

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. IPR2025-00602
Patent No. 10,174,113

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

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1003	Declaration of Dr. Brent Hanks M.D., Ph.D.
1004	Curriculum Vitae of Dr. Brent Hanks M.D., Ph.D.
1005	Postow et al., Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma., <i>N Engl J Med.</i> 2015 May 21; 372(21):2006-17. (“Postow”)
1006	RESERVED
1007	NCT01968109 Version 1, Brief Title: “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors” (Last Update Posted to clinicaltrials.gov: October 23, 2013) (“NCT-109”)
1008	Wang et al., Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. <i>J Clin Pharmacol.</i> 2009 Sep; 49(9):1012-24. (“Wang”)
1009	Brahmer et al., Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. <i>J Clin Oncology.</i> 2010 Jul 1; 28(19):3167–3175. (“Brahmer”)
1010	RESERVED
1011	Topalian et al., Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. <i>N Engl J Med.</i> 2012 Jun 28; 366(26):2443-54. (“Topalian”)
1012	Prosecution History of U.S. 16/240,316

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1013	NCT02713867 Version 2, Brief Title: “A Dose Frequency Optimization, Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received 4 Months of Nivolumab at 3 mg/ kg or 240 mg Every 2 Weeks” (Last Update Posted to clinicaltrials.gov: March 22, 2016) (“NCT-867”)
1014	NCT01844505 Version 1, Brief Title: “Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma” (Last Update Posted to clinicaltrials.gov: May 1, 2013) (“NCT-505”)
1015	International Patent Publication No. WO 2013/173223 A1 (“Cogswell”)
1016	International Patent Publication No. WO 2006/121168 A1 (“Korman”)
1017	Wolchok et al., Nivolumab plus Ipilimumab in Advanced Melanoma. <i>N Engl J Med.</i> 2013 Jun 2; 369(2):122-33. (“Wolchok”)
1018	U.S. Provisional Patent Application No. 62/153,973 (filed April 28, 2015) (“973 Provisional”)
1019	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary
1020	RESERVED
1021	Zalevsky et al., Enhanced Antibody Half-Life Improves in Vivo Activity. <i>Nat Biotechnol.</i> 2010 Feb; 28(2):157-9. (“Zalevsky”)
1022	Weber J., Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. <i>Oncologist.</i> 2007 Jul; 12(7):864-72 (“Weber”)
1023	YERVOY® FDA Approved label and prescribing information, March 2011
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1025	Philips et al., Therapeutic Uses of Anti-PD-1 and Anti-PD-L1 Antibodies. <i>Int Immunol.</i> 2015 Jan; 27(1):39-46. doi: 10.1093/intimm/dxu095. Epub 2014 Oct 16. (“Philips”)
1026	Phan et al., Cancer Regression and Autoimmunity Induced by Cytotoxic T Lymphocyte-Associated Antigen 4 Blockade in Patients with Metastatic Melanoma. <i>Proc Natl Acad Sci USA.</i> 2003 Jul 8;100(14):8372-7. doi: 10.1073/pnas.1533209100. (“Phan”)
1027	Sequence Listing of International Patent Publication No. WO 2013/173223 A1 (Nov. 21, 2013) (“Cogswell”)
1028	Callahan et al., Peripheral and Tumor Immune Correlates in Patients with Advanced Melanoma Treated with Combination Nivolumab (Anti-PD-1, BMS-936558, ONO-4538) and Ipilimumab. 2013 ASCO Annual Meeting (May 20, 2013) (Abstract) (“Callahan”)
1029	Declaration of Dr. Dhaval Shah
1030	Curriculum Vitae of Dr. Dhaval Shah
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1033	Mathijssen et al., Flat-Fixed Dosing Versus Body Surface Area-Based Dosing of Anticancer Drugs in Adults. <i>Oncologist.</i> 2007 Aug; 12(8):913-23. (“Mathijssen”)
1034	Bai et al., A Guide to Rational Dosing of Monoclonal Antibodies. <i>Clin Pharmacokinet.</i> 2012 Feb 1; 51(2):119-35. (“Bai”)
1035	Feng et al., Model-based Clinical Pharmacology Profiling of Ipilimumab in Patients with Advanced Melanoma. <i>Br J Clin Pharmacol.</i> 2014 Jul; 78(1):106-17. (“Feng”)
1036	Mould et al., Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies: Concepts and Lessons for Drug Development. <i>BioDrugs.</i> 2010 Feb 1; 24(1):23-39. (“Mould”)

Exhibit	Description
1037	Bi et al., Model-Informed Drug Development Approach Supporting Approval of the 4-Week (Q4W) Dosing Schedule for Nivolumab (Opdivo®) Across Multiple Indications: A Regulatory Perspective. <i>Ann Oncol.</i> 2019 Apr 1; 30(4):644-651. (“Bi”)
1038	Zhao et al., Model-Based Evaluation of the Efficacy and Safety of Nivolumab Once Every 4 Weeks Across Multiple Tumor Types. <i>Ann Oncol.</i> 2020 Feb; 31(2):302-309. (“Zhao”)
1039	Eisenhauer et al., New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). <i>Eur J Cancer.</i> 2009 Jan; 45(2):228-47. (“Eisenhauer”)
1040	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1041	Dirks et al., Population Pharmacokinetics of Therapeutic Monoclonal Antibodies. <i>Clin. Pharmacokinet.</i> 2010 Oct; 49(10):633-59. (“Dirks”)
1042	Lobo et al., Antibody Pharmacokinetics and Pharmacodynamics. <i>J Pharm Sci.</i> 2004 Nov; 93(11):2645-68. (“Lobo”)
1043	U.S. National Library of Medicine, National Institutes of Health <i>Food and Drug Administration Modernization Act of 1997 (FDAMA)</i> , available at https://clinicaltrials.gov/policy/reporting-requirements
1044	U.S. National Library of Medicine, National Institutes of Health, Press Release: National Institutes of Health Launches “ClinicalTrials.gov” (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html
1045	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, How to Edit Your Study Record, https://clinicaltrials.gov/ct2/manage-recs/how-edit
1046	Zarin et al., Reporting “Basic Results” in ClinicalTrials.gov, <i>Chest.</i> 2009 Jul; 136(1):295–303.

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1047	U.S. National Library of Medicine, National Center for Biotechnology Information, <i>About ClinicalTrials.gov</i> : Major milestones related to ClinicalTrials.gov and how information in the database has changed over time, available at https://clinicaltrials.gov/about-site/about-ctg
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1049	Affidavit of Nathaniel E. Frank-White (Internet Archive)
1050	Claims filed in European Patent Application No. 16725959.7 on June 18, 2018
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1052	Summons to Attend Oral Proceedings, European Patent Application No. 16725959.7 mailed on April 28, 2021
1053	Declaration of Withdrawal of European Patent Application No. 16725959.7, mailed on October 1, 2021
1054	European Patent No. EP3288980 B1
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1056	Declaration of Dr. Leonard, submitted in connection with Opposition of European Patent No. EP3288980 B1
1057	Declaration of Dr. Langguth, submitted in connection with Opposition of European Patent No. EP3288980 B1
1058	Grounds for Decision Revoking European Patent No. EP3288980 B1, mailed March 13, 2024

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1059	Examination Report mailed on October 8, 2018 in European Patent Application No. 16725959.7
1060	“Commemorating the 15th Anniversary of the Biologics Price Competition and Innovation Act,” available at: https://www.fda.gov/drugs/cder-conversations/commemorating-15th-anniversary-biologics-price-competition-and-innovation-act (accessed June 20, 2025))
1061	Bristol-Myers Squibb Company Form 10-K (Dec. 31, 2024)
1062	U.S. Patent No. 8,008,449
1063	Patent Term Extension certificate for U.S. Patent No. 8,008,449, mailed Sept. 11, 2018
1064	Notice of Final Determination Eligible for U.S. Patent No. 8,008,449, mailed Mar. 14, 2018
1065	U.S. Patent No. 9,358,289
1066	Biosimilars in the United States 2023-2027, available at: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027 (accessed June 20, 2025)
1067	Biosimilars Forum Applauds the Trump Administration for Drug Pricing Executive Order, available at: https://biosimilarsforum.org/2025/04/16/biosimilars-forum-applauds-the-trump-administration-for-drug-pricing-executive-order/ (accessed June 20, 2025)
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1069	Biosimilar-Related IPR Petitions, available at: https://biologicsshq.com/stats_entry/biosimilar-related-ipr-petitions/ (accessed June 20, 2025)
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1072	Biosimilars Council White Paper, Breaking Through on Biosimilars, Delivering More-Affordable, Innovative Medicines to America’s Patients, available at https://biosimilarscouncil.org/wp-content/uploads/2019/04/Breaking-Through-on-Biosimilars-Biosimilars-Council-White-Paper.pdf
1073	Statement of Grounds for Appeal of Decision Revoking European Patent No. EP3288980 B1, filed July 15, 2024

I. INTRODUCTION

Petitioner's challenges to the patentability of U.S. Patent No. 10,174,113 (the "'113 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 cancer, including melanoma. PO's composition of matter patent expires in December 2028.

The '113 Patent at issue in this IPR expires in 2036 and does not claim the drug itself. Instead, the challenged claims simply recite the use of an anti-PD-1 antibody and an anti-CTLA-4 antibody for a specific indication that was long known in the art at doses that were obvious in view of the art. Any differences between the claims of the '113 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 *eight years*. PO repeatedly tries to characterize the claims of the '113 Patent as more complex than they actually are (e.g., asserting that the "regimen [in the prior art] must be *gerrymandered* in a particular way to reach a *bifurcated regimen* [in the claims].” Br. 27, emphasis

added. In fact, the claims in the '113 Patent simply concern treating melanoma by: (i) administering an anti-PD-1 antibody together with an anti-CTLA-4 antibody every three weeks for about four doses using weight-based dosing, all of which was well-known in the art, then (ii) ceasing the anti-CTLA-4 antibody (which was known to have toxicity concerns) while continuing with anti-PD-1 antibody monotherapy using flat dosing. Flat dosing was common for antibodies such as nivolumab, which has a long half-life and was known not to have toxicity concerns. Notwithstanding extensive prior art, the '113 Patent claims were allowed without any art-based rejections after PO amended the claims to recite the flat dosing feature. The Petition seeks to ameliorate this Patent Office error in allowing these unpatentable claims.

Contrary to PO's assertions, the art and arguments relied upon in the Petition are not the same or substantially the same as those considered during prosecution. The Petition explains that when starting with NCT-505 or Postow—which were not of record during prosecution, and which disclose 3 mg/kg for the nivolumab monotherapy step as opposed to 1 mg/kg disclosed in Wolchok—if a POSA had decided to switch to flat dosing for the anti-PD-1 monotherapy step in view of the extensive advantages known in the art for flat dosing of antibodies that have pharmacokinetic and safety profiles like nivolumab, it would have been obvious to simply *multiply 3 mg/kg by the average body weight (80 kg) and arrive at 240 mg.*

The NCT-109 reference is not necessary for this “elementary arithmetic.” Pet. 3. Instead, it simply constitutes indisputable prior art confirming that PO was already using 240 mg of nivolumab in clinical trials—corroborating that 240 mg would have been an obvious choice when switching to flat dosing.

Petitioner’s challenge to the ’113 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;

(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 taking efficient and predictable steps to clear the path to commercialization years before its anticipated launch, by invalidating a mistakenly granted follow-on patent both to negate the challenged patent and hopefully prevent the issuance of similarly unpatentable 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 patent applications with claims directed to the use of flat doses of an anti-PD-1 antibody for treating melanoma. In one case, in response to the European Examiner’s argument that the flat dosing limitation lacks inventive step (and PO’s inability to overcome this rejection in a subsequent response), PO withdrew the application entirely. In another case, the granted patent was revoked. By contrast, for the ’113 Patent, there is no indication that the Examiner—who did not have access to later prosecution histories of related European cases—considered the advantages of flat dosing. And without access to NCT-505 and Postow, there is no indication that the Examiner considered that the disclosure of 3 mg/kg for anti-PD-1 monotherapy in these references corresponds to 240 mg for a patient of average body weight. The Patent Office committed unmistakable error—evidenced by adjudications in Europe—in allowing the challenged claims over prior art disclosing exactly what PO claims to have invented. IPR is designed to address precisely these errors and oversights and to thereby 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 filing an IPR 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 still in the process of preparing to file aBLAs to secure FDA approval to sell their products in the United States.

Third, biosimilars are critical to the public's access to potentially less expensive options for treatment, and IPRs play a valuable role in increasing 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 '113 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 improperly granted patents in advance of any BPCIA proceedings

represents the “settled expectations” of biosimilar manufacturers. And it further 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 unpatentable claims of the ’113 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 ’113 Patent was granted in error and improperly seeks to extend PO’s exclusivity for Opdivo®. This is exactly the kind of patent that IPRs should address. PO’s request for discretionary denial of IPR2025-00602 against the ’113 Patent should be denied.

II. BACKGROUND

The challenged claims concern methods of treating a melanoma tumor by administering an anti-PD-1 antibody and an anti-CTLA4 antibody. EX1001, cls. As the '113 Patent itself discusses, both these classes of antibodies had been successfully used for cancer immunotherapy long before the earliest possible priority date. EX1001, 1:42-65. Dependent claims in the '113 Patent specify that the anti-PD-1 antibody may be nivolumab (Opdivo®) and the anti-CTLA-4 antibody may be ipilimumab (Yervoy®). EX1001, cls. 10, 13, 20. BMS already obtained numerous patents covering Opdivo®, Yervoy®, and their methods of use in combination to treat cancer, including melanoma, all of which were filed long before, and will expire long before, the '113 Patent.

A. European Applications Relying on Claiming Flat Dosing of Nivolumab For Treatment of Melanoma Have Been Withdrawn or Revoked, 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 '113 Patent’s European counterpart claims have not fared well in Europe.

For example, in counterpart European Patent Application No. 16725959.7, PO pursued claims directed to the use of an anti-PD-1 antibody and an anti-CTLA4

antibody in treating melanoma, wherein the anti-PD-1 antibody was administered at a flat dose. EX1050. In a first Examination Report mailed on October 8, 2018, the Examiner noted that even though the cited art did not disclose flat dosing for the anti-PD-1 antibody, this did not render the claims inventive over the art because “No particular effect has been shown to be associated with the difference.” EX1059 at 4. This rejection based on lack of inventive step was maintained in a subsequent Examination Report (issued after the ’113 Patent granted) in which the Examiner stated that “Without a technical effect associated with the claimed difference(s), the solution represents an arbitrary solution to the problem posed, thereby not involving an inventive step.” EX1051 at 2. When PO was not able to overcome this rejection in a subsequent response, the Examiner issued a Summons to Attend Oral Proceedings. EX1052. Instead of attending the Oral Proceedings, PO chose to withdraw the application. EX1053. PO then pursued a divisional application, European Application No. 21198377.0, which has not yet undergone substantive examination.

Further, European Patent Application No. 16724512.5, which was filed by PO on the same day as the ’113 Patent and names the same sole inventor, granted on March 10, 2021 as European Patent No. EP3288980B1 with claims directed to a composition comprising nivolumab for use in treating melanoma, wherein the nivolumab is administered as a flat dose of 480 mg. EX1054. After grant, five

Notices of Opposition were filed against this patent. Opponents included extensive art and declaration evidence supporting the obviousness of flat dosing of nivolumab. EX1055, EX1056, EX1057. In the Grounds for the Decision revoking the European patent, dated March 13, 2024, the Opposition Division (OD) noted in *dicta* that a monthly flat dose of 480 mg of nivolumab for treatment of melanoma was not inventive based on disclosure in the prior art of 3 mg/kg every two weeks (which was translated to 240 mg based on an average body weight of 80 kg) and based on the known half-life of nivolumab. EX1058, at 19.4. The OD noted that “the skilled person would self-evidently choose the most convenient mode of administration that remains effective” and that “It is within the normal tasks of the person skilled in the art to verify whether a proposed regimen stands a chance of working,” which the skilled person would have been able to do in this instance due to general knowledge about the pharmacokinetic data for nivolumab. *Id.* at 19.4.6. That case is currently under appeal.

The extensive examination in these corresponding European cases related to flat dosing of nivolumab was not before the US Examiner during prosecution of the '113 patent. It stands in contrast to the U.S. prosecution history, which does not reflect any knowledge and understanding in the art related to flat dosing of nivolumab.

B. 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.¹

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

¹ Case schedules and timelines pulled from five BPCIA litigations that were terminated after trial and final judgment demonstrate that average time from Complaint filing through trial to termination is 828 days, with a maximum of 1320 days. See *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.).

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 1. By contrast, a Final Written Decision in this case would be issued far sooner and more predictably, 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.

C. PO is Attempting to Rely on the ’113 Patent to Extend its Exclusivity for Opdivo®

Opdivo® first received FDA approval in December 2014. EX1024. 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. EX1060. 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.” EX1061 at 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”) (EX1062), received patent term extension and expires on December 22, 2028. EX1063, EX1064. 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, including for treatment of melanoma, which expires in 2026. EX1065.

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 '113 Patent, which *expires in 2036* and which claims treatment of an indication that had already been disclosed in the prior art, and had already been claimed by PO. 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 DISCRETION UNDER SECTION 314(A) TO DENY INSTITUTION²

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 '113 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 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 issuance of 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 There is no previous petition concerning the '113 Patent warranting discretionary denial under the *General Plastic* factors.

2. *Fintiv* Factor 2 Disfavors Denial

A Final Written Decision will be issued in this case approximately 12 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. 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 1. 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 '113 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 ’113 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.” EX1066. 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.” EX1067. 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. EX1068, 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 and generally cost less to develop compared to originator biologics.

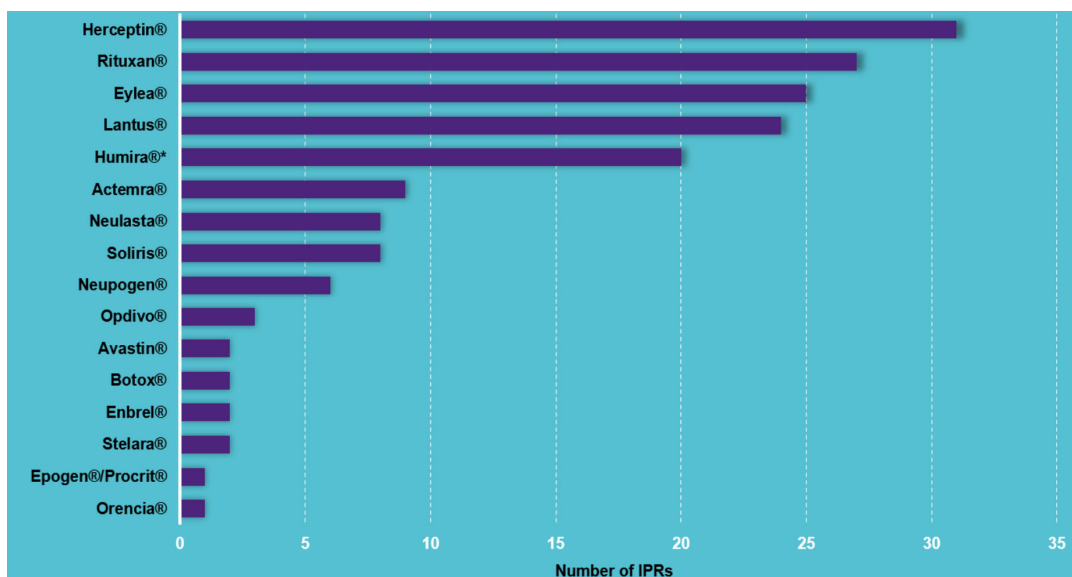
The '113 Patent represents an example of a mistakenly granted patent claiming an otherwise unpatentable method of treatment, standing in the way of fair competition by companies otherwise seeking to market biosimilars of Opdivo®. Since Opdivo® is already patented for a full statutory period, that

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 (EX1069), as reflected in the graph shown below. EX1070.



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. EX1071.

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.” EX1072, 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 '113 Patent granted in 2019, 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 '113 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 2021 withdrawal of a European counterpart to the '113 Patent (EP 16725959.7) and the 2024 revocation of European Patent No. EP3288980B1 demonstrated merits of a challenge to the '113 Patent. Petitioner has balanced an

extensive series of competing risks and incentives in bringing a challenge to the '113 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 also favor institution because the Petition's four grounds (eight if counting sub-grounds to address the effective filing dates of specific dependent claims) demonstrate clearly the obviousness of the challenged claims.

A. The Strength of the Merits Weighs Against Discretionary Denial

As the Petition explains, the challenged claims concern methods of using two categories of known checkpoint inhibitor immunotherapeutic drugs—"anti-PD-1" and "anti-CTLA-4" antibodies—to treat melanoma cancer patients. However, this precise combination had been reported as effective in treating melanoma long before the '113 Patent's earliest possible effective filing date of April 28, 2015. In fact, the combination had been disclosed by 2006. EX1016. And by 2013, positive results had already been reported in clinical trials for treating melanoma using nivolumab (an anti-PD-1 antibody) together with ipilimumab (an anti-CTLA-4 antibody). EX1017; EX1005. Combination therapy was known to improve outcomes even for PD-L1 negative melanoma tumors—notwithstanding the '113 Patent's characterization of its "invention" as recognizing the benefits of combination therapy for such tumors. Pet. 1.

PO repeatedly tries to make the challenged claims sound more complex than they actually are (e.g., asserting that the “regimen [in the prior art] must be *gerrymandered* in a particular way to reach a *bifurcated regimen* [in the claims].” Br. 27, emphasis added. In fact, the claims involve straightforward melanoma treatment methods involving: (i) administering weight-based doses of anti-PD-1 and anti-CTLA-4 antibodies once every three weeks for about 4 doses (as was well-known in the art), then (ii) ceasing the anti-CTLA-4 antibody (which had known toxicity issues) while continuing with anti-PD-1 antibody monotherapy using flat dosing. The table below compares the dosing regimen used in the NCT-505 and Postow primary references and the regimen recited in even the narrowest challenged claims:

NCT-505 and Postow	'113 Patent
(a) 1 mg/kg of an anti-PD-1 antibody and a dose of an anti-CTLA-4 antibody every three weeks for four doses, followed by (b) a weight-based dose of 3 mg/kg of the anti-PD-1 antibody once every two weeks.	(a) 1 mg/kg of an anti-PD-1 antibody and a dose of an anti-CTLA-4 antibody every three weeks for about four doses, followed by (b) a flat dose of about 240 mg once every two weeks [claims 11 and 17] or about 480 mg of the anti-PD-1

	antibody once every four weeks [claims 12 and 18].
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As the table indicates, the only difference between the challenged claims and the primary references is administering the anti-PD-1 monotherapy using a flat dose instead of a weight-based dose. As explained in the Petition, flat dosing was known to offer numerous practical benefits (e.g., improved convenience and less risk of error) relative to weight-based dosing (as disclosed in NCT-505 and Postow) for monoclonal antibodies such as nivolumab with wide therapeutic windows. “[F]ixed dosing” (another name for flat dosing) *indeed “is the approach of choice”* in such cases. EX1008, 1023; *see also* EX1034, 119, 133.

When selecting the specific flat dosage of nivolumab, POSAs would have had a reason to take the known and effective dose regimen of 3 mg/kg once every two weeks (disclosed in NCT-505 and Postow) and multiply it by 80 kg (i.e., the average weight of melanoma patients in immunotherapy trials, EX1035)—yielding a flat dose of 240 mg once every two weeks. POSAs would also have been aware that a 240 mg flat dose of nivolumab was already being used in clinical trials for treating solid tumors, including melanoma, as disclosed in NCT-109. Moreover, POSAs would have reasonably expected a 240 mg flat dose to be comparable to

the NCT-505/Postow 3 mg/kg weight-based dose given pharmacokinetic analysis reflecting nivolumab's wide therapeutic window. EX1011; EX1009.

A 480 mg dose once every four weeks (as required in challenged claims 12 and 18) is simply twice the amount at half the frequency, which POSAs would have been motivated to use since “less frequent dosing schedules” were known to be desirable for “patient convenience and compliance.” EX1021, 158. Moreover, POSAs would have reasonably expected that using a 480 mg dose once every four weeks would be comparable to a 240 mg dose once every two weeks given pharmacokinetic analysis reported for nivolumab over a dose escalation of 0.1-10 mg/kg (corresponding to 8-800 mg for an 80 kg patient)—including administration every four weeks. EX1011; EX1009. And there is no evidence of secondary considerations of non-obviousness sufficient to outweigh any of the strong obviousness arguments set forth in the Grounds.

1. PO's Misplaced Emphasis on NCT-109

PO's assertion that NCT-109 would not provide “a basis to change existing anti-PD-1 treatment regimens” (Br. 28) misapprehends Petitioner's obviousness showing. The Petition explains that when starting with NCT-505 or Postow—which were not of record during prosecution, and which disclose 3 mg/kg for the nivolumab monotherapy step—if a POSA had decided to switch to flat dosing for the anti-PD-1 monotherapy step in view of the extensive advantages known in the

art for flat dosing of antibodies that have pharmacokinetic and safety profiles like nivolumab, it would have been obvious to simply *multiply 3 mg/kg by the average body weight (80 kg) and arrive at 240 mg*. The NCT-109 reference is not necessary for this “elementary arithmetic.” Pet. 3. Instead, it simply constitutes indisputable prior art confirming that PO was already using 240 mg of nivolumab in clinical trials—corroborating that 240 mg would have been an obvious choice when switching to flat dosing. The fact that the anti-PD-1 antibody was administered with an anti-LAG-3 antibody in the clinical trial described in NCT-109 is irrelevant because NCT-109 is not cited as the basis for why one would have chosen 240 mg without any context. The Grounds in the Petition explain that one would have selected 240 mg based on elementary math starting with the cited primary references. NCT-109 simply provides additional evidence that that specific flat dose was indeed one that PO was already using in clinical trials.

PO also argues that the Petition “fails to provide any explanation why one would be motivated to modify the weight-based dosages of anti-PD-1 antibody to include a flat dose *only for the second part of the regimen*.” Br. 29, emphasis added. Aside from being factually wrong (as explained below), PO’s argument is legally irrelevant.

2. PO's Characterizations of Petitioner's Expert Testimony Are Misleading and Internally Inconsistent

PO wrongly suggests that Petitioner's expert testimony is "conclusory" (Br. 30-32)—a characterization PO advances by *selectively* quoting from Petitioner's expert declaration (EX1003).

For example, PO quotes a sentence from the declaration's paragraph 89 (Br. 31) while omitting the critical preceding sentence, which notes how the NCT-109 prior art is simply "[c]onfirming" the "logic" of how POSA would have selected 240 mg as the flat dosage for the nivolumab monotherapy (EX1003, ¶89). In the expert's own words, that logic was the "simple conversion of translating NCT-505's 3 mg/kg weight-based dosage into the actual dose a typical 80 kg clinical trial subject would receive." EX1003, ¶88.

Separately, PO excerpts a single sentence in the middle of paragraph 86 (Br. 31-32) while omitting the surrounding context—including citations to prior art—explaining why POSAs would use flat dosing for the monotherapy step while retaining NCT-505's weight-based dosing for the initial combination therapy step:

In particular, POSAs would have had reason to administer NCT-505's nivolumab monotherapy step via a flat dose while still using weight-based dosing for the earlier step involving co-administration of both nivolumab and the anti-CTLA-4 antibody ipilimumab. As compared to nivolumab, ipilimumab has a less forgiving safety profile. By early 2015, ipilimumab was known to exhibit toxicity and could cause

immune-related adverse events (“IRAEs”). EX1022 at 865. These IRAEs were “associated with tumor regression” in melanoma patients and were “dependent both on peak dosing and area under the curve.” EX1022 at 865. POSAs would have recognized that a body weight dose of ipilimumab (consistent with NCT-505’s express teachings, and later confirmed by Postow to be reasonable and efficacious) offered advantages to mitigate those toxic side effects. POSAs would have also recognized the practical benefits (such as greater convenience and streamlined protocols) of administering both ipilimumab and nivolumab according to a single dosage scheme, as opposed to administering ipilimumab via a weight-based dose and nivolumab via a flat dose. But such practical benefits are not applicable when administering nivolumab as a monotherapy (as taught in NCT-505).

EX1003, ¶86. This detailed testimony is anything but “conclusory.” And it plainly explains “why one would be motivated to modify the weight-based dosages of anti-PD-1 antibody to include a flat dose *only for the second part of the regimen.*” (Br. 29, emphasis added)—that is the nivolumab monotherapy. Yet PO not only falsely accuses Petitioner of failing to provide such an “explanation” (*id.*), but selectively and misleadingly quotes from that very explanation itself (*id.*, 30-31). Petitioner included the paragraph as a stand-alone citation. Petition, 24 (citing “Hanks, ¶89). PO’s inability to respond on the merits is telling and highlights the strength of the petition. This further weighs against discretionary denial.

VI. DISCRETIONARY DENIAL PURSUANT TO 35 U.S.C. §325(D) IS UNWARRANTED³

The Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny institution because both steps of *Advanced Bionics LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential) are satisfied. Despite the existence of extensive prior art related to flat dosing, and in contrast to the thorough analysis of flat dosing during examination in Europe, the '113 Patent claims were allowed without any prior art-based rejections after PO added the flat dosing limitation.

As detailed in the Petition, the challenged claims relate to treating melanoma by: (i) administering an anti-PD-1 antibody together with an anti-CTLA-4 antibody every three weeks for approximately four doses using standard weight-based dosing; then (ii) ceasing administration of the anti-CTLA-4 antibody while still

³ 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.

administering the anti-PD-1 antibody as monotherapy using a flat dose of 240 mg (once every two weeks) or 480 mg (once every four weeks). The 240 mg biweekly flat dose simply corresponds to what an average weight (80 kg) patient would receive via the 3 mg/kg biweekly anti-PD-1 monotherapy dose disclosed in NCT-505 and Postow. 480 mg is simply twice the amount at half the frequency (once a month), as several dependent claims specify.

Importantly, such “elementary arithmetic” underlying Petitioner’s obviousness theories (Pet. 3) is based on the 3 mg/kg biweekly anti-PD-1 monotherapy disclosure included in NCT-505 and Postow, but indisputably absent from the prior art of record. Nor is there any indication in the prosecution history that the Examiner considered the well-known advantages of flat dosing discussed in the Petition or why flat dosing would have been suitable for anti-PD-1 antibodies in particular. Despite these concepts being well-documented in the art, the Examiner either did not have such art in front of them or erred in overlooking such disclosures. In either case, consideration of both prongs of *Advanced Bionics* disfavors discretionary denial.

A. *Advanced Bionics* (1): Whether the same or substantially the same prior art or argument previously was presented to the Office

1. *Becton Dickinson* Factors: (a) The similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; and (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art.

As to *Advanced Bionics* step one, the Petition advances art and arguments not previously considered nor cumulative with art and arguments previously considered.

a. NCT-505 and Postow are not cumulative with Wolchok

All grounds in the Petition are based on primary reference NCT-505 (**Grounds 1 and 2**) or Postow (**Grounds 3 and 4**). Neither reference was of record during prosecution.

The only prior art-based rejection raised during prosecution was an anticipation rejection based on Wolchok. EX1002, 433. PO amended the anti-PD-1 monotherapy step (in which anti-PD-1 is *not* administered together with anti-CTLA4) of the claimed dosing method to distinguish Wolchok. Br. 22. As amended, and as ultimately granted, the anti-PD-1 monotherapy step (part (b) in claims 1 and 2) recites a dose of 240 mg or 480 mg for the anti-PD-1 antibody.

Each of NCT-505, Postow, and Wolchok discloses an initial step of treating melanoma using a combination of anti-PD-1 and anti-CTLA-4 antibodies (corresponding to part (a) in claims 1 and 2), followed by a second step where anti-CTLA-4 administration is ceased but anti-PD-1 administration continues (corresponding to part (b) in claims 1 and 2). However, NCT-505 and Postow disclose different parameters than Wolchok for the second step. Once anti-CTLA-4 administration is ceased, NCT-505 and Postow disclose administering **3 mg/kg** anti-PD-1 antibody (nivolumab) in the monotherapy step, whereas Wolchok discloses 1 mg/kg, as reflected below.

Prior Art	Relevant anti-PD-1 monotherapy disclosure for step 2	Of record?
NCT-505	<u>3</u> mg/kg nivolumab once <u>every two weeks</u> (EX1014, 4)	<u>No</u>
Postow	<u>3</u> mg/kg nivolumab once <u>every two weeks</u> (EX1005, 2006)	<u>No</u>
Wolchok	<i>1</i> mg/kg nivolumab once <i>every three weeks</i> (EX1017, 122)	Yes

PO wrongly argues that the difference in the second step “is immaterial to the patentability of the challenged claims” and is “beside the point.” Br. 23. In fact,

this difference underlies the Petition’s obviousness theory, which relies on “elementary arithmetic.” Pet. 3. As explained in the Petition, 3 mg/kg translates to 240 mg for a person of average body weight. Pet. 23-24; Hanks ¶88.

$$\begin{array}{r} 3 \text{ mg/kg} \text{ once every two weeks} \\ \times \quad \sim 80 \text{ kg} \\ \hline = \quad 240 \text{ mg once every two weeks} \end{array}$$

No such calculation would have been possible with only Wolchok’s disclosure of 1 mg/kg every three weeks.

Accordingly, NCT-505 and Postow represent a significantly different and more advanced starting point for the obviousness analysis for how a POSA would have arrived at the flat doses in part (b) of claims 1 and 2 than does the earlier Wolchok disclosure. By contrast, an obviousness theory based on Wolchok’s 1 mg/kg anti-PD-1 monotherapy disclosure (as opposed to 3 kg/mg as later disclosed in NCT-505 and Postow) would have required a more elaborate theory explaining why a POSA would have increased the dosage (from 1 mg/kg to 3 mg/kg) for an average weight patient while also increasing the frequency (from once every three weeks to once every two weeks).

PO has recognized this significance elsewhere. In Europe, in appealing the Decision Revoking European Patent No. 3288980B1, which claimed a flat dose of 480 mg of nivolumab monthly for treating melanoma, PO has argued that as of the

filing date of that application (which is the same filing date as the '113 Patent), *it was common general knowledge that 3 mg/kg was the preferred dose for anti-PD-1 monotherapy*. Specifically, PO states “by the current filing date, it was common general knowledge that the 3 mg/kg q2w nivolumab regimen had been approved in the USA, EU and Japan for treatment of unresectable or metastatic melanoma Importantly, this means that the skilled person knew that the selection, trialling and ultimate approval of the 3 mg/kg q2w nivolumab regimen was not arbitrary.” EX1073 at paragraphs 372-373. It is clear from PO’s statements that when administering anti-PD-1 alone (i.e., without anti-CTLA-4, as in part (b) of claims 1 and 2 in the '113 Patent), as of the filing date of the '113 Patent, the skilled person would have used 3 mg/kg as a starting point, and when considering switching to flat doses, would have used 3 mg/kg to calculate an appropriate flat dose. This supports the Petition’s obviousness theories and stands in contrast to the '113 Patent’s prosecution history. The only prior art cited in the latter was Wolchok, which PO acknowledges lacks the 3 mg/kg disclosure.

PO’s statements following revocation of EP3288980B1, which confirm the significance of the disclosure in the art of 3 mg/kg as a starting point for assessing obviousness of flat doses for nivolumab, were not of record during prosecution of the '113 Patent. Indeed, the whole line of reasoning underlying the Grounds in the Petition appears not to have been considered during prosecution of the '113 Patent.

b. PO's Misplaced Emphasis on NCT-109

PO argues that NCT-109's disclosure of 240 mg nivolumab is cumulative with that in WO2015/042246 ("Korman"), which was of record. Br. 13-19. This argument neglects Petitioner's straightforward obviousness theory. As noted above, the Petition explains that when starting with NCT-505 or Postow—which were not of record during prosecution, and which disclose biweekly administration of 3 mg/kg nivolumab without anti-CTLA-4—it would have been obvious to:

- (1) switch to flat dosing given the extensive advantages known in the art for antibodies such as nivolumab with wide therapeutic windows, and
- (2) determine the fixed dose by multiplying 3 mg/kg by 80 kg (average weight of melanoma patients in immunotherapy trials), thus arriving at 240 mg.

Pet. 3, 19-20. NCT-109 itself is simply indisputable prior art (unlike Korman, which is assigned to PO and published a month before the earliest possible priority date of the '113) confirming that "a 240 mg flat dose of nivolumab...was already being used in clinical trials for treating solid tumors, including melanoma." *Id.*, 3.

PO also wrongly accuses Petitioner of mischaracterizing NCT-109 by once referring to it as disclosing "anti-PD-1 *monotherapy* as a flat dose" rather than anti-PD-1 as a flat dose (which NCT-109 indisputably does disclose, as Petitioner

repeatedly explains throughout the petition).⁴ The Petition also recites NCT-109’s full title, which makes clear that the anti-PD-1 antibody (nivolumab) was administered *with* anti-LAG3 antibodies. Petitioner’s expert likewise explicitly referenced NCT-109’s “combination therapy.” Hanks ¶89. This teaching was not misrepresented by Petitioner.

Moreover, this point is irrelevant to the arguments made in the Petition, which did not depend on whether the disclosure in NCT-109 constituted monotherapy or not. As noted above, NCT-109 was not cited to explain why a POSA would have specifically selected 240 mg (which was instead based on simple math), but was simply cited as additional evidence to show that PO was, in fact, already using 240 mg of nivolumab in clinical trials, further supporting the argument that when switching to flat dosing, 240 mg would have been an obvious choice to try.

Because there is no overlap between the Grounds in the Petition and the one prior art rejection made during prosecution, and because the only prior art rejection made during prosecution was based on disclosures and theory that is materially

⁴ Use of the word “monotherapy” on page 17, line 10, of the Petition, was inadvertent.

different from and not cumulative in view of the disclosures and theory relied upon in the Petition's Grounds, *Advanced Bionics* Step (1) is not satisfied.

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 Factors: (c) The extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (e): Whether the Petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.**

As discussed above, the primary references relied upon in the Petition were not of record during prosecution and are not cumulative with art considered during prosecution. The Examiner cited a single prior art reference in a single anticipation rejection, and then did not make any additional prior art rejections after PO amended the claims to add a flat dosing feature.

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 has 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”).

Here, there is no indication that the Examiner—who did not have access to later prosecution histories of related European cases—considered the advantages of flat dosing. And without access to NCT-505 and Postow, there is no indication that the Examiner considered that the disclosure of 3 mg/kg for anti-PD-1 monotherapy in these references corresponds to 240 mg for a patient of average body weight. Were any similar disclosures provided in any of the other references cited but never discussed or applied against the pending claims, such failure to raise those arguments can only be attributed to the Examiner’s oversight that such teachings existed in the prior art. PO dumped over a hundred references into the prosecution record of the ’113 Patent, and PO’s arguments now that flat dosing was disclosed in there somewhere cannot explain the Examiner’s oversight in citing to them. Such conduct by the PO weighs strongly against discretionarily denying the instant Petition, which would allow claims to known and obvious treatment indications and dosing structures for anti-PD-1/anti-CTLA-4 combination therapy to stand.

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.").

The Examiner erred in failing to consider the arguments outlined in the Petition explaining why starting with the disclosure of NCT-505 or Postow, a POSA would have had reason to use a flat dose of nivolumab for the monotherapy step given the known benefits of flat dosing and given nivolumab's favorable safety profiles, and why one would have had reason to select the flat doses recited in the claims with a reasonable expectation of success. Pet. 21-23; Hanks, ¶85. The Examiner never discussed any art that disclosed increasing the dose of nivolumab after the combination therapy with ipilimumab, as disclosed by NCT-505 and Postow (EX1007, 5; EX1005, 2006), nor art disclosing the advantages of flat dosing, such as Wang (EX1008), nor the wide therapeutic window, such as Brahmer (EX1009). The Examiner erred in failing to reject the claims over the prior art or otherwise addressing these teachings of the prior art. *See, e.g., Carrier Fire & Security Americas Corp. v. Sentrilock, LLC*, IPR2021-00664, Paper 12 at 21-23 (PTAB Sept. 16, 2021) (declining to exercise discretion where "[t]he prosecution history provide[d] little insight into the Examiner's evaluation of the prior art" and the Examiner's statement that certain limitations were not in the prior art was contradicted by the petition grounds).

The Examiner further erred in not considering that such flat dosing of nivolumab would have been obvious to try, as flat doses are one of a small finite number of dosing schemes suitable for monoclonal antibodies. Hanks, ¶85; EX1036, 30; *Ex parte Anand*, Appeal 2019-001845, 2020 WL 1169599, at *9 (PTAB Mar. 4, 2020) (citing EX1036: “Mould explains that there were three known dosing regimens at the time: (1) flat dosing, (2) body-weight dosing, and (3) Bayesian individualized dosing in response to a measurement. (See Mould 30.).”)

Discretionary denial would not be appropriate.

VII. 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 8,685 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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