

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

**PATENT OWNER'S
PRELIMINARY RESPONSE**

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<i>In re Magnum Oil Tools Int’l, Ltd.</i> , 829 F.3d 1364 (Fed. Cir. 2016)	30
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<i>Sanofi-Synthelabo v. Apotex, Inc.</i> , 550 F.3d 1075 (Fed. Cir. 2008)	42, 43
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Paper 12 (P.T.A.B. Feb. 10, 2023) (Director Review: Feb. 10, 2023).....	30, 39

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35 U.S.C. § 314(a)	21
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37 C.F.R. § 42.104(b)(2), (4)	36
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37 C.F.R. § 42.108(c)	21
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<i>Office Patent Trial Practice Guide</i> , 77 Fed. Reg. 48,756 (Aug. 14, 2012)	21
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EXHIBITS

Exhibit No.	Description
EX2001	Press Release, Bristol-Myers Squibb, <i>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</i> (Mar. 25, 2011), available at https://news.bms.com/news/details/2011/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/default.aspx
EX2002	Press Release, Bristol-Myers Squibb, <i>Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration</i> (Dec. 22, 2014), available at https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx
EX2003	YERVOY, FDA Approved label and prescribing information, Rev. 5/2025
EX2004	OPDIVO, FDA Approved label and prescribing information, Rev. 5/2025
EX2005	Amgen Pipeline, available at https://www.amgenpipeline.com/
EX2006	NCT05907122, “A Study to Evaluate Similarity of ABP 206 Compared With OPDIVO® (Nivolumab) in Subjects With Resected Melanoma” (Last Update Posted Nov. 27, 2024), available at https://clinicaltrials.gov/study/NCT05907122?term=NCT05907122&rank=1
EX2007	Press Release, Amgen, <i>Amgen Reports First Quarter 2025 Financial Results</i> (May 1, 2025), available at https://www.amgen.com/newsroom/press-releases/2025/05/amgenreports-first-quarter-2025-financial-results

Exhibit No.	Description
EX2008	Press Release, Amgen, <i>Amgen Reports Fourth Quarter and Full Year 2024 Financial Results</i> (Feb. 4, 2025), available at https://www.amgen.com/newsroom/press-releases/2025/02/amgen-reports-fourth-quarter-and-full-year-2024-financial-results
EX2009	NCT01024231, “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 Mar. 22, 2022), , available at https://clinicaltrials.gov/study/NCT01024231?term=NCT01024231&rank=1&tab=history&a=43#version-content-panel
EX2010	U.S. Patent No. 8,008,449
EX2011	U.S. Patent No. 8,779,105
EX2012	U.S. Patent No. 9,084,776
EX2013	U.S. Patent No. 9,358,289
EX2014	U.S. Patent No. 9,387,247
EX2015	U.S. Patent No. 9,492,539
EX2016	U.S. Patent No. 9,492,540
EX2017	U.S. Patent No. 10,441,655
EX2018	Sharma, P., et al. <i>Novel cancer immunotherapy agents with survival benefit: recent successes and next steps</i> , 11(11) Nat. Rev. Cancer at 805-812 (2011)
EX2019	U.S. Patent No. 8,728,474
EX2020	Brittain, B., <i>Bristol Myers sues AstraZeneca over cancer-treatment patents</i> , Reuters (Mar. 18, 2022), available at https://www.reuters.com/legal/transactional/bristol-myers-sues-astrazeneca-over-cancer-treatment-patents-2022-03-18/
EX2021	Complaint, <i>Bristol-Myers Squibb Co. and E.R. Squibb & Sons, L.L.C., v. AstraZeneca Pharmaceuticals LP and AstraZeneca UK LTD.</i> , Civil Action No. 1:22-cv-00346-UNA (D. Del. filed Mar. 17, 2022)

Exhibit No.	Description
EX2022	Amgen Biosimilars, available at https://www.amgen.com/science/biosimilars
EX2023	Declaration of Peter P. Lee, M.D.
EX2024	Curriculum Vitae of Peter P. Lee, M.D.
EX2025	U.S. Food and Drug Administration, The Drug Development Process, Step 3: Clinical Research (Content current as of Jan. 4, 2018), available at https://www.fda.gov/patients/drug-development-process/step-3-clinical-research
EX2026	Wang, D.D. et al. <i>Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials</i> , J Clin Pharmacol., 2009 Sep; 49(9):1012-24
EX2027	NCT01024231, “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 Mar. 22, 2021), available at https://clinicaltrials.gov/study/NCT01024231
EX2028	Press Release, Bristol-Myers Squibb, <i>Bristol-Myers Squibb Completes Acquisition of Medarex, Inc.</i> (Sept. 1, 2009), available at https://news.bms.com/news/details/2009/Bristol-Myers-Squibb-to-Acquire-Medarex/default.aspx
EX2029	National Institutes of Health, National Cancer Institute, NCI Dictionary of Cancer Terms, Definition of “complete response” available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/complete-response (last visited July 9, 2025)
EX2030	National Institutes of Health, National Cancer Institute, NCI Dictionary of Cancer Terms, Definition of “partial response” available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/partial-response (last visited July 9, 2025)

Exhibit No.	Description
EX2031	NCT00730639, “A Phase 1 Study of Nivolumab (BMS-936558) in Subjects With Advanced or Recurrent Malignancies (MDX1106-03)” (Last Update Posted Dec. 3, 2021), available at https://clinicaltrials.gov/study/NCT00730639
EX2032	Umscheid, C.A. et al. <i>Key Concepts of Clinical Trials: A Narrative Review</i> , Postgraduate Medicine, 2011 Sep; 123:5, 194-204

BMS respectfully submits this brief requesting the Board deny institution of the Petition for *inter partes* review filed by Amgen Inc. challenging the patentability of claims 1-22 of U.S. Patent No. 9,856,320 (“the ’320 Patent”) (EX1001).

I. INTRODUCTION

The Board should deny institution because the Petition fails to establish a reasonable likelihood of unpatentability for any of the challenged claims. BMS and its collaborators revolutionized cancer treatment by developing novel methods of treating cancer by administering antibodies that bind to PD-1 and CTLA-4, two proteins involved in regulating the immune system, and altering the patient’s immune response. These groundbreaking methods of cancer treatment fall within a field known as “immunotherapy.” The PTO recognized these innovations and granted BMS multiple patents directed to anti-PD-1 and anti-CTLA-4 antibodies, and various methods of treating cancer by administering such antibodies. The ’320 Patent is one of those patents. It claims specific dosing schedules and regimens for treating cancer by administering the combination of an anti-PD-1 and an anti-CTLA-4 antibody. The innovations protected by the ’320 Patent are the result of BMS’s extensive research and clinical trials programs, and include indications covered on BMS’s label for its FDA-approved anti-PD-1 antibody OPDIVO® used in combination with its FDA-approved anti-CTLA-4 antibody YERVOY®.

In its Petition, Amgen argues that the patentability of every claim of the '320 Patent should be reassessed based on two grounds that rely on references related to the development of BMS's groundbreaking products, OPDIVO® and YERVOY®. Both of Amgen's grounds suffer from significant evidentiary defects.

In Ground 1, Amgen argues that claim 1 of the '320 Patent and its dependent claims would have been obvious in view of three references: NCT-231, Korman, and Wolchok. Amgen argues that a person of ordinary skill in the art (POSA) would have been motivated to piece together the disclosures in these references to achieve the multi-step combination therapy of the Ground 1 claims. NCT-231 is a printout of the protocol that was in place as of January 5, 2010 for BMS's clinical trial NCT01024231. BMS's clinical trial NCT01024231, which ran from December 14, 2009 to April 1, 2019, was the first of its kind to test a method of administering anti-PD-1 and anti-CTLA-4 antibodies in combination. Over the course of the trial, the protocol for NCT01024231 was amended multiple times—NCT-231 is just one early iteration of the protocol. Neither NCT-231 (the January 2010 version of the trial protocol), nor any other prior art reference discloses the dosing regimen claimed in the '320 Patent, including the specific dose combinations of the Ground 1 claims.

Amgen nevertheless argues that a POSA would have been motivated to mix-and-match doses proposed for anti-PD-1 and anti-CTLA-4 monotherapies based on

references disclosing limited human monotherapy data (Wolchok) and mouse models (Korman), and substitute those in place of the dose concentrations that were actually proposed for combination therapy in NCT-231. But Amgen fails to provide a sufficient reason or evidence for *why* a POSA would have modified an existing clinical trial for combination therapy with doses from unrelated, early-stage monotherapy regimens or mice.

Amgen also fails to present evidence to support its assertion that a POSA would have arrived at the Ground 1 claims with a reasonable expectation of success. Lacking evidentiary support for the alleged reasonable expectation of success, Amgen lays out a path that a POSA would have purportedly followed only to arrive at the conclusion that a POSA would have ended up conducting a clinical trial *just like BMS did*. Specifically, Amgen argues that a POSA would have identified some “baseline” doses and from there would “iterate the testing of various combination doses” from that starting point, administering higher and lower doses, as shown by the evolution of BMS’s NCT01024231 clinical trial. Pet., 40-41. That argument does not evidence that a POSA would have arrived at the claims with a reasonable expectation of success before May 15, 2012. It evidences Amgen’s blatant reliance on hindsight.

In Ground 2, Amgen argues that claim 5 of the '320 Patent and its dependent claims would have been obvious in view of Korman, Wolchok, and Sznol. Critically, none of those references disclose or suggest a method of treatment in which an anti-PD-1 antibody is administered as a monotherapy **subsequent to** combination therapy with an anti-PD-1 and anti-CTLA-4 antibody. Amgen does not even attempt to argue otherwise. Instead, Amgen argues that a POSA would have had a reason to add this step. But nothing cited by Amgen or its expert discloses or suggests this step. For this reason alone, Amgen's Ground 2 fails.

In addition, Amgen fails to identify or provide sufficient evidence for why a POSA would have selected **biweekly** administration for the subsequent administration of the anti-PD-1 antibody alone. Amgen argues that biweekly dosing of an anti-PD-1 antibody was disclosed in Sznol. Sznol is a preliminary report from a Phase 1 trial for anti-PD-1 monotherapy. As Dr. Lee explains, Sznol says nothing about combination therapy, much less dosing intervals in a multistep regimen where an anti-PD-1 antibody is administered alone subsequent to combination therapy. In fact, Sznol's ultimate conclusion was only that further study of anti-PD-1 blockade was warranted. And Amgen provides no other evidence—aside from an expert who just repeats the conclusory statements in the Petition—to support its argument that a

POSA would have been motivated to implement the biweekly dosing in Sznol to arrive at the Ground 2 claims.

Finally, even if Amgen had identified all of the limitations of the Ground 2 claims in the asserted references, which it did not, Ground 2 would still fail as a matter of law and fact because Amgen never evaluated the claims as a whole. Instead, Amgen dices the Ground 2 claims into three discrete parts, separately compares each to the prior art, and then through hindsight stitches the pieces back together. Amgen's hindsight-driven motivation to combine should be rejected.

For at least these reasons, Amgen failed to show there is a reasonable likelihood it will prevail with respect to any challenged claim.

II. TECHNICAL BACKGROUND

A. Immunotherapy and the PD-1 Pathway

The human immune system is formed of organs, specialized cells, and substances that protect individuals from infections and disease. T cells are one class of specialized cells that play an important role in the human immune system. One major function of T cells is to destroy pathogens and cancer cells, and to do that the T cells must distinguish between healthy cells and cells that are infected or cancerous. EX2023, ¶30; EX1001, 1:33-38. One way in which T cells facilitate this

task is through the activation or deactivation of different receptors on the T cell surface.

One of the receptors that T cells express on their surface is a protein called programmed death-1 receptor (“PD-1”). PD-1 “is a key immune checkpoint receptor expressed by activated T and B cells and mediates immunosuppression.” EX2023, ¶31. “PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA.” *Id.*; EX1001, 2:4-8. PD-1 acts as a brake on the immune system by downregulating T cell activity to prevent T cells from killing healthy cells. EX2023, ¶31. Cytotoxic T lymphocyte-associated protein 4 (“CTLA-4”) is another inhibitory receptor found on T cells that also acts as a brake on the immune system by downregulating T cell activity. *Id.*

Immunotherapy is a type of treatment that functions by taking advantage of aspects of a patient’s immune response to fight disease. EX2023, ¶32. One form of immunotherapy involves using antibodies to manipulate the immune response. *Id.* In particular and as relevant here, antibodies that bind to PD-1 (“anti-PD-1 antibodies”) and CTLA-4 (“anti-CTLA-4 antibodies”) can be used to disarm or block the activity of these inhibitory receptors. *Id.* By blocking the PD-1 and CTLA-4 inhibitory receptors, these antibodies are able to increase or activate an immune response. *Id.* More specifically, by binding to PD-1 and CTLA-4,

respectively, these antibodies shut off the brakes on the immune system, freeing the immune cells to recognize, attack and destroy cancer cells. *Id.*; EX1001, 1:57-2:25.

B. Purposes of Clinical Trials at Different Phases

The clinical testing of pharmaceutical products proceeds through phases. Importantly, the goals of the testing change as the phases proceed. EX2023, ¶33.

The primary goal of Phase 1 clinical trials is to test the safety of a new active ingredient and to gather information about a maximum tolerated dose (MTD), i.e., the maximum dose that has an acceptable level of toxicity. EX2023, ¶34; EX2032, 197 (Phase 1 trials are “designed to test the safety and maximum tolerated dose [] of a drug, human pharmacokinetics and pharmacodynamics, and ***drug-drug interactions***”). A Phase 1 trial is often the first time a new drug is tested in the clinic, making it a so-called first-in-human (FIH) study. EX2023, ¶34. The trial can include a dose escalation study, where initial doses are tested across a small number of different patients to gather preliminary information about how the body responds to different doses. *Id.* If an initial dose is found safe, then it is increased a little bit at a time as the clinicians study the safety of higher doses. EX2032, 197 (“Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a sufficient period”). Efficacy is not typically a primary objective of Phase 1 trials. It may be a secondary objective, but efficacy is

typically determined in larger trials (Phase 2 and 3) that extend over a longer period of time. EX2023, ¶34. One drug property often analyzed in a Phase 1 trial is pharmacokinetics (“PK”), which deals with how the patient’s body interacts with the drug over time, including how the drug is absorbed and eliminated, and how long the drug remains in the body after a dose. *Id.* at ¶35. Another property often evaluated in a Phase 1 trial is pharmacodynamics (“PD”), which tries to assess how the drug interacts with biological targets in the body. *Id.*

Different patients can react differently to the drug for several reasons, including stage of disease, concurrent medical conditions, genetics, age, sex, and, body weight. *Id.* at ¶36. Different body weights lead not only to different volumes for the drug to disperse within the body but can also lead to different rates and mechanisms for drug absorption and elimination from the body. *Id.* “When [a monoclonal antibody] (mAb) is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown.” EX2026, 1023; EX2023, ¶36. But again, the protocol of the Phase 1 or FIH trial is not intended as a guide for treatment methods. EX2023, ¶36. These preliminary studies are intended to test for safety and potentially gather information on PK and PD. *Id.*

The goals of Phase 2 and Phase 3 clinical trials, on the other hand, are to test the safety and efficacy of the drug in larger groups of patients. EX2023, ¶37;

EX2025, 3-4. Phase 2 trials may include dozens to several hundred patients, who are generally divided into different groups that receive either the new drug or a placebo. EX2023, ¶37; EX2025, 3-4. A Phase 2 trial may last several months to two years. EX2023, ¶37; EX2025, 3-4. The primary objective of a Phase 2 trial is typically to assess the initial efficacy of a drug on a particular disease or condition. Dose level and frequency are common secondary objectives in Phase 2 trials. EX2023, ¶37; EX2025, 3-4. Phase 2 trials are not typically large enough to conclusively establish that a drug is beneficial. EX2023, ¶37; EX2025, 3-4. They do provide some safety data about a new drug and that data is often used by researchers to design the Phase 3 protocol. EX2023, ¶37; EX2025, 3-4; EX2032, 197. According to the FDA, only about 33% of drugs that enter Phase 2 trials proceed to Phase 3 trials. EX2023, ¶37; EX2025, 4.

Phase 3 trials include hundreds to thousands of patients for the purpose of confirming efficacy and comparing the new treatment to the standard of care. EX2023, ¶38; EX2032, 198. They are typically conducted at multiple treatment centers and can last several years. EX2023, ¶38. Because of their high enrollment and long duration, Phase 3 trials provide most of the safety data necessary for drug approval. *Id.*; EX2025, 4.

The Phase 3 treatment protocol is designed based on a detailed understanding of how the drug interacts in the human body, including how body weight impacts PK and PD. EX2023, ¶39. As the Wang reference makes clear, “[t]he final dosing approach for phase 3 trials in adults should be selected based on the established body size effect on PK and PD, the therapeutic window of the mAbs, along with other factors that may impact the outcome of the study, benefit to patients, and overall drug development.” EX2023, ¶39; EX2026, 1023-24. The Phase 3 treatment protocol is intended to confirm the safety and efficacy of a method to be used in clinical practice. EX2023, ¶39.

C. BMS’s Development of OPDIVO®

BMS led the industry in developing antibodies that could be used in novel methods of immunotherapy for the treatment of cancer. BMS put its scientific breakthroughs into practice by developing an anti-CTLA-4 antibody called YERVOY® (ipilimumab) and an anti-PD-1 antibody called OPDIVO® (nivolumab). YERVOY®, approved in March 2011, was the first immune checkpoint inhibitor approved by the FDA for the treatment of cancer. EX2001. Clinical testing of OPDIVO® and YERVOY® confirmed the remarkable promise of checkpoint inhibitors as targets for immunotherapy. OPDIVO®, first approved in Japan in 2014, was the first anti-PD-1 antibody approved anywhere in the world for cancer

treatment, and, in December 2014, it was approved in the United States for the treatment of melanoma. EX2002.

Following these initial approvals, BMS continued investing in research and clinical trials aimed at developing novel dosages and treatment regimens to treat patients with cancer. BMS's groundbreaking work included extensive research related to the administration of anti-PD-1 and anti-CTLA-4 antibodies alone and in combination for the treatment of various cancers. This work is reflected in BMS's FDA-approved label for OPDIVO[®], which includes indications for non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma, head and neck cancer, malignant pleural mesothelioma, lymphoma, colorectal cancer, hepatocellular carcinomas, esophageal cancer, and gastric cancers. EX2004; *see also* EX2003.

D. Amgen

Amgen is currently developing an OPDIVO[®] biosimilar (i.e., a copy) named ABP 206. EX2005. Amgen is conducting clinical trials designed to show the similarity between ABP 206 and BMS's OPDIVO[®], so that it can rely on data BMS has spent more than a decade generating to obtain FDA approval through an abbreviated pathway. EX2006; *see also* 42 U.S.C. § 262(k). It can do so by taking advantage of the statutory scheme set forth in the BPCIA, which Congress passed as part of the Affordable Care Act in 2010. In that same statute, Congress included

protections for companies like BMS that develop innovative biologics and are targeted by biosimilar developers. 42 U.S.C. § 262(l). In particular, the BPCIA includes a step-by-step process for the identification of all patents potentially implicated by the biosimilar product and resolution of any disputes regarding those patents. 42 U.S.C. § 262(l)(3)-(6).

If approved, Amgen's biosimilar version of OPDIVO® will be sold with a label that copies information from BMS's OPDIVO® label. Although the approval date remains uncertain, Amgen has repeatedly stated that it anticipates a readout from its similarity study in the second half of this year. EX2007, 21; EX2008, 23. As Amgen has foreshadowed in its communications with investors, data from Amgen's clinical trial will undoubtedly be used for the submission of an aBLA relying on OPDIVO® as a reference product. The FDA's acceptance of Amgen's aBLA will statutorily trigger a patent resolution mechanism that begins with a series of detailed exchanges collectively known as the "Patent Dance" and culminates in the filing of a complaint for patent infringement. 42 U.S.C. § 262(l)(2)-(6). With its Petition, Amgen seeks to duplicate that work, wasting both the PTO's and the parties' resources.

III. OVERVIEW OF THE '320 PATENT

The '320 Patent is entitled “Cancer Immunotherapy by Disrupting PD-1/PD-L1 Signaling” and issued from U.S. Patent Application No. 14/400,667. It claims priority to two provisional applications, U.S. Provisional Application No. 61/647,442 filed on May 15, 2012 and U.S. Provisional Application No. 61/790,747 filed on March 15, 2013. EX1001. The '320 Patent generally provides immunotherapy methods for the treatment of a patient with cancer comprising administering to the patient a combination of anti-PD-1 and anti-CTLA-4 antibodies according to specific dosing schedules at specified dosages. EX2023, ¶¶43-47.

There are two independent claims in the '320 Patent. In Ground 1, Amgen challenges Claim 1 and its dependent claims (“Ground 1 claims”). Claim 1 sets forth a dosing schedule for combination anti-PD-1 and anti-CTLA-4 therapy for the treatment of cancer that comprises two phases—(i) an induction dosing schedule in which a patient receives multiple dosages of anti-PD-1 and anti-CTLA-4 antibodies in combination followed by a series of dosages of the anti-PD-1 antibody alone, and (ii) a maintenance dosing schedule in which the patient again receives multiple dosages of anti-PD-1 and anti-CTLA-4 antibodies in combination. EX1001, cl. 1. Claim 1 also sets forth specific dosing intervals and dosing frequencies, as well as specific dosage combinations for the induction phase combination therapy. *Id.*

In Ground 2, Amgen challenges Claim 5 and its dependent claims (“Ground 2 claims”). Claim 5 sets forth a different dosing schedule for the treatment of cancer in which the patient is administered a combination of 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, which is then followed by the subsequent administration of a dose of the anti-PD-1 antibody alone at a frequency of once every 2 weeks. EX1001, cl. 5.

IV. OVERVIEW OF THE ART

The Petition asserts two grounds for unpatentability. Ground 1 challenges the patentability of Claims 1-4, 6-12, 14-17 on obviousness grounds in view of a combination of three references, NCT-231, Korman, and Wolchok. Pet., 4. Ground 2 challenges the patentability of Claims 5, 13, 18-22 on obviousness grounds in view of a combination of three references, Korman, Wolchok, and Sznol. *Id.*

A. NCT-231

NCT-231 is a printout of the study details for clinical trial NCT01024231 that was last updated as of January 5, 2010. NCT01024231, a Phase 1 clinical trial, was a first-of-its-kind clinical trial evaluating the combination of an anti-PD-1 and an anti-CTLA-4 antibody in humans. EX2023, ¶49. In particular, NCT01024231 was a clinical trial sponsored by BMS “to assess 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.” EX1005, 4; EX2023, ¶49.

The NCT01024231 trial started on December 14, 2009 and completed on April 1, 2019. EX2023, ¶50; EX2027, 1. Complete results from the NCT01024231 trial were not posted until March 22, 2021. EX2023, ¶50; EX2027, 1. Preliminary results were published July 11, 2013. *See, e.g.*, EX2027. The NCT01024231 trial was designed as a dose escalation study, meaning that its primary objective was to identify the maximum tolerated dose. EX1005; EX2023, ¶50.

The dosage schedule in NCT-231 administered nivolumab and ipilimumab every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for an additional 4 doses, and then combination treatment with nivolumab and ipilimumab every 12 weeks for up to 8 doses. This dosage schedule was generally maintained through the course of the trial.¹ EX2023, ¶¶52-54.

¹ In later versions of the protocol PD-1 monotherapy cohorts were added, as well as Cohort 8, which implemented a different dosing regimen in which nivolumab 1 mg/kg and ipilimumab 3 mg/kg were administered every 3 weeks for 4 doses followed by nivolumab 3 mg/kg solution alone intravenously every weeks for 48 doses. EX2027, 6.

B. Korman

Korman is a PCT application, WO2006/121168, with a publication date of November 16, 2006. EX1006. It names Ono Pharmaceutical Co., Ltd. and Medarex, Inc. as applicants. *Id.* BMS acquired Medarex in September 2009, and as a result gained ownership rights in Korman. EX2028. Korman discloses isolated monoclonal antibodies that bind to PD-1, i.e., anti-PD-1 antibodies. EX1006, 22-23; EX2023, ¶56. More specifically, Korman describes the development and evaluation of the anti-PD-1 antibody, 5C4, which is the antibody that eventually became nivolumab—the active ingredient in BMS’s OPDIVO®. EX1006, 39, 74-85; EX2023, ¶56. According to Korman’s Abstract, “[t]he present invention further provides methods for using a combination immunotherapy, such as the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat hyperproliferative disease, such as cancer.” EX1006, abstract.

Examples 13-17 in Korman evaluated the administration of anti-PD-1, anti-CTLA-4, and combination anti-PD-1/anti-CTLA-4 in mouse tumor models. EX2023, ¶57; EX1006, 66, 87-95. According to Korman, “the results of Examples 14, 16, and 18 show that the combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody had a significant (synergistic) effect on tumor growth even at sub-optimal therapeutic doses as compared to treatment with either antibody alone

(i.e., the combination therapy was surprisingly more effective at subtherapeutic doses than either monotherapy).” EX2023, ¶57; EX1006, 66. Example 17, for instance, found an “unexpected synergistic effect of an anti-PD-1 antibody combined with an anti-CTLA-4 antibody, along with the surprising effectiveness of subtherapeutic levels of an anti-CTLA-4 antibody in the combination.” EX2023, ¶57; EX1006, 94. The in vivo mouse model examples in Korman do not include any information about the toxicity or adverse effects observed with respect to the combination therapy tested. The examples in Korman focus almost entirely on tumor response. EX2023, ¶57; EX1006, 87-95.

Korman contains dosage information for antibodies, including anti-PD-1 and anti-CTLA-4 antibodies. EX2023, ¶58; EX1006, 55. Korman further explains that “[t]he selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular composition of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.” EX2023, ¶58; EX1006, 55-56. Korman

does not include any human data or any examples that administer antibodies according to an induction/maintenance schedule in which antibodies are provided in combination and then followed with the administration of a single antibody alone. EX2023, ¶58.

C. Wolchok

Wolchok is an article from The Lancet Oncology journal that reports the results of a Phase 2 melanoma trial in which patients were administered a weight-based dose of ipilimumab monotherapy every three weeks for four cycles (i.e., the induction phase) followed by maintenance therapy every three months. EX2023, ¶59; EX1007, 155. In this study, a total of 214 patients were randomly assigned to receive 0.3 mg/kg (71 patients), 3.0 mg/kg (71 patients), or 10 mg/kg (72 patients). EX2023, ¶59; EX1007, Figure 1. “As the dose of ipilimumab increased, best overall response rate rose.” EX1007, 161. Complete responses² were seen in 2 patients

² “Complete Response” means “The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured.” EX2029.

administered the 10 mg/kg dose. EX2023, ¶59; EX1007, Table 2. Partial responses³ were observed in 3 patients in the 3.0 mg/kg group and 6 patients in the 10 mg/kg group. EX2023, ¶59; EX1007, Table 2. “Ipilimumab had a manageable safety profile at all three doses (table 3).” EX2023, ¶59; EX1007, 161.

A pharmacokinetic analysis was performed to evaluate whether each dose was able to achieve the target serum concentration of 20 µg/mL before the fourth dose in the induction phase. EX2023, ¶60; EX1007, 162. The analysis indicated that the “target concentration was expected to be exceeded by about 95% of patients in the 10 mg/kg group, but by only 30% and 0% in the 3 mg/kg and 0.3 mg/kg groups, respectively (figure 3B).” EX2023, ¶60; EX1007, 162. Additionally, the 10 mg/kg group “induced a greater mean rate of increase in absolute lymphocyte count than did the lower doses (figure 4).” EX2023, ¶60; EX1007, 162.

According to Wolchok, the study “results indicate that treatment with ipilimumab monotherapy at 10 mg/kg showed activity in heavily pretreated patients with advanced melanoma, with high-grade immune-related adverse events well managed with specific treatment guidelines.” EX1007, 163; EX2023, ¶61. Based

³ “Partial Response” means “A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment.” EX2030.

on these results, the authors concluded, “[f]urther investigations of ipilimumab efficacy and safety at 10 mg/kg in patients with advanced melanoma are warranted.”

EX1007, 163; EX2023, ¶61.

D. Sznol

Sznol is an abstract in the Journal of Clinical Oncology from 2010 that reports preliminary results from a Phase 1 trial in which patients were administered MDX-1106 (nivolumab) at 1 mg/kg (4 patients), 3 mg/kg (4 patients), or 10 mg/kg (8 patients) on a biweekly basis. EX1009; EX2023, ¶62. Objective tumor responses were observed in 3 patients who received a 1 mg/kg dose, 2 patients who received a 3 mg/kg dose, and 1 patient who received a 10 mg/kg dose. EX1009; EX2023, ¶62. As of the report, the 1 mg/kg and 3 mg/kg cohorts had been expanded to 16 patients and the 10 mg/kg cohort was in the process of being expanded. EX1009; EX2023, ¶62. The study did not reach a maximum tolerated dose. EX1009; EX2023, ¶62. The study concluded that “MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.... Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.” EX1009; EX2023, ¶62.

V. THE LEVEL OF SKILL IN THE ART

Solely for purposes of this Preliminary Response, BMS does not dispute Amgen's definition of a person of ordinary skill in the art ("POSA"). BMS reserves the right to present a different definition of a POSA in these proceedings, should the Board institute trial and any other proceedings regarding the '320 Patent.

VI. CLAIM CONSTRUCTION

Claim terms in IPRs are construed according to their "ordinary and customary meaning" to those of skill in the art. 37 C.F.R. § 42.100(b); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). Amgen does not argue that any terms require construction. For purposes of this Preliminary Response only, BMS agrees that none of the terms require construction.

VII. THE PETITION FAILS TO SHOW A REASONABLE LIKELIHOOD THAT AMGEN WILL PREVAIL ON A SINGLE CLAIM

The Board should deny institution of Amgen's Petition because Amgen has not shown a reasonable likelihood of prevailing with respect to any challenged claim. The Board's authority to institute *inter partes* review is limited to those circumstances where "the information presented in the petition ... and any response ... shows that there is a reasonable likelihood that petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a); *see also* 37 C.F.R. § 42.108(c). Amgen bears the burden of showing that this

statutory threshold has been met. *See, e.g., Office Patent Trial Practice Guide*, 77 Fed. Reg. 48,756 (Aug. 14, 2012) (“The Board ... may institute a trial where the petitioner establishes that the standards for instituting the requested trial are met”). In particular, a rejection under 35 U.S.C. § 103 must be supported by a clear articulation of the reasons why the claimed invention would have been obvious. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). The Supreme Court has noted that the analysis supporting an obviousness rejection should be made explicit. *KSR*, 550 U.S. at 401.

Amgen’s Ground 1 lacks sufficient evidence to establish both a motivation to combine and a reasonable expectations of success. Amgen’s Ground 2 suffers from the same defects and more. The Ground 2 references fail to disclose the subsequent administration of an anti-PD-1 antibody alone, fail to disclose biweekly dosing for an anti-PD-1 antibody administered alone following combination therapy and are the product of impermissible hindsight. For at least these reasons, Amgen failed to show there is a reasonable likelihood it will prevail with respect to any challenged claim.

A. Institution Should be Denied as to Ground 1

Amgen’s Ground 1 cobbles together combinations of antibody dosages from art without sufficient evidence or reason. It is the epitome of improper hindsight

reconstruction. BMS's clinical trials, including NCT01024231, were the first trials to evaluate combination therapy with an anti-PD-1 and an anti-CTLA-4 antibody as potential cancer immunotherapies in human patients. EX1044, 514 (Table 2); EX2018, 9-10. The combination therapy dosing regimens in the Ground 1 claims were novel, untested, and unprecedented in the field before the May 15, 2012 priority date for the '320 Patent. They are not obvious variations on known dosing as the Petition suggests.

1. A POSA Would Not Have Been Motivated to Combine NCT-231 with Korman or Wolchok and Arrive at the Ground 1 Claims

NCT-231 does not disclose any of the unique dosing combinations contained in Claim 1. Amgen nonetheless argues that every single dosing combination recited in Claim 1 would have been obvious because the art generally disclosed certain dosages for anti-PD-1 and anti-CTLA-4 antibodies, and a POSA would have allegedly engaged in an iterative process to arrive at the claimed dosages. In so arguing, Amgen incorrectly assumes a POSA would have been motivated to iterate on the dosages in NCT-231 *in the absence of any data* regarding the *combination of antibodies* being tested in humans. EX2023, ¶65. That is not how “iterative” dosing or dose escalation studies work.

Dose escalation studies, like the one described in NCT-231, function in a stepwise manner. EX2023, ¶¶66; EX2032, 197 (“Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a sufficient period”); EX1040, 709. Although there are multiple ways to design dose escalation studies, the unifying feature among these models is that they start with treating subjects with a small number of defined doses, and then based on data obtained from those treatments POSAs determine appropriate future doses to try. EX2023, ¶¶66; EX1040, 709-10. The main goal of these Phase 1 trials is to assess toxicity of the drugs being administered because the efficacy of the therapy being tested has not been determined. EX2023, ¶¶34-36; EX2032, 197. They do not randomly test any number of possible doses without reason. EX2023, ¶¶66; EX1040, 715-16 (“Overall, the choice of the dose escalation scheme for drug combination trials is as relevant as it is for first-in-human monotherapy. The recommended dosages and schedules can have a critical role in the success or failure of a combination regimen during its subsequent clinical development”). Here, Amgen never provides the reason for why a POSA would have modified NCT-231.

A POSA would have had no reason to modify an existing dosing regimen, such as the one disclosed in NCT-231, in the absence of some information about the initial combinations of dosages performed. EX2023, ¶¶68. But none of the asserted

references contain such information. NCT-231 is a protocol for a Phase 1 dose escalation study for the combination of anti-PD-1 and anti-CTLA-4 antibodies that was “[n]ot yet recruiting.” EX1005, 3; EX2023, ¶67. Its stated purpose was to “assess the safety and tolerability of treatment with [anti-PD-1 antibody] in combination with [anti-CTLA-4 antibody].” EX1005, 4; EX2023, ¶67. Its primary outcome measure was to identify the maximum tolerated dose for the antibody combination (because it was unknown at that time). EX1005, 4; EX2023, ¶¶67-68. As of May 15, 2012, the NCT01024231 clinical trial (and anti-PD-1/anti-CTLA-4 combination therapy generally) was still in its early stages and included no data on which a POSA might have relied to make the iterative changes Amgen contends would have been obvious. EX2023, ¶¶67-68; EX1005.

And Amgen points to no other references that address testing anti-PD-1 and anti-CTLA-4 combination therapy in humans. Absent some data, a POSA would not have had any reason other than hindsight to modify NCT-231 at all, much less to implement concentrations taken from Korman’s animal data or Wolchok’s anti-CTLA-4 monotherapy trial. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (“[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness”).

Amgen does not meaningfully argue otherwise. In fact, Amgen essentially admits that a POSA would rely on actual human data from the combination therapy being tested to modify existing trials in an iterative manner. Pet., 31 (“***After starting with a ‘testable hypothesis’*** ... it was also common in this field to ***test incrementally*** higher or lower concentrations”); *see also* EX1040, 709 (describing the general principle of dose escalation studies as adjusting dosage “***depending on the absence or presence of severe toxicity in the previous cohort of treated patients***”). Yet Amgen provides no such data to support Ground 1, resorting instead to hindsight to fill that gap.

2. Amgen Fails to Demonstrate a Reasonable Expectation of Success

Amgen’s argument that a POSA would have reasonably expected to successfully arrive at the claimed methods similarly lacks evidentiary support. Amgen presents its theory for reasonable expectation of success as a series of successive assertions, but Amgen fails to provide sufficient evidence to connect them to each other or the Ground 1 claims.

First, Amgen posits that 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.” Pet., 40. But Amgen does not explain why a POSA would consider dosing concentrations from Sznol (a preliminary report

from a Phase 1 monotherapy trial that is not asserted in Ground 1) and Wolchok (a report from a Phase 2 monotherapy trial) to be “baseline information” instead of the dose concentrations in its primary reference, NCT-231 (a clinical trial protocol involving multi-step combination therapy). Nor does its expert, who merely parrots the conclusory language from the Petition. EX1003 ¶144. More specifically, Amgen’s “baseline” assertion fails to account for (1) the differences between a multi-step combination therapy and monotherapy and (2) the differences between the multi-step combination therapy of the Ground 1 claims and the specific monotherapies in Sznol and Wolchok. EX2023, ¶70.

Amgen’s “baseline” assertion also fails to account for the preliminary nature and limited information in Sznol, a reference not even asserted in Ground 1, but nonetheless discussed. EX2023, ¶71. Sznol reports preliminary results for the first 16 patients treated in a Phase 1 OPDIVO[®] monotherapy trial, only 6 of which showed any response to the anti-PD-1 monotherapy. EX2023, ¶71; EX1009. The patients in Sznol were still undergoing treatment and being evaluated. EX2023, ¶71; EX1009 (“All responses are ongoing (3-13+ mo).”). And the ultimate conclusion in Sznol was that further study was warranted: “Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.” EX2023, ¶71; EX1009. Amgen ignores these facts entirely.

Second, Amgen posits that the dosing information in Wolchok and Sznol “would be bolstered by disclosure of concurrent administration of the two antibodies (EX1006, 56; EX1005, 4)...” Pet., 40. It is unclear how the “disclosure of concurrent administration” in Korman (EX1006) or NCT-231 (EX1005) would have reached any conclusions about the dosing information in Wolchok and Sznol based on Korman and NCT-231 given the differences between those references, including that (1) Korman only uses mouse models, (2) NCT-231 describes a multi-step combination therapy regimen, but provided no efficacy or toxicity data, (3) Wolchok and Sznol describe monotherapy, and (4) NCT-231 discloses different combinations of doses than the Ground 1 claims. EX2023, ¶¶73-74. Even if Amgen’s conclusory proposition made sense, it still lacks evidentiary support. Specifically, Amgen provides no evidence or explanation for its bare assertion that a POSA would have viewed the limited dose information about anti-PD-1 and anti-CTLA-4 monotherapies in Sznol and Wolchok (respectively) any differently based on combination therapies discussed in NCT-231 (EX1005) or Korman (EX1006).

Likewise, Amgen provides no evidence to support its argument that the dosing information in Wolchok and Sznol “would be bolstered by ... evidence of relative safety and efficacy for the combination therapy in animal models,” citing “EX1006, 97; EX1030, 4276; EX1045, 1” for methods directed to a brand-new combination

immunotherapy for the treatment of cancer in humans. As an initial matter, none of EX1006, EX1030, or EX1045 discuss the safety of combination therapy in their mouse tumor models. EX2023, ¶75; *see also* EX1040, 715 (“Unfortunately, preclinical models that accurately predict synergism or even additivity are not well characterized, and existing preclinical models often focus on the antitumor effects of drug combinations while ignoring their potential for creating severe toxicities.”). Furthermore, Amgen never explains what conclusions a POSA would have drawn from the mouse models to “bolster” dosing information in Wolchok or Sznol. EX2023, ¶75. Nor does its expert, who again parrots the statements in the Petition with no additional explanation other than a parenthetical quoting one of the cited references:

Amgen’s Petition	Dr. Antony Declaration
<i>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.</i>	<i>Such information would be bolstered by disclosure of concurrent administration of the two antibodies (EX1005, 4) and evidence of relative safety and efficacy for the combination therapy in animal models. EX1006, 97 (“This study indicates that, in a murine tumor model, treatment with the combination of CTLA-4 antibody and PD-1 antibody has a significantly greater effect on tumor growth than either antibody alone, even when a tumor is already well established.”); EX1030, 4276; EX1045, 1.</i>

EX1003, ¶145; *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 12 at 5 (P.T.A.B. Feb. 10, 2023) (Director Review: Feb. 10, 2023) (precedential) (affirming the Board’s denial of institution and finding “the Board was correct in giving little weight to Petitioner’s expert because the expert declaration merely offered conclusory assertions without underlying factual support and repeated, verbatim, Petitioner’s conclusory arguments”); 37 C.F.R. § 42.65(a). Thus, Amgen is left with no evidentiary support for its bare assertion. Amgen cannot carry its burden in this manner. *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness”).

That, however, is not the end of Amgen’s hollow proposal for a reasonable expectation of success. Amgen next argues that “[f]rom *there*, researchers would *iterate the testing of various combination doses* from such known concentrations (administering incrementally higher or lower concentrations as desired).” Pet., 40. In other words, Amgen argues that the collective prior art would invite a POSA to copy the inventors and pursue a path of experimentation. This is not conjecture, Amgen affirmatively acknowledges that its argument rests on following BMS’s efforts:

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.

Pet., 41. Amgen has not alleged, much less established that the April 2012 version of the NCT01024231 protocol (EX1031) is prior art; nor has it asserted the April 2012 version as a reference in Ground 1. Thus, its reliance on the April 2012 version of the protocol is improper. Moreover, the “varied and optimized” doses in the April 2012 protocol are not the product of blind selection—they were developed in an actual dose escalation study. In any event, the only thing Amgen’s argument shows is that a POSA, following **Amgen’s theory**, would NOT have arrived at the claimed doses with a reasonable expectation of success before May 15, 2012—the April 2012 protocol does not implement **any** of the dose combinations in the Ground 1 claims and the NCT01024231 clinical trial took several more years to get there.

Amgen provides no evidence to show that a POSA would have arrived at the claimed doses with a reasonable expectation of success. Amgen simply argues, without even the support of its expert, that “[i]n this way, researchers could reasonably expect similar efficacy without severe swings in toxicity.” Pet., 40-41. The fact that Amgen recognizes the inventors took an iterative approach, **by**

conducting the iterative NCT01024231 dose escalation trial, does not show a POSA lacking the data obtained by the BMS through that trial would have arrived at the Ground 1 claims with a reasonable expectation of success before May 15, 2012. It shows that Amgen's entire argument is predicated on impermissible hindsight. Amgen traced backwards from the Ground 1 claims using the approach taken by the inventors and is now trying to shoehorn the art into its theory.

Amgen's argument depends on a series of unsupported and erroneous arguments, and it is only with the benefit of hindsight that Amgen argues a POSA would have combined the Ground 1 references with a reasonable expectation of success.

* * *

Because Amgen fails to provide evidence for why a POSA would have been motivated to combine the Ground 1 references in the manner Amgen proposes and fails to provide evidence for why a POSA would have reasonably expected success in doing so, it cannot meet its burden to show a reasonable likelihood that the Ground 1 claims are unpatentable. For these reasons, the Board should deny institution.

B. Institution Should be Denied as to Ground 2

Amgen's Ground 2 fails to show a reasonable likelihood that the claims challenged under Ground 2 are unpatentable for multiple reasons. In Ground 2,

Amgen suggests that the claims would have been obvious over Korman in view of Wolchok and Sznol. But none of the Ground 2 references disclose a key limitation of the claims—subsequent administration of an anti-PD-1 antibody. For this reason alone, Amgen’s argument must fail. Amgen’s Ground 2 also suffers from errors of law and fact. Failing to anchor Ground 2 to prior art, science, or law, Amgen again turns to impermissible hindsight to reconstruct the claims in a piecemeal fashion. Just like the combination therapy of the Ground 1 claims, the methods of the Ground 2 claims were novel, untested, and unprecedented in the field before May 15, 2012.

1. The Ground 2 References Do Not Disclose or Render Obvious the “Subsequently Administering” Limitation

Every claim challenged in Ground 2 requires treatment according to a particular schedule—administering to a patient a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody “*followed by subsequently administering*” an anti-PD-1 antibody alone. EX1001, cl. 5. The Petition fails to identify this two-part dosing schedule in any combination of the asserted references. In particular, none of the Ground 2 references describes a dosing regimen in which a patient is administered an anti-PD-1 antibody alone *after* anti-PD-1/anti-CTLA-4 combination therapy. Amgen does not even attempt to identify the subsequent monotherapy administration limitation in any of Korman, Wolchok, or Sznol. Pet., 63-64. Nor could it. The Ground 2 references do not contemplate, much less

disclose a multi-step treatment regimen that utilizes both combination therapy and monotherapy. *See also* EX2023, ¶78.

Unable to identify the requirement for “subsequent administration” of an anti-PD-1 antibody alone in the asserted references, Amgen conjectures that “[i]n 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 continued anti-PD-1 monotherapy after the combination therapy. Pet., 57-58.

To the extent Amgen argues that a POSA would have been motivated to administer the anti-PD-1 antibody alone as a means to limit toxicity of the combination, that argument lacks evidentiary support. EX2023, ¶77-83. According to Amgen, the doses and frequencies of the combination therapy portion of the Ground 2 claims would have been obvious because they had purportedly already been “demonstrated safe and effective” for the anti-CTLA-4 and anti-PD-1 antibodies. Pet., 56-57. Applying ***Amgen’s rationale***, a POSA would have expected ***the combination*** to be safe and effective. Thus, a POSA would have had no reason to switch from a combination therapy to monotherapy unless there actually was some information about the efficacy or toxicity ***of the combination therapy***. EX2023, ¶77. Amgen cannot have it both ways. It provides no evidence regarding either the

efficacy or the toxicity of the specific combination therapy in the Ground 2 claims (evidence, which would of course, undermine the first part of its argument). EX2023, ¶¶77-79. Not only that, even if toxicity were a concern, Korman teaches an entirely different solution—to use subtherapeutic doses to limit the potential toxicity of the combination. EX2023, ¶80; EX1006, 66 (“In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising ***administering an anti-PD-1 antibody and a subtherapeutic dose of anti-CTLA-4 antibody*** to a subject.”); *see also id.* at 67-68. In contrast, subsequent treatment with an anti-PD-1 antibody alone is not described in any of the Ground 2 references.

Amgen offers no further explanation of its speculative theory other than to quote an isolated sentence from Fife, a review article that discusses basic aspects of peripheral T-cell tolerance and autoimmunity. Pet., 58 (“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”) (citing EX1010). Fife cannot supply a missing limitation—it is not an asserted reference. *Intel Corp. v. PACT XPP Schweiz AG*, No. 2023-1537, 2024 WL 5068112, at *1-2

(Fed. Cir. Dec. 11, 2024) (affirming the Board’s refusal to consider a reference relied on to provide a missing limitation where it was not included in the asserted grounds); *see also* 37 C.F.R. § 42.104(b)(2), (4). And in any event, Amgen never states where the missing limitation can be found in Fife.

In fact, Amgen provides no explanation for how Fife’s discussion of peripheral tolerance and autoimmunity⁴ (neither of which are cancer) would have caused a POSA to administer an anti-PD-1 antibody alone after anti-PD-1/anti-CTLA-4 combination therapy, much less for why a POSA would do so in a method for treating cancer. *See also* EX2023, ¶81. Likewise, Amgen fails to address why a POSA would have been motivated to combine the basic immunology teachings of Fife with the Ground 2 references. Amgen’s entire argument in support of the “subsequently administering” limitation is literally one sentence from a reference that is not even about—and does not disclose—subsequent administrations of anti-PD-1 antibody alone or cancer. *Id.* Even accepting Amgen’s argument that Fife

⁴ Fife is a basic immunology review article that “focuses on our current understanding of the negative regulatory molecules CTLA-4 and PD-1, their function in controlling autoimmunity, and how these molecules regulate autoreactive peripheral T cells that have escaped central tolerance.” EX1010, 167.

would have been part of the background knowledge of a POSA, the Petition is still fatally flawed because (1) it does not identify a single passage in Fife contemplating dosing regimens for cancer and (2) it does not explain how Fife would have influenced a POSA's design of multi-step dosing regimens for cancer and led a POSA to subsequently administer an anti-PD-1 antibody alone following combination therapy. *Id.* at ¶¶81-82.

Amgen nevertheless insists that its theory for subsequent administration “would have been consistent with the ‘combination followed by anti-PD-1 alone’ format disclosed” in NCT-231. Pet., 58. Like Fife, NCT-231 cannot be used to supply a missing limitation because Amgen did not assert NCT-231 as a reference in Ground 2. Even so, Amgen once again mischaracterizes NCT-231. The dosing schedule described in NCT-231 involves staged dosing of combination therapy between an induction phase and a maintenance phase, where the induction phase includes both combination therapy and PD-1 monotherapy that is followed by **additional** combination therapy. EX2023, ¶83; EX1005. NCT-231, even when combined with the Ground 2 asserted references, does not disclose the regimen in the Ground 2 claims. EX2023, ¶83; *see In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (“It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position,

to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.”). Thus, as with Fife, Amgen’s argument is fatally flawed because it provides no explanation for why a POSA would have modified the dosing regimen in NCT-231 to arrive at the dosing schedule in the Ground 2 claims. EX2023, ¶83; see *New Balance Athletics, Inc. v. Nike, Inc.*, IPR2025-00020, Paper 7 at 34-35 (P.T.A.B. June 9, 2025) (denying institution where the Petition failed to show that the combination of the art and the knowledge of a POSA discloses or suggests a missing limitation).

Finally, Amgen cites to its expert, Dr. Antony, as further support. His declaration adds nothing to the Petition. He too provides no explanation for why Amgen’s single-sentence argument satisfies the missing subsequent administration limitation. In fact, Dr. Antony repeats verbatim the same sentence and Fife quote from the Petition without providing any substantive contributions of his own, and thus, his declaration should be given no weight.

Amgen’s Petition	Dr. Antony Declaration
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	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. Pet., 57-58.	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.”). EX1003, ¶217.
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EX1003, ¶¶217, 240; *see, e.g., Xerox Corp.*, IPR2022-00624, Paper 12 at 5 (affirming the Board’s denial of institution and finding “the Board was correct in giving little weight to Petitioner’s expert because the expert declaration merely offered conclusory assertions without underlying factual support and repeated, verbatim, Petitioner’s conclusory arguments”); 37 C.F.R. § 42.65(a).

Amgen’s theory for why a POSA would have administered an anti-PD-1 antibody alone subsequent to combination therapy with anti-PD-1 and anti-CTLA-4 antibodies lacks support and improperly relies on unasserted art, which, for the reasons above, does not even satisfy the limitation.

2. The Ground 2 References Do Not Disclose Biweekly Dosing of an Anti-PD-1 Alone Administered After Combination Therapy

Amgen’s Ground 2 is fatally flawed for the additional reason that it provides no motivation for a POSA to administer an anti-PD-1 antibody alone on a **biweekly basis** subsequent to anti-PD-1/anti-CTLA-4 combination therapy. More specifically,

Amgen fails to explain why a POSA would have been motivated to administer the anti-PD-1 antibody on a more frequent basis (every two weeks) than the combination therapy (every three weeks) that precedes it.

Amgen argues that by May of 2012, 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 in Sznol.*” Pet., 58. Sznol reports preliminary results for the first 16 patients treated in a **Phase 1** OPDIVO® **monotherapy** trial. EX1009. Although Sznol observes some anti-tumor activity in 6 of the 16 patients it reports, Sznol does not reach any definitive conclusions regarding anti-PD-1 monotherapy dosing or frequency. EX2023, ¶85. The ultimate conclusion reached in Sznol is that further study of anti-PD-1 monotherapy was warranted: “Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.” EX1009. Amgen has not shown that a POSA would have administered the anti-PD-1 antibody alone biweekly following anti-PD-1/anti-CTLA-4 combination therapy based on a preliminary report from a Phase 1 trial with limited patient data like Sznol. EX2023, ¶¶84-85. Nor can it. A POSA would not have relied on such early information from a Phase 1 trial, like Sznol, for a drug that was still in the early stages of its

development to design a brand-new combination therapy. *Id.* Sznol was still trying to figure out monotherapy.

Aside from Sznol, Amgen's only other support for the argument that a POSA would have selected biweekly dosing for subsequent administration of an anti-PD-1 antibody alone is Korman's disclosure of biweekly dosing. Pet., 58 (citing EX1006, 55-56). Korman states that exemplary treatment regimens include administering antibodies anywhere from once per week to once every three to six months, and identifies "preferred dosage regimens" for monotherapy as "(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." EX1006, 55. At no point does Korman suggest that anti-PD-1 antibodies should be given on a biweekly basis when administered alone subsequent to combination therapy. EX2023, ¶¶86-87. Korman does not even recommend biweekly dosing as a preferred regimen for monotherapy. *Id.*

Thus, Amgen's Ground 2 fails for the additional reason that it fails to establish that a POSA would have been motivated select biweekly dosing from Sznol and combine it with Korman and Wolchok to arrive at the claims.

3. A POSA Would Not Have Been Motivated to Combine the Korman, Wolchok, and Sznol to Arrive at the Ground 2 Claims

The Ground 2 claims are directed to multi-step methods in which a patient is administered a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody every 3 weeks for 4 doses and is then subsequently administered an anti-PD-1 antibody alone every 2 weeks. Even if the limitations of the Ground 2 claims could all be found in the asserted references (they cannot), a POSA would have had no reason before May 15, 2012 to combine Korman, Wolchok, and Sznol in the same manner as in the Ground 2 claims. EX2023, ¶88. Amgen only does so by breaking down the claims into discrete parts and reconstructing them only with the benefit of hindsight.

In its Petition, Amgen breaks the claims into three parts: (1) Combined dosing number and frequency, (2) Subsequent dosing of Anti-PD-1 Alone, and (3) Dosing Concentrations, and argues for why those parts would have been obvious to a POSA. Pet., 56-59. In so doing, Amgen fails to consider the claims as a whole or consider why a POSA would have been motivated to arrive at the claims as a whole. By breaking the Ground 2 claims down into three discrete parts and addressing each separately, Amgen violates a primary tenant of patent law. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of

obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim.”). For this reason alone, Amgen cannot meet its burden of showing that it is more likely than not that the Ground 2 claims would have been obvious.

Amgen’s parsing of the Ground 2 claims also renders its reasoning insufficient. As an example, Amgen’s argument fails to consider the impact the initial combination treatment would have had on a subsequent treatment with an anti-PD-1 antibody alone. EX2023, ¶¶89-90. The anti-PD-1 and anti-CTLA-4 antibodies administered in the Ground 2 methods are checkpoint inhibitors. *Id.* Checkpoint inhibitors function by blocking immune signaling pathways to alter a patient’s immune response. *Id.* As a result, there is a possibility that when checkpoint inhibitors are administered together, the toxicity and/or efficacy of the inhibitors may be different than what has been observed when the inhibitors are administered alone, which will influence the dose and frequency a POSA would have selected for both combination therapy and monotherapy following combination therapy. *Id.*; EX1030, 4275-76.

In other words, a POSA would have been aware that the initial combination therapy step of administering anti-PD-1 and anti-CTLA-4 antibodies would have generated an immune response in the patient that could both enhance the toxicity and reduce the efficacy of any subsequently administered composition, including

anti-PD-1 antibodies. EX2023, ¶¶89-90; EX1030, 4275-76; EX1040, 715 (“the biochemical and biological effects of the combination may be quite complex, and the dose–toxicity relationship may depend largely on unknown pharmacokinetic and/or pharmacodynamic interactions between the agents, which could limit the administration of all drugs at their recommended dose for phase II trials as single agents”). That knowledge would have influenced a POSA’s decision-making—it is a consideration a POSA would not have ignored. EX2023, ¶¶89-90. But Amgen does ignore it. Amgen never addresses these considerations because it focuses on each “part” of the claims without regard for the others. EX2023, ¶¶89-90.

Because Amgen treats each “part” of the Ground 2 claims as independent, ignoring the potential impact the combination therapy might have on the toxicity and efficacy of subsequently administered anti-PD-1 antibody, its argument that a POSA would have been motivated to combine these references lacks sufficient evidentiary support.

* * *

The methods of treatment in the Ground 2 claims were novel and nonobvious at the time the ’320 Patent was filed. Nothing in the Petition shows otherwise—there is no reference or combination of references that disclose the methods of Ground 2. Amgen argues, without support, that the Ground 2 methods were well-

known and obvious variations on combination therapy. That position is not based on facts or evidence. It is the product of impermissible hindsight. For these reasons, Amgen cannot meet its burden to show a reasonably likelihood that the Ground 2 claims are unpatentable and the Board should deny institution.

VIII. CONCLUSION

For at least the above reasons, the Board should deny institution.

Respectfully submitted,

Date: July 10, 2025

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This paper complies with the type-volume limitation of 37 C.F.R. § 42.24.
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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE and EXHIBITS 2023 through 2032 were served on counsel of record on July 10, 2025, by filing these documents through the Patent Trial and Appeal Case Tracking System (P-TACTS), as well as delivering copies via electronic mail to the counsel of record for the Petitioner at the following addresses:

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