UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY
Patent Owner.

Case No. IPR2025-00602
Patent No. 10,174,113

PETITION FOR INTER PARTES REVIEW
UNDER 35 U.S.C. §§311-319 AND 37 C.F.R. §42.1 et seq

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

REGULATIONS

OTHER AUTHORITIES

APPENDIX LISTING OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 10,174,113 ("'113 Patent")
1002	Prosecution History of U.S. Patent No. 10,174,113
1003	Declaration of Dr. Brent Hanks M.D., Ph.D.
1004	Curriculum Vitae of Dr. Brent Hanks M.D., Ph.D.
1005	Postow et al., Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma., *N Engl J Med.* 2015 May 21; 372(21):2006-17. ("Postow")
1006	RESERVED
1007	NCT01968109 Version 1, Brief Title: "Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors" (Last Update Posted to clinicaltrials.gov: October 23, 2013) ("NCT-109")
1008	Wang et al., Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. *J Clin Pharmacol*. 2009 Sep; 49(9):1012-24. ("Wang")
1009	Brahmer et al., Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. *J Clin Oncology*. 2010 Ju1 1; 28(19):3167–3175. ("Brahmer")
1010	RESERVED
1011	Topalian et al., Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *N Engl J Med*. 2012 Jun 28; 366(26):2443-54. ("Topalian")
1012	Prosecution History of U.S. 16/240,316

Exhibit	Description
1013	NCT02713867 Version 2, Brief Title: "A Dose Frequency Optimization, Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received 4 Months of Nivolumab at 3 mg/ kg or 240 mg Every 2 Weeks" (Last Update Posted to clinicaltrials.gov: March 22, 2016) ("NCT-867")
1014	NCT01844505 Version 1, Brief Title: "Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma" (Last Update Posted to clinicaltrials.gov: May 1, 2013) ("NCT-505")
1015	International Patent Publication No. WO 2013/173223 A1 ("Cogswell")
1016	International Patent Publication No. WO 2006/121168 A1 ("Korman")
1017	Wolchok et al., Nivolumab plus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2013 Jun 2; 369(2):122-33. ("Wolchok")
1018	U.S. Provisional Patent Application No. 62/153,973 (filed April 28, 2015) ("'973 Provisional")
1019	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary
1020	RESERVED
1021	Zalevsky et al., Enhanced Antibody Half-Life Improves in Vivo Activity. *Nat Biotechnol*. 2010 Feb; 28(2):157-9. ("Zalevsky")
1022	Weber J., Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist*. 2007 Jul; 12(7):864-72 ("Weber")
1023	YERVOY FDA Approved label and prescribing information, March 2011
1024	OPDIVO FDA Approval label and prescribing information, December 2014

Exhibit	Description
1025	Philips et al., Therapeutic Uses of Anti-PD-1 and Anti-PD-L1 Antibodies. *Int Immunol*. 2015 Jan; 27(1):39-46. doi: 10.1093/intimm/dxu095. Epub 2014 Oct 16. ("Philips")
1026	Phan et al., Cancer Regression and Autoimmunity Induced by Cytotoxic T Lymphocyte-Associated Antigen 4 Blockade in Patients with Metastatic Melanoma. *Proc Natl Acad Sci USA*. 2003 Jul 8;100(14):8372-7. doi: 10.1073/pnas.1533209100. ("Phan")
1027	Sequence Listing of International Patent Publication No. WO 2013/173223 Al (Nov. 21, 2013) ("Cogswell")
1028	Callahan et al., Peripheral and Tumor Immune Correlates in Patients with Advanced Melanoma Treated with Combination Nivolumab (Anti-PD-1, BMS-936558, ONO-4538) and Ipilimumab. 2013 ASCO Annual Meeting (May 20, 2013) (Abstract) ("Callahan")
1029	Declaration of Dr. Dhaval Shah
1030	Curriculum Vitae of Dr. Dhaval Shah
1031	Declaration of Prescott Lassman
1032	Curriculum Vitae of Prescott Lassman
1033	Mathijssen et al., Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults. *Oncologist*. 2007 Aug; 12(8):913-23. ("Mathijssen")
1034	Bai et al., A Guide to Rational Dosing of Monoclonal Antibodies. *Clin Pharmacokinet*. 2012 Feb 1; 51(2):119-35. ("Bai")
1035	Feng et al., Model-based Clinical Pharmacology Profiling of Ipilimumab in Patients with Advanced Melanoma. *Br J Clin Pharmacol*. 2014 Jul; 78(1):106-17. ("Feng")
1036	Mould et al., Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies: Concepts and Lessons for Drug Development. *BioDrugs*. 2010 Feb 1; 24(1):23-39. ("Mould")

Exhibit	Description
1037	Bi et al., Model-Informed Drug Development Approach Supporting Approval of the 4-Week (Q4W) Dosing Schedule for Nivolumab (Opdivo) Across Multiple Indications: A Regulatory Perspective. *Ann Oncol*. 2019 Apr 1; 30(4):644-651. ("Bi")
1038	Zhao et al., Model-Based Evaluation of the Efficacy and Safety of Nivolumab Once Every 4 Weeks Across Multiple Tumor Types. *Ann Oncol*. 2020 Feb; 31(2):302-309. ("Zhao")
1039	Eisenhauer et al., New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *Eur J Cancer*. 2009 Jan; 45(2):228-47. ("Eisenhauer")
1040	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1041	Dirks et al., Population Pharmacokinetics of Therapeutic Monoclonal Antibodies. *Clin. Pharmacokinet*. 2010 Oct; 49(10):633-59. ("Dirks")
1042	Lobo et al., Antibody Pharmacokinetics and Pharmacodynamics. *J Pharm Sci*. 2004 Nov; 93(11):2645-68. ("Lobo")
1043	U.S. National Library of Medicine, National Institutes of Health *Food and Drug Administration Modernization Act of 1997 (FDAMA)*, available at https://clinicaltrials.gov/policy/reporting-requirements
1044	U.S. National Library of Medicine, National Institutes of Health, Press Release: National Institutes of Health Launches "ClinicalTrials.gov" (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html
1045	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, How to Edit Your Study Record, https://clinicaltrials.gov/ct2/manage-recs/how-edit
1046	Zarin et al., Reporting "Basic Results" in ClinicalTrials.gov, *Chest*. 2009 Jul; 136(1):295–303.

Exhibit	Description
1047	U.S. National Library of Medicine, National Center for Biotechnology Information, *About ClinicalTrials.gov*: Major milestones related to ClinicalTrials.gov and how information in the database has changed over time, available at https://clinicaltrials.gov/about-site/about-ctg
1048	National Library of Medicine, National Center for Biotechnology Information, ClinicalTrials.gov, *Trends and Charts on Registered Studies*, available at https://clinicaltrials.gov/about-site/trends-charts
1049	Affidavit of Nathaniel E. Frank-White (Internet Archive)

MANDATORY NOTICES

A. Real Party-In-Interest

Amgen, Inc. ("Amgen" or "Petitioner") is the Real Party-in-Interest.

B. Related Matters

A decision in this proceeding could affect or be affected by the following.

The '113 patent claims priority to U.S. Provisional Application No. 62/153,973 (filed April 28, 2015).

U.S. Patent Application No. 17/523,702 (filed on November 10, 2021), claims priority to the '113 patent. U.S. Patent Application No. 16/240,316 (filed on January 4, 2019) also claimed priority to the '113 Patent, but was abandoned.

C. Counsel and Service Information - §42.8(b)(3) and (4)

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A power of attorney is submitted with the Petition. Counsel for Petitioner consents to service of all documents via electronic mail.

I. INTRODUCTION

Amgen requests cancellation of claims 1-20 ("Challenged Claims") of U.S. Patent No. 10,174,113 (EX1001, "'113 Patent"). The Challenged Claims concern methods of using two categories of known checkpoint inhibitor immunotherapeutic drugs—"anti-PD-1" and "anti-CTLA-4" antibodies—to treat melanoma cancer patients. However, such combination immunotherapy had already been reported as effective in treating melanoma long before the '113 Patent's earliest possible effective filing date of 4/28/15. The combination had been disclosed by 2006. EX1016. By 2013, positive results had been reported in clinical trials for treating melanoma using nivolumab (an anti-PD-1 antibody) together with ipilimumab (an anti-CTLA-4 antibody). EX1017; EX1005. Favorable responses to the combination therapy (rather than nivolumab or ipilimumab monotherapy) had been reported by 2013 even in "PD-L1 negative" tumors. EX1028. Yet the '113 Patent's specification—written years later—describes the "invention" as the same thing: recognizing advantages of combination therapy over monotherapy for "PD-L1-negative melanoma tumor[s]." EX1001, 4:14-23. Moreover, fifteen of the twenty challenged claims cover treating even PD-L1-***positive*** melanoma.

Patent Owner (PO) nominally overcame an initial rejection during prosecution by adding the requirement that the combination therapy be followed by anti-PD-1 antibody monotherapy at dosages of 240 mg or 480 mg. Both issued

independent claims and most dependent claims recite these two dosages in the alternative, while other dependent claims specify just one. But neither dosage was inventive. Indeed, for a typical melanoma patient weighing 80 kg (EX1035), the 240 mg dosage corresponds precisely to a Phase III clinical trial protocol—NCT01844505 ("NCT-505")—posted to ClinicalTrials.gov on 5/1/13 and subsequently included as the '113 Patent's Example 1. EX1014. Moreover, the efficacy of this regime for treating melanoma had been confirmed in Postow—a *New England Journal of Medicine* article published on 4/20/15. EX1005.

The table below compares the dosing regimen used in the above-discussed clinical trials and the regimen recited in even the narrowest Challenged Claims:

NCT-505 and Postow	**'113 patent**
(a) 1 mg/kg of an anti-PD-1 antibody and a dose of an anti-CTLA-4 antibody every three weeks for four doses, followed by (b) a weight-based dose of 3 mg/kg of the anti-PD-1 antibody once every two weeks.	(a) 1 mg/kg of an anti-PD-1 antibody and a dose of an anti-CTLA-4 antibody every three weeks for about four doses, followed by (b) a flat dose of about 240 mg once every two weeks [claims 11 and 17] or about 480 mg of the anti-PD-1 antibody once every four weeks [claims 12 and 18].

The difference between these dosing regimens in this case is elementary arithmetic—converting the prior art weight-based dose to the claimed flat dose—because administering a flat dose of the anti-PD-1 antibody, nivolumab, to treat melanoma ***was also already well-known*** in indisputable prior art. For example, NCT01968109 ("NCT-109") discloses administering a flat dose of 240 mg nivolumab once every two weeks to patients with solid tumors, including melanoma.

Moreover, flat dosing (as disclosed in NCT-109) was known to offer numerous practical benefits (e.g., improved convenience and less risk of error) over weight-based dosing (as disclosed in NCT-505 and Postow) for monoclonal antibodies such as nivolumab with wide therapeutic windows. "***[F]ixed dosing"*** **(another name for flat dosing)** ***indeed "is the approach of choice***" in such cases. EX1008, 1023*; see also* EX1034, 119, 133.

When selecting the specific flat dosage of nivolumab, POSAs would have had a reason to take the known and effective dose regimen of 3 mg/kg once every two weeks (disclosed in NCT-505 and Postow) and multiply it by 80 kg (i.e., the average weight of melanoma patients in immunotherapy trials, EX1035)—yielding a flat dose of 240 mg once every two weeks. POSAs would also have had reason to use a 240 mg flat dose of nivolumab because it was already being used in clinical trials for treating solid tumors, including melanoma, as disclosed in NCT-109.

Moreover, POSAs would have reasonably expected a 240 mg flat dose to be comparable to the NCT-505/Postow 3 mg/kg weight-based dose given pharmacokinetic analysis reflecting nivolumab's wide therapeutic window. EX1011; EX1009.

A 480 mg dose once every four weeks (as required in Challenged Claims 12 and 18) is simply twice the amount at half the frequency, which POSAs would have been motivated to use since "less frequent dosing schedules" were known to be desirable for "patient convenience and compliance." EX1021, 158. Moreover, POSAs would have reasonably expected that using a 480 mg once every four weeks would be comparable to 240 mg once every two weeks given pharmacokinetic analysis reported for nivolumab over a dose escalation of 0.1-10 mg/kg (corresponding to 8-800 mg for an 80 kg patient)—including administration every four weeks. EX1011; EX1009.

Ground 1A demonstrates why Challenged Claims 1-4, 10, 13-15, and 19-20 would have been obvious over NCT-505 and NCT-109, while **Ground 3A** demonstrates why claims 1-6, 9-10, 13-15, and 19-20 would have been obvious over Postow and NCT-109. Even Postow—published on 4/20/15—constitutes indisputable prior art to these claims because they plainly were not effectively filed before the '113 Patent's actual 4/28/16 filing date. *See infra* §IV. **Grounds 1B and 3B** demonstrate that claims 11 and 17 would have been obvious for substantially

the same reasons as Grounds 1A and 3A, respectively, but are stated separately because the Petition's priority analysis (*infra* §IV) does not address claims 11 and 17. But NCT-505 and NCT-109 (the basis for Ground 1B) constitute indisputable prior art regardless. **Grounds 1C and 3C** demonstrate that claims 12 and 18 were obvious because a 480 mg flat dose every four weeks was an obvious variant of a 240 mg flag dose every two weeks and encompassed within the range expressly disclosed in Brahmer (EX1009). **Grounds 2 and 4** flow from Grounds 1A and 3A, respectively, and concern dependent claims 5-9 (reciting well-known details of the technique for measuring PD-L1 expression on melanoma tumors) and dependent claim 16 (reciting the well-known step of combining immunotherapy with traditional anti-cancer agents—e.g., chemotherapy). Cogswell is indisputable prior art disclosing these additional limitations.

Notwithstanding this extensive prior art, the '113 Patent claims were allowed ***without any art-based rejections*** after PO added the anti-PD-1 monotherapy limitation. None of NCT-505, NCT-109, or Postow was of record.

II. REQUIREMENTS FOR IPR

A. Grounds for Standing

Petitioner certifies that the '113 Patent is available for *inter partes* review and that Petitioner is not estopped from requesting review.

B. Identification of Challenged Claims

Petitioner requests cancellation of claims 1-20.

C. Grounds of Challenge

Ground Number and Reference(s)		Claim(s)	Basis
1A	NCT-505 and NCT-109	1-4, 10, 13-15, and 19-20	§103
1B		11 and 17	
1C		12 and 18	
2	NCT-505, NCT-109, and Cogswell	5-9 and 16	
3A	Postow and NCT-109	1-6, 9-10, 13-15, and 19-20	
3B		11 and 17	
3C		12 and 18	
4	Postow, NCT-109, and Cogswell	5-9 and 16	

Section VII details the basis for the grounds and cites additional references further exemplifying the state of the art as of the earliest alleged effective filing date. *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc*., 825 F.3d 1360, 1369 (Fed. Cir. 2016); *see also* EX1040 ("Ellis") (confirming public availability of EX1008, EX1009, EX1011, EX1017, EX1021, EX1022, EX1025, EX1026, EX1028, EX1033, EX1034, EX1035, EX1036, EX1039, EX1041, and EX1042).

III. THE '113 PATENT

The application yielding the '113 Patent was filed on 4/28/16 and claims the benefit of the '973 Provisional, filed on 4/28/15.

A. Described Embodiments

The '113 Patent discloses a method of treating melanoma comprising "combined administration of anti-PD-1 and anti-CTLA-4 antibodies at a dosing

frequency of … at least once about every 3 weeks, … for 2, 4, 6 or 8 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once about every 2 weeks….” EX1001, 23:26-37.

The patent discloses both “weight based” and “flat” dosing of the antibodies. EX1001, 7:66-8:1, 24:15-16. A “***weight based dose***” is one “calculated based on the weight of the patient,” whereas “a ***flat dose”*** is “administered to a patient without regard for the weight or body surface area (BSA) of the patient.” *Id.*, 7:52-55-8:1. However, the only data disclosed concerns weight-based doses. *See* EX1001, 26:44-38:41.

B. Person of Ordinary Skill in the Art

POSAs as of early 2015 (i.e., before the earliest possible effective filing date of 4/28/2015) would have a Ph.D. in immunology or a related field (or alternatively a M.D. with a particular focus on cancer immunotherapy) plus at least two years of experience in that field, including experience with melanoma treatments. EX1003 (“Hanks”), ¶41. The levels of education, experience and knowledge can trade off against one another. *Id*.. POSAs would also have either been (1) skilled in pharmacokinetics or (2) able to communicate as part of a team with pharmacokinetics experts if necessary.

C. Prosecution History

Original claim 1 recited a method comprising "(i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient: (a) an anti-PD-1 antibody …; and (b) an anti-CTLA-4 antibody…." EX1002, 1615. Original claim 2 recited the same but did not include limitation (i) of identifying a PD-L1-negative melanoma tumor. *Id.*

After a Preliminary Amendment (EX1002, 1400-1403), the Examiner issued an Office Action rejecting the pending claims as "anticipated by Wolchok et al. *N. Engl. J. Med*. (June 2, 2013) "Wolchok" (EX1017). EX1002, 433.

On 5/29/18, Applicant amended claims 1 and 2 to require a "***flat dose*** of the anti-PD-1 antibody of about 240 mg every two weeks or about 480 mg every four weeks" following the administration of a ***weight based dose*** of an anti-PD-1 antibody, and an anti-CTLA-4 antibody. EX1002, 68.

On 6/22/18, the Examiner rejected the claims for lacking written description support and adding new matter. EX1002, 57.

In response, Applicant cited purported support and also broadened claims 1 and 2 by removing recitation of how frequently the flat dose of PD-1 antibody is administered. *Id*., 33-39.

The Examiner in turn allowed the claims without providing any reasons for allowance. *Id.*, 19-20.

IV. EFFECTIVE FILING DATE OF CLAIMS 1-10, 12-16, AND 18-20

Claims 1-10, 12-16, and 18-20 are not entitled to the benefit of the '973 Provisional because it lacks support for a 480 mg flat dose of an anti-PD-1 antibody. Claims 1-10, 12-16, and 18-20 all recite (or depend from a claim reciting) a 480 mg flat dose of an anti-PD-1 antibody as an option or in some instances a requirement. Yet the '973 Provisional does not disclose a 480 mg flat dose. The effective filing date of claims 1-10, 12-16, and 18-20 is therefore not earlier than the '113 Patent's actual 4/28/16 filing date. §100(i)(1).[1] Patents and printed publications reasonably accessible to POSAs prior to 4/28/15 therefore constitute indisputable §102(a)(1) prior art without any possible §102(b)(1) exception.

A. Legal Standard: A Disclosure Must Provide Written Description Support For All Claimed Alternatives to Support a Priority Claim.

For a patent claim to be entitled to the benefit of an earlier provisional application, the provisional must disclose the claimed invention "in the manner provided by section 112(a)," including §112(a)'s written description requirement. §119(e).

[1] Petitioner does not concede that the provisional supports claims 11 and 17.

The written description requirement ensures "that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad Pharm. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (*en banc*). Accordingly, "all the limitations must appear in the specification." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). "It is not sufficient . . . that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to the modifications that the inventor might have envisioned, but failed to disclose." *Id.*

When a claim recites two or more options in the alternative, an adequate written description requires disclosing ***all*** claimed options—not just one. *Eden Park Illumination v. Neister*, IPR2022-00381, Paper 55, 18 (PTAB Nov. 14, 2023) ("to satisfy the written description requirement, a patent application must show that the inventor had possession of the claimed invention as a whole, including each member of a Markush group"); *Ex Parte Hassler*, 2020 WL 6781447, at *5 (PTAB Nov. 13, 2020); *Ex Parte Cotter*, 2004 WL 4979091, at *2 (BPAI Jan. 30, 2004) (finding written description not satisfied where one of two claimed alternatives was not described). Applicants cannot capture inventions that belong to the public by adding new subject matter and claiming it in the alternative.

B. The ’973 Provisional Does Not Describe Administering 480 mg of an Anti-PD-1 Antibody

The ’973 Provisional does not disclose administering 480 mg of anti-PD-1 antibody and therefore does not support any of the Challenged Claims reciting 480 mg anti-PD-1 antibody (whether as an option or a requirement). Hanks, ¶¶41-47.

Both independent claims 1 and 2 require administering “a flat dose of the anti-PD-1 antibody… of about 240 mg or ***about 480 mg***” following administration of anti-PD-1 and anti-CTLA-4 antibodies. But the ’973 Provisional nowhere discloses a ***480 mg*** dose of anti-PD-1 antibody. Hanks, ¶¶41-47. It instead merely discloses doses of the anti-PD-1 antibody of “about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, or about 300 mg.” EX1018 ¶[0111]. A 480 mg dose is never disclosed. Hanks, ¶44. The ’973 Provisional also discloses administering a flat dose of “20, 50, 75, 80, 160, 200, 240, 300, 400, 500, 750, or 1500 mg” (EX1018 ¶[0110]), but still nowhere discloses a dose of ***480 mg***, and does not use the word “about” to encompass variation around the disclosed 400 or 500 mg doses. *Id.*

While there was nothing inventive about 480 mg anti-PD-1 dosages (as detailed further below), obviousness is insufficient for adequate written description support. *Lockwood*, 107 F.3d at 1572. Independent claims 1 and 2 are therefore not supported by the ’973 Provisional.

Dependent claims 3-10, 13-16, and 19-20 do not further limit the requirement of "about 240 mg or ***about 480 mg***" anti-PD-1 antibody and thus are likewise not supported by the '973 Provisional. *See Stored Value Sols., Inc. v. Card Activation Techs., Inc.*, 499 F. App'x 5, 14 (Fed. Cir. 2012) (where dependent claims are "similarly affected" by lack of written description, they "must fall as well"). Similarly, dependent claims 12 and 18 expressly ***require*** a flat dose of "about 480 mg" and are thus also not supported by the '973 Provisional.

C. The Office Confirmed During Prosecution of a Continuation Application that the '973 Provisional Does Not Support 480 mg Anti-PD-1 Dosage Claims.

During prosecution of a continuation of the '113 Patent (U.S. Application No. 16/240,316), the Examiner found that the '973 Provisional fails to adequately describe a flat 480 mg dose of anti-PD-1 antibody. EX1012, 215.

In that prosecution, the Applicant amended the pending claims to recite a method of treating melanoma comprising administering 480 mg nivolumab once every four weeks. *Id*., 186. In response, the Examiner concluded that such claims were unpatentable over intervening art published after the '973 Provisional's filing date and before the '113 Patent's filing date. The Examiner determined that the 480 mg claims were not entitled to a priority date before the '113 Patent's actual "04/28/2016" filing date. *Id*., 215. Thereafter, that application was abandoned.

V. CLAIM INTERPRETATION

Claim terms are interpreted in accordance with "the ordinary and customary meaning" as understood by POSAs. 37 C.F.R. §42.100(b). The Board need only interpret terms to the extent necessary to resolve disputes between parties.[2] *Nidec Motor v. Zhongshan*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); 83 Fed. Reg. 51,340, at 51,353. Petitioner does not believe any term requires any outer-boundaries construction for purposes herein except as otherwise explained below.

VI. PRIOR ART TO THE '113 PATENT

A. NCT-505 (EX1014)

NCT-505 is Version 1 of a clinical trial protocol with the Brief Title "Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma." EX1014, 1. The "Last Update Posted" date for Version 1 on ClinicalTrials.gov was 5/1/13. EX1014, 3. NCT-505 was not cited or discussed during prosecution of the '113 Patent.

As explained in the accompanying declaration of Mr. Prescott Lassman, ClinicalTrials.gov publicizes clinical trial protocols, like NCT-505, as widely and

[2] Petitioners are not waiving any arguments concerning claim scope necessary for resolving other proceedings. Petitioners are also not waiving any arguments related to indefiniteness or other §112 issues, which could not have been raised in this IPR.

promptly as possible. EX1031 ("Lassman"), ¶¶17-29; *see also Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc*., IPR2022-00578, Paper 78 at 28 (PTAB Aug. 29, 2023) (citing Mr. Lassman's "intimate knowledge of, and experience with, the ClinicalTrials.gov website," which was "designed to be used by members of the public"). Pursuant to the FDA Modernization Act of 1997, the National Library of Medicine of the National Institutes of Health ("NIH") launched ClinicalTrials.gov in February 2000 to give the public better access to information on clinical studies. Lassman, ¶¶19-20. The FDA Amendments Act of 2007 later expanded the database to enable electronic searching. *Id*., ¶¶23-25.

NCT-505 (Version 1) bears a "Last update posted" date 5/1/13. EX1014, 3. The "Last update posted" date is "[t]he most recent date on which changes to a study record were made available on ClinicalTrials.gov." EX1019, 10. The "Last update posted" date for NCT-505 demonstrates that it was publicly available as of 5/1/13. Lassman, ¶¶32-42. POSAs were aware that such clinical trial protocols were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. Lassman, ¶¶26-31; Hanks, ¶¶53-54. For example, when searching ClinicalTrials.gov for clinical trials involving "nivolumab/ipilimumab" "PD-L1" when treating metastatic melanoma, NCT-505 is among the first results returned. Lassman, ¶¶30-31. NCT-505 therefore was accessible as of 5/1/13 to POSAs. *Id*., ¶¶30-42.

NCT-505 thus constitutes a printed publication under §102(a)(1) as of 5/1/13. *Grunenthal v. Antecip Bioventures*, PGR2019-00003, Paper 22, 17-18 (PTAB May 5, 2020) ("*Grunenthal*") (protocol available on ClinicalTrials.gov publicly available as of its "first posted" date). NCT-505 is thus prior art to the Challenged Claims without any exception under §102(b)(1).

B. Postow (EX1005)

Postow is an article entitled "Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma" (EX1005) and published in the New England Journal of Medicine—a journal well known to POSAs (Hanks, ¶¶56-61). It was published online at NEJM.org on 4/20/15 (EX1005, 2006) and would have commended itself to POSAs' attention immediately thereafter (Hanks, ¶56). Postow was not cited or discussed during prosecution of the '113 Patent.

Postow is §102(a)(1) prior art without any §102(b)(1) exception for Claims 1-10, 12-16, and 18-20 because such claims plainly were not effectively filed before the '113 Patent's actual 4/28/16 filing date—more than one year after Postow became publicly accessible on 4/20/15. *See supra* §IV.

Postow is also prior art to the other Challenged Claims (i.e., claims 11 and 17) because it was publicly accessible before the '973 Provisional was filed. Petitioner is not aware of any basis for either §102(b)(1) exception.

C. NCT-109 (EX1007)

NCT-109 is Version 1 of a clinical trial protocol with the Brief Title "Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors." The "Last Update Posted" date for Version 1 on ClinicalTrials.gov was 10/23/13. EX1007, 4. NCT-109 was not cited or discussed during the prosecution of the '113 patent.

As explained above as to NCT-505 (see §V.A), ClinicalTrials.gov publicizes clinical trial protocols and NCT-109's "Last Update Posted" date demonstrates that it was publicly available as of 10/23/13. Lassman, ¶¶43-50. POSAs knew that clinical trial protocols, like NCT-109, were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. Hanks, ¶62. NCT-109 thus constitutes a printed publication under §102(a)(1) as of 10/23/13. NCT-109 is thus §102(a)(1) prior art without any exception under §102(b)(1).

D. Cogswell (EX1015)

Cogswell published as International Publication No. WO 2013/173223 A1 on 11/21/13, making it §102(a)(1) prior art to the Challenged Claims without any exception under §102(b)(1). EX1015, face. Cogswell was of record during prosecution, but never applied or otherwise addressed.

VII. PRECISE REASONS FOR RELIEF REQUESTED

A. GROUNDS 1A, 1B, 1C: NCT-505 and NCT-109 Render Obvious Challenged Claims 1-4, 10-12, 13-15, and 17-20

Grounds 1A, 1B, and 1C center on NCT-505, which underlies the '113 Patent's Example 1 and discloses anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) combination therapy followed by nivolumab monotherapy to treat melanoma tumors. NCT-505 discloses a method encompassing all elements of Challenged Claims 1-4, 10-15, and 17-20 aside from administering the biweekly anti-PD-1 monotherapy as a flat dose rather than a weight-based dose. NCT-109 discloses anti-PD-1 monotherapy as a flat dose—including 240 mg nivolumab once every two weeks to treat melanoma tumors. Given the multiple known benefits of flat dosing, POSAs would have reason to modify NCT-505 to administer a flat dose of nivolumab as disclosed in NCT-109. Hanks, ¶69.

Ground 1A concerns claims 1-4, 10, 13-15, and 19-20, which encompass anti-PD-1 monotherapy flat doses of either 240 mg and 480 mg and therefore are plainly not entitled to the benefit of the '973 Provisional. *See supra* §IV.

Ground 1B concerns dependent claims 11 and 17, which require an anti-PD-1 monotherapy flat dose of 240 mg once every two weeks. With a single exception (Postow), all references cited in Ground 1A—including references relied upon merely for background teachings—constitute indisputable prior art for claims 11

and 17. And even Postow is cited in Ground 1A only as background for dependent claim 3, which recites language ***not*** included in dependent claims 11 and 17.

Ground 1C concerns dependent claims 12 and 18, which require an anti-PD-1 monotherapy flat dose of 480 mg once every four weeks. Doubling the dosage (i.e., from 240 mg to 480 mg) while also doubling the intervals between treatments (i.e., from two weeks to four weeks) was an obvious variant of the NCT505-NCT109 protocol—delivering the same amount of anti-PD-1 monotherapy while decreasing the number of injections.

Obviousness does not require that a particular claimed regimen be the only or best choice. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention."). There are indeed ***multiple*** obvious variants of NCT505-NCT109, including—but not limited to—240 mg every two weeks (per Grounds 1A-1B) and 480 mg every four weeks (per Ground 1C).

1. GROUND 1A: NCT-505 and NCT-109 Render Obvious Claims 1-4, 10, 13-15, and 19-20

NCT-505 and NCT-109 together disclose all of the dosing amounts and frequencies of anti-PD-1 and anti-CTLA-4 recited in Challenged Claims 1-4, 10, 13-15, and 19-20, and POSAs would have had reason to combine these teachings to arrive at the claimed treatment method with a reasonable expectation of success.

NCT-505, underlying the '113 Patent's Example 1, discloses the combination therapy recited in claims 1-4, 10, 13-15, and 19-20 and the weight-based combination frequency and amounts. In addition, the nivolumab anti-PD-1 antibody disclosed by NCT-505 was already being administered as a flat dose, as disclosed in NCT-109, given its wide therapeutic window and its known features as a well-tolerated and long-lasting therapeutic. Hanks, ¶74-75; EX1009, 3169, 3171. Indeed, for antibodies such as nivolumab with wide therapeutic windows, flat dosing was known to have "numerous advantages over body size-based dosing." EX1008, 1023. For example, NCT-109 discloses administering a flat dose of 240 mg nivolumab once every two weeks to melanoma patients. EX1007, 5. POSAs would have had ample reason to combine the NCT-505 and NCT-109 teachings to practice NCT-505 while obtaining the advantages of flat dosing over NCT-505's weight-based dosing for the nivolumab monotherapy.

Specifically, it would have been obvious to administer the nivolumab monotherapy at a flat 240 mg dose once every two weeks following nivolumab's coadministration with an anti-CTLA-4 antibody to treat melanoma. Hanks, ¶76.[3]

[3] Ground 1A addresses the 240 mg dosage alternative, the obviousness of which suffices to render claims 1-4, 10, 13-15, and 19-20 unpatentable. *Fresenius USA,*

For 80 kg patients—consistent with the median weight of melanoma patients in other immunotherapy clinical trials (EX1035)—a 240 mg flat dose of nivolumab once every two weeks constitutes the exact same amount of nivolumab as NCT-505's express disclosure of a weight-based dose of 3 mg/kg nivolumab once every two weeks. Hanks, ¶¶75-76.

a. NCT-505 Discloses Treating Melanoma with a Combination of Nivolumab and Ipilimumab Followed by Nivolumab Alone

NCT-505 expressly discloses treating melanoma tumors using "Nivolumab in combination with Ipilimumab." EX1014, 4.

Nivolumab—also known as "BMS-936558"—was a known anti-PD-1 antibody. Hanks, ¶¶50, 78; EX1009, 3168 ("MDX-1106 (BMS-936558/ONO-4538) is a genetically engineered, fully human…mAb specific for human PD-1"); EX1028 ("Nivolumab and ipilimumab are fully human monoclonal antibodies that block the immune checkpoint receptors PD-1 and CTLA-4, respectively"); *see also* EX1001, 17:61-67; EX1014, 4 ("Nivolumab…Other Names: BMS-936558").

Ipilimumab was a known anti-CTLA-4 antibody. Hanks, ¶79; EX1028; EX1001, 21:29-37.

Inc. v. Baxter Int'l, Inc., 582 F.3d 1288, 1298 (Fed. Cir. 2009). A 480 mg dosage would also have been obvious, per Ground 1C.

NCT-505 discloses a two-stage treatment regime—(1) co-administration of nivolumab and ipilimumab followed by (2) administration of nivolumab alone:

- In the co-administration phase, "Nivolumab 1 mg/kg solution" was "combined with Ipilimumab 3 mg/kg" and administered "intravenously every 3 weeks for 4 doses." EX1014, 4.
- In the subsequent anti-PD-1 monotherapy stage, nivolumab was administered via "3 mg/kg solution intravenously every 2 weeks." *Id*.

NCT-505 further disclosed that (i) "Progression Free Survival," (ii) "Objective Response Rate," and (iii) "OS [(Overall Survival)] based on PD-L1 expression" were outcome measures. *Id*., 5.

b. <u>Reason to Modify</u>: POSAs Would Have Had Reason to Use a Flat Dose of Nivolumab for Monotherapy Instead of the Body Weight Dose Given the Known Benefits of Flat Dosing

Given (1) the multiple known advantages of flat dosing and (2) nivolumab's favorable safety profile, POSAs would have had reason to practice NCT-505's anti-PD-1 monotherapy stage using a flat dose of nivolumab rather than the 3 mg/kg weight-based dose NCT-505 discloses. Hanks, ¶¶82-86. Nivolumab itself was "well tolerated," "dose-independent" over a wide dose range, and long-lasting ("≥ 57 days")). EX1009, 3167, 3171. Wang discloses that for antibodies with a wide therapeutic window, such as nivolumab, "[f]ixed dosing provides numerous advantages over body size–based dosing" and indeed "is the approach of choice"

provided "there is no advantage of one dosing approach over another from a PK and PD perspective." EX1008, 1023. POSAs would understand that Wang's teaching was applicable to NCT-505's nivolumab monotherapy phase because weight-based dosing of nivolumab alone did not offer pharmacokinetic advantages or practical benefits. Hanks, ¶86.

Other prior art confirms Wang's recommendations. Hanks, ¶84. For example, Mathijssen notes that flat-dosing provides advantages including "positive economic implications"; improved "safety,"; and better "patient adherence," and thus may be preferred to size-based dosing unless the drug exhibits "a narrow therapeutic window and high interindividual variability." EX1033, 918. Bai likewise teaches that most monoclonal antibodies have "a relatively large therapeutic window" and "fixed dosing is recommended" as "the first option in first-in-human studies" given flat dosing's "many practical advantages." EX1034, 119, 133. It was well known that nivolumab had a wide therapeutic window. EX1009, 3169, 3171. Further, it was also known that numerous other monoclonal antibodies—including multiple mAbs indicated for oncology—were administered via flat doses. EX1036, 25-26.

Accordingly, POSAs would have had reason to practice NCT-505's nivolumab monotherapy step using a flat dose rather than the weight-based dose disclosed in NCT-505. Hanks, ¶85; *see Intel Corp. v. PACT XPP Schweiz AG*, 61

F.4th 1373, 1379 (Fed. Cir. 2023) ("*[A]ny* need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007)). At minimum, such flat dosing of nivolumab would have been obvious to try, as flat doses are one of a small finite number of dosing schemes suitable for monoclonal antibodies. Hanks, ¶85; EX1036, 30; *Ex parte Anand*, Appeal 2019-001845, 2020 WL 1169599, at *9 (PTAB Mar. 4, 2020) (citing EX1036: "Mould explains that there were three known dosing regimens at the time: (1) flat dosing, (2) body-weight dosing, and (3) Bayesian individualized dosing in response to a measurement. (See Mould 30.).")

c. <u>The Modification</u>: 240 mg Every Two Weeks

POSAs would have had reason to select a flat dosage of 240 mg of nivolumab—as expressly disclosed in NCT-109—given the knowledge that when bodyweight-based dosing has been used previously, "[t]he dose of fixed dosing approach [is] set to the dose that would be given to a subject with median [bodyweight] by [bodyweight]-based dosing." EX1008, 1014; Hanks, ¶87.

Indeed, a flat dose of 240 mg every two weeks results from translating NCT-505's 3 mg/kg weight-based dosage into the actual dose a typical 80 kg clinical trial subject would receive. 80 kg was a typical average weight for melanoma

patients undergoing immunotherapy trials. Hanks, 88; EX1035, 108. Confirming this logic, NCT-109 discloses a clinical trial that used 240 mg nivolumab once every two weeks for treating melanoma patients. Hanks, ¶89; EX1007, 5-6 (disclosing "BMS-936558" (a.k.a. nivolumab) "240 mg solution intravenously" "every 2 weeks" for "incurable melanoma"). POSAs would thus have modified the method of treatment disclosed by NCT-505 by administering 240 mg nivolumab disclosed by NCT-109 once every two weeks following the combination therapy with nivolumab and ipilimumab (hereinafter "**NCT505–NCT109**"). Hanks, ¶90.

d. Reasonable Expectation of Success: POSAs Knew Nivolumab Had a Wide Therapeutic Window

POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 240 mg nivolumab monotherapy once every two weeks following the combination therapy would have been comparable to administering 3 mg/kg nivolumab monotherapy every two weeks following the combination therapy pursuant to NCT-505. Hanks, ¶91.

Indeed, prior art had already disclosed a flat dose of 240 mg nivolumab for melanoma treatment. NCT-109 discloses a 2013 clinical trial that used 240 mg nivolumab once every two weeks for treating melanoma patients. Hanks, ¶92; EX1007, 5-6.

Moreover, nivolumab was known to have a wide therapeutic window. Hanks, ¶93; EX1009, 3169, 3171. Brahmer discloses a "phase I study" where

"[t]hirty-nine patients with advanced metastatic melanoma … received a single intravenous infusion of [nivolumab] in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg…." *Id.*, 3167; Hanks, ¶93. For an 80 kg average weight melanoma patient (EX1035, 108), that translated into doses of 24 mg, 80 mg, 240 mg, and 800 mg. Hanks, ¶93. Brahmer discloses that across that wide range of doses, "PD-1 occupancy appeared to be ***dose-independent***." EX1009, 3171. Brahmer also discloses administration of 3 mg/kg or 10 mg/kg nivolumab every four weeks. *Id*., 3168. Topalian likewise discloses a phase I study in which melanoma patients received a dose of 0.1-10 mg/kg nivolumab once every two weeks; it reports that the "pharmacokinetics of the antibody were linear." EX1011, 2443, 2449. Given nivolumab's dose independency and linear pharmacokinetics across a wide dose range, POSAs would have expected a flat dose of 240 mg every two weeks—within the ranges tested by Brahmer and Topalian—to be comparable to a body weight dose of 3 mg/kg every two weeks. Hanks, ¶94-96. POSAs would have also expected such doses to be safe. Hanks, ¶97. Both Brahmer and Topalian report that in dose escalation studies, no maximum tolerated dose was reached even at 10 mg/kg. Id.; EX1009 at 3172; EX1011, 2443. Such reports further confirmed the safety of a 240 mg flat dose even for lightweight patients. Hanks, ¶98. 10 mg/kg translates to less than 7 mg/kg even for 80-pound patients. *Id*.

The fact that numerous other monoclonal antibodies—including those indicated for cancer treatment—had successfully been administered via flat dosing further confirms the reasonable expectation of success. Hanks, ¶99; EX1036 at 25-26 (disclosing eleven monoclonal antibodies administered via flat dosing); *Anand*, 2020 WL 1169599, at *8 (citing Mould (EX1036): "The claimed anti-beta7 antibody was not the first antibody to be found appropriate for flat dosing. We find that in light of these other antibodies those of ordinary skill would have had a reasonable expectation that flat dosing of the claimed anti-beta7 antibody would have been successful."). Indeed, nivolumab's pharmacokinetic profile tracked that of other monoclonal antibodies. EX1029 ("Shah"), ¶¶42-43.

e. Claim-by-Claim Analysis

NCT505-NCT109 satisfies every limitation of claims 1- 4, 10, 13-15, and 19-20, rendering them obvious. Hanks, ¶100.

i. Claim 1

(1) Preamble: Method for Treating Melanoma

To the extent the preamble is limiting, NCT505-NCT109 satisfies it because NCT-505 discloses a method for treating "advanced melanoma" in human patients. Hanks, ¶101; EX1014, 3.

(2) Limitation 1(i): Identifying a Patient Having a PD-L1-Negative Melanoma

NCT505-NCT109 satisfies limitation [1](i) because NCT-505 discloses that an outcome measure was "OS [(overall survival)] based on PD-L1 expression." EX1014, 5; Hanks, ¶102. NCT-505 states that identification of PD-L1 expression was to be made on "Day 1." EX1014, 5; Hanks, ¶102. POSAs would understand that assessing overall survival based on PD-L1 expression required testing patients' melanoma tumors for PD-L1 expression, thereby identifying both PD-L1-positive and PD-L1-negative melanoma tumors. Hanks, ¶103. Further, it was already known that PD-L1 negative melanoma patients were responsive to the combination of nivolumab and ipilimumab. EX1028, 1. Accordingly, POSAs would have had reason to identify patients having PD-L1 negative melanoma tumors. Hanks, ¶103. They likewise would have had a reasonable expectation of success in treating such patients using a combination of nivolumab and ipilimumab. *Id*.

(3) Limitation 1(ii)(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

NCT505-NCT109 satisfies limitation [1](ii)(a) because NCT-505 discloses that "***Nivolumab* [i.e., a known anti-PD-1 antibody] *1 mg/kg solution***" is "combined with ***Ipilimumab*** [i.e., a known anti-CTLA-4 antibody] 3 mg/kg" and

administered "intravenously every 3 weeks for 4 doses" to the patient. EX1014, 4; Hanks, ¶¶104-105. Moreover, it was well known by 2015 that anti-PD-1 and anti-CTLA-4 antibodies could be administered in combination at the "every 3 weeks for 4 doses" regimen already approved for anti-CTLA-4 antibodies. *See e.g.,* EX1025; *see also* Hanks, ¶105. Indeed, both nivolumab and ipilimumab had already been approved by the FDA. EX1023—EX1024.

(4) Limitation 1(ii)(b): Administering a Subsequent Anti-PD-1 Antibody Flat Dose of About 240 mg or About 480 mg

NCT505-NCT109 satisfies limitation [1](ii)(b) because NCT-505 discloses administering to the patient ***"Nivolumab 3 mg/kg solution intravenously every 2 weeks***" following the combination therapy. EX1014, 4; Hanks, ¶¶106-107. And NCT-109 discloses administering a flat dose of "***240 mg***" nivolumab "every 2 weeks" (EX1007, 5), including to patients with "incurable melanoma" (*id*., 6). Hanks, ¶107.

As explained above in §§VII.A.1.b-c, POSAs would have had reason to modify NCT-505's biweekly weight-based 3 mg/kg nivolumab monotherapy dose to the known alternative of a biweekly flat dose of 240 mg given the "numerous advantages" of flat dosing that were recognized by POSAs, disclosed in Wang, and confirmed in other prior art such as Bai and Mathijssen. EX1008, 1023; EX1033, 918; EX1034, 119, 133; Hanks, ¶108.

As explained above in §VII.A.1.d, POSAs would have had at least a reasonable expectation of making the substitution and achieving comparable clinical results because of nivolumab's wide therapeutic window and NCT-109's disclosure of using a 240 mg flat dose of nivolumab to treat melanoma, as well as the multiple other monoclonal antibodies that had been successfully administered via flat dosing. *See also* Hanks, ¶109; EX1009, 3167, 3169, 3171; EX1036, 25-26.

NCT505–NCT109 thus satisfies limitation 1(ii)(b), rendering claim 1 obvious. Hanks, ¶110.

ii. Claim 2

Claim 2 is similar to claim 1, but does <u>not</u> recite "identifying a patient having a PD-L1-negative melanoma tumor."

(1) Preamble: Method for Treating a Melanoma

To the extent claim 2's preamble of claim 2 is limiting, NCT505-NCT109 satisfies it for the same reason as claim 1. *See* §VII.A.1.e.i(1); Hanks, ¶¶112-113.

(2) Limitation 2(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

NCT505-NCT109 satisfies limitation 2(a) for the same reasons it discloses limitation 1(ii)(a). *See* §VII.A.1.e.i(3); Hanks, ¶¶114-115.

(3) Limitation 2(b): Administering a Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

NCT505-NCT109 satisfies limitation 2(b) for the same reasons it satisfies limitation 1(ii)(b), rendering claim 2 obvious. *See* §VII.A.1.e.i(4); Hanks, ¶¶116-117.

iii. Claim 3: Over 8 Months Progression-Free Survival and/or At Least About 10% Tumor Size Reduction

Claim 3 depends from claim 2 and requires that "the patient is characterized by (i) extended progression-free survival for over 8 months …, (ii) tumor size reduction at least about 10% …, or (iii) both (i) and (ii)." There are multiple independent reasons why claim 3 is unpatentable in view of NCT505-NCT109.

First, in the context of this particular case, claim 3's additional language should be construed as non-limiting because it merely recites the "intended result" of claim 2's method and therefore "does not result in a manipulative difference in the steps of the claim." *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc*., 246 F.3d 1368, 1376 (Fed. Cir. 2001); *see also id*. at 1375 ("The express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim."). As NCT505–NCT109 satisfies claim 2, it also, therefore, satisfies claim 3, which merely recites an intended result and is nonlimiting for that reason.

Second, even if claim 3's recited result were limiting, NCT505–NCT109 would still render it obvious because the claimed outcomes are the natural results of administering nivolumab and ipilimumab per NCT505–NCT109. "When the prior art does not expressly disclose a claim limitation, 'inherency may supply a missing claim limitation in an obviousness analysis.'" *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020). In such cases, "there is no question of a reasonable expectation of success in achieving" the recited property. *Id*. at 1332; *see also Cytiva BioProcess R&D AB v. JSR Corp*., 122 F.4th 876, 889-91 (Fed. Cir. 2024) (citing *Hospira* and reversing Board's determination that method claims reciting "inherent property" were not unpatentable as obvious).

Here, Postow discloses that administering nivolumab and ipilimumab, as disclosed by NCT-505, achieved progression-free survival for over 8 months and tumor size reduction of at least about 10%. EX1005, 2009; Hanks, ¶121. Specifically, Postow discloses that "the median progression-free survival was not reached with the combination therapy" (EX1005, 2006)—meaning that progression-free survival was well over 8 months for many patients. Hanks, ¶121. Moreover, Postow discloses a "complete response was observed in 16 patients (22%) in the combination group." EX1005, 2009. POSAs would understand this to mean that the tumor was reduced by 100% for these patients—well beyond the claimed "at least about 10%." Hanks, ¶121; EX1039, 232.

Separately, Postow discloses that nivolumab and ipilimumab, as disclosed by NCT-505, achieved a median decrease in tumor burden of 68.1% pursuant to the RECIST standard. EX1005, 2008-2009; EX1039; Hanks, ¶¶122-124.

Because nivolumab is "***dose-independent***" over a wide range of doses (EX1009, 3171), administering 240 mg nivolumab once every two weeks would have yielded substantially the same results as disclosed by Postow when administering 3 mg/kg nivolumab once every two weeks. Hanks, ¶125. The results recited by claim 3 are thus the natural result of administering the NCT505–NCT109 dosing regimen, thus rendering claim 3 obvious. *Id.* ¶¶118-125.

iv. Claim 4: Measuring PD-L1 Expression Prior to Administration

NCT505–NCT109 satisfies claim 4, thus rendering it obvious because NCT-505 discloses that one of the secondary outcome measures was "OS [(overall survival)] based on PD-L1 expression." EX1014, 5; Hanks, ¶¶126-129. POSAs would understand that to measure overall survival based on PD-L1 expression, the patients' melanoma tumor would need to be measured for PD-L1 expression. Hanks, ¶127. NCT-505 states that identification of PD-L1 expression was to be made on "Day 1." EX1014, 5; Hanks, ¶127. Moreover, POSAs would have been motivated to measure PD-L1 expression prior to administering the antibodies as required by claim 4 because that would be a logical time to take such a measurement, at least to categorize patients based on expression of this biomarker

and/or track patients' progress based on expression of this biomarker. Hanks, ¶128; EX1011, 2445 ("Immunohistochemical analysis for PD-L1 was performed on archival or newly obtained ***pretreatment*** . . . tumor specimens"). Indeed, in situations when the antibodies had eliminated the tumor, there would be nothing left to measure. Hanks, ¶128.

For these reasons and those discussed above regarding claim 1, claim 4 would have been obvious over NCT505-NCT109.

v. Claims 10 and 20: the Anti-PD-1 Antibody Is Nivolumab

NCT505–NCT109 satisfies claims 10 and 20 because NCT-505 discloses administering "nivolumab" (EX1014, 4)—the same anti-PD1 antibody disclosed in NCT-109 (EX1007, 5). Hanks, ¶¶130-131.

vi. Claim 13: the Anti-CTLA-4 Antibody Is Ipilimumab

NCT505–NCT109 satisfies claim 13 because NCT-505 discloses the anti-CTLA-4 antibody "ipilimumab." NCT-505, 4; Hanks, ¶¶`132-133.

vii. Claims 14, 15 and 19: the Anti-CTLA-4 Antibody Is from 0.1 mg/kg to 10.0 mg/kg or 3 mg/kg

NCT505-NCT109 satisfies claims 14, 15, and 19 because NCT-505 discloses administering 3 mg/kg of the anti-CTLA-4 antibody ipilimumab—the dose claimed by claims 15 and 19 and within claim 14's 0.1-10 mg/kg range. EX1014, 4; Hanks, ¶¶134-135.

2. GROUND 1B: NCT-505 and NCT-109 Render Obvious Claims 11 and 17

Dependent claims 11 and 17 are addressed separately (i.e., as Ground 1B) because *supra* Section IV does not expressly challenge their entitlement to the benefit of the 4/28/15 provisional. Nonetheless, both NCT-505 and NCT-109 constitute indisputable §102(a)(1) art regardless. Aside from Postow (EX1005), so do all other references cited in Ground 1A as further exemplifying the state of the art; all were publicly accessible to POSAs more than a year before 4/28/15. Moreover, Ground 1A cites Postow only as to dependent claim 3, which recites an ostensible limitation absent from claims 11 and 17.

Accordingly, claims 11 and 17 are unpatentable as obvious over NCT505–NCT109 for the same reasons set forth in Ground 1A. Claims 11 and 17 are identical to claims 2 and 1, respectively, aside from further specifying the flat dose monotherapy. They require the flat dose to be "about 240 mg" (rather than either "about 240 mg or about 480 mg," as recited in claims 1 and 2) and further require the flat dose to be " administered once every two weeks."

NCT505–NCT109 renders obvious claims 11 and 17. Hanks, ¶¶137-141. As explained in §§VII.A.1.b-c, above, POSAs would have administered the known flat dose of 240 mg nivolumab once every two weeks instead of the 3 mg/kg every two weeks as disclosed by NCT-505 to achieve the "numerous advantages" of flat dosing known to POSAs and disclosed by Wang. *See also* Hanks, ¶141. NCT-109

itself specifically discloses administering a flat dose of "***240 mg***" nivolumab "***every 2 weeks***" (EX1007, 5), including to patients with "incurable melanoma" (*id*., 6).

3. GROUND 1C: NCT505 and NCT109 Render Obvious Claims 12 and 18

Claims 12 and 18 depend from claims 2 and 1, respectively, which are obvious over NCT505—NCT109 per Ground 1A. Claims 12 and 18 merely require that the flat dose anti-PD-1 antibody be "about 480 mg" (as opposed to ***either*** "about 480 mg" or "about 240 mg" as in claims 1-2) and further that it be "administered once every four weeks." Such a dosage schedule would have been an obvious variant of NCT505-NCT109's flat dosage of 240 mg nivolumab every two weeks as expressly taught in NCT109 (EX1007, 5-6). Hanks, ¶¶142-143. Indeed, it was known that nivolumab had a favorable safety profile and could be administered once every four weeks (as required by claims 12 and 18) at dosages of between 0.3-10 mg/kg (EX1009, 3168)—corresponding to dosages of 24-800 mg for an average 80 kg melanoma patient (EX1035, 108); Hanks, ¶143. In the context of the '113 Patent, there was nothing patentable about optimizing such dosages and selecting a 480 mg flat dose every four weeks to achieve flat dosing's "numerous advantages" (EX1008) and deliver the same amount of nivolumab as the 240 mg dose once every two weeks (as expressly disclosed in NCT109, EX1007, 5-6)—while enhancing patient convenience and compliance levels by

reducing the number of required treatments. *See*, *e.g.*, *Yeda Rsch. v. Mylan Pharms. Inc*., 906 F.3d 1031, 1046 (Fed. Cir. 2018) (affirming Board's determination in context of a "forgiving drug" that POSAs would have been "motivated to combine [primary reference's] 40mg every other day dose with a less frequent dosing regimen, such as 3x/week"). NCT505 and NCT109 therefore also render obvious claims 12 and 18.

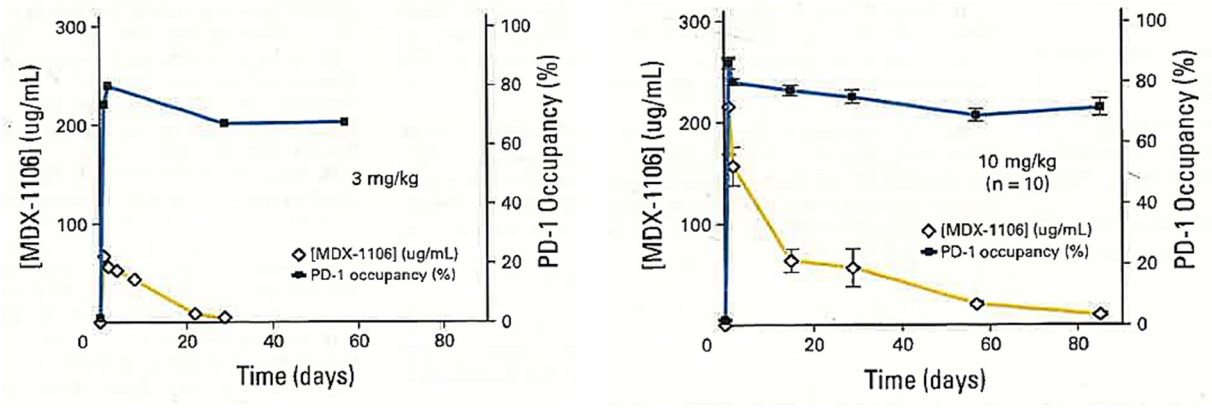
a. Reason to Use a 480 mg Dose Once Every Four Weeks

POSAs would have had reason to administer a flat dose of nivolumab once every four weeks rather than every two weeks. Hanks, ¶144. POSAs knew that "market pressures for higher patient convenience and compliance continue to drive antibody drug programs toward less frequent dosing schedules." EX1021, 158. Such issues were particularly pronounced in the context of antibodies such as nivolumab requiring infusion-based administration. Hanks, ¶144.

Furthermore, POSAs seeking to administer the nivolumab monotherapy less frequently than once every two weeks (as disclosed in both NCT-505 and NCT-109) would have had particular reason to select the four-week frequency previously disclosed by Brahmer. EX1009, 3168; Hanks, ¶145. POSAs would have thus had reason to administer nivolumab once every four weeks (disclosed in Brahmer) as an alternative to every two weeks (disclosed in NCT-505 and NCT-109). *Hoffmann-La Roche Inc. v. Apotex Inc*., 748 F.3d 1326, 1329 (Fed. Cir.

2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance."); *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1373 (Fed. Cir. 2005) ("increasing patient compliance" motivated once-weekly dose instead of a daily dose).

POSAs inclined to administer nivolumab once every four weeks would have had reason to administer it as a 480 mg flat dose. Hanks, ¶¶146-148. Brahmer investigated the pharmacokinetics and pharmacodynamics of nivolumab and taught that a 3 mg/kg dose (i.e., as taught in NCT-505)—equivalent to a 240 mg flat dose (as taught in NCT-109) for an average 80 kg melanoma patient—was nearly eliminated after 21 days (3 weeks), whereas a larger 10 mg/kg dose resulted in measurable amounts of nivolumab well past 80 days. EX1009, 3173 (*see* figures reproduced below); Hanks, ¶¶149-151; Shah, ¶¶35-43.



In selecting a flat dose of nivolumab to be administered once every four weeks as an alternative to 240 mg administered once every two weeks, 480 mg would have

been a particularly logical choice because it is twice the 240 mg dose—consistent with the doubling of time between treatments (from two to four weeks) while administering the same total amount of nivolumab as in NCT-109. Hanks, ¶147.

Thus, POSAs would have been motivated to administer a flat dose of 480 mg nivolumab once every four weeks following the combination therapy with ipilimumab as an alternative to administering 240 mg once every two weeks. Hanks, ¶¶142-148; *see also Hoffmann-La Roche*, 748 F.3d at 1329 (finding obvious a 150 mg monthly dose based on disclosure of 5 mg daily dose because 150 mg/month = "5 mg/day × 30 days/month"); *Merck*, 395 F.3d at 1373 (finding 35 mg weekly dose was obvious over disclosure of 5 mg daily dose because 5 mg/day × 7 days = 35 mg/week).

b. Reasonable Expectation that 480 mg Nivolumab Once Every Four Weeks Would Be Comparable to 3 mg/kg Once Every Two Weeks

POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 480 mg nivolumab once every four weeks following the combination therapy with nivolumab and ipilimumab was comparable to administering 240 nivolumab every two weeks per NCT505-NCT109. Shah, ¶¶19-27, 54-57; Hanks, ¶¶149-153. Indeed, pharmacokinetic modeling based on Brahmer and using techniques available to POSAs before 2015 confirms that POSAs would have expected that 480 mg dosing once every four

weeks achieves nivolumab concentrations that are always higher than those expected with 240 mg dosing once every two weeks. Shah, ¶¶28-56; EX1036, 23-24 (discussing role of "pharmacokinetic and pharmacodynamic behavior" and related modeling in supporting "flat dosing").

Moreover, NCT02713867 ("NCT-867") is a posting from ClinicalTrials.gov posted on 3/21/16 (EX1013)—over a month before 4/28/16, the earliest possible effective filing date of claims 12 and 18 (*see supra* §IV). NCT-867 disclosed using 480 mg nivolumab once every four weeks to treat cancer. *Id*., 4; Hanks, ¶152. While NCT-867 does not disclose treating melanoma, specifically, POSAs would have expected the 480 mg nivolumab dose once every four weeks to be suitable for treating melanoma, at least because Brahmer discloses that nivolumab was "well tolerated," "dose-independent" over a wide dose range and long-lasting ("≥ 57 days"), specifically for the treatment of melanoma, and tested a range of doses spanning NCT-867's flat 480 mg dose. EX1009, 3167, 3171; Hanks, ¶152.

POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 480 mg nivolumab once every four weeks following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 240 mg nivolumab every two weeks per NCT505-NCT109. Shah, ¶¶19-27, 54-57; Hanks, ¶¶149-153.

c. PO's Burden to Overcome Obviousness of 480 mg Dose Falling Within Prior Art Range

Even aside from the specific above-discussed reasons why a 480 mg flat dose every four weeks would have been an obvious selection for the nivolumab monotherapy when practicing NCT505-NCT109, it is also ***presumptively*** obvious because 480 mg falls squarely within Brahmer's dosage range. Brahmer's disclosure of doses from ".3" to "10 mg/kg" once every "4 weeks" (EX1009, 3167) constitutes a dosage of 24-800 mg for an average 80 kg melanoma patient (EX1035)." Hanks, ¶¶154-155. Accordingly, the claimed 480 mg dose falls within Brahmer's 24 mg – 800 mg dosage range. *Anand*, 2020 WL 1169599, at *9:

> As the Examiner notes, a change in concentration is normally not a patentable modification….[T]he Examiner's calculations demonstrate that the claimed range of about 100 mg to about 220 mg is not drastically different from, but rather overlaps, the range of about 0.05 mg/kg to about 10 mg/kg taught in the Fong '082 patent for an average man of 70 kg[4] (calculated to be 3.5 to 700 mg).")

[4] The claims in *Anand* concerned gastrointestinal diseases rather than melanoma. Per Feng (EX1035), assuming an average weight of 80 kg for melanoma patients is reasonable when interpreting Brahmer. Hanks, ¶143. The possibility that other

Anand exemplifies the "presumption of obviousness" when a claim falls within a prior art range. *Tyco Healthcare Grp. LP v. Mut. Pharm. Co*., 642 F.3d 1370, 1372 (Fed. Cir. 2011); *see also Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) (reversing nonobviousness finding where claimed dosage range overlapped with dosages disclosed in prior art). Because the 480 mg dose falls within Brahmer's range, "the burden of production falls upon [PO] to come forward with evidence of teaching away, unexpected results or criticality, or other pertinent objective indicia indicating" nonobviousness. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1007 (Fed. Cir. 2018). PO never presented such data in the specification (EX1001) or during prosecution (*see* EX1002). Even the FDA—applying safety and efficacy criteria inapplicable to patentability—ultimately approved the 480 mg dosage of nivolumab without requiring clinical data. EX1037-EX1038. While not necessary to find claims 12 and 18 obvious, the FDA's determination corroborates POSAs' reasonable expectation that 480 mg once every four weeks was a safe and effective dosage. *See Hoffman*, 748 F.3d at 1331 (affirming finding that "once monthly" dosage would have been obvious—noting that (1) patents did not "present data" to the claimed efficacy and (2) such

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calculations could also be reasonable does not alter the obviousness of claims 12 and 18 under this analysis. *See Fulton*, 391 F.3d at 1200.

efficacy had been "demonstrated to the FDA through a 'bridging study'" rather than actual clinical data).

d. Conclusion: Claims 12 and 18 Are Obvious

NCT505–NCT109, as practiced with a flat dose of 480 mg once every four weeks (as suggested by Brahmer) in lieu of a 240 mg flat dose once every two weeks (as disclosed in NCT-109), renders obvious claims 12 and 18. Hanks, ¶156.

B. <u>GROUND 2:</u> NCT-505, NCT-109, and Cogswell Render Obvious Claims 5-9 and 16

Claims 5-9 depend from dependent claim 4 and specify how to measure "PD-L1 expression of the melanoma tumor." Claim 16 depends from claim 2 and requires "administering an anti-cancer agent" in addition to claim 2's immunotherapy. Such techniques were already well known and recommended for cancer immunotherapy, as disclosed in Cogswell. There was nothing inventive about using them to practice NCT-505 either on its own or when implemented in view of NCT-109 to use a 240 mg flat dose. Claims 5-9 and 16 are therefore unpatentable as obvious over NCT-505 in view of NCT-109 and Cogswell.

1. Reason to Combine Cogswell with NCT505-NCT109

NCT-505 discloses a method of testing for PD-L1 expression (*see* §VII.A.1.e.i(2)), but does not specify the details of such testing. Hanks, ¶158. POSAs would have been motivated to implement NCT-505 using Cogswell's pre-treatment PD-L1 expression measurement method. *Id.*; EX1015, 125:23-25

(disclosing "***pre-treatment PD-L1 expression was measured*** by IHC in FFPE tumor specimens using the rabbit anti-PD-L1 mAb, 28-8, and an automated assay developed by Dako."). POSAs would have had reason to use Cogswell's detailed disclosure for the assessment of PD-L1 expression as disclosed by NCT-505 in combination with NCT-109 (hereinafter, "NCT505-NCT109-Cogswell"). Hanks, ¶158. Cogswell indeed expressly references NCT-505. EX1015, 53:9.

2. Reasonable Expectation of Success

POSAs would have had at least a reasonable expectation that Cogswell's detailed PD-L1 testing method would successfully measure the PD-L1 expression of melanoma tumors (i.e., as taught in NCT-505) because Cogswell discloses that its rabbit clone 28-8 "produced the most robust detection specifically of membranous PD-L1." EX1015, 35:9-12; Hanks, ¶159. POSAs would thus have had at least a reasonable expectation of successfully detecting PD-L1, as Cogswell disclosed a detection method effective at doing exactly that. Hanks, ¶159.

3. Claim-by-Claim Analysis

As discussed in §§VII.B.1-2, POSAs would have had reason to practice NCT505-NCT109 using Cogswell's detailed PD-L1 testing method and would have had a reasonable expectation of success in doing so. And as detailed below, NCT505-NCT109-Cogswell discloses all limitations of claims 5-9 and 16. For at least these reasons as well as those discussed in Ground 1A regarding why claims

2 and 4 would have been obvious as of 4/28/15 (*i.e.*, one year before the earliest priority date to which those claims are possibly entitled, *see supra* §IV), dependent claims 5-9 and 16 would have also been obvious as of this date. Hanks, ¶¶160-161.

a. Claim 5: Providing a Sample of Tumor Cells

NCT505–NCT109–Cogswell satisfies claim 5. Hanks, ¶¶162-163. NCT505–NCT109–Cogswell satisfies claim 4, from which claim 5 depends, for the reasons explained in Ground 1A. *See* §VII.A.1.e.iv. Concerning claim 5's additional requirement of providing a "test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells," Cogswell discloses provid[ing] a test tissue sample…comprising tumor cells and tumor-infiltrating inflammatory cells" in connection with cancer immunotherapy treatment. EX1015, 3:26-30; Hanks, ¶163.

b. Claim 6: Assessing the Portion of the Cells that Express PD-L1 on the Cell Surface

NCT505–NCT109–Cogswell satisfies claim 6. Hanks, ¶¶164-165. NCT505–NCT109–Cogswell satisfies claim 5 (from which claim 6 depends) for the reasons explained immediately above. Concerning claim 6's additional requirement of "assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface," Cogswell's above-quoted passage further discloses "assessing the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface." EX1015, 3:26-30.

c. Claim 7: IHC Assay on a FFPE Sample

NCT505–NCT109–Cogswell satisfies claim 7. Hanks, ¶¶166-169. NCT505–NCT109–Cogswell satisfies claim 6 (from which claim 7 depends) for the reasons explained immediately above. Concerning claim 7's additional requirements that the "test tissue sample" be a "formalin-fixed paraffin-embedded (FFPE) tissue sample" and further that the "presence of PD-L1 [be] determined using an automated IHC assay," Cogswell discloses embodiments in which "the test tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample" and "the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is [determined] by immunohistochemical (IHC) staining of the FFPE sample." EX1015, 5:18-20; Hanks, ¶¶167-168. POSAs would understand that these teachings were applicable to the earlier portions quoted in connection with claims 5 and 6. Hanks, ¶169; *see also* EX1015, 139-140 (claims 4-7).

d. Claim 8: the Anti-PD-L1 mAb Has a Heavy Variable Region Comprising the Amino Acids in SEQ ID NO: 1 and a Light Variable Region Comprising the Amino Acids in SEQ ID NO: 2

NCT505–NCT109–Cogswell satisfies claim 8. Hanks, ¶¶170-171. NCT505–NCT109–Cogswell satisfies claim 7 (from which claim 8 depends) for the reasons explained immediately above. Concerning claim 8's additional requirements concerning the anti-PD-L1 monoclonal antibody, Cogswell discloses that "[t]he clone that produced the most robust detection specifically of membranous PD-L1,

rabbit clone 28-8, was selected for the IHC assays" and that "[t]he sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively." EX1015, 35:9-12; EX1027. Cogswell's SEQ ID NOs. 35-36 match the '113 Patent's SEQ ID NOs: 1-2. Hanks, ¶171.

e. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

NCT505–NCT109–Cogswell satisfies claim 9. Hanks, ¶¶172-173. NCT505–NCT109–Cogswell satisfies claim 2 (from which claim 9 depends) for the reasons that NCT505-NCT109 satisfies claim 2. *See* §VII.A.1.e.ii. Concerning claim 9's additional requirements, Cogswell discloses "***PD-L1 positivity was defined per specimen by a 5% expression threshold***." EX1015, 111:16-18. POSAs would thus have understood Cogswell to disclose a threshold of less than 5% of tumor cells showing binding to an anti-PD-L1 antibody as being PD-L1-negative. Hanks, ¶173. Moreover, it was already known that PD-L1 negative melanoma patients responded to combined nivolumab and ipilimumab treatment—thereby motivating POSAs to include such patients (i.e., with expression thresholds under 5%) when practicing NCT505-NCT109. EX1028, 1; Hanks, ¶173.

f. Claim 16: Anti-Cancer Agent

Claim 16 depends from claim 2 and further requires "administering an anti-cancer agent." NCT505–NCT109 includes every element of claim 2, per Ground 1A. §VII.A.1.e.ii. Cogswell further discloses that a "combined PD-1 and CTLA-4

blockade may also be further combined with standard cancer treatments," including "chemotherapeutic regimes." EX1015, 63:25-27; *see also id*., 40:5-8. POSAs would have been motivated to administer chemotherapy together with nivolumab and ipilimumab per NCT505–NCT109 to "increase[e] levels of tumor antigen in the antigen presentation pathway," resulting in "synergy with a combined PD-1 and CTLA-4 blockade." *Id*., 63:29-64:1; Hanks, ¶¶175-176. POSAs would have had at least a reasonable expectation that such additional anti-cancer agents would be at least additive because Cogswell discloses that such additional anti-cancer agents demonstrated "synergy with a combined PD-1 and CTLA-4 blockade." EX1015, 63:29-64:1; Hanks, ¶¶175-176. Thus, administering an anti-cancer agent (per Cogswell) in addition to nivolumab and ipilimumab (per NCT505-NCT109) would satisfy claim 16, thus rendering it obvious. Hanks, ¶¶174-177.

C. GROUNDS 3A, 3B, and 3C: Postow and NCT-109 Render Obvious Claims 1-6, 9-10, 13-15, and 19-20

Grounds 3A, 3B, and 3C center on Postow, which confirms that the dosing regimen previously published by NCT-505 (including the combination of nivolumab and ipilimumab, followed by nivolumab monotherapy once every two weeks at 3 mg/kg) successfully treated melanoma. Thus, Postow in view of NCT-109's known 240 mg nivolumab flat dosing option discloses all of the dosing amounts and frequencies of the combination therapy recited in Challenged Claims

1-6, 9-10, 13-15, and 19-20. Hanks, ¶¶178-179. It would have been obvious to implement Postow's nivolumab monotherapy with flat dosing of 240 mg every two weeks (as disclosed in NCT-109) or alternatively 480 mg every four weeks (within Brahmer's range)—thereby delivering the same amount of nivolumab for an average 80 kg melanoma patient—for substantially the same reasons detailed in Grounds 1A, 2A, and 3A.

1. GROUND 3A: Postow and NCT-109 Render Obvious Claims 1-6, 9-10, 13-15, and 19-20

Postow and NCT-109 together disclose all of the dosing amounts and frequencies of anti-PD-1 and anti-CTLA-4 recited in Challenged Claims 1-6, 9-10, 13-15, and 19-20, and POSAs would have had reason to combine these teachings to arrive at the claimed treatment method with a reasonable expectation of success.

a. Postow Discloses Successfully Treating Melanoma with a Combination of Nivolumab and Ipilimumab Followed by Nivolumab Alone

Postow discloses that metastatic melanoma patients were administered "ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects." EX1005, 2006. Postow's combination therapy achieved a "***complete response***" in 16 [melanoma] patients (22%)" (*id.*)—meaning that melanoma tumors were eliminated completely for

those patients (Hanks, ¶182). Moreover, "the median progression-free survival ***was not reached***" (EX1005, 2006, 2009)—meaning that more than half of the patients had no cancer progression through at least 11 months (Hanks, ¶[182]). Postow concludes "the combination of ipilimumab plus nivolumab resulted in ***durable responses*** and a ***substantially higher objective response rate***, ***longer progression-free survival***, and ***higher rates of complete response*** than ipilimumab monotherapy among patients with BRAF wild-type advanced melanoma and those with BRAF-mutant advanced melanoma." EX1005, 2016.

b. <u>Reason to Modify</u>: POSAs Would Have Had Reason to Use a Flat Dose of Nivolumab Instead of the Body Weight Dose

While Postow disclosed a body weight dose of 3 mg/kg nivolumab every two weeks following coadministration with ipilimumab, POSAs would have had reason to change that body weight dose to a known flat dose for the same reasons discussed in Ground 1A. *See* §VII.A.1.b; Hanks, ¶183.

c. <u>The Modification</u>: 240 mg Every Two Weeks or 480mg Every Four Weeks

POSAs would have chosen the known 240 mg flat dose of nivolumab once every two weeks for the same reasons discussed in Ground 1A. *See* §VII.A.1.c (reasons for a 240 mg flat dose every two weeks); Hanks, ¶184. POSAs would thus have modified Postow's treatment method by administering 240 mg once every

two weeks, following the combination therapy with nivolumab and ipilimumab (hereinafter "**Postow–NCT109**"). Hanks, ¶184.

d. Reasonable Expectation of Success: POSAs Knew Nivolumab Was Long-Lasting and Had a Wide Therapeutic Window

POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 240 mg nivolumab once every two weeks following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 3 mg/kg nivolumab every two weeks as disclosed by Postow for the same reasons previously discussed in Ground 1A. *See* §VII.A.1.d (expectation of success for a 240 mg flat dose every two weeks); Hanks, ¶185. Nivolumab's wide therapeutic window confirmed such reasonable expectation. Hanks, ¶185.

e. Claim-by-Claim Analysis

Postow–NCT109 satisfies every element of claims 1-6, 9-10, 13-15, and 19-20, rendering them obvious. Hanks, ¶¶186-221.

i. Claim 1

(1) Preamble: Method for Treating a Melanoma

To the extent claim 1's preamble is limiting, Postow–NCT109 satisfies it because Postow discloses a method for treating "advanced melanoma" in human patients. Hanks, ¶187; EX1005, 2006.

(2) Limitation 1(i): Identifying a Patient Having a PD-L1-Negative Melanoma

Postow–NCT109 satisfies limitation 1(i) because Postow discloses assessing the "expression of PD-L1 on the surface of tumor cells" "in pretreatment tumor samples" (EX1005, 2008), which was then used to track any differences in efficacy depending on whether the patient had a PD-L1-positive or PD-L1-negative melanoma tumor (EX1005, 2009 ("response rate was independent of tumor PD-L1 status"), 2016 ("no significant difference in response rates between patients whose pretreatment tumors were defined as PD-L1–positive and those whose tumors were PD-L1–negative")). Hanks, ¶188. Postow discloses at least 69 patients "in the combination group" "with PD-L1-negative tumors." EX1005, 2009. Accordingly, POSAs would have treated PD-L1-negative patients in view of Postow. Hanks, ¶¶189-191.

(3) Limitation 1(ii)(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

Postow–NCT109 satisfies limitation 1(ii)(a) because Postow discloses administering to the patient "***ipilimumab [a known anti-CTLA-4 antibody] (3 mg per kilogram of body weight) combined with*** either ***nivolumab [a known anti-PD-1 antibody] (1 mg per kilogram)*** or placebo once ***every 3 weeks for four doses***." EX1005, 2006; Hanks, ¶¶192-193. Specifically, Postow discloses an "objective

response rate … [of] 55% (95% CI, 41 to 69) among patients with PD-L1–negative tumors." EX1005, 2009.

(4) Limitation 1(ii)(b): Administering a Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

Postow–NCT109 satisfies limitation 1(ii)(b). Hanks, ¶¶194-197. Postow discloses administering "***nivolumab (3 mg per kilogram)***" "every 2 weeks" after coadministration of nivolumab and ipilimumab. EX1005, 2006; Hanks, ¶194. And NCT-109 entails administering a flat dose of "***240 mg***" nivolumab "every 2 weeks" (EX1007, 5), including to "melanoma subjects" "after- receiving CTLA-4 and anti-PD-1 or PD L-1 antibody therapy" (EX1007, 6). Hanks, ¶194.

POSAs would have had reason to use NCT-109's flat 240 mg dose of nivolumab every two weeks in place of Postow's 3 mg/kg every two weeks to achieve the "numerous advantages" that Wang discloses flat doses have over body weight doses (EX1008, 1023) for the same reasons detailed in §§VII.C.1.b-c. Hanks, ¶195.

POSAs would have had at least a reasonable expectation of making the substitution and achieving comparable clinical results to Postow given nivolumab's wide therapeutic window and long-lasting effects, as well as the multiple other monoclonal antibodies known to have been successfully administered via flat

dosing, for the same reasons detailed in §VII.A.1.d. Hanks, ¶196. *See also* EX1009, 3167, 3169, 3171; EX1036, 25-26.

Postow–NCT109 thus satisfies limitation 1(ii)(b), rendering claim 1 obvious. Hanks, ¶197.

ii. Claim 2

(1) Preamble: Method for Treating a Melanoma

To the extent claim 2's preamble is limiting, Postow–NCT109 satisfies it for the same reasons as claim 1. Hanks, ¶198; EX1005, 2006; *See* §VII.C.1.e.i(1).

(2) Limitation 2(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

Postow–NCT109 satisfies limitation 2(a) for the same reasons it satisfies limitation 1(ii)(a). *See* §VII.C.1.e.i(3); Hanks, ¶¶199-200.

(3) Limitation 2(b): Administering a Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

Postow–NCT109 satisfies limitation 2(b) for the same reasons it satisfies limitation 1(ii)(b). *See* §VII.C.1.e.i(4); Hanks, ¶¶201-202.

iii. Claim 3: Over 8 Months Progression-Free Survival and/or At Least About 10% Tumor Size Reduction

Postow–NCT109 satisfies claim 3. Hanks, ¶¶203-207. Postow discloses that "the median progression-free survival was not reached with the combination therapy." EX1005, 2006; *see also id*., 2009 (describing progression-free survival

for more than 60% of patients at eight months), 2012 (Fig. 1). POSAs would understand this to mean that progression-free survival was well over 8 months for many patients. Hanks, ¶204. Moreover, Postow discloses a "complete response was observed in 16 patients (22%) in the combination group" (EX1005, 2009)—meaning that the tumor was completely eliminated (i.e., reduced by 100%), well beyond the claimed "at least about 10%." Hanks, ¶205; EX1039, 232.

Separately, Postow discloses that NCT-505's nivolumab and ipilimumab co-therapy achieved a median decrease in tumor burden of 68.1% under the RECIST standard. EX1005, 2008-2009; EX1039.[5]

As discussed in §VII.C.1.d, POSAs would have reasonably expected 240 mg flat dosing of nivolumab monotherapy (after nivolumab/ipilimumab combination therapy) to be comparable to 3 mg/kg weight-based dosing given nivolumab's wide therapeutic window and the multiple other monoclonal antibodies for which flat dosing had proven successful. Hanks, ¶207; *see also* EX1009, 3167, 3169, 3171; EX1036, 25-26.

[5] While claim 3 depends from claim 2 and is agnostic as to tumor PD-L1 status, POSAs would expect these results to apply to PD-L1 negative tumors because Postow disclosed that "[i]n the combination group, the objective response rate was independent of tumor PD-L1 status." EX1005, 2009; Hanks, ¶206.

iv. Claim 4: Measuring PD-L1 Expression

Postow–NCT109 satisfies claim 4 because Postow discloses assessing "expression of PD-L1 on the surface of tumor cells…in pretreatment tumor samples." EX1005, 2008; Hanks, ¶208.

v. Claim 5: Providing a Sample of Tumor Cells

Postow–NCT109 satisfies claim 5 because Postow discloses assessing "expression of PD-L1 on the surface of tumor cells…in pretreatment tumor samples." EX1005, 2008. POSAs would have understood that assessing such expression required obtaining tissue samples from patients. Hanks, ¶¶209-210.

vi. Claim 6: Assessing the Proportion of the Cells that Express PD-L1 on the Cell Surface

Postow–NCT109 satisfies claim 6 because Postow discloses a "tumor was considered to be PD-L1–positive if at least 5% of tumor cells showed cell-surface PD-L1 staining." EX1005, 2008; Hanks, ¶211-212. POSAs would have understood that the "at least 5%" threshold meant assessing the proportion of cells in the tissue sample expressing PD-L1 because a percentage is a proportion, and the proportion of cells expressing PD-L1 must be determined to evaluate whether the "at least 5%" threshold was met. Hanks, ¶212.

vii. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

Postow–NCT109 satisfies claim 9 because Postow discloses a "tumor was considered to be PD-L1–positive if at least 5% of tumor cells showed cell-surface PD-L1 staining" and Postow discloses at least 69 patients "in the combination group" "with PD-L1-negative tumors." EX1005, 2008-2009; Hanks, ¶¶213-214. POSAs would have understood that meant a PD-L1–***negative*** tumor would have less than 5% of tumor cells showing binding to the anti-PD-L1 antibody in the assay. Hanks, ¶214.

viii. Claims 10 and 20: the Anti-PD-1 Antibody Is Nivolumab

Postow–NCT109 satisfies claims 10 and 20 because Postow discloses the anti-PD1 antibody "nivolumab." EX1005, 2006; Hanks, ¶¶215-216.

ix. Claim 13: the Anti-CTLA-4 Antibody Is Ipilimumab

Postow–NCT109 satisfies claim 13 because Postow discloses the anti-CTLA-4 antibody "ipilimumab." EX1005, 2006; Hanks, ¶¶217-218.

x. Claims 14, 15 and 19: the Anti-CTLA-4 Antibody Is from 0.1 mg/kg to 10.0 mg/kg or 3 mg/kg

Postow–NCT109 satisfies claims 14, 15, and 19 because Postow discloses administering 3 mg/kg ipilimumab—the dose claimed by claims 15 and 19 and

within the 0.1-10 mg/kg range claimed by claim 14 . EX1005, 2006; Hanks, ¶¶219-221.

D. GROUND 3B: Postow and NCT-109 Render Obvious Claims 11 and 17

Dependent claims 11 and 17 are addressed separately because Petitioner has not expressly challenged their entitlement to the benefit of the 4/28/15 provisional. *See* §IV. But Postow was publicly accessible even before the '973 provisional was filed, and Petitioner is not aware of any basis for a §102(b)(1) exception to apply. Accordingly, claims 11 and 17 are unpatentable as obvious over Postow–NCT109 for the same reasons as Ground 3A. Claims 11 and 17 are identical to claims 2 and 1, respectively, aside from imposing additional requirements concerning the flat dose monotherapy. They require the flat dose to be "about 240 mg" (rather than either "about 240 mg or about 480 mg," as recited in claims 1 and 2) and further require the flat dose be administered biweekly. As detailed in Ground 3A, it would have been obvious in view of Postow and NCT109 to practice claims 1 and 2 using a biweekly flat dose of 240 mg nivolumab (as expressly disclosed in NCT109) to practice Postow's anti-PD1 monotherapy phase. Hanks, ¶¶222-224.

E. GROUND 3C: Postow and NCT-109 Render Obvious Claims 12 and 18

Claims 12 and 18 depend from claims 2 and 1, respectively, which are obvious over Postow-NCT109 for the reasons set forth in Ground 1A. Claims 12

and 18 merely require that the flat dose anti-PD-1 antibody be "about 480 mg" (rather than either "about 480 mg" or "about 240 mg" as in the independent claims) and further that it be "administered once every four weeks." Such a dosage schedule was an obvious variant of Postow-NCT109's flat dosage of 240 mg nivolumab every two weeks as expressly taught in NCT109 (EX1007, 5-6). Hanks, ¶¶225-228. For the same reasons explained in §VII.A.3, above, POSAs would have had reason to administer 480 mg nivolumab once every four weeks instead of 3 mg/kg every two weeks. *See also* Hanks, ¶226.

POSAs would have reasonably expected the 480 mg dose once every four weeks to have comparable efficacy and tolerability as Postow's 3 mg/kg dose for the same reasons described for Ground 1C, including nivolumab's wide therapeutic window (as disclosed in Brahmer) and related pharmacokinetic modeling. Hanks, ¶¶227-228; Shah, ¶¶19-27, 54-57; EX1009, 3171.

F. GROUND 4: Postow, NCT-109, and Cogswell Render Obvious Claims 5-9 and 16

Claims 5-9 and 16 are unpatentable as obvious over Postow, NCT-109, and Cogswell for substantially the same reasons they are obvious over NCT-505, NCT-109, and Cogswell per Ground 2. Hanks, ¶¶229-245. There is nothing inventive in practicing Postow-NCT-109 using standard methods (disclosed in Cogswell) to identify a PD-L1-negative melanoma tumor or in supplementing Postow-NCT-

109's immunotherapy with an anti-cancer agent (as also disclosed in Cogswell). *Id.* ¶229.

1. Reason to Combine

Postow discloses a specific "Dako" assay for measuring PD-L1 expression. EX1005, 2008. POSAs would have looked to Cogswell's further details concerning the Dako test. Hanks, ¶230; EX1015, 125:23-25 (disclosing "pre-treatment PD-L1 expression [using] assay ***developed by Dako***.").

2. Reasonable Expectation of Success

POSAs would have had at least a reasonable expectation of successfully combining Cogswell with Postow and NCT-109 (hereinafter "Postow–NCT109–Cogswell") because Postow references the Dako test—indicating it was suitable for the intended purpose. EX1005, 2008; Hanks, ¶231. POSAs would thus have reasonably expected Cogswell's PD-L1 testing methodology to work in measuring PD-L1 expression in Postow's melanoma tumors. Hanks, ¶231.

3. Claim-by-Claim Analysis

Postow–NCT109–Cogswell discloses every element of claims 5-9 and 16, rendering them obvious. Hanks, ¶¶232-245.

a. Claim 5: Providing a Sample of Tumor Cells

Postow–NCT109–Cogswell satisfies claim 5. Hanks, ¶¶233-234. Postow–NCT109–Cogswell satisfies claim 4 (from which claim 5 depends) for the same reasons as Ground 3A. *See* §VII.C.1.e.iv. Postow–NCT109–Cogswell also satisfies

claim 5 based on Postow's disclosure of obtaining a sample of tumor cells. EX1005, 2008 ("[T]he expression of PD-L1 on the surface of tumor cells was assessed in pretreatment tumor samples…"); Hanks, ¶234. Moreover, Cogswell discloses "immunotherapy" by which one "provide[s] a test tissue sample…comprising tumor cells and tumor-infiltrating inflammatory cells." EX1015, 3:26-30. POSAs would thus have understood Cogswell to disclose providing a sample of the tumor cells obtained from the patient as recited in claim 5. Hanks, ¶234.

b. Claim 6: Assessing the Portion of the Cells that Express PD-L1 on the Cell Surface

Postow–NCT109–Cogswell satisfies claim 6. Hanks, ¶¶235-236. Cogswell's above-quoted passage further discloses "assessing the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface." EX1015, 3:26-30; Hanks, ¶¶235-236. Postow also discloses a "tumor was considered to be PD-L1–positive if ***at least 5%*** of tumor cells showed ***cell-surface*** PD-L1 staining." EX1005, 2008; Hanks, ¶236. As discussed in Section VII.C.1.e.vi, POSAs would have understood the "at least 5%" threshold meant assessing the proportion of cells in the sample that express PD-L1 as recited in claim 6 because a percentage is a proportion, and the proportion of cells that express PD-L1 must be determined to evaluate whether the "at least 5%" threshold was met. Hanks, ¶236. POSAs

accordingly would have had reason to combine these disclosure with a reasonable expectation of success. *Id*.

c. Claim 7: IHC Assay on a FFPE Sample

Postow–NCT109–Cogswell satisfies claim 7. Hanks, ¶¶237-238. Specifically, Cogswell discloses that the "[a]nti-PD-L1 Abs of the invention also include isolated Abs selected for their ability to bind to PD-L1 in ***formalin-fixed, paraffin-embedded (FFPE) tissue specimens***" and that "pre-treatment PD-L1 expression was measured by ***IHC in FFPE tumor specimens*** using the rabbit anti-PD-L1 mAb, 28-8, and an ***automated assay*** developed by Dako." EX1015, 3:25-26, 125:23-25; Hanks, ¶238. POSAs would have reason to combine this teaching with Postow and NCT-109 with a reasonable expectation of success. *See* Section VII.F.1-2; Hanks, ¶238.

d. Claim 8: the Anti-PD-L1 mAb Has a Heavy Variable Region Comprising the Amino Acids in SEQ ID NO: 1 and a Light Variable Region Comprising the Amino Acids in SEQ ID NO: 2

Postow–NCT109–Cogswell satisfies claim 8. Hanks, ¶¶239-241. Specifically, Cogswell discloses that "[t]he clone that produced the most robust detection specifically of membranous PD-L1, rabbit clone 28-8, was selected for the IHC assays" and that "[t]he sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively." EX1015, 35:9-12; EX1027. Cogswell's SEQ ID NOs. 35-36 are identical to the '113 patent's SEQ ID NOs 1-2.

Hanks, ¶240. POSAs would have reason to combine this teaching with Postow and NCT-109 with a reasonable expectation of success. *See* Section VII.F.1-2; Hanks, ¶¶240-241.

e. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

Postow–NCT109–Cogswell satisfies claim 9. Hanks, ¶¶242-243. Cogswell discloses "***PD-L1 positivity was defined per specimen by a 5% expression threshold***." EX1015, 111:16-18. POSAs would thus have understood Cogswell to disclose a threshold of less than 5% of tumor cells showing binding to an anti-PD-L1 antibody as being PD-L1-negative. Hanks, ¶243. In addition, Postow discloses that a "tumor was considered to be PD-L1–***positive*** if ***at least 5%*** of tumor cells showed ***cell-surface*** PD-L1 staining" and Postow discloses at least 69 patients "in the combination group" "with PD-L1-negative tumors." EX1005, 2009; Hanks, ¶243. POSAs would have understood that meant a PD-L1–***negative*** tumor would have less than 5% of tumor cells showing binding to the anti-PD-L1 antibody used in the assay as required by claim 9. Hanks, ¶243. POSAs would have reason to combine this teaching with Postow and NCT-109 with a reasonable expectation of success. *See* §§VII.F.1-2; Hanks, ¶243.

f. Claim 16: Anti-Cancer Agent

Claim 16 depends from claim 2 and recites "further comprising administering an anti-cancer agent." Postow-NCT-109 discloses all elements of

claim 2, per Ground 3A. §VII.C.1.e.ii. Cogswell further teaches combining the above-discussed "PD-1 and CTLA-4 blockade…with standard cancer treatments," such as "chemotherapeutic regimes." EX1015, 63:25-27; *see also id*., 40:5-8. POSAs would have been motivated to administer chemotherapy together with nivolumab and ipilimumab according to Postow–NCT109 to "increase[e] levels of tumor antigen in the antigen presentation pathway." *Id*., 63:29-64:1; Hanks, ¶244. POSAs would have reasonably expected such additional anti-cancer agents to be additive because Cogswell discloses that, in fact, such additional anti-cancer agents achieved "synergy with a combined PD-1 and CTLA-4 blockade." EX1015, 63:29-64:1; Hanks, ¶245.

VIII. SECONDARY CONSIDERATIONS DO NOT RENDER THE CHALLENGED CLAIMS PATENTABLE

The intrinsic record does not reflect any unexpected results or other alleged secondary considerations as to the Challenged Claims. The Challenged Claims require administering anti-PD-1 monotherapy as a ***flat*** dose, whereas the specification's data concern ***weight-based*** doses. EX1001, 27:2-12; Hanks, ¶247. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc*., 97 F.4th 915, 933 (Fed. Cir. 2024) (nexus analysis must "consider the correspondence between the objective evidence and the claim scope"). Indeed, nothing in the intrinsic record ascribes any significance to the claimed dosages.

The ’113 Patent instead purports to show “that for PD-L1 negative tumors, a combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody is more suitable than a monotherapy of either an anti-PD-1 antibody or an anti-CTLA-4 antibody.” EX1001, 10:59-63. But the prior art disclosed such “combination therapy”—including for “PD-L1 negative” tumors—and highlighted its “unique features compared to either [anti-PD-1 or anti-CTLA-4] monotherapy.” EX1028, Hanks, ¶250. Consistent with that teaching, NCT-505 concerned such combination therapy and included PD-L1 negative tumors. EX1014. And Postow later further confirmed that such combination therapy yielded a “significantly greater” response rate than anti-CTLA-4 monotherapy—including in “PD-L1 negative tumors.” EX1005, 2006, 2009; Hanks, ¶250. *See Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015) (“Where objective indicia result from something other than what is both claimed and ***novel*** in the claim, there is no nexus to the merits of the claimed invention.”) (emphasis original).

IX. DISCRETIONARY DENIAL IS UNWARRANTED

No reasonable basis for discretionary denial exists.

A. Section 314(a)

There is no previous petition concerning the ’113 patent.

B. Section 324(a)

There is no co-pending litigation involving the ’113 patent.

C. Section 325(d)

Considering the two-part framework discussed in *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential), the Board should not exercise its §325(d) discretion to deny institution. The two primary references (NCT-505 and Postow) were never cited, discussed, or otherwise of record during prosecution. EX1001, References Cited; EX1002. Nor was NCT-109, which discloses a 240 mg flat dose of nivolumab following earlier combination therapy—the ostensible point of novelty PO cited to overcome Wolchok (*supra* §III.C). While Cogswell and certain other above-cited background references were of record, they were not considered in combination with either of the primary references and/or with NCT-109. *Id.*

Even if the Board considers the *Advanced Bionics* individually, the result is the same.

1. Step One: The Petition Advances Art and Arguments Not Previously Considered (Factors (a), (b), (d))

As to *Advanced Bionics* step one, the Petition advances art (including NCT-505, NCT-109, and Postow) and arguments (including obviousness) not previously considered. NCT-505, NCT-109, and Postow were not cited during prosecution. *See* §III.C. Moreover, the Examiner never made ***any*** obviousness rejection. Instead, the only rejections were under §102 and §112. *See*, *e.g.*, *Agrofresh Sol'ns. v. Lytone Ent.*, IPR2021-00451, Paper 11 at 12-13 (PTAB July 27, 2021)

(arguments were not substantially similar where teachings were used "in a different manner than the rejections made by the Examiner").

The only prior-art-based rejection during prosecution suggested anticipation by Wolchok. EX1002, 4233. NCT-505 and Postow are not cumulative of Wolchok at least because Wolchok disclosed maintaining the same dose of nivolumab throughout the regimen, including the nivolumab monotherapy phase. EX1017, 2. By contrast, NCT-505 and Postow disclose increasing the dose of nivolumab when nivolumab is administered alone to 3 mg/kg, corresponding to the claimed 240 mg dose. EX1007, 5; EX1005, 2006. Indeed, PO relied on the different dosing regimen to distinguish Wolchok. EX1002, 76-78.

2. Step Two: The Office Erred Materially (Factors (c), (e), (f))

Where "the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f)." *AB*, 10. For example, the Board has found the record was silent where the Examiner never made a prior art rejection. *Samsung Electronics Co., Ltd., et al. v. Evolved Wireless LLC*, IPR2021-00943, Paper 9 at 11 (PTAB Dec. 1, 2021); *see also Edwards Lifesciences Corp. v. Aortic Innovations*, IPR2021-01527, Paper 15, 26-27 (PTAB Mar. 17, 2022) (finding error where "the Examiner did not issue any rejections during prosecution despite prior art teachings that are closely related to the subject

matter and claims of the [challenged] patent").

Here, the Examiner never made an obviousness rejection. EX1002, 433 (anticipation rejection only). The Examiner also never discussed any art that disclosed increasing the dose of nivolumab after the combination therapy with ipilimumab, as disclosed by NCT-505 and Postow (EX1007, 5; EX1005, 2006), nor art disclosing the advantages of flat dosing, such as Wang (EX1008), nor the wide therapeutic window, such as Brahmer (EX1009). The Examiner erred in failing to reject the claims over the prior art or otherwise addressing these teachings of the prior art. *See*, *e.g.*, *Carrier Fire & Security Americas Corp. v. Sentrilock, LLC*, IPR2021-00664, Paper 12 at 21-23 (PTAB Sept. 16, 2021) (declining to exercise discretion where "[t]he prosecution history provide[d] little insight into the Examiner's evaluation of the prior art" and the Examiner's statement that certain limitations were not in the prior art was contradicted by the petition grounds).

X. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Board institute review and cancel claims 1-20.

Dated: February 28, 2025

Respectfully submitted,
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LISTING OF CHALLENGED CLAIMS

Ref.	Claim Limitation
1[pre]	A method for treating a melanoma tumor in a human patient in need thereof comprising:
1(i)	(i) identifying a patient having a PD-L1-negative melanoma tumor; and
1(ii)(a)	(ii) administering to the patient: (a) about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 ("an anti-PD-1 antibody") and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 ("an anti-CTLA-4 antibody") every three weeks for about 4 doses; followed by
1(ii)(b)	(b) a dose of the anti-PD-1 antibody, wherein the dose in (b) is a flat dose of about 240 mg or about 480 mg.
2[pre]	A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient:
2(a)	(a) about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 ("an anti-PD-1 antibody") and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 ("an anti-CTLA-4 antibody") every three weeks for about 4 doses; followed by
2(b)	(b) a dose of the anti-PD-1 antibody, wherein the dose in (b) is a flat dose of about 240 mg or about 480 mg.
3	The method of claim 2, wherein the patient is characterized by (i) extended progression-free survival for over 8 months following the administration, (ii) tumor size reduction at least about 10% compared to the tumor size prior to the administration, or (iii) both (i) and (ii).
4	The method of claim 2, further comprising measuring a PD-L1 expression on the melanoma tumor prior to the administration.

Ref.	Claim Limitation
5	The method of claim 4, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.
6	The method of claim 5, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.
7	The method of claim 6, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.
8	The method of claim 7, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2.
9	The method of claim 2, wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.
10	The method of claim 2, wherein the anti-PD-1 antibody is nivolumab.
11	The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.
12	The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
13	The method of claim 2, wherein the anti-CTLA-4 antibody is ipilimumab.
14	The method of claim 2, wherein the dose of the anti-CTLA-4 antibody is from 0.1 mg/kg to 10.0 mg/kg.
15	The method of claim 14, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.

Ref.	Claim Limitation
16	The method of claim 2, further comprising administering an anti-cancer agent.
17	The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.
18	The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
19	The method of claim 1, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.
20	The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.

CERTIFICATE OF SERVICE UNDER 37 C.F.R. §42.6 (E)(4)

I certify that on February 28, 2025, I will cause a copy of the foregoing document, including any exhibits or appendices filed therewith, to be served via Priority Mail Express at the following correspondence address of record for the patent:

Sterne, Kessler, Goldstein & Fox P.L.L.C.
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Date: February 28, 2025

/MacAulay Rush/
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Paralegal
WOLF, GREENFIELD & SACKS, P.C.

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24, the undersigned certifies that the foregoing Petition for *Inter Partes* Review contains 13,991 words excluding a table of contents, a table of authorities, Mandatory Notices under §42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: February 28, 2025

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