

Paper No. _____

Date Filed: June 10, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

IPR2025-00603
Patent No. 11,332,529

**PATENT OWNER'S REQUEST
FOR DISCRETIONARY DENIAL**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	3
A.	Immunotherapy and BMS’s Development of OPDIVO®	3
B.	The ’529 Patent	5
C.	Amgen	7
D.	Amgen’s Petition	8
III.	THE DIRECTOR SHOULD DENY INSTITUTION BECAUSE AMGEN’S CHALLENGES WILL BE RESOLVED THROUGH THE BPCIA PROCEDURES.....	9
IV.	CONCLUSION.....	13

TABLE OF AUTHORITIES

	Page(s)
Case(s)	
<i>Irhythm Techs., Inc. v. Welch Allyn, Inc.</i> , IPR2025-00363, Paper 10 (P.T.A.B. Jun. 6, 2025)	12
Statutes	
35 U.S.C. § 314(a)	2
42 U.S.C. § 262(i)	10
42 U.S.C. § 262(k)	7, 10
42 U.S.C. § 262(l)	<i>passim</i>

EXHIBITS

Exhibit	Description
EX2001	U.S. Patent No. 9,856,320
EX2002	Press Release, Bristol-Myers Squibb, <i>FDA Approves Yervoy™ (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer</i> (Mar. 25, 2011), available at https://news.bms.com/news/details/2011/FDA-Approves-YERVOY-ipilimumab-for-the-Treatment-of-Patients-with-Newly-Diagnosed-or-Previously-Treated-Unresectable-or-Metastatic-Melanoma-the-Deadliest-Form-of-Skin-Cancer/default.aspx
EX2003	Press Release, Bristol-Myers Squibb, <i>Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration</i> (Dec. 22, 2014), available at https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx
EX2004	YERVOY, FDA Approved label and prescribing information, Rev. 5/2025
EX2005	OPDIVO, FDA Approved label and prescribing information, Rev. 5/2025
EX2006	Amgen Pipeline, available at https://www.amgenpipeline.com/
EX2007	NCT05907122, “A Study to Evaluate Similarity of ABP 206 Compared With OPDIVO® (Nivolumab) in Subjects With Resected Melanoma” (Last Update Posted Nov. 27, 2024), available at https://clinicaltrials.gov/study/NCT05907122?term=NCT05907122&rank=1
EX2008	Press Release, Amgen, <i>Amgen Reports First Quarter 2025 Financial Results</i> (May 1, 2025), available at https://www.amgen.com/newsroom/press-releases/2025/05/amgen-reports-first-quarter-2025-financial-results
EX2009	Press Release, Amgen, <i>Amgen Reports Fourth Quarter and Full Year 2024 Financial Results</i> (Feb. 4, 2025), available at https://www.amgen.com/newsroom/press-releases/2025/02/amgen-reports-fourth-quarter-and-full-year-2024-financial-results
EX2010	Amgen Biosimilars, available at https://www.amgen.com/science/biosimilars

BMS respectfully submits this brief requesting discretionary denial in response to the Petition for *inter partes* review filed by Amgen Inc. challenging the patentability of claims 1-18 of U.S. Patent No. 11,332,529 (“the ’529 Patent”) (EX1001).

I. INTRODUCTION

BMS and its collaborators revolutionized cancer treatment by developing novel methods of treating by administering antibodies that bind to PD-1 and CTLA-4, two proteins involved in regulating the immune system, and altering the patient’s immune response. These groundbreaking methods of treatment for cancer fall within a field known as “immunotherapy.” The PTO recognized these innovations and granted BMS multiple patents directed to anti-PD-1 and anti-CTLA-4 antibodies, and various methods of treating cancer by administering such antibodies. The ’529 Patent is one of those patents. It claims regimens for treating cancer by administering combinations of an anti-PD-1 and an anti-CTLA-4 antibody. The innovations protected by the ’529 Patent are the results of BMS’s extensive research and clinical trials programs. They include certain indications covered on BMS’s label for its FDA-approved anti-PD-1 antibody OPDIVO® used in combination with its FDA-approved anti-CTLA-4 antibody YERVOY® for the treatment of a certain type of colorectal cancer.

In its Petition, Amgen argues that the patentability of every claim of the '529 Patent should be reassessed. Consistent with the guidance set forth in the Director's March 26, 2025 Memorandum entitled "Interim Processes for PTAB Workload Management" ("Memorandum"), the Director should exercise her discretion to deny institution of Amgen's Petition.

Specifically, the Director should exercise her discretion to deny institution of this IPR under 35 U.S.C. § 314(a) because the '529 Patent will be among the patents addressed between BMS and Amgen in the course of the statutorily provided Biologics and Price Competition Act ("BPCIA") proceedings that will initiate shortly after Amgen's filing of an abbreviated Biologics License Application ("aBLA") for its biosimilar copy of BMS's OPDIVO[®]. Amgen has repeatedly signaled to the market that it expects registrational data for its OPDIVO[®] biosimilar in the second half of this year. The FDA's acceptance of Amgen's data submission will trigger the patent litigation mechanisms of the BPCIA, beginning with the "Patent Dance." In the Patent Dance, the parties are required to exchange detailed contentions regarding both infringement and the validity of the '529 Patent. These exchanges are statutorily mandated by the BPCIA regardless of whether an IPR is instituted and they culminate in the filing of a complaint in district court. If Amgen refuses to participate in these exchanges, litigation over any patents identified in the Patent Dance is expedited. Because the parties will likely begin the Patent Dance

this year and it only takes 8-9 months to complete these extensive exchanges and begin litigation, an IPR based on this Petition will guarantee duplicative proceedings and waste PTO resources. Moreover, the Patent Dance will involve additional patents that Amgen has not challenged in IPRs. Thus, BPCIA proceedings will go forward regardless of institution here. Put simply, there is no scenario in which a favorable outcome for Amgen here will avoid BPCIA litigation.

II. BACKGROUND

A. Immunotherapy and BMS's Development of OPDIVO®

The human immune system is formed of organs, specialized cells, and substances that protect individuals from infections and disease. T cells are one class of specialized cells that play an important role in the human immune system. One major function of T cells is to destroy pathogens and cancer cells, and to do that the T cells must distinguish between healthy cells and cells that are infected or cancerous. EX2001, 1:33-38. One way in which T cells facilitate this task is through the activation or deactivation of different receptors on the T cell surface.

One of the receptors that T cells express on their surface is a protein called programmed death-1 receptor ("PD-1"). PD-1 acts as a brake on the immune system by downregulating T cell activity to prevent T cells from killing healthy cells. Cytotoxic T lymphocyte-associated protein 4 ("CTLA-4") is another inhibitory

receptor found on T cells that also acts as a brake on the immune system by downregulating T cell activity.

Immunotherapy is a type of treatment that functions by taking advantage of aspects of a patient's immune response to fight disease. One form of immunotherapy involves using antibodies to manipulate the immune response. In particular and as relevant here, antibodies that bind to PD-1 ("anti-PD-1 antibodies") and CTLA-4 ("anti-CTLA-4 antibodies") can be used to disarm or block the activity of these inhibitory receptors. By blocking the PD-1 and CTLA-4 inhibitory receptors, these antibodies are able to increase or activate an immune response. More specifically, by binding to PD-1 and CTLA-4, respectively, these antibodies shut off the brakes on the immune system, freeing the immune cells to recognize, attack and destroy cancer cells. EX2001, 1:57-2:25.

BMS led the industry in developing antibodies that could be used in novel methods of immunotherapy for the treatment of cancer. BMS put its scientific breakthroughs into practice by developing an anti-CTLA-4 antibody called YERVOY® (ipilimumab) and an anti-PD-1 antibody called OPDIVO® (nivolumab). YERVOY®, approved in March 2011, was the first immune checkpoint inhibitor approved by the FDA for the treatment of cancer. EX2002. Clinical testing of OPDIVO® and YERVOY® confirmed the remarkable promise of checkpoint inhibitors as targets for immunotherapy. OPDIVO®, first approved in Japan in 2014,

was the first anti-PD-1 antibody approved anywhere in the world for cancer treatment, and, in December 2014, it was approved in the United States for the treatment of melanoma. EX2003.

Following these initial approvals, BMS continued investing in research and clinical trials aimed at developing novel dosages and treatment regimens to treat patients with cancer. BMS's groundbreaking work included extensive research related to the administration of anti-PD-1 and anti-CTLA-4 antibodies alone and in combination for the treatment of various cancers, and is reflected in BMS's FDA-approved label for OPDIVO[®], which includes indications for non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma, head and neck cancer, malignant pleural mesothelioma, lymphoma, colorectal cancer, hepatocellular carcinomas, esophageal cancer, and gastric cancers. EX2004; EX2005.

B. The '529 Patent

The '529 Patent is titled "Methods of Treating Colorectal Cancer" and issued from U.S. Patent Application No. 16/306,290. It claims priority to U.S. Provisional Application No. 62/345,662 filed on June 3, 2016. EX1001. The '529 Patent generally provides immunotherapy methods for the treatment of a patient with a type of colorectal cancer with a high degree of microsatellite instability, known as "MSI-H" colorectal cancer.

Specifically, the '529 Patent discloses that administering an anti-PD-1 and an anti-CTLA-4 antibody in combination, including by administering specific dosages and dosing regimens, could have a beneficial effect on treating the patient's colorectal cancer. The specification then goes on to report—for the first time—the results of MSI-H colorectal cancer clinical trials performed by BMS. The first example (EX1001 at 27:35-33:47) relates to an initial clinical trial where patients were treated with either nivolumab, or a combination of nivolumab and ipilimumab. The example describes the characteristics of the enrolled patients, and details of the treatments and results of treatment, including the percentage of patients that showed an objective response rate and the percentage of patients that demonstrated progression-free survival. EX1001, 31:31-49 (Table 6); 32:6-17 (Table 7). The second example provided in the '529 Patent (EX1001, 33:50-37:26) relates to an expanded patient population from that trial and provides similar information detailing the patients' characteristics, treatments and the results of treatment, including the overall survival, progression-free survival, objective response rate and duration of response for patients who received the anti-PD-1/anti-CTLA-4 combination at a specific dose. EX1001, 35:47-37:7. In that trial, the inventors observed that the median time from the first dose to death was 8.7 months (a range of 0.1 months to 20.1 months). EX1001, 36:59-64.

There is one independent claim (claim 1) in the '529 Patent. Claim 1 covers a method of treatment comprising administering to the patient a combination of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of MSI-H colorectal cancer. Dependent claims 2 and 3 relate to specific properties of the colorectal cancer and dependent claim 4 specifies that the patient exhibits a certain overall survival or progression-free survival. Finally, dependent claims 5-18 further specify the antibodies, dosages, and/or dosing regimens implemented in the method of claim 1.

C. Amgen

Amgen is currently developing an OPDIVO[®] biosimilar (i.e., a copy) named ABP 206. EX2006. Amgen is conducting clinical trials designed to show the similarity between ABP 206 and BMS's OPDIVO[®] so that it can rely on data BMS has spent more than a decade generating to obtain FDA approval through an abbreviated pathway. EX2007; *see also* 42 U.S.C. § 262(k). It can do so by taking advantage of the statutory scheme set forth in the BPCIA, which Congress passed as part of the Affordable Care Act in 2010. In that same statute, Congress included protections for companies like BMS that develop innovative biologics that are targeted by biosimilar developers. 42 U.S.C. § 262(l). In particular, the BPCIA includes a step-by-step process for the identification of all patents potentially implicated by the biosimilar product and resolution of any disputes regarding those patents. 42 U.S.C. § 262(l)(3)-(6).

If approved, Amgen's biosimilar version of OPDIVO® will be sold with a label that copies information from BMS's OPDIVO® label. Although the approval date remains uncertain, Amgen has repeatedly stated that it anticipates a readout from its similarity study in the second half of this year. EX2008, 21; EX2009, 23. As Amgen has foreshadowed in its communications with investors, data from Amgen's clinical trial will undoubtedly be used for the submission of an aBLA relying on OPDIVO® as a reference product. EX2009, 23 (referring to ABP 206 as an OPDIVO® biosimilar). The FDA's acceptance of Amgen's aBLA will statutorily trigger a patent resolution mechanism that begins with a series of detailed exchanges collectively known as the Patent Dance that culminates in the filing of a complaint for patent infringement. 42 U.S.C. § 262(l)(2). With its Petition, Amgen seeks to duplicate that work, wasting both the PTO's and the parties' resources.

D. Amgen's Petition

Amgen filed its Petition on February 28, 2025 along with two other petitions (IPR2025-00601 and IPR2025-00602), both of which challenge patents in other families that are also owned by BMS. All three of the challenged patents claim novel methods of treating cancer with combinations of anti-PD-1 and anti-CTLA-4 antibodies. While the Petitions are substantively unique, relying on different combinations of references and different technical experts, the patents challenged in

the three Amgen Petitions all protect indications on OPDIVO®'s label and fall within the scope of patents that will be subject to the BPCIA Patent Dance and litigation.

The Petition asserts nine grounds for unpatentability—three primary grounds each divided into three sub-grounds related to different claims. Grounds 1 and 2 rely on a very short summary clinical trial protocol related to the trial ultimately performed and reported in Example 1 of the '529 Patent. *See* EX1005. Amgen argues that protocol anticipates certain claims, and that the rest of the claims in Grounds 1B through 2C would have been obvious in view of that protocol if it was combined with the teachings of 1, 2, or 3 additional references. *Pet.*, 5-6. Ground 3 relies on a publication related to PD-1 monotherapy with a competitor's anti-PD-1 antibody drug. EX1008. Amgen argues that the claims would have been obvious in view of that reference when it was combined with the teachings of 2 or 3 additional references in various combinations set forth in Grounds 3A through 3C. *Pet.*, 6.

III. THE DIRECTOR SHOULD DENY INSTITUTION BECAUSE AMGEN'S CHALLENGES WILL BE RESOLVED THROUGH THE BPCIA PROCEDURES

Consistent with the considerations provided in the Memorandum, the Petition should be denied because Amgen's challenges to the '529 Patent will be addressed by the BPCIA Patent Dance, which Congress specifically enacted as a means for resolving patent disputes that stem from the development and approval of biosimilar drugs. *See* 42 U.S.C. § 262(l). The BPCIA provides an abbreviated approval

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

The BPCIA also provides a structured framework for resolving patent litigation arising from the approval of the biosimilar drug, i.e., the Patent Dance. 42 U.S.C. § 262(l). The Patent Dance requires parties to exchange detailed validity and infringement contentions in an effort to narrow and focus the scope of any eventual patent litigation on only those patents and claims that are truly in dispute. 42 U.S.C. § 262(l)(3)-(6). Specifically, twenty days after the FDA accepts Amgen's completed application for review, Amgen "shall provide to [BMS] a copy of the application". 42 U.S.C. § 262(l)(2)(A). Then, within sixty days, BMS must provide a list of patents for which it believes a claim of infringement could reasonably be asserted. BMS will identify the patents Amgen has challenged in IPR2025-00601, -00602, and -00603, in addition to other patents that cover OPDIVO[®]. 42 U.S.C.

§ 262(l)(3)(A)(i). Then, within sixty days after BMS identifies the patents for which a claim of infringement could reasonably be asserted, Amgen must provide a detailed statement that describes, on a claim-by-claim basis, the factual and legal bases for why it believes each claim is invalid, unenforceable, and/or will not be infringed. 42 U.S.C. § 262(l)(3)(B)(ii)(I). BMS then responds (within sixty days) with its detailed statement, providing the factual and legal bases for why each claim is not invalid and will be infringed. 42 U.S.C. § 262(l)(3)(C). After the parties exchange these detailed contentions, they proceed to negotiate the scope of the resulting litigation. 42 U.S.C. §§ 262(l)(4) and (5). The Patent Dance culminates with the filing of a district court complaint. 42 U.S.C. § 262(l)(6). In effect, Congress designed the Patent Dance to be a focusing exercise that eliminates unnecessary and superfluous litigation over claims and patents not contested between the involved parties.

Based on Amgen's public statements regarding the status of its clinical trial for its OPDIVO[®] biosimilar, the parties are likely to not only begin, but also **complete** the entirety of the Patent Dance and commence litigation prior to the issuance of a final written decision here. EX2008, 21; EX2009, 23. Thus, institution in this proceeding will provide no efficiencies and serve only to duplicate the parties' efforts—contrary to Congress's intent in enacting both the BPCIA and the Leahy-Smith America Invents Act. Because the BPCIA was specifically created by Congress to provide an efficient mechanism for parties to narrow their patent

disputes prior to engaging an adjudicative body, Amgen's patentability challenges are more appropriately dealt with through the Patent Dance in the first instance and then litigation.

The '529 Patent issued on May 17, 2022 (EX1001) and Amgen began Phase III clinical trials of its OPDIVO® biosimilar on July 26, 2023 (EX2007). Amgen sells multiple biosimilar products and is a sophisticated litigant that is very familiar with the BPCIA process. EX2010. Had Amgen wanted to avoid addressing the '529 Patent through BPCIA litigation, it could have filed its IPR much sooner. *See Irhythm Techs., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10 at 3 (P.T.A.B. Jun. 6, 2025) (exercising discretion to deny institution based on settled expectations of the parties). But Amgen chose to wait and now BPCIA patent proceedings are inevitable. There is no need to duplicate efforts and waste PTO resources through an IPR when the parties will be forced to address the infringement and validity of the '529 Patent independently, regardless of institution here.

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The BPCIA establishes a step-by-step process that Congress enacted specifically for resolving patent disputes related to biosimilar approval. BMS invested billions of dollars in developing OPDIVO®, YERVOY®, and the combination treatments protected by its patents, and continues to invest in those treatments. Institution here will not avoid the Patent Dance or any resulting

IPR2025-00603

U.S. Patent No. 11,332,529

litigation—it will only waste the PTO’s and parties’ resources. This is exactly the scenario the Interim Process created in the Memorandum should be used to avoid.

IV. CONCLUSION

For at least the reasons discussed here, the Director should exercise her discretion to deny institution of Amgen’s request for IPR of the ’529 Patent.

Respectfully submitted,

Date: June 10, 2025

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IPR2025-00603

U.S. Patent No. 11,332,529

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

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

The paper contains 2,820 words, excluding the parts of the paper exempted by § 42.24(a).

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

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IPR2025-00603

U.S. Patent No. 11,332,529

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL and EXHIBITS 2001 - 2010 were served on counsel of record on June 10, 2025, by filing these documents through the Patent Trial and Appeal Case Tracking System (P-TACTS), as well as delivering copies via electronic mail to the counsel of record for the Petitioner at the following addresses:

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