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Paper 6
Date: September 27, 2024

i. 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.

IPR2024-00650
Patent 11,634,491 B2

Before DEBORAH KATZ, ROBERT A. POLLOCK, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges.*

KATZ, *Administrative Patent Judge*.

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

II. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–38 of U.S. Patent No. 11,634,491 B2 (Ex. 1001, "the '491 patent"). (Petition ("Pet."), Paper 1.) The Johns Hopkins University ("Patent Owner") filed mandatory notices identifying itself as the owner of the '491 patent. (Paper 3, 1.) Patent Owner did not file a Preliminary Patent Owner's Response.

The Director may not authorize an *inter partes* review "unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is 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). We determine whether to institute an *inter partes* review on behalf of the Director. *See* 37 C.F.R. § 42.4(a).

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner.

Upon considering the Petition and the evidence of record, we determine that Petitioner has demonstrated there is a reasonable likelihood that Petitioner would prevail in showing that at least one challenged claim is unpatentable and we institute *inter partes* review of all challenged claims on all asserted grounds. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a).

A. Real Parties-in-Interest and Related Matters

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

Both Petitioner and Patent Owner report that the litigation *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), is a related matter. (*See* Pet. 64; *see* Paper 3, 1.) Patent Owner identifies eight other related petitions for *inter partes* review that Petitioner has filed. (*See* Paper 3, 1.) These other petitions are:

Petition for *Inter-Partes* Review	**Patent**
IPR2024-00240	11,591,393
IPR2024-00622	10,934,356
IPR2024-00623	11,325,974
IPR2024-00624	11,325,975
IPR2024-00625	11.339.219
IPR2024-00647	11,649,287
IPR2024-00648	11,643,462
IPR2024-00649	11,629,187

We note that *inter-partes* review in IPR2024-00240 was instituted on June 13, 2024. (*See* IPR2024-00240, Paper 10.) Patent Owner requested Director Review of the Decision on Institution (Paper 12), which was denied

(Paper 24). In addition, *inter-partes* reviews in IPR2024-00622, IPR-00623, IPR-00624, and IPR2024-00625 were instituted on September 23, 2024.

Decisions on the other petitions are pending.

B. The '491 Patent and Challenged Claims

The '491 patent is directed to anti-cancer therapies that block immune system checkpoints, including at the PD-1 receptor. (*See* Ex. 1001, Abstr.) More specifically, the '491 patent is directed to treating cancer patients with high mutational burdens, such as found in microsatellite instable (MSI) cancer, with anti-PD-1 antibodies. (*See* Ex. 1001, 3:39–43.) The Specification discloses that pembrolizumab is a humanized monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in a clinical trial. (*See* Ex. 1001, 8:54–58.)

Claim 1 of the '491 patent recites:

> A method of treating cancer in a human patient, the method comprising:
>
> testing or having tested a biological sample obtained from a patient having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer, thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab.

(Ex. 1001, 25:36–52.) Claim 16 of the '491 patent is also independent and recites a method with similar steps, but the preamble recites: "A method of

reducing the risk of cancer progression or increasing overall survival in a human patient, the method comprising . . . ." (*Id.* 26:24–26.)

C. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–38 of the '491 patent are unpatentable based on the following grounds (*see* Pet. 3–4):

	Claims Challenged	Statutory Basis 35 U.S.C.[1] §	References
1	1–2, 4–7, 11–17, 19–22, 26–38	102	MSI-H Study Record[2] (Ex. 1005)
2	1–2, 4–7, 11–17, 19–22, 26–38	103	MSI-H Study Record (Ex. 1005), Brown[3] (Ex. 1034), Duval[4] (Ex. 1087), and Benson[5] (Ex. 1009)

[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013, before the filing of the applications to which the '491 patent claims priority. Therefore, we apply the AIA versions of Sections 102 and 103.

[2] 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") (Ex. 1005).

[3] Brown, *et al.*, *Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival*, 24 GENOME RESEARCH 743 (May 2014) (Ex. 1034) ("Brown").

[4] Duval, *et al.*, *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROC. NAT'L ACAD. SCI. 5002 (April 2004) (Ex. 1087) ("Duval").

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

3	1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	103	MSI-H Study Record (Ex. 1005), Brown (Ex. 1034), Duval (Ex. 1087), Benson (Ex. 1009), and Koh[6] (Ex. 1095)
4	2, 8, 17, 23	103	MSI-H Study Record (Ex. 1005), Brown (Ex. 1034), Duval (Ex. 1087), Benson (Ex. 1009), Koh (Ex. 1095), and Chapelle[7] (Ex. 1007)
5	3, 18	103	MSI-H Study Record (Ex. 1005), Brown (Ex. 1034), Duval (Ex. 1087), Benson (Ex. 1009), Koh (Ex. 1095), and Steinert[8] (Ex. 1008)
6	9–10, 24–25	103	MSI-H Study Record (Ex. 1005), Brown (Ex. 1034), Duval (Ex. 1087), Benson (Ex. 1009), Koh (Ex. 1095), and Salipante[9] (Ex. 1010)

[6] Koh *et al.*, *Uterine Neoplasms, Version 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. NAT'L COMPREHENSIVE CANCER NETWORK 248 (February 2014) (Ex. 1095) ("Koh").
[7] Chapelle *et al.*, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. CLINICAL ONCOLOGY 3380 (2010) (Ex. 1007) ("Chapelle").
[8] Steinert *et al.*, *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) (Ex. 1008) ("Steinert").
[9] Salipante *et al.*, *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) CLINICAL CHEMISTRY 1192 (June 2014) (Ex. 1010) ("Salipante").

7	11, 26	103	MSI-H Study Record (Ex. 1005), Brown (Ex. 1034), Duval (Ex. 1087), Benson (Ex. 1009), Koh (Ex. 1095), and Hamid[10] (Ex. 1011)

III. ANALYSIS

A. Legal Standards

"A person shall be entitled to a patent unless— (1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention." 35 U.S.C. § 102(a). To be anticipated, each and every element of the claim must be found, either expressly or inherently described, in a single prior art reference. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). When claim elements are inherently taught, the result must be a necessary consequence of what was deliberately intended, but the prior art need not demonstrate that the authors appreciated the results. *See Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999); *see Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("At the outset, this court rejects the contention that inherent anticipation requires recognition in the prior art.").

Under 35 U.S.C. § 103, a patent for a claimed invention may not be obtained,

> if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have

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

> been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which said claimed invention pertains.

Obviousness is determined by looking to the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art resolved. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). "[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

B. Level of Skill and Declarants

Petitioner presents the testimony of Alfred I. Neugut, M.D., Ph.D., M.P.H., for opinion testimony regarding what one of ordinary skill in the art would have understood at the time of filing. (*See* Ex. 1003.) Dr. Neugut testifies that he is a medical oncologist with a particular focus on gastrointestinal tract cancers, including colorectal cancers. (*See id.* ¶ 4.) Dr. Neugut testifies further that he is the Director of the Center for Pharmacoepidemiology and Health Outcomes Research in Columbia's Department of Epidemiology and Director of Global Oncology Research for Columbia's Herbert Irving Comprehensive Cancer Center. (*See id.* ¶ 5.) Dr. Neugut testifies that he sees approximately 30 patients per week to treat gastrointestinal cancers, including colorectal cancer. (*See id.* at ¶ 4)

Petitioner argues that one of ordinary skill in the art relevant to the '219 patent would have been a medical doctor or a professional in a related field with at least five years of experience with treating cancer. (*See* Pet. 11

(citing Neugut Decl., Ex. 1003 ¶19).) Petitioner argues further that the ordinarily skilled artisan would have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and to a pathologist with comparable experience. (*See id.*)

Dr. Neugut's testimony supports Petitioner's arguments regarding the level of skill that an ordinarily skilled artisan in the relevant field would have. (*See* Ex. 1003 ¶ 19.) Accordingly, in the analysis below, and in the absence of argument by Patent Owner to the contrary, we apply the level of skill set forth by Petitioner and refer to Dr. Neugut's testimony of what one of ordinary skill in the art would have understood at the time the application that became the '491 patent was filed, which does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

C. Claim Construction

Petitioner argues that we need not construe any terms of the challenged claims to resolve the underlying controversy, as any reasonable construction reads on the prior art. (*See* Pet. 10–11.)

To the extent we deem it necessary to construe the terms of the challenged claims at this point in the proceeding, we do so in the analysis below. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The Board is required to construe 'only those 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))).

D. Ground 1 – Anticipation of Claims 1–2, 4–7, 11–17, 19–22, and 26–38 *Based on the MSI-H Study Record*

Petitioner argues that the MSI-H Study Record teaches each and every element of claim 1 of the '491 patent. (*See* Pet. 16–22.) Petitioner asserts that the MSI-H Study Record was publicly available by June 10, 2013, making it prior art under 35 U.S.C. § 102(a) and not covered by any exceptions under 35 U.S.C. § 102(b). (*See id*. 7–8.)

The title of the MSI-H Study Record is "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors." (Ex. 1005, 2.) Dr. Neugut testifies that MK-3475 is pembrolizumab. (*See* Neugut Decl., Ex. 1003 ¶ 38.)

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.) The inclusion criteria for the MSI-H Study Record includes "[p]atients with MSI positive non-colorectal cancer," as well as other criteria. (*Id*. at 5.) The MSI-H Study Record provides "Arms and Interventions" as follows:[11]

[11] Petitioner relies on the testimony of Dr. Neugut and several prior art references to assert that the terms "MSI positive," "MSI-high," "MSIH," and "MSI+" were used to mean "MSI-H" by those in the art at the time. (*See* Pet. 5–6 (citing Neugut Decl., Ex. 1003 ¶ 27).)

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

(*Id.* at 4.) The chart above identifies three patient populations and states that all patients were administered pembrolizumab at 10 mg/kg every 14 days. The MSI-H Study Record provides that one primary outcome measure of the study is "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 Weeks." (*Id.*)

Petitioner argues, supported by Dr. Neugut's testimony, that the Arms and Intervention section, as well as other sections, of the MSI-H Study Record disclose a method of treating cancer in a human patient, as recited in the preamble of claim 1. (*See* Pet. 16 (citing Ex. 1003 ¶¶ 60–61).)

Petitioner argues further that the MSI-H Study Record discloses "testing or having tested a biological sample obtained from a patient" and "thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient" in the study's three study arms, one of which includes patients that have MSI-H non-colorectal cancer. (*See* Pet. 17–18, 20 (citing Ex. 1005, 2–6).) Petitioner asserts that the term "MSI-H positive" used in the MSI-H Study Record refers to "MSI-H" patients. (*See* Pet. 17.) Dr. Neugut's testimony and published prior art support this assertion. (*See* Ex. 1003 ¶¶ 27, 63; *see* Ex. 1018,[12] 293 ("MSIH (MSI high)

[12] Robinson et al., *Lynch Syndrome (Hereditary Nonpolyposis*

was considered MSI positive and MSS (MS stable)".) Petitioner also cites to an affidavit by Dr. Pardoll, a named inventor on the '491 patent, submitted during prosecution of the application that became that patent, stating that the MSI-H Study Record concerns MSI-H patients. (*See* Pet. 17 (citing Ex. 1002, (Pardoll Affidavit submitted in Application No. 17/739,278 ¶¶ 21–23).)

Petitioner argues further, relying on Dr. Neugut's testimony, that the disclosure in the MSI-H Study Record of treating patients with "MSI positive" cancer also discloses patients with mismatch repair deficiency ("dMMR"). (*See* Pet. 17.) Petitioner cites Dr. Pardoll's affidavit in the prosecution history of the '491 patent as equating the MSI-high status with the MMR deficient status of tumors. (*See* Pardoll Affidavit submitted in Application No. 17/739,278 ¶ 23 ("The preliminary results of this study demonstrated clinical responses at an unexpectedly high rate (>50% objective response rate) in the MSI-high (MMR deficient) arm but not in the MSS (MMR proficient) arm.").) Petitioner also cites Dr. Neugut, who confirms that "'MSI positive' cancer also concerns treating patients with a mismatch repair deficiency ('dMMR')." (Neugut Decl., Ex. 1003 ¶ 64 (citing Ex. 1020,[13] 251 ("Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.")).)

Colorectal Cancer) Diagnostics, 99 J. NAT'L CANCER INST. 291 (2007) (Ex. 1018).

[13] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Colon Cancer* Version 3.2014 (January 27, 2014) (Ex. 1020).

Petitioner argues that given these meanings of the terms, the MSI-H Study Record teaches testing or having tested a biological sample obtained from a patient in order to place the patient into the proper arm. (*See* Pet. 18.) Petitioner argues further that, therefore, the MSI-H Study Record teaches that to determine if a patient's cancer is MSI-H is to test for specific biomarkers. (*See* Pet. 18 (citing Neugut Decl., Ex. 1003 ¶¶ 64–66).) Dr. Neugut testifies that

> [t]he MSI-H Study Record requires testing or having tested "a biological sample obtained from a patient" in order to place the patients into the proper arm. (EX1005 at 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility).) Without that determination, patients could not have been placed into the proper arm of the study.

(Ex. 1003 ¶ 65.)

In regard to the limitations of claim 1 that recite different types of cancer, Petitioner argues that the MSI-H Study Record teaches treating patients having non-colorectal MSI-H cancer. (*See* Pet. 18.) Petitioner relies on the testimony of Dr. Neugut to argue that MSI-H was known to commonly occur in several types of cancers, including endometrial cancer, small bowel cancer, and gastric cancer. (*See id.* (citing Ex. 1003 ¶¶ 25, 67).) Petitioner cites further to prior art that states "MSI-H also occurs in ~15% of human colorectal, gastric and endometrial cancers and in lower frequencies in a minority of other tumors." (Ex. 1085[14], 675, abstract; *see* Pet. 19.)

[14] Imai & Yamamoto, *Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics*, 29(4) CARCINOGENESIS 673 (2008) (Ex. 1085).

Petitioner argues that colorectal cancer is considered along with endometrial cancer, small bowel cancer, gastric cancer in a condition called Lynch syndrome, which was known at the time to be closely associated with MSI-H. (*See* Pet. 18 (citing Neugut Decl., Ex. 1003 ¶¶ 25, 67 and Ex. 1085, 673–674).) Thus, Petitioner argues, one of ordinary skill in the art would have pictured treating patients having endometrial, small bowel, and gastric cancer with the methods taught in the MSI-H Study Record. (*See* Pet. 19 (citing Ex. 1003 ¶ 67).)

In regard to the limitation of treating the patient with a "therapeutically effective" amount of pembrolizumab "in response to determining that the patient's cancer is [MSI-H] or [dMMR]," Petitioner argues the MSI-H Study Record teaches treating patients having non-colorectal cancer with 10 mg/kg pembrolizumab every 14 days. (*See* Pet. 21 (citing Ex. 1005).) Petitioner argues that the dosage described in the MSI-H Study Record (10 mg/kg) is identical to the only dosage described in the '491 patent, which is described therein as being effective. (*See* Pet. 21 (citing Ex. 1001, 8:50–56, 13:24–30; 4:23–36, 16:4–8, 16:29–32, 19:40–21:15, Figures 2, 11).) Dr. Neugut testifies that the '491 patent demonstrates the clinical effectiveness of the treatment taught in the MSI-H Study Record. (*See* Ex. 1003 ¶ 73 (citing Ex. 1001, 4:23–36 as "showing the '[c]linical benefit to pembrolizumab according to MMR status'").)

At this point in the proceeding, Petitioner has sufficiently shown that there is a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of non-colorectal cancer patients and the determination of their MSI status, wherein non-colorectal cancer patients

determined to be microsatellite instability high or DNA mismatch repair deficient were placed into a study arm and then treated with pembrolizumab. (*See* Ex. 1005, Ex. 1003 ¶¶ 60–73.) Because treatment of the patients was performed only after MSI-H status was determined, 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. At this point in the proceeding, we interpret 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. Patent Owner has not directed us to evidence that one of ordinary skill in the art would have understood treating a patient "in response to" the determination that the patient has a condition to exclude the same treatment of other patients, such as the treatment of control patients not having the condition.

The record before us shows that Petitioner has sufficiently demonstrated a reasonable likelihood that those of ordinary skill in the art would have understood the MSI-H Study Record teaches treatment of non-colorectal cancer patients who have been determined to be microsatellite instability high or DNA mismatch repair deficient because one of the arms of the MSI-H Study Record provides for treatment of patients with "MSI Positive Non-Colorectal Cancer." (Ex. 1005, 4.) Petitioner points to

evidence that those of ordinary skill in the art would have understood that the term "MSI positive" in the MSI-H Study Record means "microsatellite instability high" or "DNA mismatch repair deficient," as recited in claim 1. (*See* Neugut Decl., Ex. 1003 ¶¶ 27, 63.) Petitioner also cites evidence showing that those of ordinary skill in the art would have understood that the term "non-colorectal cancer" in the MSI-H Study Record would include endometrial, small bowel, and gastric cancer. (*See id.* at ¶¶ 25, 67.) Petitioner cites to further evidence showing that those of ordinary skill in the art would have understood that the MSI-H Study Record uses testing to determine MSI-H status and place patients into a study arm. (*See id. at* ¶¶ 64–66.) And the Petition cites evidence showing that those of ordinary skill in the art would have understood the treatment in the MSI-H Study Record, administration of 10 mg/kg of pembrolizumab every 14 days, to be treatment with a therapeutically effective dose because it is the only dose used in the '491 patent and the results reported there showed efficacy of that dose. (*See id.* at ¶ 73 (citing Ex. 1001, 4:23–36).)

In light of this evidence, Petitioner has provided sufficient evidence to show there is a reasonable likelihood that the MSI-H Study Record teaches each and every element of claim 1 and, thus, anticipates claim 1 under 35 U.S.C. § 102. We note 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." *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012).

Accordingly, the evidence of record sufficiently shows that there is a reasonable likelihood Petitioner will prevail with respect to at least one claim challenged under Ground 1 in the Petition.

We have reviewed Petitioner's allegations regarding the MSI-H Study Record's disclosure of the additional limitations of dependent claims and find that Petitioner has sufficiently demonstrated, on this record as supported by the testimony of Dr. Neugut, that the MSI-H Study Record discloses those additional limitations. (*See* Pet. 22–36; Ex. 1003 ¶¶ 75–122.) Accordingly, we determine that there is sufficient evidence to warrant institution of review based on Ground 1 of the Petition.

E. Ground 2 – Obviousness of Claims 1–2, 4–7, 11–17, 19–22, 26–38 *Based on the MSI-H Study Record, Brown, Duval, and Benson*

Petitioner presents alternative grounds of challenge against the patentability of the claims of the '491 patent based on obviousness. (*See* Pet. 36–61.) In regard to Ground 2, challenging the patentability of claims 1–2, 4–7, 11–17, 19–22, 26–38, Petitioner cites to Brown, Duval, and Benson, in addition to the MSI-H Study Record. (*See* Pet. 40–51.) According to Petitioner, this ground of challenge is raised to address potential arguments by Patent Owner, including that (1) the MSI-H Study Record does not disclose an improved outcome and that one of ordinary skill in the art would not have expected such efficacy, (2) the MSI-H Study Record does not disclose testing a patient for MSI-H or MMR deficiency status, and/or (3) the MSI-H Study Record does not teach specific types of cancer, as well as arguments that related to dependent claims. (*See* Pet. 40.)

In regard to the first potential argument, that the MSI-H Study Record does not disclose an improved outcome and/or that such efficacy would not

have been expected, Petitioner cites to Brown as teaching that PD-1 inhibitors are inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize. (*See* Pet. 41 (citing Ex. 1034, 747).) Petitioner argues further that Duval teaches that MSI-H cancers have cells that are easy for immune cells to recognize. (*See* Pet. 41 (citing Ex. 1087, 5002).) Dr. Neugut's testimony supports Petitioner's argument that the cited teachings of Brown and Duval, as well as other references, would have motivated a person of ordinary skill in the art to obtain the results of the MSI-H Study Record. (*See* Ex. 1003 ¶¶ 124, 130, 132; *see* Pet. 41.) Petitioner argues further that Brown and Duval would have motivated one of ordinary skill in the art to obtain the results of the MSI-H Study Record by treating patients with common types of MSI-H cancers, including endometrial, small bowel, and gastric cancers. (*See* Pet. 41 (citing Ex. 1003 ¶ 130).)

Petitioner argues further that the state of the art, as demonstrated by Brown and Duval, as well as other references, would have provided one of ordinary skill in the art with a reasonable expectation of success because physicians were successfully treating patients with cancers that were known to be MSI-H with PD-1 inhibitors. (*See* Pet. 42 (citing Ex. 1003 ¶¶ 131, 132).)

According to Petitioner, these other references would have "independently urged" those of ordinary skill in the art to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, such as pembrolizumab, and would have given them a reasonable expectation of success. (*See* Pet. 43–44.) Petitioner cites, along with other references,

Pernot, which 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,[15] 3741; *see* Pet. 43.) Petitioner also cites Champiat, which states

> 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,[16] e27817-5; *see* Pet. 43.) Petitioner argues, citing Dr. Neugut's testimony, that although these references are in the context of MSI-H colorectal cancer, one of ordinary skill in the art would have understood their teachings to apply to other MSI-H cancers because small bowel cancer is often treated similarly to colorectal cancer. (*See* Pet. 43 (citing Ex. 1003 ¶ 133).)

Petitioner argues further that if Patent Owner argues the MSI-H Study Record does not expressly teach testing to determine if a patient's cancer is microsatellite instability high or DNA mismatch repair deficient, the MSI-H Study Record would have at least motivated those of ordinary skill in the art to undergo such testing to be placed in the proper study arm. (*See* Pet. 44–

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

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

45.) Petitioner also argues that testing a biological sample from a patent for MSI-H was routine in the art at the time of filing. (*See* Pet. 45, citing Ex. 1003 ¶ 135.)

Petitioner cites Benson (Ex. 1009) for its teachings of the ways in which clinical studies involving colorectal and small bowel cancer are conducted, in regard to the challenge of claims 13, 15, 28, 30, 32, 34, 36, and 38 as being obvious. (*See* Pet. 47–51 (citing Ex. 1009, 1034.) These claims require treating patients who had previously been treated with a cancer therapy drug and whose cancers had progressed or who have metastatic cancer. (*See* Ex. 1001, 26:15–28:16.) Petitioner argues that to the extent Patent Owner asserts the MSI-H Study Record does not disclose treating patients with these characteristics, Benson teaches that, under the standard of care, patients having tumors and measurable disease who would take part in a clinical study are generally patients who have had their cancer progress after previous drug therapies. (*See* Pet. 48 (citing Ex. 1009, 1034).) Petitioner cites to other references to demonstrate that, also under the standard of care, patients with tumors and measurable disease who would take part in a clinical study are patients with metastatic, advanced, and recurrent disease. (*See* Pet. 49–50 (citing Ex. 1089,[17] 17; Ex. 1094,[18] 15; Ex. 1020, 25l.)

[17] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Uterine Neoplasms* Version 1.2014 (November 27, 2013) (Ex. 1089).
[18] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) *Gastric Cancer* Version 1.2014 (May 30, 2014) (Ex. 1094).

Petitioner argues, citing Dr. Neugut's testimony, that patients in a clinical study such as the MSI-H Study Record describes would already have received standard of care treatment but that they did not respond, and would not have been expected to respond to additional standard of care treatment. (*See* Pet. 47–48 (citing Ex. 1003 ¶ 140).) Petitioner cites to Dr. Neugut's testimony that the patient population with tumors and measurable disease who would take part in a clinical study are patients with metastatic, advanced, and recurrent disease. (*See* Pet. 49–50 (citing Ex. 1003 ¶ 141).)

According to Petitioner, given the teachings of Benson, those of ordinary skill in the art would have been motivated to combine the teachings of the cited references and would have had a reasonable expectation of success in achieving the methods recited in the dependent claims 13, 15, 28, 30, 32, 34, 36, and 38. (*See* Pet. 49–50.)

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

Furthermore, to the extent the MSI-H Study Record does not disclose improved outcomes of the claimed method, testing a patient for MSI-H or MMR deficiency status, and/or specific types of cancer, Petitioner has directed us to sufficient evidence that it is reasonably likely it will prevail on at least one claim challenged under 35 U.S.C. § 103 based on the proposed

combination of cited references. Specifically, Petitioner has directed us to Brown, which teaches that PD-1 inhibitors are inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize (Ex. 1034, 747), Duval, which teaches that MSI-H cancers have cells that are easy for immune cells to recognize (*see* Ex. 1087, 5002), and Benson, which teaches processes of conducting clinical studies (*see* Ex. 1009, 1034). (*See* Pet. 41, 48.) Based on the record before us and the teachings of the references in combination, Petitioner presents a reasonable likelihood that the method of at least claim 1 would have been considered obvious by one of ordinary skill in the art. (*See* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009, 1034; *see* Ex. 1003 ¶¶ 123–143.)

Accordingly, 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.

F. Ground 3 – Obviousness of Claims 1–2, 4–7, 11, 13–17, 19–22, 26, and 28–38 *Based on the MSI-H Study Record, Brown, Duval, Benson and Koh*

Petitioner asserts a third ground of challenge based on the MSI-H Study Record, Brown, Duval, Benson, and Koh. (*See* Pet. 51–52.) According to Petitioner, Patent Owner may argue that the teachings of Benson about treating patients who had previously been treated with a prior cancer therapy drug and whose cancers had progressed or were metastatic do not apply to the challenged claims because these claims are directed towards non-colorectal cancers, such as uterine and endometrial cancer. (*See id.* at 51.) In response to this potential argument, Petitioner cites Koh, asserting

that it is directed to the ways in which clinical studies involving endometrial cancer are conducted. (*See* Pet. 51 (citing Ex. 1095, 256).)

Dr. Neugut testifies that Koh is directed to the ways in which clinical studies involving endometrial cancer are conducted, including that patients with endometrial cancer who participate in a clinical study generally would have had a tumor that had progressed following at least one prior cancer treatment and likely had metastatic cancer. (*See* Ex. 1003, ¶¶ 145, 147 (citing Ex. 1095, 256).) Petitioner cites Dr. Neugut's testimony to argue that those of ordinary skill in the art would have been motivated to combine the teachings of the MSI-H Study Record and Koh because both discuss treating patients having cancer in clinical studies. (*See* Pet. 51–52 (citing Ex. 1003 ¶¶ 148, 156).) Petitioner also argues that one of ordinary skill in the art would have had a reasonable expectation of success because such patients are normally treated in clinical studies. (*See id.*)

As explained above and based on the record before us, in light of the teachings of the references in combination, Petitioner presents a reasonable likelihood that the method of at least claim 1 would have been considered obvious by one of ordinary skill in the art. (*See* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009, 1034, Ex. 1095, 256; *see* Ex. 1003 ¶¶ 144–149.)

Accordingly, we are persuaded there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Ground 3 in the Petition.

G. Grounds 4–7 – Obviousness of Dependent Claims

Petitioner argues that certain of the dependent claims of the '491 patent are unpatentable because they would have been obvious over the

MSI-H Study Record, Brown, Duval, Benson, Koh, and other cited references, including Chapelle, Steinert, Salipante, and Hamid. (*See* Pet. 52–61.)

In regard to Ground 4, Petitioner cites Chapelle for its teaching of testing tumor tissue from a patient to determine microsatellite instability in colorectal cancer, including by using immunohistochemistry techniques, as recited in claims 2, 8, 17, and 23. (*See* Pet. 52–54 (citing Ex. 1007, 3380, 3383); *see* Neugut Decl., Ex. 1003 ¶¶ 150–159.)

In regard to Ground 5, 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 18. (*See* Pet. 54–56 (citing Ex. 1008, OF6); *see* Neugut Decl., Ex. 1003 ¶¶ 160–165.)

In regard to Ground 6, Petitioner cites to Salipante for its teaching to test a tumor for microsatellite instability high status using a PCR test or next generation sequencing on a sample, as recited in claims 9, 10, 24, and 25. (*See* Pet. 56–59 (citing Ex. 1010); *see* Neugut Decl., Ex. 1003 ¶¶ 166–177).)

In regard to Ground 7, Petitioner cites to Hamid for its teaching of administering pembrolizumab[19] intravenously, as recited in claims 11 and 26. (Pet. 59–61 (citing Ex. 1011, 134); *see* Neugut Decl., Ex. 1003 ¶¶ 178–185.)

Given the express language of the cited prior art and Dr. Neugut's testimony of how one of ordinary skill in the art would have understood

[19] Hamid refers to intravenous administration of the drug lambrolizumab, which Dr. Neugut testifies is pembrolizumab. (*See* Ex. 1003 ¶ 179 (citing Ex. 1054, 3 (“”MK-3475 (pembrolizumab formerly lambrolizumab).”).)

these teachings, Petitioner presents sufficient evidence that it is reasonably likely to prevail in showing that claims 2, 8, 17, and 23 would have been obvious over the MSI-H Study Record, Brown, Duval, Benson, Koh, and Chapelle (Ground 4; *see* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009 1034, Ex. 1095, 256, Ex. 1007, 3380, 3383; *see* Ex. 1003 ¶¶ 150–159), that claims 3 and 18 would have been obvious over the MSI-H Study Record, Brown, Duval, Benson, Koh, and Steinert (Ground 5; *see* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009, 1034, Ex. 1095, 256, Ex. 1008, OF6; *see* Ex. 1003 ¶¶ 160–165); that claims 9, 10, 24, and 25 would have been obvious over the MSI-H Study Record, Brown, Duval, Benson, Koh, and Salipante (Ground 6; *see* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009, 1034, Ex. 1095, 256, Ex. 1010; *see* Ex. 1003 ¶¶ 166–177), and that claims 11 and 26 would have been obvious over the MSI-H Study Record, Brown, Duval, Benson, Koh, and Hamid (Ground 7; *see* Ex. 1005, Ex. 1034, 747, Ex. 1087, 5002, Ex. 1009, 1034, Ex. 1095, 256, Ex. 1011, 134; *see* Ex. 1003 ¶¶ 178–185).

Accordingly, there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Grounds 4–7 in the Petition.

IV. 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 '974 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.

V. ORDER

It is hereby ORDERED that, pursuant to 35 U.S.C. § 314(a), a post-grant review of claims 1–38 of U.S. Patent 11,634,491 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter-partes* review of the '491 patent shall commence on

the entry date of this Order, and notice is hereby given of the institution of a trial.

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