

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 REQUEST
FOR DISCRETIONARY DENIAL**

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EXHIBITS

Exhibit	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/amgen-reports-first-quarter-2025-financial-results
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

Exhibit	Description
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)
EX2022	Amgen Biosimilars, available at https://www.amgen.com/science/biosimilars

BMS respectfully submits this brief requesting discretionary denial in response to 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

BMS and its collaborators revolutionized cancer treatment by developing novel methods of treating 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 combinations of an anti-PD-1 and an anti-CTLA-4 antibody. The innovations protected by the ’320 Patent are the results of BMS’s extensive research and clinical trials programs. They include certain 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. Consistent with the guidance set forth in the Director’s

March 26, 2025 Memorandum entitled “Interim Processes for PTAB Workload Management” (“Memorandum”), there are multiple independent reasons why the Director should exercise her discretion to deny institution of Amgen’s Petition.

First, the Director should deny institution under 35 U.S.C. § 325(d) because the art and arguments relied upon in both Grounds are the same or substantially the same as those considered by the Examiner during prosecution of the ’320 Patent. Amgen contends that its art and arguments are new, and suggests the Examiner erred by not considering the possibility of an obviousness rejection. This is incorrect. All three references asserted in Ground 1 were considered or are cumulative of art that was before the Examiner. Amgen’s first and primary reference, NCT-231, was before the Examiner, and its relevant contents were reviewed in connection with an anticipation rejection. Amgen argues NCT-231 is “new” because it printed a different version of the clinical trial protocol that was evaluated by the Examiner. But any fair reading of the contents of NCT-231 shows that the versions are not materially different—thus, the information Amgen relies on in the Petition is, at the very least, cumulative. Korman, another Amgen reference, was identified by the Examiner as relevant, cited in an IDS, and discussed in the specification of the ’320 Patent. Amgen’s third reference, Wolchok, was also cited in an IDS and discussed in the specification of the ’320 Patent, and is cumulative of art identified by the Examiner as relevant. Korman and Wolchok are also asserted in Ground 2, along

with another reference, Sznol—a one paragraph abstract that by Amgen’s own admission is cumulative of Korman. All of this undoubtedly shows that step one of *Advanced Bionics* is met.

Additionally, Amgen failed to satisfy its burden at step 2 of *Advanced Bionics* because it does not explain **how** the Examiner erred in a manner material to patentability. Amgen alleges that the Examiner erred by not considering the possibility of making an obviousness rejection. That is not an error at all. Rather, it is a misapprehension of how patent applications are examined. At a minimum, that allegation lacks sufficient detail to demonstrate a material error. Amgen’s second assertion of error—that the Examiner failed to consider certain dosages of anti-PD-1 and anti-CTLA-4 antibodies in combination with NCT-231—is conclusory and belied by the record. Amgen makes little effort to point out any particular or material error by the Examiner and fails to acknowledge the extent to which the Examiner considered the art. Amgen likewise presents no new facts or evidence to support this ground that justify reconsidering art that was before the Examiner during prosecution—just previously considered art and a similarly conclusory expert declaration that repeats the contents of the Petition. Here again, Amgen’s argument lacks sufficient detail to demonstrate a material error. And, because NCT-231 is not an asserted reference for Ground 2, the Examiner’s purported error of not combining

NCT-231 with other references is inapplicable to Ground 2. Amgen does not even attempt to articulate a specific error associated with Ground 2.

Second, Amgen's unpatentability challenges are substantively weak. Ground 1 relies on improper hindsight to piece together the dosing regimen in the Ground 1 challenged claims. Specifically, Amgen provides no reason for why a POSA would have modified the dosages in NCT-231 without the benefit of any human data regarding the combination therapy being tested. Amgen's Ground 2 is facially deficient because Amgen omits at least one limitation entirely. Specifically, Amgen fails to identify the requirement for "subsequent administration" of an anti-PD-1 antibody alone following combination therapy in any combination of the asserted references. Instead, Amgen resorts to background knowledge and unasserted references for this limitation, but those efforts fall short too. These significant deficiencies in Amgen's Grounds justify discretionary denial.

Third, the Director should exercise discretion to deny institution of this IPR under 35 U.S.C. § 314(a) because the '320 Patent will be among the patents addressed between BMS and Amgen in the course of the statutorily provided Biologics and Price Competition Act ("BPCIA") proceedings that will initiate shortly after Amgen's filing of an abbreviated Biologics License Application ("aBLA") for its biosimilar copy of BMS's OPDIVO®. Amgen has repeatedly signaled to the market that it expects registrational data for its OPDIVO® biosimilar

in the second half of this year. The FDA's acceptance of Amgen's data submission will trigger the patent litigation mechanisms of the BPCIA, beginning with the Patent Dance. In the Patent Dance, the parties are required to exchange detailed contentions regarding both infringement and the validity of the '320 Patent. These exchanges are statutorily mandated by the BPCIA regardless of whether an IPR is instituted, and they culminate in the filing of a complaint in district court. Because the parties will likely begin the Patent Dance this year and it only takes 8-9 months to complete these extensive exchanges and begin litigation, an IPR based on this Petition will guarantee duplicative proceedings and waste PTO resources. And the Patent Dance will involve additional patents not challenged by Amgen in IPRs. Thus, BPCIA proceedings will go forward regardless of institution here. Put simply, there is no scenario in which a favorable outcome for Amgen here will avoid BPCIA litigation.

Finally, additional relevant considerations identified in the Memorandum support discretionary denial, including how long the claims have been in force, the lack of any relevant change in law, and the extent of Amgen's reliance on expert testimony.

For all these reasons, the Director should exercise her discretion and deny institution.

II. BACKGROUND

A. Immunotherapy and BMS's Development of OPDIVO®

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. 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 acts as a brake on the immune system by downregulating T cell activity to prevent T cells from killing healthy cells. 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.

Immunotherapy is a type of treatment that functions by taking advantage of aspects of a patient's immune response to 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. By blocking the PD-1 and CTLA-4 inhibitory receptors, these antibodies are able to increase or activate an immune response. 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. EX1001, 1:57-2:25.

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. EX2003; EX2004.

B. 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.

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 subsequently 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 “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, followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.” EX1001, cl. 5.

Both Claims 1 and 5 were amended during prosecution in response to an anticipation rejection based on a 2017 version of NCT01024231 as exemplified by Ascierto. EX1002, 44-46 (August 2, 2017 response amending then claims 14 and 28); *id.* at 192-93 (May 2, 2017 Office Action). In the remarks accompanying the claim amendments, BMS directed the Examiner to a different version of the NCT01024231 protocol that was available as of April 30, 2012, and explained that neither that version of NCT01024231 nor Ascierto disclose the specific dosage combinations and dosage schedules of the amended claims. *Id.* at 51-53. On August 24, 2017, after reviewing this history and conducting another search of the prior art

(*id.* at 37-41), the Examiner issued a notice of allowance. *Id.* at 28-34. On November 21, 2017, BMS submitted another IDS that cited an even earlier version of the NCT01024231 protocol that included the same dosage cohorts as the 2012 version. *Id.* at 17. The Examiner subsequently issued a communication indicating that “Applicant’s IDS filed on 11/2[1]/2017 is acknowledged and has been considered.” *Id.* at 14. The ’320 Patent issued on January 2, 2018. *Id.* at 12.

C. 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.

D. Amgen's Petition

Amgen filed its Petition on February 28, 2025 along with two other petitions (IPR2025-00602 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 combinations of references and different technical experts, the patents challenged in

the three 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 litigation.

The Petition asserts two grounds for unpatentability. Ground 1 challenges the patentability of Claims 1-4, 6-12, and 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, and 18-22 on obviousness grounds in view of a combination of three references, Korman, Wolchok, and Sznol. *Id.* BMS will discuss the details of the asserted references in its POPR.

III. DISCRETIONARY DENIAL IS APPROPRIATE UNDER SECTION 325(d)

The Director should exercise her discretion to deny institution under Section 325(d) because the Petition presents art and arguments that were already considered by the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential). Despite this undeniable fact, Amgen submits that “[n]one of the prior art references applied in the two Grounds of this Petition were analyzed or considered against the challenged claims.” Pet., 11. That statement is incorrect. The art and arguments in the Petition are not new. Amgen’s inability to present new information or identify any material error in the examination warrants discretionary denial.

A. The Art Relied Upon in the Petition is the Same or Cumulative of Art Presented and Considered During Prosecution (*Advanced Bionics* Step 1, *Becton, Dickinson* Factors (a), (b), (d))

The art and arguments presented in the Petition were considered by the Examiner and are cumulative of the art evaluated during prosecution. The first step of the *Advanced Bionics* test is met. *Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (“whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office”); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential as to § III.C.5); *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 3 (P.T.A.B. May 19, 2025).

1. The Examiner Evaluated the Relevant Contents in NCT-231—It is Not New

The clinical trial protocol described in NCT-231 was considered and analyzed by the Examiner during prosecution. Indeed, multiple claims were rejected as anticipated by a later version of the protocol during prosecution (EX1002, 192-93), and then amended in the process of overcoming that rejection. EX1002, 44-50. Amgen argues that ***the version*** of the NCT-231 protocol relied on in the Petition is “different” than what was considered by the Examiner and therefore “not analyzed

relative to the amended claims.” Pet., 13. Amgen’s distinction is without a difference for multiple reasons.

First, the reference Amgen refers to as NCT-231 is a printout of the clinical trial protocol for BMS’s clinical trial NCT01024231 that was available on the www.clinicaltrial.gov website as of January 5, 2010 (“the 2010 protocol”). Although the Examiner relied on a different version of the clinical trial protocol, one that was available online as of April 27, 2017 (“the 2017 protocol”), as the basis for the anticipation rejection, the record makes clear that the Examiner had access to the entire NCT01024231 clinical trial history and was aware of multiple versions of the trial protocol. The Examiner accessed the 2017 protocol through the very same ClinicalTrials.gov website that Amgen used to access the 2010 protocol:

5. Claims 14, 15, and 22-35 are rejected under pre-AIA **35 U.S.C. 102(b)** as being anticipated by the data on clinical trial NCT01024231 available at clinicaltrials.gov, as evidenced by Ascierto et al. (Seminars in Oncology, October 2010, 37(5): 508-516).

EX1002, 192. As Amgen admits, “interested members of the public were aware that such clinical trial protocols were posted to ClinicalTrials.gov and would have been familiar with the available search functions for accessing such information,” including the ability to search the trial history for earlier versions. Pet., 18. Moreover, BMS cited to the NCT01024231 trial in the specification of the ’320 Patent as support for ongoing clinical trials evaluating the combination of nivolumab

and ipilimumab, thus putting the Examiner on notice of the clinical trial in its entirety. EX1001, 38:44-50. Amgen cannot reasonably argue that interested members of the public would have been aware that earlier versions of clinical trials were available and would have been familiar with how to find them, but that an experienced Examiner who did in fact access the site and was put on notice of multiple versions was oblivious to the clinical trial history.

Second, the Examiner relied on Ascierto (published in 2010) as part of the anticipation rejection, noting that Ascierto shows that NCT01024231 was public as of 2010. EX1002, 192; EX1044. Ascierto describes the status of multiple anti-PD-1 clinical trials pending at the time, including NCT01024231, and explains that BMS's anti-PD-1 antibody was being tested for toxicity at concentrations of 0.3, 1, 3, and 10 mg/kg as of 2010:

six patients received a 60-minute IV infusion of MDX-1106 at 0.3, 1, 3, or 10 mg/kg and were evaluated for toxicities on a weekly basis for 8 weeks. Dose-limiting toxicity (DLT) was defined as a treatment-related grade

EX1044, 514.

In other words, Ascierto recites the **exact same** concentrations of anti-PD-1 antibodies Amgen points to as purportedly relevant in the 2010 protocol. See Pet., 26-29; EX1005, 4. At a minimum, the 2010 protocol is cumulative of Ascierto. The Examiner also provided a list of additional references that cite to or mention

NCT01024231, all of which were published on or before April 2012, further evidencing the Examiner's familiarity and consideration of the full scope of the NCT01024231 clinical trial protocol. EX1002, 195-96. Notably, Amgen's Petition does not address the Examiner's reliance on Ascierto or citation to the other references identified in the Office Action.

Third, Amgen cannot credibly argue that the Examiner was unaware that earlier versions of the NCT01024231 protocol existed or was unaware of other antibody concentrations that had been used for anti-PD-1 and anti-CTLA-4 antibodies. BMS overcame the anticipation rejection after directing the Examiner to a 2012 version of NCT01024231 protocol ("the 2012 protocol") that implemented different antibody concentration cohorts than the 2017 protocol. EX1002, 51-53; EX1031. BMS also provided the website to access earlier versions. EX1002, 52. (citing to clinicaltrials.gov/archive/ to identify earlier versions of the protocol). And BMS submitted an IDS submitted on November 21, 2017 in which it identified another earlier version of protocol (last updated on October 17, 2011) with the same dosing cohorts as the 2012 protocol. EX1002, 14-18; EX2009. The challenged claims issued over this extensive record after BMS amended its claims to distinguish them from both the 2012 protocol *and* Ascierto. EX1002, 53 ("Therefore, neither NCT01024231, available on April 30, 2012, *nor* Ascierto anticipates amended claim 14 or 28." (emphasis added)). Amgen's recitation of the prosecution history

is silent as to Ascierto and argues that the Examiner allowed the claims to issue “without further analysis” because no new rejections were entered. Even accepting Amgen’s characterization as true (which it is not¹), it does not change the fact that the information in the NCT-231 protocol was addressed in prosecution.

Amgen nonetheless argues that the 2010 protocol should be treated as though it is brand new art based on two dosing cohorts (**Cohort 2**: 0.3 mg/kg anti-PD-1 + 10 mg/kg anti-CTLA-4; and **Cohort 3**: 1 mg/kg anti-PD-1 + 10 mg/kg anti-CTLA-4). Pet., 13. But neither of these allegedly “different intervention cohorts” are claimed in the ’320 Patent. Moreover, Amgen does not explain what is materially different about Cohorts 1 and 2 of the 2010 protocol and the information considered during prosecution.

In fact, Amgen does not appear to consider the differences material to patentability at all. In Ground 1, Amgen never relies on the “precise substance of the dosing cohorts,” from either Cohort 2 or Cohort 3 that it argues make the 2010 protocol new. Pet., 13. In its claim chart, which is presumably intended to illustrate where the claimed “concentration options” can be found in the asserted references,

¹ The Examiner reviewed BMS’s response to the Office Action, conducted an additional search of the art, reviewed references cited in subsequent IDSs, and then permitted the ’320 Patent to issue. EX1002, 13-14, 30-37.

Amgen never cites to Cohort 2 of the 2010 protocol. Pet., 25-29. Amgen cites to Cohort 2 once in Ground 1, but only for the anti-PD-1 dosage. Pet., 37. That same dosage was disclosed in Cohort 1 of the 2012 protocol that was considered by the Examiner. EX1031, 4. It is not new or materially different. Amgen cites to Cohort 3 of the 2010 protocol once in its claim chart, but again only refers to the concentration of the anti-PD-1 antibody in Cohort 3, not the precise combination of dosages it argues makes the 2010 protocol materially different from other versions. Pet., 27, 35.

As shown in the chart below, both of the anti-PD-1 antibody concentrations Amgen actually relies on from Cohorts 2 and 3 of the 2010 protocol (0.3 mg/kg (green) and 1 mg/kg (purple)) were disclosed in the 2012 protocol (EX1033, 4) that was considered by the Examiner (and disclosed in Korman as Amgen points out). Pet., 25-27. Notably, Amgen does not argue these two “new” cohorts factored into any error by the Examiner, further indicating that they are not materially different from the information considered by the Examiner.

Cohort	2010 Protocol (EX1005) Asserted by Amgen	2012 Protocol (EX1031) Presented by BMS
1	0.3 mg/kg PD-1 , 3 mg/kg CTLA-4	0.3 mg/kg PD-1 , 3 mg/kg CTLA-4
2	0.3 mg/kg PD-1 , 10 mg/kg CTLA-4	1 mg/kg PD-1 , 3 mg/kg CTLA-4
3	1 mg/kg PD-1 , 10 mg/kg CTLA-4	3 mg/kg PD-1, 3 mg/kg CTLA-4

4	3 mg/kg PD-1, 10 mg/kg CTLA-4	3 mg/kg PD-1, 10 mg/kg CTLA-4
5	10 mg/kg PD-1, 10 mg/kg CTLA-4	10 mg/kg PD-1, 10 mg/kg CTLA-4

Thus, even if it could be argued that the 2010 protocol is a new reference, Amgen's own arguments show the so-called "different intervention cohorts" are not materially different from and are cumulative of the art the Examiner considered. At bottom, Amgen printed out a nearly identical trial protocol with a different date and referred to specific combinations of dosages that are not in the claims and that Amgen never relies on again to misleadingly argue that the Examiner did not consider the reference. The PTAB should reject such gamesmanship.

Because the Petition demonstrates there is no material difference between the 2010 protocol and the multiple other versions of the NCT01024231 protocol that were expressly presented, evaluated and discussed in prosecution, there is no plausible basis on which the 2010 protocol can be viewed as "new." Likewise, the mere fact that the Examiner did not issue an obviousness rejection is not enough to consider Amgen's Ground 1 combination of references "entirely new." Pet., 13; *see Janssen Biotech, Inc., v. United States*, IPR2021-01484, Paper 10 at 29-30 (P.T.A.B. Mar. 2, 2022) (denying institution under Section 325(d) where the examiner, who was clearly familiar with the art, only issued an anticipation rejection and not an

obviousness one). As explained below, Korman and Wolchok were also before and well-known to the Examiner.

2. The Examiner Knew of and Considered Korman

Amgen contends that Korman was cited in an IDS, but never “analyzed, discussed, or applied.” Even assuming for the sake of argument that Amgen is correct, citation in an IDS is sufficient to satisfy the first step of *Advanced Bionics. Ecto World*, IPR2024-01280, Paper 13 at 4 (holding that “[b]ecause the references that Petitioner asserts in this proceeding were provided on the applicant’s IDS, the Board correctly determined that the references were previously presented to the Office.”). But Amgen is not correct. Korman was expressly addressed by the Examiner during prosecution. In the Office Action dated May 2, 2017, the Examiner provided a list of references that were identified because “they are deemed to be pertinent to the present invention.” EX1002, 195. The Examiner included in that list U.S. Patent No. 9,358,289—an issued patent in the Korman family with the same specification as the Korman reference that Amgen relies on here. The Examiner characterized the ’289 Patent as claiming “methods of treating cancer comprising administering a combination of anti-CTLA4 and anti-PD-1 antibodies.” *Id.* And there can be no dispute that the Examiner’s knowledge of the Korman family goes far beyond his description because the same Examiner was also the primary examiner on all ten applications filed in the Korman family, eight of which are now

issued patents. See EX2010; EX2011; EX2012; EX2013; EX2014; EX2015; EX2016; EX2017. If that was not enough, the specification of the '320 Patent discusses Korman's disclosures at length, including by citing to U.S. Patent No. 8,008,449 (another member of the Korman family) 17 times. EX1001, 2:19-21, 14:9-18, 14:31, 14:46-48, 15:28-35, 15:49-52, 16:9-11, 17:22-26, 18:59-60, 19:6-8, 19:36-38, 26:16-19, 28:50-52, 29:46-48, 39:16-25 (describing preclinical combo therapy observations in Korman), 44:50-51, and 69:35. This is in addition to the multiple versions cited in IDSs. EX1002, 15 (US23), 275 (1G), 276 (citing EX1006 at 2O). Thus, Korman was not merely cited in an IDS—Korman was repeatedly discussed and well-known to the Examiner. Amgen's complete failure to acknowledge the many citations to and discussion of the Korman disclosures in both the prosecution history and '320 Patent specification justify discretionary denial.

3. Wolchok was Disclosed to the Examiner and is Cumulative of Art Cited by the Examiner

As it did with Korman, Amgen downplays the extent to which Wolchok was addressed during prosecution, alleging that it too was merely cited in an IDS, but "never analyzed, discussed, or applied." Pet., 12. Again, citation on an IDS is sufficient to satisfy the first step of *Advanced Bionics. Ecto World*, IPR2024-01280, Paper 13 at 4. And here too, Wolchok was not just cited on an IDS. The specification

of the '320 Patent discusses Wolchok and expressly calls out the same dosage information relied on in both Grounds in the Petition:

Specification of the '320 Patent	Petition
“[E]xposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy has demonstrated increasing activity with increase in dose in a phase 2 trial (Wolchok et al., 2010).” EX1001, 42:52-57.	Wolchok describes the results of a Phase II, randomized, double-blind clinical trial on anti-CTLA-4 antibody therapy (ipilimumab monotherapy) in patients with pretreated advanced melanoma. EX1007, 155. Wolchok discloses the treatment arm of this study as receiving “a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months.” Pet., 20.

Thus, BMS did not merely cite to Wolchok on an IDS—BMS highlighted in the dose information that Amgen contends is relevant to patentability in its specification and directed the Examiner to Wolchok. EX1001, 42:52-57. Discretionary denial should be exercised in cases, such as this, where a Patent Owner affirmatively goes out of its way not just to cite the prior art for the Examiner, but expressly describe its contents thereby giving notice to the Examiner of its potential relevance. *See Helena Labs. Corp. v. Sebia*, IPR2024-00801, Paper 10 at 9-10 (P.T.A.B. Oct. 23, 2024) (finding prior art reference discussed in specification of challenged patent and cited on IDS to be previously presented); *Advanced Bionics*, IPR2019-01469, Paper 6 at 9 (“[The *Becton Dickson*] framework reflects a

commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.”).

Wolchok is also cumulative of other references considered by the Examiner. For example, Sharma, one of the references highlighted by the Examiner in the May 2, 2017 Office Action, describes the study in Wolchok: “In one study, patients with metastatic melanoma received different doses of ipilimumab (*0.3, 3 or 10 mg kg⁻¹*), and the results suggested an increase in response rates with higher doses³³... Ipilimumab was given *four times at 3 mg kg⁻¹ (one dose every 3 weeks)*, and patients with a documented clinical benefit could receive additional doses (termed ‘maintenance–reinduction’ doses).” EX2018, 4. There is nothing new in Wolchok material to the patentability of the challenged claims.

4. Sznol is Cumulative

Sznol, the lone reference that Amgen accurately characterizes as not being identified on an IDS or addressed by the Examiner, is also cumulative of the art and arguments considered during prosecution. Sznol describes preliminary observations from a Phase 1 trial, in which a handful of patients received “[e]scalation of biweekly [anti-PD-1 antibody] dosing at 1, 3, or 10 mg/kg IV.” EX1009, 4. As Amgen stated in its Petition, the limited details in Sznol’s single paragraph abstract are found in Korman. EX1009, 4. For example, Korman states with respect to treatment with an anti-PD-1 antibody:

For example dosages can be 0.3 mg/kg body weight, **1 mg/kg** body weight, **3 mg/kg** body weight, 5 mg/kg body weight or **10 mg/kg body** weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months.

EX1006 at 55; *see* Pet., 58 (“Korman also discloses ***bi-weekly dosing*** for anti-PD-1.”), Pet., 55 (“Korman ... provided explicit dosing disclosures for both anti-PD-1, anti-CTLA-4, and their concurrent use.”).

Additionally, Ascierto, a reference relied on by the Examiner, discusses clinical trials for anti-PD-1 monotherapy, including the trial described in Sznol, and cites to Sznol as support. EX1044, 515-16 (“A similar phase I trial was conducted on 106 patients with metastatic disease including melanoma, CRC, NSCLC, HRPC, and RCC.⁴⁴ Again, the MTD was not found and the dose of 10 mg/kg was well tolerated with fewer irAEs.”) (citing Sznol as reference 44). Sharma, identified by the Examiner as citing or mentioning NCT01024231, also describes and cites to Sznol. EX2018, 5 (citing Sznol as reference 37). Sznol’s contents were disclosed in and are plainly cumulative of the art that was before the Examiner. There is nothing new in Sznol material to the patentability of the challenged claims.

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BMS did the right thing. It cited art in the specification of the '320 Patent and ensured it was all before the Examiner.² The Examiner here being the same person who was responsible for handling much of BMS's PD-1 portfolio, including the Korman family that Amgen asserted in both Grounds of its Petition. Amgen's suggestion that the asserted art is somehow new to or unappreciated by the Examiner is incredulous and should be flatly rejected.

**B. Amgen Fails to Identify Any Material Error by the Examiner
(*Advanced Bionics Step 2, Becton, Dickinson Factors (c), (e), (f)*)**

Likely because it takes the untenable position that the asserted references are new, Amgen does not argue that the Examiner made a substantive error during Examination. Amgen instead raises two purported errors of omission, neither of which meet the threshold for material error at least because (1) Amgen failed to accurately address the extent to which the art relied on in the Petition was evaluated during prosecution, (2) Amgen failed to identify any specific teachings that impact the patentability of the challenged claims or address how the Examiner purportedly erred in his evaluation of the art, and (3) Amgen failed to present any new evidence

² This case is not like *Ecto World*, where the applicant cited to over 1,000 references during prosecution. Here, BMS cited a total of 51 patent documents and 52 non-patent references. EX1002, 15-16, 57, 65, 223, 275-280.

that warrants reconsideration of previously considered art and arguments. *See Ecto World*, IPR2024-01280, Paper 13 at 5-6 (explaining the proper bases for finding material error). As a result, Amgen cannot carry its burden to show material error. *Ocado Grp. PLC v. AutoStore Tech. AS*, IPR2021-00412, Paper 9 at 38 (P.T.A.B. July 21, 2021) (“[N]either Petitioner nor [its expert] present any argument or persuasive evidence that there was any material error by the Office. This is a required element of Petitioner’s burden to overcome our exercise of discretionary denial under Section 325(d).”).

Amgen first argues the Examiner erred by issuing an anticipation rejection rather than an obviousness rejection. Pet., 14. Amgen assumes that the “Examiner never considered whether the amended claims would have been obvious in view of earlier versions of NCT-231...or any other prior art disclosures...” because the Examiner only issued an anticipation rejection. *Id.* at 13. That speculative argument contravenes fundamental principles of patent examination. *See* MPEP (9th ed. Rev. 01.2024) § 707.05 (“The examiner must consider all the prior art references (***alone and in combination***) cited in the application or reexamination, including those cited by the applicant in a properly submitted Information Disclosure Statement.”); *id.* at § 2103 (“Under the principles of compact prosecution, ***each claim should be reviewed for compliance with every statutory requirement for patentability*** in the initial review of the application, even if one or more claims are found to be deficient

with respect to some statutory requirement. Thus, *examiners should state all reasons and bases for rejecting claims in the first Office action.*”); *id.* at § 1302.01 (“When an application is apparently ready for allowance, it should be *reviewed by the examiner to make certain that the whole application meets all formal and substantive (i.e., statutory) requirements* and that the language of the claims is enabled by, and finds adequate descriptive support in, the application disclosure as originally filed.”) (emphases added).

Amgen presents no evidence indicating that the Examiner did not read or understand the art and disclosures in the specification. On the contrary, the Examiner independently identified multiple references deemed pertinent to the present invention and described their contents. EX1002, 195-96. As explained above, this Examiner has a long history with this technology, patent family, and the asserted Korman reference. *See, e.g.*, EX2010-EX2017; EX2019. Amgen’s assertion that the Examiner erred solely because he rejected the claims as anticipated and not as obvious is not credible. It is further undermined by Amgen’s inability to identify any material difference between the 2010 protocol and the versions of NCT01024231, including the 2012 protocol, that were discussed and considered during examination.

Next, Amgen argues the Examiner erred by not discussing the anti-PD-1 and anti-CTLA-4 antibody concentrations disclosed in Korman, Wolchok, and Sznol, in

combination with the NCT-231 protocol format. Pet., 14-15 (“[This Petition] details the claimed concentration disclosures already available to a POSA via the prior art, and it provides the reason a POSA would have combined these concentrations with the NCT-231 protocol format”). Importantly, this alleged error is cabined solely to Ground 1—NCT-231 is not relied on in Ground 2. Aside from allegedly erring by not issuing an obviousness rejection, Amgen identifies no other possible error connected to the combination of references asserted in Ground 2. By definition, Amgen failed to carry its burden to show Examiner error with respect to Ground 2. *See Intel Corp. v. InterDigital, Inc.*, IPR2024-01441, Paper 13 at 18 (P.T.A.B. Apr. 1, 2025).

Regardless and as mentioned above, BMS disclosed prior art antibody concentrations in the specification of the ’320 Patent with citations to the very references relied on in Ground 1. In the Office Action, the Examiner accurately described the dosing schedule and antibody concentrations in the April 2017 version of NCT01024231:

In the instant claims, the antibody doses are 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg; in the NCT01024231 trial, the doses are 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg.
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EX1002, 193. The Examiner also independently identified multiple prior art references that discussed early versions NCT01024231, such as Ascierto. *Id.* at

195-96. The Examiner considered the information in the prior art, was fully aware of the NCT01024231 clinical protocol, and properly allowed the claims over that information.

The Examiner was not required to catalog antibody concentrations, nor does the Examiner's silence amount to a material error, particularly where, as here, both the Examiner and BMS discussed and appreciated the scope of the art. *See, e.g., Ivantis, Inc. v. Sight Sci., Inc.*, IPR2022-01540, Paper 14 at 14 (P.T.A.B. Mar. 22, 2023) ("To the extent Petitioner equates the examiner's silence in discussing relevant prior art to a material error, we are not persuaded."); *Fitesa Simpsonville, Inc. v. Proctor & Gamble Co.*, IPR2023-01451, Paper 11 at 21 (P.T.A.B. Mar. 20, 2024) ("Petitioner must demonstrate that the Examiner erred in the evaluation of the prior art, for example, by showing that the Examiner misapprehended or overlooked specific teachings in the relevant prior art"). Amgen's purported error is conclusory and without merit.

Furthermore, Amgen's unsupported assertion that its Petition fills some missing gap based on the combination of NCT-231, Korman, and Wolchok is insufficient to establish a material error related to patentability because Amgen does not rely on new information, nor does it articulate ***specific teachings*** in the asserted art that impact patentability. As mentioned above, Amgen's only argument for error focuses on precise dosing cohorts in the 2010 protocol that Amgen does not even

appear to consider material to patentability. There are no new facts or evidence in Amgen’s Petition that warrant reconsideration of the prior art. Amgen relies on an expert declaration, but, as exemplified in the chart below, that declaration largely parrots the content of the Petition and is entitled to no weight. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 12 at 5 (P.T.A.B. Feb. 10, 2023) (Director Review: Feb. 10, 2023) (precedential) (“the declaration copies, word-for-word, Petitioner’s conclusory assertions ... as though they are facts, rather than setting forth facts and evidence in support of Petitioner’s assertions”); *Halliburton Energy Serv., Inc. v. Schlumberger Tech. Corp.*, IPR2017-02072, Paper 11 at 7 (P.T.A.B. Apr. 12, 2018) (decision denying institution stating, “Mr. Todd’s testimony, which, again, merely parrots the conclusory statement ... is entitled to little, if any, weight”); *Free-Flow Packaging Int’l, Inc. v. Automated Packaging Sys., Inc.*, IPR2016-00447, Paper 7 at 10 (P.T.A.B. June 22, 2016) (“Dr. Kimmel’s declaration...does nothing more than parrot the language of the Petition word for word”); 37 C.F.R. § 42.65(a).

Amgen’s Petition	Dr. Antony Declaration
“First, NCT-231 relied upon in this Petition presents different intervention cohorts at different concentrations of dosing than the April 30, 2012 version (Version 58) of this protocol considered by the Examiner. <i>Compare</i> EX1005, 4, <i>with</i> EX1031, 4-5 (Cohorts 2 and 3 from NCT-231 (EX1005, 4) studied 0.3	“As discussed below, the NCT-231 reference relied upon in this Petition presents different intervention cohorts at different concentrations of dosing than the April 30, 2012 version (Version 58) of this protocol considered by the Examiner. <i>Compare</i> EX1005, 4, <i>with</i> EX1031, 4-5 (Cohorts 2 and 3 from

Amgen’s Petition	Dr. Antony Declaration
mg/kg anti-PD-1; 10 mg/kg anti-CTLA and 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4, respectively. These two cohorts were not included in the April 27, 2017 version of NCT-231 (EX1031, 4-5). Similarly, Cohorts 2, 3, 6, and 7 from the April 27, 2017 version to NCT-231 (EX1031, 4-5) were not included in NCT-231 (EX1005, 4)). Antony, ¶ 69.” Pet., 13.	NCT-231 (EX1005, 4) studied 0.3 mg/kg anti-PD-1; 10 mg/kg anti-CTLA and 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4, respectively. These two cohorts were not included in the April 27, 2017 version of NCT-231 (EX1031, 4-5). Similarly, Cohorts 2, 3, 6, and 7 from the April 27, 2017 version to NCT-231 (EX1031, 4-5) were not included in NCT-231 (EX1005, 4)).” EX1003, ¶ 69.

Amgen cannot cure these deficiencies by falling back on the purported strength of its Petition (which, as will be further explained in the POPR, is not strong at all). At a minimum, Amgen was required to establish that its asserted references are “not substantially the same as prior art the Examiner applied, and includes specific teachings that ‘impact patentability of the challenged claims.’” *Ecto World*, IPR2024-01280, Paper 13 at 5; *id.* at FN2 (“Petitioner’s suggestion that the Board should have scoured the Petition to cobble together an argument under the second part of *Advanced Bionics* improperly shifts Petitioner’s burden to demonstrate material error onto the Board.”). Because Amgen (1) misrepresented the scope of the art and arguments considered by the Examiner under step 1 of *Advanced Bionics*, (2) did not legitimately attempt to satisfy step 2 of the *Advanced Bionics* test for the Ground 2 claims, and (3) failed to identify a material error or new information that would lead to a different conclusion on the patentability for any challenged claim,

the Director should exercise her discretion and deny institution pursuant to Section 325(d).

C. Amgen was Required to Address Foreseeable Arguments in its Petition—the Memorandum Did Not Change That

While the Memorandum provides for separate briefing and consideration of discretionary denial issues, the Memorandum should not open the door for Amgen to present arguments regarding Section 325(d) that were not included in the Petition. The Petition was filed prior to the Memorandum's issuance. BMS's arguments regarding Section 325(d)—which focus almost entirely on the content in the prosecution history—were foreseeable. And Amgen should have addressed all foreseeable Section 325(d) issues in its Petition.

IV. THE MERITS OF THE PETITION ARE WEAK AND WEIGH IN FAVOR OF DISCRETIONARY DENIAL

As outlined in the Memorandum, the strength of the merits of a petition is relevant when considering whether to deny institution. Here, both grounds of the Petition are fatally flawed. Amgen's Ground 1 is the product of improper hindsight, while Amgen's Ground 2 omits a key limitation of the claim. The weakness of Amgen's Petition further supports discretionary denial.

A. Amgen's Ground 1 Relies on Improper Hindsight

Amgen's Ground 1 attempt to cobble together antibody dosages from art that was clearly considered during prosecution is the epitome of improper hindsight

reconstruction. The combination therapy dosing regimens in the Ground 1 claims were novel, untested, and unprecedented in the field before May 15, 2012. BMS's clinical trials, including NCT-231, were the first of their kind. EX2018, 9-10 (“Combination therapies are currently being tested *in a few ongoing clinical trials* including: ...ipilimumab plus a PD1-targeted antibody in a trial in patients with metastatic melanoma (NCT01024231).”). They are not obvious variations on known dosing as the Petition suggests.

No prior art version of NCT-231 discloses 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 identify 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. That is not how iterative dosing or dose escalation studies work.

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. But none of the asserted references contain such information. NCT-231 is a Phase 1 dose-escalation study for the

combination of anti-PD-1 and anti-CTLA-4 antibodies. EX1005. Its stated purpose was to “assess the safety and tolerability of treatment with [anti-PD-1 antibody] in combination with [anti-CTLA-4 antibody].” *Id.* at 4. Its primary outcome measure was to identify the maximum tolerated dose for the antibody combination (because it was unknown at that time). *Id.* at 5. As of May 15, 2012, NCT-231 (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. 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.

Because Amgen fails to provide a credible reason for why a POSA would have modified the references asserted in Ground 1 and relied on impermissible hindsight to reconstruct the Ground 1 claims, it cannot meet its burden to show a reasonable likelihood that the Ground 1 claims are unpatentable. For this reason, discretionary denial is warranted.

B. Amgen’s Ground 2 is Missing a Key Limitation

Every claim challenged under Ground 2 requires treatment according to a particular schedule—the patient is treated with 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 asserted 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 administration limitation in any of Korman, Wolchok, or Sznol. 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.

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. 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 (Fed. Cir. Dec. 11, 2024) at *1-2 (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 autoimmunity³ (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. Likewise, Amgen fails to address why a POSA would have been motivated to combine the teachings of Fife with the Ground 2 references. Amgen's entire argument in support of the "subsequently administering" limitation is literally one sentence and the Fife quote is not even about subsequent administrations of anti-PD-1 antibody alone or cancer. Even accepting Amgen's argument that Fife 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.

³ 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.

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. EX1005. NCT-231, even when combined with the Ground 2 asserted references, does not disclose the regimen in the Ground 2 claims. *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.

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 this single sentence satisfies the missing limitation. In fact, Dr. Antony repeats

verbatim the same single 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 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.	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.”). EX1003, ¶ 217.

EX1003, ¶ 217, 240; *see, e.g., Xerox Corp.*, IPR2022-00624, Paper 12 at 5 (“the declaration copies, word-for-word, Petitioner’s conclusory assertions ... as though they are facts, rather than setting forth facts and evidence in support of Petitioner’s assertions”); *Halliburton*, IPR2017-02072, Paper 11 at 7 (“Mr. Todd’s testimony, which, again, merely parrots the conclusory statement ... is entitled to little, if any, weight”); *Free-Flow*, IPR2016-00447, Paper 7 at 10 (“Dr. Kimmel’s

declaration...does nothing more than parrot the language of the Petition word for word”); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 25 (P.T.A.B. Jan. 24, 2019) (“Petitioner relies on conclusory, unsupported testimony to prove that Jang teaches this limitation or that the limitation is an obvious design choice, but such testimony is not sufficient.”); 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. For these reasons, Amgen cannot meet its burden to show a reasonably likelihood that the Ground 2 claims are unpatentable and discretionary denial is warranted.

V. AMGEN’S PATENTABILITY CHALLENGES ARE MORE APPROPRIATELY DEALT WITH THROUGH THE STATUTORILY CREATED BPCIA

Consistent with the considerations provided in the Memorandum, the Petition should also be denied because Amgen’s challenges to the ’320 Patent will be addressed in the BPCIA Patent Dance and litigation, which Congress specifically enacted as a means for resolving patent disputes that stem from the development and approval of biosimilar drugs. *See* 42 U.S.C. § 262(l). The BPCIA provides an abbreviated approval pathway for biosimilar drugs, including the OPDIVO® biosimilar that **Amgen is currently developing**. 42 U.S.C. § 262(k). This pathway

allows Amgen to submit an application, its aBLA, for approval of its antibody as a biosimilar version of OPDIVO®. In its aBLA, Amgen must show the FDA, among other things, that its product is highly similar to OPDIVO® and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency. 42 U.S.C. §§ 262(i)(2), 262(k)(2)(A)(i). If Amgen can make the requisite showings, the FDA will approve Amgen's product for marketing in the United States. 42 U.S.C. § 262(k)(7)(A).

The BPCIA also provides a structured framework for resolving patent litigation arising from the approval of the biosimilar drug, i.e., the Patent Dance. 42 U.S.C. § 262(l). The Patent Dance requires parties to exchange detailed validity and infringement contentions in an effort to narrow and focus the scope of any eventual patent litigation on only those patents and claims that are truly in dispute. 42 U.S.C. § 262(l)(3)-(6). The Patent Dance culminates with the filing of a district court complaint. In effect, Congress designed the Patent Dance to be a focusing exercise that eliminates unnecessary and superfluous litigation over claims and patents not contested between the involved parties.

Based on Amgen's public statements regarding the status of its clinical trial for its OPDIVO® biosimilar, the parties are likely to not only begin, but also complete the entirety of the Patent Dance and commence litigation prior to the issuance of a final written decision here. EX2007, 21; EX2008, 23. Thus, institution

in this proceeding will provide no efficiencies and serve only to duplicate the parties' efforts—contrary to Congress's intent in enacting both the BPCIA and the Leahy-Smith America Invents Act. Because the BPCIA was specifically created by Congress to provide an efficient mechanism for parties to narrow their patent disputes prior to engaging an adjudicative body, Amgen's patentability challenges are more appropriately dealt with through the Patent Dance in the first instance and then litigation.

VI. ADDITIONAL FACTORS ALSO SUPPORT DISCRETIONARY DENIAL

The Memorandum enumerates several other considerations the PTO considers relevant to discretionary denial. Several of these considerations weigh in favor of discretionary denial here. First, Amgen cites no change in law or precedent impacting patentability. Rather, the Petition relies on long-standing obviousness precedent. And, as explained above, Congress provided the parties with a distinct pathway intentionally designed to both facilitate the approval of Amgen's biosimilar for OPDIVO® and to provide a mechanism for parties to narrow and resolve their patent disputes. The '320 Patent issued more than seven years ago on January 2, 2018. EX1001. Its related family members were the subject of well-publicized litigation between BMS and AstraZeneca beginning in March 2022. EX2020 (providing a link to complaint); EX2021 (complaint asserting patents in Cogswell

family). Had Amgen wanted to avoid addressing the '320 Patent through the BPCIA, it could have filed its IPR much sooner—it began Phase III clinical trials of its OPDIVO® biosimilar on July 26, 2023. EX2006; *see also Irhythm Techs., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10 at 3 (P.T.A.B. Jun. 6, 2025) (exercising discretion to deny institution based on settled expectations of the parties). Amgen sells multiple biosimilar products and is a sophisticated litigant that is very familiar with the BPCIA process. EX2022. But Amgen chose to wait and now BPCIA patent proceedings are inevitable. There is no need to duplicate efforts and waste PTO resources through an IPR when the parties will be forced to address the infringement and validity of the '320 Patent independently regardless of institution here.

VII. CONCLUSION

For at least the reasons discussed here, the Director should exercise her discretion to deny institution of Amgen's request for IPR of the '320 Patent.

Respectfully submitted,

Date: June 10, 2025

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

IPR2025-00601

U.S. Patent No. 9,856,320

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 9,864 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: June 10, 2025

By: /Steven D. Maslowski/

Steven D. Maslowski

USPTO Registration No. 46,905

Counsel for Patent Owner

Bristol-Myers Squibb Company

IPR2025-00601

U.S. Patent No. 9,856,320

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL and EXHIBITS 2001 - 2022 were served on counsel of record on June 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: June 10, 2025

By: /Steven D. Maslowski/

Steven D. Maslowski

USPTO Registration No. 46,905

Counsel for Patent Owner

Bristol-Myers Squibb Company