

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

IPR2025-00602
Patent No. 10,174,113

**PATENT OWNER'S
PRELIMINARY RESPONSE**

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. TECHNICAL BACKGROUND.....	3
A. Immunotherapy and the PD-1 Pathway	3
B. Purposes of Clinical Trials at Different Phases	5
C. BMS's Development of OPDIVO®	7
D. Amgen	8
III. OVERVIEW OF THE '113 PATENT	10
IV. AMGEN'S PETITION AND OVERVIEW OF THE ART.....	12
A. Grounds in Amgen's Petition	12
B. Overview of the Art.....	13
1. NCT-505.....	13
2. Postow	14
3. NCT-109.....	15
4. Cogswell.....	18
V. THE LEVEL OF SKILL IN THE ART	18
VI. CLAIM CONSTRUCTION.....	19
VII. EFFECTIVE FILING DATE	19
VIII. ARGUMENT.....	19
A. Amgen's Mischaracterization of NCT-109 Undermines Every Ground in the Petition	22
1. No Motivation to Modify NCT-505 and Postow by Combining with NCT-109	23
2. No Reasonable Expectation of Success	29
B. Amgen's Strategy to Modify NCT-505 and Postow is Contradicted by the Art	31
1. Wang Teaches That Phase 3 Dosing Decisions Consider the Effect of Body Weight on PK and PD	31
2. Amgen Points to No Data on the Effect of Body Weight	33
3. Amgen's Arguments on Flat Dosing Improperly Ignore Wang's Focus on First-in-Human Testing	36
C. Amgen Fails to Address the Claims as a Whole	39
IX. CONCLUSION	42

TABLE OF AUTHORITIES

Page(s)

Cases

<i>In re Kahn</i> , 441 F.3d 977 (Fed. Cir. 2006)	20
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	20
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	19

Statutes

35 U.S.C. § 314(a)	19
42 U.S.C. § 262(k)	9
42 U.S.C. § 262(l)	9

Other Authorities

37 C.F.R. § 42.100(b)	19
37 C.F.R. § 42.108(c)	20
Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756 (Aug. 14, 2012)	20

EXHIBITS

Exhibit No.	Description
EX2001	U.S. Patent No. 9,856,320
EX2002	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
EX2003	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
EX2004	YERVOY, FDA Approved label and prescribing information, Rev. 5/2025
EX2005	OPDIVO, FDA Approved label and prescribing information, Rev. 5/2025
EX2006	Amgen Pipeline, available at https://www.amgenpipeline.com/
EX2007	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
EX2008	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/amgen-reports-first-quarter-2025-financial-results
EX2009	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
EX2010	U.S. Patent Appl. No. 15/021,102
EX2011	U.S. Patent No. 8,008,449

Exhibit No.	Description
EX2012	U.S. Patent No. 8,779,105
EX2013	U.S. Patent No. 9,084,776
EX2014	U.S. Patent No. 9,358,289
EX2015	U.S. Patent No. 9,387,247
EX2016	U.S. Patent No. 9,492,539
EX2017	U.S. Patent No. 9,492,540
EX2018	U.S. Patent No. 10,441,655
EX2019	File History, U.S. Patent Appl. No. 15/021,102, Amendment and Reply Under 37 C.F.R. § 1.111 (Apr. 9, 2018)
EX2020	File History, U.S. Patent Appl. No. 15/021,102, Notice of Allowance and Fee(s) Due (May 23, 2018)
EX2021	Amgen Biosimilars, available at https://www.amgen.com/science/biosimilars
EX2022	Declaration of Peter P. Lee, M.D.
EX2023	Curriculum Vitae of Peter P. Lee, M.D.
EX2024	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
EX2025	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 Patent Owner Preliminary Response (POPR) in response to the Petition for *inter partes* review filed by Amgen Inc. challenging the patentability of claims 1-20 of U.S. Patent No. 10,174,113 (“the ’113 Patent,” EX1001). The Board should deny institution because Amgen has not shown a reasonable likelihood of prevailing with respect to any challenged claim.

I. INTRODUCTION

BMS and its collaborators revolutionized cancer treatment by inventing novel methods of treating cancer by administering antibodies that alter the patient’s immune response by binding to PD-1 and CTLA-4, two proteins involved in regulating the immune system. These groundbreaking methods of treatment for cancer fall within a field known as “immunotherapy.” The PTO recognized these innovations and granted BMS multiple patents covering anti-PD-1 and anti-CTLA-4 antibodies, and various methods of treating cancer by administering such antibodies.

The ’113 Patent relates to methods of treating melanoma with a specific multi-part regimen that starts with a combination of weight-based doses of anti-PD-1 and anti-CTLA-4 antibodies and continues with flat (non-weight-based) doses of just the anti-PD-1 antibody. The innovations protected by the ’113 Patent are the results of BMS’s extensive investment in research and clinical trials programs. The claimed dosing regimen aligns with an approved indication on the label for BMS’s anti-PD-1

antibody OPDIVO® used in combination with its FDA-approved anti-CTLA-4 antibody YERVOY® for the treatment of melanoma.

In its Petition, Amgen argues that the patentability of every claim of the '113 Patent should be reassessed. The Board should deny institution because Amgen has not shown a reasonable likelihood of prevailing with respect to any challenged claim.

Amgen's arguments fail for multiple reasons. First, Amgen incorrectly argues in its Petition that NCT-109 discloses anti-PD-1 antibody monotherapy for treatment. But every treatment in the dose escalation study recited in NCT-109 includes an anti-LAG-3 antibody. That reference does not disclose any anti-PD-1 antibody administered as a monotherapy. This deficiency affects every Ground. A POSA would have considered significant the potential impact of the anti-LAG-3 and anti-PD-1 antibodies on each other and would not have known the precise effect on suitable antibody doses. Amgen's failure to account for the anti-LAG-3 antibody in the treatments disclosed by NCT-109, and its incorrect statement that NCT-109 describes anti-PD-1 antibody monotherapy, undermines its reliance on NCT-109 for every Ground.

Second, Amgen's proposed modification of the weight-based treatments in NCT-505 and Postow is contrary to the express teaching in its Wang reference (EX1008), which explains that the impact of body weight on pharmacokinetics and

pharmacodynamics should be assessed to determine a Phase 3 clinical dosing regimen. Amgen improperly ignores Wang's focus on modifying early first-in-human trials and instead improperly attempts to modify late-stage protocols without pointing to any information on the impact of body weight, which, as Wang explains, would be important for a POSA to make such a modification. Again, that failure undermines Amgen's argument for every one of its Grounds.

Third, Amgen fails to consider the claims of the '113 Patent as a whole. Amgen zooms in on the second part of the multipart treatment regimens of the claims, arguing that only the anti-PD-1 monotherapy part of NCT-505 and Postow would be modified to use a flat dose, while the anti-CTLA-4/anti-PD-1 combination dose would remain weight-based. But that is inconsistent with Amgen's argument that the POSA would somehow know that flat doses were the "approach of choice" for anti-PD-1 antibodies generally and is borne out of Amgen's hindsight effort to reach the claimed dosing regimen. That failure also applies to every Ground.

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. To do that the T

cells must distinguish between healthy cells and cells that are infected or cancerous. EX2001, 1:33-38; EX1001, 1:45-48; EX2022, ¶30. 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 acts as a brake on the immune system by downregulating T cell activity to prevent T cells from killing healthy cells. EX2022, ¶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. EX1001, 1:53-65; EX2022, ¶31.

Immunotherapy is a type of treatment that functions by taking advantage of pathways like these to modulate a patient’s immune response and fight disease. One form of immunotherapy involves using antibodies to manipulate the immune response. 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. EX2022, ¶31. 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. EX2001, 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. EX2022, ¶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). EX2022, ¶34; EX2025, 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.”); EX2024, 3. The Phase 1 trial is often the first time the drug is tested in the clinic, making it a so-called first-in-human (FIH) study. EX2022, ¶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. If the initial doses are safe, they are increased incrementally as the clinicians study the safety and efficacy of higher doses. EX2022, ¶34; EX2025, 197 (“Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a sufficient period.”). One drug property analyzed in these studies 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. EX2022, ¶35. Another property is

pharmacodynamics (“PD”), which tries to assess how the drug interacts with biological targets in the body. EX2022, ¶35; EX2024, 3.

Different patients can react differently to the drug for several reasons, including stage of the disease, other medical conditions, genetics, age, sex, and, importantly for the inventions of the ’113 Patent, body weight. EX2022, ¶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. EX2022, ¶36. “When an mAb is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown.” EX1008, 1023. Because the effect of body weight on PK and PD is unknown when a FIH trial begins, it is not possible to predict whether the method of treatment should proceed with weight-based dosing (for example on a milligram per kilogram basis) or flat dosing (where every patient receives the same dose regardless of body weight). For FIH trials of antibody drugs, weight-based dosing has been common because the potential doses in a dose escalation study can be evaluated based on preclinical information and because of the perception that weight-based dosing “would provide less variable exposure levels across patients.” EX1008, 1018-19. These preliminary studies are intended to test for safety and potentially gather information on PK and PD.

The primary goal of Phase 2 and Phase 3 clinical trials, on the other hand, is to test the safety and efficacy of the drug in larger groups of patients. EX2022, ¶37. Phase 2 trials often include a few hundred patients, who are sometimes split into different groups that receive either the new drug or a placebo. EX2022, ¶37; EX2024, 3-4. Phase 3 trials include hundreds or thousands of patients for the purpose of confirming efficacy and comparing the new treatment to the standard of care. EX2022, ¶38; EX2025, 198. 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. EX2022, ¶39. As the Wang reference that Amgen relies on 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.” EX1008, 1023-24. The Phase 3 treatment protocol is intended to confirm the safety and efficacy of a method to be used in clinical practice.

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. EX2002. 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. EX2003.

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 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; EX2005.

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).

III. OVERVIEW OF THE '113 PATENT

The '113 Patent, titled “Treatment of PD-L1-Negative Melanoma Using an Anti-PD-1 Antibody and an Anti-CTLA-4 antibody,” issued on January 8, 2019 and names Dr. Arvin Yang as inventor. EX1001. The '113 Patent protects certain uses of OPDIVO® for the treatment of melanoma. Specifically, the '113 Patent relates to treating patients with a multi-part regimen. In the first part, patients receive a combination of an anti-PD-1 antibody (like nivolumab) and an anti-CTLA-4 antibody (like YERVOY® (ipilimumab)). EX2022, ¶46. In that combination, the anti-PD-1 antibody doses are based on the patient’s weight. *Id.* For example, in the regimen in independent claim 2 of the '113 Patent, the patient is administered:

about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 (“an anti-PD-1 antibody”) and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 (“an anti-CTLA-4 antibody”) every three weeks for about 4 doses....

EX1001, cl. 2. This is followed by the second part of the regimen, where patients receive the anti-PD-1 antibody at “a flat dose of about 240 mg or about 480 mg.” *Id.* The flat dose is “administered to a patient without regard for the weight or body surface area (BSA) of the patient”—*i.e.*, every patient gets the same amount. EX1001, 7:52-55; EX2022, ¶47. Independent claim 1 adds a method step of “identifying a patient having a PD-L1-negative melanoma tumor.” EX1001, cl. 1.

During prosecution of the application that issued as the '113 Patent, the Examiner focused on the elements related to the flat dose of anti-PD-1 antibody. Before those claim elements were added, the Examiner rejected the pending claims as anticipated by Wolchok (EX1017), which disclosed combinations of weight-based doses of anti-PD-1 and anti-CTLA-4 antibodies. EX1002, 433. BMS amended the second part of the claimed regimen from weight-based to flat dosing of anti-PD-1 antibody, distinguishing Wolchok. EX1002, 68. BMS submitted published patent application WO 2015/042246 ("Korman") (EX1002, 161-250) in an IDS on May 29, 2018 (EX1002, 80-85), the same date that the flat dose of anti-PD-1 antibody monotherapy limitation was added to the pending claims. EX1002, 67-79. Korman describes a dose escalation study of an anti-LAG-3 antibody treatment, including in combination with anti-PD-1 antibody, but does not disclose any anti-PD-1 monotherapy. EX1002, 248, Fig. 2A. The Examiner indicated that he considered Korman along with the 22 other references submitted on the IDS. EX1002, 63-65. After the claim amendments adding the flat dosing elements, the Examiner specifically focused on whether the '113 Patent specification provided support for the use of a flat dose of PD-1 antibodies in the monotherapy part of the regimen. EX1002, 57-60. The '113 patent specification does support that regimen, and when the applicant pointed to that support, the Examiner allowed the claims. EX1002, 19-20, 37-41.

Every claim of the '113 Patent is directed to (1) weight-based dosing for the anti-PD-1/anti-CTLA-4 combination part of the regimen, and (2) flat dosing for the anti-PD-1 monotherapy part of the regimen. EX2022, ¶¶46-47. That multi-part regimen is not found in—or suggested by—the prior art. And the obviousness arguments in Amgen's Petition suffer the same fatal flaws for every claim.

IV. AMGEN'S PETITION AND OVERVIEW OF THE ART

A. Grounds in Amgen's Petition

Amgen filed its Petition on February 28, 2025 along with two other Petitions (IPR2025-00601 and IPR2025-00603), both of which challenge patents in other families that are also owned by BMS. All three of the challenged patents claim novel methods of treating cancer with combinations of anti-PD-1 and anti-CTLA-4 antibodies. While the Petitions are substantively unique, relying on different references and different technical experts, the patents challenged in the Amgen Petitions all protect indications on OPDIVO®'s label and fall within the scope of patents that would be subject to the BPCIA Patent Dance and resulting litigation.

Amgen argues that the claims of the '113 Patent would have been obvious over combinations of prior art that are gathered into four Grounds for unpatentability. To piece together the multiple parts of the claimed regimens, Amgen relies first on disclosures in NCT-505 (in Grounds 1A-C and 2) and Postow (in Grounds 3A-C and 4). Amgen points to two-part treatment regimens beginning with (1) combinations

of weight-based doses of anti-PD-1 and anti-CTLA-4 antibodies, followed by (2) monotherapy with weight-based doses of an anti-PD-1 antibody. Importantly, those prior art disclosures in NCT-505 and Postow use weight-based dosing in both the combination step and the monotherapy step.

Amgen argues that a POSA would have modified only the second part—the weight-based anti-PD-1 antibody monotherapy of the NCT-505 and Postow regimens to a flat dose. Pet., 2-3. The disclosure of a flat, monotherapy dose of an anti-PD-1 antibody, allegedly comes from NCT-109. Each and every Ground relies on the combination of either NCT-505 or Postow (for the weight-based combination) and NCT-109 (for the flat dose).

In Grounds 2 and 4, covering dependent claims 5-9 and 16, Amgen adds another reference, the Cogswell application, to its above combinations to address limitations directed to, for example, PD-L1 testing and additional therapeutic agents.

B. Overview of the Art

1. NCT-505

NCT-505 is a “Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma.” EX1014, 3. The purpose of the study was “to show that Nivolumab and/or Nivolumab in combination with Ipilimumab will extend survival compared to Ipilimumab alone.” EX1014, 4. In other words, the purpose of this Phase 3 trial was not to test various

doses, but to show efficacy. *See* EX2024, 2-5. The primary outcome measured was overall survival. EX1014, 5. Amgen points to the dosing in Arm B, where nivolumab that was administered at a weight-based dose of 1 mg/kg is combined with ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab monotherapy at 3 mg/kg every 2 weeks. EX1014, 4. NCT-505 does not suggest flat dosing and does not describe the impact of body weight on the treatment. EX2022, ¶49.

2. Postow

BMS does not concede that Postow is prior art, based on the effective filing date of the '113 Patent, but Amgen's arguments fail regardless. So for purposes of this POPR, BMS will address the merits of Amgen's arguments based on Postow.

Postow is a publication in the New England Journal of Medicine entitled, "Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma." EX1005, 2006. The article lists publication dates of April 20, 2015 and May 21, 2015. EX1005, 2006. Postow reports "the results of a randomized, double-blind trial comparing nivolumab in combination with ipilimumab with standard-of-care ipilimumab monotherapy as a first-line treatment in patients with advanced melanoma." EX1005, 2007. The primary end point was objective response. EX1005, 2008.

Like for NCT-505, Amgen points to the patients in the Postow study who received nivolumab at a weight-based dose of 1 mg/kg combined with ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab monotherapy at 3 mg/kg every 2 weeks. EX1005, 2006. Postow does not suggest flat dosing and does not describe the impact of body weight on the treatment. EX2022, ¶51.

3. NCT-109

The study in NCT-109 is entitled “A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors.” EX1007, 4. The Brief Summary in NCT-109 states that the objective of the study is “[t]o assess the safety and tolerability, characterize the dose-limiting toxicities, and identify the maximum tolerated dose of [the anti-LAG-3 antibody] BMS-986016 alone and in combination with Nivolumab in subjects with select advanced (metastatic and/or unresectable) solid tumors and to provide preliminary information on the clinical benefits of the combination.” EX1007, 4. In the first arm of the study, the anti-LAG-3 antibody (BMS-986106) is administered on its own:

Experimental: Part A-Dose Escalation: BMS-986016

BMS-986016 20, 80, 240, and 800 mg solution intravenously, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

EX1007, 5. In the second and third arms, the anti-LAG-3 antibody is administered in combination with the anti-PD-1 antibody (BMS-936558, nivolumab):

Experimental: Part B-Dose Escalation: BMS-986016 + BMS-936558

BMS-986016 3, 20, 80, and 240 mg solution + BMS-936558 80 and 240 mg solution intravenously, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

Experimental: Part C-Cohort Expansion: BMS-986016 + BMS-936558

BMS-986016 + BMS-936558 at doses selected in Part B, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

EX1007, 5. NCT-109 does not report any testing of an anti-PD-1 antibody as a monotherapy. EX2022, ¶52.

The dose escalation of anti-LAG-3 antibody with and without anti-PD-1 antibody was also described in the Korman patent application PCT/US2014/056277 (EX1002, 161-250), which was considered by the Examiner during prosecution of the '113 Patent. EX2022, ¶53. Korman, entitled “Combination of Anti-LAG-3 Antibodies and Anti-PD-1 Antibodies to Treat Tumors,” was published as WO

2015/042246 on March 26, 2015. EX1002, 161. Korman describes the same treatment arms as the NCT-109 document:

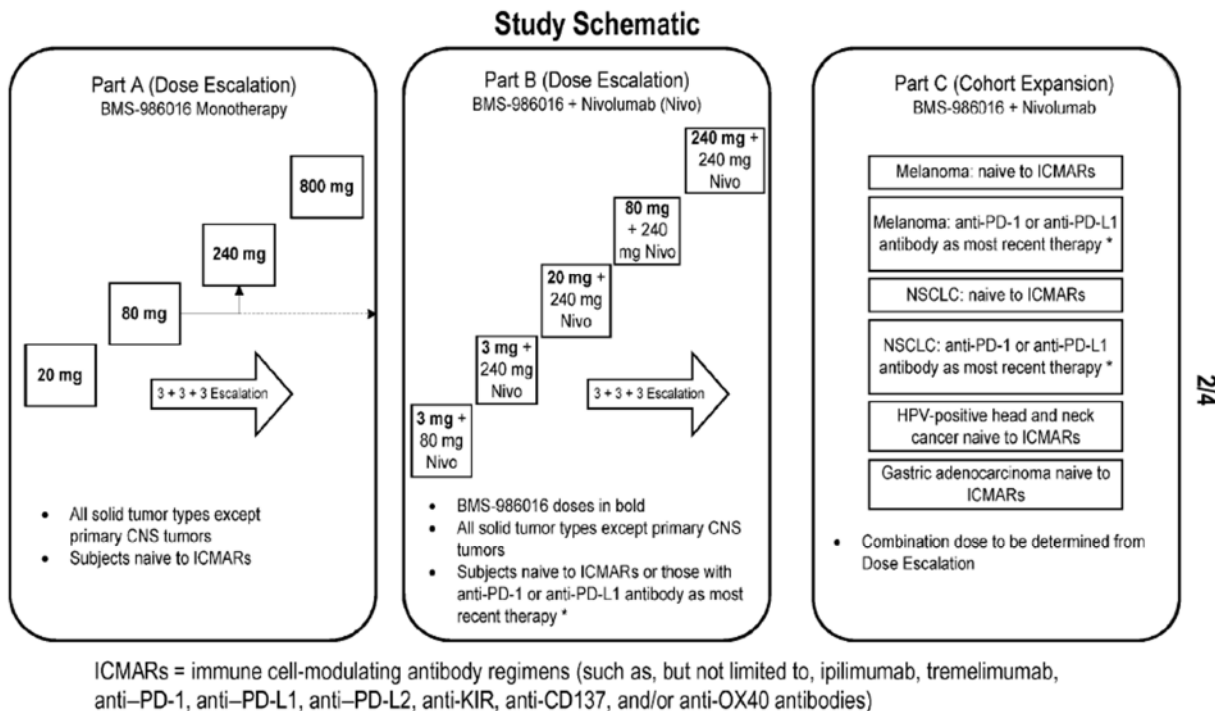


Fig. 2A

EX1002, 248, Fig. 2A. Korman goes on to describe the reasons for testing the combination of anti-LAG-3 and anti-PD-1 antibodies. First, “BMS-986016 [anti-LAG-3 antibody] has the potential to augment the frequency and severity of previously described adverse events associated with BMS-936558 [nivolumab], or to produce new toxicities.” EX1002, 202. Thus, “[t]he primary objective of the study is to assess the safety and tolerability of BMS-986016 given in combination with BMS-936558 [nivolumab] and to identify dose limiting toxicities (DLTs) and

the maximally tolerated dose (MTD) of the combination in subjects with advanced solid tumors.” EX1002, 195.

Amgen’s Petition ignores the use of the anti-LAG-3 antibody in every single dosing regimen disclosed in NCT-109. Amgen goes so far as to state that NCT-109 discloses “anti-PD-1 monotherapy as a flat dose—including 240 mg nivolumab once every two weeks to treat melanoma tumors.” Pet., 17. That is incorrect. The anti-LAG-3 antibody was central to every arm of NCT-109. Anti-PD-1 monotherapy was not part of NCT-109.

4. Cogswell

Amgen’s Petition only points to Cogswell to support claim elements other than the flat doses of anti-PD-1 antibody. Thus, all of the arguments below apply equally to all claims of the ’113 Patent, whether or not Cogswell is included in the Ground.

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 and any other proceedings regarding the ’113 Patent, should the Board institute trial.

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. EFFECTIVE FILING DATE

BMS does not concede that the claims of the ’113 Patent are not entitled to an effective filing date of April 28, 2015. But because Amgen’s arguments all fail regardless of the effective filing date, for purposes of this Preliminary Response only, BMS will not dispute that issue here. Even with a later effective filing date of April 28, 2016, the inventions in the claims were not obvious.

VIII. ARGUMENT

The Board should not institute IPR proceedings based on 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.

Each of Amgen’s arguments requires finding that a POSA would have been motivated to modify the two-part regimens in NCT-505 and Postow that start with a **weight-based** anti-PD-1/CTLA-4 antibody combination therapy and is followed by a **weight-based** anti-PD-1 antibody monotherapy. Those entirely weight-based regimens are Amgen’s starting point for every asserted Ground. For Amgen’s arguments to succeed, the entirely weight-based regimen must be specifically gerrymandered to produce a bifurcated regimen: the anti-PD-1 monotherapy changes to a flat dose, but the anti-PD-1/CTLA-4 combination therapy remains weight-based. For example, claim 2 of the ’113 Patent shows the two-part regimen with weight-based anti-PD-1 antibody in combination followed by flat dose anti-PD-1 antibody:

2. A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient:

- (a) about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 (“an anti-PD-1 antibody”) and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 (“an anti-CTLA-4 antibody”) every three weeks for about 4 doses; followed by
- (b) a dose of the anti-PD-1 antibody, wherein the dose in (b) is a flat dose of about 240 mg or about 480 mg.

Weight-based
anti-PD-1

Flat Dose
anti-PD-1

Amgen points to nothing in the prior art that would have motivated a POSA to make such a modification to the second part of the protocol, while leaving the first part of the protocol weight-based. To the contrary, Amgen argues repeatedly that flat dosing was preferred over weight-based dosing. Pet., 3, 21-23. Amgen also fails to show that the POSA would have had a reasonable expectation of success in achieving the claimed invention. Put simply, neither Amgen nor its expert point to any reference or reasoning in the art that actually suggests a POSA would have administered a dosing regimen to a patient in which the patient first receives a combination dose of anti-PD-1 and anti-CTLA-4 antibodies based on that patient’s weight and then subsequently, after months of that combination therapy, receives a flat-dose of an anti-PD-1 antibody regardless of that patient’s weight.

Amgen’s arguments on motivation and reasonable expectation of success fail for multiple reasons. First, Amgen mischaracterizes NCT-109 as disclosing anti-PD-

1 antibody monotherapy—this incorrect assertion undermines every Ground in the Petition. Second, Amgen’s proposed strategy for modifying the late-stage clinical protocols in NCT-505 and Postow is contradicted by the express disclosure of the art that Amgen cites. Third, Amgen fails to treat the claims as a whole by not showing why its proposal to change weight-based dosing to flat dosing should apply only to the anti-PD-1 antibody monotherapy part of the claimed treatment and not also to the combination with the anti-CTLA-4 antibody.

A. Amgen’s Mischaracterization of NCT-109 Undermines Every Ground in the Petition

Amgen describes NCT-109 as disclosing “anti-PD-1 monotherapy as a flat dose—including 240 mg nivolumab once every two weeks to treat melanoma tumors” (Pet., 17) and then seeks to rely on that purported monotherapy disclosure throughout its entire Petition (Pet., 19, 24, 28-29, 34-35, 47-48, 52). But there is no anti-PD-1 monotherapy in NCT-109. EX2022, ¶57. NCT-109 describes a dose escalation study of an anti-LAG-3 antibody administered alone or in combination with an anti-PD-1 antibody. Specifically, the therapies in NCT-109 are (1) an anti-LAG-3 antibody and (2) an anti-LAG-3/anti-PD-1 combination. Anti-PD-1 monotherapy is not disclosed, described, or suggested. This mischaracterization of NCT-109 dooms all of Amgen’s Grounds.

1. No Motivation to Modify NCT-505 and Postow by Combining with NCT-109

As described above, NCT-505 and Postow describe two-step dosing regimens in which anti-PD-1/anti-CTLA-4 combination therapy is followed by anti-PD-1 monotherapy. Critically, both steps in NCT-505 and Postow use weight-based dosing. Amgen suggests a POSA would have been motivated to change the monotherapy step (and only the monotherapy step) in NCT-505 or Postow from weight-based dosing to flat dosing based on the disclosure of NCT-109 and the alleged advantages of fixed dosing. Pet., 21-24. But a POSA would not have been motivated to use the anti-LAG-3/anti-PD-1 combination dose from NCT-109's Phase 1 protocol to modify the dosing strategy for an anti-PD-1 antibody monotherapy step in a totally different regimen. First, as explained in § VIII.B, *infra*, the references that Amgen relies on (Pet., 21-22) do not suggest that flat dosing was the "approach of choice" for nivolumab, or that the POSA would be motivated to change NCT-505 to use a flat dose (let alone the specifically claimed mixture of flat and weight-based doses).

Second, the POSA would not have been motivated to specifically select 240 mg as the flat dosage based on the disclosure of NCT-109.¹ In NCT-109, the authors tested the combination of anti-LAG-3 and anti-PD-1 antibodies at various doses in NCT-109 because the potential effects of one antibody on the efficacy and safety of the other were unknown. EX1007, 4 (describing the purpose of the study “[t]o assess the safety and tolerability, characterize the dose-limiting toxicities, and identify the maximum tolerated dose of BMS-986016 [anti-LAG-3 antibody] alone and in combination with Nivolumab”). In other words, despite the earlier use of anti-PD-1 antibodies (for example in NCT-505), the combination with anti-LAG-3 antibody was being tested in the dose escalation study *because* the suitable dose in the combination had the potential to be different from the dose outside the combination. The suitable dose was unknown and needed to be determined in the study. Regardless of whether flat dosing generally was considered advantageous or not, Amgen’s Petition never explains why the anti-LAG-3/anti-PD-1 antibody

¹ Claims 12 and 18 of the ’113 Patent recite a flat dose of 480 mg, but Amgen’s argument for these claims is still based on the same argument that 240 mg would have been obvious and that 480 mg was “an obvious variant” of 240 mg. Pet., 35-36, 57-58. Amgen’s incorrect argument for 240 mg therefore undermines its positions on claims 12 and 18 as well.

combination dosing would be helpful for determining an anti-PD-1 monotherapy dose, particularly where that monotherapy dose is part of a regimen in which the anti-PD-1 antibody is first administered in combination with a totally different antibody (an anti-CTLA-4 antibody) and that combination dose is administered according to a patient's weight, as in NCT-505 and Postow. EX2022, ¶58.

Reading Amgen's Petition, it would be easy to miss that the anti-LAG-3 antibody was part of NCT-109 at all. Amgen's expert Dr. Hanks only briefly mentions the anti-LAG-3 antibody (BMS-986016), suggesting that its presence would not impact the dose of anti-PD-1 antibody. According to Dr. Hanks:

POSAs would have understood that a 240 mg nivolumab dose would have been appropriate for a monotherapy as well because nivolumab and BMS-986016 have different mechanisms of action, binding to different targets, and thus a suitable dose of nivolumab in the combination therapy disclosed by NCT-109 would also have been considered a suitable dose for administering nivolumab alone.

EX1003, ¶89. Dr. Hanks cites to no evidence or prior art support for this conclusory statement.

As explained by Dr. Peter Lee, Dr. Hanks's conclusions are wrong. Both nivolumab and BMS-986016 (anti-LAG-3 antibody) target immune checkpoint molecules to modulate the immune response. EX2022, ¶61. They share this immunomodulatory function, even though they bind to different target molecules.

EX2022, ¶61. A POSA would not have understood that a suitable dose for nivolumab administered in combination with the anti-LAG-3 antibody would be a suitable dose for nivolumab administered alone, particularly when following treatment with a different combination of antibodies (anti-PD-1/anti-CTLA-4) because each combination of antibodies is going to have a different cumulative effect on the immune system. EX2022, ¶61.

Like PD-1, LAG-3 had been reported to play an important role in negatively regulating T cell activation and proliferation. EX2022, ¶62; EX1002, 162. The action of LAG-3 was linked to the exhaustion of T cells, which interferes with their ability to respond to an immune challenge. EX2022, ¶62; EX1002, 163. “Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell’s ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity.” EX1002, 163; EX2022, ¶62. Antibodies that block PD-1 or LAG-3 can remove the inhibition, releasing the brake on T cell activity. Both types of antibodies interfere with the inhibitory mechanisms that, without treatment, can lead to tumors evading the immune system. EX2022, ¶63. But this does not mean that they can be mixed, matched, or combined without regard to the effects they have on the immune system. On the contrary, the POSA would have understood that each different combination of checkpoint inhibitors may have a different effect on the immune

system than any individual checkpoint inhibitor administered alone. EX2022, ¶63. Dr. Hanks generically points to their “different mechanisms of action” as support for why a dosage would be the same for combination therapy and monotherapy, but he never accounts for what those differences are or how they impact the immune response in the context of combination or monotherapy. EX2022, ¶63. Dr. Hanks’s unsupported conclusion that the dosing of anti-PD-1 would be interchangeable between monotherapy and combination treatments simply because anti-LAG-3 and anti-PD-1 antibodies bind to different target molecules is incorrect. EX2022, ¶63.

The POSA would not have considered the doses being explored in the dose escalation study in NCT-109 to be suitable for use for nivolumab alone. EX2022, ¶64. The protocol in NCT-109 is a Phase 1 dose escalation study, meaning that the suitable dose was **not known** for the combination of anti-LAG-3 and anti-PD-1 antibodies that were the subject of the study. EX2022, ¶64. The 240 mg dose that Amgen points to was not known to be suitable, even for the combination. The dose escalation study described in NCT-109 and Korman specifically tested not only the new anti-LAG-3 antibody, but also the combination of the anti-LAG-3 antibody with various doses of anti-PD-1 antibody. EX2022, ¶65. The impact of the combination was not known ahead of time, and the doses that had been previously used for anti-PD-1 antibodies were not just assumed to be suitable for the combination. EX2022, ¶65. As Korman states, “BMS-986016 [anti-LAG-3 antibody] **has the potential to**

augment the frequency and severity of previously described adverse events associated with BMS-936558 [nivolumab], or to produce new toxicities.” EX1002, 202; EX2022, ¶65. Thus, “[t]he primary objective of the study is to assess the safety and tolerability of BMS-986016 given in combination with BMS-936558 [nivolumab] and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination in subjects with advanced solid tumors.” EX1002, 195; EX2022, ¶65. Again, the interactions between the two antibodies were not understood.

Indeed, given the lack of knowledge about the suitability of the doses in NCT-109, the POSA would not have been motivated to change the established Phase 3 treatment regimen in NCT-505, which was also used to generate the results in Postow. Those established anti-CTLA-4/anti-PD-1 antibody treatments were based on prior clinical work, and combinations were already being used at acceptable weight-based doses. Thus, a POSA would have no reason to look to a totally different antibody combination (with anti-LAG-3 antibodies) that was still being evaluated both for efficacy and toxicity and to substitute the dosing for nivolumab into the anti-CTLA-4 combination. EX2022, ¶67.

Finally, Dr. Hanks is incorrect to suggest that a dose that is suitable for “administering nivolumab alone” would necessarily be suitable for use in the claimed invention. EX2022, ¶66. The first part of the claimed treatment regimen

uses a combination of anti-CTLA-4 and anti-PD-1 antibodies for multiple rounds of treatment. As Dr. Lee explains, the POSA would have understood that the anti-CTLA-4/anti-PD-1 antibody combination treatment impacts the immune system in ways that could be durable even after the anti-CTLA-4 antibody is no longer administered. EX2022, ¶¶68. The earlier rounds of combination treatment could then affect the safety and efficacy of doses of anti-PD-1 antibody in the subsequent treatment rounds. *Id.* Thus, the situation for the claimed regimen is more complicated than a regimen where only a single antibody is used. For these reasons, the POSA would not have been motivated to modify NCT-505 or Postow based on NCT-109. EX2022, ¶¶54-68.

2. No Reasonable Expectation of Success

Amgen also relies on NCT-109 to support its argument that the POSA would have had a reasonable expectation of success for the combination of NCT-109 with NCT-505 or Postow. Pet., 24, 50. But Amgen still ignores the fact that the anti-PD-1 antibody was administered in combination with an anti-LAG-3 antibody in NCT-109. Amgen incorrectly argues that doses of the anti-PD-1 antibody from that study can be plucked out and plugged right into the protocol in NCT-505 and Postow with a reasonable expectation of success.

Contrary to Amgen's argument, the presence of the anti-LAG-3 antibody would have been central to a POSA's understanding of NCT-109, and no conclusions

would have been drawn from NCT-109 about the suitable dose for the claimed method of treatment with anti-PD-1 and anti-CTLA-4 antibodies. EX2022, ¶169. From the teachings of Amgen's prior art references, it was not known whether a 240 mg dose was the right one for the anti-PD-1/anti-LAG-3 antibody combination, it was not known whether a dose used in that specific combination would be suitable for anti-PD-1 antibody monotherapy, and it was not known whether such a dose would be suitable for use after multiple rounds of anti-CTLA-4/anti-PD-1 antibody treatment. *Id.* Determining that suitability for the anti-LAG-3/anti-PD-1 antibody combination was the purpose of the study in NCT-109. In addition, even if the anti-PD-1 antibody dose were suitable for use in the anti-LAG-3 antibody combination, for the reasons described above, that would not provide information about the suitability of the same dose for the anti-PD-1 antibody monotherapy portion of the combined anti-CTLA-4/anti-PD-1 antibody treatment in NCT-505 or Postow. Dr. Hanks's assertion that the NCT-109 dose can just be plugged into the other protocols is wholly without evidentiary support. And, as explained at length below the additional references that Amgen relies on do not suggest that the POSA would reasonably expect success with a 240 mg flat dose—they suggest that the POSA would not have a reasonable expectation of success without more information—information Amgen has not identified. *See* § VIII.B, *infra*. A POSA would not have

had a reasonable expectation of success in making Amgen's proposed modification to NCT-505 or Postow based on the combination with NCT-109. EX2022, ¶¶69-70.

B. Amgen's Strategy to Modify NCT-505 and Postow is Contradicted by the Art

Amgen argues that flat dosing has practical benefits, like improved convenience and less risk of error, and that it is the "approach of choice" for antibodies with wide therapeutic windows. Pet., 3, 19, 21-22, 28, 52. Amgen quotes the Wang reference for support (EX1008, 1023) but then ignores the totality of Wang's teaching.

Based on Wang, the POSA would not have been motivated to change the protocol in NCT-505 and Postow from weight-based to flat dosing without understanding how body weight affects the pharmacokinetic and pharmacodynamic properties of the anti-PD-1 antibody. As described below, the effect of body weight should be analyzed before making a decision about dosing for Phase 3 protocols. EX1008, 1023-24; EX2022, ¶39. None of Amgen's arguments or proposed art show how body weight affects the anti-PD-1 antibody nivolumab, and Amgen's Petition never addresses the lack of body weight data.

1. Wang Teaches That Phase 3 Dosing Decisions Consider the Effect of Body Weight on PK and PD

Each of Amgen's Grounds rely on either NCT-505 or Postow as showing treatment regimens with anti-PD-1 and anti-CTLA-4 antibodies. According to

Amgen, these protocols would be modified based on the dosage allegedly disclosed in NCT-109. Importantly, NCT-505 describes a Phase 3 protocol. The safety and efficacy of an antibody dosing regimen are the primary concerns for that Phase 3 study. EX1014, 4-5; EX2022, ¶¶38-39. Postow describes the results of a Phase 2 study testing the same weight-based regimen as in the NCT-505 Phase 3 protocol, again with the goal of assessing safety and efficacy for a group of patients. EX1005, 2007-08. At the time of Postow's publication, the POSA would have also had access to NCT-505 and would have known that the weight-based regimens were the same.

Amgen proposes that the POSA would modify the weight-based dosing in NCT-505 and Postow. But the POSA would not be motivated to make such a modification without considering "a full assessment of body size effect on PK/PD ... to determine the optimal dosing approach for phase 3 trials." EX1008, 1012. The express recommendation from the Wang reference that Amgen relies on is that ***"[w]hen sufficient data become available, a full assessment of body size effect on PK and PD should be conducted."*** The 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." EX1008, 1023-24. Importantly, "[w]hen an mAb is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown." EX1008, 1023. Bai

confirms the recommendation that “[t]he dosing strategy in later stages of clinical development could then be determined based on combined knowledge of the body weight effect on pharmacokinetics, safety and efficacy from the early clinical trials.” EX1034, 119, Abstract.

2. Amgen Points to No Data on the Effect of Body Weight

Amgen’s arguments depend on modifying the protocols in NCT-505 and Postow, but none of Amgen’s cited art or argument provides any information about the effect of body weight on the PK and PD of the anti-PD-1 antibody nivolumab, the information that should guide the dosing approach for these protocols, according to Wang. EX1008, 1012, 1023-24. Amgen points to nothing in NCT-505, Postow, or NCT-109 that shows the impact of body weight on PK or PD properties. Amgen looks outside the references in its Grounds, to the Phase 1 studies described in Brahmer (EX1009) and Topalian (EX1011), to provide additional support for its arguments. Pet., 24-25. But again, as described below, neither study describes the impact of body weight on PK or PD.

Brahmer reports a first in human, Phase 1 study of nivolumab (identified in Brahmer as MDX-1106). According to Brahmer, “[t]his phase I study sought to determine the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid tumors and to preliminarily assess antitumor activity, pharmacodynamics, and immunologic correlates.” EX1009, 3167, Abstract. More

specifically, “[t]he primary objectives were to characterize the safety and tolerability of a single dose of MDX-1106 [nivolumab] in patients with selected malignancies and to determine the maximum-tolerated dose (MTD) and pharmacokinetics.” EX1009, 3168. Brahmer’s study only included 39 patients, many of whom received only a single dose. EX1009, 3169, Table 2. All dosing was weight-based: “[s]equential cohorts of six patients received a 60-minute intravenous infusion of MDX-1106 [nivolumab] at 0.3, 1, 3, or 10 mg/kg....” EX1009, 3168. Patients with continued clinical benefit could receive additional doses. *Id.* In the study, only 12 out of 39 patients ended up receiving multiple doses. *Id.* at 3169, Table 2.

Amgen points to no evidence that Brahmer considered the impact of body weight. Amgen states that Brahmer shows that “nivolumab is ‘dose-independent’ over a wide range of doses.” Pet, 32. But that does not provide information about how the patient’s body weight impacted the properties of the antibody. Furthermore, Brahmer did not report that the efficacy of nivolumab was dose independent. Instead, the “dose-independent” result was based on testing receptor occupancy for circulating blood cells not found at the tumor site. EX1009, 3171. The connection between this in vitro assay and efficacy was unknown. According to Brahmer, “[i]t [was] unknown whether these findings in circulating lymphocytes reflect PD-1 occupancy on lymphocytes in the tumor, secondary lymphoid organs, and/or tissues.” EX1009, 3171.

Importantly, Brahmer reported no study of the effect that body weight had on the PK or PD of nivolumab. In Figure 4A, for example, Brahmer reports the “PD-1 occupancy on circulating CD3+ T cells after one infusion of MDX-1106” for single patients each receiving 0.3, 1, or 3 mg/kg, and for 10 patients receiving 10 mg/kg. EX1009, 3173. Serum concentrations of antibody were also reported. *Id.* These data do not show the impact of body weight on these characteristics. In fact, Brahmer reports no body weights from which a POSA could attempt to understand the impact of body weight on PK and PD. Amgen points to no data about that impact.

Topalian also reports the results of a Phase 1 clinical trial of nivolumab, this time with 296 patients. EX1011, 2443. “Cohorts of three to six patients per dose level were enrolled sequentially at doses of 1.0, 3.0, or 10.0 mg per kilogram of body weight.” EX1011, 2444. Like for Brahmer, Amgen points to nothing in the Topalian reference about the effect of body weight on PK or PD for nivolumab. Topalian reports that “[t]he pharmacokinetics of the antibody were linear, with a dose-proportional increase in the peak concentration and area under the curve” for 35 patients but does not report their body weights or determine whether body weight has an effect. EX1011, 2449. Topalian tested receptor occupancy on circulating cells, as in Brahmer, which Brahmer describes as having an unknown relationship with effect at the tumor site. EX1011, 2449; EX1009, 3171.

Finally, Amgen suggests in its Petition that selecting a flat dose of 240 mg nivolumab is as simple as multiplying the weight-based dose of 3 mg/kg by an average weight of 80 kg. But without information on the impact of body weight on the PK and PD, the POSA would not make and rely on that calculation. Amgen states that Wang proposes such a calculation for determining flat doses for treating patients. Pet., 23. But that is incorrect. Wang describes that calculation as part of setting up a mathematical simulation that relied on detailed information on the effect of body weight on PK for several well-studied antibodies with published population PK models. EX1008, 1014. Notably, the result of that simulation was that weight-based dosing *was better for some antibodies and flat dosing was better for others*. EX1008, 1012.

In any event, as described above, the recommendation for Phase 3 protocols was to base the dose on study of the impact of body weight. EX1008, 1023-24. That information about nivolumab is completely missing from Amgen's Grounds. Amgen has failed to show a motivation to modify NCT-505 or Postow to substitute in a flat dose.

3. Amgen's Arguments on Flat Dosing Improperly Ignore Wang's Focus on First-in-Human Testing

Amgen argues that flat dosing is the "approach of choice" for monoclonal antibodies, suggesting that the POSA would have known that flat dosing was suitable

for treating patients with nivolumab. But that ignores the fact that the Phase 3 regimen in NCT-505, the matching combination treatment regimen in Postow, and even the Phase 1 regimens in Brahmer and Topalian all used weight-based dosing. Flat dosing can hardly be considered the “approach of choice” for nivolumab to a POSA as of the priority date, and it certainly does not support Amgen’s argument that flat dosing would have been the “approach of choice” for the anti-PD-1 monotherapy step in the specific dosing regimens of the challenged claims.

In fact, Wang recommends a different course. First, as described above, the POSA would base any modification to the protocol in NCT-505 on information about the impact of body weight on PK and PD. And second, Wang’s recommendation to use flat dosing is only for first-in-human (FIH) studies, meaning the initial clinical studies to test doses. Wang “recommend[s] using fixed dosing in first-in-human (FIH) adult studies because it offers other advantages. When sufficient data become available, a full assessment of body size effect on PK/PD should be conducted to determine the optimal dosing approach for phase 3 trials.” EX1008, 1012. Again, the purpose of the first-in-human studies is to gather information about various doses. Phase 3 testing, by contrast, is done to assess safety and efficacy of the dosing protocols intended for treatment, protocols that account for the impact of body weight on PK and PD. The decision to use weight-based or flat dosing at the FIH stage is, in fact, to gather information about PK and PD.

Unlike the situation for FIH studies, by the time phase 1 and/or phase 2 studies have been completed, data become available to evaluate the effect of body size on drug exposure, PD, or efficacy and safety. A full population PK and PD analysis should be conducted, including covariate evaluation. If body size is identified as a covariate of PK or PD parameters, population and individual performances of both dosing approaches should be evaluated as described in this article. If fixed dosing is better or 2 dosing approaches are similar, fixed dosing should be used for phase 3 studies. If body size-based dosing provides significantly less variability in PK and PD, further evaluation should be conducted using available safety and efficacy data.

EX1008, 1023. Thus, Wang does not recommend changing a Phase 3 protocol, like the one in NCT-505 and also reported in Postow, in the absence of information about the effect of body weight—information Amgen has not provided. Similarly, Bai recommends “that fixed dosing should be considered as the first option in FIH studies of mAbs, when there is no prior knowledge of the body weight effect on pharmacokinetics in human adults, with the intent to assess the effect via thorough analyses of the generated clinical data.” EX1034, 132-33. These recommendations say nothing about modifying Phase 3 protocols, and no POSA would make that modification in the absence of information on the impact of body weight. EX2022, ¶39.

C. Amgen Fails to Address the Claims as a Whole

Third, the POSA would not have been motivated to change *only* the anti-PD-1 antibody monotherapy part of the NCT-505 regimen, while leaving the combination treatment alone. Indeed, that suggestion directly contradicts Amgen's arguments that a POSA would have implemented flat dosing because it was the "approach of choice." Amgen fails to consider the claims as whole, ignoring the impact of the combined administration of anti-PD-1 and anti-CTLA-4 antibodies.

The claims of the '113 Patent, taken as a whole, include administering the combination of anti-PD-1 and anti-CTLA-4 antibodies for multiple rounds, followed by the administration of anti-PD-1 antibodies. Both the anti-PD-1 and anti-CTLA-4 antibodies are checkpoint inhibitors that function by blocking immune signaling pathways to alter a patient's immune response. As a result, the POSA would have understood 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 both the dose and frequency a POSA would have selected. 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. EX2022, ¶66. And that

knowledge would have influenced a POSA's decision-making at the time—it is a consideration a POSA would not have ignored. But Amgen does ignore it. Amgen never addresses these considerations because it focuses on each “part” of the claims in isolation.

Amgen's Petition fails to provide any explanation why one would be motivated to modify the weight-based dosages of anti-PD-1 antibody to include a flat dose only for the second part of the regimen, as the claims require. According to Amgen, a POSA would have allegedly used the **combination dose** from the anti-LAG-3 trial to change the anti-PD-1 **monotherapy dose** without also changing the anti-PD-1/CTLA-4 **combination dose**. Amgen points to no prior art that suggests such a protocol, with an anti-PD-1 antibody administered sometimes at a weight-based dose and sometimes at a flat dose. In fact, such a protocol is contrary to Amgen's argument that a flat dose was somehow already known to be superior to a weight-based dose for anti-PD-1 antibodies. Pet., 3, 21-23. Likewise, Amgen's Petition never explains why weight-based dosing would have still been implemented in the anti-PD-1/CTLA-4 antibody combination part of the claimed regimen.

On this critical issue of why the anti-LAG-3/PD-1 antibody test design would be used to modify a monotherapy dose but not a combination dose for the anti-PD-1/CTLA-4 combination, Amgen again relies not on printed prior art, but on conclusory expert testimony. Dr. Hanks simply says that, for the combination dose:

POSAs would have also recognized the practical benefits (such as greater convenience and streamlined protocols) of administering both ipilimumab and nivolumab according to a single dosage scheme, as opposed to administering ipilimumab via a weight-based dose and nivolumab via a flat dose.

EX1003, ¶86. Dr. Hanks cites to nothing in support of these conclusory statements, and they run contrary to Amgen's proposed argument that flat dosing was somehow known to be the preferred substitute for weight-based dosing of anti-PD-1 antibodies, including because of "greater convenience." *See id.*; Pet., 3, 21-23. Indeed, Amgen's Petition consistently emphasizes the alleged convenience of flat dosing without ever addressing the fact that the claimed invention uses weight-based dosing for multiple rounds of treatment.

In addition, as described above, the dosing protocols are more complicated than Amgen's argument suggests. The claimed treatment regimen uses a combination of anti-CTLA-4 and anti-PD-1 antibodies for multiple rounds of treatment, and the earlier rounds of combination treatment could then affect the safety and efficacy of doses of anti-PD-1 antibody in the subsequent treatment rounds. EX2022, ¶66. Amgen never explains why its proposed modification to the second part of the regimen would be suitable after the earlier combination rounds.

Amgen's failure to consider the claims as a whole, including the weight-based administration of anti-PD-1 antibody in combination with anti-CTLA-4 antibody, undermines all of its Grounds.

IX. CONCLUSION

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

Respectfully submitted,

Date: July 10, 2025

By: /Steven D. Maslowski/
Steven D. Maslowski
USPTO Registration No. 46,905
Lead Counsel for Patent Owner

CERTIFICATE OF COMPLIANCE PURSUANT TO 37 C.F.R. § 42.24

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

The paper contains 9,021 words, excluding the parts of the paper exempted by § 42.24(a).

This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(ii) and the type style requirements of § 42.6(a)(iii)&(iv).

Respectfully submitted,

Date: July 10, 2025

By: /Steven D. Maslowski/
Steven D. Maslowski
USPTO Registration No. 46,905

Counsel for Patent Owner
Bristol-Myers Squibb Company

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE and EXHIBITS 2022 through 2025 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:

WOLF, GREENFIELD & SACKS, P.C.

Scott A. McKeown (SMcKeown-PTAB@wolfgreenfield.com)

Oona M. Johnstone (OJohnstone-PTAB@WolfGreenfield.com)

Chelsea A. Loughran (Chelsea.Loughran@WolfGreenfield.com)

Charles T. Steenburg (Charles.Steenburg@WolfGreenfield.com)

Respectfully submitted,

Date: July 10, 2025

By: /Steven D. Maslowski/

Steven D. Maslowski

USPTO Registration No. 46,905

Counsel for Patent Owner

Bristol-Myers Squibb Company