UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY
Patent Owner.

IPR2025-00601
Patent No. 9,856,320

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. 9,856,320
1002	Prosecution History of U.S. Patent No. 9,856,320
1003	Declaration of Paul A. Antony, M.D.
1004	Curriculum Vitae of Dr. Paul A. Antony
1005	NCT01024231 Version 3, Brief Title: "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma" (Last Update Posted to clinicaltrials.gov: January 5, 2010).
1006	International Patent Publication No. WO 2006/121168
1007	Wolchok et al., Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol*. 2010 Feb; 11(2):155–64.
1008	March 25, 2011 Bristol Myers Squibb Press Release announcing Ipilimumab FDA Approval, "FDA Approves YERVOY™ (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer."
1009	Sznol et al., Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1 BMS-936558/ONO4538) in patients with advanced refractory malignancies. *J Clin Oncology.* 2010 May 20; 28(15).
1010	Fife et al., Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways." *Immunol Rev.* 2008 Aug; 224:166–182.
1011	NCT00323882 Version 1, Brief Title: "Phase I/II, Open-Label, Dose-Escalation Study of MDX-010 in Patients With Metastatic Hormone-Refractory Prostate Cancer" (Last Update Posted to clinicaltrials.gov: May 10, 2006).
1012	NCT00729950 Version 1, Brief Title: "Study of MDX-010 in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma" (Last Update Posted to clinicaltrials.gov: August 8, 2008).
1013	NCT00441337 Version 1, Brief Title: "Safety and PK Study of MDX-1106 in Patients With Selected Refractory or Relapsed Malignancies" (Last Update Posted to clinicaltrials.gov: February 28, 2007).
1014	NCT00730639 Version 1, Brief Title: "A Phase 1b Study of MDX-1106 in Subjects With Advanced or Recurrent Malignancies" (Last Update Posted to clinicaltrials.gov: August 8, 2008).

1015	Parry et al., CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. *Mol Cell Biol*. 2005 Nov; 25(21):9543-53.
1016	Okazaki et al., PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol*. 2007 Jul; 19(7):813-24.
1017	NCT00094653 Version 1, Brief Title: "MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients with Melanoma" (Last Update Posted to clinicaltrials.gov: June 24, 2005).
1018	YERVOY FDA Approved label and prescribing information, March 2011
1019	Dillard et al., Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary*. 2010; 13(1):29-38.
1020	Giacomo et al., The Emerging Toxicity Profiles of Anti-CTLA-4 Antibodies Across Clinical Indications. *Semin Oncol*. 2010 Oct; 37(5):499-507.
1021	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.
1022	Pardoll D., The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012 Mar 22; 12(4):252-64.
1023	European Patent Application No. 17189595.6, Amended Claims, dated October 18, 2018.
1024	Curriculum Vitae of Prescott Lassman
1025	European Patent Application No. 17189595.6, Reply to Communication from the Examining Division, dated April 16, 2020.
1026	European Patent Application No. 17189595.6, Annex to the Communication, dated April 11, 2022.
1027	Wolchok et al., Nivolumab plus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2013 Jun 2; 369(2):122-33.
1028	Declaration of Prescott Lassman
1029	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary ("*ClinicalTrials.Gov Glossary*")
1030	Curran et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci USA.* 2010 Mar 2; 107(9):4275–4280.

1031	NCT01024231 Version 58, Brief Title: "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma" (Last Update Posted to clinicaltrials.gov: May 1, 2012).
1032	Humphrey et al., Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer. *J Natl Cancer Inst.* 2011 Aug 17; 103(16):1222–1226.
1033	European Patent Application No. 17189595.6, Notice of Withdrawal. (Sept. 20, 2022)
1034	European Patent Application No. 22196038.8 Amended claims filed after receipt of_(European) search report. (Oct. 18, 2023)
1035	European Patent Application No. 22196038.8 – Letter accompanying amendments received before examination (Oct. 18, 2023)
1036	Hodi et al., Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Nat'l Acad Sci USA*. 2003 Apr 15; 100(8):4712–4717.
1037	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 Jul 1; 28(19):3167–3175.
1038	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1039	Wolchok et al., Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. *N Engl J Med*. 2011 Jun 30; 346(26):2517-1526.
1040	Tourneau et al., Dose escalation methods in Phase 1 cancer clinical trials. *J Natl Cancer Inst.* 2009 May 20; 101(10):708–720.
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1042	Simeone et al., Immunomodulating antibodies in the treatment of metastatic melanoma: The experience with anti-CTLA-4, anti-CD137, and anti-PD1. *J Immunotoxicol*. 2012 Jul-Sep; 9(3):241-7.
1043	RESERVED
1044	Ascierto et al., Clinical Experiences with Anti-CD137 and Anti-PD1 Therapeutic Antibodies. *Semin Oncol.* 2010 Oct; 37(5):508-16.
1045	Korman et al., Activity of Anti-PD-1 in murine tumor models: Role of 'host' PD-L1 and synergistic effect of anti-PD-1 and anti-CTLA-4. *J Immunology.* 2007 Apr; 178(1_Supplement):S82 (abstract). DOI:10.4049/jimmunol.178.Supp.48.37
1046	RESERVED
1047	RESERVED

1048	RESERVED
1049	RESERVED
1050	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
1051	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 ("*Press Release: National Institutes of Health Launches "ClinicalTrials.gov"*")
1052	U.S. National Library of Medicine, National Institutes ofHealth, ClinicalTrials.gov, How to Edit Your Study Record, https://clinicaltrials.gov/ct2/manage-recs/how-edit ("*ClinicalTrials.gov, How to Edit Your Study Record*")
1053	Zarin et al., Reporting "Basic Results" in ClinicalTrials.gov. Chest. 2009 Jul; 136(1):295–303. ("*Zarin*")
1054	RESERVED
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1056	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 ("*About ClinicalTrials.gov*")
1057	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 ("*ClinicalTrials.gov Trends & Charts*")
1058	Affidavit of Nathaniel E. Frank-White (Internet Archive) ("Frank White Aff.")
1059	RESERVED
1060	RESERVED
1061	Wolchok et al., Supplementary Appendix. Nivolumab plus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2013 Jul 11; 369(2):122-33.

MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner 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:

1. United States Patent & Trademark Office

The application from which U.S. Patent No. 9,856,320 issued (U.S. App. No. 14/400,667) is a National Stage Entry of PCT/US2013/040764 filed on May 13, 2013, which claims priority to Provisional Application Nos. 61/647,442 filed on May 15, 2012, and 61/790,747 filed on March 15, 2013.

The following U.S. Patent applications claim benefit of priority to U.S. Patent No. 9,856,320: None.

2. United States Patent Trial and Appeal Board ("PTAB")

There are no proceedings before the PTAB that could affect or be affected by a decision in this proceeding.

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 1-22 ("challenged claims") of U.S. Patent No. 9,856,320 (EX1001, "'320 patent"). Independent challenged claims 1 and 5 recite methods for treating cancer by administering two well-known checkpoint inhibitors (anti-PD-1 and anti-CTLA-4) in the known format of first administering anti-PD-1 and anti-CTLA-4 antibodies together, followed by administering anti-PD-1 alone. The challenged claims also recite various options of common dosing features, all disclosed in the prior art. EX1001, cl.1. As nothing more than a broad assembly of known dosing formats, frequencies, numbers, and concentrations, all of which were disclosed in published clinical trial protocols, patent publications, and journal publications and flow from standard dosing strategies ***for these antibodies***, the challenged claims are obvious over the prior art.

Ground 1 of this Petition demonstrates why challenged claims 1-4, 6-12, and 14-17 would have been obvious to a person of ordinary skill in the art ("POSA") over the **NCT-231** clinical trial protocol[1] in view of prior art references **Korman**[2] and **Wolchok**[3]. NCT-231 is the January 5, 2010 publication of a clinical

[1] EX1005 (NCT01024231 V3 Last Update Posted, clinicaltrials.gov, Jan. 5, 2010).

[2] EX1006 (WO 2006/121168, published Nov. 16, 2006).

[3] EX1007 (*Lancet Oncol*. 2010; 11:155-64).

trial protocol disclosing the concurrent administration of anti-PD-1 and anti-CTLA-4 per the ***precise*** induction and maintenance dosing schedule recited in independent claim 1. EX1005, 4. While Patent Owner amended its claims during prosecution to avoid the specific antibody concentrations recited in NCT-231, it chose concentrations that were otherwise well-documented in different prior art. **Korman** and **Wolchok** disclose these specific claimed concentrations for anti-PD-1 and anti-CTLA-4 and ranges encompassing the same. EX1006, 55-56; EX1007, 155. These prior art concentration disclosures—having been carefully studied, and, in the case of anti-CTLA-4, approved—when taken in view of the then-common approach of POSAs to study many concentration options and optimize efficacy while minimizing toxicity, would have provided a POSA with reason to modify NCT-231 with the concentrations of Korman and Wolchok to arrive at a dosing regimen falling within the broad scope of challenged claim 1. Moreover in view of (1) the known success with similar dosing concentrations for each antibody administered alone (EX1007, EX1009), (2) the positive results with this combination in animal models (EX1030), and (3) the reliability of an iterative, dose-escalation approach to selecting dosing concentrations (EX1040), such a POSA would have had a reasonable expectation of success in implementing the NCT-231 protocol with Korman's and Wolchok's dosing concentrations.

Independent claim 5 recites a method for treating cancer by administering 1 mg/kg of anti-PD-1 and 3 mg/kg of anti-CTLA-4 antibodies every 3 weeks for 4 doses, followed by administering anti-PD-1 alone, every two weeks. **Ground 2** of this Petition explains why claims 5 and its dependent claims would have been obvious to a POSA as of May 15, 2012 over **Korman** in view **Wolchok** and **Sznol**. By 2006 (six years prior to the earliest claimed priority date of the '320 patent), concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of cancer on an "every three week" schedule had already been disclosed. EX1006, 55-56. Moreover, by 2012, POSAs understood that anti-CTLA-4 antibodies were more heavily associated with immune-related adverse events than anti-PD-1 antibodies, known to have a milder toxicity profile. EX1021, 865; EX1037, 3172; EX1022, 260; EX1044, 512, 514-515; EX1042, 243, 245. And in 2010, Sznol[4] published safety and efficacy results for dosing 1 mg/kg of anti-PD-1 antibodies bi-weekly. EX1009, 205s (2506; conclusions).

In view of their knowledge of these features of—and demonstrated results with—each claimed antibody, and in view of the known strategy of dosing with a combination-followed-by-anti-PD-1 alone format documented in published clinical trial protocols (EX1005, 4), a POSA would have had a reason to administer

[4] EX1009 (*J. Clin. Oncology* Vol. 28, No. 15, May 20, 2010).

Korman's concurrent therapy at the disclosed "every three weeks" (EX1006, 55), limited to "four cycles" [*i.e.*, doses] as proven safe and effective for the more toxic, anti-CTLA-4 antibody (EX1007, 155). And to avoid risk of additional adverse events and to maximize therapeutic efficacy and capitalize on the temporal nature of each antibody's mechanism of action (EX1010, 178), a POSA would have had a reason to continue bi-weekly dosing of anti-PD-1 as a monotherapy and would have reasonably expected success with the same.

There is no evidence that the dosing regimens recited in any of the challenged claims generated unexpectedly superior results relative to the prior art. Challenged claims 1-22 are obvious.

II. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies that the '320 patent is available for *inter partes* review. Petitioner is not estopped from requesting *inter partes* review as to the challenged claims. 37 C.F.R. § 42.104(a).

III. GROUNDS FOR UNPATENTABILITY

The table below identifies the references, applicable claims, and basis for each ground of unpatentability. 37 C.F.R. § 42.104(b); *see also* §VIII.A-B, *infra.*

Ground Number and Reference(s)		Claims	Basis
1	NCT-231 in view of Korman and Wolchok	1-4, 6-12, 14-17	35 U.S.C. § 103 (pre-AIA)
2	Korman in view of Wolchok and Sznol	5, 13, 18-22	35 U.S.C. § 103 (pre-AIA)

This Petition in supported by the Declaration of Paul Antony, M.D. ("Antony") (EX1003), ¶¶1-15.

IV. THE '320 PATENT

The '320 patent was filed as U.S. Application No. 14/400,667 ("the '667 Application") based on a National Phase Entry of PCT/US2013/040764, filed May 13, 2013. It claims the benefit of priority through the '667 Application to Provisional No. 61/647,442, filed on May 15, 2012 and Provisional No. 61/790,747, filed on March 15, 2013.

A. Challenged Claims

The '320 patent contains twenty-two claims, reproduced in Appendix I. EX1001, cls. 1-22. While discussion of certain prior art notes the demonstration of safe and effective treatment with anti-PD-1 and/or anti-CTLA antibodies, none of the challenged claims recite or require any particular level of efficacy. Dependent claim 7 broadly recites several possible therapeutic outcomes, including maintenance of stable disease. Antony, ¶59-60.

B. Person of Ordinary Skill in the Art ("POSA")

POSAs as of early 2012 (i.e., before the earliest possible effective filing date of 5/15/2012) would have a Ph.D. degree 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 cancer treatments.

Antony, ¶¶29-31. The levels of education, experience and knowledge can trade off against one another. 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. Clinical Trial Background

The first clinical trial for anti-CTLA-4 as a monotherapy commenced in the early 2000's and the drug was approved for administration to humans (as ipilimumab[5]) in 2011, for treatment of advanced melanoma. EX1036, 4713; EX1008, 1; EX1018, 1; Antony, ¶¶32-33, 47.

Similarly, clinical trials studying anti-PD-1 began as early as 2007.[6] EX1013, 1-2. In 2008, clinical trial NCT00730639 initiated the Phase 1 study of the anti-PD1 antibody nivolumab at bi-weekly dosing in subjects with advanced or recurrent malignancies. EX1014, 1, 4. Success from this trial was reported in Sznol. EX1009, 205s ("MDX-1106 [*i.e.*, nivolumab] administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg."). A POSA in 2012 would have

[5] The anti-CTLA-4 antibody "ipilimumab" is also known as "Yervoy," "BMS-734016," "MDX-010," and "MDX-101." Antony, ¶46.

[6] The anti-PD-1 antibody "nivolumab" is also known as "Opdivo," "BMS-936558," "MDX1106-4," and "ONO-4538." Antony, ¶45.

understood the phrase "biweekly" to mean, or at least suggest, "once every 2 weeks." Antony, ¶¶34, 48-49.

By December of 2009, clinical trial NCT-231 was initiated to study the ***concurrent*** dosing of anti-PD-1 and anti-CTLA-4 antibodies. EX1005, 4 (assessing "the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma"). NCT-231 discloses administration of anti-CTLA-4 and anti-PD-1 antibodies at different concentrations and on a schedule where both drugs are administered together every three weeks for 4 doses, followed by administration of anti-PD-1 alone every 3 weeks for 4 doses, followed by a maintenance dose of both antibodies again every 12 weeks for 8 doses. EX1005, 4. In 2012, a POSA would have understood an "every 12 week" dosing interval to be equivalent to, or at least suggest, an "every three months" dosing interval. Antony, ¶¶35-36, 50-51.

Though nomenclature varies and the specific terms "induction" and "maintenance" are not always used to describe dosing phases, many studies of anti-CTLA-4 and/or anti-PD-1 dating back to at least as early as 2011 utilized "induction-maintenance" dosing formats. In these dosing formats an initial (or "induction") dose of a drug at a particular frequency, number, and concentration is administered to a patient with the goal of eliciting a therapeutic response. After

that therapeutic regimen concludes, an ongoing ("maintenance") dose is administered (often at a lower concentration and/or less frequently) in order to maintain a longer-term therapeutic effect (while avoiding potential toxicities from higher concentrations or high-frequency dosing). EX1007, 155; EX1006, 55. In prior art studies of combination therapies involving anti-PD-1 and anti-CTLA-4, an "induction" phase of therapy included both an initial phase of a combined therapy followed by a phase of one of the previously combined drugs alone. Antony, ¶52; EX1005, 4; EX1039, 2518-19.

1. Toxicity Associated with Anti-CTLA-4

By May 15, 2012, two Phase 3 studies had demonstrated that anti-CTLA-4 offered a benefit in overall survival for patients with advanced melanoma, leading to the aforementioned FDA approval. EX1008, 1; EX1018, 1. However, evidence of a unique toxicity profile emerged from these trials such that by 2012 a POSA would have recognized that anti-CTLA-4 treatment often induced immune-related adverse events ("irAEs"). EX1019, 34, 35 ("The cases we present demonstrate the clinical course of autoimmune hypophysitis and consequent hypopituitarism after treatment with ipilimumab and highlight the possible role of CTLA-4 blockade in its pathogenesis."); EX1020, 499 (Abstract); EX1021, 865 (highlighting "the kinetics of antitumor responses and the relationship to IRAEs in patients receiving the CTLA-4 antibody ipilimumab"); Antony, ¶¶53-55.

In addition, studies such as Wolchok evidenced the difficulty faced by clinical trial administrators in giving anti-CTLA-4 immunotherapy to patients for extended periods of time due to the challenging irAEs associated with that drug. For each dosage arm of the study discussed in Wolchok, only a small fraction of patients even received the maintenance dosing. EX1007, 157, Fig. 1 ("Trial profile," showing significant participant loss in progression from induction to maintenance dosing of anti-CTLA-4); Antony, ¶42, 56.

2. Anti-PD-1 Exhibited a More Tolerable Safety Profile.

It was also understood by 2012, however, that treatment with anti-PD-1 antibody therapy was comparatively ***less toxic*** than treatment with anti-CTLA-4 antibody therapy. EX1037, 3172 ("While both anti-PD-1 and anti-CTLA-4 therapies are associated with irAEs, as predicted by preclinical models and consistent with the physiologic roles of these molecules, these toxicities appear to be less frequent and ***milder*** in patients receiving anti-PD-1.")[7]; EX1022, 260; EX1044, 514 (describing a "milder toxicity profile for anti-PD1 mAb as compared to that of anti-CTLA-4 mAb"); EX1042, 245 (same). This was predicted by the distinct phenotypes of Ctla4-knockout mice versus Pd1-knockout mice. EX1022, 260; EX1016, 816-18; Antony, ¶¶42-44, 57-58.

[7] Emphasis added, unless otherwise noted.

D. Prosecution History

Because the '320 patent claims a priority date of May 15, 2012, the '667 Application was examined under pre-AIA law. Original claim 14 (which ultimately issued—after cancellations and amendments—as claim 1) recited:

> A method of treating a subject afflicted with a cancer comprising administering to the subject [anti-PD-1 and anti-CTLA-4 antibodies with:]
>
> each antibody being administered in a dosage ranging from 0.1 to 20.0 mg/kg body weight in a concurrent regimen comprising [an induction dosing schedule and a maintenance dosing schedule with various options for doses and frequencies of administration.]

EX1002, 315-16. On May 2, 2017, the Examiner rejected then-pending claims 14, 15 and 22-35 as anticipated by clinical trial protocol NCT01024231 (combination BMS-936558 and ipilimumab), citing a version accessed as of April 27, 2017. *Id.* 192-93. In addition to finding that the dosing numbers and frequencies of the pending claims overlapped with those recited in the NCT0102423 trial, the Examiner found that in the pending claims, "the antibody doses are 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg" while in the NCT01024231 trial, "the doses are 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg." *Id.*, 193. The Examiner found the regimen of NCT01024231 anticipated the pending claims. *Id.*

In response, Patent Owner argued that the April 27, 2017 version of NCT01024231 relied on by the Examiner was ***not*** prior art (EX1002, 51-52) and instead offered an April 30, 2012 version. Patent Owner also amended the then-

pending, rejected claims by, *inter alia,* adding the dosing concentration options ((a) through (m)) from claim 15 to claim 14 (later issuing as claim 1), and cancelled claim 15. EX1002, 44-45, 52. Patent Owner amended claim 28 (issuing as claim 5) to recite "every 3 weeks for 4 doses, followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks." *Id*., 46.

With these amendments, Patent Owner argued that the "version of NCT01024231 available on April 30, 2012 fails to disclose the specific doses of anti-PD-1 antibody and the anti-CTLA-4 antibody recited in claim 14 and the specific dosing schedule recited in claim 28." EX1002, 52-53. The claims were allowed without further analysis. *Id.*, 28-34.

V. NO BASIS EXISTS FOR DISCRETIONARY DENIAL UNDER SECTIONS 314(A), 324(A), OR 325(D).

A. 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.

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

None of the prior art references applied in the two Grounds of this Petition were analyzed or considered against the challenged claims.

Of the four references applied in these two Grounds (NCT-231, Korman, Wolchok, and Sznol), two were cited by the Applicant in its Information Disclosure Statements but never analyzed, discussed, or applied (Korman and Wolchok). Under *Advanced Bionics* Step 1, the cited but unapplied references do not justify denying institution. *Group III Int'l v. Targus Group,* IPR2021-00371, Paper 21, at 32-33 (July 9, 2021) (Step 1 of *Advanced Bionics* not met where petition relied on prior art in IDS not applied by Examiner to reject claims); *SHDS v. Truinject Corp.*, IPR2020-00937, Paper 11, at 8-12 (Nov. 17, 2020) (Step 1 of *Advanced Bionics* not satisfied where petition combined of-record art with new art). Indeed, "[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen v. Alexion*, 2019 WL 4132683, at *25 (PTAB Aug. 30, 2019) (collecting cases); *see also* 89 Fed. Reg. 28,693, 28,700 (Apr. 19, 2024).

The third reference (Sznol) was neither cited nor mentioned anywhere in the prosecution of the '320 patent and does not justify exercise of the Board's discretion.

Use of the fourth reference (NCT-231) in this Petition likewise does not justify exercise of the Board's discretion for at least two reasons.

First, NCT-231 relied upon in this Petition presents ***different*** intervention cohorts at different concentrations of dosing than the April 30, 2012 version (Version 58) of this protocol considered by the Examiner. *Compare* EX1005, 4, *with* EX1031, 4-5 (Cohorts 2 and 3 from NCT-231 (EX1005, 4) studied 0.3 mg/kg anti-PD-1; 10 mg/kg anti-CTLA and 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4, respectively. These two cohorts were not included in the April 27, 2017 version of NCT-231 (EX1031, 4-5). Similarly, Cohorts 2, 3, 6, and 7 from the April 27, 2017 version to NCT-231 (EX1031, 4-5) were not included in NCT-231 (EX1005, 4)). Antony, ¶69. So, the precise substance of the dosing cohorts of NCT-231 was not analyzed relative to the amended claims.

Second, as discussed in §IV.D, the challenged claims were allowed after an amendment and argument in response to an anticipation rejection. The Examiner never considered whether the amended claims would have been obvious in view of earlier versions of the NCT-231 protocol (*i.e.*, NCT-231 version 3 (dated January 5, 2010) (EX1005)) or any other prior art disclosures such as those in Korman and Wolchok. Under factor (d), at a minimum, therefore, the arguments presented in this Petition are entirely new and were not considered during examination. *See, e.g., Agrofresh Sol'ns. v. Lytone Ent*., IPR2021-00451, Paper 11, at 12-13 (PTAB July 27, 2021) (arguments not substantially similar where teachings were used "in a different manner than the rejections made by the Examiner"); *see also Zip Top v.*

Stasher, IPR2018-01216, Paper 14, at 35 (PTAB Jan. 17, 2019) ("mere citation to a reference by the Examiner does not establish that the Examiner substantively considered the merits of" the reference); *SNF S.A. v. Chevron U.S.A.*, IPR2022-01534, Paper 12, at 38-40 (PTAB Apr. 19, 2023).

2. Step Two: The Office Committed Material Error (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)." *Advanced Bionics*, Paper 6 at 10. For example, the Board has found the record was silent where the Examiner never made a prior art rejection. *Samsung Elecs. Co., Ltd. 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 at 26-27 (PTAB Mar. 17, 2022) (finding error where "the Examiner did not issue *any* rejections during prosecution despite [closely related] prior art teachings").

Here, the Examiner never made an obviousness rejection. EX1002, 192-195. Nor did the Examiner discuss any art that disclosed other concentrations of anti-PD-1 or anti-CTLA-4 alone or in combination as appears in Korman, Wolchok, and Sznol (EX1006, 55-56; EX1007, 155; EX1009, 205s). This Petition fills that gap—namely, it details the claimed concentration disclosures already available to a POSA via the prior art, and it provides the reason a POSA would have combined

these concentrations with the NCT-231 protocol format, with a reasonable expectation of success. Having failed to consider this information and reject the challenged claims over these prior art disclosures, or to otherwise address these teachings of the prior art at all, the Examiner committed material error. *See*, *e.g.*, *Carrier Fire & Sec. Am.'s 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 Examiner's statement that certain limitations were not in the prior art was contradicted by petition's grounds).

B. Section 314(a)

There is no previous petition concerning the '320 patent warranting discretionary denial under the *General Plastic* factors.

C. Section 324(a)

There is no co-pending litigation involving the '320 patent warranting discretionary denial under the *Fintiv* factors.

VI. CLAIM INTERPRETATION

Claim terms are construed herein using the standard for civil actions under 35 U.S.C. § 282(b), in accordance with the ordinary 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.[8] *Nidec Motor v. Zhongshan*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); 83 Fed. Reg. 51,340, 51,353 (Oct. 11, 2018). Petitioner does not contend any claim term requires construction. Antony, ¶70.

VII. PRIOR ART TO THE '320 PATENT[9]

As detailed below, all references discussed herein are indisputable prior art under pre-AIA 35 U.S.C. §102(b) because they describe the invention of the challenged claims in printed publications more than one year prior to the '320 patent's earliest claimed priority date of May 15, 2012. While Petitioner does not concede that the challenged claims are entitled to the benefit of the May 15, 2012 provisional application, nor waive any arguments concerning priority that may be asserted in other proceedings, the Board need not address that issue herein.

A. NCT-231 (EX1005)

NCT-231 is Version 3 of a clinical trial protocol, entitled "Dose-Escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects

[8] Petitioner does not waive any arguments concerning claim scope necessary for resolving other proceedings.

[9] The Dr. Sylvia Hall-Ellis Declaration (EX1038) authenticates EX1007, EX1009, EX1010, EX1015, EX1016, EX1019, EX1020, EX1021, EX1022, EX1030, EX1032, EX1036, EX1037, EX1039, EX1040, EX1042, EX1044, EX1045.

with Unresectable Stage III or Stage IV Malignant Melanoma." Version 3 was posted on ClinicalTrials.gov on January 5, 2010. EX1005, 1, 3.

As explained in the accompanying declaration of Mr. Prescott Lassman (EX1028), ClinicalTrials.gov publicizes clinical trial protocols, like NCT-231, as widely and promptly as possible. EX1028, ¶¶15-16; *see also Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc.*, IPR2022-00578, Paper 78 at 27-28 (PTAB Aug. 29, 2023) (citing Mr. Lassman's "intimate knowledge of, and experience with, the ClinicalTrials.gov website" and noting that site is "designed to be used by members of the public"). The FDA Modernization Act of 1997 required that the National Institutes of Health ("NIH") establish a database concerning U.S. clinical trials on drugs for serious or life-threatening diseases. NIH's National Library of Medicine launched ClinicalTrials.gov in February 2000 to give the public better access to information on clinical studies. The FDA Amendments Act of 2007 later expanded the database by requiring trial sponsors to disclose additional information, enabling electronic searching. EX1028, ¶¶17-29.

NCT-231 (version 3) bears a "Last update posted" date of January 5, 2010. EX1005, 3. The "Last update posted" date is "The most recent date on which changes to a study record were made available on ClinicalTrials.gov." EX1029, 10. The "Last update posted" date for NCT-231 demonstrates that it was publicly available as of January 5, 2010. EX1028, ¶¶30-34.

POSAs and interested members of the public were aware that such clinical trial protocols were posted to ClinicalTrials.gov and would have been familiar with the available search function for accessing such information. For example, ClinicalTrials.gov offered a keyword-based "Basic Search" and an "Advanced Search" option for browsing its database. "Basic Search" allowed for keyword searching based on, *e.g.*, the name of a medical condition, intervention, or the location of a clinical trial. "Advanced Search" allowed for filtering search results by more categories. EX1028, ¶24; Antony, ¶¶71-74. A member of the public seeking information about NCT-231 would have used these keyword search options to navigate to NCT-231 and accessed publicly available information about the trial. Antony, ¶74; EX1028, ¶¶24-29. NCT-231 thus qualifies as a printed publication under §102(b) (pre-AIA) as of January 5, 2010. *Grunenthal v. Antecip Bioventures*, PGR2019-00003, Paper 22 at 17-18 (PTAB May 5, 2020) (finding protocol on ClinicalTrials.gov publicly available and therefore a "prior art printed publication"); EX1028, ¶¶30-40.

Because NCT-231 was available more than one year prior to the earliest claimed priority date of the '320 patent (May 15, 2012) it is indisputable prior art under pre-AIA §102(b).

B. Korman (EX1006)

Korman (WO2006/121168) published on Nov. 16, 2006 and is indisputable prior art to the challenged claims under pre-AIA 35 U.S.C. §102(b). EX1006, (22), (43).

In 2006, ***nearly six years*** before the earliest claimed priority date of challenged claim 1, Korman disclosed concurrent administration of anti-CTLA-4 and anti-PD-1 for the treatment of cancer in humans. EX1006, (57); *see also id.*, 16, 66; Antony, ¶79. Korman also reported that such concurrent administration exhibited synergistic effects in treating cancer in animal models. Antony, ¶80; *see also* EX1006, 66, 94-95, 98; EX1030, 4276 (left col.), 4278-4279; EX1045, 1.

Korman provides extensive dosing information for anti-PD-1 antibodies, including precise dose concentrations and ranges of acceptable concentrations, dose frequencies, and dose numbers (including in a maintenance-induction format). EX1006, 52-55. Korman recites "3 mg/kg, *i.e.,* the known dose of anti-CTLA-4 antibody" (*Id.*, 20) and indicates that anti-PD-1 and anti-CTLA-4 can be administered simultaneously per the disclosed dosages. *Id.,* 56 ("In certain embodiments, two or more monoclonal antibodies with different binding specificities (*e.g.*, anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated."); Antony, ¶¶37-38, 81-82.

C. Wolchok (EX1007)

Wolchok is a peer-reviewed journal article published in *Lancet Oncology* in 2010. Wolchok is indisputable prior art to the challenged claims under pre-AIA 35 U.S.C. §102(b).

Wolchok describes the results of a Phase II, randomized, double-blind clinical trial on anti-CTLA-4 antibody therapy (ipilimumab monotherapy) in patients with pretreated advanced melanoma. EX1007, 155. Wolchok discloses the treatment arm of this study as receiving "a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months." *Id*. Following on Wolchok's results, anti-CTLA-4 antibody monotherapy was ***approved for human use*** in 2011 by the FDA at a dose of 3 mg/kg given every three weeks for four doses. EX1008, 1; EX1018, 1; Antony, ¶¶40, 83-84. Wolchok was publicly accessible as of its publication date in 2010. EX1038, ¶¶45-52.

D. Sznol (EX1009)

Sznol is a Meeting Abstract from the 2010 ASCO Annual Meeting, published in the *Journal of Clinical Oncology* on May 20, 2010. Sznol is indisputable prior art to the challenged claim under pre-AIA 35 U.S.C. §102(b).

Sznol describes the results of a multicenter trial evaluating the safety, antitumor activity, pharmacokinetics ("PK"), and immunological correlates of

extended biweekly dosing of the anti-PD-1 antibody, MDX-1106. EX1009, 205s. Sznol studied "biweekly MDX-1106 dosing at 1, 3, or 10 mg/kg IV" in patients who had "treatment refractory metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma (MEL), or prostate cancer (CRPC), and no history of autoimmune disease." *Id.* Sznol reported that "MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg." *Id.* Antony, ¶¶39, 85-87. Sznol was publicly accessible as of its publication date of May 20, 2010. EX1038, ¶¶53-60.

VIII. PRECISE REASONS FOR RELIEF REQUESTED

A. GROUND 1: NCT-231 in View of Korman, and In Further View of Wolchok Render Obvious Claims 1-4, 6-12, and 14-17.

Challenged claim 1 recites a method of treating cancer by administering (1) an ***induction*** phase of anti-PD-1 and anti-CTLA-4 antibodies at various options of dose numbers, frequencies and optional dose concentrations ((a) through (m)), followed by administering the anti-PD-1 antibody alone at various options of dose numbers and frequencies, followed by administering, (2) a ***maintenance*** phase of the two antibodies again at various options of dose numbers and frequencies. EX1001, cl. 1. Dependent claims 2-4, 6-12, and 14-17 recite specific antibodies, dosing limitations, treatment outcomes, types of cancer, and additional combination therapies. EX1001, cls. 2-4, 6-12, 14-17. Antony, ¶89.

These claims would have been obvious to a POSA by May 15, 2012 over the 2010 published protocol of NCT-231 disclosing anti-PD-1 plus anti-CTLA-4 combination therapy dosed in the ***precise*** induction-maintenance structure claimed, in view of prior art references (Korman and Wolchok) disclosing the claimed dosing concentrations, and ranges encompassing such concentrations, of each antibody (any one of which renders the lengthy list of options unpatentable). Antony, ¶¶88, 90. Given these explicit prior art dosing disclosures—both for anti-PD-1 and anti-CTLA-4 given concurrently and in reporting success with concentrations of each antibody when administered alone—and given the standard approach of POSAs to study a variety of concentration options and optimize antibody dosing to maximize therapeutic efficacy while minimizing toxic effects, a POSA would have had reason to combine these teachings to arrive at a dosing regimen falling within the scope of challenged claim 1. *Id.*, ¶¶90-91. Moreover, given the known success with similar dosing concentrations for each antibody administered alone, the demonstrated positive results of the claimed combination in animal models, and the known reliability of an iterative approach to selecting dose concentrations, for example in a dose-escalation format, a POSA would have reasonably expected success in implementing the NCT-231 protocol with dosing concentrations disclosed in Korman and Wolchok. *Id.,* ¶92.

1. NCT-231

The "Assigned Interventions" section of NCT-231 (EX1005, 4) describes the following dosing structure:

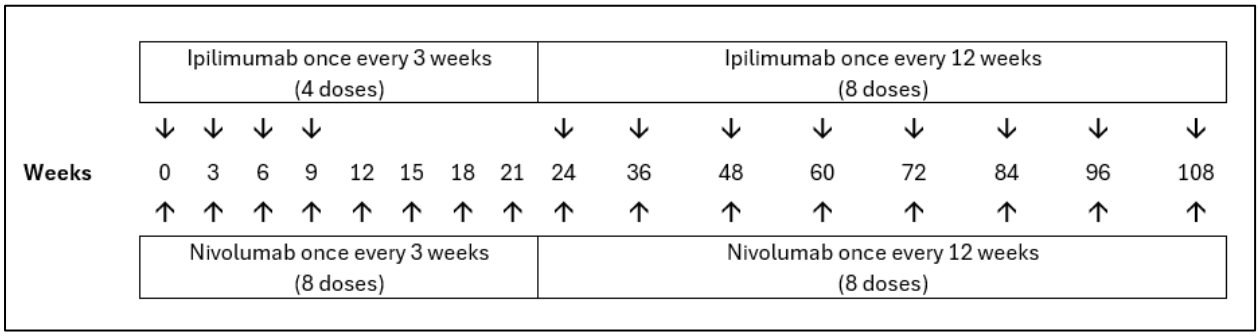
Drug: BMS-936558 (MDX1106-04) [nivolumab]

- Solution, IV, 60 min infusion, q3 weeks for 21 weeks in induction and q12 weeks for 84 weeks in maintenance

Drug: Ipilimumab

- Solution, IV, 90 minute infusion, q3 weeks for 9 weeks in induction and q12 weeks for 84 weeks in maintenance

This dosing structure is represented graphically as follows:



Antony, ¶¶75-78; EX1027; EX1061, 3 (confirming graphical depiction).

This dosing structure—an induction phase of anti-PD-1 and anti-CTLA-4 followed by anti-PD-1 alone, followed by a maintenance phase of the two antibodies—falls squarely within the scope of options presented in claim 1, where both anti-PD-1 and anti-CTLA-4 are given once every three weeks for four doses,

anti-PD-1 is given alone once every three weeks for four doses, and then both antibodies are given again once every 12 weeks for 8 doses. Antony, ¶¶93-95.

NCT-231 describes five cohorts receiving the following antibody concentrations:

C1: BMS-936558 at 0.3 mg/kg; Ipilimumab at 3 mg/kg

C2: BMS-936558 at 0.3 mg/kg; Ipilimumab at 10 mg/kg

C3: BMS-936558 at 1 mg/kg; Ipilimumab at 10 mg/kg

C4: BMS-936558 at 3 mg/kg; Ipilimumab at 10 mg/kg

C5: BMS-936558 at 10 mg/kg; Ipilimumab at 10 mg/kg

EX1005, 4; Antony, ¶¶96-97.

2. Korman, Wolchok, NCT-231

Claim 1's concentration options ((a) through (m)) were disclosed in Korman and/or in Wolchok and/or in NCT-231 itself as shown in the claim chart below. Antony, ¶¶98-107, 162.

Claim 1	**Korman**	**Wolchok**	**NCT 231 (EX1005, 4)**
(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody	"For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight." EX1006, 55. Korman discloses, "***3 mg/kg***, i.e., the known dose of anti-CTLA-4 antibody." EX1006, 56.	"217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), ***3 mg/kg (n=72)***, or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction)." EX1007, abstract.	Cohort Arm 1 0.3 mg/kg anti-PD-1; ***3 mg/kg anti-CTLA-4***
(b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (k) 0.3 mg/kg anti-PD-1 antibody and 0.3	"[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, ***5 mg/kg body weight or 10 mg/kg body weight***." EX1006, 55. Korman discloses, "***3 mg/kg***, i.e., the known dose of anti-CTLA-4 antibody." EX1006, 56.	"217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), ***3 mg/kg (n=72)***, or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction)." EX1007, abstract.	Cohort Arm 1 ***0.3 mg/kg anti-PD-1***; ***3 mg/kg anti-CTLA-4*** Cohort Arm 5 ***10 mg/kg anti-PD-1***; 10 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
mg/kg of anti-CTLA-4 antibody;			
(d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody; (l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody;	"For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight." EX1006, 55. And "[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated." EX1006, 55-56.		
(e) 0.3 mg/kg anti-PD-1 antibody	"[f]or example dosages [of anti-PD-1] can be ***0.3 mg/kg body weight***, 1 mg/kg body weight, 3		Cohort Arm 1 ***0.3 mg/kg anti-PD-1***; 3

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
and 1 mg/kg of anti-CTLA-4 antibody;	mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight." EX1006, 55. "For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight." EX1006, 55. And "[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated." EX1006, 55-56.		mg/kg anti-CTLA-4
(f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	"Preferred dosage regimens for an anti-PD-1 antibody of the invention include ***1 mg/kg body weight or 3 mg/kg body weight***." EX1006, 55.		Cohort Arm 3 ***1 mg/kg anti-PD-1***; 10 mg/kg anti-CTLA-4 Cohort Arm 4 ***3 mg/kg anti-PD-1***;

Claim 1	**Korman**	**Wolchok**	**NCT 231 (EX1005, 4)**
(g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	Anti-PD-1 antibody can be dosed "within the range of 1-10 mg/kg" and "[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated." EX1006, 55-56.		10 mg/kg anti-CTLA-4
(h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.; (i) 10 mg/kg anti-PD-1 antibody	"[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, ***5 mg/kg body weight*** **or 10 mg/kg body weight**." EX1006, 55. Anti-PD-1 antibody can be dosed "within the range of 1-10 mg/kg" and "[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-		Cohort Arm 5 ***10 mg/kg anti-PD-1***; 10 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
and 1 mg/kg of anti-CTLA-4 antibody	CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated." EX1006, 55-56.		

3. Reason To Modify NCT-231 with Korman and Wolchok

A POSA would have had reason to combine the known and studied dosing concentrations disclosed in Korman and Wolchok to arrive at ***any one*** of the dosing concentrations listed in limitations ((a) through (m)) for use in the induction-maintenance dosing structure of NCT-231 (hereinafter "NCT231-Korman-Wolchok")[10] and would have had a reasonable expectation of success in doing so. Sections 3.b.-f. below detail reasons why a POSA would have combined the prior art teachings in different ways to yield various dosing combinations, recognizing that obviousness does not require that a particular claimed regimen be

[10] A POSA would have understood that Korman's disclosure of "anti-PD-1 antibodies" to include NCT 231's reference to "BMS-936558" and Korman's disclosure of "anti-CTLA-4 antibodies" to include NCT 231's and Wolchok's reference to "ipilimumab". *See* Footnotes 5 and 6; Antony, ¶108.

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."). Antony, ¶108.

a. Knowledge-Based and Iterative Strategies For Choosing Dose Concentrations Would Have Provided a POSA With Reason to Combine NCT-231, Korman, and Wolchok.

By 2012, the immuno-oncology field understood that combinations of two or more immunotherapies could provide promising treatments for otherwise incurable cancers, particularly in situations where both antibodies demonstrated success as a monotherapy and were shown safe and efficacious as a combination in animal models. Antony, ¶109; EX1032, 1222-26. It was known by 2011 that the "[d]evelopment considerations for combination therapies" include the state of ***existing knowledge*** about "dose, efficacy, and toxicity" of the proposed compounds. EX1032, 1223-24 (Table 1). The prior art also posited that for a combination of two drugs which are both active independently, but expected to be more effective than either agent alone (as was known to be the case for anti-PD-1 combined with anti-CTLA-4 (*see* EX1006, 94; EX1030, 4279)), a POSA could administer each drug at its full dose. EX1032, 1224 ("A phase I dose-seeking trial should ideally be designed around a testable hypothesis. For example, 1) both drugs can be given at full dose"); Antony, ¶110. Moreover, POSAs understood that

"combinatorial strategies will always be easier to develop when one of the components is ***already approved*** as a single agent," providing a dosing starting point from which to build a combined regimen. EX1032, 1225; Antony, ¶111.

After starting with a "testable hypothesis" such as the studied, subtherapeutic, or approved dosing concentrations for each antibody, it was also common in this field to test incrementally higher or lower concentrations within a reasonable range to optimize a combination therapy. EX1040, 709 ("'[U]p-and-down' designs because they allow dose escalation and de-escalation.…The general principle of this design is to escalate or de-escalate the dose with diminishing fractions of the preceding dose depending on the absence or presence of severe toxicity in the previous cohort of treated patients."). Antony, ¶112.

In view of the aforementioned dosing principles for combination therapies, the many disclosed dosing options and ranges (particularly those already disclosed, studied, or approved for these checkpoint antibodies), a POSA would have had reason to apply existing knowledge to combine known, tested, and/or approved concentrations for each antibody as discussed, for example, in subsections (b) and (e), *infra*. Antony, ¶¶113-114; *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1375 (Fed. Cir. 2005) (reversing finding of non-obviousness—"The district court thus clearly erred to the extent it found lacking any motivation to

combine existing knowledge with the [prior art disclosure of dosing concentrations] to reach the claimed invention.").

A POSA would have alternatively engaged in standard iteration to "improve upon what is already generally known" by adjusting dosing concentrations within disclosed concentration ranges in assembling a dosing protocol according to the structure of NCT-231 for an anti-PD-1 plus anti-CTLA-4 therapy as discussed, for example, in section (c), (d), (e), and (f), *infra*. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); Antony, ¶115. Indeed, this would have been "'nothing more than routine' application of a well-known problem-solving strategy,…'the work of a skilled [artisan], not of an inventor"' particularly given a POSA's desire to maximize efficacy and in view of the already existing evidence of success with anti-CTLA-4 and anti-PD-1 alone and in combination. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007); *In re Peterson*, 315 F.3d 1325, 1329-30 ("A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art."); *see also In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *Tyco Healthcare Group LP v. Mutual Pharm. Co.*, 642 F.3d 1370, 1371 (Fed. Cir. 2011) (affirming that "it would have been obvious to a [POSA] to combine the preexisting 15 mg Restoril® capsule

with the dosage range" disclosed in another reference); *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods.*, IPR2013-00537, Paper 79 at 19-20 (PTAB Feb. 23, 2015) (claims unpatentable where "preponderance of the evidence establishe[d] that the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [the prior art] which would have been achievable through the use of standard clinical trial procedures… [as] the routine application of a well-known problem-solving strategy."); Antony, ¶116.

Moreover, as discussed in section IX., *infra*, Patent Owner has provided no evidence demonstrating the criticality of any of the particular claimed dosing schemes. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341-42, (Fed. Cir. 2020) (affirming obviousness where Board determined that "an optimal temperature range would have been nothing more than routine experimentation" and that Patent Owner "failed to establish criticality for the claimed temperature range"); Antony, ¶117.

b. Claim 1 Concentration Options (b) and (c)

With respect to options (b)—5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody—and (c)—10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody—a POSA seeking safe and effective concentration amounts would have had reason to utilize the explicitly disclosed concentration options for anti-PD-1 and anti-CTLA-4 found in Korman in the induction-maintenance dosing

format of NCT-231. Korman offers incremental dosing options for anti-PD-1 that overlap with the options ***already tested*** for this antibody when dosed alone (*i.e.*, Korman discloses "0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight" which overlap with the increments already demonstrated safe and efficacious for anti-PD-1 "1, 3, or 10 mg/kg"). EX1006, 55; EX1009, 205s; Antony, ¶¶118-119.

For anti-PD-1, a POSA would have reason to select the 5 mg/kg option explicitly disclosed in Korman because it is an incremental option between the 3 mg/kg and 10 mg/kg options which had already been tested and shown to be safe and efficacious. Antony, ¶120. Similarly, a POSA would have had reason to select the 10 mg/kg option explicitly disclosed in Korman because it was a known dose and had already been shown safe and effective in a study of anti-PD-1 alone. *Id.*, ¶121; EX1009, 205s. Confirming the reasonableness of this selection, a 10 mg/kg dose of anti-PD-1 was also already being tested in the NCT-231 clinical trial of the concurrent anti-PD-1 plus anti-CTLA-4 antibody therapy more than two years before May of 2012. EX1005, 4 (cohort arm 5); Antony, ¶122.

For anti-CTLA-4, Korman indicates (EX1006, 20) that 3 mg/kg of anti-CTLA-4 antibody was the "known dose" at the time (as confirmed by Wolchok and the 2011 FDA approval of the antibody for cancer therapy, and a POSA would have reason to start with or select already-known and studied dosing options when

seeking a safe therapy. Likewise, a 3 mg/kg dose of anti-CTLA-4 was already being tested in the NCT-231 clinical trial more than two years before May 15, 2012. EX1005, 4 (cohort arm 1). For at least these reasons, a POSA would have had a reason to select 5 and 10 mg/kg of anti-PD-1 antibody to administer with the already known and approved dose of 3 mg/kg of anti-CTLA-4 to arrive at claimed options (b) and (c). Antony, ¶¶123-124.

c. Claim 1 Concentration Options (f) and (g)

With respect to option (f)—1 mg/kg anti-PD-1 antibody with 1 mg/kg of anti CTLA-4 antibody—a POSA would have had reason to select a concentration of 1 mg/kg for both antibodies given the explicit disclosure in Korman that 1 mg/kg was a "preferred" dosing concentration for this drug (both specifically and at the lower bound of the disclosed range 1-10 mg/kg) and because Korman instructed that when anti-PD-1 and anti-CTLA-4 are "administered simultaneously," "the dosage of each antibody administered falls within the ranges indicated" (*i.e.*, 1-10 mg/kg). EX1006, 55-56. Likewise, a 1 mg/kg dose of anti-PD-1 was also already being tested in NCT-231. EX1005, 4 (cohort arm 3). Antony, ¶125.

Similarly, a POSA would have reason to select the other "preferred" dosing concentration for anti-PD-1 (*i.e.*, 3 mg/kg) and likewise would have followed Korman's guidance that such dose could be paired with anti-CTLA-4 where the

dose of that antibody falls within the 1-10 mg/kg range to arrive at concentration option (g). Antony, ¶¶126-127; *see also* EX1005, 4 (cohort arm 4).

d. Claim 1 Concentration Options (h), (i), and (m)

With respect to claim options (h) (5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), (i) (10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), and (m) (5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody), a POSA would have reason to select the specific recited concentrations from the listed options of anti-PD-1 (0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight), each of which was also a potentially optimal value falling within the disclosed 1-10 mg/kg range and would have then reasonably followed Korman's guidance that when "two or more monoclonal antibodies with different binding specificities (*e.g.*, anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated." EX1006, 56. Likewise, a 10 mg/kg dose of anti-PD-1 was also already being tested in NCT-231. EX1005, 4 (cohort arm 5). Antony, ¶128.

Because it was a well-known strategy to test iteratively higher and lower concentrations falling around previously known and tested concentrations and falling within disclosed concentration ranges (*see* §VIII.A.3.a, *supra*), a POSA

would have reasonably selected and tested various incremental doses within Korman's disclosed ranges (*i.e.,* 1-10 mg/kg, and 0.01-5 mg/kg). Antony, ¶129.

e. Claim 1 Concentration Option (k) and (e)

With respect to option (k) (0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody), a POSA would have had reason to explore the low effective doses disclosed in the prior art (*e.g.*, 0.3 mg/kg, as disclosed in both Korman (as to anti-PD-1) and Wolchok (as to anti-CTLA-4)) so as to maximize efficacy while reducing harmful side effects. Antony, ¶130. A POSA would have had further reason to investigate these lower doses in view of Korman's own touting of the effectiveness of this combination therapy when anti-CTLA-4 is administered at a ***subtherapeutic*** dose (*e.g.*, below 3 mg/kg). EX1006, 66, 94. And a 0.3 mg/kg dose of anti-PD-1 was also already being tested in NCT-231. EX1005, 4 (cohort arm 2); Antony, ¶¶131-132.

For similar reasons, a POSA would have had reason to try the slightly higher dose concentration of 1 mg/kg for anti-CTLA-4 as recited in claimed option (e) (0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody) with the 0.3 mg/kg dose of anti-PD-1 as both concentrations fall within Korman's disclosed range of 0.01 to 5 mg/kg and because Korman instructed that when anti-PD-1 and anti-CTLA-4 are "administered simultaneously…the dosage of each antibody falls administered within the ranges indicated." EX1006, 56; Antony, ¶133.

In view of these reasons to try a lower dose and Korman's suggestion that such would be successful, options (k) and (e) of claim 1 would have been obvious concentrations to a POSA as of May 15, 2012. *See Tyco,* 642 F.3d at 1372-77 (finding patent to insomnia drug obvious over the prior art where the only difference in the claimed invention and the prior art was the dosage amount, the prior art disclosing 15 mg temazepam capsules and the claimed invention reciting dosages of 6 mg to 8 mg in claim 1, and 7.5 mg in claim 2, because the prior art gave a motivation to try lower dosages and suggested a reasonable chance of success); Antony, ¶ 134.

f. Claim 1 Concentration Options (a), (d), (j), and (l)

With respect to concentration options (a), (d), (j), and (l), Korman discloses the dosing concentration range of 0.01 mg/kg to 5 mg/kg for anti-PD-1 antibodies, which encompasses each of these anti-PD-1 antibody concentrations and teaches that anti-PD-1 and anti-CTLA-4 "are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated." EX1006, 55-56. Additionally, for concentration option (a), both Korman and Wolchok disclose 3 mg/kg of CTLA-4. EX1006, 56; EX1007, 155; Antony, ¶135.

For the reasons set forth in §VIII.A.3.a, *supra*, a POSA would have had reason to study various options within the disclosed 0.01 to 5 mg/kg range and to optimize results towards an effective concentration combination option for anti-

PD-1 and anti-CTLA-4 antibodies. Moreover, as discussed above, a POSA would have had reason to study low, subtherapeutic doses such as 0.1 mg/kg in view of Korman's discussion of success with the same. EX1006, 66, 94; Antony, ¶136.

Confirming the rationale that various combinations of incremental concentrations between 0.1 mg/kg and 10 mg/kg for anti-PD-1 and anti-CTLA-4 antibodies in a concurrent regimen would have been obvious as the product of routine optimization of concentrations falling within a disclosed range (Korman), is the fact that many such increments were already being tested for each of these antibodies. EX1007, 155; EX1009, 205s, EX1005, 4. Antony, ¶¶137-38.

A POSA would have had reason to select any one of the claimed dosing options ((a) through (m)) by adopting the explicit (often "preferred") disclosed concentrations in Korman (confirmed by Wolchok and the FDA approval of ipilimumab and Sznol), Wolchok, or NCT-231, or by starting with low effective doses, and/or by routine experimentation of various dose options within the disclosed ranges of 1-10 mg/kg or 0.01-5 mg/kg. Antony, ¶¶139-40; *see also Boehringer Ingelheim Pharms. v. Mylan Pharms. Inc.,* 803 Fed. Appx. 397, 401-2 (Fed. Cir. 2020) (affirming obviousness of claims to administering drug in 2.5 or 5 mg doses in view of prior art disclosing a range of 1-100 mg because substantial evidence demonstrated that a POSA would have obtained the claimed dosages

through routine experimentation and that "dose ranging studies are 'conducted starting with a low dose, and sequentially moving through increasing doses'").

4. Reasonable Expectation of Success

A POSA would have understood that dosing selections for combinations of drugs is a matter of balancing safety and efficacy within certain known constraints and considerations. Antony, ¶¶141-142. As discussed in §VIII.A.3.a, *supra* (and while the challenged claims do not require any particular level of efficacy themselves), many dosing decisions for combination therapies start with information about dosing concentrations that were already known to be safe and efficacious for each drug alone. Antony, ¶143. Studies such as Sznol and Wolchok provided baseline information about anti-PD-1 and anti-CTLA-4 dosing concentrations, respectively, when each was given alone. EX1007, 155; EX1009, 205s; Antony, ¶144.

Such information would be bolstered by disclosure of concurrent administration of the two antibodies (EX1006, 56; EX1005, 4) and evidence of relative safety and efficacy for the combination therapy in animal models. EX1006, 97; EX1030, 4276; EX1045, 1. From there, researchers would iterate the testing of various combination doses from such known concentrations (administering incrementally higher or lower concentrations as desired). Antony, ¶¶145-46; EX1040, 709. In this way, researchers could reasonably expect similar efficacy

without severe swings in toxicity. This iterative approach is confirmed by the fact that the concentrations of these two antibodies were themselves varied and optimized ***within*** the context of the NCT-231 study. Antony, ¶147. By the April 2012 version of NCT-231 (Version 58), the protocol had been modified ***adding in new intermediate*** concentrations C2, C3 and anti-PD-1 alone concentrations C6, and C7). EX1031, 3-5. Antony, ¶¶148-149.

The title of NCT-231 itself is "***Dose-escalation Study***…." EX1005, 1. Thus it was clearly within the reasonable expectation of a POSA during this time (in the context of these two antibodies specifically, and particularly in view of the prior art success of these antibodies) that modifying and utilizing incrementally higher concentrations, typically trying increasing increments based on the log function of a given concentration (*i.e.*, 1, 10), or based on tenths of a given does (0.1, 1, and 0.3, 3), or doubling of doses (5, 10) would successfully yield dosing concentrations to treat cancer, as claimed. Antony, ¶150; *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."—affirming obviousness where dosage amount and frequency was deemed obvious to try); *Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1124-26 (Fed. Cir. 2015) (affirming judgment that claims to once a day method of treatment were obvious over prior art describing twice a day dosing even though

the reference was only "predictive" and not based on clinical studies, but was sufficient to give a reasonable expectation of success).

For at least these reasons, a POSA would have had both reason to select any one of the explicitly disclosed—some "preferred", some approved—options set forth in Korman and Wolchok (or select incremental or optimized concentration levels within disclosed concentration ranges) and utilize these with the intervention cohorts of NCT-231 and would have reasonably expected success in so doing. *Salix Pharms. Ltd. v. Norwich Pharms. Inc.,* 98 F.4th 1056, 1061-64 (Fed. Cir. 2024) (affirming obviousness of claims reciting 550 mg 3X daily dose of rifaximin where prior art clinical trial protocol recited twice daily doses of 550 mg and 1100 mg and prior art taught 400 mg thrice daily administration but suggested that an optimal dose may be higher); *Boehringer*, 803 Fed. Appx. at 402. Antony, ¶151.

5. Claim-by-Claim Analysis

a. Independent Claim 1

i. [1Pre] "A method of treating a human subject afflicted with a cancer comprising administering to the subject:"

To the extent claim 1's preamble is limiting, NCT231-Korman-Wolchok satisfies it because the NCT231-Korman-Wolchok method as detailed in *supra* §§VIII.A.1-4. entails treating cancer—consistent with the teachings of all three prior art references. EX1005, 3 (treatment of "Unresectable Stage III or Stage IV

Malignant Melanoma"); EX1006, (57); EX1007, 155 (Treatment of cancer "stage III (unresectable) or stage IV melanoma"); Antony, ¶¶152-56.

ii. [1A] "(a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) ('anti-PD-1 antibody'); and (b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) ('anti-CTLA-4 antibody')"

NCT231-Korman-Wolchok satisfies limitation [1A] because it entails the concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies as detailed *supra* §§VIII.A.1-4. In particular, the method of NCT231-Korman-Wolchok entails the concurrent administration of both anti-PD-1 and anti-CTLA as disclosed and tested in NCT-231 (EX1005, 4) and the disclosure of simultaneous administration of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of cancer, as described in Korman. EX1006, 56; Antony, ¶¶157-58.

iii. [1B] "(i) an induction dosing schedule … followed by (ii) a maintenance dosing schedule;"

NCT231-Korman-Wolchok satisfies limitation [1B] because this method involves concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies on a dosing schedule that falls within the options set forth in limitation [1B] as detailed *supra* §§VIII.A.1 and 3. Specifically, the clinical trial protocol described in NCT-231 discloses an ***induction*** phase of 4 doses of combination therapy given every 3

weeks, followed by 4 doses of anti-PD-1 alone given every 3 weeks, followed by a ***maintenance*** phase of 8 doses of combination therapy given every 12 weeks. EX1005, 4. The dosing structure of the NCT231-Korman-Wolchok method thus falls squarely within the scope of dosing numbers and frequencies disclosed in limitation [1B]. *Id.*; Antony, ¶¶159-60.

iv. [1C] "and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages: (a) [through (m)]."

NCT231-Korman-Wolchok satisfies limitation [1C] because it entails selecting any one of the claimed concentrations for anti-PD-1 and anti-CTLA-4 ((a) through (m)), each of which are disclosed (or fall within disclosed ranges) in Korman and Wolchok, and/or were already being tested in NCT-231. *See supra* §§VIII.A.1-4; Antony, ¶¶161-162. A POSA would have understood that dosing concentrations corresponding to options (a) through (m) would be reasonable concentrations to select for use in the protocol of NCT-231 in view of Korman's disclosure of many of these concentrations (several as "preferred"), in view of Korman's disclosure of ranges encompassing each of these concentrations, in view of the variety of similar concentrations already being tested in NCT-231 or approved from Wolchok, and in furtherance of well-known iterative dosing principles designed to find optimal concentration values within disclosed ranges. Antony, ¶163. Moreover, a POSA would have reasonably expected in applying

these disclosed concentrations to the dosing structure of NCT-231 in view of the foregoing prior art knowledge that many such doses were safe and effective for each antibody. *Id.*, ¶164.

b. Claim 2

Claim 2, depending from claim 1, further recites, "wherein the anti-PD-1 antibody is nivolumab." NCT231-Korman-Wolchok renders obvious this claimed method because as discussed *supra* §VII.A.1, the NCT-231 clinical trial protocol entails the administration of BMS-936558 (MDX1106-040) (also known as nivolumab) as the anti-PD-1 antibody. EX1005, 3. In addition, Korman discloses nucleotide sequences for a "5C4 human monoclonal antibody" (*i.e.*, Figures 4A-4B, SEQ ID NO: 60, SEQ ID NO: 4, SEQ ID NO: 67, and SEQ ID NO: 11). EX1006, 10-11. The 5C4 human monoclonal antibody disclosed in Korman is nivolumab, as confirmed by BLAST alignment. Antony, ¶¶165-67.

c. Claim 3

Claim 3, depending from claim 1, further recites, "wherein the anti-CTLA-4 antibody is ipilimumab." NCT231-Korman-Wolchok renders obvious this claimed method because as discussed *supra* §VII.A.1, the NCT-231 clinical trial protocol explicitly entails the administration of "ipilimumab." EX1005, 3. And Korman discloses, "In certain embodiments, the anti-CTLA-4 antibody is human sequence monoclonal antibody 10D1 and the anti PD-1 antibody is human sequence

monoclonal antibody, such as 17D8, 2D3, 4H1, 5C4, and 4A11." EX1006, 66. The 10D1 human monoclonal antibody disclosed in Korman is ipilimumab, as confirmed by BLAST alignment. Antony, ¶¶168-169.

d. Claim 4

Claim 4 depending from claim 1 further recites "wherein the anti-CTLA-4 antibody is administered during the induction dosing schedule once every 3 weeks for a total of 4 doses." NCT231-Korman-Wolchok renders obvious the method of claim 4 for the same reasons discussed above regarding the dosing numbers and frequencies recited in claim 1 (§§VIII.A.1 and 5.a.iii) because this method entails administering an anti-CTLA-4 antibody (ipilimumab) during the induction dosing schedule ***once every three weeks, for a total of four doses***. EX1005, 4; EX1007, 155; *see also* §VIII.A.5.c, *supra*. Antony, ¶¶170-171.

e. Claim 6

Claim 6 depending from claim 1 further recites, "wherein the administering comprises: (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 3 weeks for 4 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 3 weeks for 4 doses; followed by (ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody

and the anti-CTLA-4 antibody at a dosing frequency of once every 2 to 12 weeks for up to 8 doses."

NCT231-Korman-Wolchok renders obvious this claimed method as it entails a dosing schedule (NCT-231) falling precisely within this claim (as discussed in §VIII.A.1, *supra*) whereby the maintenance dosing frequency of NCT-231 is once every 12 weeks for 8 doses. EX1005, 4; Antony, ¶¶172-73.

f. Claim 12

Claim 12 depending from claim 1 further recites, "wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the maintenance dosing schedule" at the same (a) through (m) concentrations recited in claim 1.

NCT23-Korman-Wolchok renders obvious this claimed method as it entails the selection of any one of the concentrations explicitly disclosed in Korman and Wolchok and which would have been combined by a POSA for the reasons discussed at *supra* §VIII.A.2-4. Antony, ¶¶174-75. A POSA would have recognized such concentration options to be equally applicable to maintenance doses as they are for induction doses and would have reason to administer similar concentrations for therapeutic consistency, maintaining safety, limiting toxicity, and convenience. Confirming this, NCT-231 includes concentration information for each cohort, where the concentrations given do not change as between induction and maintenance dosing. EX1005, 4; Antony, ¶176.

In addition, Korman discloses a specific dose for anti-PD-1 given in an ***induction-maintenance*** dosing structure, with no distinction in concentration between the induction and maintenance dose. EX1006, 55 ("Preferred dosage regimens for an anti-PD-1 antibody of the invention include ***1 mg/kg*** body weight…via intravenous administration, with the antibody being given…(i) every four weeks for six dosages, ***then every three months***."). Korman also instructs that anti-PD-1 and anti-CTLA-4 can be given simultaneously per such dosing structure. *Id.*, 56. Such disclosure of "1 mg/kg" for both antibodies in a maintenance regimen satisfies at least dosing option (f) of claim 12. Antony, ¶177.

Finally, Korman also discloses 0.3 mg/kg as a concentration option for anti-PD-1, while Wolchok discloses administration of anti CTLA-4 antibodies at 10, 3, or 0.3 mg/kg in a ***maintenance*** dosing schedule. EX1006, 55; EX1007, 155 ("***0.3 mg/kg (n=72)*** every 3 weeks for four cycles (induction) followed by ***maintenance therapy every 3 months***"). In view of these maintenance dosing disclosures and as discussed in §VIII.A.3.e., a POSA would have had a reason to assemble the dosing concentration disclosures of Korman and Wolchok to arrive at the concentration option (k) (*i.e.*, 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody) and would have selected this as a maintenance concentration as this would have been a reasonable subtherapeutic dose from which to study

incrementally higher concentrations while minimizing safety and toxicity concerns. Antony, ¶¶178-79; *Boehringer,* 803 Fed. Appx. at 402.

g. Claim 14

Claim 14 depending from claim 1 further recites "wherein 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule." NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT-231. EX1005, 4; *see supra* §VIII.A.1 and A.5.a.iii. In addition, as discussed in §§VIII.A.2-3.b, 4, and 5.a.iv, administration of 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (b), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT-231. Antony, ¶¶180-82.

h. Claim 15

Claim 15 depending from claim 1 further recites, "wherein 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule." NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks

for four doses as recited in NCT-231. EX1005, 4; *see supra* §VIII.A.1 and A.5.a.iii. In addition, as discussed in §§VIII.A.2-3.c, 4, and 5.a.iv, administration of 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (f), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT-231. Antony, ¶¶183-84.

i. Claim 16

Claim 16 depending from claim 1 further recites, "wherein 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule." NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT-231. EX1005, 4; *see supra* §VIII.A.1 and A.5.a.iii. In addition, as discussed in §§VII.A.2-3.c, 4, and 5.a.iv, administration of 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (g), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT-231. Antony, ¶¶185-86.

j. Claim 17

Claim 17 depending from claim 1 further recites, "wherein 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule." NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT-231. EX1005, 4; *see supra* §VIII.A.1 and A.5.a.iii. In addition, as discussed in §§VIII.A.2-3.d, 4, and 5.a.iv, administration of 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (h), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT-231. Antony, ¶¶187-88.

k. Claim 7

Claim 7 depending from claim 1 further recites, "wherein the treatment provides a reduction in tumor size, reduction in tumor growth…partial response, or stable disease." NCT231-Korman-Wolchok renders this claim obvious as it entails a method of treatment of cancer resulting in, for example, reduction of tumor growth. Korman states: "the combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody showed an unexpected, significantly greater effect on ***reducing***

tumor growth as compared to treatment with either antibody alone (*see, e.g.*, Figures 21D, 24D, 30F and 33H-J)". EX1006, 66. Antony, ¶¶189-92.

In addition, by 2012, both anti-PD-1 and anti-CTLA-4 had demonstrated positive results in humans for outcomes such as "complete or partial response" or "objective tumor responses" when administered alone, which would have provided a POSA a reasonable expectation of success for the NCT231-Korman-Wolchok method dosed at similar concentrations. EX1007, 1 ("[O]verall response rate (the proportion of ***patients with a complete or partial response***…was 11.1% (95% CI 4.9–20.7) for 10 mg/kg, 4.2% ***(0.9–11.7) for 3 mg/kg***, and 0% (0.0–4.9) for 0.3 mg/kg (p=0.0015; trend test)."); EX1009, 205s (For bi-weekly dosing of MDX-1106, "[a]s of Dec 2009, 6/16 (37.5%) evaluable pts had ***objective tumor responses, including 3 at 1 mg/kg*** (RCC/CR, RCC/PR, MEL/PR), 2 at 3 mg/kg (NSCLC/PR, MEL/PR) and one at 10 mg/kg (MEL/PR)."); Antony, ¶193. In view of this information, a POSA would have reasonably expected some degree of similar response from the combination therapy in humans, or at the very least would have reasonably expected the maintenance of stable disease. Antony, ¶194; *see also supra* §VIII.A.4; *Salix,* 98 F.4th at 1061-62.

l. Claim 8

Claim 8 depending from claim 1 further recites, "wherein the cancer is selected from liver cancer, hepatocellular carcinoma,…cutaneous or intraocular

malignant melanoma,…non-Hodgkin's lymphoma,…and a hematologic malignancy." NCT231-Korman-Wolchok renders obvious this claimed method as it discloses a method of treatment for several cancers recited in claim 8 including melanoma, and non-Hodgkin's lymphoma. EX1006, 68. Both NCT-231 and Wolchok studied patients with "stage III (unresectable) or stage IV ***melanoma***." EX1007, 155; EX1005, 4. A POSA would have understood malignant melanoma to include stage III or IV melanoma. Antony, ¶¶195-96. Korman also discloses use of "blockade of PD-1 and CTLA-4" as treatment against various cancers including melanoma (*e.g.*, metastatic malignant melanoma), lung cancer, and non-Hodgkin's lymphoma. EX1006, 68. A POSA would have reason to enlist the method of NCT231-Korman-Wolchok to treat, for example, malignant melanoma, non-Hodgkin's lymphoma, or lung cancer, given Korman's teaching and the existence of studies (Wolchok and NCT 231, for example) treating those diseases with anti-CTLA-4 alone or in combination with anti-PD-1, and would have reasonably expected success in so doing. Antony, ¶¶197-98.

m. Claim 9

Claim 9 depending from claim 1 further recites, "wherein the hematologic malignancy is selected from multiple myeloma, B-cell lymphoma, Hodgkin lymphoma/primary mediastinal B-cell lymphoma, non-Hodgkin's lymphomas,… and precursor T-lymphoblastic lymphoma." NCT231-Korman-Wolchok renders

obvious this claimed method as it entails a method of treatment of several cancers, including Hodgkin's lymphoma and non-Hodgkin's lymphoma. EX1006, 68; Antony, ¶¶199-200.

n. Claim 10

Claim 10 depending from claim 1 further recites, "wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer." NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment of several cancers including metastatic cancer. EX1006, 60 ("The present invention is also useful for treatment of metastatic cancers…that express PD-L1."), 68; EX1007, 155; Antony, ¶¶201-203.

o. Claim 11

Claim 11 depending from claim 1 further recites, "wherein the treatment is further combined with one or more of chemotherapy, radiation, surgery..." NCT231-Korman-Wolchok renders obvious this claim as it entails a method of treatment whereby the claimed antibodies are administered with other known cancer therapies. For example, Korman discloses these precise therapeutic additions. EX1006, 70 ("A combined PD-1 and CTLA-4 blockade may also be further combined with…chemotherapeutic regimes."). And Korman provides a mechanistic explanation regarding the motivation to layer on such additional therapies—"The scientific rationale behind the combined use of PD-1 and CTLA-4

blockade with chemotherapy is that cell death, which is a consequence of the cytotoxic action of most chemotherapeutic compounds, should result in increased levels of tumor antigen in the antigen presentation pathway."). EX1006, 70; Antony, ¶¶204-06.

For at least the foregoing reasons, challenged claims 1-4, 6-12, and 14-17 are obvious over NCT231-Korman-Wolchok. Antony, ¶207.

B. GROUND 2: Korman in View of Wolchok, and in further View of Sznol Render Obvious Claims 5, 13, and 18-22.

Challenged claim 5 recites a method of treating a human subject afflicted with cancer by administering 1 mg/kg of anti-PD-1 and 3 mg/kg of anti-CTLA-4 together every 3 weeks for 4 doses, followed by administering the anti-PD-1 antibody alone every 2 weeks. EX1001, cl. 5.

By 2012, all of the features of challenged claim 5 were known. Antony, ¶¶208-09. Korman had—nearly six years earlier—provided explicit dosing disclosures for both anti-PD-1, anti-CTLA-4, and their concurrent use. EX1006, 55 ("Preferred dosage regimens for an anti-PD-1 antibody of the invention include ***1 mg/kg*** body weight…using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) ***every three weeks***; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks"); *id.*, 20 ("***3 mg/kg***, *i.e.*, the known dose of anti-CTLA-4 antibody."); *id.*, 56 ("In certain embodiments, two or more monoclonal antibodies with different binding

specificities (*e.g.*, anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case ***the dosage of each antibody administered falls within the ranges indicated*** [i.e., "within the range of 1-10 mg/kg"]."). Antony, ¶¶41, 209.

Moreover, Wolchok reported study results that would become the approved dosing schedule for anti-CTLA-4 therapy at 3 mg/kg "***once every three weeks for four cycles***." EX1007, 155 (abstract); EX1008, 1. And by 2010, Sznol reported that biweekly anti-PD-1 monotherapy had been demonstrated safe and effective at a dose of 1, 3, or 10 mg/kg. EX1009, 205s. Antony, ¶¶210-11.

As discussed below, a POSA would have had a reason to combine these prior art teachings to arrive at the method of claim 5 and its dependent claims, and would have reasonably expected success. Antony, ¶212.

1. Reason to Modify Korman with Wolchok and Sznol

a. Combination dosing number and frequency

Korman discloses that a "preferred dosage regimen" for anti-PD-1 would be "every three weeks" (EX1006, 55) while Wolchok discloses the effective treatment of melanoma with anti-CTLA-4 antibody at a dosing frequency of "every 3 weeks for four cycles." EX1007, 155 (methods). Korman also discloses the treatment of cancer using simultaneous administration of anti-PD-1 and anti-CTLA-1. EX1006, 56. In deciding at what frequency to administer Korman's concurrent therapy, a POSA would have recognized that both Korman and Wolchok disclose an "every

three week" regimen and would have deemed this frequency reasonable to use given Wolchok's success with such frequency for the relatively more toxic antibody, anti-CTLA-4. *See* §IV.C. Antony, ¶¶213-14.

By May of 2012, it was also clear that anti-CTLA-4 antibodies generated significant immune-related adverse events. *See* EX1019, 29 (abstract); EX1020, 499; EX1021, 865; EX1007, 157, Fig. 1 (significant participant loss in progression from induction to maintenance dosing of anti-CTLA-4). By contrast, a POSA would have been aware of "a milder toxicity profile for anti-PD-1 than for anti-CTLA-4." EX1042, 245 (right col.); EX1044, 512, 514; EX1037, 3172; Antony, ¶¶215-16; *see* §§IV.C., *supra*. With this information, a POSA would have been cautious with the administration of anti-CTLA-4 and chosen a frequency for any combination therapy involving this drug that was already demonstrated safe and effective. EX1007, 155. A POSA dosing a concurrent therapy including anti-CTLA-4 would reasonably have followed Korman and Wolchok's frequency disclosure of "every three weeks" limited by Wolchok's number of doses, "for four cycles." Antony, ¶¶ 42-44, 216.

b. Subsequent Dosing of Anti-PD-1 Alone

In view of the less severe toxicity profile for anti-PD-1 antibodies and the sequentially later mechanistic action of anti-PD-1 relative to anti-CTLA-4 in blocking the T-cell "off signal" to kill cancer cells, a POSA would have desired to

extend the therapeutic benefit of the combination drug by continuing patients on anti-PD-1 antibodies subsequent to the concurrent therapy. EX1010, 178 ("CTLA-4 is important for limiting T-cell activity for cells early during the immune responses. PD-1, on the other hand, limits T-cell activity in peripheral tissues and may be the last chance to prevent T-cell destruction of self-tissue resulting in autoimmunity."); Antony, ¶217. This would have been consistent with the "combination followed by anti-PD-1 alone" format disclosed for then-ongoing clinical trials. EX1005, 4. Korman also discloses bi-weekly dosing for anti-PD-1. EX1006, 55 ("An exemplary treatment regime entails administration once per week, ***once every two weeks***."). A POSA would have had reason to continue administering anti-PD-1 antibody as a monotherapy even after completion of the combination and would have looked to existing reports of success with anti-PD-1 as a monotherapy, such as the bi-weekly dosing reported by Sznol. EX1009, 205s ("MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg."). Antony, ¶¶42-44, 218.

c. Dosing concentrations

A POSA implementing the concurrent antibody therapy of Korman would have reason to dose anti-PD-1 at a concentration of 1 mg/kg given its designation by Korman as "preferred" (EX1006, 55-56) and its demonstrated success in Sznol at reducing melanoma tumors (3 patients with objective tumor responses at 1

mg/kg). EX1009, 205s (results); Antony, ¶219. Such a POSA would have also had reason to dose anti-CTLA-4 at the "known" (EX1006, 20), "stud[ied]" (EX1007, 155), and "approved" and "recommended" (EX1008, 1) 3 mg/kg concentration disclosed in both Korman and Wolchok. A POSA would have reason to look to these disclosures in view of the standard approach in the field of dosing cancer immunotherapies by starting with what had been disclosed, known, studied, and reported safe and efficacious. EX1032, 1224 (right col.), 1225. Such approach would have provided a POSA with reason to settle on concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies at 1 mg/kg of the former and 3 mg/kg of the latter. Antony, ¶220.

In sum, a POSA would have reason to administer anti-PD-1 and anti-CTLA-4 concurrently and every three weeks as disclosed in Korman, at 1 mg/kg anti-PD-1 (Korman) and 3 mg/kg of anti-CTLA-4 (Korman and Wolchok), in a manner consistent with the approved dosing scheme for anti-CTLA-4 (*i.e.*, every three weeks for four cycles) (Wolchok), and would have looked to avoid harmful toxicity and seek the additional therapeutic benefit from an extended dose of anti-PD-1 alone at its known, safe, and effective bi-weekly frequency as reported in Sznol (hereinafter, "Korman-Wolchok-Sznol"). Antony, ¶221-22.

2. Reasonable Expectation of Success

A POSA would have reasonably expected success in administering anti-PD-1 and anti-CTLA-4 antibodies concurrently as disclosed in Korman at the dosing numbers, frequencies, and concentrations disclosed in Korman, Wolchok, and Sznol, and then administering anti-PD-1 alone biweekly as taught in Sznol for the same reasons disclosed above regarding the combination of NCT-231, Korman and Wolchok. This expectation would be based on: the existing safety and efficacy demonstrated with anti-PD-1 alone at a concentration of 1 mg/kg (EX1009, 205s), the existing safety and efficacy of anti-CTLA-4 alone at a concentration of 3 mg/kg given every three weeks for four doses (EX1007, 155; EX1008, 1), the disclosure of administering anti-PD-1 and anti-CTLA-4 concurrently and the demonstrated efficacy of such concurrent administration in animal models (EX1006, 56; 99; EX1030, 4276; EX1045, 1), and the known safety and toxicity profiles of each antibody as discussed above. *See* §§IV.C.1-2. This body of knowledge would have led a POSA to reasonably anticipate success in administering 1 mg/kg of anti-PD-1 and 3 mg/kg of anti-CTLA-4 together every three weeks for four cycles, followed by administering anti-PD-1 alone, bi-weekly. Antony, ¶¶223-24.

3. Claim-By-Claim Analysis

a. Independent Claim 5

i. [5Pre] "A method of treating a human subject afflicted with a cancer comprising"

To the extent claim 5's preamble is limiting, Korman-Wolchok-Sznol satisfies it because the Korman-Wolchok-Sznol method as detailed in *supra* §§VII.B-D, and B.1-2 entails treating human cancer patients. EX1006, 1; EX1007, 155; EX1009, 205s. A POSA would have had a reason to apply the various treatment details of each prior art reference in developing a concurrent therapy using these two antibodies that would account for the safety and toxicity profiles of each and would have reasonably expected success in combining such teachings. Antony, ¶225-30; *see* §§VIII.B.1-2, *supra.*

ii. [5A] "administering to the subject 1 mg/kg of an anti-PD-1 antibody,"

Korman-Wolchok-Sznol satisfies limitation [5A] because it entails administering anti-PD-1 antibody at a concentration of 1 mg/kg, consistent with the teachings of both Korman (disclosing this concentration as "preferred" for anti-PD-1) and Sznol (demonstrating safe and effective results of treatment of refractory cancers with 1 mg/kg of anti-PD-1). EX1006, 55; EX1009, 205s; Antony, ¶231.

iii. [5B] "and 3 mg/kg of an anti-CTLA-4 antibody"

Korman-Wolchok-Sznol satisfies limitation [5B] because it entails administering anti-CTLA-4 antibody at a concentration of 3 mg/kg, consistent with the teachings of both Korman (disclosing this as the "known" concentration for anti-CTLA-4 (EX1006, 20)) and Wolchok (demonstrating safe and effective Phase II trial results of treatment of metastatic melanoma with 3 mg/kg of anti-CTLA-4). EX1007, 155. Ipilimumab was also approved by the FDA in 2011 at this concentration. EX1008, 1. A POSA would have had reason to select a safe and effective concentration of anti-CTLA-4 in Korman's concurrent administration based on ***existing data*** about the antibody's safety and efficacy and would have relied on these existing prior art disclosures to select 3 mg/kg. Antony, ¶¶232-33.

iv. [5C] "every 3 weeks for 4 doses,"

Korman-Wolchok-Sznol satisfies limitation [5C] because it entails administering anti-PD-1 antibody and anti-CTLA-4 antibody together every three weeks for four doses (or cycles). Antony, ¶234. Korman describes administering anti-PD-1 antibody on an "every three weeks" schedule and instructs that anti-PD-1 and anti-CTLA-4 can be given together (simultaneously) such that anti-CTLA-4 would also be given "every three weeks." EX1006, 55-56. Wolchok discloses the later-approved dosing regimen for anti-CTLA-4 at "every 3 weeks ***for four cycles***" EX1007, 155. In view of the greater toxicity concerns relating to administration of anti-CTLA-4 (*see* §§IV.C.1-2, *supra*), a POSA would have applied Wolchok's

four cycle dosing number to the "every three week" dosing frequency for a combination therapy involving anti-CTLA-4. Antony, ¶¶235-36; EX1007, 155; EX1008, 1. A POSA would have had reason to give anti-CTLA-4 antibody therapy—and would have understood from Korman and Wolchok that concurrent anti-PD-1 and anti-CTLA-4 therapy could reasonably be given—every three weeks for four doses. Antony, ¶237.

v. [5D] "followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks."

Korman-Wolchok-Sznol satisfies limitation [5D] because it entails the application of knowledge about the safety and toxicity of each of these antibodies to administer anti-PD-1 monotherapy following the four cycles of combination therapy. Antony, ¶238.

As discussed in §§IV.C.1-2 and VIII.B.1-2, *supra*, a POSA would have understood the toxicity risks associated with anti-CTLA-4 antibody administration and the relative tolerability of anti-PD-1 therapy. Such knowledge, combined with the desire to balance therapeutic efficacy with toxicity and patient tolerance and in recognition of the temporal nature of each antibody's mechanism of action, would have provided POSAs with reason to follow the concurrent therapy with a phase of anti-PD-1 monotherapy. Antony, ¶¶239-40. Because Sznol discloses safe and effective bi-weekly dosing of anti-PD-1 in humans, a POSA would have had

reason to apply these existing results to dose anti-PD-1 monotherapy bi-weekly. A POSA would have reasonably expected success in combining these teachings given the evidence of safety and efficacy already known to be associated with bi-weekly dosing of anti-PD-1. Antony, ¶241; EX1009, 1-2; *see* §§VII.B.1-2.

For the foregoing reasons, challenged claim 5 is obvious over Korman-Wolchok-Sznol. Antony, ¶242.

b. Claim 13

Claim 13 depending from claim 5 further recites, "wherein the anti-PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg." Korman-Wolchok-Sznol renders obvious this claimed method because it entails administering anti-PD-1 alone bi-weekly and at a dose of 3 mg/kg. As discussed above, Sznol reported safe and effective results of dosing anti-PD-1 alone bi-weekly at this precise dose (3 mg/kg) and a POSA would have looked to this existing information in selecting the precise concentration of an anti-PD-1 monotherapy following concurrent administration of anti-PD-1 and anti-CTLA-1. EX1009, 205s. Korman likewise discloses the administration of anti-PD-1 at a dose of 3 mg/kg. EX1006, 55. Antony, ¶¶243-44.

c. Claim 18

Claim 18 depending from claim 1 further recites, "wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the

tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease." Korman-Wolchok-Sznol renders obvious this claimed method for the same reasons discussed *supra* at §VIII.A.5.k, regarding claim 7. Antony, ¶245.

d. Claim 19

Claim 19 depending from claim 5 lists types of cancer which can be treated by the claimed method, including melanoma. Korman-Wolchok-Sznol renders obvious this claimed method because it entails the treatment of melanoma, and more specifically, all three prior art references of the Korman-Wolchok-Sznol method involve the treatment of melanoma. EX1006, 68; EX1007, 155; EX1009, 205s. In light of the clear therapeutic focus of these disclosures on treating melanoma, a POSA would have reason to use the Korman-Wolchok-Sznol method to treat melanoma and would have reasonably expected success in combining these teachings. Antony, ¶¶246-248.

e. Claim 20

Claim 20 depending from claim 5 further recites, "wherein the cancer is melanoma." Korman-Wolchok-Sznol renders this claimed method obvious for the same reasons discussed *supra* at §VIII.B.3.d, regarding claim 19. Antony, ¶249.

f. Claim 21

Claim 21 depending from claim 5 further recites, "wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer." Korman-Wolchok-Sznol

renders obvious this claimed method because it entails the treatment of these diseases, and more specifically, all three prior art references of the Korman-Wolchok-Sznol method involve the treatment of either advanced, or metastatic, or refractory melanoma. EX1006, 68 ("metastatic malignant melanoma"); EX1007, 155 ("advanced melanoma"); EX1009, 205s ("refractory metastatic…melanoma"). In light of the focus of these disclosures, a POSA would have reason to use the Korman-Wolchok-Sznol method to treat advanced, or metastatic, or refractory melanoma and would have reasonably expected success in combining these teachings. Antony, ¶¶250-53.

g. Claim 22

Claim 22 depending from claim 1 further recites, "wherein the treatment is further combined with one or more of chemotherapy, radiation, surgery…" Korman-Wolchok-Sznol renders this claimed method obvious for the reasons discussed *supra* at §VII.A.5.o, regarding claim 11. Antony, ¶254.

For the foregoing reasons, claims 5, 13, and 18-22 are obvious over Korman-Wolchok-Sznol. Antony, ¶255-256.

IX. SECONDARY CONSIDERATIONS DO NOT OVERCOME A FINDING OF OBVIOUSNESS.

Petitioner is unaware of any unexpected results offered by Patent Owner with respect to the challenged claims. There was no discussion of unexpected results during prosecution of the '320 patent. *See generally* EX1002. Antony, ¶257.

In prosecution of related claims with similar dosing limitations in Europe (EX1023; EX1034), Patent Owner argued that Table 10 of the '320 patent evidences unexpected results with respect to cohort 2 and 2a (EX1025, 1-2) or cohort 2. EX1035, 2. However, the dosing regimen of cohort 2 does not align with any dosing regimen recited in any challenged claim. *Compare* EX1001, Table 10, *with id.*, cl. 1. And the data in Table 10 arose from a "concurrent regimen" structure that was distinct from and irrelevant to the dosing regimen of claim 5 or any of its dependent claims. EX1001 87:4-16.[11] Antony, ¶258-59. It is axiomatic that alleged evidence of unexpected results must correspond to what is actually claimed. *In re Gartside*, 203 F.3d 1305, 1321 (Fed. Cir. 2000) (affirming Board's obviousness finding where the examples showing the alleged improvement in unexpected results "d[id] not correspond to any process within the scope of the claims"). Moreover, Patent Owner's arguments regarding the unexpected results of cohort 2 and 2a were rejected by the Examining Division in Europe, leading to Patent Owner's withdrawal of such claims. EX1026, 2-3; EX1033, 1. Antony, ¶260.

[11] There is no data in the '320 patent relating to claim 5's dosing regimen at all. EX1001, 87:4-16; Antony, ¶259.

In any case, the data presented in Table 10 fails to establish unexpected results across the full scope of claim 1 and its dependent claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). Instead, Patent Owner admitted that certain unclaimed cohorts performed ***better*** than the single cohort from Table 10 (2a) that falls within the scope of any challenged claim. EX1035, 2 ("The data in Table 10 clearly show that the dosing regimen of ***Cohort 2 has superior effects as compared to those of cohorts 1, 2a, and 3***."). Antony, ¶261. Moreover, there is no evidence that any of the concentration regimens recited in Table 10 of the '320 patent demonstrate any difference ***in kind*** relative to the prior art in objective response rate or 80% tumor reduction at 12 weeks (as opposed to a difference of degree). To the contrary, the prior art already taught the additive (and synergistic) benefits of combining these antibodies. EX1006, 66; EX1045, 1. *Galderma Labs., L.P. v. Tolmar, Inc.,*737 F.3d 731, 739 (Fed. Cir. 2013); Antony, ¶262-63.

There is no evidence of secondary considerations that would overcome the foregoing demonstration that Challenged claims 1-22 are obvious. Antony, ¶264.

X. CONCLUSION

Petitioner respectfully requests that the Board institute review and find challenged claims 1-22 of the '320 patent unpatentable.

Dated: February 28, 2025

Respectfully submitted,
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APPENDIX I: '320 PATENT CLAIMS

Claim 1
[1Pre]. A method of treating a human subject afflicted with a cancer comprising administering to the subject:
[1A] (a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) ("anti-PD-1 antibody"); and (b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) ("anti-CTLA-4 antibody");
[1B] (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses; followed by ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses; and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages:

[1C] (a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (e) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody; (k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody; (l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody; or (m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.
Claim 2
The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.
Claim 3
The method of claim 1, wherein the anti-CTLA-4 antibody is ipilimumab.
Claim 4
The method of claim 1, wherein the anti-CTLA-4 antibody is administered during the induction dosing schedule once every 3 weeks for a total of 4 doses.
Claim 5
[5Pre] A method of treating a human subject afflicted with a cancer comprising
[5A] administering to the subject 1 mg/kg of an anti-PD-1 antibody and 3 mg/kg of an anti-CTLA-4 antibody every 3 weeks for 4 doses,
[5B] followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.

Claim 6
The method of claim 1, wherein the administering comprises: (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 3 weeks for 4 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 3 weeks for 4 doses; followed by (ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2 to 12 weeks for up to 8 doses.
Claim 7
The method of claim 1, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.

Claim 8
The method of claim 1, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, cutaneous or intraocular malignant melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration-resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.
Claim 9
The method of claim 8, wherein the hematologic malignancy is selected from multiple myeloma, B-cell lymphoma, Hodgkin lymphoma/primary mediastinal B-cell lymphoma, non-Hodgkin's lymphomas, acute myeloid lymphoma, chronic myelogenous leukemia, chronic lymphoid leukemia, lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, acute lymphoblastic leukemia, mycosis fungoides, anaplastic large cell lymphoma, T-cell lymphoma, and precursor T-lymphoblastic lymphoma.
Claim 10
The method of claim 1, wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.
Claim 11

The method of claim 1, wherein the treatment is further combined with one or more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.

Claim 12

The method of claim 1, wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the maintenance dosing schedule at the following dosages:
(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
(b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
(c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
(d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(e) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
(j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody;
(k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody;
(l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody; or
(m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.

Claim 13

The method of claim 5, wherein the anti-PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg.

Claim 14

The method of claim 1, wherein 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.

Claim 15
The method of claim 1, wherein 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.
Claim 16
The method of claim 1, wherein 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.
Claim 17
The method of claim 1, wherein 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.
Claim 18
The method of claim 5, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.

Claim 19
The method of claim 5, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration-resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.
Claim 20
The method of claim 5, wherein the cancer is melanoma.
Claim 21
The method of claim 5, wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.
Claim 22
The method of claim 5, wherein the treatment is further combined with one or more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.

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:

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing Petition for *Inter Partes* Review contains 13,997 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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