

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY
Patent Owner.

Case No. IPR2025-00601
Patent No. 9,856,320

**PETITIONER'S OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF**

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LISTING OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 9,856,320
1002	Prosecution History of U.S. Patent No. 9,856,320
1003	Declaration of Paul A. Antony, M.D.
1004	Curriculum Vitae of Dr. Paul A. Antony
1005	NCT01024231 Version 3, Brief Title: “Dose-escalation Study of Combination PO-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted to clinicaltrials.gov: January 5, 2010).
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1008	March 25, 2011 Bristol Myers Squibb Press Release announcing Ipilimumab FDA Approval, “FDA Approves YERVOY™ (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer.”
1009	Sznol et al., Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1 PO-936558/ONO4538) in patients with advanced refractory malignancies. <i>J Clin Oncology.</i> 2010 May 20; 28(15).
1010	Fife et al., Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways.” <i>Immunol Rev.</i> 2008 Aug; 224:166–182.
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1023	European Patent Application No. 17189595.6, Amended Claims, dated October 18, 2018.
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1083	Biosimilar-Related IPR Petitions, available at: https://biologicsshq.com/stats_entry/biosimilar-related-ipr-petitions/ (accessed June 20, 2025)
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I. INTRODUCTION

Petitioner's challenges to the patentability of U.S. Patent No. 9,856,320 (the "'320 Patent") as being obvious over the prior art should be instituted as no reasonable basis exists for exercising discretion to deny the Petition. Rather, Patent Owner (PO) Bristol-Myers Squibb's request for discretionary denial should itself be denied.

PO markets Opdivo® (the brand name for nivolumab, an anti-PD-1 antibody) and has procured patents that cover Opdivo® and its use in combination with an anti-CTLA-4 antibody to treat various forms of cancer. PO's composition of matter patent expires in December 2028.

The '320 Patent at issue in this IPR expires in 2034 and does not claim the drug itself. Instead, the challenged claims recite a method of treating cancer by administering a combination anti-PD-1 plus anti-CTLA-4 therapy in various dosing formats that were already publicly disclosed in the prior art (both the claimed dosing frequency ("every X weeks, for Y doses") and amounts (mg/kg) for each antibody) or were the obvious dosing options as of the claimed priority date in view of the well-understood toxicity profiles of each antibody. Any differences between the claims of the '320 Patent and the prior art are trivial, are within the ordinary skill in the art of determining proper dosing, and do not justify extending patent protection on Opdivo® by another *six years*. Moreover, the claims of the

'320 Patent are overly broad and recite over a dozen variations on the combination therapy dosing. To prevail on unpatentability, the Petition need only demonstrate that a single variation would be obvious, but the Petition shows that all thirteen of these variations were known, disclosed, or the result of routine dosing optimization strategies discussed in the prior art. The Petition seeks to ameliorate this compounded Patent Office error in allowing these overbroad and obvious claims.

Petitioner's challenge to the '320 Patent raises legal and public policy factors that all weigh against discretionary denial. These include:

(1) clear and material Patent Office error as evidenced by the European Patent Office rejecting similar claims over similar prior art;

(2) timely filing of the Petition *before* any litigation has even commenced, let alone having a trial date set, and more than *three years before* the earliest date a biosimilar could launch in December 2028 (according to PO), and rejection of POs suggestion that a default rule exists prohibiting biosimilar developers from accessing IPR proceedings;

(3) a biosimilar manufacturer's taking efficient and predictable steps to clear the path to commercialization years before its anticipated launch by filing an IPR against a mistakenly granted follow-on patent both to eliminate the erroneously granted patent and hopefully prevent the issuance of similarly obvious claims.

Each of these factors, described below and more fully throughout this brief, compels a rejection of PO's request for discretionary denial.

First, outside of the US, PO's attempts to extend its patent protection have failed. In Europe, PO pursued several patents with dosing claims nearly identical to those challenged in the Petition. The European Patent Office ("EPO") rejected those claims citing similar references to those relied upon in the Petition. Effectively conceding their unpatentability, PO withdrew the claims entirely. This rejection and capitulating withdrawal of similar claims in Europe reveals the Patent Office's unmistakable error in allowing the challenged claims over prior art disclosing exactly what is recited in the claims. During prosecution of the '320 Patent, PO sought issuance of claims to dosing amounts and frequencies of Opdivo® that were already disclosed in clinical trial protocols involving combined anti-PD-1 and anti-CTLA-4 antibody administration. Although recognizing this fact, the Examiner mistakenly relied upon a version of a clinical trial protocol that was made publicly available only *after* the earliest claimed priority date of the pending application (even though prior art versions of the clinical trial protocol were available and should have been cited and relied upon by the Examiner). The Examiner's reliance on a later version of this clinical trial protocol allowed PO to remove the reference based on date. The Examiner then erroneously overlooked the prior art disclosures of the claimed doses and allowed the claims without

providing any explanation or rationale for the failure to cite the prior art protocols. IPR is designed to address precisely these errors and oversights and to avoid scenarios where otherwise unpatentable “inventions” stand in the way of healthy competition and unnecessarily tax the American public. *Microsoft Corp. v. ParTec Cluster Competence Center, GmbH*, IPR2025-00318, Paper 9, at 3 (PTAB Jun. 12, 2025) (denying request for discretionary denial—“Petitioner appears to show a material error by the Office and it is an appropriate use of Office resources to review the potential error.”).

Second, there is no parallel district court litigation. No infringement action has been filed, nor is it likely one would be filed for at least another year, if at all. Petitioner has not yet filed its abbreviated Biologics License Application (aBLA) and expects to do so later this year. Under the Biologics Price Competition and Innovation Act (BPCIA), this aBLA filing triggers a potential identification of patents believed to be valid and infringed (hereinafter the “Patent Exchange”) for a first wave of litigation. This voluntary Patent Exchange can take approximately ten months to complete before an infringement action under the BPCIA is filed. Once filed, the average time for a decision on the merits by the district court in BPCIA cases is 2.5-3.5 years. By contrast, a Final Written Decision in this IPR would be issued by October of 2026—likely years earlier than any resolution via the BPCIA procedures.

Ignoring this much faster timeline for resolution of an IPR, PO argues that because BPCIA litigation is expected in the future, IPRs should be discretionarily denied. IPR was provided by Congress to serve as an alternative to litigation. PO's argument cannot be accepted by the agency to avoid its statutory mandate.

Moreover, if credited, PO's argument would preclude all biosimilar manufacturers from ever securing recourse via IPRs as all biosimilar products developed to date have faced the potential for BPCIA litigation. The mere possibility of future litigation should not deprive biosimilar developers of access to IPRs to efficiently challenge clearly unpatentable claims while those developers are still in the process of preparing to file aBLAs to secure FDA approval to sell their products in the US.

Third, biosimilars are critical to the public's access to potentially less expensive options for treatment, and IPRs play a valuable role in enabling such access. More specifically, IPRs improve efficiency and reduce uncertainty in the development and advancement of biosimilars to commercialization by simplifying litigation and reducing the number of issues, and patents, if any, that need to be litigated before a biosimilar can launch. IPRs provide biosimilar developers the opportunity to identify erroneously granted patents and challenge their patentability prior to launch on a predictable timeline before an expert panel. And, as in this case, a successful challenge to obvious patent claims can help to prevent the issuance of similarly unpatentable patents. In addition, obtaining an IPR

decision invalidating a method of treatment patent, like the '320 Patent, before aBLA approval may help inform the biosimilar applicant's strategy about whether to obtain regulatory approval of an indication or dosing regimen that may be relevant to the patent or to omit that indication/dosing regimen from a carved-out label to reduce patent risk. In short, the continued availability of IPR proceedings to challenge mistakenly granted patents in advance of possible BPCIA proceedings represents the "settled expectations" of biosimilar manufacturers. And it advances the current Administration's mandate to increase access to biosimilars overall.

Petitioner, which is headquartered in the U.S. and employs over 28,000 people, is a world leader in the manufacture of protein-based therapeutics, such as antibodies, and has brought multiple innovative new products to the market. In the interest of serving more patients with life-altering medicines, Petitioner also applies its manufacturing and clinical development capabilities to bring biosimilar products to the market. To this end, Petitioner seeks to market a biosimilar of Opdivo® and is preparing for a launch of its biosimilar product in the US by as early as the expiration of the composition of matter patent in December 2028, if not sooner. Pursuing an IPR against the obvious claims of the '320 Patent is an important first step to clear the way for that product launch. As a leader in both innovative therapeutics and biosimilars, and as an active user of the patent system, Petitioner fully appreciates how the patent system can be utilized fairly and

effectively to drive innovation in this country while encouraging competition at the appropriate time. The '320 Patent was granted in error and improperly seeks to extend PO's exclusivity on Opdivo®. This is exactly the kind of patent that IPRs should address.

PO's request for discretionary denial of IPR2025-00601 against the '320 Patent should be denied.

II. BACKGROUND

The claims of the '320 Patent are directed to methods of treating cancer by administering an anti-PD-1 antibody and an anti-CTLA-4 antibody. EX1001, cls. As the '320 Patent itself discusses, both classes of these antibodies were known and had been used in cancer immunotherapy long before PO filed the application giving rise to the '320 Patent. EX1001, 1:33-2:25.

Challenged claim 1 recites a method of treating cancer by administering (1) an induction phase of anti-PD-1 and anti-CTLA-4 antibodies at various options of dose numbers, frequencies and optional dose concentrations ((a) through (m)), followed by administering the anti-PD-1 antibody alone at various options of dose numbers and frequencies, followed by administering, (2) a maintenance phase of the two antibodies again at various options of dose numbers and frequencies. EX1001, cl. 1. Challenged claim 5 recites a method of treating a human subject afflicted with cancer by administering 1 mg/kg of anti-PD-1 and 3 mg/kg of anti-

CTLA-4 together every 3 weeks for 4 doses, followed by administering the anti-PD-1 antibody alone every 2 weeks. EX1001, cl. 5.

Dependent claims in the '320 Patent specify that the anti-PD-1 antibody may be nivolumab (Opdivo®) and the anti-CTLA-4 antibody may be ipilimumab (Yervoy®). EX1001, cls. 2, 3. PO already obtained numerous patents covering Opdivo®, Yervoy®, and their methods of use in combination to treat cancer, all of which were filed long before, and will expire long before, the '320 Patent.

A. Technical Background

1. Clinical Trial History Relative To Anti-PD-1 And Anti-CTLA-4 Antibodies

Therapies involving the concurrent administration of anti-PD-1 antibodies and anti-CTLA-4 antibodies were undisputedly not new as of the claimed effective filing date of the '320 Patent (May 15, 2012). The first clinical trial for anti-CTLA-4 as a monotherapy commenced in the early 2000's and the drug was approved for administration to humans (as ipilimumab¹) in 2011, for treatment of advanced melanoma. EX1036, 4713; EX1008, 1; EX1018, 1; EX1003, ¶¶32-33, 47.

¹ The anti-CTLA-4 antibody "ipilimumab" is also known as "Yervoy," "BMS-734016," "MDX-010," and "MDX-101." EX1003, ¶46.

Similarly, clinical trials studying anti-PD-1 began as early as 2007.² EX1013, 1-2. In 2008, clinical trial NCT00730639 initiated the Phase 1 study of the anti-PD1 antibody nivolumab at *bi-weekly* dosing in subjects with advanced or recurrent malignancies. EX1014, 1, 4. Success from this trial was reported in Sznol. EX1009, 205s (“MDX-1106 [*i.e.*, nivolumab] administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.”).

By December of 2009, clinical trial NCT231 was initiated to study the *concurrent* dosing of anti-PD-1 and anti-CTLA-4 antibodies. EX1005, 4 (assessing “the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma”). NCT231 discloses administration of anti-CTLA-4 and anti-PD-1 antibodies at different concentrations and on a schedule where both drugs are administered together every three weeks for 4 doses, followed by administration of anti-PD-1 alone every 3 weeks for 4 doses, followed by a maintenance dose of both antibodies again every 12 weeks for 8 doses. EX1005, 4.

Though nomenclature varies and the specific terms “induction” and “maintenance” are not always used to describe dosing phases, many studies of anti-

² The anti-PD-1 antibody “nivolumab” is also known as “Opdivo®,” “BMS-936558,” “MDX1106-4,” and “ONO-4538.” EX1003, ¶45.

CTLA-4 and/or anti-PD-1 dating back to at least as early as 2011 utilized “induction-maintenance” dosing formats. In these dosing formats an initial (or “induction”) dose of a drug at a particular frequency, number, and concentration is administered to a patient with the goal of eliciting a therapeutic response. After that therapeutic regimen concludes, an ongoing (“maintenance”) dose is administered (often at a lower concentration and/or less frequently) in order to maintain a longer-term therapeutic effect (while avoiding potential toxicities from higher concentrations or high-frequency dosing). EX1007, 155; EX1006, 55.

In prior art studies of combination therapies involving anti-PD-1 and anti-CTLA-4, an “induction” phase of therapy can include both an initial phase of a combined therapy followed by a phase of one of the previously combined drugs alone. EX1003, ¶52; EX1005, 4; EX1039, 2518-19.

2. Toxicity Associated With Anti-CTLA-4

By May 15, 2012, two Phase 3 studies demonstrated that anti-CTLA-4 offered a benefit in overall survival for patients with advanced melanoma, leading to FDA approval. EX1008, 1; EX1018, 1. However, evidence of a unique toxicity profile emerged from these trials such that by 2012 a POSA would have known that anti-CTLA-4 treatment often induced immune-related adverse events (“irAEs”). EX1019, 34, 35 (“The cases we present demonstrate the clinical course of autoimmune hypophysitis and consequent hypopituitarism after treatment with

ipilimumab and highlight the possible role of CTLA-4 blockade in its pathogenesis.”); EX1020, 499 (Abstract); EX1021, 865 (highlighting “the kinetics of antitumor responses and the relationship to irAEs in patients receiving the CTLA-4 antibody ipilimumab”); EX1003, ¶¶53-55.

In addition, studies such as Wolchok evidenced the difficulty faced by clinical trial administrators in giving anti-CTLA-4 immunotherapy to patients for extended periods of time due to the challenging irAEs associated with that drug. For each dosage arm of the study discussed in Wolchok, only a small fraction of patients even received the maintenance dosing. EX1007, 157, Fig. 1 (“Trial profile,” showing significant participant loss in progression from induction to maintenance dosing of anti-CTLA-4); EX1003, ¶42, 56.

3. Anti-PD-1 Exhibited A More Tolerable Safety Profile.

It was also understood by 2012 that treatment with anti-PD-1 antibody therapy was comparatively *less toxic* than treatment with anti-CTLA-4 antibody therapy. EX1037, 3172 (“While both anti-PD-1 and anti-CTLA-4 therapies are associated with irAEs, as predicted by preclinical models and consistent with the physiologic roles of these molecules, these toxicities appear to be less frequent and *milder* in patients receiving anti-PD-1.”)³; EX1022, 260; EX1044, 514 (describing

³ Emphasis added, unless otherwise noted.

a “milder toxicity profile for anti-PD1 mAb as compared to that of anti-CTLA-4 mAb”); EX1042, 245 (same). This was predicted by the distinct phenotypes of Ctl4-knockout mice versus Pd1-knockout mice. EX1022, 260; EX1016, 816-18; EX1003, ¶¶42-44, 57-58.

B. PO’s Equivalent Claims in Europe Faced Stiff Rejection Over The Same Art Relied Upon in the Petition and Were Ultimately Withdrawn Prior To Oral Proceedings, Demonstrating USPTO Error.

The March 26, 2025 Interim Processes for PTAB Workload Management (“Memorandum”) counsels that the PTAB will consider “[w]hether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims.” The ’320 Patent’s European counterpart claimshave been rejected, and in one case withdrawn entirely, in Europe. The claims of the ’320 Patent should not be allowed to erroneously stand where such claims are being duly rejected and withdrawn in Europe for the benefit of overseas patients.

1. The Claims of EP Application No. 17189595.6 Overlap With Challenged Claim 1 And Were Stiffly Rejected and Then Withdrawn.

EP Application No. 17189595.6 was filed in 2017 seeking issuance of exemplary claim 1 (as amended):

An anti-PD-1 antibody for use in a method of treating a human subject afflicted with a cancer in combination with an anti-CTLA-4 antibody; comprising:

(i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 3 weeks, for 4 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 3 week for 4 doses; followed by

(ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2 to 12 weeks for 8 doses,

wherein the anti-PD-1 antibody and anti-CTLA-4 antibody are to be administered at dosages of: (a) 1 mg/kg of anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody or (b) 3 mg/kg of anti-PD1 antibody and 1 mg/kg of anti-CTLA-4 antibody.

Ex. 1023, 144-145 (cleaned up).

Challenged claim 1 of the '320 Patent is shown below with overlapping options from claim 1 of EP App. No. 17189595.6 highlighted in yellow.

Claim 1
[1Pre]. A method of treating a human subject afflicted with a cancer comprising administering to the subject:
[1A] (a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) (“anti-PD-1 antibody”); and (b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (“anti-CTLA-4 antibody”);

<p>[1B] (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses; followed by</p> <p>(ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses; and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages:</p>
<p>[1C] (a) ...(f)...;</p> <p>(g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;</p> <p>(h) ...<i>or</i> (m)....</p>

During prosecution of the above claim in Europe, on October 7, 2019, the EPO’s Examining Division (“ED”) asserted that the amended claims lacked novelty and inventive step over *the April 30, 2012 version of NCT01024231 [D10]* whose cohort arms recited an induction phase of concurrent anti-CTLA-4 and anti-PD-1 dosing followed by anti-PD-1 alone, followed by a maintenance phase of the two antibodies again. The ED also asserted “the establishment of dosage regimes is considered a matter of routine for the skilled person.” EX1062, 2. As was discussed at length in the Petition and will be highlighted in the sections below, the April 30, 2012 version of NCT01024231 [D10] is the same prior art reference considered by the Examiner during prosecution of the ’320 Patent around which PO narrowly amended its claims. While PO was able to skirt the specific dosing

limitations of this April 30, 2012 version of NCT01024231 via amendment, the Examiner erroneously failed to appreciate that the newly added dosing limitations were also disclosed in other versions of this clinical trial and other prior art references. *See* Pet. §VIII, *and* §§V and VI., *infra*.

In response to the foregoing communication, PO pointed to data (Table 10) and argued that the data “clearly show that the dosing regimens of ***Cohorts 2 and 2a had superior effects as compared to those of cohorts 1 and 3.***”

EX1025, 1-2.

On April 11, 2022 the ED responded that it “does not share this point of view” and that “[t]he foremost difference between the teachings of D10 and the subject-matter of claim 1 lies in a variation of the induction regime, namely splitting it between anti-PD1 plus anti-CTLA4 and anti-PD1 alone. The application did not show any technical effect/s associated with said difference/s over the state of the art over the whole breadth of the claim’s scope.” EX1026, 2-3.

Oral proceedings were scheduled for September 27, 2022, however, PO withdrew the application on September 20, 2022 (five days after Third-Party Observations were filed discussing, *inter alia*, prior art reference Korman, relied on in Grounds 1 and 2 of the Petition). EX1033.

2. Claims In European Patent Application 22196038.8 Have Been Rejected.

Similarly, in prosecuting EP Application 22196038.8, PO is seeking a claim similar to the claim recited above for EP App. No. 17189595.6. EX1034, 1 (reciting the dosing amount (a) only).

In response to a European Search Opinion finding the pending claims lacking inventive step, *again* over *NCT01024231*, PO shifted its argument relative to the prior EP 17189595.6 case, contending in this case that “[t]he data in Table 10 clearly show that the dosing regimen of *Cohort 2 has superior effects as compared to those of cohorts 1, 2a, and 3.*” EX1035, 2. While cohort 2 in Table 10 does not correspond to any of the dosing amounts recited in any of the instant challenged claims, PO’s shifting assertions regarding the allegedly superior effects of its invention only undermine its point and have, to date, failed to secure issuance of these claims in Europe. There has been no further action in the prosecution of these claims since October of 2023.

That the parallel claims of EP App Nos. 17189595.6 and 22196038.8 have been flatly rejected and, in the case of the former, withdrawn, is clear evidence of the material error of the allowance of the challenged claims of the ’320 Patent.

C. Resolving Patent Disputes Under The BPCIA

Unlike for small molecule drugs, where generic approval is linked to a mechanism for resolving patent disputes, approval of an aBLA for a biosimilar is

only linked to an *optional* litigation mechanism (BPCIA Patent Exchange and ensuing litigation) for resolving patent disputes. *Sandoz, Inc. v. Amgen, Inc.*, 582 U.S. 1, 18-19 (2017). For parties who do participate in the BPCIA Patent Exchange, litigation generally does not commence until approximately ten months after the aBLA is filed and generally runs for at least 2.5-3.5 years.⁴

Here, as PO acknowledged, Petitioner has not yet even filed an aBLA for its Opdivo® biosimilar which is still in development. Therefore, all PO can do is speculate about: (1) the timing of possible future events of aBLA filing, (2) the possible participation in the BPCIA Patent Exchange process, and (3) the possible filing of a lawsuit and time to a decision which would be expected to take at least 2.5-3.5 years after the complaint is filed. *See supra* note 4. By contrast, a Final Written Decision in this case would be issued far sooner and more predictably,

⁴ Case schedules and timelines pulled from five BPCIA litigations that were terminated after trial and final judgment demonstrate that average time from complaint through trial to termination is 828 days, with a maximum of 1320 days. *Regeneron v. Mylan*, 1:22-cv-00061 (N.D. W. Va.); *Amgen v. Hospira*, 1:15-cv-00839-RGA (D. Del.); *Immunex v. Sandoz*, No. 2:16-cv-01118 (D.N.J.); *Amgen v. Apotex*, No. 15-62081 (S.D. Fla.); *Amgen v. Apotex*, No. 0:15-cv-61631 (S.D. Fla.).

likely by October, 2026. The Petition’s filing timeline was aligned with the settled expectations of the Parties regarding fair and efficient resolution of patent disputes.

D. PO is Relying on the ’320 Patent to Extend Opdivo® Exclusivity

Opdivo® first received FDA approval in December 2014. EX1067, 20.

Pursuant to the BPCIA, enacted March 23, 2010, Opdivo® (as a reference product) is entitled to 12.5 years of regulatory (market plus pediatric) exclusivity, irrespective of patent protection, during which other companies are prevented from obtaining FDA approval to market a biosimilar version. EX1068. Opdivo®’s 12-year market exclusivity expires on December 22, 2026, while its pediatric exclusivity expires June 22, 2027. US revenue for Opdivo® in 2024 was \$9.3 billion and “revenues increased 2% in 2024 primarily due to higher average net selling prices.” EX1073, 48-50.

PO has sought additional patents related to Opdivo® and its use. The original composition of matter patent covering Opdivo®, US 8,008,449 (“the ’449 Patent”) (EX1069), received patent term extension and expires on December 22, 2028. EX1070, EX1071. The ’449 Patent family also includes another patent (US 9,358,289; “the ’289 Patent”) with claims directed to methods of administering an anti-PD-1 antibody and an anti-CTLA-4 antibody, for treatment of cancer, which expires in 2026. EX1072, cls. The table below compares claim 5 of the ’289 Patent—part of the original Opdivo® patent family and *claiming priority to 2005*

and expiring in 2026 – with claim 1 of the '320 Patent—part of a later-filed patent family *claiming priority to 2012 and expiring in 2034*. This claim comparison shows that the only differences in the claims of the '320 Patent are the dosing schedules of the two, known antibodies:

The '289 Patent (Expires in 2026)	The '320 Patent (Expires in 2034)
<p>5. A method of treating cancer in a subject having a tumor that does not express PD-L1 comprising administering to the subject a combination of a dose of an anti-PD-1 monoclonal antibody or an antigen-binding portion thereof and a dose of an anti-CTLA-4 monoclonal antibody or an antigen-binding portion thereof, wherein the combination of the anti-PD-1 antibody or antigen-binding portion thereof and the anti-CTLA-4 antibody or antigen-binding portion thereof treats cancer in the subject.</p>	<p>1. A method of treating a human subject afflicted with a cancer comprising administering to the subject: (a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) (“anti-PD-1 antibody”); and</p> <p>(b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (“anti-CTLA-4 antibody”);</p> <p>(i) [recitation of a known induction dosing schedule],</p> <p>(ii) [recitation of a known maintenance dosing schedule] and, [recitation of known doses (a) through (m) for each antibody in the induction schedule].</p>

In view of the upcoming expiry of its composition of matter patent and related patent family members such as the '289 Patent, PO sought and obtained exceedingly weak follow-on patents such as the '320 Patent, which *expires in 2034*

and which claims treatment dosing schedules (frequencies and amounts) that were disclosed in the prior art (and rejected and withdrawn in Europe, *see* §II.E. *supra*). Indeed, PO has obtained additional granted US patents (and has many more pending patent applications) related to Opdivo®. Almost all of these later filed patents claim slight and obvious variations of known uses or doses of Opdivo® and pending applications provide the potential for PO to obtain similarly obvious claims. Given this large patent landscape of questionable merit, IPRs provide an important mechanism for a biosimilar developer to reduce the scope and number of erroneously granted patents that it faces in bringing its product to market.

III. THE DIRECTOR SHOULD DECLINE TO EXERCISE HER DISCRETION UNDER SECTION 314(A) TO DENY INSTITUTION⁵

A. There Is No Parallel Litigation And Any Potential Future Litigation Would Not Be Completed Before A Final Written Decision

There is no co-pending or parallel litigation concerning the '320 Patent and PO has identified no case in which *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) has been applied to support discretionary denial in the *absence* of parallel litigation. Even were PO's speculation about a future BPCIA litigation credited, however, the facts still do not warrant discretionary

⁵ There is no previous petition concerning the '320 Patent warranting discretionary denial under the *General Plastic* factors.

denial, in particular because any litigation over Petitioner's Opdivo® biosimilar, which is currently still in development, would not be expected to be completed or even close to completion before a Final Written Decision in this IPR.

B. The *Fintiv* Factors Disfavor Denial

1. *Fintiv* Factor 1 Disfavors Denial

There is no current pending litigation between PO and Petitioner.

Consideration of a potential stay in litigation is wholly inapplicable, disfavoring denial.

2. *Fintiv* Factor 2 Disfavors Denial

A Final Written Decision will be issued in this case approximately twelve months from Institution. As discussed above, there is no current pending litigation between PO and Petitioner.

PO provides a purely speculative hypothetical timeline to assert that litigation could *commence* in 8-9 months. Br. 5. It is unclear what this speculative timeline is based on, but PO provides no support for its general estimate, which should be disregarded. To the contrary, the (pre-complaint) BPCIA Patent Exchange process itself can take approximately ten months and that process does not begin until after the aBLA has been filed. Moreover, if the Patent Exchange is initiated by the biosimilar applicant and honored by both parties, the filing of a complaint for infringement cannot occur until the Patent Exchange process is completed. And, the time through trial for a biosimilar litigation (based on existing

case data) is at least 2.5-3.5 years *after the filing of a complaint*. See *supra* note 4. Thus, even based on PO's speculation about future events, and accounting for each of these phases (time to aBLA filing, Patent Exchange process, complaint filing and litigation) resolution of any BPCIA litigation over the '320 Patent would not occur until 4-5 or more years into the future. This timeline would of course be considerably longer than the issuance of a Final Written Decision in this IPR. Thus, to credit PO's logic that IPRs should be discretionarily denied because of the *hypothetical possibility* of future BPCIA litigation, is tantamount to ruling that biosimilar developers should never be afforded the opportunity to make use of IPR and PGR proceedings at all. Given the significant uncertainty in even assessing the "proximity of the court's trial date to the Board's projected statutory deadline for a Final Written Decision," *Fintiv* factor 2 disfavors discretionary denial.

3. *Fintiv* Factors 3 And 4 Disfavor Denial

There is no parallel proceeding between PO and Petitioner in a district court. Thus, neither party nor any district court has invested any resources in a way that would support discretionary denial. Factors 3 and 4 disfavor denial.

4. *Fintiv* Factor 5 Disfavors Denial

There is no parallel proceeding between PO and Petitioner in a district court and the '320 Patent has not been the subject of any other district court or Federal Circuit proceedings. Factor 5 disfavors denial.

5. *Fintiv* Factor 6 Disfavors Denial

As discussed above, *Fintiv* Factors 1-5 disfavor discretionary denial. Thus, the Board need not consider Factor 6. *Commscope Tech. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 (PTAB Feb. 27, 2023). But, as noted herein, compelling art, prior adjudication, and the public interest all compel institution.

IV. OTHER FACTORS ALSO DISFAVOR DISCRETIONARY DENIAL

The Memorandum explicitly contemplates consideration of discretionary denial against the backdrop of “Compelling economic, public health, or national security interests” and “Settled expectations of the parties.” Memorandum, 2. All of these interests are at issue in this IPR and overwhelmingly weigh against discretionary denial.

A. Compelling Economic Interest In Accelerating Access To Biosimilars

1. Biosimilars Play A Critical Role In Advancing Access To Lower Cost Options For Treatment

Biosimilars and the BPCIA have contributed to a significant expansion of the biologics industry. As summarized by IQVIA in 2023, “The U.S. biologics market has grown 12.5% annually on average over the last five years on an invoice-price basis, faster than non-biologics, and now comprising 46% of spending.” EX1087, 1. However, compared to small-molecule drugs, biologics are more costly to produce, partly due to their complexity. The Biosimilars Forum recently noted that reference biologic drugs “were 46% of U.S. prescription drug

spending in 2022 despite only making up 3% of prescriptions. Patient and taxpayer spending on biologics increased from \$100 billion to \$260 billion (adjusted for inflation) over the last decade.” EX1088. Notably, biosimilars have been reported to consistently drive down drug costs, averaging more than 40 percent less than the reference brand at biosimilar launch, and providing \$12.4 billion in savings in 2023. EX1089, 7-9.

Petitioner has been a pioneer in the science of biotechnology—using living cells to make “large molecule” medicines, also called “biologics,” such as proteins and antibodies. Petitioner helped invent the processes and tools that built the global biotech industry—turning it into what is today the leading source of new therapies for patients—and currently has over two dozen products on the market that treat diseases as wide ranging as anemia, rheumatoid arthritis and post-menopausal osteoporosis and life-threatening illnesses like cardiovascular disease and cancer.

In view of its extensive manufacturing and clinical development capabilities for biologics, Petitioner has chosen to also apply this expertise to reach additional patients by bringing biosimilar products to the market. While innovators ought to be rewarded for making new and important biologic discoveries and deserve patent protection for those discoveries, once valid patent protection expires, the introduction of biosimilars is important for patients. Biosimilars have the potential to lower healthcare costs and bring savings to both patients and the healthcare

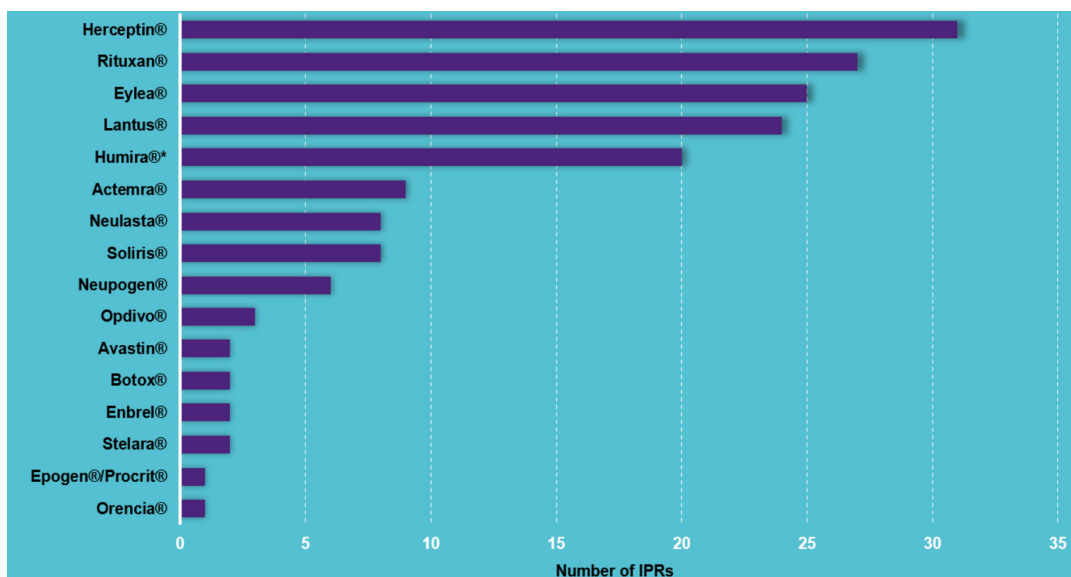
system. Biosimilars increase competition in the marketplace, generally cost less to develop compared to originator biologics.

The '320 Patent represents an example of a mistakenly granted patent claiming an otherwise unpatentable method of treatment, standing in the way of fair competition by companies otherwise seeking to market biosimilars of Opdivo®. Since Opdivo® is already patented for a full statutory period, that exclusivity should not be extended by an additional patent that recites little more than applying a known combination to a known indication.

2. IPRs Play An Important Role In Advancing Biosimilars To Market.

A first biosimilar developer for a biologic generally faces significant patent uncertainty. This is especially relevant for the development of anti-PD-1 biosimilars given the large number of indications for which these antibodies have been approved and the large numbers of patents related to these indications. Even for biosimilar developers who later participate in the Patent Exchange, IPRs can increase efficiency in biosimilar development by reducing the issues (particularly those stemming from patent office error) necessary to litigate.

IPRs have been effectively used by biosimilar developers to clear a path to market entry. Overall, approximately 165 biosimilar-related IPRs have been filed, challenging 77 patents covering 16 CDER-listed Reference Products (EX1083), as reflected in the graph shown below. EX1084.



Out of the number of patents that have been subject to biosimilar-related IPRs and litigation, approximately 23% were subject to only IPRs, meaning that disputes over those patents were resolved without the need for time-consuming and costly litigation, to the benefit of the American public. EX1085.

As noted in a White Paper published by The Biosimilars Council “IPRs lend high value to biosimilar companies by providing a more accurate picture of the patent landscape in a *timely and less-expensive manner than typical biosimilar litigation*. This value is compounded by the ability of the biosimilar manufacturer to file IPRs earlier in the development process so that there is certainty in how to proceed . . . Successful IPR challenges are *more efficient than the patent challenge* procedures in court—getting biosimilar drugs into patients’ hands faster.” EX1086, 8 (emphasis added). In view of the current Administration’s

priority to promote and accelerate biosimilar development and commercialization, IPRs such as those requested in the Petition should be evaluated on their merits.

B. The Petition Was Timely Filed In Accordance With The Settled Expectations Of The Parties

When the '320 Patent granted in 2018, Petitioner had not even begun its clinical trials on its biosimilar product, and due to the pediatric exclusivity afforded to Opdivo®, Petitioner's product cannot be approved by the FDA until June 2027. Even now, Petitioner is still preparing its aBLA and does not face an infringement lawsuit over the '320 Patent. In view of this sequence of events, Petitioner's filing of the instant petition in early 2025 was not untimely.

In addition, PO has argued in prior litigation that where a competitor initiated an IPR too early (*i.e.*, prior to having an approved product threatened by the challenged claims), it did not have standing to appeal an adverse decision. *Momenta Pharms, Inc. v. Bristol-Myers Squibb Co.*, 915 F.3d 764, 766 (Fed. Cir. 2019). PO's argument that Petitioner filed the instant IPR too late is directly contradictory to its prior arguments that IPRs filed prior to product approval were too early.

Moreover, the 2022 withdrawal of the European equivalent to the '320 Patent (EP 17189595.6) and the 2023 rejections of similar claims in EP 22196038.8 demonstrated the merits of a challenge to the corresponding U.S. Patent. Petitioner has balanced an extensive series of competing risks and

incentives in bringing a challenge to the '320 Patent and did so in a timely manner and without delay.

V. THE MERITS OF THE PETITION WEIGH AGAINST DISCRETIONARY DENIAL

The strong merits of the Petition favor institution because the two Grounds of unpatentability reveal the clear obviousness of the standard dosing recitations of the challenged claims. As the Petition explains, challenged claims 1-4, 6-12, 14-17 recite administration of anti-PD-1 and anti-CTLA-4 antibodies at a particular *frequency* and in a particular *amount*.

As Ground 1 demonstrates, the claimed *frequency* was disclosed squarely by prior art clinical trial protocol NCT231 (2010). Pet. §VIII.A.1. And the array of claimed options for dosing *amounts* were disclosed in both NCT231 (2010) and in several other prior art references (such as Korman and Wolchok). Pet. §VIII.A.2-5. The Petition explains that documented and well-known standard dosing protocol would start with known or approved dosing amounts (already disclosed in the art) for an antibody when generating a dosing scheme for its use in a combination therapy. Pet. 30-32. Alternatively, the Petition describes iterative strategies to optimize dose amounts dosing variables. Pet. 32-33. The Petition provides at least these two reasons to combine the prior art teachings, all of which are thoroughly explained in the accompanying Declaration of Dr. Paul A. Antony (EX1003).

Similarly, Ground 2 demonstrates that the dosing frequencies and amounts recited by challenged claims 5, 13, and 18-22 were disclosed in prior art references Korman, Wolchok, and Sznol and would have been obvious to a POSA to assemble with a reasonable expectation of success in light of the known and relative toxicity profiles of anti-PD-1 and anti-CTLA-4 antibodies. Pet. §VIII.B.

As discussed in the Petition, there is no evidence of secondary considerations of non-obviousness sufficient to outweigh either of the strong obviousness arguments set forth in Grounds 1 and 2. Pet. §IX. And whatever evidence PO could cite does not apply across the full scope of the claims to every variation of the dosage and schedule claimed. Moreover, if any one dosing variation claimed is obvious over the art, the entire claim is invalid.

The Petition is well-supported by the testimony of Dr. Antony, who cited exhibits in a comprehensive declaration explaining why the claimed dosing and frequencies were disclosed and would have been obvious dosing choices and the product of routine optimization of known dosing variables. While PO points to certain areas of Dr. Antony's Declaration that track the Petition, it ignores other areas where Dr. Antony went into deep technical detail to provide explanation for the reasons behind the proposed combinations of prior art. For example, PO cites to Dr. Antony's testimony where he references the "sequentially later mechanism of action of anti-PD-1 relative to anti-CTLA-4 in blocking the T-cell 'off signal' to

kill cancer cells” which is also a point made in the Petition. Br. 39. But Dr. Antony had previously explained in his declaration the distinct mechanisms of action of anti-PD-1 and anti-CTLA-4 antibodies as well as their distinct timing of action on T-cell activity to expand upon this “sequentially later mechanism of action” and provided this as a reason why a POSA would stop administration of anti-CTLA-4, but continue anti-PD-1. EX1003, ¶44. Dr. Antony’s Declaration is not a recitation of the Petition. If anything, it demonstrates that an overwhelming amount of evidence exists and should be considered in dislodging an improvidently granted extension to PO’s exclusivity.

A. Ground 1 Demonstrates The Claims Are Obvious

Ground 1 explains that challenged claims 1-4, 6-12, and 14-17 would have been obvious to a POSA by May 15, 2012 over the 2010 published protocol of clinical trial protocol NCT01024231 (NCT231 (2010)) disclosing anti-PD-1 plus anti-CTLA-4 combination therapy dosed in the *precise* induction-maintenance structure claimed, in view of prior art references (Korman and Wolchok) disclosing the claimed dosing concentrations, and ranges encompassing such concentrations, of each antibody (any one of which renders the lengthy list of options unpatentable). EX1003, ¶¶88, 90.

Quite simply, Ground 1 shows that NCT231 (2010) undisputedly discloses the exact dosing structure of the challenged claims, depicted as follows:

Weeks	Ipilimumab once every 3 weeks (4 doses)								Ipilimumab once every 12 weeks (8 doses)							
	↓	↓	↓	↓					↓	↓	↓	↓	↓	↓	↓	↓
	0	3	6	9	12	15	18	21	24	36	48	60	72	84	96	108
	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
	Nivolumab once every 3 weeks (8 doses)								Nivolumab once every 12 weeks (8 doses)							

EX1005, 4; EX1003, ¶¶75-78; EX1027; EX1061, 3 (confirming graphical depiction).

And Ground 1 undisputedly shows that all of dosing concentrations were found in the prior art (even though a finding that any one was obvious is sufficient to render the challenged claims unpatentable).

Claim 1	Korman	Wolchok	NCT231 (EX1005, 4)
(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody	<p>“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55.</p> <p>Korman discloses, “3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 56.</p>	<p>“217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.</p>	<p>Cohort Arm 1 0.3 mg/kg anti-PD-1; 3 mg/kg anti-CTLA-4</p>
(b) 5 mg/kg anti-PD-1 antibody	<p>“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1</p>	<p>“217 patients with previously treated stage III (unresectable)</p>	<p>Cohort Arm 1 0.3 mg/kg anti-PD-1; 3</p>

Claim 1	Korman	Wolchok	NCT231 (EX1005, 4)
<p>and 3 mg/kg of anti-CTLA-4 antibody;</p> <p>(c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;</p> <p>(k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody;</p>	<p>mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55.</p> <p>Korman discloses, “3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 56.</p>	<p>or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.</p>	<p>mg/kg anti-CTLA-4</p> <p>Cohort Arm 5 10 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4</p>
<p>(d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;</p> <p>(j) 0.1 mg/kg anti-PD-1</p>	<p>“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55.</p> <p>And “[i]n certain embodiments, two or more monoclonal antibodies with different</p>		

Claim 1	Korman	Wolchok	NCT231 (EX1005, 4)
antibody and 0.1 mg/kg of anti-CTLA- 4 antibody; (l) 0.5 mg/kg anti- PD-1 antibody and 0.5 mg/kg of anti-CTLA- 4 antibody;	binding specificities (e.g., anti-PD-1 and anti- CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(e) 0.3 mg/kg anti- PD-1 antibody and 1 mg/kg of anti- CTLA-4 antibody;	<p>“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55.</p> <p>“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55.</p> <p>And “[i]n certain embodiments, two or more monoclonal antibodies with different</p>		Cohort Arm 1 0.3 mg/kg anti-PD-1 ; 3 mg/kg anti- CTLA-4

Claim 1	Korman	Wolchok	NCT231 (EX1005, 4)
	binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
<p>(f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;</p> <p>(g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;</p>	<p>“Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight.” EX1006, 55.</p> <p>Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.</p>		<p>Cohort Arm 3 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4</p> <p>Cohort Arm 4 3 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4</p>

Claim 1	Korman	Wolchok	NCT231 (EX1005, 4)
<p>(h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;</p> <p>(m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.;</p> <p>(i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody</p>	<p>“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55.</p> <p>Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.</p>		<p>Cohort Arm 5 10 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4</p>

Given these explicit prior art dosing disclosures—both for anti-PD-1 and anti-CTLA-4 administered concurrently, and in reporting success with concentrations of each antibody when administered alone—and given the standard approach of POSAs to study a variety of concentration options and optimize

antibody dosing to maximize therapeutic efficacy while minimizing toxic effects, a POSA would have had reason to combine these teachings to arrive at a dosing regimen falling within the scope of challenged claim 1. EX1003, ¶¶90-91.

Moreover, given the known success with similar dosing concentrations for each antibody administered alone, the demonstrated positive results of the claimed combination in animal models, and the known reliability of an iterative approach to selecting dose concentrations, for example in a dose-escalation format, a POSA would have reasonably expected success in implementing the NCT231 (2010) protocol with dosing concentrations disclosed in Korman and Wolchok. *Id.*, ¶92.

B. Ground 1 Does Not Suffer From Hindsight

To its detriment, PO began publishing versions of its NCT231 clinical trial protocol disclosing the precise dosing structure and dosing amounts of the combination therapy that it would later try to claim *before* filing the provisional patent application on May 15, 2012 that would eventually lead to the '320 Patent. EX1005, 4. That PO made predictable, incremental, and blatantly obvious tweaks to the dosing amounts in the challenged claims when the Examiner found the *precise claimed dosing structure and dose amounts in later versions of the NCT101024231 protocol (2017, 2012)* is not the work of invention and Petitioner's revealing of the same is not the application of hindsight.

PO argues that Petitioner “fails to provide a credible reason for why a POSA would have modified the references asserted in Ground 1” (Br. 35), but this accusation is manifestly false. The Petition’s explanation for the reasons a POSA would have had to modify NCT231 (2010) with the teachings of Korman and Wolchok (and why such POSA would have had a reasonable expectation of success in the same) span over twelve (12) pages in the Petition, rely on directly analogous prior art, and fall into two categories, each of which explain why all of the dosing amounts (a) through (m) would have been obvious choices in view of the prior art.

Petitioner walked through the reasons why a POSA would have tried each and every one of the (a) – (m) dosing options, even though establishing that *any one* such option was obvious would render the challenged claims unpatentable. The Petition explained, via a published reference on dosing strategy (EX1032) and the expert testimony by Dr. Antony, who was at least a POSA as of 2012, that combination dosing strategies started with the dosing amounts that had already been tested, or approved, for each drug. Pet. 30-32. This desire to utilize existing knowledge that already had been disclosed for each antibody independently when creating combination dosing regimens was at least one reason a POSA would combine the particular dosing amounts found in Korman and Wolchok with the precise dosing regimens already disclosed in NCT231 (2010). Pet. 29-32.

In addition to this standard practice of using existing knowledge and existing approved doses, Petitioner also explained that an alternate reason a POSA would arrive at the claimed dosing amounts would have been through the routine optimization of known and disclosed doses. Pet. 32-33. Petitioner explained that even in the absence of disclosure of the exact dosing amounts (for certain of the claimed options), a POSA would have “alternatively engaged in standard iteration to improve upon what is already generally known by adjusting dosing concentrations within disclosed concentration ranges in assembling a dosing protocol according to the structure of NCT231 (2010) for an anti-PD-1 plus anti-CTLA-4 therapy as discussed, for example, in section (c), (d), (e), and (f).” Pet. 32. The desire to optimize claimed result-effective variables such as dosing amount provides yet another reason why a POSA would combine the teachings of the prior art (in counterweight to hindsight) highlighted in the Petition. *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347-48 (Fed. Cir. 2024) (affirming obviousness of claim reciting molecular weight of *S. pneumoniae* serotype of 22f glycoconjugate, where, though claimed molecular weight was not disclosed in any prior art reference, it would have been obvious because a person of ordinary skill in the art would have been motivated to optimize to provide a conjugate having improved stability and good immune response—“where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable

ranges by routine experimentation.”); *see also Amgen, Inc. v. Sandoz, Inc.*, 66 F.4th 952, 968 (Fed. Cir. 2023) (affirming obviousness of dosing claims and crediting expert testimony “establishing that it was well within a skilled artisan’s ability to titrate an apremilast dose for a patient presenting with psoriasis and that doing so would have been a routine aspect of treating [that disease]”). The Petition additionally pointed out that iterative dosing strategies were apparent from the shifting dosing cohorts of the evolving versions of the NCT01024231 clinical trial itself over time. Pet., 39-40.

Contrary to PO’s assertion, the Petition documents multiple, independent, and well-supported reasons why a POSA would have modified any one of the dosing amounts recited in the NCT231 (2010) reference to arrive at the challenged claims.

C. Ground 1 Relies On Analogous Art And PO Makes No Mention Of Secondary Considerations That Would Rebut The Petition’s Prima Facie Obviousness Demonstrations

All three references in Ground 1 are from references that disclose or discuss dosing options for anti-PD-1 antibodies, anti-CTLA-4 antibodies, or both. That each reference is analogous art to the claimed invention and this fact alone reins in hindsight bias. *LKQ Corporation v. GM Global Technology Operations LLC*, 102 F.4th 1280, 1296 (Fed. Cir. 2024) (*en banc*) (where a combination of prior art is asserted as rendering the claimed invention obvious, the “analogous art

requirement applies to each reference”—“In determining the scope of the prior art, there is no threshold similarity or ‘basically the same’ requirement to qualify as prior art. Rather, an analogous art requirement applies to each reference. The analogous art requirement reins in the scope of prior art and serves to guard against hindsight.”).

Relatedly, it is well-established that secondary considerations of nonobviousness serve “as insurance against the insidious attraction of the siren hindsight.” *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). However, PO’s discretionary denial brief makes no mention whatsoever of evidence of secondary considerations nor any previewing rebuttal of the Petition’s assertion that no such evidence exists. Pet. 66-68.

D. Ground 2 Demonstrates The Claims Are Obvious

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

By 2012, all of the features of challenged claim 5 were known. EX1003, ¶¶208-09. Korman had—nearly six years earlier—provided explicit dosing disclosures for both anti-PD-1, anti-CTLA-4, and their concurrent use. EX1006, 55 (“Preferred dosage regimens for an anti-PD-1 antibody of the invention include *I*

mg/kg body weight...using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) **every three weeks**; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks”); *id.*, 20 (“**3 mg/kg**, *i.e.*, the known dose of anti-CTLA-4 antibody.”); *id.*, 56 (“In certain embodiments, two or more monoclonal antibodies with different binding specificities (*e.g.*, anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case **the dosage of each antibody administered falls within the ranges indicated** [i.e., “within the range of 1-10 mg/kg”].”). EX1003, ¶¶41, 209.

Moreover, Wolchok reported study results that would become the approved dosing schedule for anti-CTLA-4 therapy at 3 mg/kg “**once every three weeks for four cycles.**” EX1007, 155 (abstract); EX1008, 1. And by 2010, Sznol reported that biweekly anti-PD-1 monotherapy had been demonstrated safe and effective at a dose of 1, 3, or 10 mg/kg. EX1009, 205s. EX1003, ¶¶210-11. Pet. 55-56.

The Petition further explains that by May of 2012, it was clear that anti-CTLA-4 antibodies generated significant immune-related adverse events. *See* EX1019, 29 (abstract); EX1020, 499; EX1021, 865; EX1007, 157, Fig. 1 (significant participant loss in progression from induction to maintenance dosing of anti-CTLA-4). By contrast, a POSA would have been aware of “a milder toxicity profile for anti-PD-1 than for anti-CTLA-4.” EX1042, 245 (right col.); EX1044, 512, 514; EX1037, 3172; Antony, ¶¶215-16; *see* Pet. §§IV.C., *supra*.

The Petition explains that with this information, a POSA would have been cautious with the administration of anti-CTLA-4 and chosen a frequency for any combination therapy involving this drug that was already demonstrated safe and effective. EX1007, 155. In view of such safety and adverse side effect concerns, a POSA dosing a concurrent therapy including anti-CTLA-4 would reasonably have followed Korman and Wolchok’s frequency disclosure of “every three weeks” limited by Wolchok’s number of doses, “for four cycles.” EX1003, ¶¶ 42-44, 216. Pet. 55-57. Courts recognize that for dosing claims, varying a dose in response to safety concerns, including the occurrence of side effects is a well-known, standard medical practice that may well lead to a finding of obviousness. *Amgen, Inc.*, 66 F.4th at 968, *citing Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376–77 (Fed. Cir. 2022) (“[I]t is worth noting our initial perception that, as the district court noted, varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice.”).

Finally, the Petition explains why a continued course of anti-PD-1 antibodies administered bi-weekly would have been an obvious course in view of the aforementioned safety concerns, the desire to maximize efficacy of the treatment overall, and the well-understood relative timing of the biological mechanisms of action of anti-PD-1 and anti-CTLA-4 antibodies themselves, such that a POSA

would have had a reasonable expectation of success in arriving at the dosing structure of claims 5, 13, and 18-22. Pet. 57-65.

E. The Petition’s Unpatentability Challenge To Claim 5 And Its Dependent Claims Does Not Omit A Limitation.

PO argues that the Petition failed to account for claim 5’s requirement that anti-PD-1 antibody be given alone after the combination of anti-PD-1 and anti-CTLA-4. Br. 35-39. Again, the Petition explained, in significant detail and in multiple different places, why the relative toxicity profiles of the claimed antibodies and the timing of each antibodies’ biological mechanisms of action would have motivated a POSA to stop administration of CTLA-4 after the combined 4 doses but continue the anti-PD-1 antibody therapy alone. Pet. 62-63 (discussion of limitation 5D); 57-58 (explicit discussion of reasons for “subsequent dosing of anti-PD-1 alone”); 8-9, 56-57 (discussion of high toxicity profile for anti-CTLA-4 and relatively milder toxicity for anti-PD-1).

The Petition supported this explanation with the NCT231 (2010) protocol’s induction dosing structure of administration of anti-PD-1 and anti-CTLA-4 together, followed by dosing of anti-PD-1 alone. While the overall dosing structure of NCT231 is different from claim 5 and that reference is not relied on in Ground 2, the transition in the induction phase from combined antibody therapy to anti-PD-1 *alone* confirmed what POSAs knew to be true by 2012—that anti-CTLA-4 was

too toxic to continue dosing longer than the approved “every 3 weeks for four doses.”

Dr. Antony also confirmed the factual underpinnings of the Petition’s argument that a POSA would be deeply familiar with these toxicity profiles—not just from Fife (which explains the basic timing of immune activity of anti-PD-1 and anti-CTLA-4 relative to one another), but from Wolchok and the ipilimumab approval more generally, and also through EX1019 (Dillard et al), EX1020 (DiGiacomo), 2021 (Weber). EX1003, ¶¶213-218, 224, 238-240, 45-58.

Moreover, PO fails to mention that Dr. Antony provided a fulsome explanation of how the timing of T-cell activation plays a role in these toxicity profiles and the POSAs resulting reason to discontinue anti-CTLA-4 antibody while continuing to administer anti-PD-1 alone. EX1003, ¶44 (“while adverse events were associated with anti-PD-1 antibody administration, the frequency of immune-related toxicities from anti-PD-1 treatment was understood to be less severe than with anti-CTLA4 administration as shown by research studies and at least one phase I clinical trial before 2012. *See, e.g.*, EX1022, 260; EX1037, 3167-69, 3172. Occurrence of immune related adverse events were also as predicted from the mechanisms of action of each molecule and their respective distribution throughout the body in various tissues, for instance CTLA-4 is expressed by naïve T-cells, whereas PD-1 is expressed by activated and exhausted memory T-cells. EX1022, 258; EX1037,

3168. Thus, in combination, the frequency of immune related adverse events would be expected to increase due to increased T-cell activation. *See, e.g.*, EX1022, 257-58; EX1037, 3167-69; EX1006, 60, 62, 66; *See generally*, EX1015. Finally, these distinct mechanisms of action also contribute to the distinct timing of each pathway in its impact on T-cell activity. 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.”) This full body of knowledge would have informed a POSA’s decisions in developing a method of treating cancer with concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies.”).

PO seems to suggest that because none of Korman, Wolchok, or Sznol explicitly recite “subsequently administering the anti-PD-1 antibody alone,” that combination of references in further combination with the experience and knowledge of a POSA necessarily cannot render claim 5 obvious. But that is not the test for obviousness. “A claimed invention may be obvious even when the prior art does not teach each claim limitation, so long as the record contains some reason why one of skill in the art would modify the prior art to obtain the claimed invention. Whether a person of ordinary skill in the art would have had such a reason to combine the teachings of prior art references is also a question of fact.”

Nike, Inc. v. Adidas AG, 812 F.3d 1326, 1335 (Fed. Cir. 2016) (substantial evidence supported Board’s determination that person of skill in art would have reason to modify prior art reference) *overruled on other grounds*; *see also REC Solar Pte. Ltd. v. Hanwha Solutions Corp.*, 2025 WL 251574, *2 (Fed. Cir. 2025) (nonprecedential) (for claims directed to solar-cell module, affirming finding of unpatentability, made in an IPR, for obviousness in view of a combination of two prior art references and rejecting the patentee's argument that because neither reference disclosed, expressly or inherently, a “single assembly cross-connector,” which was claimed, obviousness was not proven, the court finding that substantial evidence supported the Board's finding that a motivation to combine the two references was shown, and once that combination was made, the evidence showed that one of skill in the art would “naturally choose to fabricate the cross-connectors as a single assembly,” and thus “expert testimony [] explained why a person of ordinary skill would have found a single assembly cross-connector a ‘predictable variation’ on the prior art”).

Here, as explained in the Petition, the combination of teachings in Korman, Wolchok, and Sznol, plus a POSAs understanding of the relative toxicity profiles of the claimed antibodies and the mechanistic timing of immune action of each antibody, plus a POSA’s familiarity with the ability of patients to tolerate each drug (as demonstrated at least by Wolchok, but confirmed by the approved dosing

of anti-CTLA-4 monotherapy and confirmed by the induction phase dosing structure of NCT231 (2010)) renders obvious the dosing regimen of claim 5.

VI. DISCRETIONARY DENIAL PURSUANT TO 35 U.S.C. §325(D) IS UWARRANTED.⁶

As detailed in the Petition and explained more fully herein, the Board should not exercise its discretion under 35 U.S.C. §325(d) to deny institution in view of separate and complete consideration of both steps of *Advanced Bionics LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential).

The Grounds apply four prior art publications (in two separate §103 combinations) against the challenged claims. Those publications are Sznol (EX1009), Korman (EX1006), Wolchok (EX1007), and the clinical trial protocol NCT231 (2010) (EX1005). While Korman and Wolchok were cited on an IDS

⁶ As PO acknowledges, “the Memorandum provides for separate briefing and consideration of discretionary denial issues.” Br., 32. This separate briefing negates the need for Petitioners to address discretionary denial issues in the Petition. *See* FAQs for Interim Processes for PTAB Workload Management, FAQ No. 24. There is no indication that, for Petitions filed prior to issuance of the Memorandum, Petitioners are precluded from offering a fulsome response to a Discretionary Denial Brief even if not specifically addressed in the Petition.

(though never applied in a rejection) during prosecution, the Petition’s Grounds are materially different—and rely on materially different disclosures and combinations of disclosures—than any arguments made or art applied by the Examiner. For example, prior art reference Sznol (relied upon in Ground 2 and not cited during prosecution of the ’320 Patent at all) discloses successful clinical trial results of bi-weekly dosing of anti-PD-1, which is an element of challenged claim 5 and is not disclosed in other cited references. In any case, the Examiner’s allowance of those claims in view of the cited prior art (in striking divergence from the approach given similar claims before the EPO) constituted material error. Discretionary denial is inappropriate.

A. *Advanced Bionics* (1): Whether The Same Or Substantially The Same Prior Art Or Argument Previously Was Presented To The Office.

As set forth in the Petition, all of the challenged claims recite the administration of anti-PD-1 and anti-CTLA-4 antibodies in a particular dosing *frequency* (i.e., a number of doses, once every number of weeks) and in a particular dosing *amount*.

Claim 1 encompasses a method of treating a human subject afflicted with cancer by administering an anti-PD-1 antibody together with an anti-CTLA-4 antibody where the antibodies are given once every three weeks for four doses,

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

For the *first* combination doses (once every three weeks for four doses), the claim allows for the amounts of each antibody to be *any* of the options shown in (a) through (m) below:

- (a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
- (b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
- (c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
- (d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (e) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody;
- (k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody;
- (l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody;
- or (m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.

Challenged claim 5 (the other independent claim) recites a method of treating a human subject afflicted with cancer by administering 1 mg/kg of anti-

PD-1 and 3 mg/kg of anti-CTLA-4 together every 3 weeks for 4 doses, followed by administering the anti-PD-1 antibody alone every 2 weeks. EX1001, cl. 5.

1. *Becton Dickinson* Factor (a): The Similarities And Material Differences Between The Asserted Art And The Prior Art Involved During Examination.

a. Sznol (EX1009)

Of the four references relied upon in the Petition’s two Grounds (NCT231, Korman, Wolchok, Sznol), PO concedes that Sznol was not cited in any IDS nor used or discussed by the Examiner in any rejection. Br. 23. But contrary to PO’s assertion, Sznol is not cumulative of art of record. Br. 23-24.

Sznol discloses the positive results of a Phase 1 trial in humans *testing bi-weekly dosing* of anti-PD-1 (as recited in claim 5). While Korman mentions bi-weekly dosing and is therefore consistent with Sznol, Korman does not provide human clinical trial data of the same and so is not cumulative of Sznol’s reported data.

In addition, as discussed below, the reference Ascierto cited by the Examiner was relied on not for its substantive teachings, but for its confirmation of the public accessibility of versions of the NCT231 trial. EX1002, 192 (“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.*”). The Examiner pointed to Table 2 of Ascierto as “evidence that

the description of this trial was publicly available at least as early as October 2010.” *Id.* The Examiner did not discuss or rely on Ascierto for any mention of bi-weekly dosing of anti-PD-1 antibody and the passage of Ascierto that mentions Sznol (EX1044, 515) does not mention the bi-weekly dosing structure disclosed in that reference at all. The safe and effective bi-weekly dosing data for anti-PD-1 antibodies tested in humans as reported in Sznol is not cumulative of any other art of record.

b. NCT231 (2010) (EX1005)

The Petition relies upon prior art reference NCT231 (2010) which is a January 5, 2010 version of clinical trial NCT01024231. NCT231 (2010)’s dosing protocol is *different* from the versions of that protocol considered and applied by the Examiner during prosecution of the ’320 Patent. NCT231 was not cited in any IDS nor used or discussed by the Examiner in any rejection. PO argues that the differences between NCT231 and other protocol versions of that same clinical trial are irrelevant such that the distinction the Petition makes is “without a difference.” Br. 14. PO’s argument is sweeping and contradicts its own prosecution strategy and erroneous securance of the challenged claims of the ’320 Patent. PO’s arguments should be rejected.

i. The Entirety Of The Ongoing NCT01024231 Clinical Trial Was Not A Reference Before The Examiner.

In attempting to denigrate NCT231 (2010), PO argues that the “Examiner had access to the entire NCT01024231 clinical trial history and was aware of multiple versions of the trial protocol.” Br. 14. From this, PO draws the sweeping conclusion that the Examiner was “on notice of the clinical trial in its entirety” such that NCT231 (2010) was effectively cited and considered even though only different versions of that trial were actually cited and discussed during prosecution. Br., 14-15. PO similarly posits that “Amgen cannot credibly argue that the Examiner was unaware that earlier versions of the NCT01024231 protocol existed.” Br., 16-17. But that is flatly inconsistent with how PO itself handled the Examiner’s rejection of its claims during prosecution and imparts an unrealistic body of knowledge on examiners that is not imparted for other types of prior art.

As discussed in the Petition, when the Examiner cited a 2017 version of the NCT01024231 clinical trial, PO did not simply accept that the Examiner “was on notice of the entirety” of that clinical trial. To the contrary, PO pointed out the late date of the Examiner’s version and instead offered *an earlier version* (a 2012 version, which PO then amended around to secure its claims). In direct contrast to PO’s current argument, PO secured the challenged claims by distinguishing *different versions of the NCT01024231 clinical trial from one another*. EX1002,

53.⁷ And this would make sense in view of how prior art is treated for purposes of evaluating patent claims in the digital world. Simply because an examiner has access to the entirety of NEJM publications, does not render citation of one NEJM article tantamount to said examiner being “on notice of” the entire record of publications from that journal. Examiners must cite prior art references individually and particularly point out where in such reference the claimed material can be found. *See* MPEP 707.05(e). There is no reason, and PO offers none, for why clinical trial protocols should be treated differently.

ii. Ascierto Was Relied On As Evidence of Public Accessibility And Is Not Cumulative of NCT231.

As discussed above, the Examiner relied on Ascierto (Table 2) solely as evidence of the public accessibility of the NCT231 (2017) clinical trial version being relied upon in the rejection (which PO pointed out was erroneous because such version post-dated the claimed effective filing date of the pending claims).

⁷ PO likewise points out that it “submitted an IDS 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.” Br. 16. The fact that PO cited only to versions with the “*same dosing cohorts*” confirms Petitioner’s point. Distinct cohorts have distinct significance to the amended and now challenged claims.

EX1002, 192. There is no evidence that the Examiner relied upon the substantive dosing disclosures of Ascierto in rejecting the pending claims (logically, because all of those disclosures were found in NCT01024231 (2017) that was the heart of the rejection). EX1002, 192-193. The Examiner merely pointed to Ascierto to provide “evidence that the description of this trial was publicly available at least as early as October 2010.” EX1002, 192. For this reason alone, Ascierto is not cumulative of NCT231 (2010) relied on in the Petition.

But even if Ascierto’s full disclosure is assumed to have informed the Examiner’s rejection (despite the Examiner’s explicit statement to the contrary and lodging of a §102 rejection based on NCT010124231 (2017)), Ascierto is still not cumulative of NCT231 (2010). Nothing in Ascierto discloses a dosing structure for combined administration of anti-PD-1 and anti-CTLA-4 involving a two-part induction phase: (1) combined administration followed by anti-PD-1 alone, followed by (2) combined administration. None of the Examiner’s other cited reference involve such dosing structure. And nothing in Ascierto nor any other cited reference suggests any dosing amounts that had or could be tried with *this structure*. Instead, only NCT231 (2010) discloses this structure *precisely* while reciting many of the dosing amounts claimed as well. *See* Table in §V.A. *supra*. Thus, even if the full disclosures of Ascierto were relied upon by the Examiner

(despite evidence to the contrary), Ascierto is undoubtedly *not cumulative* of the combined therapy dosing disclosures of NCT231 (2010).

c. Korman (EX1006)

Korman was cited in a January 21, 2015 IDS but was neither mentioned, discussed, nor applied in any subsequent action. Even if Korman was “previously presented” to the Office via IDS citation or otherwise, as discussed in §VI.B., *infra*, the Examiner erred (*Advanced Bionics* factor (e)) in allowing the challenged claims where Korman was of record.

d. Wolchok (EX1007)

Wolchok was cited in a January 21, 2015 IDS but was neither mentioned, discussed, nor applied in any subsequent action. PO points to Wolchok’s appearance in the specification of the ’320 Patent, but that citation focuses on Wolchok’s dosing amounts: it fails to describe the “every 3 weeks for four cycles” dosing frequency that is central to the obviousness of the challenged claims, as discussed in the Petition. And Sharma, like Ascierto, was mentioned by the Examiner solely as a reference that “cite[s] or mention[s] clinical trial NCT01024231.” EX1002, 195-196. Even if Wolchok was “previously presented” to the Office via IDS citation or otherwise, as discussed in §VI.B., *infra*, the Examiner erred (*Advanced Bionics* factor (e)) in allowing the challenged claims where Wolchok was of record.

2. *Becton Dickinson* Factor (b): The Cumulative Nature Of The Asserted Art And The Prior Art Evaluated During Examination.

As discussed above in §VI.A.1.b., the Examiner’s application of prior art that disclosed specific dose amounts and frequencies for anti-PD-1 and anti-CTLA-4 was limited to Versions 86 (2017) and 58 (2012) of NCT01024231. While NCT231 (2017) was overcome because its publication date was later than the earliest claimed priority date of the challenged claims, Version 58 was *specifically amended around* regarding the various dose amounts recited in issued claim 1, (a) through (m). Though NCT231 (2012) did not disclose any of the amended dosing amounts ((a) through (m)), both Wolchok and Korman do contain such disclosures, and as such, are substantially *dissimilar* to NCT231 (2012).

Wolchok discloses administration of anti-CTLA-4 at the claimed dose amounts of both 0.3 mg/kg and 3 mg/kg, and at the claimed frequency of “every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months.” EX1007, 155. Similarly, Korman discloses many of the dosing amounts and frequencies for anti-PD-1 recited in the challenged claims as shown in the Table below (also including the dosing disclosures of NCT231). PO points to evidence that Korman and Wolchok were known or available to the Examiner (Br. 20-23), but *none* of these specific dosing disclosures (applicable to *many* of the optional (a)-(m) amounts) were *discussed or applied* against the amended (now

challenged) claims (which is indicative of material error as discussed in §IV.B. *infra*).

In view of: (1) the strong merits of the petition, (2) the rejection of similar claims by the EPO over similar prior art, and (3) the non-cumulative nature of disclosures relied on and analyzed in the Petition relative to distinct disclosures mentioned during prosecution of the challenged claims, the Board's careful consideration of the Petition is warranted. The Board should decline to exercise its discretion in denying the Petition.

3. *Becton Dickinson* Factor (d): The Extent Of The Overlap Between The Arguments Made During Examination And The Manner In Which Petitioner Relies On The Prior Art

There is no overlap between the argument and application of Korman, Wolchok, Sznol, and NCT231 (2010) in the Petition and the application of NCT231 (2017) and NCT231 (2012) against earlier versions of the claims that ultimately issued as the challenged claims.

As noted above, NCT231 (2017) was applied as an anticipatory reference against pending claims 14 and 15 which recited a series of dose amount combinations that were found in that version of the clinical trial protocol. PO disqualified NCT231 (2017) based on its date, but voluntarily cited NCT231 (2012) (effectively conceding that the dosing structure was in the prior art) while

simultaneously amending the claims to defeat any possible argument that the dose amounts recited in NCT231 (2012) anticipated the amended claims.

The Petition, by contrast, argues that the separate and distinct reference, NCT231 (2010), in combination with Korman and Wolchok renders claims 1-4, 6-12, 14-17 obvious, while Korman in view of Wolchok and Sznol render claim 5, 13, and 18-22 obvious. These are entirely separate and distinct bases for challenging the claims of the '320 Patent that were nowhere considered during prosecution of that patent. Discretionary denial would preclude consideration of these meritorious arguments and the very relevant but unconsidered disclosures made in these four references that highlight why the challenged claims were issued in error.

B. *Advanced Bionics* (2): Whether The Petitioner Has Demonstrated That The Office Erred In A Manner Material To The Patentability Of Challenged Claims.

1. *Becton Dickinson* Factor (c): The Extent To Which The Asserted Art Was Evaluated During Examination, Including Whether The Prior Art Was The Basis For Rejection.

As discussed above, none of the references advanced in the Petition's two grounds were substantively evaluated during examination in the combinations advanced in the Grounds of the Petition.

2. *Becton Dickinson* Factor (e): Whether The Petitioner Has Pointed Out Sufficiently How The Examiner Erred In Its Evaluation Of The Asserted Prior Art.

The Examiner made two significant mistakes in allowing the challenged claims. These errors are most starkly highlighted by the rejections lodged to nearly identical claims in Europe and PO's withdrawal of the same. *See §II.B. supra.*

First, the Examiner correctly determined that the pending claims (as of the May 2, 2017 Non-Final Rejection) recited dosing amounts and frequencies that were already disclosed in clinical trial protocols for combination therapies involving anti-PD-1 and anti-CTLA-4 antibodies. However, in arguing this very true fact, the Examiner mistakenly relied upon NCT231 (2017) that was only publicly available *after* the earliest claimed priority date of the pending application. That enabled PO to disqualify that reference, point to an earlier version of such reference (NCT231 (2012)), and amend PO's claims to dodge the dosing amounts recited in that earlier version of the clinical trial protocol.

Instead of then considering whether *any of the 57 prior versions* of the NCT01024231 clinical trial recited doses or frequencies similar to those in the amended claims, or considering whether *any other cited or uncited prior art references* disclosed such amounts or frequencies (they certainly do, as highlighted in the Petition and the Table above), such that the pending claims remained obvious over such prior art, the Examiner overlooked these disclosures and

allowed the claims without providing any explanation or rationale for the failure to conduct further analysis. *Microsoft Corp.*, IPR2025-00318, Paper 9, at 2-3 (denying request for discretionary denial where Examiner “overlook[ed] the teachings of” prior art references that were offered in combination with reference used as anticipatory during prosecution). *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21, at 19-20 (PTAB May 12, 2020) *citing Advanced Bionics* at 21 (granting institution—“By not citing such teachings [in the prior art or giving any reasons for allowance] the Examiner erred in the evaluation of the prior art ... [and] overlooked specific teachings in the relevant prior art such that error by the Office was material to the patentability of the challenged claims.”). Where “the record of the Office’s previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).” *Advanced Bionics*, 10. For example, the Board found the record was silent where the Examiner never made a prior art rejection. *Samsung Electronics Co., Ltd., et al. v. Evolved Wireless LLC*, IPR2021-00943, Paper 9 at 11 (PTAB Dec. 1, 2021); *see also Edwards Lifesciences Corp. v. Aortic Innovations*, IPR2021-01527, Paper 15, 26-27 (PTAB Mar. 17, 2022) (finding error where “the Examiner did not issue any rejections during prosecution despite prior art teachings that are closely related to the subject matter and claims of the [challenged] patent”). The Examiner’s failure to pivot

from the anticipation rejection and resulting amendment to consider the material prior art dosing disclosures in Korman, Wolchok, and Sznol, in view of the precisely claimed dosing frequency disclosures of NCT231, constitute clear error.

Finally, given the meritorious arguments set forth in the Petition and the clear disclosures of the claimed dosing frequencies and amounts provided in NCT231, Korman, Wolchok, and Sznol, the Examiner’s “failure to meaningfully address [the prior art’s] disclosure in allowing the [challenged claims] to issue...indicates that the Office erred in a manner material to the patentability of the challenged claims.” *Ironsource Ltd. v. Digital Turbine Inc.*, PGR2022-00053, Paper 10 (PTAB Mar. 17, 2023).

3. *Becton Dickinson* Factor (f): The Extent To Which Additional Evidence And Facts Presented [] Warrant Reconsideration Of The Prior Art Or Arguments.

As noted above, the Examiner’ sole prior art rejection—an anticipation rejection—was based on a mistaken citation of a clinical trial protocol that Applicant disqualified based on its publication date. EX1002, 52-53; EX1002, 28. The Examiner likewise was faced with over a hundred cited references and was examining shifting claims whose dose amounts were being amended around newly disclosed art. *Id*; *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 (PTAB May 19, 2025) (precedential as to §A) (“The Board should consider a petitioner’s argument based on the volume of the references submitted

to the Office during examination.”). All of these factors, combined with the strong merits of the Petition and the failure of PO to secure similarly obvious claims in Europe (discussed in Section V. and II.B. *supra*, respectively) demonstrate that the Examiner materially erred in allowing the challenged claims and warrant refrain from the Board’s exercise of its discretion.

VII. THE APPLICATION OF THE INTERIM MEMO IS UNCONSTITUTIONAL

The Director’s Memorandum was issued on March 26, 2025 and has been applied retroactively by PO here to petitions filed on February 28, 2025 that followed a previous administration memo. If the Memorandum and application of its newly introduced factors relating to discretionary denial are used to deny Petitioner’s statutory right to pursue *inter partes* review, then the Memorandum and its application have exceeded the Director’s powers and ignored notice-and-comment rulemaking processes. Such a denial would violate at least Petitioner’s 5th Amendment’s Due Process Clause by retroactively applying the new factors of the March Memo in contravention of statutory authority.

Petitioner reserves all rights to pursue constitutional challenges to any improper retroactive application of the Memorandum to this IPR filing.

VIII. CONCLUSION

For at least the foregoing reasons, Petitioner respectfully requests that the Director decline to exercise her discretion in denying institution and instead refer consideration to the merits panel for further review.

Respectfully submitted,

Date: July 10, 2025

/Scott A. McKeown/

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24, the undersigned certifies that the foregoing **PETITIONER'S OPPOSITION TO PATENT OWNER'S DISCRETIONARY DENIAL BRIEF** contains 13,582 words excluding; a table of contents, a table of authorities, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: July 10, 2025

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

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

I certify that on July 10, 2025, a copy of the foregoing document, including any exhibits filed therewith, is being served via electronic mail, as previously consented to by Patent Owner, upon the following:

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