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Paper 12
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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.

IPR2024-00622
Patent 10,934,356 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. 10,934,356 B2 (Ex. 1001, "the '356 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Preliminary Response identifying itself as the owner of the '356 patent. Preliminary Response ("Prelim. Resp."), Paper 6. In addition, as authorized (Paper 8), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (("Reply"), Paper 9) and Patent Owner filed Patent Owner's Sur-reply (("Sur-reply"), Paper 11).

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 fewer 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 '356 patent are unpatentable.

B. Real Parties in Interest and Related Matters

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 66. Patent Owner identifies The Johns Hopkins University as its real party-in-interest. Paper 3, 1.

The parties indicate that the '356 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. 66; Paper 3, 1. Patent Owner also reports

that Petitioner has filed eight other petitions for *inter partes* review that are related and are involved in the Maryland litigation. *See* Paper 3, 1. These other petitions are: IPR2024-00240 against U.S. Patent No. 11,591,393; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00649 against U.S. Patent No. 11,629,187; and IPR2024-00650 against U.S. Patent No. 11,634,491. We note that *inter-partes* review was instituted on June 13, 2024, in IPR2024-00240. *See* IPR2024-00240, Paper 10. Patent Owner requested Director Review of the Decision on Institution (Paper 12), which was denied (Paper 24). Decisions on the other petitions are pending.

Petitioner asserts, and Patent Owner does not dispute, that the co-pending Maryland litigation has been stayed in its entirety pending resolution of IPR2024-00240. Pet. Reply, 1 (citing Order in Maryland litigation, dated June 29, 2024, Ex. 1100, 1); *see* Sur-reply, 1 (acknowledging "the recent stay of the parties' co-pending litigation involving the '356 Patent.").

C. The '356 patent (Ex. 1001)

The '356 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '356 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 '356 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.* at 3:32–45. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:28–30.

The ’356 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., 1:51–58. According to the ’356 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.*, 2:2–7. 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., 2:59–3:2. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the ’356 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.*, 3:8–15. 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.*, 8:47–52. According to the ’356 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.*, 6:43–47.

D. The Challenged Claims

Petitioner challenges claims 1–28. Representative independent claim 1 is reproduced below:

> 1. A method for treating cancer in a patient in need thereof, comprising:
>
> determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status;
>
> administering an effective amount of pembrolizumab to the patient;
>
> determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and
>
> wherein the patient has received a prior cancer therapy drug.

Ex. 1001, 25:55–26:2.

Representative independent claim 11 is reproduced below:

> 11. A method for treating cancer in a patient in need thereof, the method comprising:
>
> detecting a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status in a tumor sample from the patient;
>
> wherein the tumor sample exhibits an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers;
>
> administering an effective amount of pembrolizumab to the patient;
>
> determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein reference patient

has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers; and

wherein the patient has received a prior cancer therapy drug.

Id., 26:31–49.

Representative independent claim 19 is reproduced below:

19. A method for treating cancer in a patient in need thereof comprising:

selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient solid tumor, the tumor having progressed following a cancer therapy;

administering an effective amount of pembrolizumab to the patient; and

determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status.

Id., 27:1–15.

Representative independent claim 23 is reproduced below:

23. A method for treating cancer in a population of cancer patients in need thereof, comprising:

administering an effective amount of pembrolizumab to patients in the population of cancer patients, which patients have a tumor that exhibits a high micro satellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, said tumor having progressed following a prior treatment; and

observing an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab.

Id., 28:1–11.

E. 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. 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").

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

F. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–28 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 6–11, 13–20, 22–24, 26–28	102	MSI-H Study Record
II	1, 6–11, 13–20, 22–24, 26, 27	103	MSI-H Study Record, Pernot, Benson
III	2–5, 11–18, 20, 21, 24, 25	103	MSI-H Study Record, Pernot, Benson, Chapelle
IV	1, 6–11, 13–20, 22–24, 26–28	103	MSI-H Study Record, Brown, Duval, Benson
V	2–5, 11–18, 20, 21, 24, 25	103	MSI-H Study Record, Brown, Duval, Benson, Chapelle
VI	18	103	MSI-H Study Record, Pernot, Benson, Chapelle, Hamid
VII	18	103	MSI-H Study Record, Brown, Duval, Benson, Chapelle, Hamid

G. 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. 11–12. Patent Owner does not argue that any claim terms require construction. *See generally* Prelim. Resp.

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 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))).

H. 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). Patent Owner does not dispute Petitioner's proposal about the POSA's qualifications. *See generally* Prelim. Resp.

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.

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 with regard to the state of the art and the asserted prior art references. *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.* ¶ 4.

Patent Owner does not contest that Dr. Neugut is qualified to testify about what one of ordinary skill would have understood at the time.

Based on the current record, we determine that Dr. Neugut is qualified to testify about what one of ordinary skill would have understood at the time of the invention.

II. 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 . . . ." 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 subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter 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. 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 [monoclonal antibodies] 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[?]" *Id.* at 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, 3738. 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.* 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. 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.* at 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.* at 747–48.

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.*

C. Ground 1 – Anticipation of Claims 1, 6–11, 13–20, 22–24, 26–28 Based on the MSI-H Study Record

1. Parties' Contentions

Petitioner contends that claims 1, 6–11, 13–20, 22–24, and 26–28 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, 6–11, 13–20, 22–24, and 26–28 is disclosed by the

MSI-H Study Record. *Id.* Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 62–128.

Petitioner contends that the MSI-H Study Record is prior art under 35 U.S.C. § 102(a) and is not covered by an exception under 35 U.S.C. § 102(b). Pet. 8. The parties agree that the MSI-H Study Record was publicly available by June 12, 2013. *Id.* at 7; Prelim. Resp. 19 ("JHU submitted the MSI-H Study Record on June 10, 2013, and it was posted on clinicaltrials.gov on approximately June 12, 2013").

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[1]

[1] 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. Pet. 6 (citing, *e.g.*, (Ex. 1018, 293 ("MSIH (MSI high) was considered MSI positive and MSS (MS stable)"; Ex. 1003 ¶ 27). Patent Owner does not contest the identifications in its Preliminary Response.

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.

Petitioner argues, in general, that the MSI-H Study Record inherently anticipates claims 1, 6–11, 13–20, 22–24, and 26–28 of the '356 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. *See* Pet. 16. Petitioner argues that the MSI-H Study Record teaches giving the claimed drug, at the only therapeutically effective dosage described in the '356 patent, and giving to the claimed patient population. *See id.* (citing Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)).

In regard to the limitation of claim 1 of the '356 patent of "determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status" tumor, Petitioner argues that the MSI-H Study Record teaches this first element of claim 1 because the MSI-H Study Record discloses three study arms, including one of the patients having MSI-H colorectal cancer and another of patients having MSI-H non-colorectal cancer. *See id.* at 17–18 (citing Ex. 1005, 4 (Arms and Interventions)). Dr. Neugut's testimony supports this argument. *See* Ex. 1003 ¶¶ 63–66. In addition, Dr. Neugut testifies that the patients determined to have defective MMR (dMMR) status are biologically the same population as patients with MSI-H status. *See id.* ¶

65 (citing Ex. 1020,[2] 51 ("Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.")).

Petitioner continues the argument that the MSI-H Study Record anticipates claim 1 of the '356 patent, citing the "Arms and Interventions" section of the MSI-H Study Record, which teaches treating patients having MSI-H colorectal cancer and MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 19 (citing Ex. 1005, 4). Petitioner cites Dr. Neugut's testimony that this teaching reads on the claim limitation "administering an effective amount of pembrolizumab to the patient," in claim 1, because the dose taught in the MSI-H Study Record is identical to the dose described as being effective in the '356 patent. *Id.* (citing Ex. 1003 ¶¶ 68–69); *see also* Ex. 1001, 4:14–27, 16:30–35, 16:56–65, 17:26–36, 21:1–22, Figs. 2, 11.

Petitioner argues that the next limitation of claim 1 of the '356 patent is a result of the method of treatment reported in the MSI-H Study Record. *See* Pet. 20–21 (citing Ex. 1005, 4–5 (Outcome Measures); Ex. 1003 ¶¶ 72–74). Petitioner argues that the MSI-H Study Record teaches actively measuring specific outcomes in patients having MSI-H cancer and cancer that is not MSI-H. Pet. 21 (citing Ex. 1005, 4–5 (Outcome Measures); Ex. 1003 ¶¶ 72–73). In support, Dr. Neugut testifies that the examples, tables, and figures of the '356 patent discuss the design and results of the MSI-H Study, as explained in the affidavit by the inventors on February 4, 2022. Ex. 1003 ¶¶ 40–41, 72–74 (citing Ex. 1001, 6:43–22:40, 3:13–15,

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

Figs. 1–13; Ex. 1005; Ex. 1002 (Part 7), 2490–2491 (February 4, 2022 Affidavit ¶¶ 22–23)).

An affidavit executed by Andrew Pardoll, M.D., an inventor named on the '356 patent, supports Dr. Neugut's testimony and provides as follows:

> 22. Our research group eventually approached Merck. Merck agreed in early 2013 to supply its then-unapproved anti-PD-1 antibody, MK-3475 (pembrolizumab) for use in the study. It was, however, the research team at Hopkins who secured IRB approval, conducted, and paid for the study. On June 12, 2013, the solicitation for patients was first posted on clinicaltrials.gov **(Exhibit D).** In my mind, the four arms allowed us to try to get at an answer to a question to which we did not know the answer–specifically whether or not patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated with MK-3475, compared with the more common MSS [microsatellite stable] or MMR proficient colon cancers. Thus, the trial covered all patients with colon cancer, MSI and MSS, but separated into two groups.
>
> 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. …

Ex. 1002 (Part 7), 2490–2491. The affidavit submitted during prosecution of the '356 patent supports the argument that an improved outcome of treating a patient with a tumor exhibiting an MSI-high or an MMR deficiency status with pembrolizumab compared to similarly treating a patient without an MSI-high or an MMR deficiency status, as recited in claim 1, is an inherent result. Furthermore, the '356 patent states: "The data from the small phase 2 trial of pembrolizumab to treat tumors with and without deficiency of MMR supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient

tumors." Ex. 1001, 6:43–47; *see also* Prelim. Resp. 6–7 ("The '356 Patent reports that mismatch repair-deficient colorectal cancers (i.e., MSI-H CRC) had an immune-related objective response rate and immune-related progression-free survival rate of 40% and 78%, respectively—a huge improvement compared to the 0% and 11% rates found in mismatch repair-proficient colorectal cancers (i.e., MSI negative CRC).").

Petitioner argues that the final limitation, "wherein the patient has received a prior cancer therapy drug," is disclosed by the MSI-H Study Record. *See* Pet. 22–24. Petitioner asserts that the MSI-H Study Record discloses treating patients with "tumors" and "measurable disease," and "patients with MSI-H colorectal cancer and non-colorectal cancer," while excluding "[p]atients who have had prior treatment with anti PD-1." *Id.* at 22 (citing Ex. 1005, 2, 4, 5–6). Petitioner thus asserts that "these disclosures demonstrate that patients would have received a prior cancer therapy drug." *Id.* (citing Ex. 1003 ¶¶ 75–80).

Petitioner asserts that "the prior art taught that patients having 'measurable' colorectal cancer in the context of the MSI-H Study Record refers to patients having metastatic and advanced cancer." *Id.* (citing Ex. 1020, 25; Ex. 1003 ¶ 76). Petitioner argues that "[i]f a patient had colorectal cancer that is curable by resection, then a practitioner would excise the tumor because surgery 'is the only way to achieve a cure.'" *Id.* (citing Ex. 1020, 7; Ex. 1048, 230; Ex. 1047, 4–7; Ex. 1003 ¶ 76). Petitioner therefore argues that "'measurable' disease in the context of a clinical study does not include cancer that is resectable for the purposes of a cure." *Id.* at 22–23.

Petitioner argues that "[p]atients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies,

such as standard of care chemotherapy, and had their cancers progress after those drug therapies." *Id.* at 23 (citing Ex. 1020, 25; Ex. 1009, 1034; Ex. 1047, 4–7; Ex. 1003 ¶ 77).

Patent Owner does not put forth substantive arguments in the Preliminary Response against Petitioner's Ground 1 for the unpatentability of claims 1, 6–11, 13–20, 22–24, and 26–28 as being anticipated by the MSI-H Study Record.

2. Discussion

Having considered the parties' positions and evidence of record, summarized above, we find sufficient evidence that Petitioner will prevail in showing that there is a reasonable likelihood that the MSI-H Study Record discloses a method for determining whether a patient has an unresectable or metastatic microsatellite instability-high tumor and administering an effective amount of pembrolizumab to the patient, as recited in claim 1 of the '356 patent. Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 63–66. At this point in the proceeding, we also find that there is sufficient evidence that there is a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have understood the inherent results of the MSI-H Study Record to be an improved outcome of treating a patient with a tumor that is MSI-H or dMMR with pembrolizumab as compared to similarly treating a reference patient having a tumor that is not MSI-high or an MMR deficient. Ex. 1003 ¶¶ 72–74. We further find that there is sufficient evidence that there is a reasonable likelihood that the MSI-H Study Record discloses treating patients who previously were treated with a prior cancer therapy drug. *Id.* ¶¶ 75–80.

Additionally, we have reviewed Petitioner's allegations regarding how the MSI-H Study Record discloses the limitations of claims 6–11, 13–20, 22–24, and 26–28, 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. 25–38; Ex. 1003 ¶¶ 81–129.

In view of the foregoing, we determine that Petitioner has established a reasonable likelihood of showing that the MSI-H Study Record anticipates claims 1, 6–11, 13–20, 22–24, and 26–28 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, 6–11, 13–20, 22–24, and 26–28 of the '356 patent.

D. Ground 2 - Obviousness over MSI-H Study Record, Pernot, and Benson

1. Petitioner's Contentions

Petitioner contends that claims 1, 6–11, 13–20, 22–24, and 26–27 are unpatentable as obvious over the combination of the MSI-H Study Record, Pernot, and Benson. *See* Pet. 40–47. Petitioner asserts that these references disclose elements that Patent Owner might argue are not taught in the MSI-H Study Record, specifically the improved outcome and efficacy recited in claim 1, testing for MSI-H or dMMR tumors, and treating patients that have progressive or metastatic disease. *See id.* at 41–47 (citing December 14, 2020, Notice of Allowance in the '549 appl., Ex. 1002 (Part 9), 3069).

Petitioner argues that Pernot teaches treating colorectal cancer and that, therefore, because the MSI-H Study Record is directed to a clinical study treating colorectal cancer patient whose cancers are MSI-H with

pembrolizumab, which is an anti-PD-1 antibody, one of ordinary skill in the art knowing the teachings of the MSI-H Study Record would have considered the teachings of Pernot. Pet. 42. Petitioner argues that Pernot teaches that colorectal cancer patients that are MSI-H are "good candidates for immunotherapy," such as PD-1 inhibitors. *See id.* (quoting Ex. 1006, 3741 ("[Colorectal cancer] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy.")).

Petitioner cites further to Dr. Neugut's testimony to argue that one of ordinary skill in the art would have been motivated to combine the disclosure of Pernot with the methods taught in the MSI-H Study Record in order to obtain the results of the MSI-H Study Record's study. *Id. at* 36 (citing Ex. 1003 ¶ 136).

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. *Id.* at 42–43. Petitioner cites to other references, for example 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.

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

Ex. 1032, e27817-5. Dr. Neugut testifies that Champiat, as well as other references, "independently urged the person of ordinary skill to treat MSI-H cancer with PD-1 inhibitors, like pembrolizumab, or other immunotherapy." Ex. 1003 ¶ 138. Citing to Dr. Neugut's testimony, Petitioner argues further that the prior art demonstrates the characteristics of cells that would have more efficacy with PD-1 inhibitors were known and that it was known that MSI-H tumors had these characteristics. Pet. 43 (citing Ex. 1003 ¶¶ 43, 45, 139).

In light of this evidence of the state of the art at that time, Dr. Neugut testifies that one of ordinary skill in the art would have wanted to obtain data from the MSI-H Study Record and would have reasonably expected success, given that pembrolizumab was already approved for another oncology indication. Ex. 1003 ¶ 177; Pet. 43. Dr. Neugut concludes that "[a]s a result of carrying out the methods in the MSI-H Study Record of treating patients having MSI-H cancer with pembrolizumab at the dosage that was applied in the clinical study, the person of ordinary skill would have seen the results that naturally flow from those methods. . . ." Ex. 1003 ¶ 177.

Petitioner also argues that the MSI-H Study Record would have motivated one of ordinary skill in the art to test patients' tumors for MSI-H because the MSI-H Study Record requires patients be placed into the proper study arm. Pet. 44–45 (citing Ex. 1003 ¶ 141 ("Testing was the way in which it was possible for the person of ordinary skill determine if the patient had the MSI-H colorectal cancer required for placement in that arm.")).

Petitioner argues further that one of ordinary skill in the art would have considered it obvious that the MSI-H Study Record discloses treating

patients with metastatic or unresectable cancer in light of the teachings of Benson. Pet. 45–47. Petitioner argues that Benson is directed to ways in which clinical studies involving colorectal cancer are conducted, which is in the same field as the MSI-H Study Record. *Id.* (citing Ex. 1003 ¶ 142). Benson teaches that under the standard of care, the patient population with tumors and measurable disease that would take part in a clinical study are patients having metastatic and advanced disease. Ex. 1009, 1034; Ex. 1003 ¶ 143. Dr. Neugut testifies further that the term "advanced cancer" refers to metastatic cancer or cancer that is so locally advanced that it is unresectable for purposes of a cure and he concludes that a person of ordinary skill would have been motivated to carry out that method of the MSI-H Study Record on colorectal cancer that was metastatic, with a reasonable expectation of success. Ex. 1003 ¶¶ 143–144.

In summary, Petitioner relies on Pernot to demonstrate that one of ordinary skill in the art would have considered patients with MSI-H tumors to be good candidates for immunotherapy, such as PD-1 inhibitors, and thus, that the ordinarily skilled artisan would have been motivated to obtain the results of the MSI-H Study Record. Pet. 41–42 (citing Ex. 1006, 3741). Petitioner relies on Benson to demonstrate that one of ordinary skill in the art would have understood the MSI-H Study Record to be directed to patients with an unresectable or metastatic tumor. *Id.* (citing Ex. 1009, 1034).

2. Patent Owner's Contentions

At this point in the proceeding, Patent Owner does not dispute Petitioner's characterization of or prior art status of either Pernot or Benson or the other references that Petitioner cites.

Patent Owner asserts that Petitioner fails to meet the particularity requirement of 35 U.S.C. § 312(a)(3) in its challenges under 35 U.S.C. § 103. Prelim. Resp. 20–29. To support this assertion, Patent Owner argues that the Petition fails to set forth a sufficient mapping of each challenged claim to the cited prior art in each of the obviousness-based grounds of unpatentability. *Id.* at 23–25. Patent Owner notes that,

> [f]or example, under the heading "Testing," Merck asserts that limitation relating to determining MSI-H status, (e.g., [1.1] "determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status") would have been obvious even if "the MSI-Study Record does not disclose such testing." (Pet., 44.) But, contrary to Merck's express framing of Ground 2, Merck does not map these limitations to either Pernot or Benson.

Id. at 23 (citing Pet. 44–45). Patent Owner next argues that the cross-references to arguments in the Petition are "ill-defined and confusing." *Id.* at 25–27. Patent Owner notes that,

> In Ground 5, for example, Merck asserts that claim 4 would have been obvious over the MSI-H Study Record in view of Brown, Duval, and Benson, and further in view of Chapelle. (Pet., 60-61.) In its one-paragraph analysis, Merck asserts that "[t]hese claims are obvious over the Ground 5 combination for the same reasons as discussed in Ground 3." (Id.) But Ground 3 relies on different prior art than Ground 5. Ground 3 relies on either the MSI-H Study Record alone, or the MSI-H Study Record in combination with Pernot and Benson, and further in view of Chapelle. (Pet., 48.) It is unclear how Ground 3 (which relies on Pernot instead of Ground 5's Brown and Duval) could provide adequate explanation for how Ground 5 renders claim 4 obvious.

Id. at 25–26. Patent Owner then argues that Petitioner relies on "a voluminous number of additional exhibits without sufficient analysis and

explanation about the relevant contents of each exhibit." *Id.* at 27. Patent Owner notes that,

> Ground 2 alone contains multiple string-cites to over 20 additional citations. (citations omitted). As in Adaptics, Merck appears to rely on the substantive disclosures of these exhibits but provides almost no analysis about their relevance or content. For example, Merck cites to exhibits 1016 and 1017 for the proposition that "Physicians were treating patients with cancers that were *known to have MSI-H subpopulations* in the prior art with PD-1 inhibitors." (Pet., 42, emphasis added.) But both of those exhibits are ***completely silent*** on whether any of the patients actually had MSI-H or dMMR cancers or were even tested for those biomarkers. In fact, those exhibits ***do not even*** contain the words "microsatellite instability," "MSI-H," or "mismatch repair." (*See* EX1016; EX1017.)

Id. at 27–28.

3. Discussion

Having considered the parties' positions and evidence of record, summarized above, we determine that the information presented in the Petition establishes that Petitioner has a reasonable likelihood of prevailing in showing that claim 1 would have been obvious in view of the MSI-H Study Record. We are persuaded that the MSI-H Study Record discloses the limitations of claim 1. Pet. 16–24. We are further persuaded that a person of ordinary skill in the art would have been motivated to modify the MSI-H Study Record with Pernot and Benson to benefit from the improved outcomes in treating MSI-H colorectal patients with the drug therapeutic. *Id.* at 41–44. We are also persuaded that a person of ordinary skill would have been motivated to test patients to determine their MSI-H status as such testing was routine in the art. *Id.* at 44–45. We are also persuaded that a person of ordinary skill would have been motivated to combine the teachings

of the MSI-H Study Record and Benson to treat patients with metastatic and advanced disease. *Id.* at 46–47.

Furthermore, as explained above with regard to Ground 1, there is sufficient evidence to show that Petitioner will prevail in showing that at least one claim is anticipated by the MSI-H Study Record. Because "[i]t is well settled that 'anticipation is the epitome of obviousness,'" we also determine that Petitioner will prevail in showing that at least one claim is obvious in view of the MSI-H Study Record. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (citation omitted).

We are not persuaded by Patent Owner's arguments that we should deny institution because the "Petition fails to set forth its obviousness arguments with the required particularity, failing to provide a sufficient mapping of each challenged claim to the cited prior art in each of the obviousness-based grounds of unpatentability and cross-referencing arguments that make no sense." Prelim. Resp. 18. Rather, we are persuaded by Petitioner's discussion providing a detailed mapping of the elements of challenged claims to the teachings of the MSI-H Study Record. *See, e.g.*, Pet. 16–24 (claim 1).

Petitioner explains that the alternative challenges under 35 U.S.C. § 103 are presented to address the potential arguments by Patent Owner that the MSI-H Study Record cannot anticipate because it did not disclose an improved outcome as required in the claims or because one of ordinary skill in the art would not have reasonably expected the efficacy recited in the claims. Pet. 40–41. Petitioner further asserts that Ground 2 is presented to address potential arguments that the MSI-H Study Record does not disclose testing or the claim limitations to metastatic disease. *Id. at* 41.

Patent Owner fails to sufficiently address Petitioner's arguments regarding the teachings of Benson that, under the standard of care, the patient population with tumors and measurable disease that would take part in a clinical study are patients having metastatic and advanced disease and that the term "advanced cancer" would indicate unresectable for purposes of a cure. *Id.* at 45–47 (citing Ex. 1009, 1034; Ex. 1003 ¶¶ 142–145). Accordingly, we are not persuaded by Patent Owner's argument that Petitioner has not met the standard for instituting *inter partes* review. Prelim. Resp. 21–22.

We disagree with Patent Owner that the Petition includes voluminous number of additional exhibits so as to run afoul of the particularity requirement of 35 U.S.C. § 312(a)(3). Prelim. Resp. 27. In reaching our decision, we have considered the arguments advanced by Petitioner in its Petition and, to the extent that additional arguments have been advanced by Petitioner in other filed exhibits, we clarify that such arguments have not been considered.

After weighing the parties' arguments set forth in the Petition and Preliminary Response, 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, Pernot, and Benson. Additionally, we have reviewed Petitioner's obvious challenges of claims 6–11, 13–20, 22–24, and 26–28 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, Pernot, and Benson renders obvious each of claims 6–11, 13–20, 22–24, and 26–28. Pet. 40–47; Ex. 1003 ¶¶ 135–145.

Accordingly, in view of the above, we institute a *inter partes* review of claims 1, 6–11, 13–20, 22–24, and 26–28 of the '356 patent.

E. Grounds 3–7 — Obviousness Based on the MSI-H Study Record, Pernot, Benson and Additional References

Petitioner argues that certain other challenged claims of the '356 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle, Hamid, Brown, and Duval. Pet. 48–63.

In regard to Grounds 3 and 5, Petitioner additionally relies on Chappelle to address the elements of claims 2–5.[4] *Id.* at 48–54, 60–61. Claim 2 depends from claim 1 and includes the limitations:

> wherein the step of determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) status includes detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence.

Ex. 1001, 26:3–7. Petitioner argues that Chapelle teaches standard methods of testing whether a tumor is MSI-H, including determining whether the patient's tumor exhibits instability in a microsatellite marker. Pet. 48–49 (citing Ex. 1007, 3380, 3383). Dr. Neugut supports this characterization of Chapelle. Ex. 1003 ¶ 150.

Claim 3 depends from claim 2 and includes the limitations:

> wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24.

[4] Petitioner's Grounds 3 and 5 challenges claims 2–5, 11–18, 20–21, and 24–25, however, Petitioner relies heavily on its contentions concerning those claims as set forth in Ground 2, which, for the sake of brevity, we do not repeat here.

Ex. 1001, 26:8–9. Petitioner argues that Chapelle teaches determining whether a microsatellite marker is BAT-25 or BAT-26. Pet. 49–50 (citing Ex. 1007, 3380–84).

> Claim 4 depends from claim 1 and includes the limitations:
>
> wherein the step of determining that the patient has a tumor that exhibits a MMR deficiency status includes detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence.

Ex. 1001, 26:10–13. Petitioner argues that Chappelle teaches that the standard method of determining whether a tumor is MSI-H also determines whether a patient exhibits a MMR deficiency. Pet. 51 (citing Ex. 1007, 3380) ("For practical purposes, MSI is equivalent to the loss of staining by immunohistochemistry (IHC) of one of the mismatch repair genes since both signify an abnormality in mismatch repair.").

> Claim 5 depends from claim 1 and includes the limitations:
>
> wherein the MMR deficiency status of the tumor is detected by immunohistochemistry.

Ex. 1001, 26:14–15. Petitioner argues that Chappelle teaches a standard method for testing for MSI-H, which includes using immunohistochemistry. Pet. 52 (citing Ex. 1007, 3380, 3384).

In view of the above, we determine that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail in establishing that claims 2–5 are rendered obvious by the combination the MSI-H Study Record, Pernot, Benson, and Chappelle (Ground 3) and by the combination of MSI-H Study Record, Brown, Duval, Benson, and Chapelle (Ground 5).

In regard to Ground 4, challenging the patentability of claims 1, 6–11, 13–20, 22–24, and 26–28, Petitioner cites to Brown, Duval, and Benson, in addition to the MSI-H Study Record. Pet. 54–60. Petitioner argues that Brown teaches that PD-1 inhibitors inherently had more efficacy when treating tumors comprised of cells that are easy for immune cells to recognize. Ex. 1034, 747. Petitioner argues further that Duval teaches that MSI-H cancers have cells that are easy for immune cells to recognize. Ex. 1087, 5002. Dr. Neugut's testimony supports Petitioner's argument that Brown and Duval would have motivated a person of ordinary skill in the art to obtain the results of the MSI-H Study Record. Ex. 1003 ¶ 171; Pet. 56. Having considered the parties' positions and evidence of record, summarized above, we determine that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail in establishing that claims 1, 6–11, 13–20, 22–24, and 26–28 are rendered obvious by the combination of MSI-H Study Record, Brown, Duval, Benson.

In regard to Grounds 6 and 7, which challenge the patentability of claim 18, Petitioner cites to Hamid, in addition to the MSI-H Study Record and the other references cited in Grounds 2, 3, and 5. Pet. 61–63. Claim 18 recites the method of claim 11, "wherein pembrolizumab is administered by intravenous infusion." Ex. 1001, 26:66–67. Petitioner argues, and Dr. Neugut agrees, that Hamid teaches infusion of pembrolizumab[5] by intravenous infusion. Pet. 62 (citing Ex. 1011, 134); Ex. 1003 ¶ 190.

In view of the above, we determine that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail

[5] Hamid refers to "lambrolizumab," which Dr. Neugut testifies is the same as prembroluzimab. *See* Ex. 1003 ¶ 186.

in establishing that claim 18 is rendered obvious by the combination of the MSI-H Study Record, Pernot, Benson, Chapelle, and Hamid (Ground 6) and by the combination of the MSI-H Study Record, Brown, Duval, Benson, Chapelle, and Hamid (Ground 7).

As described above in regard to Ground 2, Patent Owner argues that Petitioner fails to meet the particularity requirement of 35 U.S.C. § 312(a)(3) in its challenges under 35 U.S.C. § 103. *See* Prelim. Resp. 20–29. For the same reasons discussed above with regard to Ground 2, we are not persuaded by Patent Owner's arguments.

F. Discretion Under 35 U.S.C. § 314(a)

Patent Owner argues that we should exercise our discretion to deny institution of *inter partes* review in light of the parallel district court litigation. *See* Prelim. Resp. 9–18 (citing *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.) ("the Maryland litigation")); *see also* Sur-reply. Petitioner opposes Patent Owner's assertions. *See* Pet. 63–64; *see also* Reply. We look to the following factors in evaluating whether to do so:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
> 3. investment in the parallel proceeding by the court and the parties;
> 4. overlap between issues raised in the petition and in the parallel proceeding;
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Apple Inc. v. Fintiv, Inc., IPR2020-00019, Paper 11 at 5–6 (PTAB Mar. 20, 2020) (precedential). We are also guided by the Director's Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation, issued on June 21, 2022 ("Memorandum") (Ex. 1065).

Petitioner asserts, and Patent Owner does not dispute, that the co-pending Maryland litigation has been stayed in its entirety pending resolution of IPR2024-00240, which involves a related patent that is also involved in the litigation. Pet. Reply, 1 (citing Order in Maryland litigation, dated June 29, 2024, Ex. 1100, 1); Sur-reply, 1 (acknowledging "the recent stay of the parties' co-pending litigation involving the '356 Patent."). In its Memorandum Opinion, the court acknowledged that *inter partes* reviews of additional patents involved in the litigation could be instituted. *See* Ex. 1101, 3. Accordingly, the first *Fintiv* factor weighs heavily in favor of not exercising discretion to deny institution of *inter partes* review.

Because of the stay, the second and third *Fintiv* factors also weigh heavily in favor of not exercising discretion to deny institution of *inter partes* review. The stay indicates that the court's trial date will not be close to the Board's projected statutory deadline for a final written decision and that neither the court nor the parties will invest further in the parallel proceeding. *See Fintiv*, at 6 ("A district court stay of the litigation pending resolution of the PTAB trial allays concerns about inefficiency and duplication of efforts. This fact has strongly weighed against exercising the authority to deny institution under NHK."); *see also* Memorandum Opinion in Maryland litigation issued June 29, 2024, Ex. 1101, 2 (noting that the litigation is in a "relatively early stage," before depositions have been taken or paper discovery is complete, and before the parties have "invested time

and attention to developing the record and evidence for the *Markman* hearing and trial"); *contra* Prelim. Resp. 11–15.

As to *Fintiv* factors 4 and 5, although the same claims, the same prior art, and the same parties are involved in the district court proceeding, these facts do not outweigh the effect of the court's stay or the court's desire to simplify and streamline the material issues before it by waiting for the Board's decision on the patentability of the involved patents.

Patent Owner argues that *Fintiv* factor 6, particularly "[t]he weakness of [Petitioner]'s patentability challenge," indicates that institution should be denied. Prelim. Resp. 18–30; Sur-reply, 1. Because we determine that *Fintiv* factors 1–5 collectively do not favor discretionary denial, we need not determine whether compelling merits weigh in favor of institution. *See CommScope Techs. LLC v. Dali Wireless, Inc*, IPR2022-01242, Paper 23 (Feb. 27, 2023) (precedential) ("in circumstances where the Board determines that the other *Fintiv* factors 1–5 do not favor discretionary denial, the Board shall decline to discretionarily deny under *Fintiv* without reaching the compelling merits analysis.").

Patent Owner argues further that the claims challenged and issues raised in the current petition are different from the claims challenged and issues raised in IPR2024-00240, which was the basis of the court's stay in the Maryland litigation, and that the Board's determination in IPR2024-00240 does not "compel a similar result here." Sur-reply at 3. Patent Owner argues that Petitioner has engaged in "strategic delay" and "gamesmanship" that prejudice Patent Owner by creating staggered trail dates, allowing Petitioner to unfairly rely on Patent Owner's arguments in previous proceedings.

Id.; Prelim. Resp. 29–30. None of these arguments persuade us to exercise our discretion to deny institution of *inter partes* review where the District Court has stayed litigation addressing patentability of the same patent, thereby indicating that the proximity of a trial date and the investment of the parties and the court in the parallel proceeding do not merit discretionary denial.

Accordingly, we decline to exercise discretion to deny institution of a trial under 35 U.S.C. § 314(a).

III. CONCLUSION

After reviewing the merits of the Petition and Patent Owner's arguments in opposition, we are persuaded that Petitioner has met the burden to show a reasonable likelihood of prevailing on at least one challenge to claim 1. *See* 35 U.S.C. § 314(a). We are not persuaded that there is a reason to exercise the discretion provided by either 35 U.S.C. § 314(a) or § 325(d) to deny institution of trial. Accordingly, we institute trial on all grounds of challenge presented in the Petition.

We have not made a final determination as to the patentability of any challenged claim or as to the construction of any claim term. Any final determination will be based on the record developed during trial.

IV. ORDER

It is hereby ORDERED that, pursuant to 35 U.S.C. § 314(a), a *inter partes* review partes of 1, 6–11, 13–20, 22–24, and 26–28 of U.S. Patent 10,934,356 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 '356 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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