloses the administration of anti-PD-L1 antibodies intravenously.

WO874 states that the “[p]referred routes of administration for antibodies of the invention include intravenous . . . , for example by injection or infusion.” EX1027, 77:13-24; 87:26-32. Brahmer also teaches administration of an anti-PD-1 antibody to treat tumors by 60-minute intravenous infusion at 10 mg/kg. EX1019; EX1002, ¶142.

The POSA would have also known that 60 minutes is a typical infusion time and either would have started with 60 minutes or would have quickly arrived at a 60-minute infusion through routine experimentation. EX1002, ¶¶118—119, 143. WO874 teaches that dosage “regimens are adjusted to provide the optimum desired response.” EX1027, 75:7-9. WO874 also teaches that in “therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required . . . and preferably until the patient shows partial or complete amelioration of symptoms of disease.” EX1027, 76:7-18.⁸ The POSA would routinely adjust the administration

⁸ The same teachings in WO874 are included in the ’299 patent. The ’299 patent teaches that “[d]osage regimens *are adjusted* to provide the optimum desired response, *e.g.*, a therapeutic response or minimal adverse effects.” EX1001, 25:35-37. Thus, BMS has admitted, both in WO874 and the ’299 patent, that such regimens are routinely adjusted.

time in evaluating the dose and administration of an anti-PD-L1 antibody.

EX1002, ¶143; *see Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 727 (Fed. Cir. 2017) (finding patent obvious where claimed steps “would have been discovered by routine experimentation while implementing known principles”); MPEP § 2144.05(II).

For example, the POSA, in evaluating a 10 mg/kg dosage, as disclosed by WO874, would have evaluated the administration of an anti-PD-L1 antibody at various shorter and longer time intervals, such as 30 minutes or 90 minutes, in determining an appropriate administration time. EX1002, ¶¶118-119, 143. The POSA would have been motivated to investigate shorter administration times as longer administration times require considerable healthcare resources and are inconvenient for patients. *Id.* Indeed, in the context of rituximab, another monoclonal antibody on the market prior to the '299 patent's priority date, POSAs investigated and determined that an infusion time of 60 minutes was safe and effective in 2011. EX1028; EX1002, ¶118. Thus, the POSA would have been motivated to adjust the administration time to 60-minute dosing. EX1002, ¶¶114-119, 143.

The POSA would have reasonably expected that a 60-minute intravenous infusion time would succeed. Evidence of a reasonable expectation of success “may flow from the prior art references themselves, the knowledge of one of

ordinary skill in the art, or, in some cases, from the nature of the problem to be solved.” *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000). The POSA would have been aware that most chemotherapies and numerous prior-art monoclonal antibodies, including those for the treatment of cancer, on the market had been administered as intravenous infusion over 60-minute periods as is better suited for hospitals and patients. EX1002, ¶144; 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). Given the numerous approved commercial monoclonal antibodies and the routine nature of 60-minute dosing, the POSA would have been confident that the 60-minute infusion time would be operable and if they had any doubt would have routinely tested the infusion time with reasonable expectation of its success. EX1002, ¶¶118-119, 143-144.

Brahmer itself expressly discloses that its anti-PD-1 antibody, which achieved clinical responses, was administered by intravenous infusion for 60 minutes at 10 mg/kg. EX1019, 3168 (describing “60-minute intravenous

infusion”). The POSA would have been motivated to use this same infusion rate for an anti-PD-L1 antibody given Brahmer’s reported success. EX1002, ¶142.

d) “wherein the tumor is derived from a bladder cancer”

This claim limitation is disclosed by WO874, or is obvious in view of Inman.

WO874 discloses that its methods of treatment with anti-PD-L1 antibodies apply to bladder cancer. EX1027, 80:21-82:9 (“Examples of other cancers that may be treated using the methods of the invention include . . . cancer of the bladder.”); EX1002, ¶145. Inman further identifies PD-L1 as a “predictive marker” for tumor stage progression in bladder cancers and that PD-L1 plays a role in “neutralizing T cells that normally guard against cancer invasion.” EX1065, 1499, 1505. Inman further concludes that its studies “suggest that BCG induces strong PD-L1 expression in host tissues that might have important implications for antitumoral tumor immunotherapy.” *Id.*, 1505. Thus, the POSA would understand Inman to confirm that PD-L1 plays a significant role in the development of certain bladder cancers and that there was a reasonable expectation that anti-PD-L1 antibody treatments would treat those tumors. EX1002, ¶¶93-96.

e) “wherein the tumor is refractory to a platinum-based chemotherapy”

This claim limitation is obvious over WO874, NCT664, Brahmer, and the general knowledge of the POSA. EX1002; ¶147.

The inclusion criteria for the clinical trial disclosed in 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 other forms of therapy, including standard of care platinum-based chemotherapy. EX1002, ¶147; EX1021, 5 (noting that subjects who failed “prior systemic platinum-based therapy” were included in trial). Indeed, platinum-based chemotherapy was considered the standard first-line treatment for patients with bladder cancer. EX1002, ¶147 (citing EX1067, 2432 (noting that “[c]isplatin-based combination chemotherapy is considered standard first-line treatment for patients with metastatic urothelial carcinoma”)). It would have been obvious to administer anti-PD-L1 antibodies to patients who were unsuccessfully treated with platinum-based chemotherapy as immunotherapy provides an alternative mechanism to treat refractory cancers. EX1002, ¶148. POSAs understood and would have been motivated to use anti-PD-L1 antibody treatments for bladder cancers that express PD-L1 where standard treatments such as platinum-based chemotherapy failed. EX1002, ¶¶147-148.

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 would understand relapsed and/or refractory cancers to include cancers which were unresponsive to pretreatment with platinum-based chemotherapy. EX1002, ¶149.

2. Claims 2 and 3

Claim 2 depends from claim 1 and further requires that the “tumor is advanced.” EX1001, cl. 2. Claim 3 also depends from claim 1 and further requires that the “tumor is locally advanced.” EX1001, cl. 3.

Brahmer reports that its clinical trial achieved reduction of tumor activity in patients “with advanced treatment-refractory solid tumors.” EX1019, 3168; EX1002, ¶154. NCT664 also discloses subjects “with selected advanced or recurrent solid tumors.” EX1021, 2; EX1002, ¶154.

A motivation to modify or combine may be derived from the prior art reference itself, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. *DyStar Textilfarben GmbH*, 464 F.3d at 1361. Given the teachings of WO874 regarding methods of treating cancer with anti-PD-L1 antibodies in view of the disclosures of NCT664, and Brahmer, the POSA would have been motivated to treat advanced or locally advanced tumors with anti-PD-L1 antibodies. EX1002, ¶155. The POSA would have reasonably expected success, given the data in WO874 and the disclosed efficacy of other monoclonal antibodies targeting the PD-1/PD-L1 pathway. *See supra* §§VII.A and VIII.A.2.

Claims 2 and 3 are obvious. EX1002, ¶¶151-155.

3. Claim 4

Claim 4 depends from claim 1 and further requires that the “tumor is metastatic.” EX1001, cl. 4.

WO874 states that anti-PD-L1 antibodies are “also useful for treatment of metastatic cancers, especially metastatic cancers that express PD-L1.” EX1027, 81:7-9.

Claim 4 is obvious. EX1002, ¶¶156-157.

4. Claim 5

Claim 5 also depends from claim 1 and requires that the “treatment lasts more than 12 weeks.” EX1001, cl. 5.

This limitation is disclosed by NCT664 or is obvious over the general knowledge of the POSA. NCT664 describes 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.

Moreover, the POSA would understand that immunotherapy treatment should generally be sustained and that treatment under 12 weeks would be unlikely to achieve the necessary clinical progress for patients. EX1002, ¶160.

Claim 5 is obvious. EX1002, ¶¶158-160.

5. Claim 6

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

WO874 describes “pharmaceutical compositions containing the [anti-PD-L1] antibodies.” EX1027, 20:31. It describes “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.

Claim 6 is obvious. EX1002, ¶¶161-162.

6. Claim 7

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

Claim 7 is obvious. EX1002, ¶¶163-165.

7. Claims 8 and 9

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.

WO874 discloses that “[e]xamples” of pharmaceutically acceptable salts include “base addition salts.” It further discloses that one such base addition salt is “sodium” and “the like.” EX1027, 72:30-73:10. The POSA reviewing WO874 would understand that sodium chloride is a salt containing sodium. EX1002, ¶169. Furthermore, WO874 also discloses that it may “be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions.” EX1027, 73:30-31.

Claims 8 and 9 are obvious. EX1002, ¶¶166-169.

8. Claims 10 and 11

Claim 10 depends from claim 1 and additionally requires that “at least 1% of tumor cells exhibit membrane PD-L1 expression.”⁹ EX1001, cl. 10. Claim 11 also depends from claim 1 and requires that “at least 5% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 11. These claim limitations are obvious over the prior art as it would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

WO874 discloses 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. Inman teaches that PD-L1 is in fact expressed on bladder tumors. EX1065, 1505. *See also* EX1009, 2:16-23 (PD-L1 has been “confirmed” in various tumor cells lines).

Examples 7 and 8 of WO874 further discuss experiments which show that anti-PD-L1 human monoclonal antibodies promote T-cell proliferation and reverse

⁹ The '299 patent does not suggest that it was unexpected that a tumor having 1% or 5% PD-L1 expressing cells would be responsive to anti-PD-L1 therapy. Given the known role of PD-L1 in assisting tumor evasion, the POSA knew by the critical date that a tumor in which 1% or 5% of tumor cells expressed PD-L1 would be a target for anti-PD-L1 therapy. EX1002, ¶174.

the suppression of T-cell proliferation. EX1027, 101-103. Given this disclosure, it would have been obvious to the POSA that anti-PD-L1 antibody treatment should be used to treat tumors where at least 1% or 5% of tumor cells exhibit membrane PD-L1 expression, *i.e.*, minimal PD-L1 expression. EX1002, ¶174. Indeed, 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. *Id.* The POSA would have thus been motivated to treat tumors where at least 1% or 5% of tumor cells in the treated tumor exhibit membrane PD-L1 expression. EX1002, ¶¶175-177.

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. Given the teachings of WO874 in view of NCT664, Inman, and Brahmer, the POSA would have been motivated to treat a subject with bladder cancer with an anti-PD-L1 antibody where at least 1% of those tumor cells exhibit membrane PD-L1 expression with a reasonable expectation of success. EX1002, ¶175.

Claims 10 and 11 are obvious. EX1002, ¶¶170-177.

9. Claims 12-15

Claims 12-15 respectively depend from claims 1-4 and add the same limitation to each claim. Claims 12-15 each further require that the claimed

methods further comprise “administering an anti-cancer agent.” EX1001, cls.

12-17. The ’299 patent does not define the term “anti-cancer agent.” However, it does describe that “an anti-cancer agent promotes cancer regression in a subject.”

Id., 11:32-33. Thus, the POSA would understand the additional claim limitation 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.

EX1002, ¶179.

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; 88:5-7 (discussing administration “with other known therapies, *e.g.*, an anti-cancer therapy, *e.g.*, radiation.”). WO874 further describes how the “[c]o-administration of the human anti-PD-L1 antibodies, or antigen binding fragments thereof, of the present invention with chemotherapeutic agents provides two *anti-cancer agents* which operate via different mechanisms.” *Id.*, 88:12-15. WO874 thus discloses the additional limitation of claims 12-15.

Claims 12-15 are obvious. EX1002, ¶¶178-180.

10. Claims 16-21

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

WO874 discloses that “PD-L1 blockade may also be combined with standard cancer treatments,” which the POSA would understand to encompass traditional treatments such as chemotherapy and radiotherapy. EX1027, 82:32; EX1002, ¶185. WO874 goes on to disclose that “PD-L1 blockade may be effectively combined with chemotherapeutic regimes.” EX1027, 82:32-33; *see also id.*, 88:12-18. It further discloses 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 further teaches the benefits of the co-administration of additional anti-cancer agents, such as “development of resistance to drugs or a change in the antigenicity of the tumor cells which would render them unreactive with the antibody.” *Id.*, 88:15-18. WO874 discloses these additional limitations in claims 16-21.

Claims 16-21 are obvious. EX1002, ¶¶181-186.

11. Claims 22 and 23

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. Claim 23 also depends from the method of claim 1 and further requires that the “platinum-based chemotherapy comprises cisplatin, carboplatin, or both.” These additional limitations would have also been obvious over NCT664 and the general knowledge of the POSA.

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. EX1002, ¶190. Cisplatin and carboplatin are, by definition, platinum-based therapies. *Id.* 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. *Id.* 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.

Id.

It would have been obvious 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. EX1002, ¶191.

Claims 22-23 are obvious. EX1002, ¶¶187-191.

12. Claim 24

Claim 24 depends from claim 1 and further requires “wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody.” EX1001, cl. 24. This additional limitation would have also been obvious over the general knowledge of the POSA.

The POSA would have understood that the administration of an antihistamine is routine before chemotherapy and immunotherapy as they are administered to prevent hypersensitivity and infusion reactions. EX1002, ¶193; EX1068. The POSA would have thus found it obvious to administer an antihistamine prior to the obvious method of treatment in claim 1. EX1002, ¶¶192-193.

IX. GROUND 2: CLAIMS 1-5, 10-11, AND 22-24 ARE UNPATENTABLE AS OBVIOUS OVER NCT664 IN VIEW OF BRAHMER AND INMAN

A. Overview Ground 2

Claim 1-5, 10-11, and 22-23 should be canceled under 35 U.S.C. § 103 by NCT664 in view Brahmer, and/or Inman. The teachings of NCT664, Brahmer, and Inman are discussed above. *See supra* §§VII.B-D.

1. The POSA Would Have Been Motivated to Combine the Prior Art

The POSA reviewing NCT664 would have been motivated to administer an anti-PD-L1 antibody treatment for bladder tumors and combine its teachings with the disclosures of Inman and Brahmer. EX1002, ¶195. 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. *Id.*, ¶196. NCT664 disclosed a clinical trial administering an anti-PD-L1 antibody at 10mg/kg once every two weeks to treat various cancers. *Id.*, ¶197; *see supra* §§VII.B and VIII.B.1.b. As explained above, *see supra* §VIII.A.2, the POSA would have understood that the clinical trial had achieved clinical responses in treating various cancers. EXS1022, 1025, 1026.

Given that 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. EX1002, ¶198. It was known by POSAs that

certain bladder tumors express PD-L1, as taught by Inman. *See supra* §VII.D.

Thus, the POSA would have had a motivation to treat bladder tumors that express PD-L1 with anti-PD-L1 antibodies over the teachings of NCT664 in view of Inman. EX1002, ¶198.

The POSA also would have been motivated to use dosing and treatment regimens which had achieved prior clinical success. EX1002, ¶199. The POSA would have known of ongoing clinical trials regarding anti-PD-L1 antibody treatments, including NCT664, which disclosed the administration of 10 mg/kg of an anti-PD-L1 antibody once every two weeks to treat subjects. *Id.* They would also have been aware that BMS had conducted a previous clinical study with an anti-PD-1 antibody, *i.e.*, an antibody directed towards the same PD-1/PD-L1 pathway using a 60-minute intravenous infusion, and that Brahmer disclosed that this antibody had shown preliminary evidence of antitumor activity and that a response to treatment was associated with PD-L1 tumor expression. *Id.*; EX1019.

The POSA would have been motivated to combine the teachings of NCT664 with the disclosures of Inman and Brahmer. In view of the NCT664 disclosure, the POSA would have looked to the teachings of Brahmer and Inman. EX1002, ¶¶195-199.

First, in view of the POSA's knowledge of PD-L1 and its role in tumor evasion, and the PD-L1 expression on bladder tumors, and the success of

anti-PD-1 treatment (*i.e.*, MDX-1106/nivolumab), the POSA would have looked to Inman to determine PD-L1 expression patterns of on bladder tumors. *See supra* §§VII.D and VIII.B.8; EX1002, ¶198.

Second, the POSA would have been motivated to use Brahmer's infusion rate, combined with the NCT664 dosing regimen to arrive at the Challenged Claims. EX1002, ¶199. Both Brahmer and NCT664 are directed to administration of antibodies targeting the PD-1/PD-L1 pathway to cancer patients: Brahmer describes administration of an anti-PD-1 antibody; and NCT664 describes administration of an anti-PD-L1 antibody. EX1002, ¶¶197-199. Thus, the POSA would have been motivated to specifically look to Brahmer's infusion rate to apply to administration of MDX-1105. *Id.* The POSA would have expected that by also targeting the PD-1/PD-L1 pathway by antibody therapy, Brahmer's disclosure would be an obvious choice for the infusion rate for administration of MDX-1105 targeting the same pathway. *Id.*

2. The POSA Would Have Had a Reasonable Expectation of Success

The POSA, so motivated, would also have reasonably expected success using the NCT664 dosing regimen in treating bladder tumors in a human subject. EX1002, ¶200.

The prior art teaches that PD-L1 interactions with PD-1 inhibit activation and actions of T cells. *See supra*, §IV.A.1. It was also well known that preventing

PD-1/PD-L1 signaling increases the immune response against cancer cells. *See supra*, §IV.A.2. It was also well known that cancer cells, including bladder cancer cells express PD-L1, and blocking PD-1 inhibitory signaling via antibodies to PD-1 would treat these cancers. *Supra*, §IV.A.3.

The POSA also would have known of the success that anti-PD-1 clinical trials had exhibited in view of the disclosures of NCT664 and Brahmer, which showed that other monoclonal antibodies which targeted the PD-1/PD-L1 pathway had achieved clinical success. *Supra* §VIII.A.2. Indeed, Brahmer's teaching regarding nivolumab/MDX-1106 would have given the POSA a reasonable expectation of success in using an anti-PD-L1 antibody to treat tumors. NCT664 would also create a reasonable expectation of success as numerous pre-priority date publications reported on the success that MDX-1105, an anti-PD-L1 antibody, had in the NCT664 trial. These include the Hwu 2010, Topalian 2011, and Topalian 2012 references. *Supra* VIII.A.2.

As explained above, *see supra* §VI.B, even if the preamble required clinical efficacy, such efficacy would be inherent in what were already obvious claim steps over the prior art. *See Montgomery*, 667 F.3d at 1381.

B. The Prior Art Discloses Each and Every Limitation of Claims 1-5, 10-11, and 22-24

1. Claim 1

a) “A method of treating a tumor in a human subject in need thereof . . .”

NCT664 discloses a clinical trial administering an anti-PD-L1 antibody (MDX-1105) to subjects with various cancers. *Supra*, §§VII.B and VIII.B.1.a; EX1021, 3-4. NCT664 discloses that “[t]he primary purpose of this study is to determine if MDX-1105 is safe and tolerated when administered every 14 days to subjects with selected advanced or recurrent solid tumors.” EX1021, 3. The inclusion criteria included “advanced or recurrent solid tumors (renal cell carcinoma, non-small cell lung cancer, malignant melanoma, or epithelial ovarian cancer will be enrolled in the study.” *Id.* Given the reported success of the NCT664 trial, *see supra* §VIII.A.2, POSAs would expect MDX-1105 to treat tumors in human subjects.

Brahmer discloses that an anti-PD-1 antibody, nivolumab, showed evidence of anti-tumor activity in humans and that membranous PD-L1 expression was associated with tumor suppression. *Supra*, §VII.C. The POSA would understand Brahmer to also teach that an anti-PD-L1 antibody would similarly treat human tumors by affecting the same PD-1/PD-L1 pathway. *See supra* §§VII.C and VIII.B.1.a.

b) “comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks”

NCT664 discloses “MDX-1105 [intravenous] infusion, 5 cohorts, 0.3,1,3,10,15mg/kg/dose every 14 days for a total of 3 infusions” in its Phase 1 clinical trial. EX1021, 4.

c) “wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion”

It would have been obvious to administer the anti-PD-L1 antibody intravenously over 60 minutes infusion in light of Brahmer and the general knowledge of the POSA as of the priority date. Brahmer disclosed administration of an anti-PD-1 antibody to treat tumors by 60-minute intravenous infusion at 10 mg/kg. EX1019, 3168; *see supra* §§VII.C and VIII.B.1.c.

The POSA would have also, through routine experimentation, determined that a 60-minute infusion of an anti-PD-L1 antibody would be effective. *See supra* §§VII.C and VIII.B.1.c.

d) “wherein the tumor is derived from a bladder cancer”

NCT664 discloses the treatment of cancers using anti-PD-L1 antibodies. *See supra* §VII.B and VIII.B.1.d. Inman further teaches that PD-L1 is a “predictive marker” for tumor stage progression in bladder cancers and that PD-L1 plays a role in “neutralizing T cells that normally guard against cancer invasion.” EX1065, 1499, 1505. Inman further concludes that its studies “suggest that BCG induces strong PD-L1 expression in host tissues that might have important

implications for antitumoral tumor immunotherapy.” *Id.* Thus, the POSA would understand Inman to confirm that PD-L1 plays a significant role in the development of certain bladder cancers and that there was a reasonable expectation that anti-PD-L1 antibody treatments, such as those described in NCT664, would treat those tumors. EX1002, ¶¶209-210.

e) “wherein the tumor is refractory to a platinum-based chemotherapy”

This claim limitation is obvious over NCT664, Brahmer, and the general knowledge of the POSA.

The inclusion criteria for the clinical trial disclosed in NCT664 state that the treated malignancies include refractory cancers, including patients who previously failed chemotherapy or radiotherapy. EX1021, 3-4. The POSA would understand relapsed and/or refractory cancers to include subjects who were unresponsive to other forms of therapy, including standard of care platinum-based chemotherapy. EX1002, ¶¶211-213; EX1021, 5 (noting that certain subjects who failed “prior systemic platinum-based therapy” were included in trial). Indeed, platinum-based chemotherapy was considered the standard first-line treatment for patients with bladder cancer. EX1002, ¶211 (citing EX1067, 2432). It would have been obvious 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.

EX1002, ¶¶211-213. POSAs understood this well before May 2012 and would have 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. EX1002, ¶212.

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 would understand relapsed and/or refractory cancers to include cancers which were unresponsive to pretreatment with platinum-based chemotherapy. EX1002, ¶213.

2. Claims 2 (“tumor is advanced”) and 3 (“tumor is locally advanced”)

Brahmer reports that its clinical trial with 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, 2.¹⁰ The POSA would have thus been

¹⁰ Further, NCT664 involved Phase 1 clinical testing in patients “advanced or recurrent solid tumors,” and the anti-PD-L1 antibody showed preliminary evidence of activity. EX1021, 3; EX1026, 210.

motivated to treat advanced or locally advanced tumors with anti-PD-L1 antibodies. EX1002, ¶¶218-219. The POSA would have reasonably expected success given the disclosed efficacy of these monoclonal antibodies targeting the PD-1/PD-L1 pathway. *See supra* §VIII.A.2.

Claims 2 and 3 are obvious. EX1002, ¶¶215-219.

3. Claim 4 (tumor is metastatic)

NCT664 states that it treated advanced/metastatic epithelial ovarian cancer. EX1021, 3, 5. Additionally, Brahmer discloses that nivolumab was effective in treatment-refractory metastatic solid tumors. EX1019. 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. EX1002, ¶221.

Claim 4 is obvious. EX1002, ¶¶220-221.

4. Claim 5 (“treatment lasts more than 12 weeks”)

This limitation is disclosed by NCT664 or is obvious over the general knowledge of the POSA. NCT664 describes 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. Moreover, the POSA would understand that immunotherapy treatment for cancer should

generally be sustained and that treatment under 12 weeks would be unlikely to achieve the necessary clinical progress for patients. EX1002, ¶224.

Claim 5 is obvious. EX1002, ¶222-224.

5. Claims 10 (“at least 1% of tumor cells exhibit membrane PD-L1 expression”) and 11 (“at least 5% of tumor cells exhibit membrane PD-L1 expression”)

These claim limitations are obvious over the prior art as it would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

Inman discloses that PD-L1 is expressed on bladder tumors and is associated with tumor progression. *See supra* §VII.D. Thus, the POSA would understand in light of Inman that the tumor cells in the treated tumor must exhibit a minimal degree of membrane PD-L1 expression to be treated with an anti-PD-L1 antibody. The '299 patent does not suggest that it was unexpected that a tumor having 1% or 5% PD-L1 expressing cells would be responsive to anti-PD-L1 therapy. Given the known role of PD-L1 in assisting tumor evasion, the POSA knew by the critical date that a tumor in which 1% or 5% of tumor cells expressed PD-L1 would be a target for anti-PD-L1 therapy. EX1002, ¶174.

Claims 10 and 11 are obvious. EX1002, ¶¶225-232.

6. Claims 22 (“platinum-based chemotherapy is a platinum-based doublet chemotherapy”) and 23 (“platinum-based chemotherapy comprises cisplatin, carboplatin, or both”)

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

The inclusion criteria for the clinical trial disclosed in NCT664 state that the treated malignancies include relapsed/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 other forms of therapy, including standard of care platinum-based chemotherapy. EX1002, ¶236; EX1021, 5 (noting that certain subjects who failed “prior systemic platinum-based therapy” were included in trial). Indeed, platinum-based chemotherapy and platinum-based doublet chemotherapy were considered the standard first and second-line treatment for patients with bladder cancer, respectively. EX1002, ¶232 (citing EX1067, 2432). 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. EX1002, ¶236.

It would have been obvious 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. EX1002, ¶¶236-237. POSAs understood this well before May 2012 and would have been motivated to use anti-PD-L1 antibody treatments for cancers that express PD-L1, including bladder cancer, where standard treatments platinum-based chemotherapy failed. EX1002, ¶237.

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 would understand relapsed and/or refractory cancers to include cancers which were unresponsive to pretreatment with platinum-based chemotherapy. EX1002, ¶236.

Claims 22 and 23 are rendered obvious. EX1002, ¶¶233-237.

7. Claim 24 (“wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody”)

This additional limitation would have also been obvious over the general knowledge of the POSA.

The POSA would have understood that the administration of an antihistamine is routine before chemotherapy and immunotherapy as they are administered to prevent hypersensitivity and infusion reactions. EX1002, ¶239; EX1068. The POSA would have thus found it obvious to administer an antihistamine prior to the obvious method of treatment in claim 1. EX1002, ¶¶238-239.

X. GROUND 3: CLAIMS 6-9 AND 12-21 ARE UNPATENTABLE AS ARE OBVIOUS OVER NCT664 IN VIEW OF BRAHMER, INMAN, AND IRVING

A. Overview Ground 3

Claims 6-9 and 12-21 should be canceled under 35 U.S.C. § 103 by NCT664 in view of Brahmer, Inman, and Irving. The teachings of NCT664, Brahmer, and Inman are discussed above. *See supra* §§VII.B-D. In combination with these references, the teachings of Irving render obvious claims 6-9 and 12-21. The '299 patent itself provides very little description to support the additional formulation limitations of claims 7-23. It provides general laundry-list information (EX1001, 25:20-34) that is routine knowledge to the POSA and would be contained in any antibody patent or patent application, including Irving and Honjo-Freeman. EXS1058 and 1009.

The POSA would have a motivation to combine the teachings of NCT664, Brahmer, and Inman. *See supra* §IX.A.1; EX1002, ¶241. The POSA would similarly have a motivation to combine the teachings of Irving, which is similarly directed towards the use of anti-PD-L1 antibodies to treat tumors and provides further disclosures regarding the use of anti-PD-L1 antibodies in pharmaceutical compositions. *Id.*

The POSA would also have a reasonable expectation of success based on the teachings of NCT664, Inman, and Brahmer, as explained above. *See supra*

§IX.A.2; EX1002, ¶242. Irving further teaches the effectiveness of anti-PD-L1 antibodies in achieving anti-tumor activity and would support the POSA's reasonable expectation of success. *Id.*

B. The Prior Art Discloses Each and Every Limitation of Claims 6-9, 12-21

1. Claims 6 (“the anti-PD-L1 antibody is formulated in a pharmaceutical composition”) and 7 (“pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, ...”)

These limitations are disclosed by Irving. Irving discloses “anti-PD-L1 antibodies, nucleic acids encoding the same, therapeutic compositions thereof.” EX1058, Abstract. Irving discloses in great detail the various components of pharmaceutical formulations of anti-PD-L1 antibodies, including salts, antioxidants, and carriers. EX1058, [0389]; *see also* [0390]-[0397].

Claims 6 and 7 are obvious. EX1002, ¶¶243-247.

2. Claims 8 (“salt comprises a sodium salt”) and 9 (“salt comprises sodium chloride”)

Irving discloses these limitations. Irving discloses that pharmaceutically-acceptable bases include “metals such as . . . sodium,” which is a pharmaceutically-acceptable salt. EX1058, [0213]; EX1002, ¶249. It further discloses that “[p]harmaceutically acceptable” salts include those derived from base addition salts. EX1058, [214]. The POSA would understand that such salts would include sodium-derived salts such as sodium chloride. *Id.*

Claims 8 and 9 are obvious. EX1002, ¶¶248-249.

3. Claims 12-15 (“administering an anti-cancer agent”)

The ’299 patent does not define the term “anti-cancer agent.” However, it does describe that “an anti-cancer agent promotes cancer regression in a subject.” EX1001, 11:32-33. The POSA would understand the additional claim limitation to require the administration of an anti-cancer agent other than the anti-PD-L1 antibody administered intravenously by the methods of claims 1-4. *Supra*, §VIII.B.9.

Irving discloses “[i]n the treatment of cancer, any of the previously described conventional treatments for the treatment of cancer immunity may be conducted, prior, subsequent or simultaneous with the administration of the anti-PD-L1 antibodies of the invention. Additionally, the anti-PD-L1 antibodies of the invention may be adminstrered [sic] prior, subsequent or simultaneous with conventional cancer treatments, such as the administration of tumor-binding antibodies (e.g., monoclonal antibodies, toxin-conjugated monoclonal antibodies) and/or the administration of chemotherapeutic agents.” EX1058, [0429].

Claims 12-15 are obvious. EX1002, ¶¶250-252.

4. Claims 16-21 (anti-cancer agent “is a [chemotherapy/radiotherapy]”)

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.

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

Irving discloses the administration of an anti-PD-L1 antibody “in combination with a chemotherapeutic agent.” EX1058, [0032]. It discusses “[t]raditional therapies for cancer,” such as “radiation therapy” and how such “conventional treatments for the treatment of cancer immunity may be conducted . . . simultaneous with the administration the anti-PD-L1 antibodies of the invention.” *Id.*, [0428]-[0429].

Claims 16-21 are obvious. EX1002, ¶¶253-257.

XI. GROUND 4: CLAIMS 10 AND 11 ARE OBVIOUS OVER WO874 IN VIEW OF NCT664, BRAHMER, AND NAKANISHI

As explained in Ground 1, dependent claim 10 requires that “at least 1% of tumor cells exhibit membrane PD-L1 expression.” EX1001, cl. 10. Claim 11 requires that “at least 5% of tumor cells exhibit membrane PD-L1 expression.” *Id.*, cl. 11. For the reasons explained in Grounds 1 and 2, these limitations are obvious over the prior art as it would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

Claims 10 and 11 would have further been obvious over WO874 in view of NCT664, Brahmer, and Nakanishi. Nakanishi teaches that PD-L1 expression on bladder cancer is very high. EX1002, ¶¶259-260. Specifically, Nakanishi teaches that in “all 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%).” EX1066, 1175.

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. EX1002, ¶¶259-260. Nakanishi teaches that bladder cancers express PD-L1 at a percentage well above 1% and 5%. *Id.* Nakanishi also provides the motivation to use the dosing regimen of WO874 to treat bladder cancer by showing 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, EX1002, ¶¶259-260.

As in Grounds 1 and 2, the POSA would have reasonably expected success in using the dosing regimens of WO874 and NCT664, combined with the Brahmer infusion rate to achieve anti-tumor activity in human subjects. *See* §§VIII.B.1.c and IX., *supra*; EX1002, ¶261. Even if the preambles required clinical efficacy, the POSA would also reasonably expect the combination to be clinically

efficacious. *Id.* It would have been obvious to combine Nakanishi, which teaches PD-L1 expression patterns on bladder cancers, EX1002, ¶¶259-260, with WO874, NCT664 and Brahmer, since all are directed towards the use of anti-PD-L1 antibodies to disrupt the PD-1/PD-L1 pathway to treat tumors.

Claims 10 and 11 are obvious. EX1002, ¶¶258-264.

XII. SECONDARY CONSIDERATIONS CANNOT REBUT THE STRONG SHOWING OF OBVIOUSNESS

It is Patent Owner's burden to establish secondary considerations of nonobviousness to overcome Petitioner's strong *prima facie* showing of obviousness. As here, where a strong *prima facie* obviousness showing exists, the Federal Circuit has repeatedly held that secondary considerations may not dislodge the primary conclusion of obviousness. *See, e.g., Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007); *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (secondary considerations must be limited to the features of the claimed invention in order to find a nexus and the evidence of secondary considerations must be the direct result of the unique characteristics of the patent claims).

The '299 patent attributes no significance to the limitations in the claims and Patent Owner cannot show a nexus between any secondary considerations and the claims. Indeed, Petitioner is not aware of any relevant evidence of secondary considerations and there is no evidence of the claimed invention achieving

unexpected results. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). BMS does not market an anti-PD-L1 antibody product and any commercial success of an anti-PD-L1 antibody would merely be due to features which were taught by the prior art. *See Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) (“if the feature that creates the commercial success was known in the prior art, the success is not pertinent”).

XIII. DISCRETIONARY DENIAL IS NOT WARRANTED

Under 35 U.S.C. § 325(d), the Board uses a two-part framework to evaluate whether to institute: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and (2) if the first part is satisfied, whether the petition has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate BmbH*, IPR2019-01469, Paper 6 at 6-11 (P.T.A.B. Feb. 13, 2020) (precedential).

The evidence identified in this Petition was either not before the Examiner or not fully considered during prosecution. The Examiner did not cite *any prior art* in any Office Action. The only rejection issued by the Examiner was a non-final rejection based on § 112 grounds. EX1024, 216-222. WO874 was disclosed to the Office in an Information Disclosure Statement amongst 21 other references (EX1024, 198; not including the hundreds of other references included in BMS’

other Information Disclosure Statements), but it was never the subject of any prior art rejections during prosecution. NCT664 and Inman were never disclosed to the Office, and Brahmer was raised in an Information Disclosure Statement with 70 other references. EX1024, 199. None of these references were the basis for any rejection. Thus, the same art or substantially the same art or arguments were not presented to the Patent Office.

In addition, the Examiner erred by not meaningfully evaluating the references relied on by Grounds 1, 2, and 3, such as WO874, NCT664, Brahmer, and Inman. As explained above, *see supra* §§VII.A, VII.B, WO874 taught methods of treating bladder cancer with anti-PD-L1 antibodies and NCT664 discloses BMS' clinical trial of an anti-PD-L1 antibody, which POSAs knew had shown efficacy. Brahmer taught that ***tumor cell surface expression of PD-L1*** appeared to correlate with the likelihood of response to treatment and Inman taught that bladder cancers express PD-L1. *see supra* §§VII.C, VII.D. The Examiner should have determined that the claims were obvious in light of these disclosures.

In addition, the Examiner did not have the benefit of Dr. Jabbour's declaration, which explains what the POSA would have understood from the asserted references as of BMS' earliest filing date. EX1002.

Any argument for non-institution under § 325(d) is misplaced, and Dana-Farber respectfully requests that the Board institute trial on the grounds presented in this Petition.

XIV. CONCLUSION

Based on the foregoing and the accompanying expert declarations, the Challenged Claims are unpatentable as obvious. Accordingly, Petitioner requests *inter partes* review of the Challenged Claims.

Dated: December 29, 2022

Respectfully Submitted,

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Petition for *Inter Partes* Review

Certification of Word Count

I certify that the Petition for *Inter Partes* Review filed herewith has a word count of 13,957 words, as determined by the Microsoft Word word-processing software used to create this paper. The above word count excludes the table of contents, exhibit list, the certificates of service and word count, and mandatory notices.

Dated: December 29, 2022

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IPR2023-00252

Petition for *Inter Partes* Review

Certification of Service

I certify that true and correct copies of the foregoing *Inter Partes* Review of U.S. Patent No. 10,138,299 B2 and Exhibits 1001-1050 and 1058-1070 were served on December 29, 2022 via FedEx® to the attorneys of record for U.S. Patent No. 10,138,299 B2 as evidenced on Patent Center on December 29, 2022, namely:

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