

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 IPR2023-000249

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

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

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO.
10,323,092 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”)
1016	Iwai et al., <i>PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells</i> , 17(2) Int. Immunol. 133 (2004) (“Iwai 2004”)
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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1020	National Institutes of Health, <i>A Study of Atezolizumab (an Engineered Anti-Programmed Death-Ligand 1 [PDL1] Antibody) to Evaluate Safety, Tolerability Pharmacokinetics in Participants With Locally Advanced or Metastatic Solid Tumors</i> , NCT01375842 clinicaltrials.gov (June 16, 2011) (“NCT ’842”)
1021	National Institutes of Health, <i>Multiple Ascending Dose (MDX1105-01) (Anti-PDL1)</i> , NCT00729664 clinicaltrials.gov (First posted August 7, 2008) (“NCT664”)
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. 10,323,092 B2 (“the ’092 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”)
1028	Tuthill et al., <i>Rapid infusion of rituximab over 60 min</i> , 82 Eur. J. Haematol. 322 (2009) (“Tuthill 2009”)
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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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”)
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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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1049	U.S. Patent No. 10,308,714 ("the '714 patent")
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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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Statutes

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Dana-Farber Cancer Institute, Inc. (“Dana-Farber” or “Petitioner”) requests *inter partes* review (“IPR”) of claims 1-25 (the “Challenged Claims”) of U.S. Patent 10,323,092 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 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, Regeneron, AstraZeneca Pharmaceuticals LP, Novartis AG and others to invest in commercializing antibodies targeting the PD-1/PD-L1 pathway.

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

The path from invention to commercial therapeutic can sometimes lead to unexpected or surprising findings that are inventive in their own right. While time 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 '092 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 10mg/kg every two weeks to treat non-small cell lung cancer ("NSCLC"). BMS' NCT664 disclosure

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).

was highly relevant to prosecution of the pending claims, but BMS failed to disclose NCT664 to the Examiner.

NCT664 fully anticipates the Challenged Claims but for two prosecution amendments: that the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; and that at least 1% of tumor cells exhibit membrane PD-L1 expression. The '092 specification makes clear that these limitations are unremarkable, routine, predictable and nothing more than practicing the prior art for infusion time and tumor type. The '092 patent mentions infusion time only once without noting anything significant about 60 minutes as compared to other infusion times. EX1001, 67:7. 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. And as explained in Section §VII.B, Brahmer discloses that BMS' anti-PD-1 antibody, which achieved clinical response, was administered by intravenous infusion for 60 minutes at 10 mg/kg.

Similarly, the Challenged Claims merely refer in numerical terms to a similar concept that the '048 patent describes as “over-express[ion]” of PD-L1. The '092 patent describes a “threshold” level of expression as “at least 0.01%, at least 0.1%, at least 1%, or at least 5 %” of tumor cells expressing

membranous PD-L1. EX1001, 49:61-64. Interestingly, the '092 patent sets 5% as the positivity threshold for expressing PD-L1 (*see* EX1001, 62:67-63:2), which makes clear the arbitrary, non-inventive selection of “at least 1%” expression. Further, as explained in Section §VII.C, Mu teaches that NSCLC cells are significantly more likely to be positive for PD-L1 expression and that PD-L1 expression in tumor cells plays a role in resisting an immune response and promote tumor progression. Quite plainly, targeting anti-PD-L1 antibodies to tumor cells over-expressing PD-L1 and the expectation of response in populations with expression of at least 1% are taught by the art.

The '092 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 or surprising results or by overcoming technical problems encountered in drug development, but rather through superficial prosecution amendments that specify dosing parameters devoid of any unexpected or surprising result and that are untethered to solving any technical problem and unremarkable to the skilled artisan. The '092 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 Patents. 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	1-6 and 24-25	§ 103	NCT664 in view of Brahmer and Mu
2	7-23	§ 103	NCT664 in view of Brahmer, Mu, and Irving
3	1-25	§ 103	WO874 in view of Mu, NCT664, and Brahmer

³ See e.g., <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. (EXS1002 and 1003).

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

Petitioner certifies that the '092 patent is available for IPR, *see* 37 C.F.R. § 42.102(a), and that it is not barred or estopped from requesting 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 '092 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. IPR2023-00252 (P.T.A.B.) (U.S. Patent No. 10,138,299), 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
Amanda K. Antons, Ph.D. (Reg. No. 65,236) Dechert LLP 35 West Wacker Drive, Suite 3400 Chicago, IL, 60601-1608 Telephone: 312-646-5800 Facsimile: 312-646-5858	Katherine A. Helm, Ph.D. (<i>pro hac vice</i> to be applied for) Noah M. Leibowitz (<i>pro hac vice</i> to be applied for) Dechert LLP Three Bryant Park 1095 Avenue of the Americas, New York, NY, 10036-6797 Telephone: 212-698-3500 Facsimile: 212-698-3599

Please send all correspondence to lead counsel at the address shown above.

Petitioner consents to e-mail service at the following address: d-fci@dechert.com.

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 a 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 '092 patent is directed to a method of treating late-stage NSCLC 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, ¶50. When PD-L1 binds to PD-1 expressed on activated T-cells, T-cell

activity is inhibited. *Id.* PD-L1 expression 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, ¶50. 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, ¶51. 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”), 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 NSCLC. Ex 1002, ¶52.

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 '092 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, ¶54. BMS' own anti-PD-1 antibody clinical trial, NCT00441337, published in Brahmer, led to promising efficacy results in patients. In this study, many patients showed complete and partial responses, including two patients with melanoma and NSCLC showing significant tumor regression. EX1019; EX1002, ¶55.

There were also at least two ongoing 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, ¶56.

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 NSCLC. EX1021, 4. 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, ¶57.

3. NSCLC

NSCLC is a leading cause of cancer mortality. EX1051; EX1002, ¶58.

NSCLC is often diagnosed at a late stage resulting in a poor prognosis, with a 5-year survival rate after diagnosis of only 10-15%. EX1052, 5094; EX1002, ¶58.

By 2004, it was reported that most NSCLC tumors express PD-L1. EX1052, 5096; EX1002, ¶59. It was also known that higher expression of PD-L1 in NSCLC tumors correlated with poor prognosis in these patients. EX1023, Abstract; EX1002, ¶59. These findings, together with Brahmer, suggested that patients with NSCLC would benefit from treatment with an anti-PD-L1 and/or anti-PD-1 antibody. EX1002, ¶59.

V. THE '092 PATENT

A. Priority

The '092 patent issued from Application No. 16/006,493 (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 '493 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, 130-132. The original claims were not limited to any type of cancer; specific antibody; dosing regimen; or PD-L1 expression pattern in tumor cells. *Id.*

BMS filed a Preliminary Amendment on June 14, 2018, amending the claims to specify a method of treating NSCLC by administering 10 mg/kg of an anti-PD-L1 antibody every two weeks, intravenously over a period of 60 minutes. *Id.*, 178-182.

On August 10, 2018, the Examiner issued a non-final office action rejecting all pending claims. *Id.*, 218-225. The grounds of rejection included indefiniteness and obviousness.

The Examiner concluded that the claims were obvious over US20090055944 (EX1053), US20110250201 (EX1054), and US20110244546 (EX1055), in view of American Cancer Society, “What is Non-Small Cell Lung Cancer?” 2016 (EX1056), and Auperin et al. J. Clin. Oncol., 2010, 28:2181-2190 (EX1057). EX1024, 221-224. The Examiner found that the ’944 publication taught a method of treating lung cancer using a PD-L1 antibody at a dose of 10 mg/kg every two weeks and that a 60-minute infusion time was typical in the art for administration of therapeutic monoclonal antibodies. *Id.*

In response, BMS amended the base claim to add the limitation “and wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression.” *Id.*, 250-253. BMS argued that this new limitation rendered the claims non-obvious over the cited references. *Id.*, 256-259. A Notice of Allowance issued on November 28, 2018. *Id.*, 280.

BMS then filed a series of requests for continued examination, information disclosure statements, and a Terminal Disclaimer, without any substantive amendments. *Id.*, 301-407. Two further Notices of Allowance followed. *Id.*

The '092 patent issued on June 18, 2019. *Id.*, 410.

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 '092 patent’s sole independent claim provides, “[a] method of treating a late-stage non-small cell lung cancer (NSCLC) tumor in a human subject.” EX1001, cl. 1. The Board should construe this preamble as requiring administration of an anti-PD-L1 antibody with the *objective or purpose*,

i.e., intent, of treating the NSCLC tumor per the express definition in the specification. Clinical efficacy is not required.

B. The Preamble Does Not Contain a Clinical Efficacy Requirement

The preamble does not require clinical efficacy. The '092 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, 10:10-16 (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.*, 11:17-63.

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 NSCLC in May 2012. EX1002, ¶35. The preamble would require only that an anti-PD-L1 antibody be administered with the *objective or purpose, i.e., intent*, of treating the NSCLC 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.*, PTAB-IPR2021-00881, Paper 89 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. 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 Programed [*sic*] Death-Ligand 1

⁴ Even if the claims required clinical efficacy, they are obvious as there was evidence of clinical efficacy before the critical date. *See infra* §VIII.A.2.

(PD-L1).” EX1021, 4. 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 for NSCLC specified “[s]ubjects must have refractory or recurrent histologically or cytologically confirmed advanced NSCLC. The malignancy must be deemed unresectable, and subjects must have failed at least 1 prior systemic taxane-based therapy.” *Id.*, 6. 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.*, 4.

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 of the ’092 patent.

The study record for NCT664 was “First Posted” on August 7, 2008, and therefore was publicly available at least as of that date. EX1003, ¶38. As 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, ¶¶33-35. 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 '092 patents' earliest priority date.

EX1003, ¶¶33-42.

B. 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 '092 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, ¶92. 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. The observed clinical activity of MDX-1106 is most likely exerted through immunologic mechanisms rather than direct tumoricidal effects, since nonhematologic tumors do not express PD-1.” *Id.*, 3172.

The authors explain that MDX-1106 blocks PD-1’s interaction with PD-L1 and consequently “[a]nother important factor in determining outcomes may be intratumoral expression of [PD-L1]⁵, 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.*, 3172. Thus, Brahmer teaches that patients with 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

⁵ Brahmer refers to “B7-H1,” a synonym for PD-L1. EX1002, ¶93.

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.

C. Mu Teaches That NCLSC Tumors Express PD-L1 and PD-L1 Expression

Mu is a peer-reviewed journal article, published online in the journal Medical Oncology in April 2010, which is a reoccurring publication, and thus, constitutes prior art under pre-AIA 35 U.S.C. § 102(b). EX1023. Mu was not cited on the face of the '092 patent, not cited by the Examiner to reject the pending claims, nor otherwise substantively relied upon.

Mu teaches “the expression rate of PD-L1 in NSCLC was associated with histological types and overall survival.” EX1023, 682.

Mu explains that “[PD-L1] has been shown to be involved in negative regulation of immune responses through PD-1 receptor on activated T and B cells and has been thought to be an important strategy by which cancer cells evade host immune surveillance. Cancer cells expressing PD-L1 have been shown to increase

apoptosis of antigen-specific human T-cell clones and to inhibit CD4 and CD8 T-cell activation in vitro.” *Id.*

With respect to NSCLC, Mu teaches that the “[t]he percentage of PD-L1-positive cells in non-small cell lung cancer was 53.2% (58/109),” *Id.*, 684. Additionally, Mu Table 2 illustrates the percentage of PD-L1 expression in the tumor regions of NSCLC tumor specimens. *Id.*, Table 2 (mean $65.68 \pm 12.50\%$ and $37.16 \pm 9.52\%$ PD-L1:CD1 α and PD-L1:CD83 co-expressing cells, respectively).

Thus, Mu teaches that NSCLC cells are significantly more likely to be positive for PD-L1 expression and that PD-L1 expression in tumor cells plays a role in resisting an immune response and promoting tumor progression. *Id.*, 684-685; EX1002 ¶103.

D. Irving teaches Anti-PD-L1 Antibodies and Their 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 ’092 patent under 35 U.S.C. § 102(b). EX1058. Irving is cited on the face of the ’092 patent, but was not cited by the Examiner to reject the pending claims, nor otherwise substantively relied upon.

Irving developed antibodies to PD-L1 and tested them in the treatment of tumors. EX1058, [0594]-[0602] (Examples 8 and 9), Figures 9 and 10. Irving specifically claims methods of treating lung cancer. *Id.*, cls. 81, 84, and 95

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

E. WO874 Teaches the Administration of Anti-PD-L1 Antibodies to Treat Lung 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 '092 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.*, Figures 1-31; 3:10-28, 26:6-14), as well as methods of preparing anti-PD-L1 antibodies for evaluation (*id.*, 40:1-9; 51:18-52:22). It teaches that monoclonal antibodies “can be produced by a variety of techniques, including conventional monoclonal antibody methodology.” *Id.*, 55:10-15. WO874 teaches that its

methods of treatment with anti-PD-L1 antibodies can be used to treat lung cancer.

Id., 1:19-20; 80:21-82:9 (“Non-limiting examples . . . include . . . lung cancer”).

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 14 of WO874 discloses experimental evidence evaluating the binding profiles of human anti-PD-L1 antibodies with lung carcinoma tissues. *Id.*, 106:1-107:18. WO874 reports that “[w]eak to moderate staining was observed . . . in tumor cells of lung carcinoma tissues,” which the POSA would understand to reflect that anti-PD-L1 antibodies bind to human lung cancer cells and that anti-PD-L1 antibodies would reasonably be expected to treat lung tumors. *Id.*, 107:1-2; EX1002, ¶124.

In addition to these *in vitro* assays, WO874 discloses the treatment of tumors in an animal model with anti-PD-L1 antibodies. EX1002, ¶125. Example 13 discloses that mice implanted with MC38 colorectal cancer cells and treated with 10 mg/kg of anti-PD-L1 antibody 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 lung cancer. *Id.*, cl. 50.

As explained below, *see infra* §XII.A-B, while the Examiner evaluated the disclosure of WO874, the Examiner did not consider combining WO874 with NCT664, Brahmer, or Mu. This combination renders the Challenged Claims

obvious, including the sole limitation that the Examiner found was not expressly disclosed by WO874. *See infra* §XII.B.

VIII. GROUND 1: CLAIMS 1-6 AND 24-25 ARE UNPATENTABLE AS OBVIOUS OVER NCT664 IN VIEW OF BRAHMER AND MU

A. Ground 1 Overview

Claims 1-6 and 24-25 are rendered obvious under 35 U.S.C. § 103 by NCT664 in view of Brahmer and Mu.

1. The POSA Would Have Been Motivated to Combine NCT664 with Brahmer, and Mu

“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 forms of treatment for NSCLC at the time of the invention because traditional treatments, such as radiotherapy and chemotherapy were often not therapeutically effective. EX1002,

¶127. As explained above, *see supra* §VII.A, NCT664 disclosed a clinical trial administering BMS’ anti-PD-L1 antibody at 10mg/kg once every two weeks to treat NSCLC. As explained below, *see infra* §VIII.A.2, the POSA would have understood that the clinical trial had achieved clinical responses in treating NSCLC. EX1022, EX1025, EX1026. The POSA would have thus been motivated to follow NCT664 in using anti-PD-L1 antibody treatments for lung cancer. Specifically, the POSA would practice the prior art to attain the “60 minute” intravenous infusion limitation and the “at least 1%” limitation as routine determinations. EX1002, ¶¶133, 137, 161.

The POSA would have been motivated to use dosing and treatment regimens that had shown clinical responses. EX1002, ¶128. 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 with a 60-minute intravenous infusion, which was standard in the art once every two weeks to treat subjects with NSCLC. *Id.*, ¶81. Further, Brahmer disclosed that this regimen had shown preliminary evidence of antitumor activity; and that response to treatment was associated with PD-L1 tumor expression. *Id.*, ¶93; *see also Custom Accessories, Inc. v. Jeffrey–Allan Indus.*, 807 F.2d 955, 961 (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 '092 patent itself does not state that other infusion times would not work, or would be any less effective. EX1001. Rather, Patent Owner simply added this routine limitation to argue novelty where none otherwise exists. This is not a case of unexpected results at 60 minutes relative to other infusions times.

Further, NCT664 teaches the treatment of PD-L1 positive tumors. The POSA knew that NSCLC tumors are known to be PD-L1 positive and that such PD-L1 expression was associated with unfavorable outcomes, i.e., overall survival, with existing cancer therapeutics, as taught by Mu. *See supra* §VII.C. While not all NSCLC tumors are PD-L1-positive, the POSA would have been motivated to focus PD-L1 treatments on tumors that express PD-L1, which includes NSCLC tumors. EX1002, ¶161. The POSA would thus have been motivated to treat NSCLC tumors where at least 1% of the tumor cells exhibit membrane PD-L1 expression with anti-PD-L1 antibodies in light of the teachings of NCT664 in view of Mu.

Again, this is not a case of unexpected results of “at least 1%” expression relative to other percentages. The '092 patent describes overexpression as “at least 0.01%, at least 0.1%, at least 1%, or at least 5%” of tumor cells expressing membranous PD-L1, EX1001, 49:61-64, and sets 5%—not 1%—as the positivity threshold for expressing PD-L1 (*see* EX1001, 62:67-63:2). The claimed selection

of “at least 1%” expression was arbitrary and non-inventive, and obvious in light of NCT664 in view of Mu.

The POSA would have been motivated to combine the teachings of NCT664 with the teachings of Mu and Brahmer. In view of the NCT664 disclosure, the POSA would have looked to the teachings of Mu and Brahmer.

First, in view of the POSA’s knowledge of PD-L1 and its role in tumor evasion, the expression of PD-L1 on lung cancers, and the success of anti-PD-1 treatment (*i.e.*, MDX-1106/nivolumab), Mu would have motivated the POSA to determine PD-L1 expression patterns on NSCLC tumors. EX1002, ¶105. Mu specifically teaches that NSCLC tumors express PD-L1. Mu itself provides the motivation to use the dosing regimen of NCT664 to treat NSCLC by showing that “PD-L1 positive lung cancer cells was significantly related to a poor prognosis,” and concluding that “PD-L1 plays a role in disease progression.” EX1023, 686-687, EX1002, ¶101. The POSA would have been motivated to target the PD-L1 pathway via the dosing regimen of NCT664 in view of Mu. EX1002, ¶140.

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, ¶141. Both Brahmer and NCT664 are directed to administration of antibodies to NSCLC patients – Brahmer describing administration of an anti-PD-1 antibody and NCT664 describing administration of an anti-PD-L1 antibody.

EX1002, ¶141. 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 would also have reasonably expected success using the NCT664 dosing regimen with Brahmer's infusion rate in treating late-stage NSCLC tumors in a human subject.

As explained above, the claims do not require clinical efficacy. *See* §VI.B, *supra*.⁶ Thus, all that is required is that the POSA reasonably expects that the dosing regimen 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)

⁶ Even if the preamble required clinical efficacy, the POSA would have had a reasonable expectation of successfully treating NSCLC patients with the claimed dosing regimen for the reasons discussed *infra*.

(“Petitioner need not establish a reasonable likelihood of a successful phase III trial or FDA approval to demonstrate obviousness”).

The prior art teaches that PD-L1 interactions with PD-1 inhibit activation 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. *Id.* The POSA knew that NSCLC 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 Brahmer’s disclosure.⁷ The POSA was aware that MDX-1106, *i.e.*, nivolumab, had undergone clinical trials where anti-tumor clinical activity was observed, including in NSCLC. EX1019, at 3169; *see also* EX1029. The POSA would understand that the successful clinical results of nivolumab, BMS’ anti-PD-1 immunotherapy, teaches that other antibodies that disrupt PD-

⁷ 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 anti-PD-1 antibodies, and at least two ongoing clinical trials studying the safety and efficacy of anti-PD-L1 antibodies prior to the ’092 patent, discussed *supra*.

1/PD-L1 interaction would be successful in treating tumors that express PD-L1.

EX1002, ¶143.

It was also well known that tumor cells expressing PD-L1 are responsive to treatment with anti-PD-L1 antibodies. Indeed, Brahmer found a correlation between membranous PD-L1 expression on tumor cells and the likelihood of tumor response to treatment by an anti-PD-1 antibody. EX1002, ¶144; EX1019, 3170. Brahmer explicitly teaches that “tumor cell surface expression of [PD-L1] may be a predictor of responsiveness to PD-1 blockade.” *Id.*, 3712. The POSA thus would have reasonably expected an anti-PD-L1 antibody to successfully treat tumors expressing PD-L1 in light of the nivolumab clinical trials. EX1002, ¶144. The anti-PD-L1 antibody would be expected to attack the same pathway as the anti-PD-1 antibody and disrupt the PD-1/PD-L1 interaction that gives rise to tumor evasion. EX1002, ¶144. Thus, Brahmer teaches the POSA that an anti-PD-L1 antibody is reasonably likely to achieve a clinical response.

The fact that the POSA, at the time of the alleged invention of the '092 patent, would have looked to PD-1 (nivolumab/MDX-1106) clinical trials to gauge the likelihood of success of a method of treatment using a PD-L1 antibody 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.

The POSA would thus have reasonably expected anti-PD-L1 monoclonal antibodies to treat NSCLC tumors in light of these prior art disclosures as it was known that monoclonal antibodies targeting the PD-1/PD-L1 pathway achieved successful clinical outcomes. EX1002, ¶146. *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 knew even more. The POSA also knew that the specific methods of treatment disclosed by NCT664, and claimed by the ’092 patent, were successful. Numerous pre-priority date publications report on the success of MDX-1105 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 (EX2026) 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.”

Thus, the POSA would have had a reasonable expectation of success in using the NCT664 dosing regimen combined with Brahmer’s infusion rate to achieve anti-tumor activity in human subjects. Even if the preambles required clinical efficacy, the POSA would also reasonably expect that the combination would be clinically efficacious given these disclosures.

Moreover, 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 at 1381. Similarly, as each step of the claim body is obvious in light of NCT664, Brahmer, and Mu, any efficacy required by the preamble would be inherent in carrying out those claim steps. EX1002, ¶148 (discussing Brahmer 2012 and showing the efficacy is inherent).

B. The Prior Art Discloses Each & Every Limitation of Claims 1-6 and 24-25

1. Claim 1

a) “A method of treating a late stage non-small cell lung cancer (NSCLC) tumor in a human subject . . .”

NCT664 discloses a clinical trial administering an anti-PD-L1 antibody (MDX-1105/BMS-936559) to subjects with advanced or recurrent NSCLC. *Supra*, §VII.A; EX1021. 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.” *Id.*, 3. The inclusion criteria included various cancers, including “*non-small cell lung cancer*.” *Id.*, 5 (emphasis added).

The ’092 patent does not define “late stage” NSCLC, but dependent claim 2 requires “wherein the tumor is Stage IV NSCLC.” EX1001, cl. 2. Thus, “late stage” of claim 1 must include at least Stage IV. Stage IV cancer is “advanced” as disclosed by NCT664. EX1002, ¶150.

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 clinical trial. EX1021, 5.

The antibody MDX-1105 was known in the art prior to the critical date. EX1030 at [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.”).

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 NCT664, the general knowledge of the POSA, and Brahmer as of the critical date.

The POSA would have also known that 60 minute 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. Infusion-time is a results effective variable, and the POSA would have routinely optimized the infusion time in evaluating the administration of an anti-PD-L1 antibody. EX1002, ¶133; *see e.g., Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724 (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 anti-PD-L1 antibody dosage, as disclosed by NCT664, would have evaluated the administration of anti-PD-L1 antibody at various shorter and longer time intervals, such as 30 minutes or 90 minutes, in determining an appropriate administration time for an anti-PD-L1 antibody. EX1002, ¶134. 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.*, ¶133. Indeed, in the context of rituximab, another monoclonal antibody on the market prior to the '092 patent's priority date, POSAs investigated and determined that an infusion time of 60 minutes was safe and effective in 2011 and reduced the impact on healthcare resources and patients. EX1028; EX1002 ¶133. Thus, the POSA would have been motivated to adjust the administration time to 60-minute dosing. EX1002 ¶133.

The POSA would have had a reasonable expectation of success with a 60-minute intravenous infusion time. 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 known that most chemotherapies and all kinds of commercial antibodies, regardless of the nature of the treatment, had been administered intravenously over 60-minute periods as a standard and routine protocol and as is better suited for hospitals and patients. *See, e.g.,* EX1002, ¶133; 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 these commercially-approved 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, ¶156. *See Pfizer, Inc*, 480 F.3d at 1364 (“[O]nly a reasonable expectation of success, not a guarantee, is needed.”).

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 with an anti-PD-1 antibody. EX1002, ¶154.

d) “wherein the subject is pretreated for a chemotherapy and a radiotherapy”

This claim limitation is disclosed by NCT664, or is obvious in light of NCT664 and Mu.

The inclusion criteria for the clinical trial disclosed in NCT664 state that the treated “[s]ubjects must have *refractory* or recurrent histologically or cytologically confirmed advanced NSCLC.” EX1021, 5 (emphasis added). As of the priority date, POSAs understood that chemotherapy and radiotherapy were first line treatments for NSCLC. EX1002, ¶127. The POSA would understand that patients that were afflicted with refractory tumors would have been pretreated with chemotherapy and radiotherapy. *Id.*, ¶157. Thus, NCT664 discloses administration of an anti-PD-L1 antibody to patients whose pretreatment with chemotherapy and radiotherapy was ineffective. *Id.*

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 teaches that numerous patients had previously been treated with chemotherapy and radiation therapy. *Id.*, 3169. The POSA would understand relapsed and/or refractory cancers to include cancers which were

unresponsive to pretreatment with chemotherapy and radiotherapy, as taught by Brahmer. EX1002, ¶158.

Mu teaches that “chemotherapy and radiotherapy have low efficacy” against lung cancer. EX1023, 682. Thus, it would have been obvious to administer immunotherapy, including anti-PD-L1 antibodies, to patients whose pretreatment with chemotherapy and radiotherapy was ineffective. EX1002, ¶159.

e) “and wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression”

It would be obvious to the POSA that the tumor being treated with an anti-PD-L1 antibody must express PD-L1.

Mu, Table 2, illustrates the percentage of PD-L1 expression in the tumor regions of NSCLC tumor specimens it studied. EX1023, Table 2 (mean $65.68 \pm 12.50\%$ and $37.16 \pm 9.52\%$ PD-L1:CD1 α and PD-L1:CD83 co-expressing cells, respectively). *See also* EX1009, 2:16-23 (PD-L1 has been “confirmed” in various tumor cells lines).

The “at least 1%,” limitation covers any range of PD-L1 expression between 1% and 100%. EX1002, ¶137. The prior art, including Mu, disclosed that NSCLC tumors expressed PD-L1 in amounts that fall within this range and that PD-L1 expression assists tumors to evade an immune response. EX1002, ¶160. This overlap “establishes a prima facie case of obviousness.” *Genentech, Inc. v. Hospira, Inc.*, 946 F. 3d 1333, 1340-41 (Fed. Cir. 2020).

Thus, Mu teaches the POSA that NSCLC cells are significantly more likely to be positive for PD-L1 expression, and that PD-L1 expression in tumor cells plays a role in resisting an immune response and promoting tumor progression. EX1023; EX1002, ¶105. Given the teachings of NCT664 in view of Mu, the POSA would have been motivated to treat a subject with NSCLC with an anti-PD-L1 antibody where at least 1% of tumor cells exhibit membrane PD-L1 expression. EX1002, ¶160.

Additionally, in 2012, treatment options for NSCLC tumors were extremely limited. EX1002, ¶137. The POSA would have been motivated to administer an anti-PD-L1 antibody as long as the tumor expressed PD-L1, even if such expression was as low as 1%. *Id.*⁸ Thus, the limited nature of treatment at the time

⁸ The '092 patent describes PD-L1 expression as “at least 0.01%, at least 0.1%, at least 1%, or at least 5 %” and does not suggest that it was unexpected that a tumor having 1% PD-L1 expressing cells would be responsive to anti-PD-L1 therapy relative to the other ranges disclosed. Given the known role of PD-L1 in assisting tumor evasion, the POSA knew by the critical date that a tumor in which 1% of tumor cells expressed PD-L1 would be a target for anti-PD-L1 therapy. EX1002, ¶129.

would further provide the POSA with significant motivation to treat a tumor with 1% PD-L1 expression on tumor cells with an anti-PD-L1 antibody, particularly in light of Mu's teachings.

Thus, NCT664 in view of Brahmer and Mu renders claim 1 obvious.

EX1002, ¶¶149-162.

2. Claims 2 and 3

Claim 2 depends from claim 1 and further requires that the “tumor is Stage IV NSCLC.” EX1001, cl. 2. Claim 3 also depends from claim 1 and further requires that the “tumor is advanced or recurrent.” EX1001, cl. 3. These limitations are disclosed by the prior art or obvious to the POSA.

The POSA would understand that PD-L1 positive NSCLC tumors would be responsive to anti-PD-L1 antibodies regardless of stage as the PD-1/PD-L1 mechanism is no different depending on stage. EX1002, ¶168. It would be obvious for the POSA to treat all stages of NSCLC with an anti-PD-L1 antibody. *Id.*

Brahmer also 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 that its subjects were “with selected advanced or recurrent solid tumors.” EX1021. The POSA would understand this to encompass Stage IV tumors. EX1002, ¶167.

Mu discloses an analysis of subjects whose Stage I - III⁹ NSCLC tumors had been surgically removed. EX1023, 683; EX1002, ¶106. Mu analyzed the survival time of each patient whose tumors had been surgically removed. Figure 2 of Mu illustrates that “PD-L1-positive lung cancer cells were significantly related to a poor prognosis” following surgical resection of stage I and II tumors. EX1023, 685, Figure 2. Given Mu’s disclosure, it would have been obvious to the POSA to treat NSCLC tumors that are PD-L1 positive and that recurred after the subject previously had stage I and/or stage II tumors surgically removed. EX1002, ¶167.

The POSA thus would have been motivated to treat advanced or recurrent tumors, including Stage IV NSCLC tumors, with anti-PD-L1 antibodies. EX1002, ¶167.

Claims 2 and 3 are obvious. EX1002, ¶¶163-168.

⁹ Stage IV tumors are routinely needle biopsied, rather than surgically removed. EX1002, ¶167. Thus, the POSA would have understood the focus of Stage I-III in Mu based on this practical limitation, and that PD-L1-expression patterns in Stage IV would be consistent with *e.g.*, Stage III tumors. *Id.*

3. Claim 4

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

NCT664 states that it treated advanced/metastatic epithelial ovarian cancer. EX1021. 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 in light of Brahmer. EX1002, ¶170.

Claim 4 is obvious. EX1002, ¶¶169-170.

4. Claim 5

Claim 5 also depends from claim 1 and requires that the “subject has previously had a stage I and/or II tumor that has surgically been removed.” EX1001, cl. 5.

Mu discloses an analysis of subjects whose Stage I, II, or III NSCLC tumors had been surgically removed. EX1023, 683; EX1002, ¶106. Figure 2 of Mu illustrates that “PD-L1-positive lung cancer cells were significantly related to a poor prognosis” following surgical resection of stage I and II tumors. EX1023, 685, Figure 2. It would have been obvious to the POSA to treat NSCLC tumors

that are PD-L1 positive where the subject previously had stage I and/or stage II tumors that had been surgically removed. EX1002, ¶172.

Claim 5 is obvious. EX1002, ¶¶171-172.

5. Claim 6

Claim 6 also depends from claim 1 and requires that the “treating lasts more than 12 weeks.” EX1001, cl. 6.

This limitation is disclosed by NCT664 or is obvious in light of the general knowledge of the POSA. NCT664 describes that “[t]he maximum duration of study drug treatment for a subject is 2 years.” EX1021, 4. 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, ¶175.

Claim 6 is obvious. EX1002, ¶¶173-175.

6. Claims 24 and 25

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

The POSA, based on the teaching of Mu, would have been motivated to determine whether tissues in patients being treated according to its methods express PD-L1 prior to treatment. Mu teaches that not all NSCLC tumors are PD-L1 positive. EX1023, 684. Thus, it would have been obvious to determine if the NSCLC tumor expresses PD-L1 prior to treatment.

Mu also discloses that “immunohistochemistry” was performed to detect the expression of PD-L1. *Id.*, 683. By May 15, 2012 immunohistochemistry techniques were well-known and widely used. EX1002, ¶178. The POSA would have been aware of routine immunochemistry techniques to measure PD-L1 expression, as reported by Mu itself.

Claims 24 and 25 are obvious. EX1002, ¶¶176-178.

IX. GROUND 2: CLAIMS 7-23 ARE UNPATENTABLE AS OBVIOUS OVER NCT664 IN VIEW OF BRAHMER, MU, AND IRVING

A. Ground 2 Overview

Claims 7-23 should be canceled as obvious under 35 U.S.C. § 103 over NCT664 in view Brahmer, Mu, and Irving. The teachings of NCT664, Brahmer, and Mu are discussed above. *See supra* §§VII.A-C. In combination with these references, the additional teachings of Irving render obvious claims 7-23. The ’092 patent itself provides very little description to support the additional formulation limitations of claims 7-23. It provides general laundry-list information (EX1001, 25:23-37) that is routine knowledge to the POSA and would be

contained in any antibody patent or patent application, including Irving and Honjo-Freeman. EXS1058, 1009.

As explained above, the POSA would have a motivation to combine the teachings of NCT664, Brahmer, and Mu. *See supra* §VII.A.1. 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. EX1002, ¶¶184-185.

The POSA would also have a reasonable expectation of success based on the teachings of NCT664, Mu, and Brahmer, as explained above. *See supra* §VII.A.2. 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. EX1002, ¶¶111-112.

B. The Prior Art Discloses Each & Every Limitation of Claims 7-23

1. Claims 7-9

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

depends from claim 7, requires that “the pharmaceutical composition comprises a preservative, a wetting agent, an emulsifying agent, a dispersing agent, or any combination thereof.” *Id.*, cl. 9.

Irving discloses “anti-PD-L1 antibodies, nucleic acid encoding the same, [and] therapeutic compositions thereof.” EX1058, Abstract. Irving discloses in great detail various components of pharmaceutical formulations of anti-PD-L1 antibodies, including salts, antioxidants, and carriers. *Id.*, [0389]; *see also* [0390]-[0397]. Irving further discloses preservatives ([0217]) and wetting agents ([0395]).

Claims 7-9 are obvious. EX1002, ¶¶182-185.

2. Claims 10 and 11

Claim 10, which depends from claim 8, further requires that the pharmaceutically acceptable “salt comprises a sodium salt.” EX1001, cl. 10.

Claim 11, which also depends from claim 8, requires that the pharmaceutically acceptable “salt comprises sodium chloride.” EX1001, cl. 11.

These claim limitations are disclosed by Irving, which teaches antibodies “formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol” EX 1058, [0625].

Claims 10 and 11 are obvious. EX1002, ¶¶186-187.

3. Claims 12-17

Claims 12-17 respectively depend from claims 1-6 and add the same limitation to each claim. Claims 12-17 each further require that the claimed methods comprise “administering an anti-cancer agent.” EX1001, cls. 12-17. The ’092 patent does not specifically 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, ¶190.

Irving discloses “the anti-PD-L1 antibodies of the invention may be adminstrered [*sic*] prior, subsequent or simultaneous with conventional cancer treatments, such as the administration of tumor-binding antibodies (e.g., monoclonal antibodies, toxin-conjugated monoclonal antibodies) and/or the administration of chemotherapeutic agents.” EX1058, [0492].

Claims 12-17 are obvious. EX1002, ¶¶188-190.

4. Claims 18-23

Claims 18-23 respectively depend from claims 12-17 and add the same limitation to each claim. Claims 18-23 each further require that the additionally

administered “anti-cancer agent” of claims 12-17 “is an anti-CTLA-4 antibody.” EX1001, cls. 18-23.

This claim limitation is disclosed by Irving. Specifically, Irving discloses “an article of manufacture comprising any of the above described anti-PD-L1 compositions in combination with at least one BNCA molecule. In one aspect, the BNCA molecule is an antibody, antigen binding antibody fragment, BNCA oligopeptide, BNCA RNAi or BNCA small molecule. In another aspect, the B7 negative costimulatory molecule is selected from the group consisting of: CTLA-4, PD-1, PD-L1, PD-L2, B7.1, B7-H3 and B7-H4.” EX1058, [0031].

Claims 18-23 are obvious. EX1002, ¶¶191-192.

X. GROUND 3: CLAIMS 1-25 ARE UNPATENTABLE AS OBVIOUS OVER WO874 IN VIEW OF MU, NCT664, AND BRAHMER

A. Ground 3 Overview

Claims 1-25 should be canceled as obvious under 35 U.S.C. § 103(a) over WO874 in view of Mu, NCT664, and Brahmer.

An overview of the WO874, NCT664, Brahmer, and Mu references was provided above. *See supra* §§VII.A-C, VII.E.

1. The POSA Would Have Been Motivated to Combine WO874, Mu, NCT664, and/or Brahmer

The POSA reviewing WO874 would have been motivated to administer anti-PD-L1 antibody treatment for NSCLC tumors and combine its teachings with the disclosures of Mu, NCT664, and Brahmer. EX1002, ¶196. As explained

above, *see supra* §VIII.A.1, POSAs were interested in exploring alternative forms of treatment for NSCLC because traditional treatments were often not therapeutically effective. *Id.* And WO874 discloses that anti-PD-L1 antibodies are useful to treat various cancers, including lung cancer. The POSA would have been motivated to pursue anti-PD-L1 antibody treatments for lung cancer in light of WO874.

The POSA would have been motivated to treat NSCLC tumors with anti-PD-L1 antibodies, as Mu taught that they were PD-L1 positive. *See* §§VII.C, VII.A.1, *supra*. The same POSA would have been aware of NCT664, which disclosed a dosing regimen of 10 mg/kg once every two weeks as achieving anti-tumor activity in subjects with NSCLC. EX1002, ¶198. The POSA would have been aware of Brahmer's disclosure of an anti-PD-1 antibody successfully intravenously infused for 60 minutes. *Id.*

The POSA would have been motivated to combine WO874 specifically with Mu, NCT664, and/or Brahmer. First, as explained above, in view of the POSA's knowledge of PD-L1 and its role in tumor evasion, the POSA would have looked to Mu to determine the PD-L1 expression patterns on NSCLC tumors. *See* §VIII.A.1, *supra*; EX1002, ¶199.

Second, also explained above, the POSA would have been motivated to use Brahmer's infusion rate, combined with the dosing regimen of NCT664 to arrive at the Challenged Claims. *See* §VIII.A.1, *supra*; EX1002, ¶200.

Third, the success of the use of anti-PD-L1 and anti-PD-1 antibodies (see EXS1019, 1022, 1025, 1026), would have motivated the POSA to look to the ongoing successful clinical trial. EX1002, ¶200. The POSA would have been specifically motivated to look to NCT664, which disclosed the use of anti-PD-L1 antibodies for the treatment of NSCLC using the same dosage as that of WO874. *Id.*

The POSA thus would have been motivated to combine the dosing regimen teachings of these references with WO874. EX1002, ¶200.

Techniques for generating human monoclonal antibodies were well-known by persons of skill (EX1002, ¶201), as disclosed by WO874. EX1027, 56:1-58:16. Thus, it would have been routine for the skilled artisan to generate anti-PD-L1 antibodies based on the teachings of WO874. EX1002, ¶201. Indeed, one of the specific anti-PD-L1 antibodies disclosed in WO874 is antibody "12A4." EX1027, Fig. 2A, 2B; EX1002, ¶201. This is the *same antibody*, MDX-1105, that was the subject of the clinical trial NCT664. EX1002, ¶201. The POSA would have focused on antibody "12A4", one of the specific antibodies disclosed by WO874 and was later reported as efficacious. *Id.*

The POSA thus would have been motivated to supplement the teachings of WO874 in light of the disclosures of NCT664 and Brahmer regarding antibodies directed towards the PD-1/PD-L1 pathway.

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 NSCLC in a human subject. The '092 specification concedes 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, 11:18-31 (emphasis added). Consistent with this disclosure, WO874 provides a reasonable expectation of success regarding the use of an anti-PD-L1 antibody to treat tumors, including lung tumors. EX1027, 21:1-6; 1:19-20; 80:21-82:9.

WO874 discloses *in vitro* experimental data and *in vivo* experiments that disclose the treatment of tumors in an animal model using anti-PD-L1 antibodies. See §VII.E, *supra*; EX1002, ¶203. WO874 also discloses that such animal model data can be “*predictive of efficacy* in human tumors” and that “inhibition” can also be evaluated “in vitro” with “assays known to the skilled practitioner.” EX1027, 77:4-8 (emphasis added).

Mu teaches the expression of PD-L1 on NSCLC tumors and that PD-L1 expression on NSCLC tumor cells plays a role in resisting an immune response and promoting tumor progression. EX1002, ¶105. Thus, WO874 in view of Mu provides a reasonable expectation of success for the administration of anti-PD-L1 antibodies to treat NSCLC tumors.

Similarly, the disclosures of NCT664 and Brahmer showed that other monoclonal antibodies that target the PD-1/PD-L1 pathway had achieved clinical success. *Supra* §VIII.A.2; EXS1019, 1022, 1025, 1026.

As explained above, *see supra* §VIII.A.2, even if the preamble required clinical efficacy, such efficacy would be inherent in what already were obvious claim steps in light of the prior art. *See Montgomery*, 667 F.3d at 1381.

B. The Prior Art Discloses Each & Every Limitation of Claims 1-25

1. Claim 1

a) “A method of treating a late stage non-small cell lung cancer (NSCLC) tumor in a human subject . . .”

This limitation is disclosed by WO874 in view of NCT664, Brahmer, and Mu.

WO874 discloses methods of treating cancers in human subjects using anti-PD-L1 antibodies. EX1027, 21:1-6. WO874 also discloses that PD-L1 expression has been found in several murine and human cancers, including lung, ovarian, and colon cancer. *Id.*, 1:19-20; 80:21-82:9. NCT664 discloses a clinical

trial administering an anti-PD-L1 antibody (MDX-1105/BMS-936559) to subjects with NSCLC, which showed success. EX1021; EX1022. Brahmer reports that an anti-PD-1 antibody, nivolumab, showed evidence of anti-tumor activity in humans and that membranous expression of PD-L1 was associated with tumor suppression. EX1002, ¶208. The POSA would thus understand from WO874, NCT664, and Brahmer that an anti-PD-L1 antibody would achieve anti-tumor activity by targeting the same pathway as an anti-PD-1 antibody. *Id.*

While WO874 does not expressly delineate NSCLC as treatable with anti-PD-L1 antibodies, it teaches the treatment of lung cancer with anti-PD-L1 antibodies. The POSA would understand that there are only two types of lung cancer—small cell and non-small cell lung cancer. EX1002, ¶207. The POSA would also have understood that the vast majority of lung cancer presents itself as NSCLC. *Id.* Thus, the POSA would understand the teachings of WO874 to encompass both types of lung cancer, including NSCLC as WO874 does not state that its antibodies are only applicable to small cell lung cancer. EX1002, ¶207 (explaining that the overwhelming majority of lung cancer seen in patients is NSCLC). *See Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147, 152 (Fed. Cir. 2022) (“The prior art may be deemed to disclose each member of a genus when, reading the reference, a person of ordinary skill can ‘at once envisage each member of this limited class.’”).

The POSA would also understand from Mu that NSCLC is a type of cancer which can express PD-L1 such that an anti-PD-L1 antibody would be useful to treat it. *Id.* Mu teaches the presence of PD-L1 on NSCLC cells and its association with a poor prognosis for subjects with NSCLC. *See supra* §VII.C. It thus would have been obvious to apply the methods of treatment disclosed in WO874 to subjects with NSCLC given Mu’s disclosure of the presence of PD-L1 on NSCLC cells and its association with a poor prognosis for those subjects. EX1002, ¶214.

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

As discussed above, *see supra* §VIII.B.1, NCT664 discloses this claim element.

In addition, 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.

As explained above, it was also known by at least March 2010, which was before the ’092 patent’s priority date, that “MDX-1105,” as used in NCT664, was disclosed in WO874. *Id.*, [0177]. Thus, the POSA would have known that the specific antibody used in NCT664, which achieved clinical responses, was disclosed by WO874. EX1002, ¶210.

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, Brahmer, and the general knowledge of the POSA as of the priority date.

WO874 discloses the administration of anti-PD-L1 antibodies intravenously in its disclosed methods. *Id.*, 77:13-24 (“Preferred routes of administration for antibodies of the invention include intravenous ...”); 87:26-32.

As discussed above, it would have been obvious to administer the anti-PD-L1 antibody intravenously over 60 minutes infusion in view of Brahmer and the general knowledge of the POSA as of the priority date. *See* §VIII.B.1, *supra*. As explained in Ground 1, through routine experimentation the POSA also would have determined that a 60-minute infusion of an anti-PD-L1 antibody would be appropriate and desirable. *Id.*

d) “wherein the subject is pretreated for a chemotherapy and a radiotherapy”

As discussed above in Ground 1, NCT664 discloses this limitation, or it would be obvious in light of the additional teachings of Brahmer and Mu, or is obvious in light of the knowledge of the POSA at the time of the invention. *See supra* §VIII.B.1.

e) “and wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression”

This claim limitation is obvious in light of 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, including human lung cancer and that PD-L1 plays a role in “tumor immunity.” EX1027, 1:19-21. The POSA would understand that NSCLC is the most common form of human lung cancer and was known to express PD-L1. EX1002, ¶214. 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% of tumor cells exhibit membrane PD-L1 expression. *Id.* Indeed, if there were no membrane PD-L1 expression in any of the tumor cells, the tumor would not be a practical target for treatment with an anti-PD-L1 antibody. EX1002, ¶75. The POSA thus would have been motivated to treat tumors where at least 1% of tumor cells in the treated tumor exhibit membrane PD-L1 expression. EX1002, ¶214.

As explained above, *see supra* §VII.B-C, Mu and Brahmer teach that NSCLC cells can be PD-L1 positive and that PD-L1 expression on tumors is predictive of responsiveness to PD-1/PD-L1 blockade. Given the teachings of WO874 in view of Mu, NCT664, and Brahmer, the POSA would have been motivated to treat a subject with NSCLC 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, ¶215.

As explained above, *see supra* §VIII.B.1, the prior art disclosed that NSCLC tumors expressed PD-L1 in amounts that fall within the claimed 1% and 100% range and that PD-L1 assists tumors to evade an immune response, thus establishing a prima facie case of obviousness. EX1002, ¶137.

Claim 1 is obvious. EX1002, ¶¶205-216.

2. Claims 2 (“tumor is Stage IV NSCLC”) and 3 (“tumor is advanced or recurrent”)

As explained above with respect to Ground 1, *see supra* §VIII.B.2, the limitations of claims 2 and 3 would be obvious. 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 that its subjects were patients “with selected advanced or recurrent solid tumors.” EX1021.¹⁰

¹⁰ The clinical trial reported in NCT664 involved “testing in patients with *advanced* solid tumors” and the anti-PD-L1 antibody showed preliminary evidence of activity. EX1026, 210 (emphasis added).

The POSA thus would have been motivated to treat advanced or recurrent tumors, including Stage IV NSCLC tumors, with anti-PD-L1 antibodies. EX1002, ¶221. The POSA also would have had a reasonable expectation of success, as explained above, given the data in WO874 and the disclosed efficacy of other monoclonal antibodies targeting the PD-1/PD-L1 pathway. *See supra* §§VIII.A.2, X.A.2.

Claims 2 and 3 obvious are obvious. EX1002, ¶¶217-221.

3. Claim 4 (“tumor is metastatic”)

This limitation is disclosed by WO874. WO874 states that the anti-PD-L1 antibodies of its disclosure are “also useful for treatment of metastatic cancers, especially metastatic cancers that express PD-L1.” EX1027, 81:7-9.

Claim 4 is obvious. EX1002, ¶¶222-223.

4. Claim 5 (“subject has previously had a stage I and/or II tumor that has surgically been removed”)

This claim limitation is obvious in light of WO874 in view of Mu.

As explained in Ground 1, Mu discloses an analysis of subjects whose Stage I, II, or III NSCLC tumors had been surgically removed. EX1023, 683; EX1002, ¶225.

Claim 5 is obvious. EX1002, ¶¶224-225.

5. Claim 6 (“treating lasts more than 12 weeks”)

As explained in Ground 1, this limitation is disclosed by NCT664 or is obvious in light of the general knowledge of the POSA. NCT664 describes that “[t]he maximum duration of study drug treatment for a subject is 2 years.” EX1021, 4. This describes treatment that lasts more than 12 weeks.

Claim 6 is obvious. EX1002, ¶¶226-228.

6. Claim 7 (“the anti-PD-L1 antibody is formulated in a pharmaceutical composition”)

This limitation is disclosed by WO874, which describes “pharmaceutical compositions containing the [anti-PD-L1] antibodies.” EX1027, 20:31. It teaches formulating its anti-PD-L1 antibodies in “a composition, e.g., a pharmaceutical composition, containing one or a combination of monoclonal antibodies . . . of the present invention, formulated together with a pharmaceutically acceptable carrier.” *Id.*, 72:7-11.

Claim 7 is obvious. EX1002, ¶¶229-230.

7. Claim 8 (“pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, ...”)

This claim limitation is disclosed by WO874. WO874 discloses that the “pharmaceutical compounds of the invention may include one or more pharmaceutically acceptable salts.” *Id.*, 72:30-31. It further discloses that its compositions “also may include a pharmaceutically acceptable anti-oxidant.” *Id.*,

73:11-12. WO874 also teaches that there are “suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention.” *Id.*, 73:19-20.

Claim 8 is obvious. EX1002, ¶¶231-232.

8. Claim 9 (“the pharmaceutical composition comprises a preservative, a wetting agent, an emulsifying agent, a dispersing agent, ...”)

WO874 discloses this limitation. WO874 describes that its pharmaceutical compositions “may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents.” *Id.*, 73:26-27.

Claim 9 is obvious. EX1002, ¶¶233-234.

9. Claims 10 (“salt comprises a sodium salt”) and 11 (“salt comprises sodium chloride”)

WO874 discloses these limitations. 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.” *Id.*, 72:30-73:10. The POSA reviewing WO874 would understand that sodium chloride is a salt containing sodium. EX1002, 236. 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 10 and 11 are obvious. EX1002, ¶¶235-236.

10. Claims 12-17 (“administering an anti-cancer agent”)

The '092 patent does not specifically define the term “anti-cancer agent.”

As discussed above, *see supra* §IX.B.3, the POSA would understand this to simply require the administration of an anti-cancer agent other than the anti-PD-L1 antibody administered intravenously.

This limitation is disclosed by WO874. WO874 discloses how the antibody “can be administered before, after or concurrently with the agent or can be co-administered with other known therapies, e.g., an anti-cancer therapy, e.g., radiation.” EX1027, 88:5-7. WO874 further describes how “[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 (emphasis added). WO874 thus discloses the additional limitation of claims 12-17 as it discloses methods of administering anti-PD-L1 antibodies that further comprise a step of administering an additional anti-cancer agent.

Claims 12-17 are obvious. EX1002, ¶¶237-239.

11. Claims 18-23 (“anti-cancer agent” is “an anti-CTLA-4 antibody”)

This limitation is disclosed by WO874. WO874 teaches that “[o]ther antibodies which may be used to activate host immune responsiveness can be used in combination with anti-PD-L1” antibodies. *Id.*, 83:31-33. WO874 then

identifies such antibodies, including “antibodies which block the activity of negative costimulatory molecules such as CTLA-4,” *i.e.*, anti-CTLA-4 antibodies. *Id.*, 84:3-10; EX1002, ¶241. Furthermore, Example 13 of WO874 describes the *in vivo* efficacy of a combination therapy utilizing both anti-PD-L1 antibodies and anti-CTLA-4 antibodies. EX1027, 105:11-31.

Claims 18-23 are obvious. EX1002, ¶¶240-242.

12. Claims 24 (“measuring membranous PD-L1 expression on tumor cells prior to administering the anti-PD-L1 antibody”) and 25 (“the measuring comprises an immunohistochemistry”)

The POSA, based on the teaching of WO874, would have been motivated to determine whether tissues in patients being treated according to its methods express PD-L1 prior to treatment in view of Mu. Mu teaches that not all NSCLC tumors are PD-L1 positive. *See supra* §VII.C. Given the teachings of WO874 that anti-PD-L1 antibodies treat cancer by binding to PD-L1 expressed on the membrane of tumor cells, it would have been obvious to the POSA to measure PD-L1 expression by a patient’s tumor prior to treatment. EX1002, ¶244.

As explained in Ground 1, Mu also discloses that “immunohistochemistry” was performed to detect the expression of PD-L1. *See* §VIII.B.6, *supra*; EX1023.

Claims 24 and 25 are obvious. EX1002, ¶¶243-245.

XI. 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 '092 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 and any commercial success by an anti-PD-L1 antibody would 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”).

XII. 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 (PTAB Feb. 13, 2020) (precedential). Factors (a), (b), and (d) from *Becton, Dickinson* relate to whether the art and arguments presented are the same or substantially the same as those previously presented to the Office. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of the art or arguments. *Id.*, 10.

A. The Grounds Are Not the Same, Substantially the Same, or Cumulative of Arguments Made During Prosecution

Becton, Dickinson factors (a), (b), and (d) favor institution. Grounds 1-3 of this Petition do not present the same or substantially the same prior art or arguments made during prosecution.

Grounds 1 and 2 rely on NCT664, Brahmer, and Mu. NCT664, the primary reference relied upon, describes the clinical trial of MDX-1105, an anti-PD-L1

antibody. As described above, the POSA knew in 2010 that this antibody had demonstrated clinical response. Yet, BMS did not disclose its own NCT664 trial during prosecution. BMS also did not disclose Mu, which discloses the association between PD-L1 expression and NSCLC, and was thus not addressed during prosecution. While Brahmer was disclosed in an Information Disclosure Statement, Brahmer was not the subject of any Examiner rejection or discussed by the Examiner in any Office Action or elsewhere during prosecution. Thus, both Grounds 1 and 2 include prior art which was not disclosed during prosecution.¹¹

The prior art in Grounds 1 and 2 is also materially different from the prior art relied upon by the Examiner and is not cumulative. The only clinical trial that BMS provided to the Examiner was a disclosure of a trial regarding an anti-PD-1 antibody. EX1024, 205. BMS never disclosed NCT664—a clinical trial directed at *an anti-PD-L1 antibody*. None of the references relied upon by the Examiner in the non-final rejection relate to or discuss this clinical trial. *Id.*, 217-225. None of the references relied upon by the Examiner included any human clinical trial data with either an anti-PD-1 antibody (Brahmer) or an anti-PD-L1 antibody (NCT664).

¹¹ The Examiner did not review Irving's teachings in light of NCT664, Brahmer, or Mu or issue any rejection based on Irving. EX1024, 217-225.

The same is true for Ground 3 which relies on the combination of WO874, NCT664, Brahmer, and Mu. During prosecution, the Examiner rejected BMS' proposed claims under pre-AIA 35 U.S.C. § 103(a) as being obvious over Korman (US2009/0055944; EX1053) in view of Smith (US2011/0250201; EX1054) and Hansen (US2011/0244546; EX1055). *Id.*, 221-225.

Korman is the U.S. publication of the corresponding PCT application and contains the same disclosure as WO874, and the Examiner determined that it taught almost every element of the claims. The Examiner determined it taught a method of treating lung cancer by administering an anti-PD-L1 antibody. *Id.* The Examiner further found Korman taught the administration of an anti-PD-L1 antibody at a 10 mg/kg dose once every two weeks by intravenous infusion and that the method of treating NSCLC is inherent in Korman's teachings. *Id.* The Examiner also found that it would have been obvious that the anti-PD-L1 treatment taught by Korman should be "applied to NSCLC patients previously treated with chemotherapy and radiotherapy." *Id.*, 222. The Examiner also determined that that it was "typical in the art at the time of the invention . . . to administer therapeutic antibodies by 60 minutes-long intravenous infusion," and that it would have been obvious as other therapeutic monoclonal antibodies were successfully infused over 60 minutes. *Id.*, 222-223. Thus, the Examiner determined that Korman taught each of these claim elements.

During prosecution, BMS ***did not dispute*** any of these findings. *Id.*, 254-259. Instead, BMS added a single limitation, *i.e.*, “wherein at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression” and argued that Korman did not teach or suggest treating NSCLC with an anti-PD-L1 antibody wherein at least 1% of tumor cells exhibit membranous PD-L1 expression. *Id.*, 258. The Examiner then allowed the claims with no explanation. *Id.*, 280-285.

The Examiner’s reliance on Korman does not warrant a § 325(d) rejection. Ground 3 relies on the combination of ***four references***, three of which—NCT664, Brahmer, and Mu—were not disclosed during prosecution, are materially different from the prior art raised during prosecution, or were not addressed by the Examiner. These additional references disclose the association of PD-L1 expression on tumors, including NSCLC tumors, with anti-PD-1/anti-PD-L1 treatment. Since the Examiner purported to allow the claims in light of the *added limitation* that “at least 1% of tumor cells in the tumor exhibit membrane PD-L1 expression,” these references’ teachings regarding the known association between tumor PD-L1 expression (including on NSCLC tumors) and the effectiveness of anti-PD-1/anti-PD-L1 therapy are particularly relevant to the claims’ patentability. Thus, the same or substantially the same prior art was not previously before the Office ***with respect to the combination*** in Ground 3. *See Volkswagen Group of America, Inc. v. Michigan Motor Technologies LLC*, IPR2020-00169, Paper 8

(PTAB June 2, 2020) (the same or substantially the same art was not before the Office when one asserted reference applied by the Examiner was combined with art not previously before the Examiner).

Additionally, NCT664 is not cumulative of Korman. NCT664, a clinical trial disclosure is meaningfully noncumulative over Korman's disclosure of the dose administration and infusion time. NCT664 describes a clinical trial in patients, which cannot be performed ethically without a reasonable basis to do so, including scientific validity based on pre-clinical data. EX1002, ¶81.

The remaining references are not cumulative and are materially different from the Smith (EX1054) and Hansen (EX1055) references. While the Examiner relied upon Smith and Hansen for the disclosure of a 60-minute intravenous infusion, Brahmer discloses a 60-minute intravenous infusion for *an anti-PD-1 antibody, i.e., an antibody that targets the same pathway as an anti-PD-L1 antibody*. EX1019, 3168. Neither Smith nor Hansen relate to PD-1 or PD-L1. *See* EX1054 (referring to IL-6 antagonists); EX1055 (anti-CD74 antibodies).

Thus, *Becton, Dickinson* factors (a), (b), and (d) favor institution for Ground 2 as well.

B. The Petition Demonstrates a Material Examiner Error

Even if the Board were to determine that Ground 3 of this Petition raises substantially the same art, institution is appropriate due to “material error by the

Office.” *Advanced Bionics, LLC*, IPR2019-01469, Paper 6 at 10. Factors (c), (e), and (f) of *Beckton, Dickinson* relate to whether the petitioner has demonstrated such an error and favor institution. *Id.*

As explained above, *see supra* §V.B, the Examiner did not meaningfully address the obviousness of the added “at least 1%” limitation. BMS did not provide any argument as to why this limitation would make the claims non-obvious. BMS simply argued that none of the cited references disclose this specific limitation. EX1024, 256-259. And the ’092 patent itself sets 5% as the positivity threshold for expressing PD-L1, not 1%. EX1001, 62:67-63:2. The Examiner did not consider Mu, which teaches that NSCLC cells are significantly more likely to be positive for ***PD-L1 expression***, further suggesting PD-L1 expression in tumor cells plays a role in promoting tumor progression. EX1023, 684. As explained by Dr. Jabbour, anti-PD-L1 antibodies are—by their very nature—designed to work on tumors that ***express PD-L1***. EX1002, ¶75. It is nonsensical to treat a tumor with an anti-PD-L1 antibody if the tumor cells do not express a minimal level of PD-L1. The converse is also true—the POA would have understood that anti-PD-L1 antibodies are specifically designed to treat PD-L1-expressing tumors. *Id.*

The Examiner did not meaningfully evaluate the prior art in Ground 3 such as NCT664 and Brahmer. As explained above, *see supra* §§VII.A, VIII.A.2,

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.

EX1019, 3167. The Examiner should have determined that the additional limitation of “at least 1%” tumor cells being PD-L1 positive was obvious in light of these disclosures. Simply put—an anti-PD-L1 antibody is not useful for tumors that do not express PD-L1, at least minimally. This is why the limitation that the Examiner apparently found was not expressly taught by Korman remained obvious to the POSA.

It was widely known before the '092 patent that many different types of tumor cells express PD-L1 both in the cytoplasm and on the membrane (*see e.g.*, EX1015, 309). The 1%-limitation merely requires that a minimal cell quantity in the tumor exhibit PD-L1 membrane expression. The Examiner thus erred by removing the obviousness rejection and allowing the claims based on the 1% limitation.

While the disclosure of WO874 was part of the basis of one prior art rejection, the other references relied on by Ground 3—NCT664, Brahmer, and Mu—were not. Thus, many of the references relied upon for Ground 3 were not relied upon for any prior art rejection (factor (c)). This Petition also demonstrates how the Examiner erred by not finding that the claims would still be obvious in

light of the prior art despite the addition of the “1%” limitation (factor (d)). This Petition presents new arguments, expert testimony by the POSA, and new references which show that each of the limitations, including the 1% limitation, are obvious (factor (e)). A § 325(d) rejection is inappropriate in this case. *See Edwards Lifesciences Corp. v. Boston Scientific SciMed, Inc.*, IPR2017-01295, Paper No. 9 at 27 (PTAB Oct. 25, 2017) (declining to exercise § 325(d) discretion where Examiner did not consider whether a claim amendment “may have been obvious” “in combination with additional prior art”).

XIII. 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

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Certification of Word Count

I certify that the Petition for *Inter Partes* Review filed herewith has a word count of 13,961 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

/Amanda K. Antons/

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IPR2023-00249

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. 10,323,092 B2 and Exhibits 1001-1060 and 1069-1070 were served on December 29, 2022 via FedEx® to the attorneys of record for U.S. Patent No. 10,323,092 B2 as evidenced on Patent Center on December 29, 2022, namely:

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