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Paper 6
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

IPR2024-00647
Patent 11,649,287 B2

Before DEBORAH KATZ, SHERIDAN K. SNEDDEN, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background and Summary

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–36 of U.S. Patent No. 11,649,287 B2 (Ex. 1001, "the '287 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '287 patent. Paper 3. Patent Owner did not file a Preliminary Response.

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the information presented in the Petition, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving the unpatentability of at least one of claims 1–36 of the '287 patent.

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 65. Patent Owner identifies Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '287 patent is involved in *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), filed November 29, 2022. Pet. 65; Paper 3, 1. Petitioner has also filed petitions for *inter partes* review of the following patents asserted against

Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 65; Paper 3, 1.

D. The '287 patent (Ex. 1001)

The '287 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '287 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.*, Abstract. More specifically, the '287 patent is directed to treating cancer patients with high mutational burdens, such as those found in microsatellite instable ("MSI") cancer, with anti-PD-1 antibodies. *Id.*, 3:38–53. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:32–34.

The '287 patent explains that

> [t]he PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including auto-immune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors.

Id., 1:55–62. According to the '287 patent, "[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types." *Id.*, 2:6–5. However, the specification describes that

> in reports of the effects of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment, . . . What was different about this single patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id., 2:63–3:6. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '287 patent describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id.*, 3:14–21. The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id.*, 8:52–56. According to the '287 patent, "[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors." *Id.*, 6:52–56.

E. The Challenged Claims

Petitioner challenges claims 1–36. Representative independent claim 1 is reproduced below:

> 1. A method for treating colorectal cancer in a human patient, the method comprising:
>
> in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,

wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.

Ex. 1001, 24:42–52.

Representative independent claim 11 is reproduced below:

11. A method for reducing the risk of progression of colorectal cancer in a human patient, the method comprising:

in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,

wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.

Id., 25:8–19.

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1005, MSI-H Study Record, ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1 ("MSI-H Study Record"); also available at *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-BPG, ECF 1, Complaint, Exhibit B (11/29/22) ("MSI-H Study Record").

Ex. 1006, Pernot et al., *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) WORLD J. GASTROENTEROLOGY 3738 (April 2014) ("Pernot").

Ex. 1007, Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J CLIN ONCOLOGY 3320 (2010) ("Chapelle").

Ex. 1008, Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) ("Steinert").

Ex. 1009, Benson et al., *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. NAT'L COMPREHENSIVE CANCER NETWORK 1028 (July 2014) ("Benson").

Ex. 1011, Hamid et al., *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) NEW ENG. J. MEDICINE 134 (July 2013) ("Hamid").

Petitioner also relies on the Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) to support its contentions.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–36 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 2, 4–8, 11, 12, 14–18, 21–36	102	MSI-H Study Record
II	1, 2, 4–8, 11, 12, 14–18, 21–36	103	MSI-H Study Record, Pernot
III	2, 9, 10, 12, 19, 20	103	MSI-H Study Record, Pernot, Chapelle
IV	3, 13	103	MSI-H Study Record, Pernot, Steinert
V	6, 7, 16, 17, 26, 28, 30–36	103	MSI-H Study Record, Pernot, Benson
VI	8, 18	103	MSI-H Study Record, Pernot, Hamid

H. Claim Construction

The challenged claims should be read in light of the Specification, as it would be interpreted by one of ordinary skill in the art. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech.*, Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question." (internal quotation marks omitted)); *see also* 37 C.F.R. § 42.100(b) (stating that claims are construed in IPRs according to the same standard as used in federal court).

Petitioner contends that we need not construe any terms of the challenged claims to resolve the issues presented in the Petition. Pet. 11.

We determine that no express construction of any claim term is necessary to determine whether to institute *inter partes* review. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). To the extent further discussion of the meaning any claim term is necessary to our decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

I. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art ("POSA" or "POSITA") at the time of the invention

> would be a medical doctor or a professional in a related field with at least five years of experience with treating cancer. . . . The POSA would also have experience in or access to a person with

> knowledge of clinical studies for therapeutics and how they work and a pathologist with comparable experience. . . . The inherent anticipation and obviousness grounds discussed herein would not change due to a modestly lesser or greater level of experience.

Pet. 11–12 (citing Ex. 1003 ¶ 19).

For this Decision, we adopt and apply Petitioner's proposal above, which does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

II. ANALYSIS

A. Introduction

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Moreover, a petitioner should not "place the burden on [the Board] to sift through information presented by the Petitioners, determine where each element [of the challenged claims] is found in [the cited references], and identify any differences between the claimed subject matter and the teachings of [the cited references.]" *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9 at 25 (PTAB May 22, 2014).

Anticipation is a question of fact, as is the question of what a prior art reference teaches. *In re NTP, Inc.*, 654 F.3d 1279, 1297 (Fed. Cir. 2011). "Because the hallmark of anticipation is prior invention, the prior art

reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Whether a reference anticipates a claim is assessed from the skilled artisan's perspective. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) ("[T]he dispositive question regarding anticipation [i]s whether one skilled in the art would reasonably understand or infer from the [prior art reference's] teaching that every claim element was disclosed in that single reference." (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991))).

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness.[1] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The obviousness inquiry also typically requires an analysis of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). A petitioner cannot prove obviousness with "mere conclusory statements." *In re Magnum Oil Tools*

[1] Patent Owner does not present any objective evidence of nonobviousness (i.e., secondary considerations) for the challenged claims at this time.

Int'l, Ltd., 829 F.3d 1364, 1380 (Fed. Cir. 2016). Rather, a petitioner must articulate a sufficient reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive*, 842 F.3d 1376, 1382 (Fed. Cir. 2016).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

B. Summary of the Cited Prior Art

1. MSI-H Study Record (Ex. 1005)

The title of the MSI-H Study Record is "Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors." Ex. 1005, 1. MK-3475 is also known as pembrolizumab. *See* Ex. 1054, 3 (disclosing that "Nivolumab . . . and MK-3475 (pembrolizumab formerly lambrolizumab) . . . are humanized MAb that block the interaction between PD-1 and its ligands and demonstrate durable responses in patients with advanced melanoma."); *see also* Ex. 1069 (titled "ANTITUMOR ACTIVITY OF PEMBROLIZUMAB (PEMBRO; MK-3475) . . . .")).

The MSI-H Study Record includes a "Brief Summary," explaining that

> [t]his study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers.

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in

patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" Ex. 1005, 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

Ex. 1005, 4. The chart above identifies three patient populations and the therapeutic intervention to be provided.

2. Pernot (Ex. 1006)

Pernot is an article titled "Colorectal Cancer and Immunity: What We Know and Perspectives." Ex. 1006, 3739. Pernot discloses that "Comprehension of antitumor immune response and combination of the different approaches of immunotherapy may allow the use of effective immunotherapy for treatment of colorectal cancer in the near future." *Id.*, 3738. More specifically, Pernot discloses that "[m]icrosatellite instability (MSI) is associated with CRC in patients with Lynch syndrome." *Id.*, 3740. Pernot states that "CRC associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy." *Id.*, 3741.

3. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated

DNA nucleotide units in microsatellites," which "arises in tumors with deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2*, *MLH1*, *MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.*, 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.*, 3380, 3384.

4. Steinert (Ex. 1008)

Steinert is an article titled "Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer." Ex. 1008, OF1. Steinert discloses a detailed genomic and phenotypic analyses of single colorectal cancer–derived circulating tumor cells (CTC). *Id.* Steinert describes that "[a]mplified gDNA of CTC and tumor tissue samples was tested for microsatellite instability (MSI) using the markers NR21, NR24, and BAT 25." *Id.*, OF2. Steinert describes that the analyses of single cancer-derived CTC found disparities in key mutations, including MSI, in comparison to the primary tumor. *Id.*, OF4. "MSI at one or more markers . . . was detected in CTC from 2 patients (of 25 with complete MSI data sets; 7.7%, Fig. 2C). In 1 patient, two of 11 tested CTC were MSI despite a microsatellite stable (MSS) tumor (Table 1)." *Id.* In one patient, "[t]hree single CTC were classified as MSI-high level (MSI-H) and showed a mutation in the coding region of the *ELAVL* gene." *Id.*, OF6.

5. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic

disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id.*, 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.*, 1034.

6. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

C. Ground 1: Anticipation of Claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 by the MSI-H Study Record

1. Petitioner's Contentions

Petitioner contends that claims 1–2, 4–8, 11–12, 14–18, and 21–36 are anticipated by the MSI-H Study Record. Pet. 15–39. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how each element of claims 1–2, 4–8, 11–12, 14–18, and 21–36 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1002 ¶¶ 50–127.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference

may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 15–16. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 17. Relying on those cases, Petitioner contends that "the MSI-H Study Record inherently anticipates claims 1–2, 4–8, 11–12, 14–18, and 21–36 of the '287 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 18.

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '287 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 15.

a) Independent Claim 1

Like Petitioner, our analysis focuses on independent claim 1. *See id.* at 29–30 (relying substantially on analysis of claim 1 for independent claim 11). Petitioner's contentions with regard to claim 1 are summarized below.

(1) [1.pre]: "A method for treating colorectal cancer in a human patient, the method comprising:"

Petitioner argues that, in general, the MSI-H Study Record anticipates claim 1 of the '287 patent because it "teaches the claimed drug, given at the

only therapeutically effective dosage described in the '287 patent, and given to the claimed patient population." Pet. 18. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating human MSI positive colorectal cancer patients, as recited in the preamble of claim 1.[2] *Id.* (citing Ex. 1003 ¶¶ 59–60; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)).

> *(2) [1.1]: "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,"*

Petitioner argues that the MSI-H Study Record anticipates the limitation in claim 1 of treating with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient" because the Arms and Interventions section discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 19–21; *see also* Ex. 1003 ¶ 64–65 ("The MSI-H Study Record's discussion of treating patients with 'MSI positive' cancer also concerns treating patients with a mismatch repair deficiency ('dMMR')").

Petitioner also relies on Dr. Neugut's testimony to assert that the dosage described in the MSI-H Study Record is the same as the dosage described as being effective in the '287 patent. Pet. 19–20 (citing Ex. 1003 ¶ 63); *see* Ex. 1001 4:23–36, 8:52–56, 13:28–30.)

[2] We need not decide whether the preamble is limiting as we find that the MSI-H Study Record discloses the preamble.

(3) *[1.2]: "wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient."*

Petitioner argues further that the Arms and Interventions section of the MSI-H Study Record teaches the limitation in claim 1 of "wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." Pet. 22–23. Petitioner relies on Dr. Neugut's testimony that, "in order to place the patients into the proper arm, the MSI-H Study Record required a biological sample from the patient that had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." *Id.* at 23; Ex. 1003 ¶ 68.

2. Discussion

Having considered the information presented in the Petition, summarized above, we are persuaded by Petitioner that the MSI-H Study Record teaches treating colorectal cancer patients after they were determined to be microsatellite instability high or DNA mismatch repair deficient with pembrolizumab. *See* MSI-H Study Record, Ex, 1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003, ¶¶ 58–62. We are also persuaded that Petitioner has sufficiently shown that there is a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of colorectal cancer patients and the determination of their MSI status — all colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were treated

with pembrolizumab. Whether or not other patients were treated or enrolled in the study does not detract from this teaching.[3] Accordingly, we are persuaded by Petitioner that, on this record, the MSI-H Study Record discloses each element of claim 1.

In view of the above, we determine that Petitioner has sufficiently shown a reasonable likelihood of establishing that the MSI-H Study Record anticipates claim 1. Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

Additionally, we have reviewed Petitioner's allegations regarding how the MSI-H Study Record discloses the limitations of 2, 4–8, 11–12, 14–18, and 21–36 and find that Petitioner has sufficiently demonstrated, on this record and as supported by the testimony of Dr. Neugut, that the MSI-H Study Record expressly or inherently discloses those additional limitations. Pet. 23–39; Ex. 1003 ¶¶ 50–127.

3. Conclusion

For the foregoing reasons, we determine that Petitioner has established a reasonable likelihood of showing that the MSI-H Study Record

[3] Because treatment of the patients was performed only after MSI-H status was determined, there is evidence that the MSI-H Study Record teaches treating the patients "in response to" determining their MSI-H status. The MSI-H Study Record describes other patients being enrolled and treated with pembrolizumab, including colorectal cancer patients determined to be MSI-H and colorectal cancer patients determined not to be MSI-H. For the purposes of this Decision, we interpreted the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients. The parties are invited to address this issue at trial.

anticipates claims 1–2, 4–8, 11–12, 14–18, and 21–36 for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Accordingly, we institute a *inter partes* review of claims 1–2, 4–8, 11–12, 14–18, and 21–36 of the '287 patent.

D. Ground 2: Obviousness of Claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 over MSI-H Study Record and Pernot

1. Petitioner's Contentions

Petitioner presents a challenge to claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 of the '287 patent under 35 U.S.C. § 103, as an alternative to the challenge under 35 U.S.C. § 102, reportedly to address potential arguments by Patent Owner. Pet. 43–44. Petitioner expects Patent Owner's arguments to be that the MSI-H Study Record cannot anticipate because it does not disclose an improved outcome and does not teach "testing, or having tested, a biological sample obtained from a patient," as required in claim 1, because these points were noted in the Notice of Allowance for a related patent and/or taught or suggested by Pernot. *See* Pet. 44 (citing December 14, 2020, Notice of Allowance in application 16/144,549, Ex. 1022 (part 11), 3073).

For example, Petitioner cites Pernot as teaching that colorectal cancer patients are good candidates for immunotherapy, such as the PD-1 inhibitor pembrolizumab, to address the expectation of success in the method of claim 1. Pet. 44 (citing Ex. 1006, 3741). Pernot states "[colorectal cancers] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy." Ex. 1006, 3740–41; Pet. 10. Petitioner argues, citing Dr. Neugut's testimony, that Pernot would have motivated one of ordinary

skill in the art to obtain the results of the MSI-H Study Record. Pet. 45 (citing Ex. 1003 ¶ 131).

Petitioner also argues that the state of the art indicates one of ordinary skill would have had a reasonable expectation of success in the claimed method because successful treatment with a PD-1 inhibitor of a colorectal cancer patient having an MSI-H tumor was reported in the prior art. Pet. 45–47 (citing Ex. 1003 ¶¶ 132–135). Specifically, Petitioner refers to Lipson[4] for its reporting of the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor, albeit different from pembrolizumab:

> A 71-year-old male with [colorectal cancer] underwent a right hemicolectomy in October 2003, revealing a moderately differentiated adenocarcinoma with metastases to 4 of 16 pericolonic lymph nodes and vascular and perineural invasion [G_2, pT3N2; *microsatellite instability (MSI)-high genotype]*. He received adjuvant 5-fluorouracil (5-FU) and leucovorin; however, a CT scan the following year revealed metastatic disease. Over the subsequent 3 years, the patient received multiple chemotherapeutic regimens with temporary response but then progression at multiple lymph node sites (gastrohepatic, portacaval, and peripancreatic); therapies included FOLFOX, irinotecan, bevacizumab, and cetuximab. Chemotherapy was last administered in April 2007. The patient began therapy with anti-PD-1 at 3 mg/kg per dose in July 2007 after documentation of disease progression, and received 5 doses over the next 9 months. *CT scans conducted 8 and 12 weeks after a single dose of anti-PD-1 showed a partial response (Fig. 1A). A [complete remission] was achieved in January 2008, and periodic CT and PET scans have revealed no evidence of recurrence since then.* The patient was most

[4] Ex. 1057, Lipson et al, *Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody*, 19(2) CLINICAL CANCER RESEARCH 462 (January 2015).

> recently evaluated in April 2011, at which time he had not received any antineoplastic therapy for 3 years and had no evidence of disease recurrence.

Ex. 1057, 463–64 (emphasis added); Pet. 45.

Petitioner cites to other references as "independently urg[ing] the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab." Pet. 45 (citing Ex. 1003 ¶ 133). For example, Petitioner cites to Champiat,[5] which teaches:

> Moreover, if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1 and 2, early onset), all of which display severe genomic instability.

Ex. 1032, e27817-5.

Petitioner argues further that the MSI-H Study Record itself would have rendered it obvious to test patients for MSI-H because one of ordinary skill in the art would have been motivated to and would have expected success in carrying out the methods taught in the MSI-H Study Record. Pet. 47–48 (citing Ex. 1003 ¶¶ 131–135). In particular, Petitioner argues that the MSI-H Study Record discusses treating colorectal cancer patients having MSI-H colorectal cancer in one arm, which would have at least motivated one of ordinary skill in the art to test for MSI-H because it would have been necessary to

[5] Ex. 1032, Champiat et al, *Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy*, 3(1) OncoImmunology e27817-1 (January 2014).

place the patients into the correct arm of the study. *Id.* Petitioner argues further that one of ordinary skill in the art would have expected success testing MSI-H positive patients because it was routine in the art. *Id.* (citing Ex. 1003 ¶ 136).

2. Discussion

As explained above in regard to Ground 1, on this record we determine that sufficient evidence exists to institute on the anticipation ground based on the MSI-H Study Record. For the same reasons, we determine the evidence is sufficient to proceed on Ground 2. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("It is well settled that 'anticipation is the epitome of obviousness.'") (citation omitted).

Furthermore, we note that, to the extent the MSI-H Study Record does not disclose the limitation of "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab," the record before us supports this limitation being rendered obvious by Pernot and the MSI-H Study Record. Specifically, because Pernot teaches that colorectal cancer patients are good candidates for immunotherapy, the evidence of the current record shows that one of ordinary skill in the art would have had a reason to use to PD-1 inhibitors to treat colorectal cancers. Ex. 1006, 3741; Ex. 1003 ¶ 136. Additionally, the focus in the MSI-H Study Record on a clinical study treating colorectal cancer patients who had been determined to be MSI-H with pembrolizumab indicates that it would have been obvious to test for this condition before treatment.

The additional references discussed by Petitioner contribute further to a reasonable likelihood that Petitioner will prevail. For example, Libson reports the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor (Ex. 1057, 463-64) and Champiat discusses evaluating the clinical activity of PD-1 agents in DNA mismatch repair, such as MSI+, colorectal cancer (Ex. 1032, e27817-5). Pet. 44 (citing Ex. 1003 ¶ 49). Thus, based on the current record, we determine that Petitioner presents a reasonable likelihood that the method of claim 1 would have been considered obvious by one of ordinary skill in the art.

Accordingly, in view of the above, we are persuaded that there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Ground 2 in the Petition.

A. Grounds 3–6: Obviousness Based on the MSI-H Study Record, Pernot, and Additional References

Petitioner argues that certain of the dependent claims of the '393 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle, Steinert, Benson, and Hamid. Pet. 48–62.

In regard to Ground 3, Petitioner cites Chapelle for its teaching of testing tumor tissue from a patient to determine microsatellite instability in colorectal cancer, as recited in claims 2, 9–10, 12, and 19–20. Pet. 48–47 (citing Ex. 1007, 3380, 3383; Ex. 1003 ¶¶ 138, 141). Petitioner also cites Chappelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claim 9. Pet. 49–50 (citing Ex. 1007, 3380–84; Ex. 1003 ¶¶ 143–144.

In regard to Ground 4, Petitioner contends that claims 3 and 13 would have been obvious over the combination of the MSI-H Study Record,

Pernot, and Steinert. Pet. 51–53. Petitioner cites Steinert for its teaching of testing body fluid to determine whether a tumor is microsatellite instability high, as recited in claims 3 and 16. *Id.* (citing Ex. 1008, OF6; Ex. 1003 ¶ 155).

In regard to Ground 5, Petitioner contends that claims 6–7, 16–17, 26, 28, and 30–36 would have been obvious over the combination of the MSI-H Study Record, Pernot, and Benson. Petitioner cites to Benson for its teaching of a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer, as recited in claims 6–7, 16, 17, 26, 28, and 30–36. Pet. 51–57 (citing Ex. 1009, 1034; Ex. 1003 ¶¶ 159–178.)

In regard to Ground 6, Petitioner contends that claims 8 and 18 would have been obvious over the combination of the MSI-H Study Record, Pernot, and Hamid. Petitioner cites to Hamid for its teaching of administering pembrolizumab intravenously, as recited in claims 8 and 18. Pet. 60–63 (citing Ex. 1011, 134; Ex. 1003 ¶ 166).

Having considered the information presented in the Petition, summarized above, we find Petitioner has established a reasonable likelihood of prevailing with respect to at least one claim challenged under each of Grounds 3–6. Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of the challenged claims of the '287 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v.*

Iancu, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"); 37 C.F.R. § 42.108(a). At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response). In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board's Rules.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–36 of the '287 patent is hereby instituted on the grounds set forth in the Petition, commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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