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. IPR2025-00603
Patent No. 11,332,529

PETITION FOR INTER PARTES REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.1 et seq

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MANDATORY NOTICES

A. Real Party-In-Interest

Amgen, Inc. ("Amgen" or "Petitioner") is the Real Party-in-Interest.

B. Related Matters

A decision in this proceeding could affect or be affected by the following:

U.S. Patent Application No. 18/787,822 (filed July 29, 2024) claims the benefit of the priority of the filing date of the '529 Patent. U.S. Application No. 17/724,399 (filed April 19, 2022) also claimed the benefit of the '529 Patent's priority date, but is abandoned.

C. Counsel and Service Information - § 42.8(b)(3) and (4)

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A power of attorney is submitted with the Petition. Counsel for Petitioner consents to service of all documents via electronic mail.

I. INTRODUCTION

Amgen Inc. ("Petitioner") requests cancellation of claims 1-18 ("Challenged Claims") of U.S. Patent No. 11,332,529 (EX1001, "'529 Patent"). The Challenged Claims concern known methods of using two categories of known checkpoint inhibitor immunotherapeutic drugs—specifically, "anti-PD-1" and "anti-CTLA-4" antibodies—to treat colorectal cancer tumors "exhibiting a high degree of microsatellite instability (MSI-H)," in which the body's DNA mismatch repair (MMR) system malfunctions.

However, the exact same claimed anti-PD-1/anti-CTLA-4 combination had already been established as effective in treating various other cancers prior to the '529 Patent's earliest possible effective filing date of 6/3/16. *E.g.*, EX1009 (combination therapy to treat kidney cancer); EX1011 (combination therapy to treat melanoma); EX1052 (combination therapy to treat lung cancer). For example, the specific combination of the anti-PD-1 antibody nivolumab and the anti-CTLA-4 antibody ipilimumab—both FDA-approved and commercially available prior to 6/3/16—had been shown to yield a "numerically longer progression-free survival and a higher rate of response than did nivolumab alone in" a melanoma study. EX1011, 31. Nivolumab and ipilimumab are the antibodies disclosed in the '529 Patent's preferred embodiments and recited in the most specific dependent claims.

The prior art also touted such immunotherapies as promising for treating MSI-H colorectal cancer tumors as claimed. For example, Xiao highlighted "the microsatellite instable subset of colorectal cancer" as "a ***particularly good candidate*** for" such "checkpoint blockade immunotherapy." EX1010, 16.[1] Earlier literature indeed had reported promising results using anti-PD-1 antibodies such as nivolumab to treat MSI-H colorectal cancers. *E.g.*, EX1037, 463 (2013 article reporting "[d]urable complete response in [MSI-H] colorectal cancer" treated with nivolumab); EX1008, 2509 (2015 article reporting "clinical benefit" of anti-PD-1 antibody therapy for MSI-H colorectal cancer).

The above-noted Xiao reference (touting MSI-H colorectal cancer as a "particularly good candidate" for checkpoint immunotherapy) highlighted then-ongoing studies using anti-PD-1 antibodies and further taught that "[c]ombinations" with other checkpoint inhibitors such as "CTLA-4" would "likely follow." EX1010, 18. Earlier reports had already taught that anti-PD-1 and anti-CTLA-4 antibodies served "complementary roles" and together achieved synergistic effects. *E.g.*, EX1013, 123, 130-132 (citing EX1012).

Consistent with Xiao's teaching and this additional background knowledge, the "NCT-188" clinical study protocol publicly available as of February 2014

[1] All emphasis added.

disclosed treating MSI-H colorectal cancer using a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody. EX1005. NCT-188—sponsored by Patent Owner ("PO")—describes treatment methods mirroring most Challenged Claims.

Ground 1A details how NCT-188 anticipates Challenged Claims 1 and 4-14. NCT-188's relevant disclosures are essentially identical to the supporting disclosures for those claims. While the '529 Patent discloses the results of the NCT-188 study whereas the NCT-188 protocol does not, such absence is irrelevant. For example, Challenged Claim 1—the sole independent claim—does not recite any such results or otherwise include any efficacy requirement. Yet it purports to exclude the public from practicing the method that NCT-188 publicly disclosed years before the '529 Patent's earliest possible effective filing date. Challenged Claims 1 and 4-14 therefore wrongly withdraw previously known treatment methods from the public domain.

Grounds 1B and 1C detail how NCT-188 in view of other prior art renders obvious the remaining dependent claims. Claims 2-3 recite known characteristics of MSI-H tumors—properties highlighted in prior art (Zhang) recommending the same MSI testing methodology for colorectal cancer as that disclosed in NCT-188. Claims 15-18 require that the anti-PD-1 monotherapy following the initial anti-PD-1/anti-CTLA combination be delivered as a "flat dose" independent of a patient's weight. While NCT-188 discloses weight-based anti-PD-1 monotherapy, flat

dosing was a well-known alternative, and other prior art specifically disclosed a flat dose of 240 mg of the anti-PD-1 antibody nivolumab—consistent with even the most specific dependent claim and the amount of nivolumab administered to average-weight patients even under NCT-188's weight-based dosing.

Grounds 2A-2C correspond to Grounds 1A-1C, respectively, while incorporating additional prior art teachings confirming that a person of ordinary skill in the art (POSA) would have reasonably expected success when administering anti-PD-1 antibodies together with anti-CTLA-4 antibodies as claimed.

Grounds 3A-3C concern a separate and independent basis for finding all claims unpatentable—one centering on clinical ***results***. Le (EX1008) disclosed that MSI-H status "predicted clinical benefit of immune checkpoint blockade" with anti-PD-1 antibodies (EX1008, 2509) and highlighted how anti-PD-1 antibodies achieved a response in MSI-H colorectal cancer. Moreover, the above-identified Xiao article (EX1010) noted such studies (including Le) and reasoned combinations of anti-PD-1 antibodies and other checkpoint molecules such as anti-CTLA "***will likely follow***." Given these teachings, POSAs would have turned to Hammers (EX1009), which discloses combined anti-PD-1/anti-CTLA-4 immunotherapy using particular antibodies at particular dosages over particular intervals satisfying independent claim 1 and dependent claims 4-14. Claims 2-3

and 15-18 likewise would have been obvious over Le-Xiao-Hammers in view of secondary references for the same reasons they would have been obvious over NCT-188 in view of those same references.

Notwithstanding this extensive prior art, the Examiner allowed the '529 Patent claims ***without any art-based rejections***. While PO suggested that it was inventive to target colorectal cancer "exhibit[ing] a high degree of microsatellite instability ('MSI-H')" (EX1002, 2546), NCT-188, Le, and Xiao all confirm the opposite. Yet, the Examiner never addressed NCT-188 or Le, and Xiao was not of record at all.

II. REQUIREMENTS FOR IPR

A. Grounds for Standing

Petitioner certifies that the '529 patent is available for *inter partes* review and that Petitioner is not estopped from requesting such review as to the challenged claims.

B. Identification of Challenged Claims

Petitioner requests cancellation of claims 1-18 of the '529 patent.

C. Grounds of Challenge

Ground Number and Reference(s)		Claim(s)	Basis
1A	NCT-188	1 and 4-14	§102
1B	NCT-188 and Zhang	2-3	
1C	NCT-188 and NCT-109	15-18	

Ground Number and Reference(s)		Claim(s)	Basis
2A	NCT-188, Postow, and Xiao	1 and 4-14	§103
2B	NCT-188, Zhang, Postow, and Xiao	2-3	
2C	NCT-188, NCT-109, Postow, and Xiao	15-18	
3A	Le, Xiao, and Hammers	1 and 4-14	
3B	Le, Xiao, Hammers, and Zhang	2-3	
3C	Le, Xiao, Hammers, and NCT-109	15-18	

Section VI details the basis for the grounds and cites additional references further exemplifying the state of the art as of the earliest alleged effective filing date. *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016); *see also* EX1058 ("Ellis") (confirming public availability of EX1011, EX1012, EX1013, EX1014, EX1020, EX1021, EX1024, EX1026, EX1027, EX1028, EX1029, EX1030, EX1037, EX1038, EX1039, EX1041, EX1048, EX1049, EX1050, EX1052, EX1053, EX1054, and EX1055 on or before 5/31/15; EX1047 by 6/17/15; and EX1034 by 12/1/15).

III. BACKGROUND OF THE '529 PATENT

A. Person of Ordinary Skill in the Art

POSAs as of early 2016 (i.e., before the earliest possible effective filing date of 6/3/16) would have a Ph.D. in immunology or a related field (or alternatively a M.D. with a particular focus on cancer immunotherapy) plus at least two years of experience in that field, including experience with colorectal cancer treatments. Monjazeb, ¶¶38-40. The levels of education, experience and knowledge can trade

off against one another. POSAs would also have either been (1) skilled in pharmacokinetics or (2) able to communicate as part of a team with pharmacokinetics experts if necessary.

B. Prosecution History

The '529 Patent issued from a PCT application filed on 6/2/17 and claims the benefit of a provisional application filed 6/3/16.

The Examiner issued a restriction between method and kit claims and stated that "the technical feature of a PD-1 antibody and a CTLA-4 antibody …does not make a contribution over the prior art in view of Wolchok [EX1013] which discloses method[s] of treatment comprising administering a PD-1 antibody and a CTLA-4 antibody." EX1002, 2542.

PO then selected the method claims while stating that Wolchok did not teach treating patients with tumors "derived from a colorectal cancer" and administering "(1) an anti-PD-1 antibody, and (ii) an anti-CTLA-4 antibody; wherein the tumor exhibits a high degree of microsatellite instability ('MSI-H')." EX1002, 2546.

The Examiner subsequently rejected the claims under 35 U.S.C. §112 as not enabling for "a method of treating any tumor ***derived from*** a colorectal cancer." EX1002, 2553-2554. However, the Examiner indicated that pending claim 2—specifying that "the tumor ***is*** a colon cancer or a rectal cancer"—would be allowable if rewritten in independent form. *Id*. PO in turn amended claim 2 as

suggested (*id*., 2576), and the Examiner issued a notice of allowance (*id*., 2586).

In sum, aside from citing Wolchok in the Restriction Requirement, the Examiner never discussed any prior art.

IV. CLAIM INTERPRETATION

Claim terms are construed herein using the standard used in civil actions under §282(b), in accordance with the ordinary meaning as understood by POSAs and the patent's prosecution history. 37 C.F.R. §42.100(b). The Board need only interpret terms to the extent necessary to resolve disputes between parties.[2] *Nidec Motor v. Zhongshan*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); 83 Fed. Reg. 51,340, 51,353 (Oct. 11, 2018). Petitioner does not believe any term requires any outer-boundaries construction for purposes herein except as otherwise explained below.

V. PRIOR ART TO THE '529 PATENT

As detailed below, all references discussed herein are indisputable §102(a)(1) prior art without any exception under §102(b)(1) because they were publicly available more than one year before the '529 Patent's earliest possible effective filing date (6/3/16). Accordingly, while Petitioner does not concede that

[2] Petitioner does not waive any arguments concerning claim scope necessary for resolving other proceedings. Nor does Petitioner waive any arguments related to indefiniteness or other §112 issues, which could not have been raised in this IPR.

the Challenged Claims are entitled to the benefit of the 6/3/16 provisional application, nor waive any arguments concerning priority relevant to other proceedings, the Board need not address that issue herein.

A. NCT-188 (EX1005)

NCT-188 is Version 1 of a clinical trial protocol with the Brief Title "A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)." EX1005, 4. The "Last Update Posted" date for Version 1 on ClinicalTrials.gov was 2/11/14. EX1005, 4.

As explained in the accompanying declaration of Mr. Prescott Lassman (EX1016, "Lassman"), ClinicalTrials.gov publicizes clinical trial protocols, like NCT-188, as widely and promptly as possible. Lassman, ¶¶16-28; *see also Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc*., IPR2022-00578, Paper 78 at 28 (PTAB Aug. 29, 2023) (citing Mr. Lassman's "intimate knowledge of, and experience with, the ClinicalTrials.gov website" and noting that site is "designed to be used by members of the public"). Pursuant to the FDA Modernization Act of 1997, the National Library of Medicine of the National Institutes of Health ("NIH") launched ClinicalTrials.gov in February 2000 to give the public better access to information on clinical studies. Lassman, ¶¶18-19. The FDA Amendments Act of 2007 later required additional information, enabling electronic searching. *Id.*, ¶¶22-24.

NCT-188 (Version 1) bears a "Last update posted" date of 2/11/14. EX1005, 4. The "Last update posted" date is "[t]he most recent date on which changes to a study record were made available on ClinicalTrials.gov." EX1018, 10. The "Last update posted" date for NCT-188 demonstrates that it was publicly available as of 2/11/14. Lassman, ¶¶31-38. POSAs were aware that such clinical trial protocols were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. Lassman, ¶¶25-30; Monjazeb, ¶¶67-68. For example, when searching ClinicalTrials.gov for clinical trials involving "nivolumab" and concerning "Microsatellite High (MSI-H) Colon Cancer," NCT-188 is the first study returned in the results. Lassman, ¶30. NCT-188 therefore was accessible as of 2/11/14 to interested members of the public. Lassman, ¶¶31-41.

NCT-188 thus constitutes a printed publication under §102(a)(1) as of 2/11/14. *Grunenthal v. Antecip Bioventures*, PGR2019-00003, Paper 22, 17-18 (PTAB May 5, 2020) (finding protocol on ClinicalTrials.gov publicly available as of its "first posted" date and therefore a "prior art printed publication").

Although nominally of record during prosecution (*see* EX1002, 221, 2164, 2840, 2865, 2873, 2890), NCT-188 was not discussed or applied. Moreover, while NCT-188 was cited in a PCT search report and related opinion prepared by the EPO (see EX1002, 104-111), the opinion overlooked that NCT-188 discloses administering nivolumab ***together with ipilimumab*** rather than administering

nivolumab alone. *See* EX1002, 109.

B. Zhang (EX1006)

Zhang is an article entitled "Era of Universal Testing of Microsatellite Instability in Colorectal Cancer" and published 2/15/13 in the World Journal of Gastrointestinal Oncology—a journal readily accessible to POSAs as of the earliest alleged effective filing date. Monjazeb, ¶69; *see also* Ellis, ¶¶45-52 (confirming Zhang's accessibility by 2/15/13).

Zhang was not of record during prosecution. EX1001, 1-3.

C. NCT-109 (EX1007)

NCT-109 is Version 1 of a clinical trial protocol with the Brief Title "Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors." EX1007, 4. The "Last Update Posted" date for Version 1 on ClinicalTrials.gov was 10/23/13. EX1007, 4.

ClinicalTrials.gov publicizes clinical trial protocols (*see* §V.A) and NCT-109's "Last Update Posted" date demonstrates that it was publicly available as of 10/23/13 (Lassman, ¶¶42-52). POSAs knew that clinical trial protocols, like NCT-109, were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. Monjazeb, ¶71. Accordingly, NCT-109 constitutes a printed publication under §102(a)(1) as of 10/23/13. *Grunenthal*, PGR2019-00003, Paper 22 at 17-18.

NCT-109 was not of record during prosecution. EX1001, 1-3.

D. Le (EX1008)

Le is an article entitled "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency" (EX1008) and published in the New England Journal of Medicine—a journal well known to POSAs (Monjazeb, ¶¶72-73). Le has an associated appendix (EX1032) and protocol (EX1040). Monjazeb, ¶72.

Le was published online at NEJM.org on "May 30, 2015" (EX1008, 2509) and would have commended itself to POSAs' attention immediately thereafter given the nature of the field and the New England Journal of Medicine's well-known status (Monjazeb, ¶73). An unrelated article submitted to a different journal on 6/1/15 cited Le—confirming Le's public accessibility more than a year before the '529 Patent's earliest alleged effective filing date. EX1047 (footnote 2); Monjazeb. ¶73; *see also* Ellis, ¶¶53-64 (confirming accessibility of Le, Le's appendix, and Le's protocol) by 2/15/13.

Further, the Internet Archive (also known as the "Wayback Machine") archived Le on 6/2/15. EX1019, 7. *See Valve Corp. v. Ironburg Inventions Ltd.*, 8 F.4th 1364, 1375-76 (Fed. Cir. 2021) (affirming reliance on Wayback Machine to establish public accessibility).

Le was cited in an IDS filed 4/12/19. EX1002, 223. Le was not discussed or applied by the Examiner.

E. Postow (EX1031)

Postow is an article entitled "Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma" (EX1031) and published online at NEJM.org on 4/20/15 (EX1031, 1); it would have commended itself to POSAs' attention immediately thereafter. Monjazeb, ¶¶74-75. A separate article citing Postow published online at NEJM.org on 5/31/2015. EX1011, 34 (footnote 13). *See also* Ellis, ¶¶274-281 (confirming Postow's accessibility by 4/20/15).

Postow was not of record during prosecution. EX1001, 1-3.

F. Hammers (EX1009)

Hammers is an abstract for a poster presentation at the Annual Meeting of the American Society of Clinical Oncology (ASCO) entitled "Expanded Cohort Results from CheckMate 016: A phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC)" and published on 5/20/15 in the Journal of Clinical Oncology (EX1009)—a journal well known to POSAs (Monjazeb, ¶76); *see also* Ellis, ¶¶65-72 (confirming Hammers' accessibility by 5/20/15). Additionally, Hammers' disclosure was presented to POSAs at the 5/29/15-6/2/15 ASCO Annual Meeting. Monjazeb, ¶76.

Hammers was not of record during prosecution.

G. Xiao (EX1010)

Xiao is an article entitled "The Microsatellite Instable Subset of Colorectal Cancer is a Particularly Good Candidate for Checkpoint Blockade

Immunotherapy" and published on 1/15/15 in Cancer Discovery—a journal well known to POSAs (Monjazeb, ¶77); *see also* Ellis, ¶¶73-80 (confirming Xiao's accessibility by 1/11/15).

Xiao was not of record during prosecution.

VI. PRECISE REASONS FOR RELIEF REQUESTED

A. GROUND 1A: NCT-188 Anticipates Claims 1 and 4-14

NCT-188 anticipates independent claim 1 and dependent claims 4-14 because NCT-188 discloses all elements of these claims—including the same antibodies, the same dosages, and the same MSI-H colorectal cancer tumors. Monjazeb, ¶79. Claims 1 and 4-14 wrongly purport "to exclude the public from practicing" NCT-188 and are therefore anticipated by it. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

NCT-188's disclosures are in all relevant respects identical to those in the '529 Patent. While the patent discloses treatment results whereas NCT-188 does not, this is immaterial for multiple reasons.

First, independent claim 1 and dependent claims 5-14 do not require any particular result. Claim 1 merely concerns "treating a subject," and the '529 Patent defines "[t]reatment" as "refer[ring] to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of" reversing or alleviating a disease or its symptoms. EX1001, 11:6-12;

Monjazeb, ¶¶80-81. A subject is "treated" whether or not the treatment is successful. *See* EX1001, 11:6-12 ("***objective of*** reversing, alleviating," etc.); Monjazeb, ¶81; *see also United Therapeutics Corp. v. Liquidia Techs., Inc*., 74 F.4th 1360, 1369 (Fed. Cir. 2023) ("method of treating pulmonary hypertension" did not require showing safety or efficacy).

Second, "anticipation does not require the actual creation or reduction to practice of the prior art subject matter." *Schering*, 339 F.3d at 1380. In this context of claimed treatment methods, an earlier disclosure of such method can anticipate a later claim even if the earlier disclosure "merely proposed the administration of [the drug] for treatment" rather than "actually doing so." *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012). This can be true even if the claim "include[s] an efficacy requirement" (as dependent claim 4 here ostensibly does) because "efficacy is inherent in carrying out the claim steps." *Id*. at 1381; *see also In re Couvaras*, 70 F.4th 1374, 1380 (Fed. Cir. 2023) (explaining that "[n]ewly discovered results of known processes directed to the same purpose are not patentable") (citing *Montgomery*).

Consistent with *Montgomery*, the Board has recognized clinical trial protocols can anticipate when—as here—the factual record supports such determination. *See*, *e.g*., *Celltrion,* IPR2022-00578, Paper 78 at 23-33 (prior art clinical trial protocol anticipated claims); *see also Merck Sharp & Dohme LLC v.*

Johns Hopkins Univ., IPR2024-00240, Paper 10 at 11-19 (PTAB June 13, 2024) (instituting review based on ground that "MSI-H Study Record" anticipated claimed method of treating MSI-H colorectal cancer).

1. NCT-188 (EX1005)

The Official Title of NCT-188 (Version 1) is "A Phase 2 Clinical Trial of Nivolumab and ***Nivolumab Plus Ipilimumab*** in Recurrent and Metastatic ***Microsatellite High (MSI-H) Colon Cancer***." EX1005, 4. NCT-188 discloses treating patients with MSI-H colon cancer with nivolumab and ipilimumab, followed by nivolumab monotherapy, with the "purpose…to examine if ***Nivolumab*** alone or ***in combination with Ipilimumab*** will demonstrate a meaningful objective response rate in patients with recurrent and metastatic ***colon cancer*** who also have ***a specific biomarker in their tumors***." EX1005, 4.

NCT-188 describes identifying tumors by MSI status and identifying the response rate "in all MSI-High subjects." EX1005, 4-5; Monjazeb, ¶¶83-84.

NCT-188 discloses four different arms involving the co-administration of nivolumab and ipilimumab. EX1005, 5.[3] In each case, the initial treatment phase

[3] NCT-188's alternative nivolumab monotherapy arm does not alter the anticipatory nature of the co-administration arms. *Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1381-83 (Fed. Cir. 2015).

involved co-administration every three weeks for four doses. EX1005, 5; Monjazeb, ¶85. During this phase, the arms featured the following dosages:

Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)
-1	0.3	1
1	1	1
2a	1	3
2b	3	1

EX1005, 5.

NCT-188 further discloses that each co-administration arm (i.e., administering both nivolumab and ipilimumab) included a subsequent phase in which patients received nivolumab alone. Monjazeb, ¶86; EX1005, 5 ("…followed by Nivolumab 3mg/Kg IV every 2 weeks until disease progression"). The table below summarizes the NCT-188 disclosure concerning the co-administration study arms:

	Initial Co-Administration Phase (once every three weeks for four doses)		**Subsequent Monotherapy Phase (once every two weeks until disease progression)**
Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)	Nivolumab (mg/kg)
-1	0.3	1	3
1	1	1	3
2a	3	3	3
2b	3	1	3

EX1005, 5; Monjazeb, ¶86.

2. NCT-188 is Enabling

"[A]nticipation does not require actual performance of suggestions in a disclosure," but instead "only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Moreover, NCT-188 is presumed enabling as a prior art printed publication, and it is PO's burden to demonstrate otherwise. *See Apple Inc. v. Corephotonics, Ltd*., 861 F. App'x 443, 449 (Fed. Cir. 2021); *Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01336, Paper 27 at 23-24 (PTAB Feb. 23, 2022).

NCT-188 provides such an enabling disclosure regardless because POSAs could readily practice the disclosed methods without undue experimentation. Monjazeb, ¶87. NCT-188's "Dose Level 2b" discloses the same inclusion criteria (i.e., patients with MSI-H colorectal cancer) and treatment parameters (i.e., "Nivolumab 3mg/Kg IV combined with Ipilimumab 1 mg/Kg IV every 3 weeks for 4 doses followed by Nivolumab 3mg/Kg IV every 2 weeks") later disclosed in the '529 Patent. Monjazeb, ¶88. *See Murray & Poole Enterprises Ltd. v. Institut de Cardiologie de Montreal*, IPR2023-01064, Paper 49 at 29 (PTAB Jan. 14, 2025) (holding that study protocol was enabling because it indicated "what patient population to treat, when to start treatment, the duration of treatment, and how much [drug] to administer").

While NCT-188 does not disclose treatment results, "proof of efficacy is not required for a prior art reference to be enabling." *Impax Lab'ys, Inc. v. Aventis Pharms. Inc*., 468 F.3d 1366, 1383 (Fed. Cir. 2006). Although not required, the prior art demonstrated that the nivolumab/ipilimumab treatment disclosed in NCT-188 was efficacious, confirming enablement. For example, Lipson-2013 reported that nivolumab achieved a "[d]urable complete response in [MSI-H] colorectal cancer." EX1037, 463-464; *see also Merck*, IPR2024-00240, Paper 10 at 23 (instituting review: "Li[p]son reports the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor."). Moreover, Duraiswamy reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy in a colon carcinoma mouse model. EX1053, 3595; Monjazeb, ¶89.

3. Claim-by-Claim Analysis

a. Independent Claim 1

(1) [1.PRE] "A method of treating a subject afflicted with a tumor derived from a colorectal cancer…"

To the extent the preamble is limiting, NCT-188 satisfies it by disclosing "[a] method of treating a subject afflicted with a tumor derived from a colorectal cancer." Monjazeb, ¶91. NCT-188 indeed concerns "[a] Phase 2 Clinical Trial…in…Colon Cancer." EX1005, 4; Monjazeb, ¶91. It discloses that participating patients must have "[h]istologically confirmed colorectal cancer"

including "[m]easurable disease by CT or MRI" with ongoing "[t]umor imaging assessments" of the patients. EX1005, 5; Monjazeb, ¶91.

Even if "treating" were interpreted to require efficacy (despite the specification's plain language to the contrary, as detailed above), NCT-188 would satisfy such a requirement because NCT-188's disclosures mirror those in the '529 Patent. Monjazeb, ¶92. Where the claim steps are the same, "efficacy is inherent in carrying out the claim steps" because it "inevitably" flows from the treatment. *In re Montgomery*, 677 F.3d at 1381. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Ben Venue*, 246 F.3d at 1376; *see also Merck*, IPR2024-00240, Paper 10 at 29 (instituting review of claims to efficacious treatment of MSI-H colorectal cancer using PD-1 inhibitor: "We are persuaded that a reference need not show the efficacy of treatment if the steps were taught in the prior art."); *Murray*, IPR2023-01064, Paper 49 at 29 ("[E]fficacy is inherent in carrying out the protocol disclosed in the art.") (citing *Montgomery*, 677 F.3d at 1381).

(2) [1.A] "administering to the subject:
(i) an anti-PD-1 antibody, and
(ii) an anti-CTLA-4 antibody"

NCT-188 satisfies [1.A] because it discloses "administering to the subject: (i) an anti-PD-1 antibody, and (ii) an anti-CTLA-4 antibody"—specifically, administering nivolumab together with ipilimumab. EX1005, 4 ("A Study

of…Nivolumab Plus Ipilimumab"); 5 (dosing information including "Nivolumab 3 mg/[k]g IV combined with Ipilimumab 1 mg/[k]g IV every 3 weeks for 4 doses"); *see also* §VI.A.1; Monjazeb, ¶93.

POSAs would have understood that nivolumab is an anti-PD-1 antibody previously approved by the FDA for treating multiple cancers. *See* Monjazeb, ¶94; EX1020, 180, 183.

POSAs would have understood that ipilimumab is an anti-CTLA-4 antibody previously approved by the FDA for treating melanoma. *See* Monjazeb, ¶95; EX1021; EX1046; EX1048.

(3) [1.B] "the tumor is a colon cancer or a rectal cancer"

NCT-188 satisfies [1.B] because it discloses a method of treating a cancer tumor in which "the tumor is a colon cancer or a rectal cancer." EX1005, 4 ("Phase 2 Clinical Trial …in Recurrent and Metastatic Microsatellite High (MSI-H) ***Colon Cancer***"); 5 (patients must have "[h]istologically confirmed colorectal cancer" and "[m]easurable disease by CT or MRI"); Monjazeb, ¶96. "Colorectal" means "relating to or affecting the colon and rectum." Monjazeb, ¶¶96-97; EX1022, Merriam-Webster Dictionary (definition of colorectal). Accordingly, POSAs would have understood that NCT-188 concerned treating colorectal cancer tumors. Monjazeb, ¶97.

(4) [1.C] "the tumor exhibits a high degree of microsatellite instability (MSI-H)"

NCT-188 satisfies [1.C] because it discloses treating a tumor that "exhibits a high degree of microsatellite instability (MSI-H)." Monjazeb, ¶98. In particular, NCT-188 concerns "Microsatellite High (***MSI-H***) Colon Cancer." EX1005, 4. It identifies the response rate "in all MSI-High subjects" as one of the study's primary outcome measures. EX1005, 5; Monjazeb, ¶98.

Neither [1.C] nor any other aspect of claim 1 requires testing the tumor to identify whether it exhibits MSI-H. Monjazeb, ¶99. However, even if [1.C] were interpreted to require a testing step, NCT-188 discloses "[t]esting for MSI Status" as an inclusion criterion. EX1005, 5; Monjazeb, ¶99.

b. Dependent Claim 4: Survival of At Least About One Month Following Treatment

Claim 4 depends from claim 1 and requires that, after administration, the subject exhibits either "a progression-free survival of at least about one month" or "an overall survival of at least about one month." Overall survival refers to the length of time "patients diagnosed with the disease are still alive." EX1023 (defining "overall survival"); Monjazeb, ¶¶100-102. Given that any patient exhibiting a "progression-free survival of at least about one month" would necessarily still be alive at the time (i.e., one month after treatment), claim 4 merely recites that a patient receiving the treatment specified in claim 1 remain

alive approximately one month after treatment. Monjazeb, ¶102.

Aside from this statement of intended effect, claim 4 is identical to independent claim 1 and does not "require any additional required structure or condition." *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018). Accordingly, in the present case, claim 4's wherein clause is merely a "non-limiting statement…of intended effect." *Id*.; *see also Murray*, IPR2023-01064, Paper 49 at 18 ("wherein" clause was "not limiting and merely describes [treatment's] intended result"). Aside from disclosing the co-administration of "3 mg/kg nivolumab+1 mg/kg ipilimumab" (identical to NCT-188's "Dose Level 2b"), the '529 Patent does not disclose any other pertinent treatment parameters. Monjazeb, ¶¶102-105. Nor does the '529 Patent otherwise disclose any other difference as between the patients who fell above (versus below) "[t]he median time from the first dose to death or the last known alive date" of "8.7 months." EX1001, 36:62-63. All method steps are "performed the same way whether or not the patient" survives at least one month after administration. *Murray*, IPR2023-01064, Paper 49 at 18 (clinical protocol anticipated method of treatment claim).

In any event, even if claim 4's wherein clause did ostensibly limit the claim, it would not render the claim patentable over NCT-188. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers Squibb*, 246 F.3d at 1376. NCT-188's Dose

Level 2b entails the same process later disclosed in the '529 Patent for the same purpose—treating MSI-H colorectal cancer. Monjazeb, ¶106; *see also id*., ¶107 (discussing EX1034). PO cannot distinguish NCT-188 merely by specifying the desired result. Claim 4 is therefore anticipated by NCT-188.

c. Dependent Claims 5-14: Specific Antibody and/or Dosage Requirements

(1) Claim 5: Anti-PD-1 Antibody is Nivolumab or Pembrolizumab

NCT-188 satisfies the additional limitation of claim 5 because it discloses a treatment method in which "the anti-PD-1 antibody is nivolumab or pembrolizumab"—specifically, treatment using nivolumab. EX1005, 4 ("A Study of…***Nivolumab*** Plus Ipilimumab…"), 2-3 (dosages with nivolumab); Monjazeb, ¶109.

(2) Claim 6: Anti-CTLA-4 Antibody Dosage

NCT-188 satisfies the additional limitations of claim 6 because it discloses a treatment method in which "the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks." Monjazeb, ¶110. In particular, NCT-188 discloses treatments using ipilimumab (an anti-CTLA-4 antibody) dosed at 1 and 3 mg/kg every 3 weeks. EX1005, 5. Accordingly, NCT-188 discloses multiple dosages falling within the claimed 0.1-10.0 mg/kg range with a frequency of every 3 weeks, as recited in claim 6. Monjazeb, ¶111.

(3) Claim 7: Anti-CTLA-4 Antibody is Ipilimumab or Tremelimumab

NCT-188 satisfies claim 7's additional limitation because it discloses a treatment method in which "the anti-CTLA-4 antibody is ipilimumab or tremelimumab." NCT-188 describes dosing with ipilimumab (an anti-CTLA-4 antibody). EX1005, 4 ("A Study of …Nivolumab Plus ***Ipilimumab***"), 2-3 (describing dosing with ipilimumab). Monjazeb, ¶¶112-113.

(4) Claim 8: Anti-PD-1 Antibody Dosage

NCT-188 satisfies claim 8's additional limitations because it discloses a treatment method in which "the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks." Monjazeb, ¶114. In particular, NCT-188 discloses treatment methods using nivolumab (an anti-PD-1 antibody) at doses of 0.3 mg/kg every 3 weeks, 1 mg/kg every 3 weeks, and 3 mg/kg every 3 weeks. EX1005, 5. Accordingly, NCT-188 discloses multiple dosages within the range of 0.1 mg/kg to 10.0 mg/kg and a frequency of every 3 weeks, as recited in claim 8. Monjazeb, ¶114.

(5) Claim 9: Anti-PD-1 and Anti-CTLA-4 Dosages

NCT-188 satisfies claim 9's additional limitation because it discloses multiple treatment arms in which the dosages of anti-PD-1 and anti-CTLA-4 antibodies satisfies at least one of the four recited scenarios separated by an "or."

Any one of those arms suffices to satisfy the limitation. *See Brown v. 3M*, 265 F.3d 1349, 1352 (Fed. Cir. 2001).

In particular, NCT-188 discloses three of the four alternatives recited in claim 9. *See* Monjazeb, ¶¶115-116:

Claim 9 option	anti-PD-1 antibody (mg/kg) (e.g., nivolumab)	anti-CTLA-4 antibody (mg/kg) (e.g., ipilimumab)	Arm designation in NCT-188
(i)	1	1	Dose Level 1
(ii)	1	3	Dose Level 2a
(iii)	3	1	Dose Level 2b

NCT-188's disclosures of dose levels 1, 2a, and 2b therefore each separately anticipates claim 9.

(6) Claim 10: Subsequent Anti-PD-1 Monotherapy

Claim 10 depends from claim 9 and further requires "the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy."

NCT-188 satisfies claim 10's additional limitations because it satisfies claim 9 (as detailed above) and further discloses that each arm of the study (i.e., featuring nivolumab and ipilimumab co-therapy) was followed by an anti-PD-1 monotherapy—specifically, administering "Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression." EX1005, 5. Monjazeb, ¶¶118-119. NCT-188's disclosures of dose levels 1, 2a, and 2b each separately anticipate claim 10 because

POSAs would understand that each NCT-188 arm was followed by the nivolumab monotherapy. Monjazeb, ¶119.

(7) Claim 11: Anti-PD-1 and Anti-CTLA-4 Dosages and Duration.

Claim 11 depends from claim 1 and recites "wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once about every 3 weeks for a total of 12 weeks."

NCT-188 satisfies this limitation because it discloses "Dose Level 2b: Nivolumab [an anti-PD-1 antibody] ***3 mg/[k]g*** IV combined with Ipilimumab [an anti-CTLA-4 antibody] ***1 mg/[k]g*** IV every ***3 weeks for 4 doses***…" EX1005, 5. Accordingly, the dosage is the same and the time period—every 3 weeks for 4 doses—corresponds to a total of 12 weeks. Monjazeb, ¶¶120-121.

(8) Claim 12: Combination of Claims 10 and 11

Claim 12 depends from claim 11 and is otherwise identical to claim 10. NCT-188 anticipates claim 12 for the same reasons. *See* §VI.A.3.c(6); Monjazeb, ¶122.

(9) Claim 13: Anti-PD-1 Monotherapy Administered Once About Every Two Weeks

Claim 13 depends from claim 12 and recites "the anti-PD-1 antibody monotherapy is administered once about every 2 weeks."

NCT-188 satisfies this limitation by disclosing that the anti-PD-1 antibody

monotherapy provided after the combination therapy phase is administered every 2 weeks. EX1005, 5 ("followed by Nivolumab 3mg/Kg IV ***every 2 weeks***"); Monjazeb, ¶¶123-124.

(10) Claim 14: Anti-PD-1 Monotherapy of 3 mg/kg Administered Once About Every Two Weeks

Claim 14 depends from claim 12 and recites "the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks."

NCT-188 satisfies this limitation by disclosing that the anti-PD-1 antibody monotherapy is dosed at 3 mg/kg once every 2 weeks. EX1005, 5 ("followed by Nivolumab 3mg/Kg IV ***every 2 weeks***"); Monjazeb, ¶¶125-126.

B. GROUND 1B: NCT-188 and Zhang Render Obvious Claims 2-3

Dependent Challenged Claims 2-3 recite characteristics of the MSI-H colon or rectal tumor treated by claim 1's immunotherapy method. Those characteristics specify well-known details concerning MSI-H status, which concerns losses of function in a patient's MMR (mismatch repair) system. Monjazeb, ¶127; EX1039, 3380.

Claim 2 depends from claim 1 and recites several characteristics in the alternative, any which suffices to practice the claimed method. One option is that "at least one protein encoded by DNA MMR genes is not detected in the tumor."

EX1001, 37:36-45. The absence of one or more MMR proteins is consistent with MSI-H status. Monjazeb, ¶128.

Claim 3 depends from claim 2 and specifies that the "DNA MMR genes" may be "any combination" of five genes. EX1001, 37:46-48. All five of the recited genes were well known to POSAs as related to MMR. Monjazeb, ¶129 (discussing EX1006, EX1024, and EX1025).

As shown below, Zhang discloses the characteristics specified in claims 2 and 3.

1. Zhang (EX1006)

Zhang, (entitled "Era of universal testing of microsatellite instability in colorectal cancer") explains that, as of 2013, "[i]ncreased emphasis has been placed on the importance of MSI testing for all newly diagnosed individuals with [colorectal cancers]." EX1006, Abstract. Zhang discloses that "MSI is detected indirectly by ***demonstrating absence of expression of MMR proteins*** by immunohistochemical staining (IHC), or more directly by polymerase chain reaction (PCR)-based amplification of specific microsatellite repeats." EX1006, 14; Monjazeb, ¶¶131-132. Further, Zhang discloses that "[t]he principle of using IHC of MMR proteins to indirectly indicate the presence of MSI is that the absence of one or more of the MMR proteins can cause MSI." EX1006, 14.

2. Reason to Combine NCT-188 and Zhang

As discussed in §VI.A.1, NCT-188 discloses treating MSI-H colorectal cancer tumors and specifies "[t]esting for MSI Status" as one of the "Inclusion Criteria." EX1005, 5; Monjazeb, ¶133. POSAs implementing NCT-188 would thus have reason to screen prospective patients for MSI-H status per NCT-188's Inclusion Criteria and to achieve NCT-188's "primary outcome measure[]" of determining the "[o]bjective response rate (ORR) in all MSI-High subjects." EX1005, 5; Monjazeb, ¶133. Zhang discloses criteria to identify MSI-H status. Moreover, POSAs would have had reason to consider Zhang because it concerns colorectal cancer and was published in a journal about "Gastrointestinal Oncology." Monjazeb, ¶134. Zhang teaches the desirability of "MSI testing for all newly diagnosed" colorectal cancer patients. EX1006, 12. Accordingly, POSAs would be motivated to use Zhang's MSI-H criteria to further define MSI-H status as disclosed in NCT-188 when "[t]esting for MSI Status" as NCT-188 discloses prior to treating patients for colorectal cancer. Monjazeb, ¶¶134-135.

Further, POSAs would have had reason to implement NCT-188 using Zhang's methodology of "***demonstrating absence of expression of MMR proteins*** by immunohistochemical staining (IHC)" (EX1006, 14) because such staining was a well-known methodology that could be readily implemented without special equipment or genetic testing. Monjazeb, ¶¶135-136; *see also* EX1006, 14 (noting

that "[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system"). NCT-188 implemented using Zhang's disclosed method of "***demonstrating absence of expression of MMR proteins"*** to determine MSI-H status—using commercially available antibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 as disclosed in Zhang—is hereinafter referenced as "NCT-188-Zhang."

3. Reasonable Expectation of Success

POSAs would have had a reasonable expectation of success in combining NCT-188 and Zhang given that Zhang's immunohistochemical staining methodology for detecting MSI status was a well-known and reliable technique that could be implemented using readily available equipment. Monjazeb, ¶137.

4. Claim-by-Claim Analysis of NCT-188-Zhang

a. Claim 2

Claim 2 depends from claim 1 and recites that the tumor meets one or more of three characteristics, one of which is that "at least one protein encoded by DNA MMR genes is not detected in the tumor."

NCT-188-Zhang renders obvious claim 2 because the combination involves implementing NCT-188's inclusion criteria of "testing for MSI status" based on Zhang's disclosure of detecting MSI via "immunohistochemical staining (IHC)." EX1006, 14; Monjazeb, ¶¶138-139. Zhang's disclosed IHC method involves

testing the tumor to determine if it "indicate[s] the presence of MSI" via "***the absence of one or more of the MMR proteins***." EX1006, 14. POSAs would understand that "one or more of the MMR proteins" means "at least one protein encoded by DNA MMR genes." Monjazeb, ¶140. Accordingly, detecting MSI positive colon or rectal cancer pursuant to NCT-188-Zhang entails determining that "at least one protein encoded by DNA MMR genes is not detected in the tumor." Monjazeb, ¶140.

b. Claim 3

Claim 3 depends from claim 2 and recites that "the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof."

NCT-188-Zhang renders obvious claim 3 because Zhang teaches identifying MSI status using immunohistochemical staining "of MMR proteins to indirectly indicate the presence of MSI" through the "absence of one or more of the MMR proteins." EX1006, 14. Zhang explains that "[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system." EX1006, 14. In particular, as explained in §VI.B.2, the NCT-188-Zhang combination entails using commercially available antibodies (as disclosed in Zhang) to indicate the presence or absence of MLH1, PMS2, MSH2 and MSH6. *See also* Monjazeb, ¶¶141-42. Accordingly, NCT-188-Zhang involves treating patients in which the "DNA MMR

genes" of claim 2 include MLH1, PMS2, MSH2 and MSH6. Monjazeb, ¶142. That group satisfies the additional requirement of claim 3 because it includes "***MSH2***, ***MLH1***, ***MSH6***, ***PMS2***, PMS1, ***or any combination thereof.***"

C. GROUND 1C: NCT-188 and NCT-109 Render Obvious Claims 15-18

Claims 15-18 depend directly or indirectly from dependent claim 12 and require that the "anti-PD-1 antibody monotherapy" be administered as a "flat dose"—that is, administering all patients the same dose "without correction for body size or other (pharmacological) parameters." EX1029, 918; Monjazeb, ¶143.

Such flat dosing (also known as fixed dosing) was a well-known technique—including in anti-PD-1 antibody cancer treatments such as NCT-109—recognized as offering numerous advantages over weight-dependent dosages. *See* §§VI.C.1-VI.C.3. Accordingly, NCT-188 in view of NCT-109 ("NCT-188-NCT-109") renders obvious claims 15-18. Monjazeb, ¶¶144-45.

1. NCT-109 (EX1007)

The Official Title of NCT-109 (Version 1) is "A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors." EX1007, 4.

NCT-109 discloses administering flat doses of nivolumab (identified as

BMS-936558), including 80 and 240 mg dosages (Parts B–C). EX1007, 5; Monjazeb, ¶¶146-147.

2. Reason to Combine NCT-188 and NCT-109

As discussed in §VI.A.3.c(6) (concerning dependent claim 10), NCT-188 discloses anti-PD-1 antibody monotherapy at a weight-based dose of 3 mg/kg after completing the anti-PD-1/anti-CTLA-4 co-therapy. *See* EX1005, 5 ("…followed by Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression").

POSAs would appreciate that flat dosing offers advantages over weight-based dosing for the nivolumab monotherapy. Monjazeb, ¶¶148-149. For example, a 2009 article (Wang) about flat dosing of monoclonal antibodies explains that it offered "numerous advantages over body size–based dosing," including greater convenience and lower costs. EX1030, 1023.

Given these advantages, it was known that "when there is no advantage of one dosing approach over another from a PK and PD perspective, ***fixed dosing is the approach of choice***" for monoclonal antibodies. *Id.* Such understanding was applicable to NCT-188's nivolumab monotherapy phase because weight-based dosing of nivolumab alone did not offer PK or PD-related advantages and likewise did not offer any particular practical benefit in this nivolumab monotherapy phase. Monjazeb, ¶¶149-150.

Other prior art confirms Wang's recommendations. Monjazeb, ¶¶151-152.

For example, Mathijssen notes that flat-dosing provides advantages including "positive economic implications"; "safety" benefits; and better "patient adherence," such that it may be preferred to size-based dosing unless the drug exhibits "a narrow therapeutic window and high interindividual variability in exposure." EX1029, 918. Bai likewise teaches that most monoclonal antibodies have "a relatively large therapeutic window" and "fixed dosing is recommended" as "the first option in first-in-human studies" given flat dosing's "many practical advantages." EX1055, 133. It was well known that nivolumab had a wide therapeutic window. EX1050, 3169, 3171.

Accordingly, POSAs would have had reason to practice NCT-188's nivolumab monotherapy step using a flat dose of nivolumab rather than NCT-188's weight-based dose. Monjazeb, ¶¶153-154.

In particular, POSAs would have had reason to select a flat 240 mg nivolumab dose—consistent with one of the dosages expressly disclosed in NCT-109—given the knowledge that when bodyweight-based dosing has been used previously, "[t]he dose of fixed dosing approach [is] set to the dose that would be given to a subject with median [bodyweight] by [bodyweight]-based dosing." EX1030, 1014; Monjazeb, ¶155. Under that approach, NCT-188's disclosure of 3 mg/kg nivolumab translates to 240 mg nivolumab from the simple conversion of multiplying NCT-109's 3 mg/kg by the ~80 kg weight of typical subjects

participating in other cancer immunotherapy studies. Monjazeb, ¶¶155-156; EX1041, 108 (reporting mean body weight of 80.11 kg for ipilimumab).

Practicing NCT-188 with a 240 mg flat dose of nivolumab for the nivolumab monotherapy phase is henceforth referenced as "NCT-188-NCT-109." Aside from substituting the 240 mg flat dose of nivolumab in place of the 3 mg/kg weight-based dose, NCT-188-NCT-109 is identical to NCT-188 and therefore satisfies dependent claim 12 (from which claims 15-18 depend) for the reasons detailed in §VI.A.3.c(8).

3. Reasonable Expectation of Success

POSAs would have had a reasonable expectation of success when practicing NCT-188 with a 240 mg flat dose of nivolumab once every two weeks for the nivolumab monotherapy phase (i.e., in place of NCT-188's 3 mg/kg nivolumab once every two weeks) given that it reflects the amount of nivolumab specified by NCT-188 for an average weight (80 kg) patient. Monjazeb, ¶157. 240 mg flat dosing of nivolumab was also a well-established dosing strategy for various other tumor types—further confirming the reasonable expectation of success when using this technique to practice NCT-188. *See* EX1043, ¶¶ [0002], [0096], [0187] (240 mg nivolumab for lung cancer); Monjazeb, ¶158. Moreover, a dose escalation study had reported that nivolumab was tolerated at dosages up to 10 mg/kg across multiple cancer types (EX1049, 2445)—further confirming the safety of a 240 mg

flat dose even for lightweight patients. Monjazeb, ¶158. For example, 240 mg nivolumab corresponds to less than 7 mg/kg even for a 36 kg (80 pound) patient. Monjazeb, ¶158.

4. Claim-by-Claim Analysis

a. Claim 15: Anti-PD-1 Antibody Monotherapy Administered as a Flat Dose

NCT-188-NCT-109 satisfies claim 15 because "the anti-PD-1 antibody monotherapy is administered as a flat dose"—specifically, a 240 mg flat dose of nivolumab—as detailed in §VI.C.2. Monjazeb, ¶159. Accordingly, NCT-188 in view of NCT-109 renders claim 15 obvious.

b. Claim 16: Anti-PD-1 Antibody Monotherapy Administered as a Flat Dose of About 240 mg Once About Every 2 Weeks

NCT-188-NCT-109 satisfies claim 16 because "the anti-PD-1 antibody monotherapy is administered at a flat dose of about 240 mg once about every 2 weeks" as detailed in §VI.C.2. Monjazeb, ¶160. Accordingly, NCT-188 in view of NCT-109 renders claim 16 obvious.

Indeed, as noted in §VI.C.2, a 240 mg flat dose of nivolumab reflects the amount of nivolumab that would be administered to an 80 kg patient (i.e., consistent with average weight of humans generally and in patients enrolled in, for example, an ipilimumab study, *see* EX1041) under NCT-188's disclosed 3 mg/kg weight-based nivolumab dose. Monjazeb, ¶161.

c. Claim 17: Anti-PD-1 Antibody is Nivolumab

NCT-188-NCT-109 satisfies claim 17 because it satisfies claim 16 (as detailed immediately above) and further because the anti-PD-1 antibody used is nivolumab—per both NCT-188 and NCT-109. *See* NCT-109, 2-3 EX1005, 5; EX1007, 5; Monjazeb, ¶162.

d. Claim 18: Anti-CTLA-4 Antibody is Ipilimumab

NCT-188-NCT-109 satisfies claim 18 because it satisfies claim 17 (as detailed immediately above) and further because the anti-CTLA-4 antibody used in the combination therapy phase of the treatment is ipilimumab—consistent with NCT-188's discussion. *See* EX1005, 4 ("A Study of …Nivolumab Plus Ipilimumab"), 5 (describing dosing with ipilimumab); Monjazeb, ¶163. The combination therapy disclosures in NCT-188 are not impacted by substituting NCT-109's 240 mg flat dosing of nivolumab in place of NCT-188's weight-based dosing of nivolumab for the anti-PD-1 monotherapy. Monjazeb, ¶163.

D. GROUNDS 2A-2C: Addition of Postow and Xiao to Grounds 1A-1C

As detailed in Ground 1A, NCT-188 is enabling and anticipates claims 1 and 4-14. However, even if PO disputed NCT-188's enablement and/or argued that the claims require some efficacy not disclosed by or inherent from NCT-188, such theories would be immaterial in view of Postow and Xiao. Monjazeb, ¶164.

Postow discloses the same dosage schedule as NCT-188's Dose Level 2a

(i.e., 1 mg/kg nivolumab and 3 mg/kg ipilimumab every three weeks for four doses, followed by 3 mg/kg nivolumab monotherapy every two weeks) and further discloses that such treatment yielded "durable responses"—indeed, "substantially higher objective response rate, longer progression-free survival, and higher rates of complete responses than ipilimumab monotherapy." EX1031, 1-5; Monjazeb, ¶165; *see also* EX1011, 31 (reporting that "combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone").

While Postow's clinical results concerned melanoma patients, Xiao specifically referenced anti-PD-1 colorectal cancer clinical trials such as NCT-188 and emphasized that "***[c]ombinations*** with IDO, LAG-3, ***CTLA-4***, and other checkpoints will likely follow." EX1010, 18; Monjazeb, ¶166.

Given Postow and Xiao, POSAs would have reasonably expected NCT-188's disclosures (including but not limited to Dose Level 2a) to be efficacious and would have implemented NCT-188 to maximize the likelihood of such efficacy. Monjazeb, ¶167. Other teachings further confirm such expectation and the high level of skill in the art. *Id*. For example, Lipson-2013 reported that even nivolumab alone achieved a "[d]urable complete response in [MSI-H] colorectal cancer." EX1037, 463-464; *see also Merck*, IPR2024-00240, Paper 10 at 23 (instituting review: "Li[p]son reports the successful treatment of a colorectal

cancer patient having MSI-H status with a PD-1 inhibitor."). Moreover, synergistic effects of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model. EX1053, 3595, 3599-3600; Monjazeb, ¶168.

Ground 2A therefore establishes that claims 1 and 4-14 are at minimum obvious over NCT-188 (as detailed in Ground 1) in view of Postow and Xiao. Monjazeb, ¶¶169-171. As to dependent claim 4 (i.e., the only claim reciting clinical results), POSAs would have had reason to take steps consistent with medical best practices to maximize survival time, and further would have reasonably expected patients undergoing the combination therapy to survive at least one month as recited in claim 4. *Id*. Medical literature predicted "the use of effective immunotherapy for treatment of colorectal cancer in the near future." EX1038, 3738; Monjazeb, ¶171. NCT-188's schedules themselves confirm that more than one month survival was expected. EX1005, 5 ("Tumor imaging assessments will occur every 6 weeks from the date of first dose (+/-1 wk) for the first ***24 weeks***, then every 12 wks (+/-1 wk) thereafter…"; "The final analysis of the primary endpoint will occur ***at least 6 months*** after the last enrolled subject's first dose…").

For the same reasons, **Ground 2B** establishes that claims 2-3 are at minimum obvious over NCT-188 and Zhang (as in Ground 1B) in further view of Postow and Xiao. Monjazeb, ¶172. Xiao specifically discusses MSI-H (i.e., MSI)

colorectal cancer and discusses how it can result from "mutation of DNA mismatch repair genes," which Zhang details. EX1010, 16.

Likewise, **Ground 2C** establishes that claims 15-18 are at minimum obvious over NCT-188 and NCT-109 (as in Ground 1C) in further view of Postow and Xiao. Xiao specifically identifies LAG-3 (along with PD-1 and CTLA-4) as among the checkpoint molecules expressed in MSI colorectal cancer, and NCT-109 concerns a clinical trial testing the effectiveness of anti-LAG-3 antibodies with or without anti-PD-1. Monjazeb, ¶173.

E. GROUND 3A: Le, Xiao, and Hammers Render Obvious Claims 1 and 4-14

Le in view of Xiao and Hammers ("Le-Xiao-Hammers") renders obvious claims 1 and 4-14. Monjazeb, ¶174.

1. Le (EX1008)

Le describes results of a phase 2 study "evaluat[ing] the clinical activity of pembrolizumab, an [anti-PD-1] immune checkpoint inhibitor" in 41 patients across three cohorts:

- the first—cohort A—including patients with mismatch repair-***deficient*** [i.e., MSI-H] colorectal adenocarcinomas;
- the second—cohort B—including patients with mismatch repair-***proficient*** colorectal adenocarcinomas; and
- the third—cohort C—including patients with other types of cancers

that were mismatch repair-***deficient***.

EX1008, 2509-10; Monjazeb, ¶175 (also citing EX1026, 1043; EX1027, 5248; EX1028, 2417)

Le reported markedly better results when using pembrolizumab to treat cohort A (i.e., MSI-H colorectal cancer patients) as compared to cohort B (i.e., microsatellite stable ("MSS") colorectal cancer patients). EX1008, 2513; Monjazeb, ¶176:

	MSS Colorectal Cancer	MSI-H Colorectal Cancer
Objective Response Rate	0%	40%
Progression-Free Survival Rate	11%	78%
Disease Control Rate	11%	90%

EX1008, 2514. Further, Le disclosed that among MSS patients, median progression-free survival was only "2.2 months… and the median overall survival was 5.0 months," whereas for MSI-H patients neither survival criteria was reached. *Id.*; Monjazeb, ¶176.

Given these results, Le concluded that "mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors." EX1008, 2516; Monjazeb, ¶177. The results supported Le's hypothesis based on an earlier study reporting that of "33 patients with colorectal cancer" "only 1 of

[the] 33" had responded to treatment with another anti-PD-1 antibody (i.e., nivolumab) (EX1008, 2510; EX1049; EX1050; EX1051). Despite that low percentage, the colorectal cancer tumor of the single responsive patient "was mismatch repair-deficient." EX1008, 2510 (citing EX1037); Monjazeb, ¶¶177-178.

2. Xiao (EX1010)

Xiao is a January 2015 article entitled "The Microsatellite Instable Subset of Colorectal Cancer is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy." EX1010. Reviewing earlier work, Xiao highlights how anti-PD-1 therapies could be combined with antibodies targeting other checkpoints such as CTLA-4 to treat MSI-H colorectal cancer. EX1010, 16.

Specifically, Xiao summarizes an earlier study and notes how it determined that "compared with [microsatellite stable] tumors, [microsatellite instable] tumors highly upregulate expression of multiple immune checkpoints, including programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)." *Id.* Xiao identified PD-1 and CTLA-4 as two of the checkpoints upregulated in MSI-H colorectal cancer tumors. *Id.*

Xiao also notes that all of these upregulated checkpoints—including PD-1 and CTLA-4—were "currently being targeted clinically with inhibitors." EX1010, 18. More specifically, Xiao stated that "[t]he FDA approved a CTLA-4 monoclonal antibody (mAB; ipil[i]mumab) in 2010 and a PD-1 mAb

(pembrolizumab) in 2014 for melanoma treatment." *Id.*; Monjazeb, ¶¶179-181.

Xiao also reported that "two clinical trials have been initiated to test PD-1 blockage in patients with MSI colorectal cancer" and stated that "[c]ombinations with IDO, LAG-3, ***CTLA-4***, and other checkpoints will likely follow." EX1010, 18; Monjazeb, ¶182.

3. Hammers (EX1009)

Hammers is a published poster abstract describing "[a] phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma." Hammers, 1. Hammers reports that patients received either (i) 3 mg/kg nivolumab + 1 mg/kg ipilimumab; (ii) 1 mg/kg nivolumab and 3 mg/kg ipilimumab, or (iii) 3 mg/kg nivolumab and 3 mg/kg ipilimumab, each administered once every three weeks for four doses and followed by 3 mg/kg nivolumab every two weeks until disease progression or toxicity. *Id.*; Monjazeb, ¶183.

	First Phase: Combination therapy once every 3 weeks for 4 doses		Second Phase: Monotherapy every 2 weeks until progression or toxicity
Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)	Nivolumab (mg/kg)
(i)	3	1	3
(ii)	1	3	3
(iii)	3	3	3

Hammers reported that arm (iii) "showed early toxicity and did not proceed to expansion" but that the other two arms were expanded and that results of the

study "confirm[ed] initial safety findings and promising antitumor activity for [nivolumab] + [ipilimumab] in [patients] with [metastatic renal cell carcinoma]." *Id.* Hammers reported that the results "appear encouraging and support further development of this combination." *Id.*; Monjazeb, ¶184.

4. Reason to Combine Le, Xiao, and Hammers

Given Le's positive results concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer patients (EX1008, 2512-2515), Xiao's teaching that "[c]ombinations" with other checkpoints such as CTLA-4 "will likely follow" (EX1010, 18) would have motivated POSAs to treat MSI-H colorectal cancer patients (as disclosed in Le) using the therapeutic regimes disclosed in Hammers—including (1) the combination of anti-PD-1 and anti-CTLA-4 antibodies followed by (2) anti-PD-1 monotherapy. Monjazeb, ¶185. This combination—detailed below—is henceforth referenced as "Le-Xiao-Hammers."

a. Given Le's Favorable Results, Xiao Would Have Motivated POSAs to Combine Anti-PD-1 and Anti-CTLA-4 Antibodies to Treat MSI-H Colorectal Cancer

There are multiple reasons why POSAs considering how to leverage Le's favorable results concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer would have looked to Xiao's teachings concerning combined anti-PD-1 and anti-CTLA-4 antibody therapy. Monjazeb, ¶186.

For one, Xiao indicates that "two clinical trials have been initiated to test

PD-1 blockade in patients with MSI colorectal cancer" and "[c]ombinations with IDO, LAG-3, CTLA-4, and other checkpoints will likely follow." EX1010, 18. Xiao cites to a separate reference (Llosa, EX1014) confirming that one of those trials was NCT01876511—the same trial whose results Le subsequently disclosed. EX1010, 18 (reference 3); EX1014, 49 ("Indeed, based on these findings, two clinical trials testing anti-PD-1 antibodies in patients selected based on MSI have been initiated (***NCT01876511*** and NCT02060188)."); EX1008, 2509 ("This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab….ClinicalTrials.gov number, ***NCT01876511***."); Monjazeb, ¶187.

The fact that Le reports positive results concerning one of the "two clinical trials" referenced in Xiao "to test PD-1 blockade in patients with MSI colorectal cancer" (EX1010, 18) would have motivated POSAs to follow Xiao's teaching concerning desirable next steps following the successful completion of the NCT01876511 study. Monjazeb, ¶188. Further, POSAs would have understood Xiao as disclosing that such next steps would likely include combinations with anti-CTLA-4 antibodies. *Id*. While Xiao also refers to other checkpoints such as "IDO" and "LAG-3," POSAs would have understood that Xiao highlights CTLA-4 given Xiao's teaching that ipilimumab was already FDA approved. EX1010, 18; Monjazeb, ¶188; *see also* EX1044, 1:37-38 (disclosing "combination of anti-

CTLA-4 and anti-PD-1 antibodies, to treat cancer"); EX1045, 9:52-55 (disclosing "an anti-PD-1 antibody…combined with anti-CTLA-4"); EX1054 (article entitled "CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy"); *Ex Parte Mak*, Appeal 2020-003831, 2021 WL 302992, at *3 (PTAB Jan. 27, 2021) ("Callahan [EX1054] clearly provides [POSAs] with motivation to pursue cancer therapies that involve the combination of CTLA-4 and PD-1.").

In addition, Le and Xiao are complementary and concern the same problem of understanding why anti-PD-1 antibodies had shown limited efficacy in treating colorectal cancer despite their success in treating various other cancers. Monjazeb, ¶189. Le highlights how "mismatch-repair deficiency occurs in a small fraction of advanced colorectal cancers"—prompting Le's hypothesis (confirmed by Le's data) "that mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors." EX1008, 2510. Similarly, Xiao notes that "[m]icrosatellite instable (MSI) colorectal cancer comprises approximately 15% of sporadic colorectal cancer" (EX1010, 16) and further that "most MSI colorectal cancers typically present with lower-stage disease than MSS colorectal cancers," such that "the MSI subtype represents only 5% to 6% of the stage IV colorectal cancer population"—meaning that there were likely "few MSI patients in PD-1 and PD-L1 clinical trials." EX1010, 16-18. POSAs would recognize that Xiao's inference aligned with Le's determination that while "only 1 of 33 patients

with colorectal cancer" treated in a PD-1 clinical trial "had a response to this treatment," that patient's tumor "was mismatch repair deficient." EX1008, 2510; Monjazeb, ¶190. This consistency reinforces why POSAs would have looked to Xiao's teachings—including the combination of anti-PD-1 and anti-CTLA-4 antibodies—when considering how to leverage Le's favorable results. Monjazeb, ¶190.

b. Hammers Discloses a Particular Combination Therapy of Anti-PD-1 and Anti-CTLA Antibodies To Which POSAs Would Have Looked Given The Teachings in Le and Xiao

Given the combined teachings of Le and Xiao indicating that it would be desirable to treat MSI-H colorectal cancer patients using a combination therapy involving both anti-PD-1 and anti-CTLA-4 antibodies, POSAs would have had reason to look to Hammers for the details of such combination therapy because Hammers discloses favorable results using anti-PD-1 and anti-CTLA-4 antibodies to treat renal-cell carcinoma. EX1009 ("nivolumab [i.e., an anti-PD-1 antibody] in combination with ipilimumab [i.e., an anti-CTLA antibody] in metastatic renal cell carcinoma"). Monjazeb, ¶191. Renal-cell carcinoma is one of the types of cancer for which Le taught anti-PD-1 antibodies had shown "remarkable clinical responses," with the "expression of PD-1 ligands…on the surface of tumor cells" being a significant "predictive biomarker of response to PD-1 blockade." EX1008, 2510. Given this teaching and Le's determination that the objective response rate

when treating MSI-H colorectal cancer using anti-PD-1 antibodies was comparable to that when treating other MSI-H cancers using anti-PD-1 antibodies (EX1008, 2513), POSAs would have looked to the Hammers protocol as a suitable guide for implementing Xiao's suggestion of combination therapy for MSI-H colorectal cancer. Monjazeb, ¶¶192-193.

Each of Hammers' two expanded arms (i.e., featuring either 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab or 1 mg/kg of nivolumab and 3 mg/kg of ipilimumab) would have been obvious to implement in view of the positive results disclosed in Hammers for such combination therapies. Monjazeb, ¶¶194-195.

This combined method—involving testing colorectal cancer patients to determine whether their tumors were MSI-H (as disclosed in Le) and then treating such patients using a combination therapy incorporating both anti-PD-1 and anti-CTLA-4 antibodies (as suggested by Xiao) with the particular protocol disclosed by Hammers—is henceforth referenced as Le-Xiao-Hammers.

5. Reasonable Expectation of Success

POSAs would have had a reasonable expectation of success when implementing Le-Xiao-Hammers given:

(1) the favorable clinical results disclosed in Le and Lipson-2013 (referenced in Le) concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer; coupled with

(2) the favorable clinical results in Hammers and other prior art references teaching the benefits of combined anti-PD-1 and anti-CTLA-4 antibody therapy as compared to monotherapy alone for a variety of cancers.

Monjazeb, ¶196.

Given Le and Lipson-2013, POSAs would have had a reasonable expectation of success when using anti-PD-1 immunotherapy to treat MSI-H colorectal cancer. The results in Le and Lipson-2013 tracked other prior art teachings that MSI-H colorectal cancers were "good candidates for immunotherapy." EX1038, 3740-41. Lipson-2013 in particular, provided a reasonable expectation of success in using nivolumab (i.e., the anti-PD-1 antibody disclosed in Hammer) in place of the different anti-PD-1 antibody disclosed in Le given Lipson-2013's reports that nivolumab achieved a "[d]urable complete response in [MSI-H] colorectal cancer." EX1037, 463-464; *see also Merck*, IPR2024-00240, Paper 10 at 23 (instituting review: "Li[p]son reports the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor."); Monjazeb, ¶197.

Further, based on Hammers and other medical literature, POSAs would have had a reasonable expectation that the combination of anti-PD-1 and anti-CTLA immunotherapy would also effectively treat MSI-H colorectal cancer and achieve

even better results than those observed with anti-PD-1 immunotherapy alone. Monjazeb, ¶¶198-199. For example, Curran taught that "the CTLA-4 and PD-1 inhibitory pathways appeared to be nonredundant" (EX1012, 4275) and the "combination blockade … leads to ***synergistic*** levels of tumor rejection" (*Id.*, 4278). Similarly, Larkin found that "the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone." EX1011, 31. Moreover, in the specific context of colorectal cancer, Duraiswamy (EX1053) reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model. EX1053, 3595, 3599-3600.

6. Claim-by-Claim Analysis

Le-Xiao-Hammers discloses every element of claims 1, 4, and 5-14, thus rendering them obvious. Monjazeb, ¶200.

a. Independent Claim 1

(1) [1.Pre] "A method of treating a subject afflicted with a tumor derived from a colorectal cancer…"

To the extent claim 1's preamble is limiting, Le-Xiao-Hammers satisfies it because the Le-Hammers-Xiao method as detailed in §VI.E.4 entails treating colorectal cancer—consistent with the teachings in both Le and Xiao. Le discloses treating subjects afflicted with a tumor derived from a colorectal cancer. *See* Le, 2509-2510; Monjazeb, ¶201. Additionally, Xiao discloses treating colorectal

cancer patients. EX1010, Summary; Monjazeb, ¶201. Specifically, Xiao concludes that "the [microsatellite instable] subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy." EX1010, Summary. Xiao also reports that "two clinical trials [including Le] have been initiated …in patients with MSI colorectal cancer." EX1010, 18; Monjazeb, ¶201.

(2) [1.A] "administering to the subject: (i) an anti-PD-1 antibody, and (ii) an anti-CTLA-4 antibody"

Le-Xiao-Hammers satisfies [1.A] because it entails administering both an anti-PD-1 antibody and an anti-CTLA-4 antibody as detailed in §VI.E.4 — consistent with the teachings in both Xiao and Hammers as well as related disclosures in Le. Monjazeb, ¶202. Xiao references then-ongoing clinical trials "test[ing] PD-1 blockade in patients with MSI colorectal cancer" (one of which was the trial for which Le subsequently reported favorable results) and suggests that a combination with CTLA-4 would "likely follow." EX1010, 18; Monjazeb, ¶202. And Hammers discloses administering an anti-PD-1 antibody (nivolumab) and an anti-CTLA-4 antibody (ipilimumab) when treating a different type of cancer (i.e., renal cell carcinoma) expressly referenced in both Le and Xiao. EX1009; Monjazeb, ¶202.

(3) [1.B] "the tumor is a colon cancer or a rectal cancer"

Le-Xiao-Hammers satisfies [1.B] because it entails treating colon or rectal

cancer patients as detailed in §VI.E.4 —consistent with the teachings in both Le and Xiao. Monjazeb, ¶203. Le describes treating colon or rectal cancer. EX1008, 2509-2510 (discussing cohorts A and B including patients with colorectal adenocarcinomas); Monjazeb, ¶203. Similarly, Xiao describes treating colorectal cancer tumors. EX1010, summary, 1; Monjazeb, ¶203. "Colorectal" means "relating to or affecting the colon and rectum." EX1022 (defining colorectal); Monjazeb, ¶204. POSAs would understand that both Le and Xiao concern treatment of colon or rectal cancer, as opposed to other cancers derived from colorectal cancer. Monjazeb, ¶204; *cf.* §III.B (detailing prosecution history and amendment in response to §112 rejection).

(4) [1.C] "the tumor exhibits a high degree of microsatellite instability (MSI-H)"

Le-Xiao-Hammers satisfies [1.C] because it entails treating MSI-H colon or rectal cancer tumors as detailed in §VI.E.4—consistent with the teachings in both Le and Xiao. Monjazeb, ¶205.

Le describes evaluating treatment of patients with mismatch repair-deficient colorectal cancers as compared to mismatch repair-proficient colorectal cancers. EX1008, 2509. POSAs would understand that mismatch repair deficient corresponds to MSI-H, and mismatch repair proficient corresponds to MSS. Monjazeb, ¶¶206-207. Specifically, Le explains that it identified mismatch-repair status based on microsatellite instability. EX1008, 2512. *see also* EX1032, 5

(Appendix 1 to Le, disclosing assessment of MSI status using five microsatellites to determine mismatch repair status); EX1001, 2:2-5 ("Some colorectal cancers are associated with a high degree of microsatellite instability (MSI-H), which results from impaired DNA mismatch repair.").

Xiao discloses that "[microsatellite instable] tumors highly upregulate expression of multiple immune checkpoints." EX1010, 16. Xiao concludes that "the [microsatellite instable] subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy." *Id*., Summary.

b. Dependent Claim 4: Survival of At Least About One Month Following Treatment

Le-Xiao-Hammers renders obvious claim 4 for at least two separate and independent reasons.

First, as detailed in §VI.A.3.b, claim 4's "wherein" clause (i.e., reciting that after administration, the subject either "exhibit a progression-free survival of at least about one month" or "exhibit an overall survival of at least about one month") recites a non-limiting statement of intended effect.

Second, even if the wherein clause were deemed to limit claim 4 in some form, it would still be inherent in Le-Xiao-Hammers because the recited outcome (i.e., patients surviving at least one month) is the natural result of administering 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab as disclosed in Hammers. "When the prior art does not expressly disclose a claim limitation, 'inherency may

supply a missing claim limitation in an obviousness analysis.'" *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020). Here, the result would be inherent because Le reported that median overall and progression-free survival were not reached after twelve months for patients receiving anti-PD-1 therapy alone, meaning that at the time of analysis, greater than half of the patients were still alive and without evidence of disease progression. EX1008, Fig. 2; Monjazeb, ¶210. Accordingly, at least this result would be inherent in the combination therapy. *See* §§VI.E.4-VI.E.5; Monjazeb, ¶210.

Alternatively, POSAs would expect to achieve these results with at least a reasonable expectation of success, given the clinical results disclosed in Le, Lipson-2013, and Hammers. Monjazeb, ¶211. Such reasonable expectation is further confirmed by the '529 Patent's disclosures concerning the effect of administering 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab to patients with MSI-H colorectal cancer. *See* EX1001, 36:59-37:7; Figs. 12A, 12B; Monjazeb, ¶212. And beyond these dosages, the '529 Patent does not disclose any additional manipulative steps to increase the likelihood of patient survival beyond any point. Accordingly, the '529 Patent's specification confirms that the natural result of administering Hammers' disclosed dosages (i.e., 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab) to MSI-H colorectal cancer patients is that such patients survive at least one month following treatment.

c. Claims 5-14: Specific Antibody and/or Dosage Requirements

Le-Xiao-Hammers renders dependent claims 5-14 obvious because, as detailed in §VI.E.4, it would have been obvious in view of these references to treat MSI-H colorectal cancer patients by administering an anti-PD-1 antibody and an anti-CTLA-4 antibody (thereby rendering independent claim 1 obvious, as detailed in §VI.E.6.a) and in particular to use the treatment regime disclosed in Hammers of (1) 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab once every three weeks for four doses followed by (2) 3 mg/kg of nivolumab once every two weeks. Those parameters satisfy all additional requirements of claims 5-14.

(1) Claim 5

Claim 5 recites "the anti-PD-1 antibody is nivolumab or pembrolizumab." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering nivolumab as the anti-PD-1 antibody. EX1009, 251s; Monjazeb, ¶¶213-214.

(2) Claim 6

Claim 6 recites "the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering ipilimumab (i.e., an anti-CTLA-4 antibody) at a dose of 1 mg/kg

once every three weeks. EX1009, 251s; Monjazeb, ¶215.

(3) Claim 7

Claim 7 recites "the anti-CTLA-4 antibody is ipilimumab or tremelimumab." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering ipilimumab (i.e., an anti-CTLA-4 antibody). EX1009, 251s; Monjazeb, ¶216.

(4) Claim 8

Claim 8 recites "the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering nivolumab (i.e., an anti-PD-1 antibody) at a dose of 3 mg/kg once every three weeks. EX1009, 251s; Monjazeb, ¶217.

(5) Claim 9

Claim 9 recites four different treatment regimes in the alternative, one of which requires administering 3 mg/kg of an anti-PD-1 antibody and 1 mg/kg of an anti-CTLA-4 antibody. Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering nivolumab (i.e., an anti-PD-1 antibody) at a dose of 3 mg/kg and ipilimumab (i.e., an anti-CTLA-4 antibody) at a dose of 1 mg/kg. EX1009, 251s; Monjazeb, ¶218.

(6) Claim 10

Claim 10 depends from claim 9 and recites "the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy." Monjazeb, ¶219. "Monotherapy" refers to "the use of a single drug to treat a particular disorder or disease." EX1036; *see also* Monjazeb, ¶219; EX1015. Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because Hammers' treatment regime entails a combination therapy administering nivolumab (i.e., an anti-PD-1 antibody) together with ipilimumab (i.e., an anti-CTLA-4 antibody) satisfying claim 9 (as detailed immediately above) followed by nivolumab monotherapy. EX1009, 251s; Monjazeb, ¶220.

(7) Claim 11

Claim 11 recites "wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once about every 3 weeks for a total of 12 weeks." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime entails administering nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg once every 3 weeks for 4 doses (i.e., a total of 12 weeks). EX1009, 251s; Monjazeb, ¶221.

(8) Claim 12

Claim 12 depends from claim 11 and is otherwise identical to claim 10 in

that it recites the same "anti-PD-1 antibody monotherapy." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime satisfies claim 11 and also includes a subsequent anti-PD-1 antibody monotherapy phase as discussed above in connection with claim 10. Monjazeb, ¶222.

(9) Claim 13

Claim 13 depends from claim 12 and recites "the anti-PD-1 antibody monotherapy is administered once about every 2 weeks." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime satisfies claim 12 and further because the anti-PD-1 antibody monotherapy is administered once every 2 weeks. EX1009, 251s ("Q2W"); Monjazeb, ¶223.

(10) Claim 14

Claim 14 depends from claim 12 and recites "the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks." Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the Hammers treatment regime satisfies claim 12 and further because the anti-PD-1 antibody monotherapy is administered at a dosage of 3 mg/kg nivolumab once every 2 weeks. EX1009, 251s ("N 3 mg/kg IV Q2W"); Monjazeb, ¶224.

F. GROUND 3B: Le, Xiao, Hammers, and Zhang Render Obvious Claims 2-3

Le in view of Xiao and Hammers and further in view of Zhang ("Le-Xiao-Hammers-Zhang") renders obvious claims 2-3.

1. Reason to Combine Zhang With Le-Xiao-Hammers

As discussed in §VI.E.4, the Le-Xiao-Hammers method entails treating MSI-H colorectal cancer tumors—consistent with Xiao's teaching "that the MSI subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy" (EX1010, 16) and Le's report that "mismatch repair status predicted clinical benefit" of such checkpoint immunotherapy" (EX1008, 2509). Given these teachings and the corresponding purpose of the Le-Xiao-Hammers method, POSAs implementing such method would have tested patients presenting with colorectal cancer to determine whether their tumors were mismatch repair deficient (i.e., MSI-H) or proficient. Monjazeb, ¶¶226-227.

Zhang discloses such criteria to identify MSI-H status. Moreover, Zhang is expressly directed to colorectal cancer and was published in a journal about "Gastrointestinal Oncology." EX1006, 12; Monjazeb, ¶228. In particular, Zhang teaches the desirability of "MSI testing for all newly diagnosed individuals with CRC" (i.e., colorectal cancer). EX1006, 12. Accordingly, POSAs would be motivated to use the MSI-H criteria of Zhang to determine whether colorectal cancer patients would be likely to benefit from the method of treatment rendered

obvious by Le-Xiao-Hammers. Monjazeb, ¶228.

In particular, POSAs would have had reason to implement Le-Xiao-Hammers using Zhang's methodology of "***demonstrating absence of expression of MMR proteins*** by immunohistochemical staining (IHC)" (EX1006, 14) because such staining was a well-known methodology that could be readily implemented without special equipment and/or the need for genetic testing. Monjazeb, ¶229; *see also* EX1006, 14 (noting that "[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system"). Le-Xiao-Hammers implemented using Zhang's disclosed method of "***demonstrating absence of expression of MMR proteins"*** to determine MSI-H status (EX1006, 14)—including the use of commercially available antibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 as disclosed in Zhang—is hereinafter referenced as "Le-Xiao-Hammers-Zhang."

2. Reasonable Expectation of Success

POSAs would have had a reasonable expectation of success in combining Le-Xiao-Hammers and Zhang given that Zhang's immunohistochemical staining methodology for detecting MSI status was a well-known and reliable technique that could be implemented using readily available equipment. Monjazeb, ¶230. The fact that Le's protocol—made publicly available at the same time as Le—

recognized "immunohistochemistry" as a basis "for determining MSI" (EX1040, 16)—further confirms POSAs' reasonable expectation that Zhang's immunohistochemical staining methodology would be suitable for the Le-Xiao-Hammers method. Monjazeb, ¶230.

3. Claim-by-Claim Analysis

a. Claim 2

Le-Xiao-Hammers-Zhang renders claim 2 obvious for substantially the same reasons as NCT-188-Zhang, discussed in §VI.B.4.a. Monjazeb, ¶¶231-32.

b. Claim 3

Le-Xiao-Hammers-Zhang renders claim 3 obvious for substantially the same reasons as NCT-188-Zhang, discussed in §VI.B.4.b. Monjazeb, ¶233.

G. GROUND 3C: Le, Hammers, Xiao, and NCT-109 Render Obvious Claims 15-18

Le in view of Hammers and Xiao and further in view of NCT-109 ("Le-Hammers-Xiao-NCT-109") renders obvious claims 15-18.

1. Reason to Combine NCT-109 With Le-Xiao-Hammers

Consistent with the protocol disclosed in Hammers, Le-Xiao-Hammers as detailed in §VI.E.4 discloses anti-PD-1 antibody monotherapy at a weight-based dose of 3 mg/kg after conclusion of the anti-PD-1 and anti-CTLA-1 antibody combination therapy. *See* EX1009, 251s ("then [nivolumab] 3 mg/kg IV Q2W until progression or toxicity"). Given the advantages of flat dosing over weight-based

dosing as detailed in §VI.C.2 concerning the combination of NCT-188 and NCT-109, POSAs would have had reason to modify Le-Xiao-Hammers in view of NCT-109 (disclosing flat dosing with nivolumab), for the reasons discussed in §VI.C.2. Monjazeb, ¶¶234-235.

Le-Xiao-Hammers implemented using flat dosing for the monotherapy (as opposed to the weight-based dosing disclosed in Hammers) is henceforth referenced as "Le-Xiao-Hammers-NCT-109."

2. Reasonable Expectation of Success

POSAs would have had a reasonable expectation of success in combining Le-Xiao-Hammers and NCT-109 for the same reasons detailed in §VI.C.3 concerning NCT-188-NCT-109. In particular, POSAs would have reasonably expected success when practicing Le-Xiao-Hammers with a 240 mg flat dose of nivolumab once every two weeks for the nivolumab monotherapy phase (i.e., in place of the 3 mg/kg nivolumab once every two weeks as disclosed in Hammers for the monotherapy phase) given that it reflects the amount of nivolumab specified by Hammers for a patient having 80 kg body weight—consistent with the average weight of patients in other immunotherapy studies. EX1041; Monjazeb, ¶236.

3. Claim-by-Claim Analysis

a. Claim 15

Le-Hammers-Xiao-NCT-109 renders claim 15 obvious for substantially the

same reasons as NCT-188-NCT-109, discussed in §VI.C.4.a. Monjazeb, ¶237.

b. Claim 16

Le-Hammers-Xiao-NCT-109 renders claim 16 obvious for substantially the same reasons as NCT-188-NCT-109, discussed in §VI.C.4.b. Monjazeb, ¶238.

c. Claim 17

Le-Hammers-Xiao-NCT-109 renders claim 17 obvious for substantially the same reasons as NCT-188-NCT-109, discussed in §VI.C.4.c. Monjazeb, ¶239.

d. Claim 18

Le-Hammers-Xiao-NCT-109 renders claim 18 obvious for substantially the same reasons as NCT-188- NCT-109, discussed in §VI.C.4.d. Monjazeb, ¶240.

VII. SECONDARY CONSIDERATIONS DO NOT RENDER THE CHALLENGED CLAIMS PATENTABLE

"[S]econdary considerations are not an element of a claim of anticipation" and thus irrelevant to Ground 1A. *Cohesive Technologies, Inc. v. Waters Corp*., 543 F.3d 1351, 1364 (Fed. Cir. 2008).

Petitioner is not aware of any ostensible secondary considerations relevant to the §103-based grounds. None were suggested or addressed by the Examiner.

Moreover, Grounds 1B-1C, 2B-2C, and 3B-3C relate exclusively to Challenged Claims for which the '529 Patent lacks corresponding data. Monjazeb, ¶243. While the specification discloses MSI-H colorectal cancer treatment results generally, it never specifies whether any such results concern tumors satisfying the

specific MSI-H characteristics recited in Challenged Claims 2-3. Monjazeb, ¶244. Nor does the specification disclose any results concerning treatments involving flat dosing as required by Challenged Claims 15-18. Monjazeb, ¶245. Nor does the file history (EX1002) reflect any data beyond that included in the '529 Patent.

Finally, to the extent PO may allege that the '529 Patent's dataset is relevant to Grounds 2A or 3A, such results would have been expected given the prior art. Anti-PD-1 antibodies were known to be effective in treating MSI-H colorectal cancer. EX1008, 2514 (reporting that "median progression-free survival and median overall survival were not reached" for MSI-H colorectal cancer patients treated with pembrolizumab); EX1037, 463 (reporting "Durable complete response in [MSI-H] colorectal cancer" treated with nivolumab); Monjazeb, ¶246. Earlier literature had also disclosed synergistic effects when combining anti-PD-1 and anti-CTLA-4 antibodies. Monjazeb, ¶¶247-257 (discussing EX1011, EX1013, EX1031, EX1052, EX1053, and EX1054).

Given this existing literature, there was nothing surprising or unexpected about the '529 Patent's disclosed results. Monjazeb, ¶257.

Nor is there anything "in the record to establish the statistical significance of the comparative survival data." *Mak*, 2021 WL 302992, at *4 (citing Callahan [EX1054] and affirming obviousness rejection of claims to combined anti-PD-1/anti-CTLA-4 treatment despite alleged unexpected results).

While the file history includes a PCT written opinion prepared by the EPO (EX1002, 104-111) suggesting that the PCT application's specific "dosing schedule" (including "3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab") purportedly achieved "the surprising result of prolonged progression free survival compared to those patients receiving nivolumab monotherapy," this statement is immaterial to the patentability of the Challenged Claims under U.S. law.

For one, none of the Challenged Claims recites a dosage schedule "commensurate in scope" with the PCT application's dosing schedule. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). For example, independent claim 1 encompasses ***any*** dosage of ***any*** anti-PD-1 antibody together with ***any*** dosage of ***any*** anti-CTLA-4 antibody.[4] NCT-188 anticipates such method. *See* §VI.A. Even

[4] The ISA opinion neglected that NCT-188 disclosed administering 3 mg/kg nivolumab together with 1 mg/kg ipilimumab. *Cf*. EX1002, 109 ("D3 [NCT-188] describes a Phase 2 clinical trial investigating the ***treatment of the anti-PD-1 antibody nivolumab*** on patients with microsatellite unstable colorectal cancer."). Based at least in part on this misinterpretation of NCT-188, the opinion wrongly suggested that PCT claim 8 (reciting the combination of anti-PD-1 and anti-CTLA-4 antibodies for treating MSI-H colorectal cancer) "appears to be novel." EX1002,

the most specific dependent claims are significantly broader than and/or otherwise different from the application's dosage schedule (using nivolumab and ipilimumab). Dependent claim 11 is not limited to nivolumab and ipilimumab. Moreover, dependent claims 15-18 require flat dosage of the anti-PD-1 antibody monotherapy, whereas the application dosage schedule in the PCT application (as well as that in the '529 Patent) is limited to weight-based doses.

Separately, the EPO search report neglected the numerous references (including EX1011—EX1013, EX1031, and EX1052—EX1054) teaching the synergistic benefit of administering nivolumab together with ipilimumab. Monjazeb, ¶¶258-265. For example, Larkin (EX1011) had previously disclosed that patients receiving nivolumab together with ipilimumab (including 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab) achieved markedly higher progression-free survival than patients receiving nivolumab alone—11.5 months versus 6.9 months. EX1001, 24-26; Monjazeb, ¶262. Yet Larkin was not identified in the PCT search report or otherwise of record during prosecution of the '529 Patent. Nor were other above-discussed references such as Postow, Hammers, and Xiao. Nothing in the record indicates any consideration of purported "unexpected

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109, 112-113. Notably, however, the opinion also indicated such combination lacked "inventive step." *Id*., 1110.

[results] compared with the ***closest prior art***" as required by U.S. law. *In re Baxter Travenol Lab'ys*, 952 F.2d 388, 392 (Fed. Cir. 1991); *see also Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012) (upholding obviousness determination: "[T]o show that the cooling effect of the combination…was unexpected, Wrigley needed to demonstrate that the results were unexpected to a significant degree ***beyond what was already known*** about the effect of combining [the agents].").

VIII. NO BASIS EXISTS FOR DISCRETIONARY DENIAL

No reasonable basis for discretionary denial exists under §§314(a), 324(a), or 325(d).

A. Section 314(a)

There is no previous petition concerning the '529 patent warranting discretionary denial under the *General Plastic* factors.

B. Section 324(a)

There is no co-pending litigation involving the '529 patent warranting discretionary denial under the *Fintiv* factors.

C. Section 325(d)

Considering the two-part framework discussed in *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential), the Board should not exercise its §325(d) discretion to deny institution. ***No*** prior art reference included in ***any*** ground was ***ever*** cited or

analyzed in a rejection. EX1002.

1. Step One: The Petition Advances Art and Arguments Not Previously Considered (Factors (a), (b), (d))

As to *Advanced Bionics* step one, the Petition advances art and arguments not previously considered. None of Zhang, NCT-109, Postow, Hammers, and Xiao were cited during prosecution. *See* §III.B. Nor was Petitioner's declaration evidence of record. Moreover, the Examiner never made any art-based rejection. Instead, the only rejection was under §112. Accordingly, under factor (d), at a minimum, the arguments regarding the art are entirely new and were not considered during examination. *See*, *e.g.*, *Agrofresh Sol'ns. v. Lytone Ent.*, IPR2021-00451, Paper 11 at 12-13 (PTAB July 27, 2021) (arguments not substantially similar where teachings were used "in a different manner than the rejections made by the Examiner").

2. Step Two: The Office Erred Materially (Factors (c), (e), (f))

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)." *AB*, 10. For example, the Board has found the record was silent where—as here (*see* §III.B)—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). Indeed, other than the observation in the context of a restriction requirement that

"Wolchok … discloses method of treatment comprising administering a PD-1 antibody and a CTLA-4 antibody," the record is silent as to the Examiner's understanding of the art. *See* §III.B; EX1002, 2542. Accordingly, the Examiner erred in failing to reject the claims over 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 Examiner's statement that certain limitations were not in the prior art was contradicted by petition's grounds); *Satco Products Inc. v. Regents of the Univ. of California*, IPR2021-00662, Paper 13 at 25 (PTAB Nov. 8, 2021) (where examiner initialed references but "did not rely on any … to reject claims," Board was "not persuaded that the Examiner evaluated these references sufficiently").

For example, while PO distinguished Wolchok as not involving treatment of MSI-H colorectal cancer (EX1002, 2546), the Examiner apparently overlooked NCT-188, which describes administering a PD-1 antibody and a CTLA-4 antibody (like Wolchok) to treat MSI-H colorectal cancer (***unlike Wolchok***).[5]

[5] As discussed in §VII, the ISA opinion describes NCT-188 as merely "investigating the treatment of the ***anti-PD-1 antibody nivolumab*****";** it overlooks that NCT-188 described administering nivolumab ***together with the anti-CTLA***

IX. CONCLUSION

The Board should institute review and cancel claims 1-18.

Dated: February 28, 2025

Respectfully submitted,
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antibody ipilimumab. Nor is there any indication the Examiner considered the ISA opinion. Indeed, the Examiner allowed the claims even though they align with claims the ISA opinion deemed to lack an inventive step. *See* §VII.

CLAIM LISTING

Claim 1
1. A method of treating a subject afflicted with a tumor derived from a colorectal cancer, comprising
administering to the subject: (i) an anti-PD-1 antibody, and (ii) an anti-CTLA-4 antibody;
wherein the tumor is a colon cancer or a rectal cancer; and
wherein the tumor exhibits a high degree of microsatellite instability (MSI-H).
Claim 2
2. The method of claim 1, wherein the tumor exhibits one or more characteristics selected from the group consisting of:
(a) the tumor comprises a germline alteration in at least two DNA mismatch repair genes (MMR genes);
(b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
(c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
(d) any combination thereof.
Claim 3
3. The method of claim 2, wherein the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.
Claim 4
4. The method of claim 1, wherein:
(i) the subject exhibits a progression-free survival of at least about one month after the administration, or
(ii) the subject exhibits an overall survival of at least about one month after the administration.
Claim 5
5. The method of claim 1, wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.
Claim 6

6. The method of claim 1, wherein the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.
Claim 7
7. The method of claim 1, wherein the anti-CTLA-4 antibody is ipilimumab or tremelimumab.
Claim 8
8. The method of claim 1, wherein the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.
Claim 9
9. The method of claim 1, wherein:
(i) the anti-PD-1 antibody is administered at a dose of about 1 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight;
(ii) the anti-PD-1 antibody is administered at a dose of about 1 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 3 mg/kg body weight;
(iii) the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight; or
(iv) the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 3 mg/kg body weight.
Claim 10
10. The method of claim 9, wherein the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.
Claim 11
11. The method of claim 1, wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once about every 3 weeks for a total of 12 weeks.
Claim 12

12. The method of claim 11, wherein the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.
Claim 13
13. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered once about every 2 weeks.
Claim 14
14. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks.
Claim 15
15. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered as a flat dose.
Claim 16
16. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered at a flat dose of about 240 mg once about every 2 weeks.
Claim 17
17. The method of claim 16, wherein the anti-PD-1 antibody is nivolumab.
Claim 18
18. The method of claim 17, wherein the anti-CTLA-4 antibody is ipilimumab.

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

I certify that on February 28, 2025, I will cause a copy of the foregoing document, including any exhibits or appendices filed therewith, to be served via Priority Mail Express at the following correspondence address of record for the patent:

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Date: February 28, 2025

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Paralegal
WOLF, GREENFIELD & SACKS, P.C.

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing Petition for *Inter Partes* Review contains 13,992 words excluding a table of contents, a table of authorities, Mandatory Notices under § 42.8, 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: February 28, 2025

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