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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.

IPR2024-00649
Patent 11,629,187 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 1–28 of U.S. Patent No. 11,629,187 B2 (Ex. 1001, "the '187 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '187 patent. Paper 3. Patent Owner has not filed a Preliminary Response ("Prelim. Resp.").

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 by the parties, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of claims 1–28 of the '187 patent are unpatentable.

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 64. Patent Owner identifies Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '187 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. 64; 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; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00647 against U.S. Patent No. 11,649,287; 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. 64; Paper 3, 1.

D. The '187 patent (Ex. 1001)

The '187 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '187 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 '187 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 '187 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 responses. 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 '187 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.*, 2:6–9. However, the specification describes that

> in reports of PD-1 blockade in human tumors, only one of 33 colorectal cancer (CRC) patients responded to this treatment. . . . What was different about this 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 '187 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.*, 8:52–58. According to the '187 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 1–28. Representative independent claim 1 is reproduced below:

> 1. A method for treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer, the method comprising:
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small

> bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer with a therapeutically effective amount of pembrolizumab based on a determination that the solid tumor has progressed following at least one prior cancer treatment, and further based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.

Ex. 1001, 25:5–27.

Representative independent claim 11 is reproduced below:

> 11. A method for reducing the risk of progression of a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment in a patient, the method comprising:
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.

Id., 25:49–26:12.

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. 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").

Ex. 1034, Brown et al., *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) GENOME RESEARCH 743 (May 2014) ("Brown").

Ex. 1087, Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 5002 (2004) ("Duval").

Ex. 1095, Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. NAT'L COMPREHENSIVE CANCER NETWORK 248 (February 2014) ("Koh").

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 1–28 would have been unpatentable on the following grounds (Pet. 3–4):

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 2, 4–7, 9–12, 14–17, 19–28	102	MSI-H Study Record
II	1, 2, 4–7, 9–12, 14–17, 19–28	103	MSI-H Study Record, Brown, Duval, Benson
III	1, 2, 4–7, 9–12, 14–17, 19–28	103	MSI-H Study Record, Brown, Duval, Benson, Koh
IV	2, 8, 12, 18	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Chapelle
V	3, 13	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Steinert
VI	7, 17	103	MSI-H Study Record, Brown, Duval, Benson, Koh, 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 argues 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. Matal*, 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 (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 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, Inc.*, 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

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

"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. 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.

3. 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.

4. 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.

5. 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.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.*, 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic

mutations have . . . elevated expression of *CTLA4* and *PDCD1*," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.*, 747–748.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.* (emphasis omitted).

8. Koh (Ex. 1095)

Koh is an article titled "Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology." Ex. 1095, 248. Koh describes that "[t]he NCCN Guidelines for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management." *Id.*, Abstract. Koh discloses that patients having endometrial cancer who were enrolled in a clinical study would generally have had a tumor that had progressed after at least one prior cancer treatment and metastatic cancer. *Id.*, 256.

C. Ground 1: Anticipation of Claims 1, 2, 4–7, 9–12, 14–17, and 19–28 by the MSI-H Study Record

1. Petitioner's Contentions

Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, and 19–28 are anticipated by the MSI-H Study Record. Pet. 13–38. 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, 4–7, 9–12, 14–17, and 19–28 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 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. 13–14. 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. 16. Relying on those cases, Petitioner contends that "[t]he MSI-H Study Record inherently anticipates [c]laims 1–2, 4–7, 9–12, 14–17, [and] 19–28 of the '187 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 16.

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 '187 patent, and given to

the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "[i]f 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. 14.

a) Independent Claim 1

Like Petitioner, our analysis focuses on independent claim 1. *See id.* at 32–34 (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 reducing the risk of progression of a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment in a patient, the method comprising:"*

Petitioner argues that, in general, the MSI-H Study Record anticipates claim 1 of the '187 patent because it "teaches the claimed drug, given at the only therapeutically effective dosage described in the '187 patent, and given to the claimed patient population." Pet. 16–17. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating patients having non-colorectal MSI-H cancer, as recited in the preamble of claim 1.[2] *Id.* at 18 (citing Ex. 1003 ¶¶ 38–41, 59–63; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)). Petitioner contends that the MSI-H Study Record concerns the treatment of solid tumor and further contends

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

that "MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel cancer, and gastric cancer." Pet. 17–18 (citing Ex. 1005, 2 (Study Identification), 5–6 (Eligibility); Ex. 1048, 228, 230–3; Ex. 1085, 673, 675; Ex. 1086, 14; Ex. 1003 ¶¶ 25, 60–61, 63).

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses the preamble of claim 1.

(2) [1.1]: "in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating a patient"

Petitioner argues that the MSI-H Study Record anticipates this limitation in claim 1 because the Arms and Interventions section treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 19–21; *see also* Ex. 1003 ¶¶ 65–67 ("The MSI-H Study Record's discussion of treating patients with 'MSI positive' cancer also concerns treating patients with a mismatch repair deficiency ('dMMR')").

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

(3) [1.2]: "having a solid tumor"

This limitation is identical to limitation [1.pre], discussed above, and met for the same reasons. Pet. 21.

(4) [1.3]: "selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer"

This limitation is identical to limitation [1.pre], discussed above, and met for the same reasons. Pet. 21.

(5) [1.4]: "with a therapeutically effective amount of pembrolizumab"

Petitioner 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 '187 patent. Pet. 21–22 (citing Ex. 1003 ¶¶ 70–73; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)); *compare* Ex. 1001 4:23–36, 8:51–58, 13:30–37.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

(6) [1.5]: "based on a determination that the solid tumor has progressed following at least one prior cancer treatment"

Petitioner alleges that the MSI-H Study Record discloses the above limitation, because the MSI-H Study Record requires the enrolled patients to have "tumors" and "measurable disease," which Dr. Neugut testifies would include metastatic and advanced non-colorectal cancers in the context of the MSI-H Study Record. Pet. 23 (citing Ex. 1005, 2–6 (Study Identification, Study Design, Eligibility); Ex. 1020, 25; Ex. 1003 ¶¶ 74–75). According to Dr. Neugut, the MSI-H Study Record indicated that, "before receiving treatment based on the MSI-H Study Record, patients would have generally

received a prior cancer therapy drug and had their solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 74.

Dr. Neugut testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer "would have generally received at least one prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after that drug therapy." *Id.* ¶ 76 (citing Ex. 1089 at PDF p. 17 (endometrial); Ex. 1020, 25 (small bowel); Ex. 1091, 12, 15 (gastric cancer patients would generally receive a standard first line therapy, unless diagnosis was late stage)). Dr. Neugut observes that the Eligibility section of the MSI-H Study Record takes care to exclude patients having had prior treatment with certain antibodies. Ex. 1003 ¶ 74. Dr. Neugut interprets this exclusion as supporting his opinion that such patients would have received a prior cancer therapy drug to treat their tumor because otherwise, the study would not have purposefully excluded these antibodies, and because if the prior therapies had worked, these patients would not have participated in the MSI-H Study Record. *Id.* Dr. Neugut cites to a poster presentation describing the MSI-H Study Record as requiring that patients have "progressive disease" and have had prior therapies. *Id.* ¶ 79.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

> *(7) [1.6]: "and further based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency."*

Petitioner contends that the Arms and Interventions section of the MSI-H Study Record teaches this limitation in claim 1. Pet. 27–28.

Specifically, Petitioner contends that "the MSI-H Study Record discloses treating three study arms, one of which consists of patients having MSI positive non-colorectal cancer—that is non-colorectal cancer that exhibits an instability of more than one microsatellite marker and a deficiency of one or more mismatch repair markers." *Id.* (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); Ex. 1007, 3382–3383; Ex. 1003 ¶ 80). Petitioner also 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 28; Ex. 1003 ¶ 81.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

2. Discussion

Having considered the information presented in the Petition, summarized above, we determine that Petitioner has sufficiently shown a reasonable likelihood of establishing that the MSI-H Study Record discloses each element of 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, 4–7, 9–12, 14–17, and 19–28 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.

For the foregoing reasons, we determine that Petitioner has established a reasonable likelihood of showing that the MSI-H Study Record anticipates claims 1, 2, 4–7, 9–12, 14–17, and 19–28 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, 4–7, 9–12, 14–17, and 19–28 of the '187 patent.

D. Ground 2: Obviousness of Claims 1, 2, 4–7, 9–12, 14–17, and 19–28 over MSI-H Study Record, Brown, Duval, and Benson

1. Petitioner's Contentions

Petitioner presents a challenge to claims 1, 2, 4–7, 9–12, 14–17, and 19–28 of the '187 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. 41–42. Petitioner expects Patent Owner to argue that the MSI-H Study Record cannot anticipate because it does not disclose an improved outcome and does not disclose "testing of a biological sample obtained from the patient," as required in claim 1. *Id.* Petitioner contends those elements are rendered obvious by the additional disclosures of Brown, Duval, and Benson. *Id.* at 42–53.

For example, Petitioner cites Brown for its disclosure "that PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize." *Id.* at 43 (citing Ex. 1034, 747; Ex. 1003 ¶¶129, 135). Petitioner relies on Duval for its disclosure "that MSI-H cancers have cancer cells that are easy for immune cells to recognize." *Id.* (citing Ex. 1087, 5002; Ex. 1003 ¶¶ 131, 135). Petitioner contends, citing Dr. Neugut's testimony, that Brown and Duval would have motivated one of ordinary skill in the art "to treat patients

having common types of MSI-H cancers, including endometrial, small bowel, and gastric cancer in the MSI-H Study." *Id.* (citing Ex. 1003 ¶ 135).

Petitioner contends that the state of the art indicates one of ordinary skill would have had a reasonable expectation of success in the claimed method because "[p]hysicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art with PD-1 inhibitors." Pet. 43 (citing Ex. 1003 ¶ 136). Petitioner further contends that "Brown and other prior art also taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are already infiltrated by many immune cells. *Id.* at 44 (Ex. 1034, 747; Ex. 1037, 2; Ex. 1003 ¶ 137).

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. 44 (citing Ex. 1003 ¶ 138). For example, Petitioner cites to Champiat,[3] 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

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

success in carrying out the methods taught in the MSI-H Study Record. Pet. 46–48 (citing Ex. 1003 ¶¶ 140–143). In particular, Petitioner argues that the MSI-H Study Record discusses treating patients having MSI-H cancer in two arms, 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 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.* at 47 (citing Ex. 1003 ¶ 141).

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 solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient," the record before us supports this limitation being rendered obvious by the combination of MSI-H Study Record, Brown, Duval, and Benson. For example, 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 MSI-H cancer because "Brown and Duval teach that PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize, and that all MSI-H cancer, such as endometrial, small bowel, and gastric cancer, have cancer

cells that are easy for immune cells to recognize." Pet. 44 (Ex. 1034, 743; Ex. 1087, 5002; Ex. 1003 ¶¶ 131, 135, 137). Additionally, the MSI-H Study Record is directed to a clinical study treating patients having MSI-H non-colorectal cancer with pembrolizumab indicates that it would have been obvious to test for this condition before treatment. Ex. 1003 ¶ 135.

Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

After considering the information presented in the Petition, we determine that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail in establishing that claim 1 is rendered obvious by the combination of the MSI-H Study Record, Brown, Duval, and Benson. Additionally, we have reviewed Petitioner's obvious challenges of claims 2, 4–7, 9–12, 14–17, and 19–28 and find that Petitioner has sufficiently demonstrated, on this record and as supported by the testimony of Dr. Neugut, that the combination of the MSI-H Study Record, Brown, Duval, and Benson renders obvious each of claims 2, 4–7, 9–12, 14–17, and 19–28.

Accordingly, in view of the above, we institute a inter partes review of claims 1, 2, 4–7, 9–12, 14–17, and 19–28 of the '187 patent.

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

In Ground 3, Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, 19–28 of the '187 would have been obvious over the references discussed in Grounds 1 and 2 and further in view of Koh. Pet. 53–54. In Ground 4, Petitioner contends that claims 2, 8, 12, and 18 would have been obvious over the references discussed in Grounds 1 and 2 and further in view of Koh and Chapelle. *Id.* at 54–55. In Ground 5, Petitioner contends that claims 3

and 13 would have been obvious over the references discussed in Grounds 1 and 2 and further in view of Koh and Steinert. *Id.* at 58–59. In Ground 6, Petitioner contends that claims 7 and 17 would have been obvious over the references discussed in Grounds 1 and 2 and further in view of Koh and Hamid. *Id.* at 59–61.

Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

We have reviewed Petitioner's contentions as to the remaining grounds and are persuaded, on this record, that Petitioner's arguments and evidence are sufficient to show a reasonable likelihood that Petitioner would prevail in proving unpatentability of at least one claim in challenged in each of Grounds 3–6. However, the burden remains on Petitioner to prove unpatentability of each challenged claim. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

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 '187 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 1–28 of the '187 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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