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Paper 60
Date: September 18, 2025

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.

IPR2024-00625
Patent 11,339,219 B2

Before DEBORAH KATZ, SUSAN L.C. MITCHELL, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges.*

KATZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner, Merck Sharp & Dohme LLC, filed a Petition to institute an *inter partes* review of all claims, namely claims 1–8 of U.S. Patent No. 11,339,219 B2 ("the '219 patent") pursuant to 35 U.S.C. § 311(a). (Paper 1 ("Pet.").) Patent Owner, The Johns Hopkins University, filed a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). (Paper 5 ("Prelim. Resp.").) In addition, as authorized (*see* Ex. 3001), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (Paper 8) and Patent Owner filed Patent Owner's Sur-Reply (Paper 10). We granted the Petition and instituted an *inter partes* review. (Paper 11 ("Decision" or "Dec.").)

During trial, Patent Owner filed a Patent Owner Response to the Petition (Paper 35 (confidential Paper 32) ("PO Resp.")), Petitioner filed a Reply (Paper 53 (confidential Paper 50) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 57 (confidential Paper 54) ("PO Sur-reply"). The parties declined to present oral arguments in this proceeding. (*See* Paper 58.)

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

determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–8 of the '219 patent are unpatentable.

A. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. (*See* Pet. 55.) Patent Owner identifies The Johns Hopkins University as its real party-in-interest. (*See* Paper 3, 1.)

B. Related Matters

Both Petitioner and Patent Owner report that the litigation *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), is a related matter. (*See* Pet. 55; Paper 4, 1.)

In addition, several other *inter partes* reviews are related to this proceeding, including IPR2024-00622, challenging the claims of U.S. Patent No. 10,934,356; IPR2024-00623, challenging claims of U.S. Patent No. 11,325,974 B2; IPR2024-00624, challenging the claims of U.S. Patent No. 11,325,975 B2; IPR2024-00647, challenging claims of U.S. Patent No. 11,649,287 B2; IPR2024-00648, challenging claims of U.S. Patent No. 11,643,462 B2; IPR2024-00649, challenging claims of U.S. Patent No. 11,629,187 B2; IPR2024-00650, challenging claims of U.S. Patent No. 11,634,491 B2.

IPR2024-00240 is also related. Claims 1–42 of U.S. Patent No. 11,591,393 B2 were held to be unpatentable in that proceeding. (*See Merck*

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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 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.

Sharp & Dohme, LLC v. The Johns Hopkins Univ., IPR2024-00240, Paper 90 (PTAB June 9, 2025), Final Written Decision.) Patent Owner's request for Director Review of that decision was denied. (*Id.*, Paper 93.)

C. The '291 Patent

The application that became the '291 patent was filed on December 22, 2020, claiming priority to a number of continuation applications and also to provisional application 62/190,977, which was filed July 10, 2015. (*See* Ex. 1001, codes (22), (60).) The '291 patent cites another provisional application, filed November 13, 2014, but Patent Owner claims priority only to July 10, 2015. (*See* PO Resp. 5, n.3.)

The '291 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor, in several different types of cancer patients. (*See* Ex. 1001, Abstract.) More specifically, the '291 patent is directed to treating cancer patients with high mutational burdens, such as found in microsatellite instable (MSI) cancer, with anti-PD-1 antibodies. (*Id.* at 3:35–49.) The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in a clinical trial. (*Id.* at 8:50–54.)

Claim 1 of the '291 patent recites:

> A method for treating cancer in a patient in need thereof comprising:
>
> selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor, and
>
> 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 a MSI-high or a MMR deficiency status.

(*Id.* at 25:32–26:8.)

The parties refer to the term "microsatellite instability high" as "MSI-H" and the term "mismatch repair deficient" as "dMMR." The parties agree that testing a tumor to determine whether it is either MSI-H or dMMR is considered the equivalent of testing for the other condition, and refer most often to MSI-H as the identified condition. (*See* Pet. 6; PO Resp. 5, n.2.)

D. Evidence

Petitioner relies, *inter alia*, on the following evidence in the grounds of challenge.

Name	**Reference**	**Exhibit**
MSR (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	1005
Pernot	Pernot et al., *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) WORLD J. GASTROENTEROLOGY 3738 (April 2014)	1006
Chapelle	Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. CLINICAL ONCOLOGY 3380 (2010)	1007
Benson	Benson et al., *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. NAT'L COMPREHENSIVE CANCER NETWORK 1028 (July 2014)	1009
Hamid	Hamid et al., *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) NEW ENG. J. MEDICINE 134 (July 2013)	1011
Brown	Brown et al., *Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival*, 24 GENOME RESEARCH 743	1034

	(May 2014)	
Duval	Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROC. NAT'L ACAD. SCI. 5002 (April 2004)	1087

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–8 are unpatentable on the following grounds:

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1–4, 6–8	102	MSR
2	1–4, 6–8	103	MSR, Pernot, Benson
3	5	103	MSR or MSR, Pernot, Benson, and Chapelle
4	1–4, 6–8	103	MSR, Brown, Duval, and Benson
5	5	103	MSR, Brown, Duval, Benson, and Chapelle
6	8	103	MSR or MSR, Pernot, Benson, Chapelle, and Hamid
7	8	103	MSR, Brown, Duval, Benson, Chapelle, and Hamid

[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 '291 patent claims priority. Therefore, we apply the AIA versions of Sections 102 and 103.

II. ANALYSIS

A. Legal Standards

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

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

> if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.

Obviousness is determined by looking to the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art resolved. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). "[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged

claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

B. Level of Ordinary Skill in the Art and Declarants

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

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would have been a medical doctor, or a professional in a related field, with experience treating cancer or access to those with experience in clinical studies of therapeutics and to a pathologist with this experience. (*See* Pet. 12 (citing Ex. 1003 ¶ 19).) To Patent Owner, 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. (*See* 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 '219 patent claims a method of treating a human patient with colorectal cancer having certain characteristics using pembrolizumab and the

main prior art reference cited by Petitioner discloses testing pembrolizumab to treat human patients. (*See* Ex. 1001, 25:35–36, Ex. 1005.) Accordingly, the relevant field of Patent Owner's claims is treating human patients for colorectal 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 '291 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.

C. 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.").

D. Ground 1: Anticipation over the MSR

Petitioner argues that claims 1–4 and 6–8 are anticipated under 35 U.S.C. § 102 by the MSI-H Study Record. (*See* Pet. 15–26.)

1. MSI-H Study Record ("MSR")

The MSR 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 MSR was published on a government web site on June 10, 2013, more than two years before the priority date of the '219 patent on July 10, 2015. (*See* Pet. 7 (citing Ex. 1005, 3, Ex. 1003 ¶ 36).)

> The MSR 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 MSR are "[i]mmune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" (Ex. 1005, 4–5.) The MSR 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. (*See* Pet. 6 (citing, e.g., (Ex. 1018, 293 ("MSIH (MSI high) was considered MSI positive and MSS (MS stable)"); Neugut Decl., Ex. 1003 ¶ 26).) 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.*)

2. Claim 1

a) Preamble: "[a] method for treating cancer in a patient in need thereof comprising"

Petitioner cites the teaching in the Arms and Interventions section as a method of treating cancer patients, as recited in the preamble of claim 1. (*See* Pet. 18–19 (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 ¶ 58).)

Patent Owner does not raise any arguments regarding this limitation, and neither party argues that the preamble is limiting. To the extent that the preamble is limiting, we agree with Petitioner that the MSR teaches the preamble.

b) Element 1.1: "selecting a patient who has an unresectable or metastatic,"

Petitioner argues that the limitation in claim 1 of "selecting a patient who has an unresectable or metastatic" tumor, is taught in the MSR because the MSR teaches that the patients treated have "tumors" and "measurable

disease." (*See* Pet. 19 (citing Ex. 1005, 5 (Eligibility).) Petitioner relies on Dr. Neugut's testimony that these patients would have metastatic and advanced cancers. (*See* Ex. 1003 ¶¶ 59–63.) Dr. Neugut testifies that, in the context of the MSR, advanced cancer refers to metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. (*See* Ex. 1003 ¶ 59 (citing Ex. 1078, 1278 ("Advanced colorectal cancer can be defined as colorectal cancer that at presentation or recurrence is either metastatic or so locally advanced that surgical resection is unlikely to be carried out with curative intent.").) Dr. Neugut testifies further that clinical trials that involve "measurable" colorectal cancer in the context of the MSR would not include cancer that is resectable for the purposes of a cure because the patient could be cured by surgery and a practitioner would excise the tumor as the only way to achieve a cure. (*See* Neugut Decl. ¶ 60 (citing Ex. 1020, 7 (providing chemotherapy for advanced or metastatic disease only when the cancer is "locally unresectable or medially inoperable").) According to Dr. Neugut, it would be highly unusual if the MSR 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 ¶ 61.) Dr. Neugut concludes that "the person of ordinary skill would have concluded that a method [of] treating patients who had metastatic and advanced cancer is found in the MSI-H Study." (Ex. 1003 ¶ 63.)

Dr. Neugut further cites references that indicate those of ordinary skill in the art considered the MSR to include patients with metastatic colorectal cancer. (*See id.* ¶ 62 (citing Ex. 1049, 444).) Specifically, one 2015 publication refers to the clinical trial number of the MSR and states:

"pembrolizumab is being tested in metastatic tumors with microsatellite instability, including colorectal cancer (NCT01876511)." (Ex. 1049, 444.) Another 2015 publication, entitled "Novel Therapies in Development for Metastatic Colorectal Cancer," refers to the MSR ("NCT01876511") as a "Phase II clinical trials in development investigating immunotherapy in MSI-H mCRC," wherein "mCRC" is defined as metastatic colorectal cancer. (Ex. 1050, S2, S4.)

Patent Owner argues that "measurable disease" is very different from the "metastatic cancer" required in claim 1. (*See* PO Resp. 6.) Patent Owner argues that "measurable disease" in the context of cancer means only that the cancer has a minimum size, not that it is metastatic, which Patent Owner argues was conceded by Petitioner's witness, Dr. Neugut. (*See* PO Resp. 7 (citing Ex. 1048, 230–31, Ex. 2163, 14:9–15:12; Ex. 2072 ¶¶ 96–100).)

Patent Owner argues further that the missing disclosure of "unresectable or metastatic" cancer in the MSR cannot be cured by attorney argument, because the law "does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them." (*See* PO Resp. 7 (citing *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274–75 (Fed. Cir. 2017).) Patent Owner cites Benson as explaining that "when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy," that "NCCN [provider of the guidelines] believes that the best management for ***any cancer patient*** is in a clinical trial," and that "[p]articipation in clinical trials is especially encouraged." (Ex. 1009, 1, 2; *see* PO Resp. 8.) According to Patent Owner, this means that a patient could

have been enrolled in the MSR, even with tumor that was not unresectable or metastatic and, thus, this limitation is not inherent to the MSR. (*See* PO Resp. 8–9.)

"In an anticipation analysis, the dispositive question is whether a skilled artisan would 'reasonably understand or infer' from a prior art reference that every claim limitation is disclosed in that single reference." *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020). Extrinsic evidence, such as declarations and depositions may be considered when it is used to explain, but not expand, the meaning of a reference. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (holding that the depositions and declarations of skilled workers were properly used to show what those skilled in the art would have known about the prior art). Although Patent Owner argues that a missing element cannot be filled by what an ordinarily skilled artisan would have envisioned, Petitioner's argument is based on what one of ordinary skill in the art would have understood from what the MSR expressly teaches. (*See* Pet. 20 ("Indeed, prior art concerning the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had 'metastatic tumors.' (EX1049, 444; *see also* EX1050, S4; EX1003, ¶62.)").) Unlike the facts of *Nidec*, where a missing signal could have been envisioned but was not present, we are persuaded by the evidence Petitioner presents that those of ordinary skill in the art understood the MSR express disclosure to include patients with unresectable or metastatic tumors because references referring to the study underlying the MSR discuss the inclusion of patients with metastatic tumors in the study.

Even if Dr. Neugut's reasoning that the reference to "measurable" disease in the MSR would have indicated patients having metastatic cancer is flawed, we are persuaded by Petitioner's evidence of publications referring to the MSR as a study of metastatic colorectal cancer, and we are further persuaded that one of ordinary skill in the art would have understood the MSR to disclose treating patients having metastatic colorectal cancer with pembrolizumab. (*See* Ex. 1049, 444, Ex. 1050, S4.) Patent Owner does not address this evidence. Instead, Patent Owner acknowledges that "the MSR discloses treating cancer patients ***that could*** be within the claimed subset," but argues that the MSR does not inherently anticipate results later obtained by treating *only* patients within the claimed subset. (*See* Pet. Sur-Reply 5–6.) We are persuaded, though, that Petitioner's challenge is based on what one of ordinary skill in the art would have understood from the MSR (that patients who had an unresectable or metastatic tumor were selected), not on what is inherent to the disclosure of the MSR.

We are persuaded that one of ordinary skill in the art at the time would have understood the MSR to teach selecting a patient "who has an unresectable or metastatic," as required in claim 1.

c) *Element 1.2: "microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor, and"*

Petitioner argues that the MSR teaches selecting patients with a "microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor" because the MSR discloses three study arms, including one arm with patients having MSI-H colorectal cancer and another arm with patients having MSI-H non-colorectal cancer. (*See* Pet. 21–23 (citing Ex. 1005, 4 (Arms and Interventions)).) Dr. Neugut's testimony supports this argument. (*See* Ex. 1003 ¶¶ 64–68.) Dr. Neugut testifies that the

patients determined to have defective MMR (dMMR) status are biologically the same as patients with MSI-H status. (*See* Ex. 1003 ¶ 66 (citing Ex. 1020, 51 ("Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.")).)

Patent Owner does not dispute that the MSR teaches selecting a patient who has a tumor characterized as MSI-H or MMR deficient.

The arguments and evidence that Petitioner cites persuade us that the MSR teaches this element of claim 1.

d) Element 1.3: "administering an effective amount of pembrolizumab to the patient"

Petitioner argues that the MSR teaches treating patient populations having both MSI-H colorectal cancer and MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days, which is a teaching of administering an effective amount of the drug to a patient. (*See* Pet. 23 (citing Ex. 1005, 4).) Dr. Neugut's testimony supports Petitioner's argument that the dose taught in the MSR is identical to the dose described as being effective in the '219 patent. (*See* Pet. 23 (citing Ex. 1003 ¶¶ 69–73); *see* Ex. 1001, 4:19–32, 8:48–54, 13:22–28, 16:1–8, 16:60–17:3, 19:55–21:20, Figures 2, 11.) Petitioner argues further that any efficacy required in the claim is inherent to that dosage because the '219 patent shows that dosage to be effective. (Pet. 23 (citing Ex. 1003 ¶ 70).)

Patent Owner argues that one of ordinary skill in the art would not have known whether the amount of pembrolizumab taught in the MSR would be effective in MSI-H/dMMR patients because the MSR does not provide results. (*See* PO Resp. 9–16.) According to Patent Owner, the MSR fails to inherently teach the effective amount of pembrolizumab because it is merely a study proposal. (*See id.* at 9–10.) Patent Owner does not dispute

that the MSR discloses an amount of pembrolizumab that is effective at achieving the therapeutic results (an improved outcome in a selected patient compared to a reference patient), as required in the '219 patent.

As discussed in detail below, we are not persuaded that the lack of results in the MSR prevents the MSR from inherently anticipating claim 1. Instead, we are persuaded by Petitioner's argument that because the MSR teaches an amount of pembrolizumab that was shown to be effective, the limitation of "administering an effective amount of pembrolizumab to the patient" is disclosed by the MSR.

e) Element 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 a MSI-high or a MMR deficiency status."

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. (*See* Pet. 25–26 (citing Ex. 1003 ¶¶ 40–41, 69–76).) Petitioner argues that the MSR teaches actively measuring specific outcomes in patients having an MSI-H tumor and a non-MSI-H or non-dMMR tumor. (*See* Pet. 26 (citing Ex. 1003 ¶ 75).) In support, Dr. Neugut testifies that the examples, tables, and figures of the '219 patent discuss the design and results of the MSI-H Study, as explained in an affidavit submitted by the inventors during prosecution on February 4, 2022. (*See* Ex. 1003 ¶¶ 40–41, 74– 76, (citing Ex. 1001, 3:16–18, 6:48–22:15, Figures 1–13; Ex. 1005; Ex. 1002, 295–96 (February 4, 2022, Affidavit ¶¶ 22–23)).)

Specifically, Dr. Pardoll, a named inventor on the '219 patent, cited to "Exhibit D," the MSR, in his prosecution affidavit. (*See* Ex. 1002, 361; *compare* Ex. 1005.) Dr. Pardoll testified:

> 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, 295–96.) The affidavit supports Petitioner's argument that the improved outcome of treating a patient with a tumor exhibiting an MSI-high or an MMR deficiency status with pembrolizumab, compared to similarly treating a patient without an MSI-high or an MMR deficiency status is an inherent result because the treatment would necessarily provide the result.

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 ['219 patent] is irrelevant." (Pet. 26 (citing *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003).)

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. (*See* PO Resp. 9–16.) 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. (*See* PO Resp. 10–11; 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 MSR does not disclose treating a cancer patient with pembrolizumab when the patient has "unresectable or metastatic" MSI-H cancer. (*See* PO Resp. 11; PO Sur-Reply 2.) As discussed above, though, we are persuaded by the statements in contemporaneous references citing the MSR that one of ordinary skill in the art would have understood the study to involve patients with "unresectable or metastatic" MSI-H cancer. (*See* 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 argues further that because the MSR 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; *see* 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 MSR 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. 12–14; *see* Ex. 2072 ¶ 108; Ex. 2130 ¶¶ 10–13.)

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded. But knowledge of the results is not a component of the analysis of anticipation. *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 Kris. 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 MSR, 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 without a tumor that was not MSI-H or dMMR, and Patent Owner does not dispute that the amount of pembrolizumab disclosed in the MSR (10 mg/kg every 14 days; *see* Ex. 1005, 4) is the same as the amount provided in the '219 patent as being effective (10 mg/kg every 14 days; *see* Ex. 1001, 8:48-54, 13:22–28).

Regardless of the inventors' intent in publishing the MSR as a Stage II clinical trial on the www.clinicaltrials.gov website, as discussed above, we determine that the MSR 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 MSR 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 MSR discloses selecting a patient with a condition recited in claim 1 and treating with the drug at the amount 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. (*See* PO Resp. 14.) But because we find that

the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H cancer, we are persuaded that the MSR 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 MSR could have provided results or was sufficient for full regulatory approval does not change that the MSR teaches Patent Owner's claimed steps. We have no reason to doubt that the disclosure in the MSR of the steps recited in claim 1 produces the efficacy element required in claim 1, whether or not this efficacy was disclosed in the MSR or was known when it was published. *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 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. (*See* PO Resp. 15–16; PO Sur-Reply 4–5.) Patent Owner asserts that if its inventors had filed a "data-less provisional application mirroring the MSR" before the MSR 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. (*See* PO Resp. 15.)

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 (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*, 21 USPQ2d 1892 (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. 26 (citing *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003).) According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the '219 patent is irrelevant. (*See* Pet. 26.)

Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSR 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 MSR, 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. (*See* 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 MSR was published before the inventors filed an application to protect their patent rights, the MSR 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 MSR discloses an experimental use that does not qualify as prior art. (*See* PO Resp. 16–23.) Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. (*See id.* at 16 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998).) According to Patent Owner, the experimental use negation applies to the MSR under a 13-factor analysis provided in *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002). (*See* PO Resp. 17–23.) 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 MSR on the government website under federal law. (*See* PO Resp. 18–20.) 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. (*See id.* at 19–20.) 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 21.)

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 MSR 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 MSR 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 MSR.

3. Claims 2–4 and 6–8

Petitioner argues that claims 2–4 and 6–8 are anticipated by the MSR. (*See* Pet. 26–30.) Patent Owner presents the arguments discussed above regarding the limitations of claim 1, but does not present arguments or direct us to evidence against these challenges that are specific to the limitations of dependent claims 2–4 and 6–8.

Both claims 2 and 3 further limit the outcome exhibited by the patients selected and administered pembrolizumab, as recited in claim 1. (*See* Ex. 1001, 26:9–16.) Specifically, claims 2 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," and claim 3 recites "[t]he method of claim 2, wherein the ORR is an immune-related ORR (irORR), or wherein the PFS is an immune-related progression-free survival (irPFS)." (*Id.*)

Petitioner argues that these outcomes are inherent to the methods taught in the MSR. (*See* Pet. 26–28 (citing Ex. 1003 ¶¶ 77–80).) We agree with Petitioner because, as discussed above, we are persuaded that the steps recited in claim 1 are taught by the MSR 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.

Claims 4 recites "[t]he method of claim 2, wherein the outcome is assessed in the patient within approximately 20 weeks after administering pembrolizumab." (Ex. 1001, 16–18.) Petitioner cites the Primary Outcomes Measure section the MSR, which discloses one measure as being

"[i]mmune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)" and another measure as being "[o]bjective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)." (Ex. 1005, 4; *see* Pet. 28.) Petitioner argues that this disclosure reads on this limitation because it discloses measuring the relevant outcomes at 20 weeks. (*See* Pet. 28 (citing Ex. 1003 ¶¶ 81, 82).) We agree.

Claim 6 recites "[t]he method of claim 1, wherein the cancer is a metastatic cancer." and claim 7 recites "[t]he method of claim 1, wherein the cancer is a metastatic colorectal cancer." (Ex. 1001, 29–32.) Petitioner cites to evidence, as discussed above, that physicians understood the MSR to indicate patients had metastatic colorectal tumors. (*See* Pet. 29 (citing Ex. 1049, 444; Ex. 1050, S4; Ex. 1003, ¶¶ 59–63, 83, 84).) As discussed above, we agree with Petitioner that the references to the study described in the MSR indicate one of ordinary skill in the art would have understood the MSR to include patients with metastatic tumors. Accordingly, we agree with Petitioner that the methods of claims 6 and 7 are anticipated by the MSR.

Claim 8 recites "The method of claim 1, wherein pembrolizumab is administered by intravenous infusion." (Ex. 1001, 26:33–34.) Petitioner argues that the prior art, including the pembrolizumab package insert, demonstrates that pembrolizumab was administered intravenously for the

treatment of cancer. (*See* Pet. 30 (citing Ex. 1055,[4] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."), Ex. 1003, ¶ 85.) We are persuaded by Petitioner's evidence that claim 8 is anticipated by the MSR.

4. Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of claims 1–4 and 6–8. Accordingly, we determine that claims 1–4 and 6–8 are anticipated by the MSR.

E. Grounds 2 and 4: Obviousness of claims 1–4 and 6–8

Petitioner argues that the same claims challenged under Ground 1 as being anticipated by the MSR would also have been obvious over the MSR, Pernot, and Benson (Ground 2) or over Brown, Duval, and Benson (Ground 4). (*See* Pet. 34–41 and 43–49.) Petitioner states that Grounds 2 and 4 are presented as an alternative to the challenge in Ground 1 that claims 1–4 and 6–8 are anticipated by the MSR. (*See* Pet. 34, 43.)

In regard to Ground 2, Petitioner cites Pernot as teaching that colorectal cancer patients are good candidates for immunotherapy, such as the PD-1 inhibitor pembrolizumab, to address the expectation of success in the method of claim 1. (*See* Pet. 31 (citing Ex. 1006, 3741).) Pernot states "[colorectal cancers] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena,

[4] Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf. (September 4, 2014) (Ex. 1055.)

making them good candidates for immunotherapy." (Ex. 1006, 3740–41; *see* Pet. 31.) Petitioner argues, citing Dr. Neugut's testimony, that Pernot would have motivated one of ordinary skill in the art to obtain the results of the MSI-H Study Record. (*See* Pet. 34–36 (citing Ex. 1003 ¶ 93).)

Petitioner cites Benson as teaching that, under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (*See* Pet. 40 (citing Ex. 1009, 1034; Ex. 1003 ¶ 100).)

In regard to Ground 4, challenging the patentability of claims 1–4 and 6–8, Petitioner cites to Brown, Duval, and Benson, in addition to the MSI-H Study Record. (*See* Pet. 43–49.) 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. (*See* Pet. 44 (citing Ex. 1034, 747).) Petitioner argues further that Duval teaches that MSI-H cancers have cells that are easy for immune cells to recognize. (*See* Pet. 44 (citing Ex. 1087, 5002).) Dr. Neugut's testimony supports Petitioner's argument that Brown and Duval would have motivated a person of ordinary skill in the art to obtain the results of the MSR. (*See* Ex. 1003 ¶¶ 110, 112, 114; *see* Pet. 44.)

Patent Owner argues that the MSR does not anticipate the challenged claims and that neither Pernot nor Benson supplies limitations that Patent Owner asserts are "missing" from the MSR. (*See* PO Resp. 23.) Specifically, Patent Owner argues that the MSR does not teach the limitation of "unresectable or metastatic" MSI-H cancer or the limitation of improved outcome in MSI-H patients, deficiencies that are not cured by the other cited prior art. (*See id.* (citing Ex. 2072, ¶¶ 122–170).)

As discussed above, we are not persuaded that the MSR fails to teach the limitations Patent Owner cites, or any other limitations of claims 1–4 and 6–8, because we are persuaded that the MSR anticipates claims 1–4 and 6–8. As discussed above, we determined that claims 1–4 and 6–8 are anticipated by the MSR. Therefore, they would have been rendered obvious by the MSR as well. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("It is well settled that 'anticipation is the epitome of obviousness.' [citations omitted]").

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. (*See* PO Resp. 49–87.) The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. (*See id.*) Because we determine, as discussed above, that the method recited in independent claim 1 is anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of 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 2–4 and 6–8, which we determine are anticipated by the MSR.

Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1–4 and 6–8 as being obvious over the MSR alone or along with other references cited in Grounds 2 and 4.

F. Grounds 3 and 5: Obviousness of claim 5.

Grounds 3 and 5 challenge the patentability of claim 5, which recites:

> The method of claim 1, wherein the unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor exhibits instability in a microsatellite marker, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, or
>
> wherein the unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor exhibits a deficiency of a mismatch repair marker is POLE, POLDI, or MYH.

(Ex. 1001, 26:19–28.) In Grounds 3 and 5, Petitioner argues, relying on Dr. Neugut's testimony, that Chapelle teaches standard methods of testing whether a tumor is MSI-H, including determining whether the patient's tumor exhibits instability in a microsatellite marker, such as BAT-25 or BAT-26. (*See* Pet. 42 (citing Ex. 1007, 3380, 3383; Ex. 1003 ¶ 107).) For example, Chapelle states that "'a standard test' using a '[p]anel consisting of … BAT26, BAT25' has 'stood the test of time.'" (Ex. 1007 at 3382.) Dr. Neugut testifies that one of ordinary skill in the art would have been motivated to treat a patient with an unresectable or metastatic MSI-H dMMR tumor, wherein the tumor exhibits instability in the BAT-25 and BAT-26 microsatellite marker, and would have expected success in doing so, in light of the teachings of Chapelle. (*See* Ex. 1003 ¶¶ 105–108.)

We find that the record as recounted above supports Petitioner's challenges of claim 5 in Grounds 3 and 5.

Patent Owner does not raise specific arguments against the obviousness of claim 5 and does not direct us to specific evidence demonstrating that a method using the recited microsatellite markers would not have been obvious to one of ordinary skill in the art. Regarding claim 5, Patent Owner only argues that:

> The prior art in Grounds 3 and 5-7 does nothing to fill the Petition's deficiencies regarding either the treating "unresectable or metastatic cancer," 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 '219 Patent.

(PO Resp. 48.) As discussed above, we are persuaded that the MSR is not deficient as anticipatory prior art because it fails to teach selecting patients with "unresectable or metastatic cancer" or providing an "outcome that is improved." Thus, we are not persuaded that any of the grounds of challenge fail if the additional references Petitioner cites do not teach the elements of "unresectable or metastatic cancer" or an "outcome that is improved."

Patent Owner raises arguments against Petitioner's reliance on the prior art references in addition to the MSR, but because we are persuaded that the MSR anticipates, and therefore renders obvious the limitations of claim 1, we are not persuaded by these arguments. For example, Patent Owner argues that Pernot fails to teach or suggest treating MSI-H patients with pembrolizumab or any other PD-1 inhibitor and that Brown does not disclose a connection between the efficacy of PD-1 inhibitors and a patient's MSI-H status. (*See* PO Resp. 25–26 (citing Ex. 2072 ¶¶ 118, 119, 140–142.) Patent Owner argues further that Duval supports the hypothesis that MSI-H tumors are non-immunogenic and that these patients are poor candidates for immunotherapy, rather than providing an expectation of success in achieving the outcome recited in the challenged claims. (*See* PO Resp. 27–28 (citing Ex. 2072 ¶ 120).) Because the MSR teaches selecting a patient as recited in claim 1 and administering pembrolizumab as recited in claim 1, even if Patent Owner is correct about the teachings of Pernot, Brown, and Duval, claim 5 is unpatentable as being obvious because the MSR teaches the

elements of claim 1 and we are persuaded that Chapelle discloses methods for testing whether a tumor is MSI-H, including by determining whether the tumor exhibits instability in the microsatellite marker BAT-25 or BAT-26.

Similarly, Patent Owner argues that Petitioner applies the wrong legal standard regarding a reasonable expectation of success in the methods of claim 1, but because, as discussed above, we are persuaded that the steps of claim 1 are expressly taught in the MSR, 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 of such treatment being inherent. (*See* PO Resp. 29–48.) Patent Owner does not argue that one of ordinary skill in the art would not have had a reasonable expectation of success in a method wherein an MSI-H tumor exhibits instability in the BAT-25 or BAT-26 marker, as recited in dependent claim 5. Because we are persuaded by the evidence Petitioner presents regarding claim 1, we are persuaded that Petitioner has met its burden of presenting a *prima facie* case for the obviousness of claim 5.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. (*See* PO Resp. 49–87.) The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. (*See id.*) Because we determine, as discussed above, that the method recited in independent claim 1 is anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of the subject matter recited in 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.").

In order to show that objective evidence renders the method of claim 5 non-obvious, Patent Owner must show a nexus between the subject matter recited in claim 5 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 argues that there is a nexus between the development and commercialization of pembrolizumab and the patented method of treatment recited in the challenged claims, citing, *inter alia*, the package insert for Keytruda® (pembrolizumab), but Patent Owner does not direct us to evidence of a nexus to MSI-H or MMR deficient tumors that exhibit instability in the microsatellite markers recited in claim 5 and the unexpected results, commercial success, or other objective measures of non-obviousness flowing from these additional limitations. (*See* PO Resp. 50–63 (citing Ex. 2129, Ex. 2072 ¶ 190, Ex. 2090 ¶¶ 82–92).) Patent Owner directs us only to evidence regarding determining MSI-H status and then using Keytruda® to treat MSI-H cancer patients, which we determine to be anticipated by the MSR. (*See* PO Resp. 60.)

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 id.* 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 method 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 any dependent claim. For example, Patent Owner fails to direct us to evidence that a method of treating cancer in a patient "wherein the unresectable or monitoring tumor burden in melanoma patients undergo metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor exhibits instability in a

microsatellite marker, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24," as recited in claim 5, demonstrated unexpected results or commercial success.

Following a review of the evidence, including Patent Owner's evidence of secondary considerations with regard to the subject matter of claim 1, we conclude that Petitioner has demonstrated by a preponderance of the evidence that the method of claim 5 would have been obvious. Grounds 6 and 7: Obviousness of claim 8.

Grounds 6 and 7 challenge the patentability of claim 8, which recites: "The method of claim 1, wherein pembrolizumab is administered by intravenous infusion." (Ex. 1001, 26:33–34.)

As discussed above, we are persuaded that the MSR anticipates the method of claim 8 because Petitioner demonstrates that pembrolizumab was administered intravenously for the treatment of cancer, as evidenced by the package insert. (*See* Ex. 1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003, ¶ 85.) Because "'anticipation is the epitome of obviousness,'" the preponderance of the evidence supports Petitioner's challenge of claim 8 as being obvious. *In re McDaniel*, 293 F.3d at 1385.

In the alternative, we are persuaded by Petitioner's arguments in Grounds 6 and 7 that Hamid teaches administering pembrolizumab (called "lambrolizumab") intravenously. (Pet. 50 (citing Ex. 1011, 134; Ex. 1003 ¶ 130–134).) Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have been motivated to combine the teachings of the MSR and other references with Hamid because the MSR discloses administering pembrolizumab, Hamid demonstrates success in

treating patients with advanced cancer with pembrolizumab, and the prior art only discloses intravenous administration of pembrolizumab to treat cancer patients. (*See* Pet. 50 (citing Ex. 1011, 134; *see also* Ex. 1055, 1, Ex. 1003 ¶¶ 132–133).) Petitioner argues that one of ordinary skill in the art would have had a reasonable expectation of success in administering pembrolizumab intravenously, given that administering pembrolizumab intravenously had been successful in the past. (*See id.*)

Patent Owner does not argue or direct us to evidence to the contrary. Patent Owner also fails to present objective evidence of non-obviousness that demonstrates a nexus to intravenous administration of pembrolizumab as recited in claim 8. (*See* PO Resp. 50–63.) 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 MSR. As discussed above, we are not persuaded by this evidence that the method of claim 8 would not have been obvious because the evidence Patent Owner cites is related only to what was known in the prior art and is of no relevance to the obviousness inquiry of Grounds 6 and 7. *See Yita*, 69 F.4th at 1363–65; *Ethicon Endo-Surgery, Inc. v. Covidien LLp*, 812 F.3d 1023, 1034 (Fed. Circ. 2016).

We find that the record supports Petitioner's arguments in regard to the challenges of claim 8 in Grounds 6 and 7.

III. CONCLUSION[5]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–8 of the '219 patent are unpatentable.

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1	102	MSR	1–4, 6–8	
2	103	MSR, Pernot, Benson	1–4, 6–8	
3	103	MSR, or MSR, Pernot, Benson, and Chapelle	5	
4	103	MSR, Brown, Duval, and Benson	1–4, 6–8	
5	103	MSR, Brown, Duval, Benson, and Chapelle	5	
6	103	MSR, or MSR, Pernot, Benson, Chapelle, and Hamid	8	
7	103	MSR, Brown,	8	

[5] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
		Duval, Benson, Chapelle, and Hamid		
Overall Outcome			1–8	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–8 of the '219 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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