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Paper 63
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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.

IPR2024-00623
Patent 11,325,974 B2

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

NEWMAN, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

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. Paper 5. In addition, as authorized (*see* Paper 7), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (Paper 8) and Patent Owner filed Patent Owner's Preliminary Sur-reply (Paper 10). We granted the Petition and instituted an inter partes review. Paper 11.

During trial, Patent Owner filed a Patent Owner Response to the Petition (Paper 34 (confidential Paper 31) ("PO Resp.")), Petitioner filed a Reply (Paper 52 (confidential Paper 49) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 56 (confidential Paper 54) ("PO Sur-reply"). The parties declined to present oral arguments in this proceeding. *See* Paper 57.

We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial.[1] For the reasons discussed below, we

[1] To the extent this Final Written Decision includes portions of the record that are presently sealed, the parties may meet and confer concerning whether any portions of this Decision should be redacted before it is made available to the public. If any party maintains that redactions to the Final Written Decision should be made, that party may, within seven (7) days of entry of the Final Written Decision, submit a proposed redacted and publicly-available version of the Final Written Decision along with a motion to seal explaining why the redactions are necessary and outweigh any public interest in the redacted information. Any opposition to such motion must be filed within ten (10) days after the motion is filed. If no motion is filed within the timeline set forth above or if the parties otherwise inform the

determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–7 of the '974 patent are unpatentable.

B. Real Parties in Interest

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

In addition, several other *inter partes* reviews are related to this proceeding, including: IPR2024-00622 against U.S. Patent No. 10,934,356 B2; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00240 against U.S. Patent No. 11,591,393 B2; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00649 against U.S. Patent No. 11,629,187; and IPR2024-00650 against U.S. Patent No. 11,634,491. Pet. 60; Paper 3.

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

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Board (via email to trials@uspto.gov) that no redactions are necessary, the Final Written Decision will be made available to the public in unredacted form.

death-1 ("PD-1") receptor. *Id.* at Abstract. More specifically, the '974 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 3:35–49. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.* at 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. at 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.* at 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. at 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.* at 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.* at 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.* at 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").

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. §[2]	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, 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 parties do not assert constructions of any terms recited in the challenged claims other than that their ordinary and customary meanings should apply. *See* 37 C.F.R. § 42.100(b) (2020) (requiring claims to be construed "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.").

[2] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013, before the filing of the applications to which the '974 patent claims priority. Therefore, we apply the AIA versions of Sections 102 and 103.

I. Level of Ordinary Skill in the Art

The parties rely on the testimony of witnesses for their opinions on what one of ordinary skill in the art ("POSA") would have known and understood at the relevant time. Specifically, Petitioner relies primarily on the testimony of Alfred L. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies primarily on the testimony of Nils Lonberg, Ph.D. (Ex. 2072).

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 contends that the ordinarily skilled artisan would have had a medical or graduate-level degree, or equivalent work experience, in the fields of immunology, genetics, or a related field and would have experience (i) conducting immunology research relating to oncology, (ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. PO Resp. 5–6 (citing Ex. 2072 ¶¶ 31–32, 86–94). Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '974 patent claims a method of treating a patient with cancer having certain characteristics, who has previously received a cancer treatment drug, with pembrolizumab, and determining patient outcome, and

the main prior art reference cited by Petitioner discloses testing pembrolizumab to treat human patients. *See* Ex. 1001, 24:28–43, Ex. 1005.) Accordingly, the relevant field of Patent Owner's claims is treating human patients for cancer, as well as testing existing compounds for use in treatment modalities.

In light of the extent of the relevant field, we determine that the level of skill in the art relevant to the claims of the '974 patent is not limited to knowledge of and experience with conducting research relating to oncology or developing and conducting clinical trials, but includes knowledge of and experience with treating cancer patients with immunotherapy compounds, identifying the conditions these patients may have, and understanding the literature regarding clinical trials for such colorectal cancers and the associated conditions and immunotherapy.

J. Qualifications of Declarants to Testify on Understanding of POSA

Petitioner presents the testimony of Dr. Neugut 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. *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. *Id.* ¶ 5. Dr. Neugut testifies that he sees approximately 30 patients per week to treat gastrointestinal cancers, including colorectal cancer. *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 Dr. Neugut's qualifications, as summarized above, we determine that Dr. Neugut is qualified to testify about what one of ordinary skill would have understood at the time of the invention.

Patent Owner presents the testimony of Dr. Longberg 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. 2072.

Dr. Longberg testifies that he is a trained medical biologist and biochemist and has training in drug discovery, including working on "antibody therapies that target and modulate immune-attenuating pathways to activate patient immune responses to cancer cells (so-called "checkpoint blockade" therapies)." Ex. 2072 ¶¶ 2–4. Dr. Longberg testifies that he has worked in drug discovery groups at two different drug discovery companies and currently is an Executive in Residence at Canaan Partners. *Id.* ¶ 5. Dr. Longberg testifies that he is an inventor on over 60 patents in the fields of immunology and oncology and has authored over 40 manuscripts in peer reviewed journals. *Id.* ¶ 6.

Petitioner does not contest that Dr. Longberg is qualified to testify about what one of ordinary skill would have understood at the time. Based on Dr. Longberg's qualifications, as summarized above, we determine that Dr. Longberg 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. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The obviousness inquiry also typically requires an analysis of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). A petitioner cannot prove obviousness with "mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Rather, a petitioner must articulate a sufficient reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive*, 842 F.3d 1376, 1382 (Fed. Cir. 2016).

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

Petitioner argues that claims 1–3 and 5–7 are anticipated under 35 U.S.C. § 102 by the MSI-H Study Record. *See* Pet. 15–36.

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

The MSI-H Study Record reports a "Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors." Ex. 1005, 1. The

parties' witnesses agree that MK-3475 is pembrolizumab, the compound recited in claim 1. *See* Neugut Decl., Ex. 1003 ¶ 38; *see* Lonberg Decl., Ex. 2072 ¶ 68. Patent Owner does not dispute Petitioner's assertion that the MSI-H Study Record was published on a government web site on June 10, 2013, more than two years before the priority date of the '974 patent on July 10, 2015. *See* Pet. 7 (citing Ex. 1005, 3, Ex. 1003 ¶ 36). However, Patent Owner disputes the MSI-H Study Record's status as prior art. *See* PO Resp. 18–24. We summarize the MSI-H Study Record, and then address its status as prior art.

a) Summary of MSI-H Study Record

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[3]

[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.

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, including "MSI Positive Colorectal Cancer," "MSI Negative Colorectal Cancer," and "MSI Positive Non-Colorectal Cancer," and the same therapeutic intervention for each of the populations: "MK-3475 10 mg/kg every 14 days." *Id.*

b) Prior Art Status of MSI-H Study Record

Patent Owner argues that the MSI-H Study Record discloses an experimental use that does not qualify as prior art. PO Resp. 18–24. Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. *Id.* at 18 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998). According to Patent Owner, the experimental use negation applies to the MSI-H Study Record under a 13-factor analysis provided in *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002). PO Resp. 19–24. For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test treatment in humans, there being no animal models, and had to publish the MSI-H Study Record on the government website under federal law. PO Resp. 21–22. Patent Owner argues further that the inventors had control over the MSI-H clinical study and that the field of cancer treatment was highly unpredictable, among other facts. *Id.* at 21. Patent Owner argues that "[a]t the time of the MSR's

posting, the claimed invention was not, nor could it have been, ready for patenting. The clinical study that ultimately collected the data reported in the patent specification and supporting the patent claims had not and could not have commenced before the MSR was posted." PO Resp. 22.

In *City of Elizabeth*, the Supreme Court was concerned that "[i]t is sometimes said that an inventor acquires an undue advantage over the public by delaying to take out a patent, inasmuch as he thereby preserves the monopoly to himself for a longer period than is allowed by the policy of the law," but held that "when the delay is occasioned by a bona fide effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended," the experiment use exception can preserve the inventor's rights. *City of Elizabeth v. Am. Nicholson Pavement Co*., 97 U.S. 126, 137 (1877).

With regard to whether Patent Owner could have filed an earlier patent application for the claimed subject matter, Patent Owner asserts that if its inventors had filed a "data-less provisional application mirroring the MSR" before the MSI-H clinical study was published, it would have been unable to satisfy the requirements of §101 and §112, creating a "catch-22 scenario" wherein Patent Owner would not have been able to secure patent protection. PO Resp. 15–16. Patent Owner cites *Barry v. Medtronic, Inc*., 914 F.3d 1310, 1322 (Fed. Cir. 2019), *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010), and *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005), in support, asserting that these cases hold that a specification cannot provide merely prophetic examples, that it must demonstrate possession by the inventors, and that it must convey that the claimed invention benefits the public. PO Resp. 15–16.

Petitioner disagrees, arguing that "[i]t is well established . . . that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112." Pet. Reply 9–10 (citing *In re '318 Patent Infringement Litig*., 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"); *Ex parte Balzarini*, 1991 WL 332576 (BPAI 1991) (holding that even in situations where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials)). Petitioner argues that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." Pet. 16 (citing *Schering Corp. v. Geneva Pharms.,* 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citations omitted)). According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the '974 patent is irrelevant. *Id.* at 16–18.

Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSI-H clinical study and was denied an earlier filing date. Contrary to Patent Owner's argument that it could not file a patent application without results from the MSI-H clinical study, we note that the inventors filed a provisional patent application on November 13, 2014, which, although also filed more than a year after the publication of the MSI-H clinical study, disclosed no clinical results or data. Ex. 1001, cover; Ex. 1030, 1. After considering the parties' arguments, we are not persuaded by Patent Owner's assertion that the inventors could not have filed an earlier application to at least attempt to secure a priority date before the MSI-H clinical study was publicly available. We are not persuaded that the law prevented Patent Owner from obtaining an earlier filing date. Instead, we are persuaded by Petitioner's argument

that because the MSI-H clinical study was published before the inventors filed an application to protect their patent rights the MSI-H clinical study is prior art for the information it discloses.

2. Claim 1

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. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility) Ex. 1003 ¶ 59).

Patent Owner does not raise any arguments regarding this limitation. 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 had 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.* ¶ 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.* ¶¶ 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.

Patent Owner does not raise any arguments regarding this limitation. *See generally* PO Resp. We are persuaded that one of ordinary skill in the art at the time would have understood the MSI-H Study Record to teach "*wherein a tumor sample obtained from the patient has been determined to*

[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.

exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers," as required in claim 1.

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

Petitioner, through the testimony of Dr. Neugut, alleges that the MSI-H Study Record anticipates this limitation. *See* Pet. 23–26. Per the MSI-H Study Record, patients participating in the study 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 further 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, which the ordinarily skilled artisan would have understood could have been administered as cancer drugs. Ex. 1003 ¶¶ 70, 78 (excluding anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies). 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. Based on Dr. Neugut's testimony, Petitioner concludes that the ordinary artisan would have reasonably understood that the MSI-H Study Record anticipates this limitation. Pet. 25 (citing, e.g., *Genentech, Inc. v. Hospira, Inc*., 946 F.3d 1333, 1340 (Fed. Cir. 2020).

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 64–67. Dr. Oberstein testifies that because the eligibility criteria stated in the MSI-H Study Record requires patients to have "measurable disease," one of ordinary skill in the art would have expected a patient to have undergone prior cancer therapies and would have had their cancer progress after those therapies prior to enrollment. *Id.* ¶ 64. Dr. Oberstein testifies that it is reasonable to assume that patients would typically have received the two standard chemotherapy regimens before trying a novel therapeutic agent. *Id*. ¶ 65.

Patent Owner argues that the MSI-H Study Record cannot anticipate this limitation because it is "silent on whether eligible patients ***must*** have had a prior treatment and have progressed after receiving that prior

treatment." PO Resp. 6 (citing Ex. 1005, 5–6) (emphasis original). Patent Owner asserts that Petitioner's declarant, Dr. Neugut agreed with this statement. *Id.* (citing Ex. 2163, 99:13–21).

Patent Owner criticizes case law cited by Petitioner for the proposition that inherent anticipation can be found where one of ordinary skill in the art could reasonably infer claim limitations from a single prior art reference. *Id.* at 7–8 (citing, e.g., Pet. 25 (citing cases)). Patent Owner asserts that Petitioner's cited cases apply only where "the express disclosure establishes that a POSA would understand the limitation was ***necessarily*** present" and not merely generally present, as Petitioner argues. PO Resp. 8–9 (emphasis original). Patent Owner cites *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274–75 (Fed. Cir. 2017) and *VirnetX Inc. v. Apple Inc.*, 2023 WL 6933812, at *4 (Fed. Cir. Oct. 20, 2023) in support of its argument against inherency of limitation [1.2], asserting that missing limitations cannot be added despite being immediately envisioned. *Id.* at 6–7. Rather, Patent Owner argues, the express disclosure of the MSI-H Study Record does not establish that an ordinarily skilled artisan would understand the limitation was necessarily present, and thus Petitioner's cited cases do not apply. PO Resp. 8.

Patent Owner cites Dr. Lonberg's testimony that the MSI-H Study Record refers only to prior treatment by stating the "***exclusion*** of individuals who had received certain prior treatments" and disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSI-H Study Record. PO Resp. 9 (citing Ex. 2072 ¶ 96 ("While measurable cancer refers to a cancer that has a minimum size (e.g., as determined by imaging), this has little to do with whether or not a patient's cancer has progressed after the patient received prior therapies."). But Dr. Lonberg fails to testify that one

of ordinary skill in the art would not have understood the MSI-H Study Record in 2013 to teach treating patients who had received prior/different cancer therapies, wherein the patients' cancer had progressed after the patients received the prior/different cancer therapies.

On balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSI-H Study Record. We find Dr. Neugut's and Dr. Oberstein's testimony, and Dr. Lonberg's lack of clear testimony to the contrary, persuasive as to this issue. In addition, we are not persuaded by the case law cited by Patent Owner regarding inherent anticipation. *See* PO Resp. 6–7. Rather, we agree with Petitioner that the correct inquiry is whether the skilled artisan would have understood that all limitations are disclosed in the prior art. *See* Pet. 34–35; Pet. Reply 12–13.

In light of the cited testimony, we are persuaded that Petitioner has met its burden of proving that a skilled artisan would reasonably have understood or inferred that the limitation for a patient having received a prior cancer therapy drug to treat the tumor was disclosed in the MSI-Study Record. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSI-H Study Record, not what it inherently discloses. *Contra* PO Resp. 6–9.

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 '974 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.

Patent Owner does not raise any arguments regarding this limitation. *See generally* PO Resp. We are persuaded that one of ordinary skill in the art at the time would have understood the MSI-H Study Record to teach "administering an effective amount of pembrolizumab to the patient," as required in claim 1.

> 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. *Compare id. with* Ex. 1001, 6:48–52 ("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.")

Petitioner argues that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. Thus, actual administration of [pembrolizumab] to patients before the critical date of the ['974 patent] is irrelevant." Pet. 29 (citing *Schering*, 339 F.3d at 1380).

Patent Owner argues that the MSR does not disclose outcomes of the study and, therefore, does not teach that a patient administered pembrolizumab and having a tumor with MSI-H or dMMR status would exhibit an improved outcome compared to a reference patient administered pembrolizumab and not having a tumor with MSI-H or dMMR, as required in claim 1. PO Resp. 10–15. Patent Owner argues that *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), cited by Petitioner, fails to support the assertion of inherent anticipation of the claimed method. PO Resp. 11–15; Pet. 17 ("In *In re Montgomery*, the Federal Circuit held that a document disclosing a planned clinical study inherently anticipated method of treatment claims even where the method of treatment had not yet been practiced."). Patent Owner attempts to distinguish the facts of *Montgomery* from the facts at issue here by arguing that, in *Montgomery*, the disclosure of the prior art was identical to the patent itself, whereas here the MSI-H Study Record does not disclose treating a cancer patient with pembrolizumab when "the patient has received a prior cancer therapy drug" or that the cancer "progressed following a [cancer therapy/prior treatment]." PO Resp. 11–15; PO Sur-Reply 1–6. We are unpersuaded. Rather, we are persuaded by the statements in contemporaneous references citing the MSI-H Study Record that one of ordinary skill in the art would have understood the study to involve patients with unresectable or metastatic MSI-H cancer. Ex. 1049, 444; Ex. 1050 S4. Accordingly, we are not persuaded that the facts here

differ from those in *Montgomery* as much as Patent Owner argues, wherein both prior art references teach the steps recited in the challenged claims. See *Montgomery*, 677 F.3d at 1380 ("We see no error in the Board's uncontested conclusion that HOPE discloses the administration of ramipril to patients diagnosed as in need of stroke treatment or prevention.").

Patent Owner also argues that the MSI-H Study Record does not expressly disclose any results that would have led to the ordinarily skilled artisan understanding whether the amount of perbrolizumab used would be effective or any potential outcome from its use. *Id.* at 10–11. Patent Owner further argues that MSI-H Study Record does not inherently disclose the claimed results. *Id.* at 11–15. Patent Owner argues further that because the MSI-H clinical study "did not disclose the claimed but unperformed method" and is only an initial submission for an experimental trial that had not yet begun recruiting patients or obtaining experimental data, it was merely an "invitation to investigate" from which the results recited in claim 1 would not "inevitably flow." PO Resp. 11–12; PO Sur-Reply 2–3. Patent Owner argues that the inventors knew that other checkpoint inhibitor drugs used to treat colorectal cancer patients were "resoundingly ***unsuccessful***," and that treatment of other types of cancer "beyond the initial success in melanoma and non-small cell lung cancer had failed." PO Resp. 12 (citing Ex. 2090 ¶ 57). According to Patent Owner, "the MSR was a far cry from meeting *Montgomery's* inevitability requirement for inherent anticipation" and that, in contrast to *Montgomery*, the MSI-H Study Record only describes a study to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. PO Resp. 11–16; Ex. 2072 ¶ 109; Ex. 2130 ¶¶ 10–13.

We do not doubt that the inventors were unaware of the results of the study described in the MSI-H Study Record before it was concluded. But knowledge of the results is not a component of the analysis of anticipation, the challenges at issue here. *See Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc*., 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [the prior art]. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.") After analysis of the full record, we are persuaded that the results recited in claim 1 would follow from the steps taught in the MSI-H Study Record, for the reasons and based on the evidence Petitioner cites above. For these same reasons, we are unpersuaded by Patent Owner's argument that it was unknown whether the amount of pembrolizumab recited in claim 1 would be effective in producing an improved outcome compared to a reference patient with 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 Patent Owner does not dispute that the amount of pembrolizumab disclosed in the MSI-H Study Record (10 mg/kg every 14 days; *see* Ex. 1005, 4) is the same as the amount provided in the '974 patent as being effective (10 mg/kg every 14 days; Ex. 1001, 8:48–52, 13:50–52). Regardless of the inventors' intent in publishing the MSI-H Study Record as a Stage II clinical trial on the www.clinicaltrials.gov website, as discussed above, we determine that the MSI-H Study Record teaches selecting a patient with a metastatic MSI-H or dMMR tumor and administering an amount of pembrolizumab that would be effective. *See*, e.g., Ex. 1005, 4 (Arms and Interventions). The result of drug treatment inherently follows its administration. The MSI-H Study Record does not

merely suggest that pembrolizumab may be useful in some unidentified subset of patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the MSI-H Study Record discloses selecting a patient with a condition recited in claim 1 and treating with an effective amount of pembrolizumab as recited in claim 1. *Contra Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (holding that the prior art did not inherently anticipate where it failed to mention specific vitamin deficiencies, instead merely inviting further experimentation to find associations with metabolic perturbations). *Montgomery* states that "even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps," referring to a claimed method of treating or preventing stroke, which was held to be anticipated by the publication of a proposed study. 677 F.3d at 1381.

Patent Owner attempts to distinguish the size and apparent surety of the study in *Montgomery* from the MSR. PO Resp. 15. But because we find that the MSI-H Study Record teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H cancer, we are persuaded that the MSI-H Study Record inherently discloses the results of selection of patients and administration of the drug treatment recited in those steps. *See Bristol-Myers*, 246 F.3d at 1376. Whether or not the MSI-H Study Record could have provided results or was sufficient for full regulatory approval does not change that the MSI-H Study Record teaches Patent Owner's claimed steps. We have no reason to doubt that the disclosure in the MSI-H Study Record of the steps recited in claim 1 produces the efficacy element required in claim 1, whether or not this efficacy was disclosed in the MSI-H Study Record or was known when it was published. *See Mehl/Biophile Intern. Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999)("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.").

Patent Owner argues that Merck's interpretation of inherency law cannot be correct because it would effectively preclude the patenting of unexpectedly effective methods of treating human patients. PO Resp. 15– 16; PO Sur-Reply 5–6. Patent Owner asserts that if its inventors had filed a "data-less provisional application mirroring the MSR" before the MSI-H Study Record was published, it would have been unable to satisfy the requirements of §101 and §112, creating a "catch-22 scenario" wherein Patent Owner would not have been able to secure patent protection. PO Resp. 16. Patent Owner cites *Barry v. Medtronic, Inc*., 914 F.3d 1310, 1322 (Fed. Cir. 2019), *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010), and *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005), in support, asserting that these cases hold that a specification cannot provide merely prophetic examples, that it must demonstrate possession by the inventors, and that it must convey that the claimed invention benefits the public. *Id.* at 15–16. Petitioner disagrees, arguing that "[i]t is well established . . . that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112." Pet. Reply 9–10 (citing *In re '318 Patent Infringement Litig*., 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"); *Ex parte Balzarini*, 1991 WL 332576 (BPAI 1991) (holding that even in situations where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials)).

Petitioner responds that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." Pet. 16 (citing *Schering*, 339 F.3d at 1380). According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the '974 patent is irrelevant. *Id.* Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSI-H Study Record and was denied an earlier filing date. Contrary to Patent Owner's argument that it could not file a patent application without results from the MSI-H Study Record, we note that the inventors filed a provisional patent application on November 13, 2014, which, although also filed more than a year after the publication of the MSR, disclosed no clinical results or data. Ex. 1001, cover; Ex. 1030, 1. After considering the parties' arguments, we are not persuaded by Patent Owner's assertion that the inventors could not have filed an earlier application to at least attempt to secure a priority date before the MSR was publicly available. We are not persuaded that the law prevented Patent Owner from obtaining an earlier filing date. Instead, we are persuaded by Petitioner's argument that because the MSI-H Study Record was published before the inventors filed an application to protect their patent rights, the MSI-H Study Record is prior art for the information it discloses, including the steps recited in claim 1 and any results that would inherently result from these steps.

Patent Owner argues further that the MSI-H Study Record discloses an experimental use that does not qualify as prior art. PO Resp. 18–24. Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. *Id.* at 18 (citing *Pfaff v. Wells Elecs., Inc*., 525 U.S. 55, 64 (1998). According to Patent

Owner, the experimental use negation applies to the MSI-H Study Record under a 13-factor analysis provided in *Allen Eng'g Corp.*, 299 F.3d at 1353. PO Resp. 19–24. For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test treatment in humans, there being no animal models, and had to publish the MSI-H Study Record on the government website under federal law. PO Resp. 19–21. Patent Owner argues further that the inventors had control over the MSI-H clinical study and that the field of cancer treatment was highly unpredictable, among other facts. *Id.* at 21. Patent Owner argues that "[a]t the time of the MSR's posting, the claimed invention was not, nor could it have been, ready for patenting. The clinical study that ultimately collected the data reported in the patent specification and supporting the patent claims had not and could not have commenced before the MSR was posted." *Id.* at 22.

In City of Elizabeth, the Supreme Court was concerned that "[i]t is sometimes said that an inventor acquires an undue advantage over the public by delaying to take out a patent, inasmuch as he thereby preserves the monopoly to himself for a longer period than is allowed by the policy of the law," but held that "when the delay is occasioned by a bona fide effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended," the experiment use exception can preserve the inventor's rights. *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 137 (1877).

Because we are not persuaded that Patent Owner could not have filed an earlier application, we are not persuaded that the experimental use doctrine is properly applied in this case. Given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted

as prior art in other cases, we are not persuaded by Patent Owner's arguments that the MSI-H clinical study is not available as prior art against the challenged claims. *See*, *e.g.*, *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir.), cert. denied, 145 S. Ct. 567 (2024), and cert. denied, 145 S. Ct. 983 (2024).

After considering the parties' arguments and evidence, we are persuaded that the MSR teaches the efficacy requirement of claim 1, wherein a patient with an unresectable or metastatic MSI-H tumor and administered an effective amount of pembrolizumab would have an improved outcome over a reference patient that had been also administered pembrolizumab, but whose tumor does not exhibit an MSI-H status.

In summary, the preponderance of the evidence supports Petitioner's argument that the MSI-H Study Record teaches each and every element of claim 1. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claim 1 is anticipated by the MSI-H Study Record.

3. Dependent Claim 2

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.

Petitioner argues that this limitation "is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.2], "the patient having received a prior cancer therapy drug to treat the tumor." Pet 29–30 (citing Pet. 23–26, Ex. 1003 ¶¶ 81–82).

Patent Owner's arguments against this limitation, with one exception, were directed together with its arguments against limitation [1.2]. *See* PO

Resp. 6–16. As we addressed those arguments above with respect to limitation [1.2], we focus here on the argument unique to dependent claim 2.

Patent Owner's arguments regarding limitation [1.2] were equally made against the limitation "wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug." *See* PO Resp. 6–16 (arguing, e.g., that the MSI-H Study Record "is silent on whether eligible patients ***must*** have had a prior treatment and have progressed after receiving that prior treatment"). We find these arguments equally unpersuasive for the same reasons addressed above. Namely, we are persuaded that Petitioner has established by a preponderance of the evidence that patients having metastatic and advanced colorectal cancer who chose to participate in a clinical study such as 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." *See* Pet. 24 (citing Ex. 1020, PDF p. 25; Ex. 1009, 1034; Ex. 1047, 4–7; Ex. 1003¶ 69).

4. Dependent Claim 3

Claim 3 further limits the outcome exhibited by the patients selected and administered pembrolizumab, as recited in claim 1. Ex. 1001, 24:48–51. Specifically, claim 3 recites "[t]he method of claim 1, 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.*

Petitioner argues that the MSI-H Study Record discloses measuring objective "response rate, progression-free survival, and overall survival," which outcomes are "inherent to the methods of the MSI-H Study Record." *Id.* (citing MSI-H Study Record Ex. 1005, 4–5 (Outcome Measures), discussion regarding claim 1 (*see* Pet. 26–28 (citing Ex. 1003 ¶¶ 77–80)).

As discussed above, we are persuaded by Petitioner that the steps recited in claim 1 are taught by the MSI-H Study Record and the efficacy of those steps would be inherent to them. *See Montgomery*, 677 F.3d at 1385; *Schering Corp.*, 339 F.3d at 1377.

Patent Owner does not present separate arguments against Petitioner's challenge to claim 3. *See, e.g.*, PO Resp. 6–16. For the reasons discussed above regarding claim 1, we are persuaded that claim 3 is anticipated by the MSI-H Study Record.

5. Dependent claims 5 and 6

Claim 5 further recites "wherein the cancer is a metastatic cancer." *Id.* at 24:59–60. Claim 6 further recites "wherein the cancer is a metastatic colorectal cancer." *Id.* at 24:61–62.

Petitioner asserts that its arguments related to limitation [1.2] above ("the patient having received a prior cancer therapy drug to treat the tumor") apply equally to establish that patients in the MSI-H Study Record would have had metastatic cancer. Pet. 31 (citing arguments related to limitation [1.2]). Petitioner further cites prior art regarding the MSI-H Study Record as indicative that "the physicians understood postings on clinicaltrials.gov indicated that patients had "metastatic tumors." *Id.* (citing Ex. 1049, 444; Ex. 1050, S4; Ex. 1003 ¶¶ 86–90).

Patent Owner argues that the MSI-H Study Record does not disclose treatment of metastatic colorectal cancer and that the disclosure of "measurable disease" is not a teaching of metastatic colorectal cancer because "measurable disease" is not synonymous with metastatic cancer. PO Resp. 17–18. In support, Patent Owner cites to Dr. Neugut's testimony that "metastatic" and "measurable" are "totally different terms," wherein

metastatic tumors are not necessarily measurable. PO Resp. 17–18. (citing Ex. 2163:14:9–15:12).)

Even if Dr. Neugut's reasoning that the reference to "measurable" disease in the MSI-H Study Record would have indicated patients having metastatic cancer is flawed, we are persuaded by Petitioner's evidence of publications referring to the MSI-H Study Record as a study of metastatic colorectal cancer that one of ordinary skill in the art would have understood the MSI-H Study Record to disclose treating patients with metastatic colorectal cancer. *See* Ex. 1049, 444; Ex. 1050, S4. Patent Owner does not address this evidence.

As discussed above, we agree with Petitioner that the references to the study described in the MSI-H Study Record indicate one of ordinary skill in the art would have understood the MSI-H Study Record to include patients with metastatic tumors. Accordingly, we agree with Petitioner that the methods of claims 5 and 6 are anticipated by the MSI-H Study Record.

6. Dependent Claim 7

Claim 7 recites "The method of claim 1, wherein pembrolizumab is administered by intravenous infusion." Ex. 1001, 24:63–64.

Petitioner argues that the prior art, including the pembrolizumab package insert, demonstrates that pembrolizumab was administered intravenously for the treatment of cancer. *See* Pet. 31–32 (citing Ex. 1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."), Ex. 1003 ¶¶ 89–90. We agree.

Patent Owner does not present separate arguments against Petitioner's challenge to claim 7. *See, e.g.*, PO Resp. 6–16.

For the reasons discussed above, we are persuaded that claim 7 is anticipated by the MSI-H Study Record.

7. Conclusion

The preponderance of the evidence supports Petitioner's argument that the MSI-H Study Record teaches each and every element of claims 1–3 and 5–7. Accordingly, we determine that claims 1–3 and 5–7 are anticipated by the MSI-H Study Record.

C. Grounds 2 and 4 – Obviousness of Claims 1–3 and 5–7

1. Summary of Additional Asserted Prior Art

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.* at 3738. More specifically, Pernot discloses that "[m]icrosatellite instability (MSI) is associated with CRC in patients with Lynch syndrome." Ex. 1006, 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.* at 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.* at 1029. Benson

discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. Ex. 1009, 1034.

c) 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.* 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.

d) 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.*

2. Petitioner's Contentions

a) Ground 2 – Obviousness over MSI-H Study Record, Pernot, and Benson

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 . . . .

Ex. 1003 ¶ 101. 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 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).)

b) Ground 4 – Obviousness over MSI-H Study Record, Brown, Duval, and Benson

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 incorporates its earlier allegations regarding claim 1, and argues that any elements not disclosed by the MSI-H Study Record would have been obvious to the ordinary artisan in view of the additional asserted prior art. *Id.* at 51–52.

Petitioner also argues the artisan would have been motivated to carry out the claimed method and would have had a reasonable expectation of success in doing so. Pet. 53.

3. Patent Owner's Contentions

Patent Owner argues that the MSI-H Study Record does not anticipate the challenged claims and that none of Pernot, Benson, or Duval supplies limitations that Patent Owner asserts are "missing" from the MSI-H Study Record. PO Resp. 25–26. Specifically, Patent Owner argues that the MSI-H Study Record does not teach the "prior cancer therapy"/"progressed following a [cancer therapy/prior treatment]" required by the independent claim 1 or the "metastatic" limitation of dependent claims 5 and 6. *Id.* Thus, Petitioner's "obviousness challenges necessarily fail." *Id.* at 25. Patent Owner also argues that Benson advocates clinical trials as first-line therapy as opposed to after progression of cancer and drug treatment. *Id.* at 25–26.

4. Discussion

Because "anticipation is the epitome of obviousness," we are persuaded that the claims Petitioner challenges as being anticipated by the MSI-H Study Record would have been obvious over the MSI-H Study Record and other references, for the reasons discussed above. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002). Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1–3 and 5–7 as being obvious over the MSI-H Study Record alone.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. PO Resp. 50–85. The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed

methods. PO Resp. 50–85. Because we determine, as discussed above, that the method recited in claims 1–3 and 5–7 is anticipated by the MSI-H Study Record, Patent Owner's objective evidence of non-obviousness is not persuasive as to the patentability of these claims. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("secondary considerations are not an element of a claim of anticipation.").

Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1–3 and 5–7 as being obvious over the MSI-H Study Record alone or along with other references cited in Ground 2 and/or Ground 4.

D. Remaining Grounds: Obviousness Based on the MSI-H Study Record, Pernot, Brown, Duval, Benson, Chapelle and Hamid

Petitioner argues that dependent claims 4 and 7 of the '974 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle and Hamid. Pet. 45, 54–57. Because, as discussed above, we determined that claim 7 is anticipated by the MSI-H Study Record, it would have been obvious under the MSI-H Study Record alone. *In re McDaniel*, 293 F.3d at 1385. Accordingly, we review Petitioner's obviousness challenges only for remaining claim 4.

1. Summary of Additional Asserted Prior Art, 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. Ex. 1007, 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.* at 3380, 3384.

2. Petitioner's Contentions

In Grounds 3 and 5, Petitioner additionally relies on Chappelle to address the elements of claim 4. Pet. 45–46. Claim 4 recites

> The method of claim 1 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.

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, 132.

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." Pet. 46 (citing Ex. 1001, 6:21–22; 6:31–34; Ex. 1003 ¶ 113).

We find that the record as recounted above supports Petitioner's arguments.

3. Patent Owner's Contentions

Patent Owner argues that Petitioner has not shown claim 4 would have been obvious over the prior art in Grounds 3 and 5.[5] PO Resp. 49–50. Patent Owner argues that the additional art cited to show obviousness of the additional limitations in claim 4, Chapelle, does not cure the deficiencies in Petitioner's case to show that the prior art disclosed or suggested claim 1's requirement that the patient "received a prior cancer therapy drug" or the "outcome that is improved" limitation, or the requirement that a POSA "would have reasonably expected to achieve success in the treatment" claimed by the '974 Patent. PO Resp. 49–50. Patent Owner does not argue that claim 4's additional limitations render its method non-obvious. Patent Owner makes certain general arguments in response to Petitioner's obviousness challenges, which we address below.

Patent Owner argues that Petitioner applies the wrong legal standard to argue that there would have been a reasonable expectation of success in the methods recited in independent claim 1. PO Resp. 31–50. For example, Patent Owner argues that neither the MSI-H Study Record, Pernot, any other reference cited by Petitioner, nor the state of the art provides a reasonable expectation in using MSI status as an indicator of successful treatment with

[5] Patent Owner alleges the same for each of claims 1–7 with respect to Grounds 3 and 5–7. Pet. 49–50. We address only claim 4 here.

pembrolizumab. PO Resp. 32–49. Because, as discussed above, we are persuaded that the steps of the methods recited in claim 1 is expressly taught in the MSI-H Study Record, anticipating the limitations of independent claim 1, we are persuaded that Petitioner has established that one of ordinary skill in the art would have had a reasonable expectation of success in achieving a method comprising these steps, with the results being inherent. *See MEHL/Biophile*, 192 F.3d at 1366 ("Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the articles' authors did not appreciate the results."). Further, Petitioner presents persuasive evidence that one of ordinary skill in the art would have had a reasonable expectation of success in making a method that tests whether the tumor sample from the patient exhibits an instability of one or more microsatellite markers, wherein the microsatellite marker is one of the markers that was known by persons of skill in the art at the time of the invention, as recited in claim 4. Patent Owner does not argue or present evidence to the contrary. Accordingly, we are persuaded that Petitioner has met its burden of presenting a *prima facie* case for the obviousness of the claim 4.[6]

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 50–85. The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. *Id.* Because we determine, as discussed above, that the methods recited in the independent claims are anticipated by the MSI-H

[6] Having already concluded that Petitioner has demonstrated the obviousness of claims 1–3 and 5–7, we do not reassess that conclusion here, but the same assessment would apply.

Study Record, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of independent claim 1. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("secondary considerations are not an element of a claim of anticipation."). Similarly, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of dependent claims 2, 3, and 5–7, which we determine are anticipated by the MSI-H Study Record.

Regarding dependent claim 4, which Petitioner challenges only on obviousness grounds, Patent Owner must show a nexus between the claimed method and the evidence of non-obviousness. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("to be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a 'nexus' to the claims, *i.e.*, there must be 'a legally and factually sufficient connection' between the evidence and the patented invention. . . . Ultimately, '[t]he patentee bears the burden of showing that a nexus exists.'" (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988), *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999)).

Patent Owner does not direct us to evidence of a nexus to limitations recited in dependent claim 4, which recites testing that comprises assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24 and mismatch repair markers POLE, POLDl, or MYH. Thus, even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claim 1 alone, not the limitations of claim 4. PO Resp. 50–85. Patent Owner directs us only to evidence regarding treating patients determined to have MSI-H colorectal cancer with pembrolizumab, which we

determine to be anticipated by the MSI-H Study Record. PO Resp. 50–85. When evidence of a "secondary consideration is exclusively related to a single feature that is in the prior art," our reviewing court has held the evidence is of no relevance to the obviousness inquiry. *See Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1363–65 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 499 (2023) (distinguishing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330–31 (Fed. Cir. 2016)); *see also Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."). In *Yita*, the prior art taught close-conformance of a floor tray with the walls of a vehicle foot well, which one of ordinary skill in the art would have had reason to use in combination with other prior-art teachings to arrive at the claimed invention. *See Yita*, 69 F.4th at 1359–61. The court held that because the asserted evidence of secondary consideration related exclusively to close-conformity, the evidence was not persuasive of non-obviousness, even though the claimed floor tray was coextensive with the product that produced the evidence. *See* 69 F.4th at 1364–65 ("The coextensiveness inquiry bears only on the presumption of nexus; it does not decide the overall nexus question.").

Because Patent Owner directs us only to evidence that the methods recited in claim 1 produced evidence of secondary considerations, we are not persuaded that this evidence is persuasive of the non-obviousness of the specific methods recited in the dependent claim 4. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient wherein testing was confirmed to show that the tumor had one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24 and or mismatch repair markers

POLE, POLDl, or MYH, as recited in claim 4, demonstrated unexpected results or commercial success.

Accordingly, Petitioner has demonstrated by a preponderance of the evidence that the method of claim 4 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

4. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSI-H Study Record and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claim 4 is rendered obvious by the MSI-H Study Record and the other cited references.

a) 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 the MSI-H Study Record, Pernot, Benson, and Chapelle, or the MSI-H Study Record, Brown, Duval, Benson, and Chapelle.

III. CONCLUSION

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–7 of the '974 patent are unpatentable.

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–3, 5–7	102	MSI-H Study Record	1–3, 5–7	
1–3, 5–7	103	MSI-H Study Record, Pernot, Benson	1–3, 5–7	
4	103	MSI-H Study Record or MSI-H Study Record, Pernot, Benson, Chapelle	4	
1–3, 5–7	103	MSI-H Study Record, Brown, Duval, Benson	1–3, 5–7	
4	103	MSI-H Study Record, Brown, Duval, Benson, Chapelle	4	
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	7	
Overall Outcome			1–7	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–7 of the ’974 patent have been shown to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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Patent 11,325,974 B2

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