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Paper 11
Entered: September 23, 2024

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.

IPR2024-00623
Patent 11,325,974 B2

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

NEWMAN, *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 1–7 of U.S. Patent No. 11,325,974 B2 (Ex. 1001, "the '974 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Preliminary Response identifying itself as the owner of the '974 patent. Preliminary Response ("Prelim. Resp."), Paper 5. In addition, as authorized (*see* Paper 7), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (("Reply"), Paper 8) and Patent Owner filed Patent Owner's Preliminary Sur-reply (("Sur-reply"), Paper 10).

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 1–7 of the '974 patent is unpatentable, and we institute *inter partes* review of all challenged claims on all asserted grounds. *Id.*

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 60. Patent Owner identifies The Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '974 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. 60; Paper 3, 1. 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 June, 2024, Ex. 1100, 1); *see* PO Sur-Reply, 1 (acknowledging "the recent stay of the parties' co-pending litigation involving the '972 Patent.").)

Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 (instituted June 13, 2024[1]) against U.S. Patent No. 11,591,393. Pet. 60; Paper 3, 1.

D. The '974 patent (Ex. 1001)

The '974 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '974 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 '974 patent is directed to treating cancer patients with high mutational burdens, such as

[1] We note that trial 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).

those found in microsatellite instable ("MSI") cancer, with anti-PD-1 antibodies. *Id.*, 3:35–49. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:30–31.

The '974 patent explains that

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

Id., 1:53–60. According to the '974 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.*, 2:4–2:7. 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 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., 2:60–3:3. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '974 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.*, 3:11–18. 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.*, 8:50–55. According to the '974 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.*, 6:48–52.

E. The Challenged Claims

Petitioner challenges claims 1–7. Representative independent claim 1 is reproduced below:

> 1. A method for treating cancer in a patient in need thereof,
>
> wherein a tumor sample obtained from the patient has been determined to exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers, the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:
>
> administering an effective amount of pembrolizumab to the patient;
>
> wherein 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 an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers.

Ex. 1001, 24:27–43.

F. Evidence

Petitioner relies upon information that includes the following.

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

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

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

Ex. 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.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–7 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–3, 5–7	102	MSI-H Study Record
2	1–3, 5–7	103	MSI-H Study Record, Pernot, Benson
3	4	103	MSI-H Study Record or MSI-H Study Record, Pernot, Benson, Chapelle
4	1–3, 5–7	103	MSI-H Study Record,

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
			Brown, Duval, Benson
5	4	103	MSI-H Study Record, Brown, Duval, Benson Chapelle
6	7	103	MSI-H Study Record or MSI-H Study Record, Pernot, Benson, Chapelle, Hamid
7	7	103	MSI-H Study Record, Brown, Duval, Benson, Chapelle, Hamid

H. Claim Construction

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

Petitioner argues that we need not construe any terms of the challenged claims to resolve the issues presented in the Petition. Pet. 12. Patent Owner does not argue that any claim terms require construction. *See* Prelim. Resp.

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))).

I. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art ("POSA") 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. 12–13 (citing Ex. 1003, ¶ 19). Patent Owner does not dispute Petitioner's proposal about the POSA's qualifications and does not contest that Dr. Neugut is qualified to testify about what one of ordinary skill would have understood at the time. *See* 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 Standard

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

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

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

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

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

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

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

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

B. Ground 1: Anticipation by MSI-H Study Record (Claims 1–3 and 5–7)

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

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

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

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

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune

related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" *Id.*, 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows[3]

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

2. The Parties' Contentions

The parties agree that the MSI-H Study Record was publicly available by June 12, 2013. (*See* Pet. 7; *see* 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"). In its Preliminary Response, Patent Owner does not dispute Petitioner's argument (*see* Pet. 8) 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). *See* Prelim. Resp.

Petitioner argues, in general, that the MSI-H Study Record inherently anticipates claims 1–3 and 5–7 of the '974 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. Pet. 18.

[3] 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.*, (Exs. 1010, 1193; 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.

Petitioner argues that the MSI-H Study Record teaches giving the claimed drug at the only therapeutically effective dosage described in the '974 patent to the claimed patient population. Pet. 18 (citing Ex. 1005, 4 (Arms and Interventions); 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility)).

Patent Owner does not offer substantive arguments in the Preliminary Response against Petitioner's Ground 1 challenging claims 1–3 and 5–7 as being anticipated by the MSI-H Study Record. *See* Prelim. Resp. We review Petitioner's allegations for each limitation of representative claim 1 below.

a) *[1.pre]: "A method for treating cancer in a patient in need thereof,"*

Petitioner alleges that the Arms and Interventions section of the MSI-H Study Record discloses a method for treating cancer. Pet 19 (citing Ex. 1003 ¶ 59). We need not address whether the preamble is limiting as we agree that, to the extent it is limiting, the MSI-H Study Record discloses a cancer treatment method. *See* Ex. 1005, 3 (describing a study of administering antibody to three different cancer patient populations).

b) *[1.1]: "wherein a tumor sample obtained from the patient has been determined to exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers,"*

Petitioner alleges that the MSI-H Study Record discloses the above limitation because each study participant has their cancer biopsied, and two of the study arms have patients with MSI-H cancers, which Petitioner alleges are cancers that "exhibit[] an instability of more than one microsatellite marker and a deficiency of one or more mismatch repair

markers." Pet. 19–20 (citing Ex. 1005, 2–4). Petitioner cites to Chapelle[4] as evidence that a portion of colorectal cancer tumors include instability of more than one microsatellite marker and a deficiency of one or more mismatch repair markers. Pet. 20 (citing Ex. 1007, 3382–83). Petitioner also offers the testimony of Dr. Neugut in support. *Id.*, (citing Ex. 1003 ¶¶ 60–66). Dr. Neugut opines that two of the MSI-H Study Record selected patient populations (study arms) having MSI-H cancers (tumors), which "exhibit an instability of more than one microsatellite marker and a deficiency of one or more mismatch repair markers." *Id.* at ¶ 61.

Dr. Neugut testifies that a POSA would have understood that taking a biopsy of the patient tumor to determine if the patient qualified for the study would have tested for MSI-H status because "determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status in order to place the patients into the proper arm." *Id.* at ¶¶ 62–63. Dr. Neugut testifies that the POSA would generally have understood "MSI positive" patents to refer to "MSI-H" patients and that "the MSI-H Study Record's discussion of treating patients with 'MSI positive' cancer to also include treating patients with a mismatch repair deficiency ('dMMR')" because the population of defective mismatch repair status is the same as the high instability population. *Id.* ¶¶ 64–65. Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

[4] Chapelle, A. and Heather Hampel, Clinical Relevance of Microsatellite Instability in Colorectal Cancer. 28(20): J. CLIN ONC. 3380–87 (July 10, 2010). Ex. 1007.

c) *[1.2]: "the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:"*

Petitioner alleges that the MSI-H Study Record discloses the above limitation, which requires that the recited patient must have "tumors" and "measurable disease," which Dr. Neugut testifies would include metastatic and advanced colorectal cancers in the context of the MSI-H Study Record. *See* Pet. 23 (citing Ex. 1005, 2–6 (Study Identification, Study Design, Eligibility); Ex. 1020, 25; Ex. 1003 ¶ 68). Dr. Neugut testifies that advanced cancer would be metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. *See id.* 23–24 (citing Ex. 1048, 230; Ex. 1047, 4–7; Ex. 1003 ¶¶ 67–72; Ex. 1020, 7 ("If 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.'")). According to Dr. Neugut, it would be highly unusual if the MSI-H Study Record did not indicate inclusion of patients with metastatic and advanced cancer because the study was not directed to local treatments, such as radiation or surgery. *See* Ex. 1003 ¶ 68.

Dr. Neugut testifies that patients with metastatic and advanced cancer whose cancer is too advanced for resection "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." Ex. 1003 ¶ 69 (citing Ex. 1020, 25; Ex. 1009, 1034; Ex. 1047, 4–7.) Dr. Neugut observes that the Eligibility section of the MSI-H Study Record takes care to exclude patients having had prior treatment with certain antibodies. *Id.* ¶ 70. Dr. Neugut interprets this exclusion as supporting his opinion that such patients would have received a prior cancer therapy drug to treat their tumor because otherwise, the study would not have

purposefully excluded these antibodies, and because if the prior therapies had worked, these patients would not have participated in the MSI-H Study Record. *Id.* Dr. Neugut cites to a poster presentation describing the MSI-H Study Record as requiring that patients have "progressive disease" and have had prior therapies. *Id.* ¶ 72.

Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

d) [1.3]: "administering an effective amount of pembrolizumab to the patient;"

For this limitation, Petitioner cites the "Arms and Interventions" section of the MSI-H Study Record, which teaches treating patients having MSI-H colorectal cancer and also patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 26 (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 '219 patent. Pet. 27 (citing Ex. 1003 ¶¶ 40–41, 73–77); *see* Ex. 1001, 4:19–32; 16:3–8, 16:61–17:3, 20:20–21, Figures 2, 11.

Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

e) [1.4]: "wherein 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 an instability of the one or more microsatellite

> *markers or a deficiency of the one or more mismatch repair markers."*

Petitioner argues that the final limitation of claim 1 is an inherent result of the method of treatment reported in the MSI-H Study Record. Pet. 28–29 (citing Ex. 1003 ¶¶ 73–80). Petitioner argues that the MSI-H Study Record teaches actively measuring specific outcomes in patients having MSI-H cancer and in patients having cancer that is not MSI-H. *Id.* at 29 (citing Ex. 1003 ¶ 79). In support, Dr. Neugut testifies that the examples, tables, and figures of the '974 patent discuss the design and results of the MSI-H Study, as explained in the affidavit by the inventors on February 4, 2022. (*See* Ex. 1003 ¶¶ 38–41, 74–76, (citing Ex. 1001, 3:16–18, 6:48–22:15, Figures 1–13; Ex. 1005; Ex. 1002, 295–296 (February 4, 2022, Affidavit ¶¶ 22–23).)

Dr. Neugut further cites to an affidavit executed by Andrew Pardoll, M.D., an inventor named on the '974 patent, citing to Exhibit D, which we understand to be the MSI-H Study Record. Ex. 1003 ¶ 40 (citing Ex. 1002, 335–343, Affidavit ¶ 22, June 8, 2020, Affidavit, ¶¶ 27–28.) The testimony in that Affidavit supports Dr. Neugut's testimony and explains that

> 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, 270–271.) This affidavit, submitted during prosecution of the '974 patent, supports the argument that an improved outcome of treating a patient with a tumor exhibiting an MSI-high or a MMR deficiency status with pembrolizumab compared to similarly treating a patient without an MSI-high or a MMR deficiency status, a recited in claim 1, is an inherent result. Patent Owner does not dispute this result in the Preliminary Response. *See* Prelim. Resp. 7 ("The '974 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).").

Furthermore, the '974 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, 6:48–52.

3. Discussion

Patent Owner does not offer substantive arguments in the Preliminary Response against Petitioner's Ground 1 for the unpatentability of claims 1–3 and 4–7 as being anticipated by the MSI-H Study Record. *See* Prelim. Resp.

On this record, we find sufficient evidence that Petitioner will prevail in showing that there is a reasonable likelihood that the MSI-H Study

Record teaches a method for treating cancer in a patient having an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers and having received a prior cancer therapy drug, and administering an effective amount of pembrolizumab to the patient, as recited in claim 1 of the '974 patent. *See* MSI-H Study Record, Ex, 1005, 4 (Arms and Interventions); *see also id*., 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); *see* Neugut Decl., Ex. 1003 ¶¶ 59–72. On this record, we 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 MMR deficient. *See* Neugut Decl., Ex. 1003 ¶¶ 73–80.

4. Dependent Claims 2, 3 and 5–7

Claim 2 further recites "wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug." Ex. 1001, 24:44–47. Claim 3 further recites "wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival (OS)." *Id.* at 24:48–51. Claim 5 further recites "wherein the cancer is a metastatic cancer." *Id.* at 24:59–61. Claim 6 further recites "wherein the cancer is a metastatic colorectal cancer." *Id.* at 24:62–64. Claim 7 further recites "wherein pembrolizumab is administered by intravenous infusion." *Id.* at 24:63–65.

We have reviewed Petitioner's allegations regarding how the MSI-H Study Record discloses the additional limitations of dependent claims 2, 3,

and 5–7, and find that Petitioner has sufficiently demonstrated, on this record and as supported by the testimony of Dr. Neugut, 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 would disclose those additional limitations. *See* Pet. 29–32; Ex. 1003 ¶¶ 81–90.

5. Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that at least one of the challenged claims of the '974 patent is unpatentable. Accordingly, we institute an *inter partes* review of claims 1–3 and 5–7 of the '974 patent.

C. Grounds 2–7

Petitioner incorporates its allegations that claims 1–3 and 5–7 are anticipated by the MSI-H Study Record, but presents alternative grounds challenging against the patentability of claims 1–3 and 5–7 based on obviousness in Grounds 2 and 4. *See* Pet. 36–45; 46–54. Petitioner also challenges claim 4 as obvious in Grounds 3 and 7. *See* Pet. 46–46; 54. Petitioner also argues that claim 7 is obvious on two alternative bases in Grounds 6 and 7. *See* Pet. 55–56.

Patent Owner raises a global argument against institution of trial for Grounds 2–7: Patent Owner argues that we should exercise our discretion to deny institution of *inter partes* review under 35 U.S.C. § 314(a) in light of the parallel district court litigation and the *Fintiv*[5] factors. *See* Prelim. Resp. 9–33 (citing *Merck Sharp & Dohme LLC v. The Johns Hopkins University*,

[5] *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential).

1:22-cv-03059-JRR (D. Md.) ("the Maryland litigation")); *see also* Sur-reply 1–3. Because both of Patent Owner's arguments for discretionary denial address the merits of Petitioner's challenges and do not themselves argue the merits, we analyze the merits of Petitioner's Grounds 2–7 before turning to Patent Owner's arguments.

1. Ground 2: Obviousness over MSI-H Study Record, Pernot, and Benson (Claims 1–3 and 5–7)

a) Summary of Pernot (Ex. 1006)

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

b) Summary of 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.

c) Petitioner's Contentions

Petitioner incorporates its allegations that claims 1–3 and 5–7 are anticipated by the MSI-H Study Record, but presents alternative grounds based on obviousness. *See* Pet. 32–56. For Ground 2, Petitioner alleges claims 1–3 and 5–7 are obvious over the teachings in the MSI-H Study Record, Pernot and Benson. Pet. 36–45. Petitioner asserts that Pernot, and Benson disclose elements that Patent Owner might argue are not taught in the MSH-I Study Record, specifically the improved patient outcome and drug efficacy recited in claim 1, testing for MSI-H or dMMR tumors, and treating patients that have characteristics related to progressive or metastatic disease. *Id.*

(1) Allegations Regarding Pernot

Petitioner argues that Pernot teaches treating colorectal cancer and that one of ordinary skill in the art knowing the teachings of the MSI-H Study Record would have considered the teachings of Pernot 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. Pet. 37 (citing Ex. 1003 ¶ 97). Petitioner argues that Pernot teaches that colorectal cancer patients that are MSI-H are "good candidates for immunotherapy," such as PD-1 inhibitors. *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 also argues that the state of the art indicates one of ordinary skill would have had a reasonable expectation of success in the claimed method because successful treatment with a PD-1 inhibitor of a colorectal cancer patient having an MSI-H tumor was reported in the prior art. Pet. 38

(citing, e.g., Ex. 1057, 463–64 (reporting patient with MSI-H status advanced colorectal cancer who had not responded to prior chemotherapy treatment had cancer resolved through administration of PD-1 inhibitor, albeit a different inhibitor from pembrolizumab)). *See also* Ex. 1003 ¶ 98 (Dr. Neugut opining that the study described in Ex. 1057 would have motivated the POSA to pursue the claimed method). Petitioner additionally argues that independent sources urged the treatment of MSI-H cancer with "PD-1 inhibitors or other immunotherapy, like pembrolizumab." Pet. 38 (citing e.g., Ex. 1032, e27817-5; Ex. 1003 ¶ 99). Petitioner further argues that the prior art taught PD-1 inhibitors were more effective when treating tumors "comprised of cancer cells that are easy for immune cells to recognize" such as MSI-H tumors. Pet. 38–39 (citing, e,g., Ex. 1085, 673–74. *See also* Ex. 1003 ¶¶ 43–46, 96–101 (Dr. Neugut's testimony citing numerous studies showing that "the literature had also discussed that MSI-H tumors exhibited the characteristics that were most relevant for PD-1 efficacy" and that this knowledge would have motivated the POSA to "obtain the data from the MSI-H Study").

> Petitioner also argues, through Dr. Neugut, that
>
> [a]s a result of carrying out the methods in the MSI-H Study Record of treating MSI-H colorectal patients 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 . . . .

Dr. Neugut opines 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. *See* Pet. 40–42 (citing Ex. 1003 ¶¶ 97, 98).

(2) Allegations Regarding Benson

Petitioner argues 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. 42–45. 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.* at 42–43 (citing Ex. 1009, 1034; Neugut Decl., Ex. 1003 ¶ 104). Petitioner alleges that 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. *Id.* at 43 (citing Ex. 1009, 1034; Neugut Decl., Ex. 1003 ¶ 105). Dr. Neugut testifies 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 concludes that a POSA would have been motivated to carry out that the method of the MSI-H Study Record on colorectal cancer that was metastatic, with a reasonable expectation of success. Neugut Decl., Ex. 1003 ¶¶ 105, 106.

In summary, Petitioner argues that the MSI-H Study Record teaches all limitations of claim 1, while relying 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. 36–42 (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. Pet. 42–45 (citing Ex. 1009, 1034).)

d) Discussion

Patent Owner does not dispute Petitioner's characterization of or prior art status of either Pernot or Benson. *See* Prelim. Resp.

On this record, we find that there is sufficient evidence of a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have been motivated to obtain the results of MSI-H Study Record, having been informed by Pernot's disclosures that patients with MSI-H tumors would be good candidates for immunotherapy, and understanding through Benson's disclosures that the patients in this study would be patients with an unresectable or metastatic tumor.

e) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that at least one of claims 1–3 and 5–7 is unpatentable based on the combined teachings of MSI-H Study Record, Pernot, and Benson.

2. Ground 3 Obviousness over MSI-H Study Record or MSI-H Study Record, Pernot, Benson, and Chapelle (Claim 4)

Claim 4 depends from claim 1 and further recites "wherein the tumor sample from the patient exhibits an instability of one or more microsatellite markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, or wherein the tumor sample from the patient exhibits a deficiency of one or more mismatch repair markers, wherein the mismatch repair marker is POLE, POLDl, or MYH." Ex. 1001, 52–58.

a) Summary of 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.* at 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.* at 3380, 3384.

b) Petitioner's Contentions

Petitioner argues that Chapelle teaches standard methods of testing whether a tumor is MSI-H, and that the methods have been successful in determining whether the patient's tumor exhibits instability in a microsatellite marker, such as BAT-25 or BAT-26. Pet. 45–46 (citing Ex. 1007, 3380, 3383). Dr. Neugut supports this characterization of Chapelle, and opines that the POSA would have considered Chapelle to be in the same field of art. *See* Ex. 1003 ¶¶ 110–111.

Petitioner argues that a POSA would have been motivated, based on the teachings of the MSH-I Study record, Pernot, Benson, and Chapelle, to determine "whether the tumor sample from the patient exhibits an instability of one or more microsatellite markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24." Pet. 45 (citing Ex. 1003 ¶ 112). Petitioner further argues the artisan would have had a reasonable expectation of success in the method because Chapelle's method of testing was well known and "does not affect the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors." *Id.* at 46 citing Ex. 1001, 6:21–22; 6:31–34; Ex. 1003, ¶ 113).

a) Discussion

Patent Owner does not dispute Petitioner's characterization of or prior art status of Chapelle. *See* Prelim. Resp.

On this record, we find that there is sufficient evidence of a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have been motivated to obtain the results of the MSI-H Study Record as discussed above (*see* Section II.C.1), and further motivated to test patient samples to assess whether the tumors exhibited an instability of one or more microsatellite markers (e.g., BAT-25, BAT-26, MONO-27, NR-21 or NR-24) based on Chapelle's disclosure of the testing method, and the information that could be obtained about the specific deficiency through the testing.

b) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that claim 4 is unpatentable based on the combined teachings of MSI-H Study Record, Pernot, Benson, and Chapelle.

3. Ground 4: Obviousness over MSI-H Study Record, Brown, Duval, and Benson (Claims 1–3 and 5–7)

a) Summary of Brown (Ex. 1034)

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

"reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.*, 747–48.

b) Summary of 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) Petitioner's Contentions

Petitioner incorporates its allegations that claims 1–3 and 5–7 are anticipated by the MSI-H Study Record, but presents an alternative ground alleging claims 1–3 and 5–7 are obvious over the teachings in the MSI-H Study Record, Brown, Duval, and Benson to supplement the allegations in Ground 1 that a POSA would have known that a PD-1 inhibitor would provide an improved outcome to patients having MSI-H cancers in patients with progressive disease and to show that testing for MSI-H cancers was known. Pet. 46–54.

With regard to claim 1, Petitioner argues that Brown teaches that PD-1 inhibitors were inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 48

(citing Ex. 1034, 747L Ex. 1003 ¶¶ 115 119.). Petitioner argues further that Duval teaches that MSI-H cancers have cells that are easy for immune cells to recognize. *Id.* (citing Ex. 1087, 5002; Ex. 1003 ¶¶ 117, 119). Petitioner argues that the combined teachings would have motivated a person of ordinary skill in the art to obtain the results of the MSI-H Study Record because the POSA would have "reasonably expected patients to respond" sufficiently to obtain the data based on the disclosures of Brown, Duval, and Benson. *Id.* at 49–50 (citing Ex. 1003 ¶¶ 124, 125).

Regarding the dependent claims 2, 3 and 5–7, Petitioner alleges the teachings discussed above at Section II.C.1.(c)(2).

d) Discussion

Patent Owner does not dispute Petitioner's characterization of or prior art status of either Brown or Duval. *See* Prelim. Resp.

On this record, we find that there is sufficient evidence of a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have been motivated to obtain the results of MSI-H Study Record, having been informed by Brown and Duval's disclosures that patients with MSI-H tumors would be good candidates for immunotherapy, and understanding through Benson's disclosures that the patients in this study would be patients with an unresectable or metastatic tumor.

e) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that at least one of claims 1–3 and 5–7 is unpatentable based on the combined teachings of MSI-H Study Record, Brown, Duval, and Benson.

4. Ground 5: Obviousness over MSI-H Study Record, Brown, Benson, and Chapelle (Claim 4)

a) Petitioner's Contentions

Petitioner incorporates its contentions from Ground 3 with regard to the teachings of MSI-H Study Record, Brown, and Benson. Pet. 54 (citing Ex. 1003 ¶ 132). Petitioner also incorporates its contentions from Ground 3 with regard to how Chapelle discloses the additional limitation of standard methods of testing whether a tumor is MSI-H, which has been successful in determining whether the patient's tumor exhibits instability in a microsatellite marker, such as BAT-25 or BAT-26. *Id.* (citing allegations regarding Ground 3). Petitioner argues that a POSA would have been motivated, based on the teachings of the MSH-I Study record, Brown, Benson, and Chapelle, for the same reasons discussed in its allegations in Ground 3. *Id.*

b) Discussion

On this record, we find that there is sufficient evidence of a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have been motivated to obtain the results of the MSI-H Study Record as discussed above (*see* Section II.C.1), and further motivated to test patient samples to assess whether the tumors exhibited an instability of one or more microsatellite markers (e.g., BAT-25, BAT-26, MONO-27, NR-21 or NR-24) based on Chapelle's disclosure of the testing method.

c) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that claim 4 is unpatentable based on the combined teachings of MSI-H Study Record, Brown, Benson, and Chapelle.

5. Ground 6: Obviousness over MSI-H Study Record or MSI-H Study Record, Pernot, Benson, Chapelle, and Hamid (Claim 7)

Claim 7 depends from claim 1 and further recites "wherein pembrolizumab is administered by intravenous infusion." Ex. 1001, 24:63–65.

a) Summary of 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.*

b) Petitioner's Contentions

Petitioner incorporates its contentions regarding anticipation from Ground 1 with regard to the teachings of the MSI-H Study Record, and Petitioner's contentions regarding obviousness from Ground 3 with regard to the teachings of the MSI-H Study Record, Pernot, Benson, and Chapelle. Pet. 55. With regard to claim 7's limitation that pembrolizumab be administered by intravenous infusion, Petitioner cites to Hamid's disclosure that pembrolizumab can be administered by intravenous infusion. *Id.* (citing Ex. 1011, 134; Ex. 1003 ¶¶ 134, 136). Petitioner alleges that a POSA would have been motivated to combine the teachings of these references to arrive at the method of the MSI-H Study Record, and to administer pembrolizumab

by intravenous infusion, particularly as the prior art discloses administration of pembrolizumab by intravenous infusion for treating cancer patients. *Id.* at 55–56 (citing Ex. 1011, 134; Ex. 1055, 1; Ex. 1003, ¶ 138). Petitioner further alleges that, given the prior art's demonstrated success in administration of pembrolizumab by intravenous infusion for treating cancer patients, the POSA would have had a reasonable expectation of success.

c) Discussion

Patent Owner does not dispute Petitioner's characterization of or prior art status of Hamid. *See* Prelim. Resp.

On this record, we find that there is sufficient evidence of a reasonable likelihood that Petitioner will prevail in showing that one of ordinary skill in the art would have been motivated to obtain the results of the MSI-H Study Record as discussed above (*see* Section II.C.1), and further motivated to administer pembrolizumab by intravenous infusion based on Hamid's disclosure of the method.

d) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that claim 7 is unpatentable based on the combined teachings of MSI-H Study Record, Pernot, Benson, Chapelle, and Hamid.

6. Ground 7: Obviousness over MSI-H Study Record, Brown, Duval, Benson, Chapelle, and Hamid (Claim 7)

a) Petitioner's Contentions

Petitioner incorporates its contentions from Ground 6 with regard to the teachings of MSI-H Study Record, Duval, Benson, Chapelle, and Hamid. Pet. 56 (citing Ex. 1003 ¶ 140). Petitioner argues that the additional

limitation of administration of pembrolizumab by intravenous infusion is obvious in light of Hamid's disclosure as discussed in Ground 6.

a) Discussion

The difference between Grounds 6 and 7 is the substitution of Brown for Pernot in Ground 7 to establish that PD-1 inhibitors inherently were more effective when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize.[6] *See*, e.g., Pet. 48. On this record, we find there is sufficient evidence that the teachings of the proposed combination with Brown substituted for Pernot in combination with MSI-H Study Record, Duval, Benson, Chapelle, and Hamid would have made it obvious to a POSA to obtain the results of the MSI-H Study Record as discussed above (*see* Section II.C.1), and to have been motivated to administer pembrolizumab by intravenous infusion. *See* Ex. 1003 ¶¶ 133–139.

b) Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that claim 7 is unpatentable based on the combined teachings of the MSI-H Study Record, Brown, Duval, Benson, Chapelle, and Hamid.

*D. Patent Owner's Procedural Challenge Unde*r 35 U.S.C. § 312(a)(3)

Having determine that Petitioner's Grounds 1–7 have substantive merit, we turn to Patent Owner's procedural challenge.

[6] The Petition incorporates contentions from Ground 6 that alleges Pernot as prior art as opposed to Brown in Ground 7. *Compare* Pet. 55 and 56.

Patent Owner argues that Petitioner fails to meet the particularity requirement of 35 U.S.C. § 312(a)(3) in all of its challenges under 35 U.S.C. § 103. *See* Prelim. Resp. 4–5, 23–32. According to Patent Owner, the Petition fails to set forth, with particularity, a sufficient mapping of each challenged claim to the cited prior art in each of the obviousness-based grounds of unpatentability. *Id.* at 24. Patent Owner argues that,

> [f]or example, in one ground (Ground 2), as explained below, the Petition identifies the claim limitation at issue (limitation [1.1]) but not the cited prior art that allegedly teaches or suggests that limitation. In that same ground, the Petition goes on to identify prior art but then fails to set forth the claim limitation allegedly taught or suggested by that prior art. In other words, in each situation, the Petition fails to properly relate the prior art to the claims.

Id. at 24–25 (internal citations to Petition omitted)

We are not persuaded by Patent Owner's arguments that we should deny institution because the Petition advances ambiguous or unclear grounds of unpatentability for obviousness. Prelim. Resp. 24. We agree with Patent Owner that in certain circumstances, the Petition lacks clarity in its allegations due to reliance on incorporation of earlier arguments. *See, e.g.*, Prelim. Resp. at 29–30, describing Petitioner's incorporation of arguments from Ground 6 which relies in part on different prior art. As we have concluded, regarding Ground 1, that Petitioner has shown a reasonable likelihood that it will prevail in establishing that the MSI-H Study Record anticipates claims 1–3 and 5–7, and because Petitioner's independent allegations against claim 4 in Grounds 5 and 6 are sufficiently clear, we decline to deny institution in response to this procedural argument.

Patent Owner also argues that Petitioner relies on "a voluminous number of additional exhibits without sufficient analysis and explanation

about the relevant contents of each exhibit." Prelim. Resp. 30–32. We are not persuaded that Petitioner's inclusion of these references is a reason to decline institution as the cited references appear to be cited to show the knowledge of a POSA. *See Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1337 (Fed. Cir. 2020) ("[T]he inquiry into whether any 'differences' between the invention and the prior art would have rendered the invention obvious to a skilled artisan necessarily depends on such artisan's knowledge.").

After weighing the parties' arguments and reviewing the evidence relied on in the Petition, as set forth above in Section II.C, we determine that there is sufficient evidence to indicate a reasonable likelihood Petitioner will prevail on at least one claim challenged under 35 U.S.C. § 103 in each of Grounds 2–7 in the Petition. Furthermore, Patent Owner does not challenge Petitioner's arguments that the MSI-H Study Record anticipates claims 1–4 and 6–8 of the '974 patent and, as explained above, there is sufficient evidence to show that Petitioner will prevail in showing that those claims are unpatentable as anticipated. We decline to deny institution in response to Patent Owner's procedural argument.

E. Discretionary Denial

1. 35 U.S.C. § 325(d)[7]

Under 35 U.S.C. § 325(d):

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take

[7] Patent Owner does not expressly identify its argument as a request for exercise of discretion to deny institution under 35 U.S.C. § 325(d), but rather argues under Factor 6 of the *Fintiv* analysis, "other circumstances that impact the Board's exercise of discretion, including the merits." Prelim.

> into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

Thus, we have the discretion to deny institution when the prior art cited in Petitioner's challenges was previously presented to the Office. To determine whether denial under § 325(d) is appropriate, we look to the parties' evidence of

> (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph). We apply a two-part test to analyze these factors, as articulated in *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential), wherein we ask

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the

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Resp. 18–23. We address the argument separately here for completeness as Patent Owner appears to argue for discretionary denial under § 325(d).

> Office erred in a manner material to the patentability of challenged claims.

(*Id.* at 8.)

Petitioner argues that discretionary denial is not appropriate because the Examiner did not fully consider the information in the MSI-H Study Record during prosecution of the '974 patent. Pet. 9–10, 58–59. Petitioner acknowledges that the Examiner considered the MSI-H Study Record during prosecution of an application that was in the chain of priority of the '974 patent, namely application 16/144,549 ("the '549 application"), which issued as U.S. Patent No. 10,934,356 ("the '356 patent"). *Id.* at 9 (citing Ex. 1022, August 26, 2020, Non-Final Rejection 26–27. However, Petitioner argues that the Examiner erred in allowing the claims of the '356 patent over the MSI-H Study Record "on the rationale that [the MSI-H Study Record] did not affirmatively disclose the results flowing from the disclosed treatment." *Id.* at 9–10 (citing Ex. 1022, December 14, 2020, Notice of Allowance, 3. The Examiner stated:

> Clinical Trial Announcement NCT01876511 does not teach the mental step of determining that the patient with a MSI-high or MMR deficiency status who has been treated with pembrolizumab exhibits an improved outcome compared to a patient who has been treated with pembrolizumab but does not have such a status. The announcement contemplates evaluating this parameter as primary and secondary outcome measures of the proposed clinical trial. (Page 3/8.) On its own, however, the announcement does not establish why the person of ordinary skill in the art would have reasonably expected the claimed outcome. In particular, the announcement does not establish a reasonable expectation of observing claim 41's objective response rate of about 12%-96% in MSI-high or MMR-deficiency patients treated with pembrolizumab.

December 14, 2020, Notice of Allowability, Ex. 1022 (part 11), 3073.

Petitioner argues that the Examiner's requirement for an express disclosure of an inherent result "was incorrect as a matter of law, particularly given the evidence that the methods in the MSI-H Study Record were, in fact, shown to be effective." Pet. 59. Petitioner argues that the Examiner erred in not considering whether the MSI-H Study Record inherently anticipates the methods claimed in the '356 patent and, thus, discretionary denial is inappropriate for the challenges presented in the Petition. Pet. 9, 59.

Patent Owner argues that discretion to deny is appropriate because the Examiner repeatedly considered the MSI-H Study Record and updates to the record that were provided during prosecution of the '974 patent and at least six other related applications examined before the '974 patent was allowed. Prelim. Resp. 18–22 (citing Ex. 1002 (part 1), 466, 470; Ex 1001, 4; Ex. 2010, 1; Ex. 2011, 1; Ex. 2012, 1; Ex. 2014, 1; Ex. 2015, 1; Ex. 2054, 1; Ex. 2021; Ex. 2018, 9–12, Ex. 2019, 10–13, Ex. 1022, 3009–12, 3039–49, 3072–74; Ex. 2020, 5). Patent Owner argues that the Examiner's numerous considerations of the MSI-H Study Record are indicated by signatures on Information Disclosure Statements, reliance on the reference in rejections, discussions in interviews, and explanation in the "reasons for allowance" notification in at least some of these applications. *Id.* Patent Owner points specifically to the Examiner's consideration of the MSI-H Study Record in the prosecution of related applications 15/611,017 and the '549 patent prior to allowance of the claims in the '974 patent. *Id*. at 20–21.

Turning to the *Becton, Dickinson* factors, even if we consider the MSI-H Study Record to have been fully considered during prosecution of the application that became the '974 patent and, even if we consider that the MSI-H Study Record would have been the basis for a rejection had it not

been discounted in the prosecution of prior applications (factors (a) through (c)), we are persuaded that these considerations do not indicate we should deny institution in this case. As discussed above, at this point in the proceeding, we agree with Petitioner that, on the record before us, Petitioner has sufficiently shown that the MSI-H Study Record teaches the steps of at least claim 1 of the '972 patent — treating a patient who has received a prior cancer therapy drug to treat a MSI-H or MMR deficient tumor, administering an effective amount of pembrolizumab, and observing an improved outcome in the patient as compared to a patient without a MSI-H or MMR deficient tumor – inherently where it does not teach them expressly. *See* Section II.B. Thus, we agree with Petitioner that the Examiner erred by failing to appreciate the teachings of the prior art when the claims were allowed over the MSI-H Study Record on the rationale that the art did not affirmatively disclose an improved outcome or that one or ordinary skill would not have expected such efficacy. *See* Pet. 59. We are persuaded that a reference need not show the efficacy of treatment if the steps were taught in the prior art. *See Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999):

> MEHL/Biohile does not dispute on appeal that the laser operating parameters disclosed in the article substantially coincide with those disclosed in the patent. Accordingly, to the extent that the embodiment in the patent achieves hair depilation, so does the Polla method. Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results.

We disagree with Patent Owner that merely because the Examiner considered the MSI-H Study Record during prosecution, we should exercise discretion to deny institution of *inter partes* review because we are

persuaded that Petitioner has pointed out sufficiently that the Examiner failed to appreciate the inherent disclosures in the asserted prior art.

2. 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 co-pending litigation between the parties and "under the *Fintiv* factors." Prelim Resp. 4, 9–33; Sur-reply 1–3. Petitioner opposes Patent Owner's assertions. Pet. 57–58; Reply 1–3.

35 U.S.C. § 314(a) states that

> [t]he Director may not authorize an inter partes review to be instituted 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.

The language of § 314(a) expressly provides the Director with discretion to deny institution of a inter partes review. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 1231, 2140 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."); Consolidated Trial Practice Guide November 2019 ("CTPG") at 55, https://www.uspto.gov/TrialPracticeGuideConsolidated.

In exercising the Director's discretion under § 314(a), the Board may consider "events in other proceedings related to the same patent, either at the Office, in district court, or the ITC." CTPG at 58. *NHK Spring* explains that the Board may consider the advanced state of a related district court proceeding, among other considerations, as a "factor that weighs in favor of denying the Petition under § 314(a)." *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 20 (PTAB Sept. 12, 2018) (precedential). Additionally, the Board's precedential order in *Apple Inc. v. Fintiv, Inc.*,

IPR2020-00019, Paper 11 at 5—6 (PTAB Mar. 20, 2020) (precedential) ("the *Fintiv* Order") identifies several factors for analyzing issues related to the Director's discretion to deny institution in view of related litigation, with the goal of balancing efficiency, fairness, and patent quality.

When considering related litigation, the Board evaluates the following factors ("*Fintiv* factors"):

> 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.

Fintiv Order at 5–6. In evaluating these factors, "the Board takes a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6.

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. *See* Reply 1 (citing Order in *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), dated June 29, 2024, Ex. 1100, 1); *see* Sur-Reply 1 (acknowledging "the recent stay of the parties' co-pending litigation involving the '974 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.)

"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." *Fintiv*, at 6. Accordingly, the stay of the co-pending Maryland litigation indicates that the first *Fintiv* factor weighs heavily against exercising discretion to deny institution of *inter partes* review in this proceeding.

The litigation stay is pending resolution of related proceeding IPR2024-00240, which has a statutory deadline of June 13, 2025, one year from its date of institution. *See* IPR2024-00240, Paper 10 (June 13, 2024, Decision on Institution). Institution in this proceeding would result in a final written decision by September 24, 2025. Accordingly, trial in the co-pending Maryland litigation will be after the Board's projected statutory deadline for a final written decision in this matter. *See* 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 (filed before the stay was enacted)). In addition, neither the court nor the parties will invest further in that parallel proceeding during the stay. Thus, as a result of the stay, the second and third *Fintiv* factors also weigh heavily against exercising discretion to deny institution of *inter partes* review.

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 the merits of Petitioner's arguments, indicates that institution should be denied. *See* Prelim. Resp. 18–33; Sur-reply, 1–2.) Patent Owner repeats many of the arguments presented in the Preliminary Response to argue that the merits of Petitioner's challenges should guide us to use our discretion to deny institution. Sur-reply 2.

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 at 4–5 (Feb. 27, 2023) (precedential) ("[I]n 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 differ from the claims challenged and issues raised in IPR2024-00240, which was the basis of 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 2– 3. Patent Owner argues that Petitioner has engaged in "strategic delay" and "gamesmanship" that prejudice Patent Owner by creating staggered trial dates, thereby allowing Petitioner to unfairly rely on Patent Owner's arguments in previous proceedings. *Id.* at 3; *see also* Prelim. Resp. 32–33.

None of these arguments persuades us that we should exercise our discretion to deny institution of *inter partes* review where the District Court

has stayed litigation addressing patentability of a related patent, 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 considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that the challenged claims of the '974 patent are unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"); 37 C.F.R. § 42.108(a). At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

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

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–7 of U.S. Patent 11,325,974 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 '974 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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