ADDENDUM INDEX

Johns Hopkins University v. Merck Sharp & Dohme LLC
Nos. 26-1020, 26-1021, 26-1184, 26-1185, 26-1188, 26-1189, 26-1209, 26-1210, 26-1211

U.S. Patent No. 11,643,462 B2	Appx793-826
U.S. Patent No. 11,629,187 B2	Appx827-859
U.S. Patent No. 11,634,491 B2	Appx860-893

Trials@uspto.gov
571-272-7822

Paper 53
Date: September 23, 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.

IPR2024-00647
Patent 11,649,287 B2

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

SNEDDEN, *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 1–36 of U.S. Patent No. 11,649,287 B2 (Ex. 1001, "the '287 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '287 patent. Paper 3. Patent Owner did not file a Preliminary Response.

We instituted trial on September 27, 2024. Paper 6 ("Inst. Dec."). During trial, Patent Owner filed a Patent Owner Response. Paper 29 (confidential Paper 25) ("PO Resp."). Petitioner filed a Reply (Paper 46 (confidential Paper 43) ("Pet. Reply")) and Patent Owner filed a Sur-reply (Paper 51 (confidential Paper 48) ("PO Sur-reply")). The parties declined to present oral arguments in this proceeding. Paper 50.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 65. Patent Owner identifies Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '287 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. 65; Paper 3, 1. Petitioner has also filed

petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 65; Paper 3, 1.

D. The '287 patent (Ex. 1001)

The '287 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '287 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.*, Abstract. More specifically, the '287 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.*, 3:38–53. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:32–34.

The '287 patent explains that

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

Id., 1:55–62. According to the '287 patent, "[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate

with poor prognosis and survival in various cancer types." *Id.*, 2:6–5. However, the specification describes that

> in reports of the effects of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment, . . . What was different about this single patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id., 2:63–3:6. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '287 patent describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id.*, 3:14–21. The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id.*, 8:52–56. According to the '287 patent, "[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors." *Id.*, 6:52–56.

E. The Challenged Claims

Petitioner challenges claims 1–36. Representative independent claim 1 is reproduced below:

> 1. A method for treating colorectal cancer in a human patient, the method comprising:
>
> in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA

mismatch repair deficient with a therapeutically effective amount of pembrolizumab,

wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.

Ex. 1001, 24:42–52.

Representative independent claim 11 is reproduced below:

11. A method for reducing the risk of progression of colorectal cancer in a human patient, the method comprising:

in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,

wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.

Id. at 25:8–19.

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" or "MSR").

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. 1008, Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) ("Steinert").

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").

Petitioner also relies on the Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150) to support its contentions.

Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072), Dung Le, M.D. (Ex. 2130) and Richard Goldberg, M.D. (Ex. 2090).

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–36 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 2, 4–8, 11, 12, 14–18, 21–36	102	MSI-H Study Record
II	1, 2, 4–8, 11, 12, 14–18, 21–36	103	MSI-H Study Record, Pernot
III	2, 9, 10, 12, 19, 20	103	MSI-H Study Record, Pernot, Chapelle
IV	3, 13	103	MSI-H Study Record, Pernot, Steinert
V	6, 7, 16, 17, 26, 28, 30–36	103	MSI-H Study Record, Pernot, Benson
VI	8, 18	103	MSI-H Study Record, Pernot, Hamid

H. Claim Construction

We construe claims "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." 37 C.F.R. § 42.100(b) (2020).

Claim 1 requires treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient . . . ." Ex. 1001, 24:42–52. Petitioner argues that the discussion in the MSR of treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. *See* Pet. 19 (citing Ex. 1005, 2–5). For the purposes of our decision whether to institute review, we interpreted the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients. Inst. Dec. 17 n.3.

Patent Owner argues that our construction "disregards the critical ***causal*** relationship between 'determining' and 'treating' steps expressed by the claims," wherein the causal relationship establishes that "***only*** CRC patients determined to be MSI-H are treated." PO Resp. 5. According to Patent Owner, the construction of "in response to" should be that the phrase means "in reaction to." *Id.* at 5.

Patent Owner argues that if the inventors had intended the claimed method to encompass merely treating patients "after" a determination of the patient's MSI-H status, they would have used the word "after" in their claims, citing use of the word "after" in other claims. *Id*. at 6. Because the cited language is in claims that depend on claim 1, Patent Owner argues that the term "in response to" must have a different meaning from "after." *Id*.

Patent Owner argues further that the Specification of the '287 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H. PO Resp. 7. Specifically, Patent Owner cites the disclosure in the '287 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. Ex. 1001, 3:58–60.

According to Patent Owner, one of ordinary skill in the art would have understood from this distinction in recommended treatments that "in response to" describes administering the claimed treatment only as a reaction to the determination that the patient's cancer is MSI-H. PO Resp. 7. According to Patent Owner, "[t]he contrary view advanced by the Board

improperly renders meaningless the 'in response to' step of the claim." *Id.* Patent Owner argues further that under our initial construction, "the claims would cover treatment administered to MSI-H patients for any reason or no reason at all—even accidental treatment would be covered. Such a reading is entirely inconsistent with the teaching of the specification." *Id.*

We agree with Patent Owner that the phrase "in response to" in claim 1 requires a causal relationship wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is treated with 10 mg/kg of pembrolizumab every 14 days. In claim 1, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having colorectal cancer to determine that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the art anticipates claim 1. We are not persuaded that claim 1 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment *only* as a reaction to the determination that the patient's cancer is MSI-H, and that, if treatment were administered to patients for any other reason after testing confirmed that the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the term "in response to" would be

meaningless. PO Resp. 7. But, as Petitioner argues, claim 1 does not exclude treatment of other patients who are not MSI-H or dMMR, if the colorectal cancer patient from whom the biological sample is obtained and tested is determined not to be microsatellite instability high or mismatch repair deficient. *See* Pet. Reply 9 ("JHU advocates for a construction that excludes a treatment in which pembrolizumab is administered to patients that do not have MSI-H. Such unclaimed negative limitations should not be read into claim terms."). Claim 1 does not mention any other patients or define patient populations to be excluded from treatment. Claim 1 provides that if the colorectal cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab.

Here, we further note that the method of claim 1 uses the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim.). The use of the open-ended transitional phrase "comprising" in claim 1 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner's arguments about the interpretation the Examiner used during prosecution do not persuade us otherwise. PO Resp. 7–8. Patent Owner cites to the Examiner's reasons for allowance in a related patent (U.S. 11,591,393), which states that the cited prior art "does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed." Ex. 2302, 8. According to Patent Owner, the term "based on" does not mean "after," but requires a causal relationship. PO Resp. 8. Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that claim 1 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. The Examiner's reasoning does not indicate that claim 1 excludes treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one determined to be MSI-H or dMMR, as Patent Owner implies. PO Resp. 8–10. Patent Owner argues that "Merck's only dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." *Id.* at 9 (citing Ex. 2160, 24). But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 excludes treating any patient other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a ***reaction***, as that of

an organism to any of its parts, to a ***specific*** stimulus." Ex. 2160, 24–25. This construction does not limit the scope of claim 1 to contemplating the treatment of any patients other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued "[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion about what behavior the claims cover." *Id.* at 25. Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now.

Patent Owner argues further that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that its witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a determination that the patient's tumor is MSI-H. PO Resp. 9 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 90–91). Neither of these statements persuades us that claim 1 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of claim 1 excludes treating any patient other than the one tested and confirmed to be MSI-H.

Patent Owner cites *Am. Calcar, Inc. v. American Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011), in support of the claim construction that the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H, but not when the patient is MSI-stable. PO Resp. 9–10. In that case, the Federal Circuit determined that, in claims directed to systems for identifying a service provided when a vehicle needs

service, the term "the processing element identifying one of the plurality of providers *in response to* the vehicle condition" means "that the second event occur in reaction to the first event." *Am. Calcar*, 651 F.3d at 1324, 1340. The court continued, by explaining that "[t]he language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction." *Id.* at 1340. We note that, as explained above, we agree the claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claim 1 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claim 1 to require testing a biological sample obtained from a patient having colorectal cancer to determine that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient, and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient. We are not persuaded that claim 1 either requires or excludes other patients or steps because claim 1 does not recite any other steps or contain negative limitations.

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 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) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be "a medical doctor or a professional in a related field with at least five years of experience with treating cancer" and "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." Pet. 11–12 (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. PO Resp. 5 (citing Ex. 2072 ¶¶ 31–32, 81–89). Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '287 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, 24:42–52; Ex. 1005. Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds.

In the Decision to institute trial, we adopted Petitioner's uncontested proposal defining that the level of skill in the art, presented above. Dec. 7–8. Neither party directs us to evidence of the level of skill in the art beyond what we considered for institution of trial. Having considered Patent Owner's positions and evidence of record, however, we determine that the level of skill also 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 cancers and the associated conditions and immunotherapy.

II. ANALYSIS

A. Introduction

"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. Summary of the Cited Prior Art

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

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

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

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

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

related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" Ex. 1005, 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

Ex. 1005, 4. The chart above identifies three patient populations and the therapeutic intervention to be provided.

2. Pernot (Ex. 1006)

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

3. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with

deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.*, 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.*, 3380, 3384.

4. Steinert (Ex. 1008)

Steinert is an article titled "Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer." Ex. 1008, OF1. Steinert discloses a detailed genomic and phenotypic analyses of single colorectal cancer–derived circulating tumor cells (CTC). *Id.* Steinert describes that "[a]mplified gDNA of CTC and tumor tissue samples was tested for microsatellite instability (MSI) using the markers NR21, NR24, and BAT 25." *Id.*, OF2. Steinert describes that the analyses of single cancer-derived CTC found disparities in key mutations, including MSI, in comparison to the primary tumor. *Id.*, OF4. "MSI at one or more markers . . . was detected in CTC from 2 patients (of 25 with complete MSI data sets; 7.7%, Fig. 2C). In 1 patient, two of 11 tested CTC were MSI despite a microsatellite stable (MSS) tumor (Table 1)." *Id.* In one patient, "[t]hree single CTC were classified as MSI-high level (MSI-H) and showed a mutation in the coding region of the *ELAVL* gene." *Id.*, OF6.

5. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical

Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id.*, 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.*, 1034.

6. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

C. Ground 1: Anticipation of Claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 by the MSI-H Study Record

Petitioner contends that claims 1–2, 4–8, 11–12, 14–18, and 21–36 are anticipated by the MSI-H Study Record. Pet. 15–39. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how each element of claims 1–2, 4–8, 11–12, 14–18, and 21–36 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1002 ¶¶ 50–127.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single

anticipating reference." Pet. 15–16. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 17. Relying on those cases, Petitioner contends that "the MSI-H Study Record inherently anticipates claims 1–2, 4–8, 11–12, 14–18, and 21–36 of the '287 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 18.

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '287 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 15.

1. Independent Claim 1

Like the parties, our analysis focuses on independent claim 1. *See e.g.,* Pet. 29–30 (relying substantially on analysis of claim 1 for independent claim 11).

a) [1.pre]: "A method for treating colorectal cancer in a human patient, the method comprising:"

Petitioner argues that, in general, the MSI-H Study Record anticipates claim 1 of the '287 patent because it "teaches the claimed drug, given at the only therapeutically effective dosage described in the '287 patent, and given to the claimed patient population." Pet. 18. Specifically, Petitioner cites to

the teaching in the Arms and Interventions section of a method of treating human MSI positive colorectal cancer patients, as recited in the preamble of claim 1.[1] *Id.* (citing Ex. 1003 ¶¶ 59–60; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)).

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 this limitation.

> b) *[1.1]: "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab," and*
>
> *[1.2]: "wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient."*

Petitioner argues that the MSI-H Study Record anticipates the limitation in claim 1 of treating with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient" because the Arms and Interventions section discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 19–21; *see also* Ex. 1003 ¶ 64–65 ("The MSI-H Study Record's discussion of

[1] We need not decide whether the preamble is limiting as we find that the MSI-H Study Record discloses the preamble.

treating patients with 'MSI positive' cancer also concerns treating patients with a mismatch repair deficiency ('dMMR')").

Petitioner also relies on Dr. Neugut's testimony to assert that the dosage described in the MSI-H Study Record is the same as the dosage described as being effective in the '287 patent. Pet. 19–20 (citing Ex. 1003 ¶ 63); *see* Ex. 1001 4:23–36, 8:52–56, 13:28–30.

Petitioner argues further that the Arms and Interventions section of the MSI-H Study Record teaches the limitation in claim 1 of "wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." Pet. 22–23. Petitioner relies on Dr. Neugut's testimony that, "in order to place the patients into the proper arm, the MSI-H Study Record required a biological sample from the patient that had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." *Id.* at 23; Ex. 1003 ¶ 68.

Patent Owner first argues that the MSR is silent with respect to testing a patient for MSI-H before administering pembrolizumab. PO Resp. 1–2. Patent Owner cites Dr. Neugut's testimony that the MSR does not expressly teach determining a patient's MSI status before enrollment in the study. PO Resp. 13 (citing Ex. 2163, 102:20–103:1 ("Q. And is there anything in this study protocol that says a patient's MSI status would need to be determined before enrollment? A. 'Before enrollment' being before they were recruited into the study? . . . A. No.")).

Petitioner disagrees with Patent Owner's characterization of what the MSR teaches about the timing of testing for MSI status. Petitioner argues

that Patent Owner's arguments fail to consider that enrolling enough colorectal cancer patients who were also MSI-H would not have been easy and, thus, testing before enrollment would be required to obtain enough MSI-H patients for the small 71-patient study. Pet. Reply 11–12. In support of Petitioner's argument, Dr. Oberstein testifies that

> the MSI-H Study Record describes in the Study Design section that the anticipated enrollment of the study is 71 patients. (EX1005, 4 (Study Design).) Given the low incidence of MSI-H in the colorectal cancer population that would be treated in the MSI-H Study, a POSA would understand that the MSI-H Study Record requires that a patient is tested to determine whether the patient is MSI-H before being enrolled and treated in the study. (*See* EX2072, ¶50 ("[A] small percentage of cancer patients (including CRC patients) were MSI-H"); EX1138, 91:4-17; *see also* EX1003, ¶¶58-63; EX1007, 3380, 3382.) Otherwise, with an anticipated enrollment of 71 total patients, the POSA would understand that there would not be enough MSI-H colorectal cancer patients treated in the study to measure the outcomes described by the MSI-H Study Record. (*See* EX1005, 4-5 (Outcome Measures).)

Ex. 1150 ¶ 67. According to Dr. Oberstein, "a colorectal cancer patient could not 'meet the eligibility criteria' [of the MSR] and begin treatment without first determining whether the colorectal cancer patient's cancer was MSI-H." Ex. 1150 ¶ 65. Thus, Dr. Oberstein testifies that to conduct the study disclosed in the MSR, the researchers would have needed to determine a patient's MSI status before enrollment and subsequent treatment. Patent Owner does not cite to evidence contradicting Dr. Oberstein's testimony about the incidence of MSI-H colorectal cancer or the circumstances of carrying out the study disclosed in the MSR.

Petitioner argues further that "the existence of multiple arms only underscores the need for MSI testing before the patient is placed into the appropriate arm and treated according to the MSR." Pet. Reply 10. Petitioner explains that MSI-H non-colorectal cancer patients were enrolled in the study, but not MSI-stable non-colorectal cancer patients. *Id.* Citing Dr. Oberstein's testimony, Petitioner argues that "the MSR describes the study as 'non-randomized', and therefore would not be understood by a POSA to describe an 'all-comers' study, where 'patients are ***randomly assigned*** [to receive treatment] regardless of biomarker status.'" Pet. Reply 11 (citing Ex. 1150 ¶¶ 64–67). Again, Patent Owner does not direct us to evidence contradicting Dr. Oberstein's testimony.

Patent Owner cites publications about the design of "all-comers" studies and randomized clinical trials with biomarkers, in general, but does not cite to the evidence that specially addresses the MSR or the incidence of MSI-H in colorectal cancer patients, as does Dr. Oberstein's testimony. PO Resp. 13 (citing Ex. 2026, 1; Ex. 2027, 2). Dr. Lonberg, Patent Owner's witness, testifies that the MSR is silent about the timing of testing and "leaves open the possibility that a colorectal cancer patient be tested for MSI-H ***after*** they are already tested," but he does not testify that one of ordinary skill in the art would not have understood from the MSR that testing would occur before treatment. (Ex. 2072 ¶¶ 98–99.)

We are persuaded by Dr. Oberstein's testimony that one of ordinary skill in the art would have known from the circumstances of carrying out the study disclosed in the MSR that patients would have been tested for the MSI status of their colorectal cancer before treatment with pembrolizumab and that, because of the patient's enrollment in the study, the patient would have

been treated with a therapeutically effective amount of pembrolizumab. Thus, we are persuaded that one of ordinary skill in the art would have understood that the MSR teaches the two steps recited in claim 1: 1) testing a biological sample obtained from a patient having colorectal cancer to determine that the patient's colorectal cancer is MSI-H or dMMR and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient (e.g., limitations 1.1 and 1.2 of claim 1).

Patent Owner argues further that the MSR does not disclose treating a colorectal patient "in response to" determining that the colorectal cancer is MSI-H or dMMR. PO Resp. 10. Patent Owner argues that the MSR discloses recruiting subjects for two colorectal cancer-related arms and administering pembrolizumab to all the enrolled patients, including to those who were ultimately determined to be MSI-stable. PO Resp. 11–12. According to Patent Owner, this means that colorectal cancer patients were not treated "in response to" a determination of their MSI status because they received treatment with pembrolizumab regardless of the ultimate result of their MSI test. *Id.* at 12 (citing Ex. 2072 ¶¶ 100–107); PO Sur-Reply 4–5. Patent Owner argues that because both MSI-H and MSI-stable patients are treated regardless of the outcome of their MSI/MMR test, there is no causal relationship between the determining step and the treatment step. PO Resp. at 14–15.

Patent Owner argues that Dr. Oberstein concedes the MSR proposes treating both MSI-H and MS-stable colorectal cancer patients in the same way. PO Sur-Reply 6 (citing Ex. 2404, 283:8–284:10). According to Patent

Owner, Petitioner and Dr. Neugut "disregard[s] the MSI-stable CRC patients who are also administered pembrolizumab." PO Resp. 15–16. According to Patent Owner, if the MSR requires treating MSI-stable and MSI-H colorectal cancer patients in the same way, the treatment cannot be "'in response to determining that the colorectal cancer is [MSI-H]' as required by every claim of the '287 Patent." PO Sur-Reply 6. Patent Owner argues that the Petition provides no analysis of treating patients "in response to" determining their MSI status, as required in claim 1. PO Resp. 15.

As discussed above, we do not construe claim 1 to exclude treating other patients, such as patients who are not MSI-H, because it does not recite any steps or limitations other than testing a biological sample from a patient having colorectal cancer to determine if the cancer is MSI-H or dMMR and, in response to a determination that the colorectal cancer is MSI-H or dMMR, treating the patient with a therapeutically effective amount of pembrolizumab. Because claim 1 does not include any steps or limitations regarding the treatment or non-treatment of any other patient, we are not persuaded by Patent Owner's arguments that because the MSR teaches treating other patients, the steps recited in claim 1 are not taught. Instead, we are persuaded by Petitioner's arguments and evidence that the MSR teaches testing a colorectal cancer patient for MSI status and, in response to determining that the colorectal cancer is MSI-H, treating the patient with a therapeutically effective amount of pembrolizumab.

Patent Owner next disputes Petitioner's reliance on *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), to support the assertion of inherent anticipation of the claimed method. PO Resp. 23–24; 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 argues 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 claimed by the '287 Patent did not "inevitably flow." PO Resp. 23.

Patent Owner argues, citing the testimony of inventor Le, that at the time the MSR was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. PO Resp. 24 (citing Ex. 2130 ¶ 21 ("There were then and still are no animal models that accurately represent the response of human MSI-H cancers to checkpoint inhibitors.")). Patent Owner argues that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the MSR was not assured. PO Resp. 24–27 (citing Ex. 2090 ¶ 52). According to Patent Owner, "the MSR was a far cry from meeting *Montgomery's* inevitability requirement for inherent anticipation" and the MSR only describes a study to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than being designed to secure regulatory approval. PO Resp. 25–26; *see* Ex. 2072 ¶ 123; 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 we are not persuaded the MSR is so vague it does not teach the steps expressly recited in claim 1. 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 testing a biological sample from a colorectal cancer patient to determine if the cancer is MSI-H or dMMR and treating patients with MSI-H or dMMR colorectal cancer with a therapeutically effective amount of pembrolizumab in response to the determination the cancer is MSI-H or dMMR. (*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 colorectal cancer patients or suggest that some unidentified drug may be useful for MSI-H colorectal cancer patients. Instead, the MSR discloses testing for the condition recited in claim 1 and treating with the drug recited in claim 1 if the condition is met. *See 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 pertubations).

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. 26–27. But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, 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."). 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.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. PO Resp. 27–33. 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 27 (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). PO Resp. 28–33. 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. PO Resp. 28–29. 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 29–33. Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." *Id.* at 31.

Petitioner disagrees, arguing that "[i]t is well established that there is no requirement under §101 or §112 that evidence from human clinical trials must be provided for patentability." 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.)).

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support a patent reinforces the importance of experimental use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment." PO Sur-Reply 13. But 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. We are not persuaded by Patent Owner's assertion that "there can be no question" that Patent Owner could not have filed an earlier application to secure a priority date before the MSR was publicly available.

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, particularly given that clinical trial protocols

published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See 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).

Patent Owner argues "[a]s a matter of policy, Merck's interpretation of inherency law cannot be correct because it makes patenting a surprisingly effective method of treatment impossible." PO Resp. 33. Again, Patent Owner asserts that a "dataless provisional application mirroring the MSR before the MSR was published (before any clinical study had begun)," would not have satisfied the requirements of 35 U.S.C. § 101 and § 112. *Id.* As explained above, this argument is unpersuasive at least in part because Patent Owner filed a provisional application without data, albeit after the MSR was publicly available. Patent Owner argues that under a "policy" finding claim 1 to be anticipated, Patent Owner's only other option was to pursue "unsupported claims that would likely be unpatentable." PO Resp. 34. Patent Owner fails to support this argument with evidence that under our controlling statutes and precedents Patent Owner is correct.

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.

2. Independent Claim 11

Patent Owner does not present separate arguments against Petitioner's challenge to claim 14 as being anticipated by the MSR. (*See, e.g.* PO Resp. 12, 19 (referring to claims 1 and 11 together).) For the reasons

discussed above regarding claim 1, we are persuaded that claim 11 is anticipated by the MSR.

3. Dependent Claims

a) Claims 7, 17, 26, 28, 30, 32, 34, and 36

Petitioner argues that claims 7, 17, 26, 28, 30, 32, 34, and 36 are anticipated by the MSR. Pet. 26–28, 31–39. These claims each require the patient to have received a "prior cancer therapy," and the patient's cancer to have progressed "subsequent to the prior treatment" or "following the prior cancer therapy." Petitioner argues that because the MSR discloses that patients eligible for the study must have "tumors" and "measurable disease," one of ordinary skill in the art would have known that the patients would have received prior drug therapies and that their cancers would have progressed after these therapies. Pet. 26 (citing Ex. 1003 ¶¶ 81–86).

Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have known the reference to "measurable cancer" in the MSR would include patients with metastatic and advanced cancer, not resectable cancer, because patients whose tumors are resectable can be cured by surgery. *Id.* (citing Ex. 1003 ¶ 82). Petitioner argues further, relying again on Dr. Neugut's testimony, that patients with metastatic and advanced cancer who would participate in a clinical study would have generally received at least two other prior drug therapies, such as standard care chemotherapy, and would have had their cancer progress after these therapies. *Id.* at 26–27 (citing Ex. 1003 ¶ 83). Dr. Neugut testifies: "the person of ordinary skill would have found it highly unusual for that patient population, patients who had received two prior drug treatments

and had their cancer progress after those treatments, to not be included in the MSI-H Study Record." Ex. 1003 ¶ 83.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 75–78. Dr. Oberstein testifies that because the eligibility criteria stated in the MSR 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 receiving those therapies prior to enrollment in the MSR. Ex. 1150 ¶ 76. 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.* at 77.

"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). We credit Dr. Neugut's and Dr. Oberstein's testimony about what one of ordinary skill in the art would have understood after reviewing the MSR.

Patent Owner argues that Petitioner fails to meet the burden to show inherent anticipation of the limitations of these dependent claims. PO Resp. 17–19. Patent Owner argues that the MSR is silent about whether

eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for a finding of inherency." *Id*. at 17.

Patent Owner cites evidence to show that, instead, it was known that some cancer patients can proceed directly to clinical trials even without prior treatment. *Id.* at 17–19. First, Patent Owner cites published guidelines for the management of patients with gastric cancer. *Id.* at 18 (citing Ex. 2164, 533, 537). But Patent Owner fails to explain the flow diagrams in the cited pages of this publication and, although there is mention of "clinical trial" for "Unresectable locally advanced, Locally recurrent or metastatic disease," it is not clear that clinical trial participation is recommended in the absence of different or prior cancer therapy. Ex. 2164, 533, 537. Patent Owner also cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." Ex. 1009, 2.

Patent Owner's evidence is directed to the general knowledge in the field, not to the specific understandings of one of ordinary skill in the art when reviewing the MSR, such as the testimony of a witness regarding the content of the MSR. Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression" and that three years later it was updated with a statement requiring prior cancer treatment, but he does not directly contradict Dr. Neugut's or Dr. Oberstein's testimony about the MSR as it was published in 2013. Ex. 2072 ¶ 108 (citing Ex. 2165); PO Resp. 19. Dr. Lonberg disagrees with Dr. Neugut's interpretation of the

term "measurable disease" in the MSR. Ex. 2072 ¶ 108 ("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 MSR 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 the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. As Patent Owner argues, the MSR was updated in 2016 to add the "express requirement for prior treatment." PO Resp. 19. We have considered this argument but find that this update alone does not indicate that the MSR as it appeared in 2013 was not within the scope of the challenged claims. *See* Ex. 1150 ¶ 77 (Dr. Oberstein testifying that "it is reasonable to assume that patients would typically receive [the two standard chemotherapy regimens (FOLFOX and FOLFIRI) for colorectal cancer] before trying a novel therapeutic agent."). It is also not clear why the MSR was updated – was it a change to the study or merely a clarification? The update by itself is not dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients who had received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitations of claims 7, 17, 26, 28, 30, 32, 34, and 36 were disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. *Contra* PO Resp. 17–19.

Accordingly, we are persuaded that claims 7, 17, 26, 28, 30, 32, 34, and 36 are anticipated by the MSR.

b) Claims 6 and 16

Petitioner argues that claims 6 and 16 are anticipated by the MSR. Pet. 24–25, 31. Claims 6 and 16 require that the colorectal cancer recited in claim 1 or claim 11, respectively, be metastatic colorectal cancer. Petitioner argues that the MSR discloses a clinical study treating colorectal cancer patients with "tumors" and "measurable disease." *Id.* (citing Ex. 1005, 2, 4, 5–6). Petitioner relies on Dr. Neugut's testimony that, in the context of the MSR, the treated patients would have had metastatic cancer. *Id.* (citing Ex. 1003 ¶¶ 76–80). Dr. Neugut testifies that "measurable" disease in the context of a study record studying a new drug refers to patients having metastatic and advanced cancer. Ex. 1003 ¶ 77. According to Dr. Neugut, one of ordinary skill would therefore have understand that the MSR teaches treating patients with metastatic cancer and locally advanced cancer that is unresectable for purpose of a cure. *Id.* Dr. Neugut testifies further that not including metastatic patients in such a study would be highly unusual because the drug treatment would not be a local cure, whereas radiation or surgery could be. *Id.*

Petitioner argues further that other prior art, referring to the MSR indicates that physicians understood the MSR to be for patients with metastatic tumors. Pet. 25 (citing Ex. 1049, 444; Ex. 1050, S4; Ex. 1003 ¶ 79. 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 the MSR 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. 21. 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. 20 (citing Ex. 2163:14:9–15:12.)

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 that one of ordinary skill in the art would have understood the MSR to disclose treating patients with metastatic colorectal cancer. *See* Ex. 1049, 444; Ex. 1050, S4. Patent Owner does not address this evidence.

We are persuaded by Petitioner's evidence that claims 6 and 16 are anticipated by the MSR.

c) Claims 21–25, 27, 29, 31, 33, and 35

Claims 21–25, 27, 29, 31, 33, and 35 are directed to the therapeutic effects of treating the patient of independent claim 1 or 11 with pembrolizumab. For example, claims 21–24 require that the treatment increases the "median progression free survival" or "median overall survival" of MSIH CRC patients compared to those of MSI-stable CRC patients. Claims 25, 27, 29, 31, 33, and 35 recite a method that "results in" response rates and probabilities of progression-free survival for MSI-H or dMMR colorectal cancer patients. Petitioner argues that because the MSR teaches treating patients having MSI-H colorectal cancer patients with 10 mg/kg of pembrolizumab every 14 days it is inherently effective in achieving the results recited in claims 21–25, 27, 29, 31, 33, and 35. Pet. 32–39 (citing Ex. 1003 ¶¶ 111–113).

Patent Owner argues that the MSR does not disclose the results recited in these claims and, thus, does not anticipate them. PO Resp. 21–23. Patent Owner relies on Dr. Neugut's and Dr. Lonberg's testimony to argue that one of ordinary skill in the art could not have known the outcome of the MSR study and would have had no way of knowing whether the amount of pembrolizumab was effective in promoting survival or reduced the risk of cancer progression, or that it provided any objective response rate or progression free survival rate. *Id.* (citing Ex. 2072 ¶¶ 114–117, 178–179; Ex. 2163, 111:20–112:2, 114:22–24, 115:25–116:7, 147:18–148:2).

As Patent Owner argues, to show inherent anticipation Petitioner must show that the results recited in the challenged claims are necessarily present

in the disclosure of the MSR. PO Resp. 22–23; *see also Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.")). But Patent Owner also argues that Petitioner must show that inherent limitations would be recognized by those of ordinary skill in the art, citing *Continental Can Co. USA, Inc. v. Monsanto Co*., 948 F.2d 1264, 1268 (Fed. Cir. 1991). PO Resp. 22–23. The Federal Circuit, however, has expressly "reject[ed] the contention that inherent anticipation requires recognition in the prior art." *See Schering*, 339 F.3d at 1377–1378 ("Thus, in *Continental Can,* this court did not require past recognition of the inherent feature, but only allowed recourse to opinions of skilled artisans to determine the scope of the prior art reference.").

Because, as discussed above in regard to claims 1 and 11, the MSR teaches testing a biological sample obtained from a colorectal cancer patient to determine if the cancer is MSI-H or dMMR and in response to determining that the colorectal cancer is MSI-H or dMMR, treating the patient with a therapeutically effective amount of pembrolizumab, we are persuaded that the results of such steps would be inherent even if they had not yet been reported. "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering*, 339 F.3d at 1380.

Accordingly, we are persuaded that claims 21–25, 27, 29, 31, 33, and 35 are anticipated by the MSR.

d) Claims 2, 4, 5, 8, 12, 14, 15, and 18

Petitioner argues that claims 2, 4, 5, 8, 12, 14, 15, and 18 are also anticipated by the MSR. Pet. 23–24, 29–31. Patent Owner does not argue to the contrary.

Briefly, Petitioner argues that claims 2 and 12, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSR because the Eligibility Criteria section of the MSR requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies that one of ordinary skill in the art would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. Ex. 1005, 5–6; Ex. 1003 ¶ 70.

Petitioner argues that claims 4, 5, 11, and 14, which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient is anticipated by the MSR because the MSR teaches treating colorectal cancer patients whose tumors are determined to be MSI-H or dMMR. Pet. 24, 30 (citing Ex. 1003 ¶¶ 72–75).

Petitioner argues that claims 8 and 18, which require the pembrolizumab to be administered to the patient intravenously is anticipated by the MSR because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. Pet. 29, 31 (citing Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1054, 3; Ex. 1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003 ¶¶ 87–88).

In view of the above, we are persuaded by Petitioner's uncontested evidence that each of claims 2, 4, 5, 8, 12, 14, and 15 are anticipated by the MSR.

4. Conclusion

For the foregoing reasons, we determine that the preponderance of the evidence supports Petitioner's argument that the MSI-H Study Record teaches each and every element of the challenged dependent claims. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claims 1–2, 4–8, 11–12, 14–18, and 21–36 are anticipated by the MSI-H Study Record.

D. Ground 2: Obviousness of Claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 over MSI-H Study Record and Pernot

Petitioner presents a challenge to claims 1, 2, 4–8, 11, 12, 14–18, and 21–36 of the '287 patent under 35 U.S.C. § 103, as an alternative to the challenge under 35 U.S.C. § 102. Pet. 43–44. 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. Pet. 44 (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, making them good candidates for immunotherapy." Ex. 1006, 3740–41; Pet. 18. 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. Pet. 45 (citing Ex. 1003 ¶ 131).

Patent Owner argues that "Pernot does not disclose testing patients for MSI-H status or treating them with pembrolizumab." PO Resp. 35.

Because "anticipation is the epitome of obviousness," we are

persuaded that the claims Petitioner challenges as being anticipated by the MSR would have been obvious over the MSR 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, 2, 4–8, 11, 12, 14–18, and 21–36 as being obvious over the MSR alone.

E. Remaining Grounds: Obviousness Based on the MSI-H Study Record, Pernot, and Additional References

Petitioner argues that certain dependent claims of the '297 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle, Steinert, Benson, and Hamid. Pet. 48–62. Because, as discussed above, we determined that some of these claims are anticipated by the MSR, they also would have been obvious by MSR alone. *In re McDaniel*, 293 F.3d at 1385. Accordingly, we review Petitioner's obviousness challenges only for the claims not deemed anticipated.

1. Claims 9 and 19: Obviousness over the MSR, Pernot, and Chapelle

Claims 9 and 19 recite the methods of claims 1 and 11, respectively, "wherein the biological sample was tested by a method comprising immunohistochemistry testing, next generation sequencing or PCR testing." Petitioner cites Chapelle for its teaching of testing tumor tissue from a patient to determine microsatellite instability in colorectal cancer, as recited in claims 9, 10, 19, and 20. Pet. 49–51 (citing Ex. 1007, 3380–84; Ex. 1003 ¶ 143–144). Petitioner also cites Chappelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claims 9 and 19. *Id.* Those methods include testing with PCR.

Id. Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) with Chapelle's standard methods for testing for MSI-H, including testing with immunohistochemistry, and would have had an expectation of success in doing so because the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. *Id.*

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

2. Claims 10 and 20: Obviousness over the MSR, Pernot, and Chapelle

Claims 10 and 20 recite the methods of claims 1 and 11, respectively, "wherein the biological sample was tested by a method comprising assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24." Petitioner cites Chapelle for its teaching of Chappelle's standard methods for testing for MSI-H, including a test for MSI-H that "was proposed as a standard test for MSI" and has "stood the test of time" comprises testing for "two mononucleotide repeats (BAT26, BAT25)." Pet. 50–51 (citing Ex. 1003 ¶ 145; Ex. 1007, 3382). Petitioner contends that "[a] method wherein the biological sample was tested by a method comprising assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24 would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. *Id.* (citing Ex. 1003 ¶¶ 145–147).

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

3. Claims 3 and 13: Obviousness over the MSR, Pernot, and Steinert

Claims 3 and 13 recite the method of claim 1 or 11, respectively, "wherein the biological sample is a body fluid from the patient." Petitioner contends that claims 3 and 13 would have been obvious over the combination of the MSI-H Study Record, Pernot, and Steinert. Pet. 51–53. Petitioner cites Steinert for its teaching of testing body fluid to determine whether a tumor is microsatellite instability high. *Id.* (citing Ex. 1008, OF6; Ex. 1003 ¶ 155).

Petitioner argues that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) and Steinert because the MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H and Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. *Id.* (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 153–156). Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have had a reasonable expectation of success given that the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. Pet. 52 (citing Ex. 1001, 6:25–26 ("Testing of MSI can be accomplished by any means known in the art"), 6:35–38; Ex. 1003 ¶ 155).

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

4. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 9, 10, 13, 19, and 20 as being obvious. (*See, e.g.,* PO Resp. 52–57 (arguing that Petitioner relies on Chapelle, Steinert, Benson,

Salipante, and Hamid for "discrete limitations unrelated to" the "in response to" limitation of the independent claims or the expectation of success in the recited methods).) That is, Patent Owner argues against all of the obviousness challenges together, without arguing that any of the limitations recited in the dependent claims renders the method of claim 1 or 11 non-obvious.

Patent Owner argues only 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 claims 1 and 11. (*See* PO Resp. 38–45.) For example, Patent Owner argues that neither the MSR, 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 pembrolizumab. *Id.* at 42–44. Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, 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 Int'l 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 articles' authors did not appreciate the results."). 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 for MSI-H with immunohistochemistry, polymerase chain reaction, or next generation sequencing, that uses a bodily fluid, or that uses intravenous administration

of pembrolizumab, as recited in the challenged dependent claims, and 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 challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 53–83. 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 MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 11. *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, 4–8, 12, 14–18, and 21–36, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 9, 10, 13, 19, 20), Patent Owner must show a nexus between the claimed methods 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 mentions a nexus between the Keytruda® (pembrolizumab) label for testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claims 9 and 19. PO Resp. 58. But Patent Owner does not direct us to evidence of a nexus to limitations recited in the dependent claims, for example to claims 3 and 13, which recite testing a biological sample that is a bodily fluid, claims 10 and 20, which recite 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.

Even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 11, not the limitations of the claims Petitioner challenges as being obvious. PO Resp. 53–83. 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. When evidence of a "secondary consideration that 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 methods recited in claims 1 and 11 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claim 3, or "wherein the biological sample was tested by a method comprising immunohistochemistry testing, next generation sequencing or PCR testing," as recited in claim 9, demonstrated unexpected results or commercial success.

Accordingly, Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 3, 9, 10, 13, 19, and 20 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

5. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSR and the

other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 3, 9, 10, 13, 19, and 20 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[2]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–36 of the '287 patent are unpatentable. In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–8, 11, 12, 14–18, 21–36	102	MSR	1, 2, 4–8, 11, 12, 14–18, 21–36	
1, 2, 4–8, 11, 12, 14–18, 21–36	103	MSR, Pernot	1, 2, 4–8, 11, 12, 14–18, 21–36	
2, 9, 10, 12, 19, 20	103	MSR, Pernot, Chapelle	2, 9, 10, 12, 19, 20	
3, 13	103	MSR, Pernot, Steinert	3, 13	
6, 7, 16, 17, 26, 28, 30–36	103	MSR, Pernot, Benson	6, 7, 16, 17, 26, 28, 30–36	
8, 18	103	MSR, Pernot, Hamid	8, 18	
Overall Outcome			1–36	

[2] 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).

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–36 of the '287 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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Matthew Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 90
Date: June 9, 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.

IPR2024-00240
Patent 11,591,393 B2

Before DEBORAH KATZ, SHERIDAN K. SNEDDEN, 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 1–42, of U.S. Patent No. 11,591,393 B2 ("the '393 patent") pursuant to 35 U.S.C. § 311(a). (Paper 1 ("Pet.") 1, 3–5.) 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 9). We granted the Petition and instituted an *inter partes* review. (Paper 10 ("Decision" or "Dec.").)

During the review, Patent Owner filed a Patent Owner Response to the Petition (Paper 38 (confidential Paper 40) ("PO Resp.")), Petitioner filed a Reply (Paper 61 (confidential Paper 64) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 67 (confidential Paper 70) ("PO Sur-reply").

An oral hearing was held March 31, 2025. A transcript of the hearing is of record in this case. (Paper 86 (confidential Paper 87).)

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 1–42 of the '393 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. 67.) Patent Owner identifies The Johns Hopkins University as its real party-in-interest. (*See* Paper 4, 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. 67; Paper 4, 1.)

In addition, several other inter partes reviews are related to this proceeding, including IPR 2024-00622, 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; IPR2024-00625, challenging claims of U.S. Patent No. 11,339,219 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.

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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.

C. The '393 Patent

The application that became the '393 patent was filed on September 2, 2021, 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 '393 patent cites another provisional application, filed November 13, 2014, but Patent Owner claims priority only to July 10, 2015. (*See* PO Resp. 4, n.2.)

The '393 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor, in colorectal cancer ("CRC") patients. (*See* Ex. 1001, Abstract.) More specifically, the '393 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 3:40–53.) 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 8:52–56.)

Claim 1 of the '393 patent recites:

> A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising:
>
> testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and
>
> in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.

(*Id.* at 25:40–50.) Independent claim 14, the only other independent claim, is similar and recites the same steps of "testing" and "in response to

determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating . . . ." (*Id.* at 26:17–28.)

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 for 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. 4, n.1.)

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
Steinert	Steinert et al., Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer, 74(6) Cancer Research OF1 (March 2014)	1008
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
Salipante	Salipante et al., Microsatellite Instability Detection by Next Generation Sequencing, 60(9)	1010

	Clinical Chemistry 1192 (2014)	
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

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–42 are unpatentable on the following grounds:

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42	102	MSR
2	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24–25, 27–42	103	MSR, Pernot
3	2, 8, 15, 21	103	MSR, or MSR, Pernot, Chapelle
4	3, 16	103	MSR, or MSR, Pernot, Steiner
5	7, 20, 29, 30, 32, 34, 36–42	103	MSR, or MSR, Pernot, Benson
6	9, 10, 22, 23	103	MSR, or MSR, Pernot, Salipante
7	11, 12, 24, 25	103	MSR, or MSR, Pernot, Hamid
8	13, 26	103	MSR, or MSR, Pernot, Steinert, 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 '393 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.[3] (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2001) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be 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

[3] Patent Owner states that Dr. Neugut does not qualify as one of ordinary skill in the art and that, therefore, his testimony is flawed and unreliable. (PO Resp. 5, n.3.) Patent Owner does not present a full explanation, referring only to arguments made in the Patent Owner's Preliminary Response. (*See id.*) Incorporating arguments by reference is prohibited. *See* 37 C.F.R. § 42.6(a)(3) ("*Incorporation by reference; combined documents.* Arguments must not be incorporated by reference from one document into another document. Combined motions, oppositions, replies, or other combined documents are not permitted."). Dr. Neugut testifies that he has experience treating cancer and has knowledge of clinical studies for therapeutics and how they work. (*See* Ex. 1003 ¶¶ 4–13.) In the absence of appropriate argument to the contrary by Patent Owner, we are persuaded that Dr. Neugut is qualified to present opinion testimony. We are not persuaded that we should disregard his testimony in general, absent specific argument about specific testimony.

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 (citing Ex. 2072 ¶¶ 31–32, 83).) Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

As we discussed in the Decision to institute trial, the '393 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, 25:40–50, Ex. 1005; *see* Decision 8–9.) Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds. Neither party directs us to evidence of the level of skill in the art beyond what we considered for institution of trial.

In the Decision to institute trial, we determined that the level of skill in the art relevant to the claims of the '393 patent is not limited to knowledge of and experience with conducting research relating to oncology or developing and conducting clinical trials. (*See* Dec. 8–9.) We determined that the level of skill also includes knowledge of and experience with treating colorectal 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. (*See id.*) Because the parties do not present additional evidence or argument, we maintain that determination.

C. Claim Construction

We construe claims "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." 37 C.F.R. § 42.100(b) (2020).

Claim 1 requires treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient . . . ." (Ex. 1001, 25:47–50.) Petitioner argues that the discussion in the MSR of treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. (*See* Pet. 21 (citing Ex. 1005, 2–5.)) For the purposes of our decision whether to institute review, we agreed and stated that we interpreted this claim step as meaning "the treatment of colorectal cancer patients after they have been determined to be microsatellite instability high or DNA mismatch repair deficient."[4] (Decision 17.)

Patent Owner argues[5] that our construction "disregards the critical ***causal*** relationship between 'determining' and 'treating' steps expressed by

[4] Neither party proposed a construction of the claim term "in response to" prior to institution of review. (*See* Pet. 11–12; PO Prelim. Resp. 18–19 ("JHU does not formally construe any claim terms at this time because the deficiencies in the Petition highlighted in this POPR do not turn on claim construction. . . . Merck implicitly construes the term 'in response to' to have no meaning at all").)

[5] Patent Owner requested that the Director review our Decision, arguing that we "*sua sponte* went beyond the bounds of the Petition to erroneously

the claims," wherein the causal relationship establishes that the "'treating' step is performed (and only performed) in response to (i.e., as a reaction to) determining the patient's cancer is MSI-H." (PO Resp. 6–7.) According to Patent Owner, the construction of "in response to" should be that the phrase means "in reaction to." (*Id.* at 6.)

Patent Owner argues that if the inventors had intended the claimed method to encompass merely treating patients "after" a determination of the patient's MSI-H status, they would have used the word "after" in their claims, citing use of the word "after" in other claims. (*Id.* at 7 (citing Ex. 1001, 25:66–7, 26:44–46, 26:63–64 (claims 7, 20, 27, which require that "the patient's cancer had progressed after the patient received the different cancer therapy.")).) Because the cited language is in claims that depend on claim 1, Patent Owner argues that the term "in response to" must have a different meaning from "after." (*Id.*)

Patent Owner argues further that the Specification of the '393 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H. (*See* PO Resp. 8.) Specifically, Patent Owner cites the disclosure in the '393 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. (Ex. 1001, 3:54–67.)

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construe, and then supply, a claim limitation missing from Merck's inherent anticipation and obviousness analyses." (Paper 12, 1.) Patent Owner's request was denied. (*See* Paper 24.)

According to Patent Owner, one of ordinary skill in the art would have understood from this distinction in recommended treatments that "in response to" describes administering the claimed treatment only as a reaction to the determination that the patient's cancer is MSI-H. (*See* PO Resp. 8.) According to Patent Owner, "[t]he contrary view advanced by the Board improperly renders meaningless the 'in response to' step of the claim." (*Id.*) Patent Owner argues further that under our initial construction, "the claims would cover treatment administered to MSI-H patients for any reason or no reason at all—even accidental treatment would be covered. Such a reading is entirely inconsistent with the teaching of the specification." (*Id.*)

We agree with Patent Owner that the phrase "in response to" in claim 1 requires a causal relationship wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is treated with 10 mg/kg of pembrolizumab every 14 days. We further agree that this relationship is different than the use of the term "after" in claims 7, 20, and 27, wherein patients must be treated with a different cancer therapy, and wherein the cancer must have later progressed for the treatment to be within the scope of these claims. (Ex. 1001, 25:66–7, 26:44–46, 26:63–64.) In claim 1, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having colorectal cancer to determine that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the

patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the art anticipates claim 1. We are not persuaded that claim 1 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment *only* as a reaction to the determination that the patient's cancer is MSI-H, and that, if treatment were administered to patients for any other reason after testing confirmed that the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the term "in response to" would be meaningless. (*See* PO Resp. 8.) But, as Petitioner argues, claim 1 does not exclude treatment of other patients who are not MSI-H or dMMR, if the colorectal cancer patient from whom the biological sample is obtained and tested is determined not to be microsatellite instability high or mismatch repair deficient. (*See* Pet. Reply 9 ("JHU advocates for a construction that excludes a treatment in which pembrolizumab is administered to patients that do not have MSI-H. Such unclaimed negative limitations should not be read into claim terms.").) Claim 1 does not mention any other patients or define patient populations to be excluded from treatment. Claim 1 provides that if the colorectal cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab.

Here, we further note that the method of claim 1 uses the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a

method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim.). The use of the open-ended transitional phrase "comprising" in claim 1 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner's arguments about the interpretation the Examiner used during prosecution do not persuade us otherwise. (*See* PO Resp. 8–9.) Patent Owner cites to the Examiner's reasons for allowance, which state that the cited prior art "does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed." (Ex. 1002, 544.) According to Patent Owner, the term "based on" does not mean "after," but requires a causal relationship. (*See* PO Resp. 9.) Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that claim 1 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. The Examiner's reasoning does not indicate that claim 1 excludes treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one determined to be MSI-H or dMMR, as Patent Owner implies. (*See* PO Resp. 9–10.) Patent Owner argues that "Merck's only

dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." (PO Resp. 9–10 (citing Ex. 2160, 24).) But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 excludes treating any patient other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a ***reaction***, as that of an organism to any of its parts, to a ***specific*** stimulus." (Ex. 2160, 24–25.) This construction does not limit the scope of claim 1 to contemplating the treatment of any patients other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued "[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion about what behavior the claims cover." (*Id.* at 25.) Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now.

Patent Owner argues further that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that its witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a determination that the patient's tumor is MSI-H. (*See* PO Resp. 10 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 84–85).) Neither of these statements persuades us that claim 1 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of

claim 1 excludes treating any patient other than the one tested and confirmed to be MSI-H.

Patent Owner cites *Am. Calcar, Inc. v. American Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011), in support of the claim construction that the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H, but not when the patient is MSI-stable. (*See* PO Resp. 10–11.) In that case, the Federal Circuit determined that, in claims directed to systems for identifying a service provided when a vehicle needs service, the term "the processing element identifying one of the plurality of providers *in response to* the vehicle condition" means "that the second event occur in reaction to the first event." *Am. Calcar*, 651 F.3d at 1324, 1340. The court continued, by explaining that "[t]he language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction." *Id.* at 1340. We note that, as explained above, we agree the claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claim 1 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claim 1 to require testing a biological sample obtained from a

patient having colorectal cancer to determine that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient, and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient. We are not persuaded that claim 1 either requires or excludes other patients or steps because claim 1 does not recite any other steps or contain negative limitations.

D. Ground 1: Anticipation over the MSR

Petitioner argues that claims 1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42 are anticipated under 35 U.S.C. § 102. (*See* Pet. 15–37.)

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, 2.) The parties' witnesses agree that MK-3475 is pembrolizumab, the compound recited in claim 1. (*See* Neugut Decl., Ex. 1003 ¶ 37; *see* Lonberg Decl., Ex. 2001, ¶ 65.) 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 '393 patent on July 10, 2015. (*See* Pet. 7 (citing Ex. 1005, 3, Ex. 1003 ¶ 35).)

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[6]:

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.*)

Petitioner cites the teaching in the Arms and Interventions section as a method of treating human MSI positive colorectal cancer patients, as recited in the preamble of claim 1. (*See* Pet. 18 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility)).) Petitioner argues that the

[6] 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.

claimed methods are anticipated by the MSR even if the recited steps had not been performed yet because any efficacy requirement in the claims would be inherent to the steps. (Pet. 18–22.) Petitioner argues that the challenged claims are directed to the methods disclosed in the MSR. (*See id.* at 18.)

2. Claim 1

a) *Preamble "[a] method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising"*

Petitioner argues that the MSR teaches "[a] method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient," as recited in the preamble of claim 1. (Pet. 18 (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 53–57).) Petitioner relies on Dr. Neugut's testimony that the MSR provides three study arms, including one arm that treats human patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days and measuring specific outcomes, such as overall survival and progression-free survival. (Ex. 1003 ¶¶ 53–57.)

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 this limitation.

b) Elements 1.1 and 1.2: "testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab."

Petitioner argues that the MSR teaches "testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient," as recited in claim 1, because the Arms and Interventions section of the MSI-H Study Record teaches "testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient," in order to put patients into the proper arm of the study. (*See* Pet. 20–21 (citing Ex. 1003 ¶ 58).) Petitioner relies on Dr. Neugut's testimony that the study required testing because "[p]lacing patients into that proper arm would not be possible without first determining that the patient's tumor was MSI-H." (Ex. 1003, ¶ 58.)

Petitioner argues further that the MSR teaches treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient," as required in claim 1, because the Arms and Interventions section discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (*See* Pet. 21–23 (citing Ex. 1003 ¶¶ 59–63).) Petitioner argues that the MSR teaches treating the patient with a "therapeutically effective amount" of

pembrolizumab because the recited amount, 10 mg/kg, is identical to the dosage described as being "therapeutically effective" in the '393 patent. (Pet. 21–22 (citing Ex. 1001, 8:50–56, 13:24–30).) Petitioner asserts that any efficacy required in the claim is inherent to that dosage because the '393 patent shows that dosage to be effective. (Pet. 22 (citing Ex. 1001, 4:23–36, 16:4–8, 16:29–32, 19:40–21:15, Figs. 2, 11.)

Petitioner relies on Dr. Neugut's testimony that the MSR discusses treating a patient with 10 mg/kg of pembrolizumab every 14 days "in response to a patient meeting the eligibility criterion of having MSI-H colorectal cancer." (Pet. 21 (citing Ex. 1003 ¶ 59).) Dr. Neugut testifies that the '393 patent uses the same dosage of pembrolizumab and employs the same methods as the MSR and demonstrates the efficacy of treating patients having MSI-H colorectal cancer with 10 mg/ml of pembrolizumab every 14 days. (Ex. 1003 ¶ 61 (citing Ex. 1001, 8:52–56, 13:28–30).) Dr. Neugut concludes that "the person of ordinary skill would have concluded that the limitation was found in the MSI-H Study Record," referring to the limitation in claim 1 of treating the patient "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." (Ex. 1003 ¶ 63.)

Patent Owner first argues that the MSR is silent with respect to testing a patient for MSI-H before administering pembrolizumab. (*See* PO Resp. 12.) Patent Owner cites Dr. Neugut's testimony that the MSR does not expressly teach determining a patient's MSI status before enrollment in the study. (PO Resp. 14 (citing Ex. 2163, 102:20–103:1 ("Q. And is there anything in this study protocol that says a patient's MSI status would need to

be determined before enrollment? A. 'Before enrollment' being before they were recruited into the study? . . . A. No.")).)

Petitioner disagrees with Patent Owner's characterization of what the MSR teaches about the timing of testing for MSI status. Petitioner argues that Patent Owner's arguments fail to consider that enrolling enough colorectal cancer patients who were also MSI-H would not have been easy and, thus, testing before enrollment would be required to obtain enough MSI-H patients for the small 71-patient study. (*See* Pet. Reply 13.) In support of Petitioner's argument, Dr. Oberstein testifies that

> the MSI-H Study Record describes in the Study Design section that the anticipated enrollment of the study is 71 patients. (EX1005, 4 (Study Design).) Given the low incidence of MSI-H in the colorectal cancer population (about 15%), and even lower in the metastatic colorectal cancer population that would be treated in the MSI-H Study, the POSA would understand that the MSI-H Study Record requires that a patient is tested to determine whether the patient is MSI-H before being enrolled and treated in the study. (*See* EX2072, ¶50 ("[A] small percentage of cancer patients (including CRC patients) were MSI-H"); EX1138, 91:4-17; *see also* EX1003, ¶¶58-63; EX1007, 3380, 3382.) Otherwise, with an anticipated enrollment of 71 total patients, the POSA would understand that there would not be enough MSI-H colorectal cancer patients treated in the study to measure the outcomes described by the MSI-H Study Record. (*See* EX1005, 4-5 (Outcome Measures).)

(Ex. 1150 ¶ 68.) According to Dr. Oberstein, "a colorectal cancer patient could not 'meet the eligibility criteria' [of the MSR] and begin treatment without first determining whether the colorectal cancer patient's cancer was MSI-H." (Ex. 1150 ¶ 66.) Thus, Dr. Oberstein testifies that to conduct the study disclosed in the MSR, the researchers would have needed to determine

a patient's MSI status before enrollment and subsequent treatment. Patent Owner does not cite to evidence contradicting Dr. Oberstein's testimony about the incidence of MSI-H colorectal cancer or the circumstances of carrying out the study disclosed in the MSR.

Petitioner argues further that "the existence of multiple arms only underscores the need for MSI testing before the patient is placed into the appropriate arm and treated according to the MSR (particularly considering the lack of any fourth arm to accommodate patients with non-CRC MSI negative cancers)." (Pet. Reply 11.) Petitioner explains that MSI-H non-colorectal cancer patients were enrolled in the study, but not MSI-stable non-colorectal cancer patients. (*See id.*) Citing Dr. Oberstein's testimony, Petitioner argues that it would not make sense to determine their MSI status of non-colorectal patients before treatment, to determine if they should be enrolled, but to determine the MSI status of non-colorectal cancer patients only after treatment. (*See* Pet. Reply 12 (citing Ex. 1150 ¶¶ 61–70).) Again, Patent Owner does not direct us to evidence contradicting Dr. Oberstein's testimony.

Patent Owner cites publications about the design of "all-comers" studies and randomized clinical trials with biomarkers, in general, but does not cite to the evidence that specially addresses the MSR or the incidence of MSI-H in colorectal cancer patients, as does Dr. Oberstein's testimony. (*See* PO Resp. 15 (citing Ex. 2026, 1; Ex. 2027, 2).) Dr. Lonberg, Patent Owner's witness, testifies that the MSR is silent about the timing of testing and "leaves open the possibility that a colorectal cancer patient be tested for MSI-H ***after*** they are already tested," but he does not testify that one of

ordinary skill in the art would not have understood from the MSR that testing would occur before treatment. (Ex. 2072 ¶¶ 92–93.)

We are persuaded by Dr. Oberstein's testimony that one of ordinary skill in the art would have known from the circumstances of carrying out the study disclosed in the MSR that patients would have been tested for the MSI status of their colorectal cancer before treatment with pembrolizumab and that, because of the patient's enrollment in the study, the patient would have been treated with a therapeutically effective amount of pembrolizumab. Thus, we are persuaded that one of ordinary skill in the art would have understood that the MSR teaches the two steps recited in claim 1: 1) testing a biological sample obtained from a patient having colorectal cancer to determine that the patient's colorectal cancer is MSI-H or dMMR and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's colorectal cancer is determined to be microsatellite instability high or DNA mismatch repair deficient (e.g., limitations 1.1 and 1.2 of claim 1).

Patent Owner argues further that the MSR does not disclose treating a colorectal patient "in response to" determining that the colorectal cancer is MSI-H or dMMR. (*See* PO Resp. 11.) Patent Owner argues that the MSR discloses recruiting subjects for two colorectal cancer-related arms and administering pembrolizumab to all the enrolled patients, including to those who were ultimately determined to be MSI-stable. (*See* PO Resp. 13–14.) According to Patent Owner, this means that colorectal cancer patients were not treated "in response to" a determination of their MSI status because they received treatment with pembrolizumab regardless of the ultimate result of their MSI test. (*See id.* (citing Ex. 2072 ¶¶ 94–101); PO Sur-reply 6.)

Patent Owner argues that because both MSI-H and MSI-stable patients are treated regardless of the outcome of their MSI/MMR test, there is no causal relationship between the determining step and the treatment step. (*See id.* at 16–17.)

Patent Owner argues that Dr. Oberstein concedes the MSR proposes treating both MSI-H and MS-stable colorectal cancer patients in the same way. (*See* PO Sur-Reply 8 (citing Ex. 2024, 283:8–284:10).) According to Patent Owner, Petitioner and Dr. Neugut "completely ignor[e] the MSI-stable CRC patients who are also administered pembrolizumab." (PO Resp. 18.) According to Patent Owner, if the MSR requires treating MSI-stable and MSI-H colorectal cancer patients in the same way, the treatment cannot be "'in response to determining that the colorectal cancer is [MSI-H]' as required by every claim of the '393 Patent." (PO Sur-Reply 8.) Patent Owner argues that the Petition provides no analysis of treating patients "in response to" determining their MSI status, as required in claim 1. (*See* PO Resp. 17.)

As discussed above, we do not construe claim 1 to exclude treating other patients, such as patients who are not MSI-H, because it does not recite any steps or limitations other than testing a biological sample from a patient having colorectal cancer to determine if the cancer is MSI-H or dMMR and, in response to a determination that the colorectal cancer is MSI-H or dMMR, treating the patient with a therapeutically effective amount of pembrolizumab. Because claim 1 does not include any steps or limitations regarding the treatment or non-treatment of any other patient, we are not persuaded by Patent Owner's arguments that because the MSR teaches treating other patients, the steps recited in claim 1 are not taught. Instead,

we are persuaded by Petitioner's arguments and evidence that the MSR teaches testing a colorectal cancer patient for MSI status and, in response to determining that the colorectal cancer is MSI-H, treating the patient with a therapeutically effective amount of pembrolizumab.

Patent Owner next disputes Petitioner's reliance on *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), to support the assertion of inherent anticipation of the claimed method. (*See* PO Resp. 25–29; 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 argues 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 claimed by the '393 Patent did not "inevitably flow." (PO Resp. 25.)

Patent Owner argues, citing the testimony of inventor Le, that at the time the MSR was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. (*See* PO Resp. 26 (citing Ex. 2130 ¶ 20).) Patent Owner argues that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the MSR was not assured. (PO Resp. 26–27 (citing Ex. 2090 ¶ 52; Ex. 2024; Ex. 1013).) According to Patent Owner, "the MSR was a far cry from meeting *Montgomery's* inevitability requirement for inherent anticipation" and the MSR only describes a study to test the hypothesis that MSI-H might correlate with a response to treatment with

pembrolizumab, rather than being designed to secure regulatory approval. (PO Resp. 27–28; *see* Ex. 2072 ¶ 117.)

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded, but we are not persuaded the MSR is so vague it does not teach the steps expressly recited in claim 1. 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 testing a biological sample from a colorectal cancer patient to determine if the cancer is MSI-H or dMMR and treating patients with MSI-H or dMMR colorectal cancer with a therapeutically effective amount of pembrolizumab in response to the determination the cancer is MSI-H or dMMR. (*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 colorectal cancer patients or suggest that some unidentified drug may be useful for MSI-H colorectal cancer patients. Instead, the MSR discloses testing for the condition recited in claim 1 and treating with the drug recited in claim 1 if the condition is met. *See 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 pertubations).)

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. 28.) But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, 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."). 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.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. (*See* PO Resp. 29–36.) 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 29 (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. 31–36.) 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. 30–32.) 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 32–36.) Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." (*Id.* at 34.)

Petitioner disagrees, arguing that "[i]t is well established that there is no requirement under §101 or §112 that evidence from human clinical trials must be provided for patentability." (Pet. Reply 19 (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 notes that Patent Owner 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. (Pet. Reply 19–20 (citing Ex. 1001, cover; Ex. 1030, 1).)

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support a patent reinforces the importance of experimental use negation, especially in highly unpredictable fields such as cancer treatment." (PO Sur-Reply 13–14 (footnote omitted).) But 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. We are not persuaded by Patent Owner's assertion that "there

can be no question" that Patent Owner could not have filed an earlier application to secure a priority date before the MSR was publicly available.

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, particularly given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See 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).

Patent Owner argues "[a]s a matter of policy, Merck's interpretation of inherency law cannot be correct because it makes patenting a surprisingly effective method of treatment impossible." (PO Resp. 36.) Again, Patent Owner asserts that a "dataless provisional application mirroring the MSR before the MSR was published (before any clinical study had begun)," would not have satisfied the requirements of 35 U.S.C. § 101 and § 112. (*Id.*) As explained above, this argument is unpersuasive at least in part because Patent Owner filed a provisional application without data, albeit after the MSR was publicly available. Patent Owner argues that under a

"policy" finding claim 1 to be anticipated, Patent Owner's only other option was to pursue "unsupported claims that would likely be unpatentable." (PO Resp. 38.) Patent Owner fails to support this argument with evidence that under our controlling statutes and precedents Patent Owner is correct.

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. Independent Claim 14

Patent Owner does not present separate arguments against Petitioner's challenge to claim 14 as being anticipated by the MSR. (*See, e.g.* PO Resp. 12, 19 (referring to claims 1 and 14 together).) For the reasons discussed above regarding claim 1, we are persuaded that claim 14 is anticipated by the MSR.

4. Dependent claims

a) Claims 7, 20, 32, 34, 36, 38, 40, and 42

Petitioner argues that claims 7, 20, 32, 34, 36, 38, 40 and 42 are anticipated by the MSR. (*See* Pet. 25–37.) These claims each require the patient to have received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." (Ex. 1001, 25:65–67, 26:43–46, 27:10–12, 27:19–21, 27:28–30, 28:7–9, 28:17–19, 28:26–28.) Petitioner argues that because the MSR discloses that patients eligible for the study must have "tumors" and "measurable disease," one of ordinary skill in the art would have known that the patients would have received prior drug therapies and that their cancers

would have progressed after these therapies. (*See* Pet. 25 (citing Ex. 1003 ¶¶ 68–72).)

Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have known the reference to "measurable cancer" in the MSR would include patients with metastatic and advanced cancer, not resectable cancer, because patients whose tumors are resectable can be cured by surgery. (*See* Pet. 25 (citing Ex. 1003 ¶ 69.) Petitioner argues further, relying again on Dr. Neugut's testimony, that patients with metastatic and advanced cancer who would participate in a clinical study would have generally received at least two other prior drug therapies, such as standard care chemotherapy, and would have had their cancer progress after these therapies. (*See* Pet. 26 (citing Ex. 1003 ¶ 70.) Dr. Neugut testifies: "the person of ordinary skill would have understood that treating patients who had received prior/different cancer therapies, and the patients' cancer had progressed after the patients received the different cancer therapies was found in the MSI-H Study Record." (Ex. 1003 ¶ 72.)

Dr. Oberstein testifies that he agrees with Dr. Neugut. (*See* Ex. 1150 ¶¶ 75–78.) Dr. Oberstein testifies that because the eligibility criteria stated in the MSR requires patients to have "measurable disease," one of ordinary skill in the art would have expected a patient to have undergone at least two prior and/or different cancer therapies and would have had their cancer progress after those therapies prior to enrollment. (*See* Ex. 1150 ¶ 77.) 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. (*See id.*)

"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). We credit Dr. Neugut's and Dr. Oberstein's testimony about what one of ordinary skill in the art would have understood after reviewing the MSR.

Patent Owner argues that Petitioner fails to meet the burden to show inherent anticipation of the limitations of these dependent claims. (*See* PO Resp. 19–22.) Patent Owner argues that the MSR is silent about whether eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for a finding of inherency." (*Id.* at 20.)

Patent Owner cites evidence to show that, instead, it was known that some cancer patients can proceed directly to clinical trials even without prior treatment. (*See id.*) First, Patent Owner cites published guidelines for the management of patients with gastric cancer. (*See* Ex. 2164, 533, 537.) But Patent Owner fails to explain the flow diagrams in the cited pages of this publication and, although there is mention of "clinical trial" for "Unresectable locally advanced, Locally recurrent or metastatic disease," it

is not clear that this is recommended in the absence of different or prior cancer therapy. (*Id.*) Patent Owner also cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." (Ex. 1009, 2.)

Patent Owner's evidence is directed to the general knowledge in the field, not to the specific understandings of one of ordinary skill in the art when reviewing the MSR, such as the testimony of a witness regarding the content of the MSR. Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression" and that three years later it was updated with a statement requiring prior cancer treatment, but he does not directly contradict Dr. Neugut's or Dr. Oberstein's testimony about the MSR as it was published in 2013. (*See* Ex. 2072 ¶ 102 (citing Ex. 2165); *see* PO Resp. 21–22.) Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. (*See* Ex. 2072 ¶ 102 ("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 MSR 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 the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. As Patent Owner argues, the MSR was updated in 2016, wherein "[p]atients

with colon cancer must have received at least two prior cancer therapy regimens," but the claims of the cited claims of the '393 patent encompass only one prior therapy. Therefore, the update does not by itself indicate the MSR as it appeared in 2013 was not within the scope of the challenged claims. (*See* Ex. 1150 ¶ 77.) It is also not clear why the MSR was updated – was it a change to the study or merely a clarification? The update by itself is not dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients who had received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would "reasonably understand or infer" that the limitations of claims 7, 20, 32, 34, 36, 38, 40, and 42 were disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. (*Contra* PO Resp. 19–22.)

Accordingly, we are persuaded that claims 7, 20, 32, 34, 36, 38, 40, and 42 are anticipated by the MSR.

b) Claims 29 and 30

Petitioner argues that claims 29 and 30 are anticipated by the MSR. (*See* Pet. 31–33.) Claims 29 and 30 require that the colorectal cancer recited in claim 1 or claim 14, respectively, be metastatic colorectal cancer. (*See* Ex. 1001, 27:1–4.) Petitioner argues that the MSR discloses a clinical study

treating colorectal cancer patients with "tumors" and "measurable disease." (*See* Pet. 31 (citing Ex. 1005, 2, 4, 5–6).) Petitioner relies on Dr. Neugut's testimony that in the context of the MSR, the treated patients would have had metastatic cancer. (Pet. 31–32 (citing Ex. 1003 ¶¶ 87–90).) Dr. Neugut testifies that "measurable" disease in the context of a study record studying a new drug refers to patients having metastatic and advanced cancer. (*See* Ex. 1003 ¶ 88.) Dr. Neugut testifies further that patients whose cancer was resectable for the purposes of a cure would not be included in the context of a study record for a new drug because if the cancer could be surgically removed, it would be to achieve a cure. (*See id.* (citing Ex. 1047 at 4–7; Ex. 1020 at 7).) According to Dr. Neugut, one of ordinary skill would therefore have understand that the MSR teaches treating patients with metastatic cancer and locally advanced cancer that is unresectable for purpose of a cure. (*See* Ex. 1003 ¶¶ 88–89.) Dr. Neugut testifies further that not including metastatic patients in such a study would be highly unusual because the drug treatment would not be a local cure, whereas radiation or surgery could be. (*See id.*)

Petitioner argues further that other prior art, referring to the MSR indicates that physicians understood the MSR to be for patients with metastatic tumors. (*See* Pet. 32–33 (citing (Ex. 1049, 444; *see also* Ex. 1050, S4; Ex. 1003 ¶ 90.) 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 the MSR 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. (*See* PO Resp. 22.) 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. (*See* PO Resp. 23 (citing Ex. 2163:14:9–15:12).)

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 that one of ordinary skill in the art would have understood the MSR to disclose treating patients with metastatic colorectal cancer. (*See* Ex. 1049, 444; Ex. 1050, S4.) Patent Owner does not address this evidence.

We are persuaded by Petitioner's evidence that claims 29 and 30 are anticipated by the MSR.

c) Claims 4, 17, 31, 33, 35, 37, 39, and 41

Claims 4, 17, 31, 33, 35, 37, 39, and 41 are directed to the therapeutic effects of treating the patient of independent claim 1 or 14 with pembrolizumab. For example, claims 4 and 17 require that the patient is treated with an amount of pembrolizumab "shown in a clinical trial" to be effective in promoting progression-free survival or to reduce the risk that MSI-H or dMMR colon cancer will progress. (Ex. 1001, 25:57–59, 26:35–36.) Claims 31, 33, 35, 37, 39, and 41 recite "result in" response rates and

probabilities of progression-free survival for MSI-H or dMMR colorectal cancer patients. (*See* Ex. 1001, 27:5–8, 27:13–17, 27:22–25, 28:1–4, 28:10–14, 28:20–23.) Petitioner argues that because the MSR teaches treating patients having MSI-H colorectal cancer patients with 10 mg/kg of pembrolizumab every 14 days it is inherently effective in achieving the results recited in claims 4, 17, 31, 33, 35, 37, 39, and 41. (*See* Pet. 24, 29, 33–37 (citing Ex. 1003 ¶¶ 40, 60–62, 65, 79, 92, 95, 97, 99, 101, 103).)

Patent Owner argues that the MSR does not disclose the results recited in these claims and, thus, does not anticipate them. (*See* PO Resp. 23–25.) Patent Owner relies on Dr. Neugut's and Dr. Lonberg's testimony to argue that one of ordinary skill in the art could not have known the outcome of the MSR study and would have had no way of knowing whether the amount of pembrolizumab was effective in promoting survival or reduced the risk of cancer progression, or that it provided any objective response rate or progression free survival rate. (*See id.* (citing Ex. 2072 ¶¶ 111, 172, Ex. 2163, 111:20–112:2, 115:25–116:7, 114:22–24).)

As Patent Owner argues, to show inherent anticipation Petitioner must show that the results recited in the challenged claims are necessarily present in the disclosure of the MSR. (*See* PO Resp. 24; *see also Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.")). But Patent Owner also argues that Petitioner must show that inherent limitations would be recognized by those of ordinary skill in the art, citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit, however, has expressly

"reject[ed] the contention that inherent anticipation requires recognition in the prior art." *See Schering*, 339 F.3d at 1377–1378 ("Thus, in *Continental Can,* this court did not require past recognition of the inherent feature, but only allowed recourse to opinions of skilled artisans to determine the scope of the prior art reference.").

Because, as discussed above in regard to claims 1 and 14, the MSR teaches testing a biological sample obtained from a colorectal cancer patient to determine if the cancer is MSI-H or dMMR and in response to determining that the colorectal cancer is MSI-H or dMMR, treating the patient with a therapeutically effective amount of pembrolizumab, we are persuaded that the results of such steps, as recited in claims 4, 17, 31, 33, 35, 37, 39, and 41 would be inherent even if they had not yet been reported. "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering*, 339 F.3d at 1380.

Accordingly, we are persuaded that claims 4, 17, 31, 33, 35, 37, 39, and 41 are anticipated by the MSR.

d) Claims 2, 5, 6, 11, 12, 15, 18, 19, 24, 25, 27, and 28

Petitioner argues that claims 2, 5, 6, 11, 12, 15, 18, 19, 24, 25, 27, and 28 are also anticipated by the MSR. (*See* Pet. 23–31.) Patent Owner does not argue to the contrary.

Briefly, Petitioner argues that claims 2 and 15, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSR because the Eligibility Criteria section of the MSR requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies that one of ordinary skill in the art would have understood that a biopsy of a

patient's tumor obtains tumor tissue for testing. (*See* Ex. 1005, 5–6; Ex. 1003 ¶ 64.)

Petitioner argues that claims 5, 6, 18, and 19, which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient is anticipated by the MSR because the MSR teaches treating colorectal cancer patients whose tumors are determined to be MSI-H. (*See* Pet. 24, 30 (citing Ex. 1003 ¶¶ 66, 67, 80, 81).)

Petitioner argues that claims 11 and 12, which require the pembrolizumab to be administered to the patient intravenously is anticipated by the MSR because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. (*See* Pet. 27–28 (citing Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1054, 3; Ex. 1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003, ¶¶ 73, 74).)

Petitioner argues that claims 27 and 28, which recite "further comprising testing or having tested the patient for progression of the colorectal cancer after the treatment" (Ex. 1001, 26:62–67) were anticipated by the MSR because one of ordinary skill in the art would have understood that an "[i]mmune-related ***progression*** free survival (irPFS) rate," as disclosed in the Primary Outcome Measures section of the MSR, is a test for disease progression. (*See* Pet. 31 (citing Ex. 1005, 4–5, Ex. 1048, 236; Ex. 1003 ¶¶ 85, 86).)

We are persuaded by Petitioner's uncontested evidence that each of claims 2, 5, 6, 11, 12, 15, 18, 19, 24, 25, 27, and 28 are anticipated by the MSR.

e) Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of the challenged dependent claims. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claims 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 are anticipated by the MSR.

E. Ground 2: Obviousness over the MSR or the MSR and Pernot

Petitioner argues that the same claims challenged under Ground 1 as being anticipated by the MSR would also have been obvious over the MSR alone or the MSR and Pernot. (*See* Pet. 42–46.)

Patent Owner argues that "under Ground 2 Merck does not address any specific dependent claim, and thus has not met its burden with respect to the obviousness of any dependent claim, particularly the two groups of claims that are independently patentable over Ground 2 . . . ." (PO Resp. 55–56.)

Because "anticipation is the epitome of obviousness," we are persuaded that the claims Petitioner challenges as being anticipated by the MSR would have been obvious over the MSR and other references, for the reasons discussed above. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002). (*See* Pet. Reply 21.) Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 as being obvious over the MSR alone.

F. Grounds 3–8: Obviousness over the MSR and Other References.

Petitioner argues that the MSR and other prior art references render certain dependent claims obvious. (*See* Pet. 46–65.) Because, as discussed above, we determined that some of these claims are anticipated by the MSR,

they would have been rendered obvious by the MSR as well. Accordingly, we review Petitioner's obviousness challenges only for the claims not included in Ground 1 based on anticipation.

1. Claims 8 and 21: Obviousness over the MSR, Pernot, and Chapelle

Claims 8 and 21 recite the method of claim 1 or 14, respectively, "wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample." (Ex. 1001, 26:1–3, 26:47–49.)

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. 43 (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, making them good candidates for immunotherapy." (Ex. 1006, 3740–41; *see* Pet. 10.) 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. 43 (citing Ex. 1003 ¶ 108).)

Petitioner also cites Chapelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claim 8. (*See* Pet. 48 (citing Ex. 1007, 3380, 3384; Ex. 1003 ¶¶ 117, 120).)

Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) with Chapelle's standard methods for testing for MSI-H, including testing with immunohistochemistry, and would have had an expectation of success in doing so because the method of testing for MSI-

H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. (*See* Pet. 48–49 (citing (Ex. 1003 ¶¶ 117, 120).)

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

2. Claims 3 and 16: Obviousness over the MSR, Pernot, and Steinert

Claims 3 and 16 recite the method of claim 1 or 14, respectively, "wherein the biological sample is a body fluid from the patient." (Ex. 1001, 25:53–54, 27:31–32.)

Petitioner cites Steinert for its teaching of testing a body fluid to determine whether a tumor is microsatellite instability high. (*See* Pet. 49–50 (citing Ex. 1008, OF6; Neugut Decl., Ex. 1003 ¶ 127).)

Petitioner argues that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) and Steinert because the MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H and Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. (*See* Pet. 49–50 EX1008, OF6; EX1003 ¶ 127.) Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have had a reasonable expectation of success given that the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. (*See* Pet. 50 (citing Ex. 1001, 6:25–26 ("Testing of MSI can be accomplished by any means known in the art"), 6:35–38; Ex. 1003 ¶ 127).)

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

3. Claims 9, 10, 22, and 23: Obviousness over the MSR, Pernot, and Salipante

Claims 9 and 22 recite the methods of claims 1 and 14, respectively, "wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample." (Ex. 1001, 26:4–6, 26:50–52.) Claims 10 and 23 recite the methods of claims 1 and 14, respectively, "wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample." (Ex. 1001, 26:7–9, 26:53–55.)

Petitioner cites to the teaching in Salipante of testing a tumor for microsatellite instability high using a PCR test or next generation sequencing on a sample. (*See* Pet. 58–60 (citing Ex. 1010, 1192–1193; Ex. 1003 ¶¶ 155, 159.))

Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have been motivated to combine the MSI-H Study Record (alone or combined with Pernot) and Salipante because the MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H and Salipante teaches standard methods of testing whether a tumor was MSI-H using a PCR test on the sample or next generation sequencing. (*See* Pet. 58–60 (citing Ex. 1003 ¶¶ 155, 159).) Petitioner argues further, again citing Dr. Neugut's testimony, that one of ordinary skill in the art would have had a reasonable expectation of success because the method of testing for MSI-H does not affect the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and because a polymerase chain reaction test was known, as acknowledged in the '393 patent. (*See* Pet. 58–60 (citing Ex. 1001, 6:25–26; 8:10–15; Ex. 1003 ¶¶ 156, 160).)

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

4. Claims 13 and 26: Obviousness over the MSR, Pernot, Steinert, and Hamid

Claims 13 and 26 recite the methods of claims 3 and 16, respectively, wherein the biological sample tested is a body fluid and "wherein the pembrolizumab is administered to the patient intravenously." (Ex. 1001, 26:14–15, 26:60–61.)

Petitioner cites Hamid for its teaching of administering pembrolizumab (called "lambrolizumab") intravenously. (Pet. 61–63 (citing Ex. 1011, 134; Neugut Decl., Ex. 1003 ¶ 166).) Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have had a motivation to combine the MSR (alone or combined with Pernot) and 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. 61–62 (citing Ex. 1011, 134; *see also* Ex. 1055, 1, Ex. 1003 ¶¶ 168–169).) 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.*)

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

5. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 8–10, 13, 16, 21–23, and 26 as being obvious. (*See,*

e.g., PO Resp. 55–57 (arguing that Petitioner relies on Chapelle, Steinert, Benson, Salipante, and Hamid for "discrete limitations unrelated to" the "in response to" limitation of the independent claims or the expectation of success in the recited methods).) That is, Patent Owner argues against all of the obviousness challenges together, without arguing that any of the limitations recited in the dependent claims renders the method of claim 1 or 14 non-obvious.

Patent Owner argues only 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 claims 1 and 14. (*See* PO Resp. 39–55.) For example, Patent Owner argues that neither the MSR, 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 pembrolizumab. (*See id.* at 41–55.) Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, 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."). Petitioner presents persuasive evidence that one of ordinary skill in the art would had a reasonable expectation of success in making a method that tests for MSI-H with immunohistochemistry, polymerase chain reaction, or next generation sequencing, that uses a bodily fluid, or that uses

intravenous administration of pembrolizumab, as recited in the challenged dependent claims, and 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 challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. (*See* PO Resp. 57–91.) 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 methods recited in the independent claims are anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 14. *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, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8, 9, 10, 13, 16, 21, 22, 23, 26), Patent Owner must show a nexus between the claimed methods 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 mentions a nexus between the Keytruda® (pembrolizumab) label for testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claims 8, 9, 21, and 22. (*See* PO Resp. 62.) But Patent Owner does not direct us to evidence of a nexus to limitations recited in the dependent claims, for example to claims 3 and 16, which recite testing a biological sample that is a bodily fluid, claims 10 and 23, which recite testing that comprises carrying out next generation sequencing, or claims 13 and 26, which recite pembrolizumab administered intravenously.

Even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 14, not the limitations of the claims Petitioner challenges as being obvious. (*See* PO Resp. 68–91.) 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. 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 methods recited in claims 1 and 14 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claim 3, or "wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample," as recited in claim 10, demonstrated unexpected results or commercial success.

Accordingly, Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 3, 8, 9, 10, 13, 16, 21, 22, 23, and 26 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

6. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSR and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[7]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–42 of the '393 patent are unpatentable.

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42	102	MSR	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42	
1, 2, 4–7, 11, 12,	103	MSR, Pernot	1, 2, 4–7, 11, 12, 14,15,	

[7] 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
14, 15, 17–20, 24, 25, 27–42			17–20, 24, 25, 27–42	
2, 8, 15, 21	103	MSR, or MSR, Pernot, Chapelle	2, 8, 15, 21	
3, 16	103	MSR, or MSR, Pernot, Steiner	3, 16	
7, 20, 29, 30, 32, 34, 36–42	103	MSR, or MSR, Pernot, Benson	7, 20, 29, 30, 32, 34, 36–42	
9, 10, 22, 23	103	MSR, or MSR, Pernot, Salipante	9, 10, 22, 23	
11, 12, 24, 25	103	MSR, or MSR, Pernot, Hamid	11, 12, 24, 25	
13, 26	103	MSR, or MSR, Pernot, Steinert, Hamid	13, 26	
Overall Outcome			1–42	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–42 of the '393 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.

IPR2024-00240
Patent 11,591,393 B2

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Matthew Chun
Todd Miller
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
mchun@fr.com
miller@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 64
Date: October 28, 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.

IPR2024-00622
Patent 10,934,356 B2

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

SNEDDEN, *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 1–28 of U.S. Patent No. 10,934,356 B2 (Ex. 1001, "the '356 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Preliminary Response. In addition, as authorized (Paper 8), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (Paper 9) and Patent Owner filed Patent Owner's Sur-reply (Paper 11).

We instituted trial on September 23, 2024. Paper 12 ("Inst. 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 45 (confidential Paper 42) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 50 (confidential Paper 47) ("PO Sur-Reply")). The parties declined to present oral arguments in this proceeding. 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. For the reasons discussed below, we determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–28 of the '356 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. 66. Patent Owner identifies The Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '356 patent is involved in *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), filed November 29, 2022. Pet. 66; Paper 3, 1.

In addition, several other *inter partes* reviews are related to this proceeding, including IPR2024-00240 against U.S. Patent No. 11,591,393; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00649 against U.S. Patent No. 11,629,187; and IPR2024-00650 against U.S. Patent No. 11,634,491.

D. The '356 patent (Ex. 1001)

The '356 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '356 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.* at Abstract. More specifically, the '356 patent is directed to treating cancer patients with high mutational burdens, such as those found in microsatellite instable ("MSI . . . in DNA mismatch repair ("MMR-deficiency"). *Id. at* 1:28–30.

The '356 patent explains that

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

Ex. 1001, 1:51–58. According to the '356 patent, "[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types." *Id*. at 2:2–5. However, the Specification describes that

> in reports of the effects of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment. . . . What was different about this single patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id. at 2:59–3:2. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '356 patent describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id*. at 3:8–15. The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id*. at 8:47–52. According to the '356 patent, "[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors." *Id*. at 6:43–47.

E. The Challenged Claims

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

> 1. A method for treating cancer in a patient in need thereof, comprising:

determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status;

administering an effective amount of pembrolizumab to the patient;

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

wherein the patient has received a prior cancer therapy drug.

Ex. 1001, 25:55–26:2.

Representative independent claim 11 is reproduced below:

11. A method for treating cancer in a patient in need thereof, the method comprising:

detecting a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status in a tumor sample from the patient;

wherein the tumor sample exhibits an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers;

administering an effective amount of pembrolizumab to the patient;

determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers; and

wherein the patient has received a prior cancer therapy drug.

Ex. 1001, 26:31–49.

Representative independent claim 19 is reproduced below:

> 19. A method for treating cancer in a patient in need thereof comprising:
>
> selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient solid tumor, the tumor having progressed following a cancer therapy;
>
> administering an effective amount of pembrolizumab to the patient; and
>
> determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status.

Id. at 27:1–15.

Representative independent claim 23 is reproduced below:

> 23. A method for treating cancer in a population of cancer patients in need thereof, comprising:
>
> administering an effective amount of pembrolizumab to patients in the population of cancer patients, which patients have a tumor that exhibits a high micro satellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, said tumor having progressed following a prior treatment; and
>
> observing an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab.

Ex. 1001, 28:1–11.

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" or "MSR").

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

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

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

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

Ex. 1034, Brown et al., *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) GENOME RESEARCH 743 (May 2014) ("Brown").

Ex. 1087, Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 5002 (2004) ("Duval").

Petitioner also relies on the Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150) to support its contentions.

Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2001), Dung Le, M.D. (Ex. 2130), and Richard Goldberg, M.D., (Ex. 2090).

G. Asserted Grounds of Unpatentability

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

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 6–11, 13–20, 22–24, 26–28	102	MSR
2	1, 6–11, 13–20, 22–24, 26, 27	103	MSR, Pernot, Benson
3	2–5, 11–18, 20, 21, 24, 25	103	MSR, Pernot, Benson, Chapelle
4	1, 6–11, 13–20, 22–24, 26–28	103	MSR, Brown, Duval, Benson
5	2–5, 11–18, 20, 21, 24, 25	103	MSR, Brown, Duval, Benson, Chapelle
6	18	103	MSR, Pernot, Benson, Chapelle, Hamid
7	18	103	MSR, 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. Pet. 10–11; PO Resp. 6.

We determine that no express construction of any claim term is necessary to resolve the dispute between the parties. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)). We construe claims "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." 37 C.F.R. § 42.100(b) (2020).

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 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. Pet. 11 (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. 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 '356 patent claims a method of treating a human patient with cancer having certain characteristics using pembrolizumab and the main prior art reference cited by Petitioner, MSR, discloses testing

pembrolizumab to treat human patients. *See*, *e.g.*, Ex. 1001, 25:55–26:2; 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 '356 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.

II. ANALYSIS

A. Legal Standards

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

(Fed. Cir. 2003) ("At the outset, this court rejects the contention that inherent anticipation requires recognition in the prior art.").

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

> if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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

B. Summary of the Cited Prior Art

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

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

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

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

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" *Id.* at 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

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

2. Pernot (Ex. 1006)

Pernot is an article titled "Colorectal cancer and immunity: What we know and perspectives." Ex. 1006, 3738. Pernot discloses that "Comprehension of antitumor immune response and combination of the different approaches of immunotherapy may allow the use of effective immunotherapy for treatment of colorectal cancer in the near future." *Id.*

More specifically, Pernot discloses that "[m]icrosatellite instability (MSI) is associated with CRC in patients with Lynch syndrome." 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.

3. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id*. at 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id*. at 3380, 3384.

4. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id*. at 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id*. at 1034.

5. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.* at 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic mutations have . . . elevated expression of CTLA4 and PDCD1," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.* at 747–48.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses

that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.*

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

Petitioner contends that claims 1, 6–11, 13–20, 22–24, and 26–28 are anticipated by the MSI-H Study Record. Pet. 13–38. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how each element of claims 1, 6–11, 13–20, 22–24 and 26–28 is disclosed by the MSI-H Study Record. *Id.* Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 62–128.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 15–16. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 17. Relying on those cases, Petitioner contends that "the MSI-H Study

Record inherently anticipates claims 1, 6–11, 13–20, 22–24 and 26–28 of the '356 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 16.

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '356 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 13–14.

Independent claims 1 and 11 each require that, prior to receiving treatment according to the claimed method, the patient must have received a prior cancer therapy drug, while independent claims 19 and 23 require that the patient's tumor must have progressed following a cancer therapy. Independent Claims 1, 11, and 19 also require knowledge of the outcome of the study initiated by the MSR. Like Petitioner, our analysis focuses on independent claim 1. *See e.g.,* Pet. 27–29 (relying substantially on analysis of claim 1 for independent claim 11), 31–32 (relying substantially on analysis of claim 1 for independent claim 19), 33–35 (relying substantially on analysis of claim 1 for independent claim 23).

1. Independent 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.

Pet. 16 (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 ¶ 62).

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]: "determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status;"

Petitioner argues that the MSI-H Study Record teaches this first element of claim 1 because the MSI-H Study Record discloses three study arms, including one with patients having MSI-H colorectal cancer and another of patients having MSI-H non-colorectal cancer. Pet. 17–18 (citing Ex. 1005, 4 (Arms and Interventions)). Dr. Neugut's testimony supports this argument. *See* Ex. 1003 ¶¶ 63–66. In addition, Dr. Neugut testifies that the patients determined to have defective MMR (dMMR) status are biologically the same population as patients with MSI-H status. *Id.* ¶ 65 (citing Ex. 1020,[1] 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.

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

c) Element [1.2]: "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. Pet. 19 (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 '356 patent. *Id.* (citing Ex. 1003 ¶¶ 67–71); *see* Ex. 1001, 4:14–27, 8:45–51, 13:45–52, 16:30–35, 16:56–65, Figures 2, 11.) Petitioner argues further that any efficacy required in the claim is inherent to that dosage because the '356 patent shows that dosage to be effective. Pet. 19–20.

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 '356 patent.

d) Element [1.3]: "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and"

Petitioner argues that element 1.3 of claim 1 is a result of the method of treatment reported in the MSI-H Study Record. *See* Pet. 20–21 (citing Ex. 1005, 4–5 (Outcome Measures); Ex. 1003 ¶¶ 72–74). Petitioner argues that the MSI-H Study Record teaches actively measuring specific outcomes in patients having MSI-H cancer and cancer that is not MSI-H. Pet. 21 (citing Ex. 1005, 4–5 (Outcome Measures); Ex. 1003 ¶¶ 72–73). In support,

Dr. Neugut testifies that the examples, tables, and figures of the '356 patent discuss the design and results of the MSI-H Study. Ex. 1003 ¶¶ 40–41, 72–74 (citing Ex. 1001, 6:43–22:40, 3:13–15, Figs. 1–13; Ex. 1005.

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

> 22. Our research group eventually approached Merck. Merck agreed in early 2013 to supply its then-unapproved anti-PD-1 antibody, MK-3475 (pembrolizumab) for use in the study. It was, however, the research team at Hopkins who secured IRB approval, conducted, and paid for the study. On June 12, 2013, the solicitation for patients was first posted on clinicaltrials.gov **(Exhibit D).** In my mind, the four arms allowed us to try to get at an answer to a question to which we did not know the answer–specifically whether or not patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated with MK-3475, compared with the more common MSS [microsatellite stable] or MMR proficient colon cancers. Thus, the trial covered all patients with colon cancer, MSI and MSS, but separated into two groups.
>
> 23. The preliminary results of this study demonstrated clinical responses at an unexpectedly high rate (>50% objective response rate) in the MSI-high (MMR deficient) arm but not in the MSS (MMR proficient) arm. . . .

Ex. 1002 (Part 7), 2490–2491 (February 4, 2022, Affidavit ¶¶ 22–23) (citing "Exhibit D," the MSR). That affidavit, submitted during prosecution of the '356 patent, supports the argument that an improved outcome of treating a patient with a tumor exhibiting an MSI-high or an MMR deficiency status with pembrolizumab compared to similarly treating a patient without an MSI-high or an MMR deficiency status, as recited in claim 1, is an inherent result because the treatment would necessarily provide the result. *Compare*

id. with Ex. 1001, 6:43–47 ("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 ['356 patent] is irrelevant." Pet. 21 (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. 10–17. 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. 15 ("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 received a prior cancer therapy drug" or "the tumor having progressed following a [cancer therapy/prior treatment]." PO Resp. 11–12; PO Sur-Reply 2. We are unpersuaded. Rather, 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. 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. 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. 13 (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. 13–15; 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 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 [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 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 '356 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 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. PO Resp. 15. 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. PO Resp. 15–17; 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. 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. 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*, 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. 21 (citing *Schering*, 339 F.3d at 1380). According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the '356 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 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. 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. PO Resp. 18–25. 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 MSR 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. 19–25. 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. PO Resp. 20–22. 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." *Id.* at 23.

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.

e) Element [1.4]: "wherein the patient has received a prior cancer therapy drug."

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

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

Petitioner argues that "[p]atients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies." *Id.* at 23 (citing Ex. 1020, 25; Ex. 1009, 1034; Ex. 1047, 4–7; Ex. 1003 ¶ 77). To that point, Dr. Neugut testifies that

patients with metastatic and advanced endometrial, small bowel, and gastric cancer "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 ¶ 77 (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 other antibodies. *Id.* at ¶ 75–76 ("[T]he person of ordinary skill would have understood that the MSI-H Study Record recognizes that patients would have received prior cancer drug therapies, and because of that makes it a point to exclude those that received '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.* ¶ 79.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 64–67. Dr. Oberstein testifies that because the eligibility criteria stated in the MSR 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 MSR is silent about whether eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for an inherency finding." PO Resp. 7–8.

Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression." Ex. 2072 ¶ 96; PO Resp. 9. Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. 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 MSR 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 the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitation for a solid tumor that has progressed following at least one prior cancer treatment was disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. *Contra* PO Resp. 6–9.

2. Independent Claims 11, 19 and 23

Patent Owner does not present separate arguments against Petitioner's challenge to claims 11, 19 and 23 as being anticipated by the MSR. *See, e.g.* PO Resp. 10–16 (referring to claims 1, 11, 19 and 23 together). For the reasons discussed above regarding claim 1, we are persuaded that claims 11, 19 and 23 are anticipated by the MSR.

3. Dependent Claims 6–10, 13–18, 20, 22, 24, and 26–28

Petitioner argues that claims 6–10, 13–18, 20, 22, 24, and 26–28 are anticipated by the MSR. Pet. 25–37. Patent Owner presents the arguments discussed above regarding the limitations of independent claims 1, 11, 19, and 23, but does not present arguments or direct us to evidence against these challenges that are specific to the limitations of dependent claims 6–10, 13–18, 20, 22, 24, and 26–28. As summarized below, we find that the record supports Petitioner's arguments.

a) Claims 6 and 15

Claims 6 and 15 depend from claims 1 and 11, respectively, and each requires the patient to have received a "prior cancer therapy" (*see supra*, Section II.c.1.e (Element 1.4)), and the patient's cancer to have progressed "after the patient received the prior cancer therapy drug." Petitioner argues that the additional limitations of claims 6 and 15 are anticipated by the MSR and "addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]." Pet. 25, 30 (citing Ex. 1003 ¶¶ 81, 99–100). We agree.

b) Claims 7, 16 and 22

Petitioner argues that claims 7, 16, and 22 are anticipated by the MSR. Pet. 25–26, 30–31, 33. 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 7, 16, and 22.

Claims 7, 16, and 22 depend from claims 1, 11, and 19 respectively, and further limit the outcome exhibited by the patients selected and administered pembrolizumab, as recited in claims 1, 11, and 19. Specifically, claims 7, 16, and 22 recite, "wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival."

Petitioner argues that these outcomes are inherent to the methods taught in the MSR. Pet. 26–28 (citing Ex. 1003 ¶¶ 77–80).) We agree with Petitioner because, as discussed above, we are persuaded that the steps recited in claims 1, 11, and 19 are taught by the MSR and the efficacy of those steps would be inherent to practicing the method recited in the steps. *See Montgomery*, 677 F.3d at 1385; *Schering Corp.*, 339 F.3d at 1377.

c) Claims 8, 17, and 27

Petitioner argues that claims 8, 17, and 27 are anticipated by the MSR. Pet. 25–26, 30, 33. 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 8, 17, and 27.

Claims 8 and 17 depend from claims 7 and 16, respectively, and further recite, "wherein the outcome is assessed in the patient at 20 weeks after administering pembrolizumab." Claim 27 depends from claim 23 and further recites, "wherein the objective response rate is assessed in the

population of cancer patients at 20 weeks after administering pembrolizumab."

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)." Pet. 26 (citing Ex. 1005, 4–5 (Outcome Measures)). Petitioner argues that this disclosure reads on this limitation because it discloses measuring the relevant outcomes at 20 weeks. *Id.* (citing Ex. 1003 ¶ 85). We agree.

d) Claims 9, 10, 13, 14, and 26

Petitioner argues that claims 9, 10, 13, 14, and 26 are anticipated by the MSR. Pet. 24–25, 31. Claims 9 and 10 require that the cancer recited in claim 1 be metastatic cancer or metastatic colorectal cancer, respectively. Claims 13 and 14 require that the cancer recited in claim 11 be metastatic cancer or metastatic colorectal cancer, respectively. Claim 26 requires that the cancer recited in claim 23 be metastatic cancer.

Petitioner argues that the MSR discloses a clinical study treating colorectal cancer patients with "tumors" and "measurable disease." Pet. 22–24, 27 (citing Ex. 1005, 2, 4, 5–6). Petitioner relies on Dr. Neugut's testimony that in the context of the MSR, the treated patients would have had metastatic cancer. *Id.* (citing Ex. 1003 ¶¶ 75–80, 86). Dr. Neugut testifies that "measurable" disease in the context of a study record studying a new drug refers to patients having metastatic and advanced cancer.

Ex. 1003 ¶ 76. According to Dr. Neugut, one of ordinary skill would therefore have understand that the MSR teaches treating patients with metastatic cancer and locally advanced cancer that is unresectable for purpose of a cure. *Id*. Dr. Neugut testifies further that not including metastatic patients in such a study would have been highly unusual because the drug treatment would not be a local cure, whereas radiation or surgery could be. *Id*.

Petitioner argues further that other prior art, referring to the MSR indicates that physicians understood the MSR to be for patients with metastatic tumors. Pet. 27 (citing Ex. 1049, 444; Ex. 1050, S4; Ex. 1003 ¶ 86. 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 the MSR 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. 18 (citing Ex. 2163:14:9–15:12).)

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 that one of ordinary skill in the art would have understood the MSR to disclose treating patients with metastatic colorectal cancer. *See* Ex. 1049, 444; Ex. 1050, S4. Patent Owner does not address this evidence.

In view of the above, we are persuaded by Petitioner's evidence that claims 9, 10, 13, 14 and 26 are anticipated by the MSR.

e) Claim 18

Petitioner argues that claim 18 is also anticipated by the MSR. Pet. 31. Patent Owner does not argue to the contrary.

Claim 8 recites "The method of claim 11, wherein pembrolizumab is administered by intravenous infusion." Petitioner argues that the prior art, including the pembrolizumab package insert, demonstrates that pembrolizumab was administered intravenously for the treatment of cancer. *Id.* (citing Ex. 1055,[2] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1003 ¶¶ 104–105.) We are persuaded by Petitioner's evidence that claim 18 is anticipated by the MSR.

f) Claims 20 and 24

Claims 20 and 24 depend from claims 1 and 23, respectively, and further recite, "wherein the tumor exhibits instability of a microsatellite marker." Petitioner argues that claim 20 and 24 is anticipated by the MSR. Pet. 32–33, 35–36. Specifically, Petitioner contends that "all tumors that are

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

MSI-H exhibit instability in more than one microsatellite marker." *Id.* at 32–33. Patent Owner does not argue to the contrary. We find that the record as supports Petitioner's arguments. *See* Ex. 1003 ¶ 112 (citing Ex. 1010, 1193, 1196; Ex. 1018, 293; Ex. 1019, 1065).

g) Claim 28

Claim 28 depends from claim 23 and further recites, "wherein the cancer is not colorectal cancer." Pet. 36–38. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating patients having non-colorectal MSI-H cancer. *Id.* at 36 (citing Ex. 1003 ¶¶ 125–129; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)).

Patent Owner does not argue to the contrary. *See* PO Resp. 6–25.

We are persuaded by Petitioner's uncontested evidence that claim 28 is anticipated by the MSR. Pet. 36–38 (Ex. 1005, 2–5; Ex. 1003 ¶¶ 125–29).

4. Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of claims 1, 6–11, 13–20, 22–24, and 26–28. Accordingly, we determine that claims 1, 6–11, 13–20, 22–24, and 26–28 are anticipated by the MSR.

D. Grounds 2 and 4 – Obviousness of Claims 1, 6–11, 13–20, 22–24, and 26–28

In Ground 2, Petitioner contends that claims 1, 6–11, 13–20, 22–24, and 26–27 are unpatentable as obvious over the combination of the MSI-H Study Record, Pernot, and Benson. Pet. 40–47. In Ground 4, Petitioner challenges the patentability of claims 1, 6–11, 13–20, 22–24, and 26–28, citing MSR, Brown, Duval, and Benson. Pet. 54–60. Patent Owner opposes

Petitioner's allegations in Grounds 2 and 4. PO Resp. 26–27. We address the parties' arguments and evidence with regards to Grounds 2 and 4 below.

1. Petitioner's Contentions

a) Ground 2

Petitioner asserts that these references disclose elements that Patent Owner might argue are not taught in the MSI-H Study Record, specifically the improved outcome and efficacy recited in claim 1, testing for MSI-H or dMMR tumors, and treating patients that have progressive or metastatic disease. *Id.* at 41–47 (citing December 14, 2020, Notice of Allowance in the '549 appl., Ex. 1002 (Part 9), 3069).

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

Petitioner cites further to Dr. Neugut's testimony to argue that one of ordinary skill in the art would have been motivated to combine the disclosure of Pernot with the methods taught in the MSI-H Study Record in order to obtain the results of the MSI-H Study Record's study. *Id.* at 42 (citing Ex. 1003 ¶ 136).

Additionally, Petitioner argues that the state of the art indicates one of ordinary skill would have had a reasonable expectation of success in the claimed method because successful treatment with a PD-1 inhibitor of a colorectal cancer patient having an MSI-H tumor was reported in the prior art. *Id.* at 42–43. Petitioner cites to other references, for example Champiat,[3] which teaches:

> Moreover, if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)- deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1 and 2, early onset), all of which display severe genomic instability.

Ex. 1032, e27817-5. Dr. Neugut testifies that Champiat, as well as other references, "independently urged the person of ordinary skill to treat MSI-H cancer with PD-1 inhibitors, like pembrolizumab, or other immunotherapy." Ex. 1003 ¶ 138. Citing to Dr. Neugut's testimony, Petitioner argues further that the prior art demonstrates the characteristics of cells that would have more efficacy with PD-1 inhibitors were known and that it was known that MSI-H tumors had these characteristics. Pet. 43 (citing Ex. 1003 ¶¶ 43–46, 139).

In light of this evidence of the state of the art at that time, Dr. Neugut testifies that one of ordinary skill in the art would have wanted to obtain data from the MSI-H Study Record and would have reasonably expected success,

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

given that pembrolizumab was already approved for another oncology indication. Ex. 1003 ¶¶ 137–40; Pet. 43. Dr. Neugut concludes 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 ¶ 140.

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

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

colorectal cancer that was metastatic, with a reasonable expectation of success. Ex. 1003 ¶¶ 143–144.

In summary, Petitioner relies on Pernot to demonstrate that one of ordinary skill in the art would have considered patients with MSI-H tumors to be good candidates for immunotherapy, such as PD-1 inhibitors, and thus, that the ordinarily skilled artisan would have been motivated to obtain the results of the MSI-H Study Record. Pet. 41–42 (citing Ex. 1003 ¶ 136; 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 a metastatic tumor. *Id.* at 46–47 (citing Ex. 1009, 1034).

b) Ground 4

In Ground 4, Petitioner relies on Brown for its teaching that PD-1 inhibitors inherently had more efficacy when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 55 (citing Ex. 1034, 747). Petitioner relies on Duval for its teaching that MSI-H cancers have cells that are easy for immune cells to recognize. *Id.* (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 MSI-H Study Record. Ex. 1003 ¶¶ 170–177; Pet. 56.

2. Patent Owner's Contentions

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. PO Resp. 25–26. Specifically, Patent Owner argues that the MSR does not teach the "prior cancer

therapy"/"progressed following a [cancer therapy/prior treatment]" required by the independent claims or "metastatic" limitation of dependent claims 9–10, 13–15, and 26. *Id.* Thus, Petitioner's "obviousness challenges necessarily fail." *Id.* at 26.

3. Discussion

Because "anticipation is the epitome of obviousness," we are persuaded that the claims Petitioner challenges as being anticipated by the MSR would have been obvious over the MSR 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, 6–11, 13–20, 22–24, and 26–27 as being obvious over the MSR alone.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. PO Resp. 52–85. 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 method recited in claims 1, 6–11, 13–20, 22–24, and 26–28 is anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive as to the patentability of claims 1, 6–11, 13–20, 22–24, and 26–28. *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, 6–11, 13–20, 22–24, and 26–28 as being obvious

over the MSR alone or along with other references cited in Ground 2 and/or Ground 4.

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

Petitioner argues that certain dependent claims of the '356 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle and Hamid. Pet. 48–62. Because, as discussed above, we determined that some of these claims are anticipated by the MSR, they also would have been obvious by MSR alone. *In re McDaniel*, 293 F.3d at 1385. Accordingly, we review Petitioner's obviousness challenges only for the claims not deemed anticipated (i.e., claims 2–5, 12, 21 and 25).

1. Petitioner's Contentions

In Grounds 3 and 5, Petitioner additionally relies on Chappelle to address the elements of claims 2–5, 12, 21 and 25. *Id.* at 48–54, 60–61. Claims 2–5, 12, 21 and 25 provide as follows:

> 2. The method of claim 1, wherein the step of determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) status includes detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence.
>
> 3. The method of claim 2, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24.
>
> 4. The method of claim 1, wherein the step of determining that the patient has a tumor that exhibits a MMR deficiency status includes detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence.
>
> 5. The method of claim 1, wherein the MMR deficiency status of the tumor is detected by immunohistochemistry.

> 12. The method of claim 11, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21, or NR-24.
>
> 21. The method of claim 20, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24.
>
> 25. The method of claim 24, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24.

Ex. 1001, 26:3–16, 26:50–51, 27:18–19, 28:13–14.

Regarding claims 2 and 4, Petitioner argues that Chapelle teaches standard methods of testing whether a tumor is MSI-H, including determining whether the patient's tumor exhibits instability in a microsatellite marker. Pet. 48–51, 60–61 (citing Ex. 1007, 3380, 3383). Dr. Neugut supports this characterization of Chapelle. Ex. 1003 ¶¶ 149–151. Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) with Chapelle's standard methods for testing for MSI-H, including testing with immunohistochemistry, and would have had an expectation of success in doing so because the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. Pet. 48–49.

Regarding claims 3, 12, 21 and 25, Petitioner argues that Chapelle teaches determining whether a microsatellite marker is BAT-25 or BAT-26. *Id.* at 49–50 (citing Ex. 1007, 3380–84). For example, Chappelle teaches that "a standard test" using a "[p]anel consisting of . . . BAT26, BAT25" has "stood the test of time." *Id.* at 50 (citing Ex. 1007, 3382.)

Regarding claim 5, Petitioner argues that Chappelle teaches a standard method for testing for MSI-H, which includes using immunohistochemistry. Pet. 52 (citing Ex. 1007, 3380, 3384). "[T]he POSA would have had

motivation to combine the MSI-H Study Record (whether alone or combined with Pernot and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so." *Id.* (citing Ex. 1003 ¶ 158.)

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

2. Patent Owner's Contentions

Patent Owner does not raise specific arguments against any of the challenges to claims 2–5, 12, 21 and 25 as being obvious. *See, e.g.,* PO Resp. 25–52. That is, Patent Owner argues against all of the obviousness challenges together, without arguing that any of the limitations recited in the dependent claims render the methods of independent claims 1, 11, 19 or 23 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 the independent claims. PO Resp. 32–51. For example, Patent Owner argues that neither the MSR, 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 pembrolizumab. *Id.* at 34–55. Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, 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 Int'l 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 articles' authors did not appreciate the results."). 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 for MSI-H with immunohistochemistry or that uses intravenous administration of pembrolizumab, as recited in the challenged dependent claims, and 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 challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 52–85. 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 MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1, 11, 19 and 23. *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 6–10, 13–18, 20, 22, 24 and 26–28, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 2–5, 12, 21 and 25), Patent Owner must show a nexus between the claimed methods 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 mentions a nexus between the Keytruda® (pembrolizumab) label for testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claim 5. PO Resp. 56. But Patent Owner does not direct us to evidence of a nexus to limitations recited in the dependent claims, for example to claims 3, 12, 21 and 25, which recite 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. Thus, even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1, 11, 19 and 23, not the limitations of the claims 3, 12, 21 and 25. PO Resp. 53–61. 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. *Id.* 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 methods recited in claims 1, 11, 19, and 23 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the MMR deficiency status of the tumor is detected by immunohistochemistry," as recited in claim 5, demonstrated unexpected results or commercial success.

Accordingly, Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 2–5, 12, 21 and 25 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

3. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSR and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 2–5, 12, 21 and 25 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[4]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–28 of the '356 patent are unpatentable.

[4] 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).

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 6–11, 13–20, 22–24, 26–28	102	MSR	1, 6–11, 13–20, 22–24, 26–28	
1, 6–11, 13–20, 22–24, 26, 27	103	MSR, Pernot, Benson	1, 6–11, 13–20, 22–24, 26, 27	
2–5, 11–18, 20, 21, 24, 25	103	MSR, Pernot, Benson, Chapelle	2–5, 11–18, 20, 21, 24, 25	
1, 6–11, 13–20, 22–24, 26–28	103	MSR, Brown, Duval, Benson	1, 6–11, 13–20, 22–24, 26–28	
2–5, 11–18, 20, 21, 24, 25	103	MSR, Brown, Duval, Benson, Chapelle	2–5, 11–18, 20, 21, 24, 25	
18	103	MSR, Pernot, Benson, Chapelle, Hamid	18	
18	103	MSR, Brown, Duval, Benson, Chapelle, Hamid	18	
Overall Outcome			1–28	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–28 of the ’356 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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Matthew Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 63
Entered: November 6, 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.

IPR2024-00623
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.

IPR2024-00623
Patent 11,325,974 B2

For PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

For PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Matthew Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 63
Date: November 4, 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.

IPR2024-00624
Patent 11,325,975 B2

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

SNEDDEN, *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 1–4, 6–10, and 12–15 of U.S. Patent No. 11,325,975 B2 (Ex. 1001, "the '975 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Preliminary Response. Preliminary Response ("Prelim. Resp."), Paper 5. In addition, as authorized (Paper 7), Petitioner filed a Preliminary Reply to Patent Owner's Preliminary Response (Paper 8) and Patent Owner filed a Preliminary Sur-reply (Paper 10).

We instituted trial on September 23, 2024. 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 53) ("PO Sur-Reply")). The parties declined to present oral arguments in this proceeding. 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. For the reasons discussed below, we determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–4, 6–10, and 12–15 of the '975 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. 63. Patent Owner identifies The Johns Hopkins University as its real party-in-interest. Paper 3, 1 (Mandatory Notices) .

C. Related Matters

The parties indicate that the '975 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. 63; Paper 3, 1. Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 63; Paper 3, 1.

D. The '975 patent (Ex. 1001)

The '975 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '975 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.* at Abst. More specifically, the '975 patent is directed to treating cancer patients with high mutational burdens, such as those found in microsatellite instable ("MSI") cancer, with anti-PD-1 antibodies. *Id.* at 3:32–45. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.* at 1:26–28.

The '975 patent explains that

> [t]he PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including auto-immune reactions.

> The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors.

Id. at 1:49–56. According to the '975 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 1:67–2:3. However, the specification describes that

> in reports of the effects of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment. . . . What was different about this single patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id. at 2:57–3:1. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '975 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 3:8–14. 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 8:47–52. According to the '975 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 6:44–48.

E. The Challenged Claims

Petitioner challenges claims 1–4, 6–10, and 12–15. Representative independent claim 1 is reproduced below:

1. A method for treating cancer in a patient in need thereof,

wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, comprising:

administering an effective amount of an anti-PD-1 antibody 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 the anti-PD-I antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and

wherein the patient has received a prior cancer therapy drug.

Ex. 1001, 25:51–66.

Representative independent claim 9 is reproduced below:

9. A method for treating cancer in a patient in need thereof,

wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:

administering an effective amount of an anti-PD-1 antibody 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 the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient.

Id. at 26:28–42.

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" or "MSR").

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 RSCH. 743 (May 2014) ("Brown").

Ex. 1087, Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 5002 (2004) ("Duval").

Petitioner also relies on the Declarations of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150) to support its contentions.

Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072), Dung Le, M.D. (Ex. 2130), and Richard Goldberg, M.D., (Ex. 2090).

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–4, 6–10, and 12–15 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1–3, 6–10, 13–15	102	MSR
II	1–3, 6–10, 13–15	103	MSR, Pernot, Benson
III	4, 12	103	MSR, Pernot, Benson, Chapelle
IV	1–3, 6–10, 13–15	103	MSR, Brown, Duval, Benson
V	4, 12	103	MSR, Brown, Duval, Benson, Chapelle
VI	8	103	MSR, Pernot, Benson, Chapelle, Hamid
VII	8	103	MSR, 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. Pet. 11–12; PO Resp. 6.

We determine that no express construction of any claim term is necessary to resolve the dispute between the parties. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). We construe

claims "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." 37 C.F.R. § 42.100(b) (2020).

I. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art ("POSA" or "POSITA") at the time of the invention

> would be a medical doctor or a professional in a related field with at least five years of experience with treating cancer. . . . The POSA would also have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and a pathologist with comparable experience. . . . The inherent anticipation and obviousness grounds discussed herein would not change due to a modestly lesser or greater level of experience.

Pet. 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. PO Resp. 6 (citing Ex. 2072 ¶¶ 31–32, 86–94). Thus, Petitioner and Patent Owner characterize one of ordinary skill in the art differently. Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '975 patent claims a method of treating a human patient with cancer having certain characteristics using pembrolizumab and the main prior art reference cited by Petitioner, MSR, discloses testing pembrolizumab to treat human patients. *See*, *e.g.*, Ex. 1001, 25:50–66;

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 '975 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.

II. ANALYSIS

A. Legal Standards

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

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

> if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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

B. Summary of the Cited Prior Art

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

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

The 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 "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 MSR provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

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

2. Pernot (Ex. 1006)

Pernot is an article titled "Colorectal Cancer and Immunity: What We Know and Perspectives." Ex. 1006, 3738. Pernot discloses that "Comprehension of antitumor immune response and combination of the different approaches of immunotherapy may allow the use of effective immunotherapy for treatment of colorectal cancer in the near future." *Id.* More specifically, Pernot discloses that "[m]icrosatellite instability (MSI) is associated with CRC in patients with Lynch syndrome." *Id.* at 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.

3. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.* at 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.* at 3380, 3384.

4. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id.* at 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.* at 1034.

5. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in

patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.* at 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic mutations have . . . elevated expression of CTLA4 and PDCD1," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.* at 747–48.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with

immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.*

C. Ground 1: Anticipation by MSI-H Study Record

Petitioner contends that claims 1–3, 6–10, and 12–15 are anticipated by the MSR. Pet. 18–33. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSR and provides a detailed claim analysis addressing how each element of 1–3, 6–10, and 12–15 is disclosed by the MSR. *Id.* Petitioner supports this interpretation of the MSR with Dr. Neugut's testimony. Ex. 1003 ¶¶ 34–50.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 15–16. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 17. Relying on those cases, Petitioner contends that "the MSI-H Study Record inherently anticipates claims 1–3, 6–10, and 13–15 of the '975 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 18.

Petitioner argues further that the treatment described in the MSR is written description support for the claimed method because the MSR teaches the claimed drug, given at the only therapeutically effective dosage

described in the '975 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 16.

Independent claims 1 and 9 each require that, prior to receiving treatment according to the claimed method, the patient must have received a prior cancer therapy drug. Each claim also requires knowledge of the outcome of the treatment method so as to assess whether the outcome is improved as compared to a reference patient. Claims 1 and 9 differ in the reference patient for assessing an improved outcome, where the reference patient recited in claim 1 "has a tumor that does not exhibit a MSI-high or a MMR deficiency status" and the reference patient recited in claim 9 "has a tumor that does not exhibit a MSI-high status or is MMR proficient." Ex. 1001, cl.1, cl.3. Like Petitioner, our analysis focuses on independent claim 1. *See*, *e.g.*, Pet. 31–32 (relying substantially on analysis of claim 1 for independent claim 9).

1. Independent Claim 1

a) Preamble: "A method for treating cancer in a patient in need thereof, comprising:"

To begin, 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. 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 ¶ 62).

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]: "wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status,"

Petitioner argues that the MSR teaches this first element of claim 1 because the MSR discloses three study arms, including one of patients having MSI-H colorectal cancer and another of the patients having MSI-H non-colorectal cancer. Pet. 19–21 (citing Ex. 1005, 4 (Arms and Interventions)). Dr. Neugut's testimony supports this argument. Ex. 1003 ¶¶ 60–64. In addition, Dr. Neugut testifies that the patients determined to have defective MMR (dMMR) status are biologically the same population as patients with MSI-H status. Ex. 1003 ¶ 62 (citing Ex. 1020,[1] 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.

c) Element [1.2]: "administering an effective amount of an anti-PD-1 antibody to the patient;"

Petitioner continues the argument that the MSR anticipates claim 1 of the '975 patent, citing the "Arms and Interventions" section of the MSR, which teaches treating patients having MSI-H colorectal cancer and MSI-H

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

non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 21 (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 MSR is identical to the dose described as being effective in the '975 patent. *Id.* at 21–22 (citing Ex. 1003 ¶¶ 40–41, 67); Ex. 1001, 4:14–27, 8:44–50, 13:18–24, 16:1–8, 16:65–17:7, 19:40–21:18, Figs. 2, 11. Petitioner argues further that any efficacy required in the claim is inherent to that dosage because the '975 patent shows that dosage to be effective. *Id.*

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 '975 patent.

> d) *Element [1.3]: "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 the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient."*

Petitioner argues that the next limitation of claim 1 of the '975 patent is an inherent result of the method of treatment reported in the MSR. Pet. 23–24 (citing Ex. 1003 ¶¶ 65–72). Petitioner argues that the MSR teaches actively measuring specific outcomes in patients having MSI-H cancer and cancer that is not MSI-H. *Id.* (citing Ex. 1003 ¶ 71). In support, Dr. Neugut testifies that the examples, tables, and figures of the '975 patent discuss the design and results of the MSI-H Study, as explained in the affidavit by the inventors on February 4, 2022. Ex. 1003 ¶¶ 40–41, 67–68 (citing Ex. 1001, 6:44–18:55, 3:12–14, Figs. 1–13; Ex. 1005).

An affidavit executed by Andrew Pardoll, M.D., an inventor named on the '975 patent, 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. 1022 (Part 9), 2490–2491. That affidavit, submitted during prosecution of the '975 patent, supports the argument that an improved outcome of treating a patient with a tumor exhibiting an MSI-high or an MMR deficiency status with pembrolizumab compared to similarly treating a patient without an MSI-high or an MMR deficiency status, as recited in claim 1, is an inherent result because the treatment would necessarily provide the result. *Compare id.*, *with* Ex. 1001, 6:44–48 ("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 ['975 patent] is irrelevant." Pet. 24 (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 MSR does not disclose treating a cancer patient with pembrolizumab when "the patient has received a prior cancer therapy drug" or "the tumor having progressed following a [cancer therapy/prior treatment]." PO Resp. 11–12; PO Sur-Reply 2. We are unpersuaded. Rather, 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. 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. 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. 13 (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. 13–15; 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 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) ("[T]he 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 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 '975 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 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. PO Resp. 15. 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. PO Resp. 15–17; 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. 16–17. 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. 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) ("[H]uman 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. 16–17 (citing *Schering*, 339 F.3d at 1380). According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the '975 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 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. 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. PO Resp. 18–25. 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 MSR under a 13-factor analysis provided in *Allen Engineering Corp. v. Bartell Industries, Inc*., 299 F.3d 1336, 1353 (Fed. Cir. 2002). PO Resp. 19–25. 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. *Id.* at 20–22. 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." *Id.* at 23.

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.

e) Element [1.4]: "wherein the patient has received a prior cancer therapy drug."

Petitioner argues that the final limitation of claim 1, "wherein the patient has received a prior cancer therapy drug," is disclosed by the MSR.

Pet. 24–27. Petitioner asserts that the MSR discloses treating patients with "tumors" and "measurable disease," and that "patients with MSI-H colorectal cancer and non-colorectal cancer," while excluding "[p]atients who have had prior treatment with anti PD-1." *Id.* at 26 (citing Ex. 1005, 5–6). Petitioner thus asserts that "these disclosures demonstrate that patients would have received a prior cancer therapy drug." *Id.* at 25 (citing Ex. 1003 ¶¶ 73–78).

Petitioner asserts that "the prior art taught that patients having 'measurable' colorectal cancer in the context of the MSR refers to patients having metastatic and advanced cancer." *Id.* (citing Ex. 1020, 25; Ex. 1003 ¶ 76). Petitioner argues that "[i]f a patient had colorectal cancer that is curable by resection, then a practitioner would excise the tumor because surgery 'is the only way to achieve a cure.'" *Id.* (citing Ex. 1020, 7; Ex. 1048, 230; Ex. 1047, 4–7; Ex. 1003 ¶ 74). Petitioner therefore argues that "'measurable' disease in the context of a clinical study does not include cancer that is resectable for the purposes of a cure." *Id.* at 25.

Petitioner argues that "[p]atients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies." *Id.* at 26. To that point, Dr. Neugut testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer "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 ¶ 75 (citing Ex. 1020, 25; Ex. 1009, 1034; Ex. 1047, 4–7). Dr. Neugut observes that the Eligibility section of the MSR takes care to exclude patients having had prior treatment

with certain other antibodies. *Id.* ¶ 76 ("[T]he person of ordinary skill would have understood that the MSR recognizes that patients would have received prior cancer drug therapies, and because of that makes it a point to exclude those that received '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 MSR. *Id.* Dr. Neugut cites to a poster presentation describing the MSR as requiring that patients have "progressive disease" and have had prior therapies. *Id.* ¶ 78.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 64–67. Dr. Oberstein testifies that because the eligibility criteria stated in the MSR 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 MSR is silent about whether eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for an inherency finding." PO Resp. 7–8.

Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression." Ex. 2072 ¶ 96; PO Resp. 9. Dr.

Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. 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 MSR 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 the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitation for a solid tumor that has progressed following at least one prior cancer treatment was disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. *Contra* PO Resp. 6–9.

2. Independent Claim 9

Patent Owner does not present separate arguments against Petitioner's challenge to claim 9 as being anticipated by the MSR. *See*, *e.g.*, PO Resp. 10–17 (referring to claims 1 and 9 together). For the reasons discussed above regarding claim 1, we are persuaded that claim 9 is anticipated by the MSR.

3. Dependent Claims 2 and 15

Claims 2 and 15 depend from claims 1 and 9, respectively, and further recite, "wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug." Patent Owner contends that the MSR "is silent on whether eligible patients ***must*** have had a prior treatment and have progressed after receiving that prior treatment." PO Resp. 7 (citing Ex. 1005, 5–6). Petitioner argues that the additional limitations of claims 2 and 15 are anticipated by the MSR and "addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]." Pet. 28–29, 33 (citing Ex. 1003 ¶ 79). We agree and rely on our analysis set forth above.

4. Dependent Claims 6, 7, 13, and 14

Petitioner argues that claims 6, 7, 13, and 14 are anticipated by the MSR. Pet. 30–31, 33. Claims 6 and 7 require that the cancer recited in claim 1 be metastatic cancer or metastatic colorectal cancer, respectively. Claims 13 and 14 require that the cancer recited in claim 9 be metastatic cancer or metastatic colorectal cancer, respectively. Petitioner argues that the MSR discloses a clinical study treating colorectal cancer patients with "measurable disease." *Id.* at 24, 30 (citing Ex. 1003 ¶¶ 82–83). Petitioner relies on Dr. Neugut's testimony that in the context of the MSR, the treated patients would have had metastatic cancer. Ex. 1003 ¶¶ 82–83 (citing Ex. 1049, 444; Ex. 1050, S4).

Dr. Neugut further testifies that "measurable" disease in the context of a clinical study for a new drug refers to patients having metastatic and advanced cancer. Ex. 1003 ¶ 74. According to Dr. Neugut, one of ordinary skill would therefore have understand that the MSR teaches treating patients with metastatic cancer and locally advanced cancer that is unresectable for

purpose of a cure. *Id*. Dr. Neugut testifies that not including metastatic patients in such a study would have been highly unusual because the drug treatment would not be a local cure, whereas radiation or surgery could be. *Id*.

Petitioner argues further that other prior art references citing the MSR demonstrate that physicians understood the MSR to be for patients with metastatic tumors. Pet. 30 (citing Ex. 1049, 444; Ex. 1050, S4). 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 the MSR 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. 18 (citing Ex. 2163:14:9–15:12).

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 that one of ordinary skill in the art would have understood the MSR to disclose treating

patients with metastatic colorectal cancer. *See* Ex. 1049, 444; Ex. 1050, S4. Patent Owner does not address this evidence.

In view of the above, we are persuaded by Petitioner's evidence that claims 6, 7, 13, and 14 are anticipated by the MSR.

5. Dependent Claims 3, 8, and 10

Petitioner argues that claims 3, 8, and 10 are anticipated by the MSR. Pet. 29–31, 33. Patent Owner presents the arguments discussed above regarding the limitations of independent claims 1 and 9, but does not present arguments or direct us to evidence that are specific to the limitations of dependent claims 3, 8, and 10. As summarized below, we find that the record supports Petitioner's arguments.

a) Claims 3 and 10

Petitioner argues that claims 3 and 10 are anticipated by the MSR. Pet. 29–30, 33. 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 3 and 10.

Claims 3 and 10 depend from claims 1 and 9, respectively, and further recite, "wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival." Claims 3 and 10 therefore further limit the outcome exhibited by the patients selected and administered pembrolizumab, as recited in claims 1 and 9. Petitioner argues that these outcomes are inherent to the methods taught in the MSR. Pet. 29–30, 33 (citing Ex. 1003 ¶¶ 80–81, 91).

We agree with Petitioner because, as discussed above, we are persuaded that the steps recited in claims 1 and 9 are taught by the MSR and the efficacy of those steps would be inherent to practicing the method recited in the steps. *See Montgomery*, 677 F.3d at 1385; *Schering Corp.*, 339 F.3d at 1377.

b) Claim 8

Claim 8 recites "The method of claim 1, wherein the anti-PD-1 antibody is administered by intravenous infusion."

Petitioner argues that claim 8 is also anticipated by the MSR. Pet. 31. Petitioner argues that the prior art, including the pembrolizumab package insert, demonstrates that pembrolizumab was administered intravenously for the treatment of cancer. *Id.* (citing Ex. 1055,[2] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1011, 134 ("We administered [pembrolizumab] intravenously.")); Ex. 1003 ¶¶ 84–85. Patent Owner does not argue to the contrary.

Having considered the parties' positions and evidence of record, summarized above, we are persuaded by Petitioner's evidence that claim 8 is anticipated by the MSR.

6. Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of claims 1–3, 6–10, and 12–15. Accordingly, we determine that claims 1–3, 6–10, and 12–15 are anticipated by the MSR.

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

D. Grounds 2 and 4 – Obviousness of Claims 1–3, 6–10, and 13–15

In Ground 2, Petitioner contends that claims 1–3, 6–10, and 13–15 are unpatentable as obvious over the combination of the MSI-H Study Record, Pernot, and Benson. Pet. 37–45. In Ground 4, Petitioner challenges the patentability of claims 1–3, 6–10, and 13–15, citing MSR, Brown, Duval, and Benson. Pet. 49–57. Patent Owner opposes Petitioner's allegations in Grounds 2 and 4. PO Resp. 25–50. We address the parties' arguments and evidence with regards to Grounds 2 and 4 below.

1. Petitioner's Contentions

a) Ground 2

Petitioner asserts that these references disclose elements that Patent Owner might argue are not taught in the MSR, specifically the improved outcome and efficacy recited in claim 1, testing for MSI-H or dMMR tumors, and treating patients that have progressive or metastatic disease. *Id.* at 38–41 (citing December 14, 2020, Notice of Allowance in the '549 appl., Ex. 1002 (Part 9), 3069).

Petitioner argues that Pernot teaches treating colorectal cancer and that, therefore, because the MSR is directed to a clinical study treating colorectal cancer patient whose cancers are MSI-H with pembrolizumab, which is an anti-PD-1 antibody, one of ordinary skill in the art knowing the teachings of the MSR would have considered the teachings of Pernot. Pet. 39. 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 cites further to Dr. Neugut's testimony to argue that one of ordinary skill in the art would have been motivated to combine the disclosure of Pernot with the methods taught in the MSR in order to obtain the results of the MSR's study. Pet. 42 (citing Ex. 1003 ¶ 101).

Additionally, Petitioner argues that the state of the art indicates one of ordinary skill would have had a reasonable expectation of success in the claimed method because successful treatment with a PD-1 inhibitor of a colorectal cancer patient having an MSI-H tumor was reported in the prior art. *Id.* at 39–40. Petitioner cites to other references, for example Champiat,[3] which teaches:

> Moreover, if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)- deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1 and 2, early onset), all of which display severe genomic instability.

Ex. 1032, e27817-5. Dr. Neugut testifies that Champiat, as well as other references, "independently urged the person of ordinary skill to treat MSI-H cancer with PD-1 inhibitors, like pembrolizumab, or other immunotherapy." Ex. 1003 ¶ 103. Citing to Dr. Neugut's testimony, Petitioner argues further that the prior art demonstrates the characteristics of cells that would have more efficacy with PD-1 inhibitors were known and that it was known that

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

MSI-H tumors had these characteristics. Pet. 43 (citing Ex. 1003 ¶¶ 43, 45, 104).

In light of this evidence of the state of the art at that time, Dr. Neugut testifies that one of ordinary skill in the art would have wanted to obtain data from the MSR and would have reasonably expected success, given that pembrolizumab was already approved for another oncology indication. Ex. 1003 ¶¶ 102–105; Pet. 40–41. Dr. Neugut concludes that "[a]s a result of carrying out the methods in the MSR 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 ¶ 105.

Petitioner also argues that the MSR would have motivated one of ordinary skill in the art to test patients' tumors for MSI-H because the MSR requires patients to be placed into the proper study arm. Pet. 41–42 (citing Ex. 1003 ¶ 106 ("Testing was the way in which it was possible for the person of ordinary skill [to] determine if the patient had the MSI-H colorectal cancer required for placement in that arm.")).

Petitioner argues further that one of ordinary skill in the art would have considered it obvious that the MSR 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 MSR. *Id.* (citing Ex. 1003 ¶ 107). Benson teaches that under the standard of care, the patient population with tumors and measurable disease that would take part in a clinical study are patients having metastatic and advanced disease. Ex. 1009, 1034; Ex. 1003 ¶ 108. Dr. Neugut testifies further that the term "advanced cancer" refers to metastatic cancer or cancer

that is so locally advanced that it is unresectable for purposes of a cure and he concludes that a person of ordinary skill would have been motivated to carry out that method of the MSR on colorectal cancer that was metastatic, with a reasonable expectation of success. Ex. 1003 ¶¶ 108–109.

b) Ground 4

In Ground 4, Petitioner relies on Brown for its teaching that PD-1 inhibitors inherently had more efficacy when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 51 (citing Ex. 1034, 747). Petitioner relies on Duval for its teaching that MSI-H cancers have cells that are easy for immune cells to recognize. *Id.* (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. Ex. 1003 ¶¶ 121–31.

2. Patent Owner's Contentions

Patent Owner argues that the MSR does not anticipate the challenged claims and that neither none of Pernot, Benson, Brown, Duval supplies limitations that Patent Owner asserts are "missing" from the MSR. PO Resp. 25–26. In particular, Patent Owner argues that none of the cited references teach the "prior cancer therapy"/"progressed following a [cancer therapy/prior treatment]" element required by the independent claims or "metastatic" element of dependent claims 6–7 and 13–14, and that, thus, Petitioner's "obviousness challenges necessarily fail." *Id.* at 25. For example, Patent Owner further contends that Benson "did not require prior treatment, progression on a prior therapy, or metastatic disease before a patient is enrolled in clinical trials." *Id.* at 26.

3. Discussion

Because "anticipation is the epitome of obviousness," we are persuaded that the claims Petitioner challenges as being anticipated by the MSR would have been obvious over the MSR 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, 6–10, and 13–15 as being obvious over the MSR alone.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. PO Resp. 51–86. 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 method recited in claims 1–3, 6–10, and 13–15 is anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive as to the patentability of claims 1–3, 6–10, and 13–15. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("[S]econdary considerations are not an element of a claim of anticipation.").

Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1–3, 6–10, and 13–15 as being obvious over the MSR alone or along with other references cited in Ground 2 and/or Ground 4.

E. Grounds 3 and 5: Obviousness Based on the MSI-H Study Record, Pernot, Brown, Duval, Benson, and Chapelle

In Grounds 3 and 5, Petitioner builds upon its assertions presented in Grounds 2 and 4 and further relies on Chappelle to address the elements of claims 4 and 12. Pet. 46–49, 57. Claims 2 and 12 depend from claims 1 and 9, respectively, and recite,

> wherein the patient has been determined to have a tumor that exhibits a MSI-high status when instability of a microsatellite marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24; or
>
> wherein the patient has been determined to have a tumor that exhibits a MMR deficiency status when deficiency of a mismatch repair marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the mismatch repair marker is POLE, POLD1, or MYH.

Ex. 1001, claims 4 and 12.

Petitioner argues that Chapelle teaches standard methods of testing whether a tumor is MSI-H, including determining whether the patient's tumor exhibits instability in a microsatellite marker. Pet. 46–49, 57 (citing Ex. 1007, 3380, 3383). Dr. Neugut supports this characterization of Chapelle. Ex. 1003 ¶¶ 113–117. Petitioner also argues that Chapelle teaches determining whether a microsatellite marker is BAT-25 or BAT-26. *Id.* at 49 (citing Ex. 1007, 3380–84). For example, Chappelle teaches that "a standard test" using a "[p]anel consisting of . . . BAT26, BAT25" has "stood the test of time." *Id.* (citing Ex. 1007, 3382).

Moreover, Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) with Chapelle's standard methods for testing for MSI-H and would have had an expectation of success in doing so because the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. Pet. 47–48.

Patent Owner presents the arguments discussed above regarding the limitations of independent claims 1 and 9, but does not present arguments or

direct us to evidence that are specific to the limitations of dependent claims 4 and 12. *See*, *e.g.*, PO Resp. 25–50. That is, Patent Owner argues against all of the obviousness challenges together, without arguing that any of the limitations recited in dependent claims 4 and 12 render the methods of independent claims 1 or 9 non-obvious. Patent Owner, however, makes certain general arguments in response to Petitioner's obviousness challenges, which we address below.

To begin, 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 the independent claims. PO Resp. 32–50. For example, Patent Owner argues that neither the MSR, 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 pembrolizumab. *Id.* at 33–50. Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, 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 Int'l 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 articles' authors did not appreciate the results."). 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 for MSI-H as recited in the challenged dependent claims, and 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 challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 51–86. 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 MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 9. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("[S]econdary considerations are not an element of a claim of anticipation.").

Regarding the dependent claims 4 and 12, Patent Owner must show a nexus between the claimed methods and the evidence of non-obviousness. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("[T]o 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 mentions a nexus between the Keytruda® (pembrolizumab) label for testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claim 5. PO Resp. 52. But Patent Owner does not direct us to evidence of a nexus to limitations recited in dependent claims 4 and 12, which recite 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. Thus, even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 9, not the limitations of the claims 4 and 12. PO Resp. 52–62. 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. *Id.* 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 methods recited in claims 1 and 9 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 claims.

Accordingly, Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 4 and 12 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

F. Grounds 6 and 7: Obviousness Based on the MSI-H Study Record, Pernot, Brown, Duval, Benson, Chapelle and Hamid

Petitioner argues that dependent claim 8 of the '975 patent is unpatentable as obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle and Hamid. Pet. 58–60. Because, as discussed above, we determined that claim 8 is anticipated by the MSR, claim 8 also would have been obvious over MSR alone. *In re McDaniel*, 293 F.3d at 1385. Accordingly, the preponderance of the evidence supports Petitioner's challenges of claim 8 as being obvious over the MSR alone or along with other references cited in Ground 6 and/or Ground 7.

III. CONCLUSION[4]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–4, 6–10, and 12–15 of the '975 patent are unpatentable.

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[4] 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).

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–3, 6–10, 13–15	102	MSR	1–3, 6–10, 13–15	
1–3, 6–10, 13–15	103	MSR, Pernot, Benson	1–3, 6–10, 13–15	
4, 12	103	MSR, Pernot, Benson, Chapelle	4, 12	
1–3, 6–10, 13–15	103	MSR, Brown, Duval, Benson	1–3, 6–10, 13–15	
4, 12	103	MSR, Brown, Duval, Benson, Chapelle	4, 12	
8	103	MSR, Pernot, Benson, Chapelle, Hamid	8	
8	103	MSR, Brown, Duval, Benson, Chapelle, Hamid	8	
Overall Outcome			1–4, 6–10, 12–15	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–4, 6–10, and 12–15 of the ’975 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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Anita Meiklejohn
Matthew Chun
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
meiklejohn@fr.com
mchun@fr.com

Trials@uspto.gov
571-272-7822

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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd G. Miller

Anita L. Meiklejohn
Matthew L. Chun
Frank E. Scherkenbach
Corrin N. Drakulich
Christina D. Brown-Marshall
Casey M. Kraning
Madelyn S. McCormick
Sarah E. Jack
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
mchun@fr.com
miller@fr.com
IPR52261-0005IP1@fr.com

Trials@uspto.gov
571-272-7822

Paper 56
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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.

IPR2024-00648
Patent 11,643,462 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 1–30 of U.S. Patent No. 11,643,462 B2 (Ex. 1001, "the '462 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '462 patent. Paper 3, 1. Patent Owner did not file a Preliminary Patent Owner Response.

We instituted trial on September 27, 2024. Paper 6 ("Inst. Dec."). During trial, Patent Owner filed a Patent Owner Response. Paper 29 (confidential Paper 25) ("PO Resp."). Petitioner filed a Reply (Paper 45 (confidential Paper 42) ("Pet. Reply")) and Patent Owner filed a Sur-Reply (Paper 50 (confidential Paper 47) ("PO Sur-Reply")). The parties declined to present oral arguments in this proceeding. Paper 49.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).[1]

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[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

B. Real Parties in Interest

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

C. Related Matters

The parties indicate that the '462 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. 64; Paper 3, 1. Petitioner states that the U.S. District Court for the District of Maryland entered an order granting Petitioner's Motion to Stay on July 1, 2024. Paper 5, 1.

Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; IPR2024-00240 against U.S. Patent No. 11,591,393; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR-00624 against U.S. Patent No. 11,325,975; and IPR2024-00625 against U.S. Patent No. 11,339,219. *See, e.g.*, Pet. 64; Paper 3, 1.

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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.

D. The '462 patent (Ex. 1001)

The '462 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '462 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.*, Abstract. More specifically, the '462 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.*, 3:38–53. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:33–34.

The '462 patent explains that

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

Id., 1:55–62. According to the '462 patent, "[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types." *Id.*, 2:6–9. However, the Specification describes that

> in reports of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment. . . . What was different about this single patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id., 2:63–3:6. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '462 patent

describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id.*, 3:14–21. The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id.*, 8:52–58. According to the '462 patent, "[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors." *Id.*, 6:53–57.

E. The Challenged Claims

Petitioner challenges claims 1–30. Representative independent claim 1 is reproduced below:

> 1. A method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, the method comprising:
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> testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
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> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.

Ex. 1001, 25:52–26:2.

Representative independent claim 11 is reproduced below:

> 11. A method for prescribing a treatment for a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior cancer treatment, the method comprising:
>
> testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, prescribing treatment with a therapeutically effective amount of pembrolizumab for the patient
>
> determined to have a tumor that is microsatellite instability high or DNA mismatch repair deficient.

Ex. 1001, 26:26–43.

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

Ex. 1008, Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) ("Steinert").

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").

Ex. 1095, Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. NAT'L COMPREHENSIVE CANCER NETWORK 248 (February 2014) ("Koh").

Ex. 1096, Ajani et al., *Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines*, 11(5) J. NAT'L COMPREHENSIVE CANCER NETWORK 531 (May 2013) ("Ajani").

Petitioner also relies on the declarations of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150) to support its contentions.

Patent Owner relies on the declarations of Nils Lonberg, Ph.D. (Ex. 2072), Dung Le, M.D. (Ex. 2130), and Richard Goldberg, M.D. (Ex. 2090) Ph.D., M.P.H. (Ex. 1003), to support its contentions.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 2, 4–7, 9–12, 14–17, 19–30	102	MSI-H Study Record
2	1, 2, 4–7, 9–12, 14–17, 19–30	103	MSI-H Study Record, Brown, Duval, Benson
3	1, 2, 4–7, 9–12, 14–17, 19–24	103	MSI-H Study Record, Brown, Duval, Benson, Koh
4	1, 2, 4–7, 9, 11, 12, 14–17, 19, 25, 26	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani
5	2, 8, 12, 18	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Chapelle
6	3, 13	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Steinert
7	7, 17	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Hamid

H. Claim Construction

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

Claim 1 requires treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the solid tumor

is microsatellite instability high or DNA mismatch repair deficient . . . ." Ex. 1001, 25:52–26:2. Petitioner argues that the discussion in the MSI-H Study Record of treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. Pet. 25–26 (citing Ex. 1005, 2–6; Ex. 1003 ¶¶ 76–79).

Patent Owner argues that our construction "disregards the critical ***causal*** relationship between 'determining' and 'treating'/'prescribing' steps in the claims," wherein the causal relationship establishes that "***only*** patients determined to be MSI-H are treated." PO Resp. 6 (emphases original). According to Patent Owner, the construction of "in response to" should be that the phrase means "in reaction to." *Id.*

Patent Owner argues that if the inventors had intended the claimed method to encompass merely treating patients "after" a determination of the patient's MSI-H status, they would have used the word "after" in their claims, citing use of the word "after" in claims in a related patent. *Id.* at 7. Because the cited language is in claims that depend on claim 1, Patent Owner argues that the term "in response to" must have a different meaning from "after." *Id.*

Patent Owner argues further that the Specification of the '462 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is only performed as a reaction to determining the patient's cancer is MSI-H. PO Resp. 7–8. Specifically, Patent Owner cites the disclosure in the '462 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. Ex. 1001, 3:64–67.

According to Patent Owner, one of ordinary skill in the art would have understood from this distinction in recommended treatments that "in response to" describes administering the claimed treatment only as a reaction to the determination that the patient's cancer is MSI-H. PO Resp. 8. Patent Owner argues further that "[i]f 'in response to' meant merely 'after,' the claims would cover treatment administered to MSI-H patients for any reason or no reason at all," which is a reading "inconsistent with the specification." *Id.*

We agree with Patent Owner that the phrase "in response to" in claim 1 requires a causal relationship wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is treated with 10 mg/kg of pembrolizumab every 14 days. In claim 1, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having cancer to determine that the patient's cancer is microsatellite instability high or mismatch repair deficient, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the art anticipates claim 1. We are not persuaded that claim 1 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment only as a reaction to the determination that the patient's cancer is MSI-H, and that, if treatment were administered to patients for any other reason after testing confirmed that the

patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the term "in response to" would be meaningless. PO Resp. 7–8. We agree that claim 1 provides that if the cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab. But claim 1 does not exclude treatment of other cancer patients whose tumors were confirmed *not* to be MSI-H or dMMR, when tested; claim 1 does not mention any other patients or define patient populations to be excluded from treatment. This is so because the method of claim 1 uses the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp*., 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim."). The use of the open-ended transitional phrase "comprising" in claim 1 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner's argues that the prosecution history of the '462 patent supports its claim construction. PO Resp. 8–9. Patent Owner cites to the Examiner's reasons for allowance in a related patent (U.S. 11,591,393), which states that the cited prior art "does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed." *Id.* at 8 (citing Ex. 2302, 8). According to Patent

Owner, the term "based on" does not mean "after," but requires a causal relationship. *Id.* Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that claim 1 requires anything other than testing a cancer patient and, if the cancer is determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. The Examiner's reasoning does not indicate that claim 1 excludes treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one tested and confirmed to be MSI-H or dMMR, as Patent Owner implies. PO Resp. 9–10. Patent Owner argues that "Merck's only dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean 'as the reaction specifically to.'" *Id.* at 9 (citing Ex. 2160, 24[2]). But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 excludes treating any patient other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a reaction, as that of an organism to any of its parts, to a specific stimulus." Ex. 2160, 24–25. Petitioner's arguments do not limit the scope of claim 1 to treating only patients tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued "[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA

[2] Patent Owner cites to page 30 of Exhibit 2160, which is page 24 of the underlying document.

knows what it means, invites legal error and jury confusion about what behavior the claims cover." *Id.* at 25. Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now.

Patent Owner further argues that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that its witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a determination that the patient's tumor is MSI-H. PO Resp. 9–10 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 98–100). Neither of these statements persuades us that claim 1 requires anything other than testing a cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of claim 1 excludes treating any patient other than the one tested and confirmed to be MSI-H or dMMR.

Patent Owner cites *Am. Calcar, Inc. v. American Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011), in support of the claim construction that the "treating" step is only performed as a reaction to determining the patient's cancer is MSI-H, but not when the patient is MSI-stable. PO Resp. 10. In *Am. Calcar*, the Federal Circuit determined that, in claims directed to systems for identifying a service provided when a vehicle needs service, the term "the processing element identifying one of the plurality of providers in response to the vehicle condition" was construed to mean "that the second event occur in reaction to the first event." 651 F.3d at 1324, 1340. The court explained that "[t]he language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction." *Id.* at 1340.

We note that, as explained above, we agree the claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claim 1 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claim 1 to require testing a biological sample obtained from a patient having cancer to determine that the patient's cancer is microsatellite instability high or mismatch repair deficient, and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient. We are not persuaded that claim 1 either requires or excludes other patients or steps because claim 1 does not recite any other steps or contain negative limitations.

I. Level of Ordinary Skill in the Art and Declarant

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) and Paul E. Oberstein, M.D., (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be "a medical doctor or a professional in a related field with at least five years of experience with treating cancer" and "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." Pet. 11 (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. PO Resp. 5–6 (citing Ex. 2072 ¶¶ 31–32, 91–99). Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects. The '462 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, 25:5–27; Ex. 1005. Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds. In the Decision to institute trial, we adopted Petitioner's uncontested proposal defining that the level of skill in the art, presented above. Inst. Dec. 8. Neither party directs us to evidence of the level of skill in the art beyond what we considered for institution of trial. Having considered Patent Owner's positions and evidence of record, however, we determine that the level of skill also 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 cancers and the associated conditions and immunotherapy.

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. Summary of the Cited Prior Art

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

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

3475 is also known as pembrolizumab. *See* Ex. 1054,[3] 3 (disclosing that "Nivolumab . . . and MK-3475 (pembrolizumab formerly lambrolizumab) . . . are humanized MAb that block the interaction between PD-1 and its ligands and demonstrate durable responses in patients with advanced melanoma."); *see also* Ex. 1069 (titled "ANTITUMOR ACTIVITY OF PEMBROLIZUMAB (PEMBRO; MK-3475) . . . .")).

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

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

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" *Id.* at 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

[3] Ascierto et al., *Future Perspectives in Melanoma Research: Meeting Report from the "Melanoma Bridge", Napoli, December 5th-8th 2013*, 12 J. TRANSLATIONAL MEDICINE 277 (October 2024).

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

2. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.* at 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.* at 3380, 3384.

3. Steinert (Ex. 1008)

Steinert is an article titled "Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer." Ex. 1008, OF1. Steinert discloses detailed genomic and phenotypic analyses of single colorectal cancer–derived circulating tumor cells (CTC). *Id.* Steinert describes that "[a]mplified gDNA of CTC and tumor tissue samples was tested for microsatellite instability (MSI) using the markers NR21, NR24, and BAT 25." *Id.* at OF2. Steinert describes that the analyses of single cancer-derived CTC found disparities in key mutations, including MSI, in comparison to the primary tumor. *Id.* at OF4. "MSI at one or more markers . . . was detected in CTC from 2 patients (of 25 with complete MSI data sets; 7.7%, Fig. 2C). In 1 patient, two of 11 tested CTC were MSI despite a microsatellite stable (MSS) tumor (Table 1)." *Id.* In one patient, "[t]hree

single CTC were classified as MSI-high level (MSI-H) and showed a mutation in the coding region of the *ELAVL* gene." *Id.* at OF6.

4. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id.*, 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.* at 1034.

5. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or

PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.* at 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic mutations have . . . elevated expression of CTLA4 and PDCD1," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.* at 747–48.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.*

8. Koh (Ex. 1095)

Koh is an article titled "Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology." Ex. 1095, 248. Koh describes that "[t]he NCCN Guidelines for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management." *Id.*, Abstract. Koh discloses that patients having endometrial cancer who were enrolled in a clinical study would generally have had a tumor that had progressed after at least one prior cancer treatment and metastatic cancer. *Id.* at 256.

9. Ajani (Ex. 1096)

Ajani is an article titled "Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines." Ex. 1096, 531. Ajani discloses "evidence- and consensus-based recommendations for a multidisciplinary approach for the management of patients with gastric cancer." *Id.* Ajani discloses that "combined modality therapy has been used as an adjunct to surgery to improve survival rates in patients with localized resectable cancer." *Id.* Because "gastric cancer is often diagnosed at an advanced stage," Ajani describes that "HER2 testing is now recommended for all patients with metastatic disease at the time of diagnosis." *Id.* at 544. According to Ajani, "[t]he selection of appropriate systemic therapy should be based on the patient's performance status and HER2 status." *Id.*

C. Ground 1: Anticipation by MSI-H Study Record

1. Prior Art Status of MSI-K Study Record

Patent Owner argues that the MSI-H Study Record discloses an experimental use that does not qualify as prior art. PO Resp. 26–32. We address this threshold issue before proceeding with the analysis of claim 1.

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 26 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 65 (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. 27–32. For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test the 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. 27–28. 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 28. 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 30.

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 experimental 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. 24–25. 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. 24–25.

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*, 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. 13–14 (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 '462 patent is irrelevant. *Id.* at 13–16.

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. Accordingly, we proceed to analyze Petitioner's contentions in Ground 1.

2. Petitioner's Contentions

Petitioner contends that claims 1–2, 4–7, 9–12, 14–17, and 19–30 are anticipated by the MSI-H Study Record. Pet. 13–37. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how each element of claims 1–2, 4–7, 9–12, 14–17, and 19–30 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 50–128.

Additionally, Petitioner cites the holding in *Schering Corp.*, 339 F.3d at 1377, that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 13–14. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 15. Relying on those cases, Petitioner contends that "the MSI-H Study Record inherently anticipates claims 1–2, 4–7, 9–12, 14–17, and 19–30 of the '462 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 16.

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '462 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 13.

a) Independent Claim 1

Like the parties, our analysis focuses on independent claim 1. *See e.g.,* Pet. 30–31 (relying substantially on analysis of claim 1 for independent claim 11). We analyze the parties' contentions with regard to the limitations of claim 1 below.

(1) [1.pre]: "A method for treating a patient"

Petitioner argues that the MSI-H Study Record discloses a method of treating a patient that is the method set forth in this claim. Pet. 16. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating patients having non-colorectal MSI-H cancer, as recited in the preamble of claim 1.[4] *Id.* (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria); Ex. 1003 ¶¶ 59–60).

Patent Owner does not argue that the MSI-H Study Record does not disclose a method of treating a patient. *See, generally*, PO Response. We are persuaded that one of ordinary skill in the art at the time would have

[4] We need not decide whether the preamble is limiting as we find that the MSI-H Study Record discloses the preamble.

understood the MSI-H Study Record to teach "*a method for treating a patient*," as recited in [1.pre].

(2) [1. pre.b]: "having a solid tumor"

Petitioner contends that the MSI-H Study Record discloses that its patients have both tumors and measurable disease. Pet. 17 (citing Ex. 1005, 2 (Study Identification), 5–6 (Eligibility)). Petitioner contends that "[m]easurability is a property of solid tumors," and that the MSI-H Study Record patients therefore had solid tumors. *Id.* (citing Ex. 1048, 228, 230–31; Ex. 1003, ¶¶ 60–61).

Patent Owner does not argue that the MSI-H Study Record does not disclose a method of treating a patient having a solid tumor. *See, generally*, PO Response. We are persuaded that one of ordinary skill in the art at the time would have understood the MSI-H Study Record to teach the method applied to a patient "*having a solid tumor*," at recited in [1.pre.b].

(3) [1.pre.c]: "selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer"

Petitioner contends that "MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel cancer, and gastric cancer." Pet. 17 (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria); Ex. 1085,[5] 673, 675; Ex. 1003

[5] Imai et al., *Carcinogenesis and Microsatellite Instability: The Interrelationship Between Genetics and Epigenetics*, 29(4) CARCINOGENESIS 673 (2008).

¶¶ 25, 60–61, 63). Petitioner relies on Dr. Neugut's testimony that endometrial, small bowel cancer, and gastric cancer are "common in Lynch syndrome, which was known at the time to be closely related to MSI-H." Ex. 1003 ¶ 63 (citing Ex. 1085, 673–74 ("DNA mismatch repair (MMR) deficiency results in a strong mutator phenotype and high-frequency microsatellite instability (MSI-H), which are the hallmarks of tumors arising within Lynch syndrome.")); *see also* Ex. 1085, 673 ("Tumors of the Lynch syndrome . . . and some sporadic gastrointestinal and endometrial cancers belong to the MSI pathway."). Thus, "the person of ordinary skill would have immediately pictured treating [patients with endometrial, small bowel, and gastric cancer] with the MSI-H Study Record's methods" and that "the person of ordinary skill would have concluded that the limitation [listing recited types of cancer] was found in the MSI-H Study Record." Ex. 1003 ¶¶ 63–64. Petitioner argues that, based on this disclosure, an ordinary skilled artisan would have "envisaged treating patients having endometrial, small bowel, and gastric cancer" using the MSI-H methods. *Id.* at 17–18.

To begin, Patent Owner argues that the MSI-H Study Record cannot anticipate because it does not expressly or inherently disclose the claimed MSI-H cancers. PO Resp. 10–14. Patent Owner contends that the MSI-H Study Record provides no details or guidance about cancer types to be included in the third arm of patients, but only describes its third arm as "MSI Positive Non-Colorectal Cancer." *Id.* at 10 (citing 1005, 4); *see also id.* ("Other than specifying the participant's cancer must be noncolorectal, the MSR provides no details or guidance about cancer types to be included in that third arm."). Patent Owner further contends that "MSI Positive Non-Colorectal Cancer" is a large genus "comprising a large, and unknown, number of species" such that a person of ordinary skill in the art "would not

envisage all its species, let alone the claimed subset of those species, based on the bare disclosure in the MSR." PO Resp. at 14; *see also* PO Sur-Reply 3 (Petitioner "identifies no common properties of non-CRC MSI-H cancer, or any other way a POSITA would have recognized the MSR discloses those cancers."); *Id.* at 4 (Petitioner "has not shown that a POSITA would at once envisage the ***entire*** genus—meaning every one of its constituent species—based on the MSR."). Patent Owner acknowledges that the MSI-H Study Record discloses the "third arm" disclosed in the MSI-H Study Record "was open to all-comers with any MSI-H cancer other than CRC," but argues that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of the genus. PO Resp. 10–11 (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006), *Metabolite Lab'ys, Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)).

Next, Patent Owner argues that the Petition did not provide evidence of the number of species in the genus of "MSI Positive Non-Colorectal Cancers" and does not contend that one of ordinary skill would immediately appreciate the full scope of the genus. *Id.* at 13. Instead, Patent Owner argues that Petitioner focused on whether MSI-H was known to occur in its "hand-picked set of cancers." *Id.* (citing Pet. 17). According to Patent Owner, the issue of whether MSI-H was known to occur in these cancers (endometrial, gastric, and small bowel cancer) is irrelevant because it overlooks the other MSI-H cancers recited in claim 1 and ignores the "unclaimed non-[colorectal] MSI-H cancers." *Id.* at 12. According to Patent Owner, the size of the non-colorectal cancers included in the MSI-H Study Record is large and there is no support for a conclusion that a person

of ordinary skill in the art could have at once envisaged each member. *Id.* at 13.

Patent Owner argues that the Petition overstates the understanding one of ordinary skill in the art would have of MSI-H cancers. PO Resp. at 12 (citing Ex. 2072 ¶ 103). According to Patent Owner, only endometrial cancer "was tested for MSI-H as a part of standard care at the time of the invention—and it was only tested to identify familial susceptibility (not in relationship to treatment)." *Id.* (citing Ex. 2090 ¶ 79). Patent Owner further cites inventor Le's testimony that the MSI-H Study Record investigators had difficulty recruiting MSI-H patients for the non-colorectal cancer arm of the study because such testing was not routinely done in non-colorectal cancers. *Id. at 12–13* (citing Ex. 2130 ¶ 12). This evidence, though, does not persuade us of what one of ordinary skill in the art would have understood from the disclosure of the MSI-H Study Record.

In contrast, the testimony of Patent Owner's witness, Dr. Goldberg, supports Petitioner's argument of the knowledge in the art at the time, wherein Dr. Goldberg testifies that "[w]hile many clinical oncologists were aware that patients with Lynch Syndrome had a defect in DNA mismatch repair, they associated MSI testing with young onset colorectal and endometrial cancer and patients with a family history of colorectal and/or endometrial cancer." Ex. 2090 ¶ 79. Similarly, during his deposition, Dr. Goldberg also agreed that endometrial, gastric, and small-bowel cancers would come to mind when he saw a reference to MSI-high non-colorectal cancer. *See* Ex. 1243, 115:5–116:22 (Q. And so does endometrial cancer come to mind when you see reference to MSI-high non-colorectal cancers? . . . A. Yes. Q. As . . . a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does gastric cancer come to mind? . . . A.

I believe it was listed among the items that I stated when you asked me what comes to mind. So the answer is yes. Q. As a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does small bowel cancer come to mind? . . . A. Yes."). Patent Owner does not direct us to other evidence contradicting Petitioner's argument that MSI-H was known to occur in endometrial, small bowel, and gastric cancer. Pet. 18.

Patent Owner argues that the Petition does not consider the breadth of the genus disclosed in the MSI Study Record and does not argue or provide evidence to show that one of ordinary skill in the art could have envisaged each species within that genus. PO Resp. 11–14. We are not persuaded that either the size of the genus in the MSI Study Record or whether one of ordinary skill in the art would have been able to envisage every species within it is dispositive of whether the MSI Study Record anticipates claim 1, where one of ordinary skill in the art would have known that specific cancers recited in claim 1 would be included in the MSI Study Record. As Petitioner argues, claim 1 requires that "a patient…***selected from the group consisting of*** [the listed cancers]" be tested and treated. Pet. Reply 10 (emphasis original). Claim 1 does not require that the patient have each and every one of the sixteen listed cancers to anticipate the claim. Rather, claim 1 requires testing a sample from "a patient" with one of the recited types of cancer and treating the patient. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.").

Patent Owner argues further that *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009), supports its position, requiring that one of ordinary skill in the art must at once envisage all MSI-H non-colorectal cancer types included

in the MSI Study Record, not just one or even a subset of the claimed cancer types, in order for the MSI Study Record to anticipate claim 1. PO Sur-Reply 2. *Gleave* states:

> For the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law. *Compare Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) (rejecting "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list") with *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). This distinction collapses when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can "at once envisage each member of this limited class." *Eli Lilly*, 471 F.3d at 1376. In that limited circumstance, a reference describing the genus anticipates every species within the genus. *See Perricone*, 432 F.3d at 1377.

In re Gleave, 560 F.3d at 1337–38. This portion of *Gleave*, cited by Patent Owner, does not hold that a reference anticipates *only* when all species either disclosed in the reference or recited in the challenged claim can be envisioned, but rather that when each species of the prior art genus could be envisaged, the genus is anticipatory.

Nothing in *Gleave* or any other reference cited by Patent Owner refutes the patent law concept that a claim encompassing a species is anticipated if a prior art disclosure leads to a genus small enough that a person of ordinary skill in the art would at once envisage the claimed species. *See Brown*, 265 F.3d at 1351; *In re Slayter*, 276 F.2d 408, 411 (CCPA 1960) ("[A] generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus."); *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989) (holding that a claim reciting a

genus of twenty-one specific chemical species in a Markush group is anticipated by prior art that discloses two of the chemical species).

Patent Owner attempts to distinguish *Brown* by arguing that its holding is limited to anticipation of a claimed genus through disclosure of individual species, whereas the facts of this case involve the disclosure of a genus. PO Resp. 14. Because the facts before us, including the testimony of Patent Owner's witness, indicate that one of ordinary skill in the art would have immediately understood that the third arm of the study described in the MSI-H Study Record includes patients with cancers recited in claim 1, including endometrial, gastric, and small-bowel cancers, we are persuaded that one of ordinary skill in the art would have understood that the MSI-H Study Record discloses species that fall within the scope of claim 1. Ex. 2090 ¶ 79; Ex. 1243, 115:5–116:22; Ex. 1085, 673–75; Ex. 1086,[6] 14; Ex. 1003 ¶¶ 25, 63; Ex. 1005, 4. We are not persuaded that where species falling within the scope of claim 1 were previously known and disclosed in MSI-H Study Record, that claim 1 is patentable over the MSI-H Study Record. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage'" the claimed arrangement or combination." (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

After considering the parties' arguments and the evidence presented, we are persuaded that one of ordinary skill in the art at the time would have

[6] Cheung et al., *Current Advance in Small Bowel Tumors*, 44(1) CLINICAL ENDOSCOPY 13 (2011).

understood the MSI-H Study Record to teach "a method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer," and thus teaches the corresponding limitation of claim 1 by anticipating the genus of the recited cancers.

(4) [1.pre.d]: "that has progressed following at least one prior treatment, the method comprising:"

Petitioner alleges that the MSI-H Study Record discloses that, to participate, eligible patients must have "tumors" and "measurable disease," which Dr. Neugut testifies would include metastatic and advanced non-colorectal cancers in the context of the MSI-H Study Record. Pet. 19–21 (citing Ex. 1005, 2–6 (Study Identification, Study Design, Eligibility (excluding patients with prior PD-1 and other antibody treatment); Ex. 1003 ¶ 65). According to Dr. Neugut, in the context of the MSI-H Study Record and its disclosures, "the person of ordinary skill would have concluded that patients in the MSI-H study would have generally received a prior cancer therapy drug and had their solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 65.

Dr. Neugut further testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer "would have generally received at least one other prior drug therapy, such as standard of care chemotherapy, and had their cancers progress following that drug therapy." *Id.* ¶ 67 (citing Ex. 1089 at PDF p. 17 (endometrial); Ex. 1020 at PDF p. 25 (small bowel); Ex. 1094 at PDF p. 12, 15 (gastric cancer patients would generally receive a standard first line therapy, unless diagnosis was late stage)). 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.

Ex. 1003 ¶ 68. 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 patients treated with these antibodies. *Id.* Rather, if the prior therapies had worked, these patients would not have participated in the MSI-H Study Record due to their progressing disease. *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.* ¶ 70.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 63–69. 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.* at ¶ 65. 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.*

Patent Owner argues that the MSI-H Study Record is silent about whether eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for an inherency finding." PO Resp. 16–17.

Patent Owner cites evidence to show that, instead, it was known that some cancer patients can proceed directly to clinical trials even without prior treatment. *Id.* at 17–19. First, Patent Owner cites published guidelines for the management of patients with gastric cancer. *Id.* at 17 (citing Ex. 1096, 533, 537; Ex. 2072 ¶ 106). But Patent Owner fails to explain the flow

diagrams in the cited pages of this publication and, although there is mention of "clinical trial" for "Unresectable locally advanced, locally recurrent or metastatic disease," it is not clear that this is recommended in the absence of different or prior cancer therapy. Ex. 1096, 533, 537. Second, Patent Owner cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." Ex. 1009, 1029.[7]

Patent Owner's evidence is directed to general knowledge in the field, not to the specific understandings of one of ordinary skill in the art when reviewing the MSI-H Study Record, such as is provided by Dr. Neugut's declaration testimony regarding the content of the MSI-H Study Record. Patent Owner cites Dr. Lonberg's testimony that the MSI-H Study Record "says ***nothing*** about . . . cancer progression." Ex. 2072 ¶ 105; PO Resp. 18. Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSI-H Study Record. *Id.* ¶ 106 ("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.

[7] We cite to the reference's published page number.

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. As Patent Owner argues, the MSI-H Study Record was updated in 2016 to add the "express requirement for a prior treatment." PO Resp. 18 (citing Ex. 2165, 8; Ex. 2166, 8). We have considered this argument but find that this update alone does not indicate that the MSI-H Study Record as it appeared in 2013 was outside the scope of the challenged claims. *See* Ex. 1150 ¶ 65 (Dr. Oberstein testifying that "it is reasonable to assume that patients would typically receive [the two standard chemotherapy regimens (FOLFOX and FOLFIRI) for colorectal cancer] before trying a novel therapeutic agent."). It is also not clear whether the MSI-H Study Record was updated to reflect a change to the study or merely a clarification. The update by itself is not dispositive evidence of whether one of ordinary skill in the art would have understood the 2013 version of the MSI-H Study Record to teach treating patients who had received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitation for a solid tumor that has progressed following at least one prior cancer treatment was disclosed in the MSI-H 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. 15–19.

> *(5) [1.1]: "testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and"*

Petitioner contends that the Arms and Interventions section of the MSI-H Study Record teaches this limitation in claim 1. Pet. 23–25. Specifically, Petitioner contends that this section of "the MSI-H Study Record discloses three study arms, one of which consists of patients having MSI-H non-colorectal cancer. *Id.* at 23 (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility). Petitioner contends that "MSI positive" patients identified in the MSI-H Study Record are MSI-H patients as taught by the prior art as affirmed by an inventor during prosecution. *Id.* (citing Exs. 1010, 1193, 1196; Ex. 1018, 293; Ex. 1019, 1065; Ex. 1003, ¶¶ 27, 72; June 28, 2022, Declaration of Dr. Pardoll, 7–8, ¶¶ 21–23). Dr. Neugut testifies that the MSI-H Study Record's description of treating patients with "MSI-H positive" cancer "also discloses treating patients with a mismatch repair deficiency ("dMMR") because MSI-H is caused by dMMR. *Id.* at 24 (citing Ex. 1010, 1192; Ex. 1003, ¶¶ 27–29, 73).

Petitioner also relies on Dr. Neugut's testimony that "the MSI-H Study Record required testing or having tested 'a biological sample obtained from a patient' in order to place the patients into the proper arm." *Id.* (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); Ex. 1003 ¶ 74).

In view of the above, and after review of the entire record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation. Patent Owner does not argue to the contrary. *See generally*, PO Resp.

> (6) *[1.2]: "in response to determining that the solid tumor microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab."*

Petitioner argues that the MSI-H Study Record anticipates this limitation in claim 1 because the Arms and Interventions section discloses treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 25–26 (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); *see also* Ex. 1003 ¶¶ 76–79 (Dr. Neugut's testimony that the dosage described in the MSI-H Study Record is the same as the dosage described as being therapeutically effective in the '462 patent); *compare* Ex. 1001, 4:23–36, 8:51–58, 13:30–37. Petitioner argues that, based on the identity of the dosage, "any required efficacy is thus inherent to that dosage." Pet. 25 (citing Ex. 1003 ¶¶ 40–41, 77–78).

Patent Owner does not argue the identity or efficacy of the dosage of pembrolizumab. *See generally*, PO Resp.

Patent Owner argues that the MSI-H Study Record does not disclose treating any of the 16 cancers recited in claim 1 "in response to determining that the patient's cancer is [MSI-H]" because nothing in the MSI-H Study Record teaches identifying any of the claimed cancer types as having the MSI-H biomarker and, in response to that determination, treating with pembrolizumab. PO Resp. 15 (citing Ex. 2072 ¶ 104).

As explained above, we are persuaded by Petitioner's arguments and the cited evidence that one of ordinary skill in the art would have understood and envisaged the MSI-H Study Record to include patients with at least

endometrial, small bowel, or gastric cancers. We are further persuaded that the MSI-H Study Record teaches treating these patients in response to the determination that these patient's tumors were MSI-H in the third arm of the MSI-H Study Record. Patent Owner's arguments about the failure of the MSI-H Study Record to expressly identify any of the cancers recited in claim 1 do not persuade us otherwise. Instead, we are persuaded that one of ordinary skill in the art would have understood that the MSI-H Study Record teaches testing a patient with a non-colorectal cancer, such as endometrial, small bowel, or gastric cancers, to determine if the patient has an MSI-H tumor and, if the tumor is determined to be MSI-H, treating the patient with an amount of pembrolizumab described as being therapeutically effective in the '462 patent.

Accordingly, we are persuaded that the MSI-H Study Record teaches this limitation of claim 1.

(7) Patent Owner's Remaining Arguments.

In addition to arguing that the MSI-H Study Record does not teach specific elements recited in claim 1, Patent Owner argues that the MSI-H Study Record cannot anticipate claim 1 because it does not inherently disclose the clinical results of the study described in the MSI-H Study Record and because the MSI-H Study Record proposed an experimental use disqualifying it as prior art. PO Resp. 20–32.

Patent Owner argues that Petitioner inappropriately relies on *In re Montgomery*, 677 F.3d at 1381, 1385, to support the assertion of inherent anticipation of the claimed method. PO Resp. 20–24; Pet. 15 ("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 argues

that because the MSI-H Study Record 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 claimed by the '187 Patent did not "inevitably flow." PO Resp. 21. Patent Owner cites the testimony of inventor Le to argue that, at the time the MSI-H Study Record was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. *Id.* (citing Ex. 2130 ¶¶ 10, 22). Patent Owner argues further that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the MSI-H Study Record was not assured. *Id.* at 21–22 (citing Ex. 2090 ¶ 57; Ex. 2024[8]; Ex. 1013[9]). According to Patent Owner, "the MSR was a far cry from meeting *Montgomery*'s inevitability requirement for inherent anticipation," being design only to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. PO Resp. 22–24; Ex. 2072 ¶ 118.

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 we are not persuaded that the MSI-H Study Record is so vague it does not teach the steps expressly recited in claim 1. Regardless of the inventors' intent in publishing the MSI-H Study Record as a Stage II clinical trial on the

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[8] Brahmer et al., *Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*, 28(19) J. CLIN. ONCOLOGY 3167 (July 1, 2010).

[9] Topalian et al., Safety, *Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer*, 366(26) NEW ENG. J. MED. 2443 (June 28, 2012).

www.clinicaltrials.gov website, as discussed above, we determine that one of ordinary skill in the art would have known that the MSI-H Study Record teaches testing a biological sample from a patient having either endometrial, small bowel, or gastric cancer to determine if the patient's cancer is MSI-H or dMMR and, if so, treating the patient with a therapeutically effective amount of pembrolizumab. *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 cancer patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the MSI-H Study Record discloses testing patients with cancers known to be associated with MSI-H, as recited in claim 1, and treating with the drug recited in claim 1 if the cancer was determined to be MSI-H. *See Metabolite Labs.*, 370 F.3d at 1367 (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 MSI-H Study Record. PO Resp. 23–24. 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 colorectal cancer, we are persuaded that the MSI-H Study Record anticipates the results of administration of the drug treatment recited in those steps. *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."). 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.

(8) Summary for Claim 1

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.

b) Independent Claim 11

Patent Owner does not present separate arguments against Petitioner's challenge to claim 11 as being anticipated by the MSI-H Study Record. *See*, *e.g.*, PO Resp. 15, 16 (referring to claims 1 and 11 together). For the reasons discussed above regarding claim 1, we are persuaded that claim 11 is anticipated by the MSI-H Study Record.

c) Dependent Claims

(1) Claims 6, 16, 24, 28, and 30

Petitioner argues that claims 6, 16, 24, 28, and 30 are anticipated by the MSI-H Study Record. Pet. 28, 32, 34, and 36. Claims 6, 16, 24, 28, and 30 each require that the cancer treated according to the claimed method is "metastatic." As discussed above, the MSI-H Study Record indicated that, "before receiving treatment based on the MSI-H Study Record, patients would have generally received a prior cancer therapy drug and had their

solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 65; *see also id.* ¶ 86 ("the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had 'metastatic tumors.'") (citing Ex. 1049,[10] 444; Ex. 1050,[11] S4). Specifically, one 2015 publication refers to the clinical trial number of the MSI-H Study Record 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 MSI-H Study Record ("NCT01876511") as "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 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 cancer because "measurable disease" is not synonymous with metastatic cancer. PO Resp. 19–20. 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. *Id.* (citing Ex. 1003 ¶ 68; 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

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[10] Matikas et al., *The Place of Targeted Agents in the Treatment of Elderly Patients with Metastatic Colorectal Cancer*, 7(1) CANCERS 439 (March 13, 2015).
[11] Lee et al., *Novel Therapies in Development for Metastatic Colorectal Cance*r, 7(4 Supp. 1) GASTROINTESTINAL CANCER RESEARCH S2 (September 2015).

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.

We are persuaded by Petitioner's evidence that claims 6, 16, 24, 28, and 30 are anticipated by the MSI-H Study Record.

d) Claims 2, 4, 5, 7, 9, 10, 12, 14, 15, 17, 19–23, 25–27, and 29

Petitioner argues that claims 2, 4, 5, 7, 9, 10, 12, 14, 15, 17, 19–23, 25–27, and 29 are also anticipated by the MSI-H Study Record. Pet. 27–29, 32–36. Patent Owner does not argue these claims separately.

Briefly, Petitioner argues that claims 2 and 12, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSI-H Study Record because the Eligibility Criteria section of the MSI-H Study Record requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies that one of ordinary skill in the art would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. Ex. 1005, 5–6; Ex. 1003 ¶ 80.

Petitioner argues that claims 4, 5, 14, 15, 22, 23, 26, 27, and 29, which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient, are anticipated by the MSI-H Study Record because the MSI-H Study Record teaches treating colorectal cancer patients whose tumors are determined to be MSI-H or dMMR. Pet. 27, 28, 32, 35, and 36 (citing Ex. 1003 ¶¶ 82–85, 104–105, 112–115, 120–123, 126).

Petitioner argues that claims 7 and 17, which require the pembrolizumab to be administered to the patient intravenously is anticipated

by the MSI-H Study Record because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. Pet. 28–29, 32 (citing Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1054,[12] 3; Ex. 1055,[13] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003 ¶¶ 88–89).

Petitioner argues that claims 9, 10, 19, 20, 21, 25, and 29, which require the solid tumor to be, endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer. *See* Pet 29, 33, 35–36 (citing Ex. 1089, 39; Ex. 1003 ¶¶ 90–91, 92–93, 108–111, 118–119, 126)

In view of the above, we are persuaded by Petitioner's evidence that each of claims 2, 4, 5, 7, 9, 10, 12, 14, 15, 17, 19–23, and 25–27 are anticipated by the MSI-H Study Record.

3. Conclusion

For the foregoing reasons, we determine that the preponderance of the evidence supports Petitioner's argument that the MSI-H Study Record teaches each and every element of the challenged dependent claims. We are not persuaded otherwise by Patent Owner's arguments pertaining to these

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[12] Ascierto, et al., "*Future perspectives in melanoma research: meeting report from the "Melanoma Bridge", Napoli, December 5th-8th 2013"* J. TRANSLATNL. MED. 12:277, 1–29 (2014).
[13] September 4, 2014 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

claims. Accordingly, we determine that claims 1–2, 4–7, 9–12, 14–17, and 19–30 are anticipated by the MSI-H Study Record.

D. Ground 2: Obviousness over MSI-H Study Record, Brown, Duval, and Benson

Petitioner presents alternative grounds of challenge to claims 1–2, 4–7, 9–12, 14–17, and 19–30 of the '462 patent under 35 U.S.C. § 103, as an alternative to the challenge under 35 U.S.C. § 102, to address certain arguments by Patent Owner. Pet. 41–51. In regard to Ground 2, challenging the patentability of claims, Petitioner cites to Brown, Duval, and Benson, in addition to the MSI-H Study Record. *Id.* According to Petitioner, this ground of challenge is raised to address potential arguments by Patent Owner that the MSI-H Study Record cannot anticipate because (1) the MSI-H Study Record does not disclose an improved outcome and that one of ordinary skill in the art would not have expected such efficacy, (2) the MSI-H Study Record does not disclose testing a patient for MSI-H or MMR deficiency status, and/or (3) the MSI-H Study Record does not teach specific types of cancer, as well as arguments that related to dependent claims. Pet. 41.

In regard to the first potential argument, that the MSI-H Study Record does not disclose an improved outcome and/or that such efficacy would not have been expected, Petitioner cites to Brown as teaching that PD-1 inhibitors are inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 42 (citing Ex. 1034, 747). 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). Dr. Neugut's testimony supports Petitioner's argument that the cited teachings of Brown and Duval, as well as other references, would have

motivated a person of ordinary skill in the art to obtain the results of the MSI-H Study Record. *See* Ex. 1003 ¶¶ 124, 130, 132, 136. Petitioner argues further that Brown and Duval would have motivated one of ordinary skill in the art to obtain the results of the MSI-H Study Record by treating patients with common types of MSI-H cancers, including endometrial, small bowel, and gastric cancers. Pet. 42–43 (citing Ex. 1003, ¶ 136).

Petitioner argues further that the state of the art, as demonstrated by Brown and Duval, as well as other references, would have provided one of ordinary skill in the art with a reasonable expectation of success because physicians were actively treating patients with cancers that were known to be MSI-H with PD-1 inhibitors. Pet. 43 (citing Ex. 1016; Ex. 1017; Ex. 1003 ¶¶ 131–132).

According to Petitioner, these other references would have "independently urged" those of ordinary skill in the art to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, such as pembrolizumab, and would have given them a reasonable expectation of success. Pet. 44–45. Petitioner cites, along with other references, Pernot, which states "[colorectal cancers] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy." Ex. 1006,[14] 3741; *see* Pet. 43. Petitioner also cites Champiat, which states that

> if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MSI)+

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

> colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1 and 2, early onset), all of which display severe genomic instability.

Ex. 1032,[15] e27817-5; *see* Pet. 43. Petitioner argues, citing Dr. Neugut's testimony, that although these references are in the context of MSI-H colorectal cancer, one of ordinary skill in the art would have understood their teachings to apply to other MSI-H cancers because small bowel cancer is often treated similarly to colorectal cancer. Pet. 44 (citing Ex. 1003 ¶ 139).

Petitioner argues further that if Patent Owner argues the MSI-H Study Record does not expressly teach testing to determine if a patient's cancer is microsatellite instability high or DNA mismatch repair deficient, the MSI-H Study Record would have at least motivated those of ordinary skill in the art to undergo such testing to be placed in the proper study arm. Pet. 45–46 (citing Ex. 1003 ¶ 141). Petitioner also argues that testing a biological sample from a patent for MSI-H was routine in the art at the time of filing. *Id.*, 45 (citing Ex. 1003 ¶ 141).

Regarding claims 6, 16, 24, 28, and 30, challenged under 35 U.S.C. § 103, Petitioner cites Benson (Ex. 1009) for its teachings of the ways in which clinical studies involving colorectal and small bowel cancer are conducted. *See* Pet. 48–51 (citing Ex. 1009, 1034.) These claims require treating patients who had previously been treated with a cancer therapy drug and whose cancers had progressed or who have metastatic cancer. *See* Ex. 1001, 26:11–27:17. Petitioner argues that, to the extent Patent Owner

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

asserts the MSI-H Study Record does not disclose treating patients with these characteristics, Benson teaches that, under the standard of care, patients having tumors and measurable disease who would take part in a clinical study are generally patients who have had their cancer progress after previous drug therapies. Pet. 49 (citing Ex. 1009, 1034). Petitioner cites to other references to demonstrate that, also under the standard of care, patients with tumors and measurable disease who would take part in a clinical study are patients with metastatic, advanced, and recurrent disease. Pet. 49–50 (citing Ex. 1089,[16] 17; Ex. 1094,[17] 15; Ex. 1020,[18] 251).

Petitioner argues, citing Dr. Neugut's testimony, that patients in a clinical study such as the MSI-H Study Record describes would be patients who had already received standard of care treatment but did not respond to this treatment, and would not have been expected to respond to additional standard of care treatment. Pet. 50–51 (citing Ex. 1003 ¶ 147). Petitioner further cites to Dr. Neugut's testimony that the patient population with tumors and measurable disease who would take part in a clinical study are patients with metastatic, advanced, and recurrent disease. *Id.* (citing Ex. 1003 ¶ 147).

According to Petitioner, given the teachings of Benson, those of ordinary skill in the art would have been motivated to combine the teachings

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[16] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2014 (November 27, 2013) (Ex. 1089).
[17] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1.2014 (May 30, 2014) (Ex. 1094).
[18] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014) (Ex. 1020).

of the cited references and would have had a reasonable expectation of success in achieving the methods recited in dependent claims 6, 16, 24, 28, and 30. *See* Pet. 50–51.

For the reasons stated above in our discussion of Ground 1, 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. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("anticipation if the epitome of obviousness").

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. PO Resp. 55–82. 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 claims 1–2, 4–7, 9–12, 14–17, and 19–30 are 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, 2, 4–7, 9–12, 14–17, and 19–28 as being obvious over the MSI-H Study Record alone.

E. Grounds 3–7: Obviousness over MSI-H Study Record in combination with Brown, Duval, Benson, and Koh, or additionally references.

Petitioner argues that certain dependent claims of the '462 patent are unpatentable because they are obvious over the MSI-H Study Record, Brown, Duval, Benson, and Koh (Ground 3), additionally in combination with Ajani (Ground 4), additionally in combination with Ajani and Chapelle

(Ground 5), additionally in combination with Ajani and Steinert (Ground 6), and additionally in combination with Ajani and Hamid (Ground 7). Pet. 52–61. Because, as discussed above, we determine that claims 1–2, 4–7, 9–12, 14–17, and 19–30 are anticipated by the MSI-H Study Record, they also would have been obvious over MSI-H Study Record alone in each of Grounds 3–7 for the reasons discussed above. *In re McDaniel*, 293 F.3d at 1385. In the discussion that follows, we review Petitioner's obviousness challenges for the claims not addressed in Ground 1—that is, claims 3, 8, 13, and 18.

1. Claims 8 and 18: Obviousness over the MSI-H Study Record, Brown, Duval, Benson, Koh, Chapelle

Claims 8 and 18 recite the methods of claims 1 and 11, respectively, "wherein the step of testing or having tested comprises assessing one or more of BAT-25, BAT-26, MONO-27, NR-21 and NR-24." Ex. 1001, 26:16–18, 26:56–59.

Petitioner cites Chapelle for its teaching of Chappelle's standard methods for testing for MSI-H, including a test for MSI-H that has "stood the test of time" and comprises "assessing one or more of: BAT-25, BAT-26, MONO-27, NR-21 and NR-24, in order to test whether a tumor is MSI-H." Pet. 56–57 (citing Ex. 1003 ¶ 169; Ex. 1007, 3380, 3382–3383). Petitioner contends that a POSA would have been motivated to "combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Chapelle to assess one or more of: BAT-25, BAT-26, MONO-27, NR-21 and NR-24, in order to test whether a tumor is MSI-H." *Id.* at 57 (citing Ex. 1003 ¶ 169). 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. 57 (citing Ex. 1001, 6:16–17; 6:26–29; Ex. 1003 ¶ 169).

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

2. Claims 3 and 13: Obviousness over the MSI-H Study Record, Brown, Duval, Benson, Koh, and Steinert

Claims 3 and 13 recite the method of claim 1 or claim 11, respectively, "wherein the biological sample is a body fluid from the patient." Ex. 1001, 26:5–6, 26:46–47. Petitioner cites Steinert for its teaching of testing body fluid to determine whether a tumor is microsatellite instability high. Pet. 58–59 (citing Ex. 1008, OF1; Ex. 1003 ¶¶ 173, 175).

Petitioner argues that one of ordinary skill in the art would have been motivated to combine the MSI-H Study Record (alone or combined with Brown, Duval, and Benson) and Steinert because the MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H and because Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. Pet 58 (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 173, 175). Petitioner also argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have had a reasonable expectation of success given that the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. *Id.* at 59 (citing Ex. 1001, 6:26–27 ("Testing of MSI can be accomplished by any means known in the art"), 6:36–39; Ex. 1003 ¶ 176).

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

1. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 8, 13, and 18 as being obvious. *See generally* PO Resp. That is, Patent Owner argues against all of the obviousness challenges together, without *arguing* that any of the limitations recited in the dependent claims renders the method of claim 1 or 11 non-obvious.

Patent Owner asserts that Petitioner alleges an incorrect legal standard for reasonable expectation of success because Petitioner asserts that the ordinarily skilled artisan would have wanted to obtain the data from the MSH-H Study Record to determine the outcome of patients, rather than alleging that the artisan would have reasonably expected to achieve success in the treatment. PO Resp. 36–38 (citing Pet. 42, 44). We are not persuaded. Petitioner's statements explain why an artisan interested in treating MSI-H cancers would have been motivated to read and understand the MSI-H Study Record. *See, e.g.*, Pet. 42 (stating that the artisan "would have expected all patients having MSI-H tumors to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study, thus observing the inherent properties of treating MSI-H patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record.") This statement is followed by reasoning as to why the artisan would have further examined Brown and Duval (*id.*) and Benson (*id.* at 48). We are not persuaded that these statements are relevant as the correct inquiry on reasonable expectation of success is whether an ordinarily skilled artisan, armed with all of the knowledge from the identified references in combination, would have a reasonable expectation of success in practicing the claimed method. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 966 (Fed. Cir. 2014).

Furthermore, as discussed above, we have concluded that the MSI-H Study Record inherently anticipates claims 1 and 11. Therefore, Petitioner's burden in showing a reasonable expectation of success with regard to claims 3, 8, 13 and 18 distills to whether an ordinarily skilled artisan would have a reasonable expectation of success in practicing the additional limitations only. *See also Cytiva Bioprocess v. JSR Corp.*, Dec. 4, 2024 CAFC "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." (citing *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020).) We are persuaded that Petitioner has shown that the artisan would have had a reasonable expectation of success in practicing the additional limitations of the claimed methods of claims 3, 8, 13 and 18, as discussed above.

Similarly, we are not persuaded by Patent Owner's argument that the ordinarily skilled artisan would not have been motivated to treat the claimed cancers in the claimed way as it pertains to claims 3, 8, 13 and 18. PO Resp. 52–54. We are persuaded that Petitioner has shown that the artisan would have been motivated to combine the MSI-H Study record with Steinert to make the subject matter of claims 1 and 13, and with Chapelle to make the subject matter of claims 8 and 18.

Finally, Patent Owner presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 55–82. 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 Study Record, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 11. *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, 4–7, 9, 10, 12, 14–17, and 19–28, which we determine are anticipated by the MSI-H Study Record.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8, 13, 18), Patent Owner must show a nexus between the claimed methods 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 the dependent claims, for example to claims 3 and 13, which recite testing a biological sample that is a bodily fluid, claims 8 and 18, which recite 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.

Even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 11, not the additional limitations of the claims Petitioner challenges as being obvious. PO Resp. 55–83. Patent Owner directs us only to evidence regarding treating patients determined to have certain MSI-H cancers with pembrolizumab, which we determine to be anticipated by the MSI-H Study

Record. *Id.* at 58. 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 methods recited in claims 1 and 11 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claim 3, or "wherein the at least one marker comprises BAT-25, BAT-26, MONO-27, NR-21 or NR-24," as recited in claim 8, demonstrated unexpected results or commercial success.

Accordingly, having considered the evidence of record as a whole, we determine that Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 3, 8, 13, and 18 would have been obvious. We are not persuaded to the contrary by Patent Owner's arguments or evidence of second secondary considerations.

III. CONCLUSION[19]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–30 of the '462 patent are unpatentable. In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–7, 9–12, 14–17, 19–30	102	MSI-H Study Record	1, 2, 4–7, 9–12, 14–17, 19–30	
1, 2, 4–7, 9–12, 14–17, 19–30	103	MSI-H Study Record, Brown, Duval, Benson	1, 2, 4–7, 9–12, 14–17, 19–30	
1, 2, 4–7, 9–12, 14–17, 19–24	103	MSI-H Study Record, Brown,	1, 2, 4–7, 9–12, 14–17, 19–24	

19 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, Koh		
1, 2, 4–7, 9, 11, 12, 14–17, 19, 25, 26	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani	1, 2, 4–7, 9, 11, 12, 14–17, 19, 25, 26	
2, 8, 12, 18	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Chapelle	2, 8, 12, 18	
3, 13	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Steinert	3, 13	
7, 17	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Hamid	7, 17	
Overall Outcome			1–30	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–30 of the ’462 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.

For PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

For PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Matthew Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 52
Date: September 23, 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.

IPR2024-00649
Patent 11,629,187 B2

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

SNEDDEN, *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 1–28 of U.S. Patent No. 11,629,187 B2 (Ex. 1001, "the '187 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '187 patent. Paper 3. Patent Owner did not file a Preliminary Response.

We instituted trial on September 27, 2024. Paper 6 ("Inst. Dec."). During trial, Patent Owner filed a Patent Owner Response. Paper 29 (confidential Paper 25) ("PO Resp."). Petitioner filed a Reply (Paper 45 (confidential Paper 42) ("Pet. Reply")) and Patent Owner filed a Sur-Reply (Paper 50 (confidential Paper 47) ("PO Sur-Reply")). The parties declined to present oral arguments in this proceeding. Paper 49.

We have jurisdiction under 35 U.S.C. § 6(b). After considering the full record developed through trial, we determine that Petitioner has proved by a preponderance of the evidence that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e). Our reasoning is explained below, and we issue this Final Written Decision under 35 U.S.C. § 318(a).[1]

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[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

B. Real Parties in Interest

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

C. Related Matters

The parties indicate that the '187 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. 64; Paper 3, 1. Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 64; Paper 3, 1.

D. The '187 patent (Ex. 1001)

The '187 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '187 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.* at Abstract. More specifically, the '187 patent is directed to treating cancer patients with high mutational burdens,

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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.

such as those found in microsatellite instable ("MSI") cancer, with anti-PD-1 antibodies. *Id.* at 3:38–53. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:32–34.

The '187 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 1:55–62. According to the '187 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 2:6–9. However, the Specification describes that

> in reports of PD-1 blockade in human tumors, only one of 33 colorectal cancer (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 2:63–3:6. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '187 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 3:14–21. 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 8:52–58. According to the '187 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 6:52–56.

E. The Challenged Claims

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

> 1. A method for treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer, the method comprising:
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer with a therapeutically effective amount of pembrolizumab based on a determination that the solid tumor has progressed following at least one prior cancer treatment, and further based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.

Ex. 1001, 25:5–27.

Representative independent claim 11 is reproduced below:

> 11. A method for reducing the risk of progression of a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine

cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment in a patient, the method comprising:

in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.

Id. at 25:49–26:12.

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" or "MSR").

Ex. 1007, Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. CLIN. ONCOLOGY 3380 (2010) ("Chapelle").

Ex. 1008, Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) ("Steinert").

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").

Ex. 1095, Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. NAT'L COMPREHENSIVE CANCER NETWORK 248 (February 2014) ("Koh").

Petitioner also relies on the declarations of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150) to support its contentions.

Patent Owner relies on the declarations of Nils Lonberg, Ph.D. (Ex. 2072), Dung Le, M.D. (Ex. 2130) and Richard Goldberg, M.D. (Ex. 2090).

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–28 would have been unpatentable on the following grounds (Pet. 3–4):

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 2, 4–7, 9–12, 14–17, 19–28	102	MSI-H Study Record
II	1, 2, 4–7, 9–12, 14–17, 19–28	103	MSI-H Study Record, Brown, Duval, Benson
III	1, 2, 4–7, 9–12, 14–17, 19–28	103	MSI-H Study Record, Brown, Duval, Benson, Koh
IV	2, 8, 12, 18	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Chapelle
V	3, 13	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Steinert

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
VI	7, 17	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Hamid

H. Claim Construction

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

Claim 1 requires treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient . . . ." Petitioner argues that the discussion in the MSR of treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. Pet. 19–20 (citing Ex. 1005, 2–5; Ex. 1003 ¶¶ 61–66).

Patent Owner argues that our construction "disregards the critical ***causal*** relationship between 'determining' and 'treating' steps expressed by the claims," wherein the causal relationship establishes that "***only*** patients determined to be MSI-H are treated." PO Resp. 6. According to Patent Owner, the construction of "in response to" should be that the phrase means "in reaction to." *Id.*

Patent Owner argues that if the inventors had intended the claimed method to encompass merely treating patients "after" a determination of the patient's MSI-H status, they would have used the word "after" in their claims, citing use of the word "after" in other claims. PO Resp. 7. Because the cited language is in claims that depend on claim 1, Patent Owner argues that the term "in response to" must have a different meaning from "after." *Id*.

Patent Owner argues further that the Specification of the '187 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H. PO Resp. 7–8. Specifically, Patent Owner cites the disclosure in the '187 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. Ex. 1001, 3:54–66.

According to Patent Owner, one of ordinary skill in the art would have understood from this distinction in recommended treatments that "in response to" describes administering the claimed treatment only as a reaction to the determination that the patient's cancer is MSI-H. PO Resp. 8. Patent Owner argues further that "[i]f 'in response to' meant merely 'after,' the claims would cover treatment administered to MSI-H patients for any reason or no reason at all," which is a reading "inconsistent with the specification." *Id*.

We agree with Patent Owner that the phrase "in response to" in claim 1 requires a causal relationship wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is

treated with 10 mg/kg of pembrolizumab every 14 days. In claim 1, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having cancer to determine that the patient's cancer is microsatellite instability high or mismatch repair deficient, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the art anticipates claim 1. We are not persuaded that claim 1 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment *only* as a reaction to the determination that the patient's cancer is MSI-H, and that, if treatment were administered to patients for any other reason after testing confirmed that the patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient, the term "in response to" would be meaningless. PO Resp. 7. But claim 1 does not exclude treatment of other patients who are not MSI-H or dMMR, if the cancer patient from whom the biological sample is obtained and tested is determined not to be microsatellite instability high or mismatch repair deficient. Claim 1 does not mention any other patients or define patient populations to be excluded from treatment. Claim 1 provides that if the cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab.

Here, we further note that the method of claim 1 uses the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp*., 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim."). The use of the open-ended transitional phrase "comprising" in claim 1 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner's arguments about the interpretation the Examiner used during prosecution do not persuade us otherwise. PO Resp. 8–9. Patent Owner cites to the Examiner's reasons for allowance in a related patent (U.S. 11,591,393), which states that the cited prior art "does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed." *Id.* at 7 (citing Ex. 2302, 8). According to Patent Owner, the term "based on" does not mean "after," but requires a causal relationship. PO Resp. 8. Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that claim 1 requires anything other than testing a cancer patient and, if the cancer is determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. The Examiner's reasoning does not indicate that claim 1 excludes treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one determined to be MSI-H or dMMR, as Patent Owner implies. PO Resp. 9–10. Patent Owner argues that "Merck's only dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." *Id.* at 9 (citing Ex. 2160, 24[2]). But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 excludes treating any patient other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a ***reaction***, as that of an organism to any of its parts, to a ***specific*** stimulus." Ex. 2160, 24–25. This construction does not limit the scope of claim 1 to contemplating the treatment of any patients other than the one tested and determined to be MSI-H or dMMR. Before the District Court, Petitioner argued "[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion about what behavior the claims cover." *Id.* at 25. Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now.

Patent Owner argues further that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that its witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a

[2] Patent Owner cites to page 30 of Exhibit 2160, which is page 24 of the underlying document.

determination that the patient's tumor is MSI-H. PO Resp. 9 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 98–100). Neither of these statements persuades us that claim 1 requires anything other than testing a cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of claim 1 excludes treating any patient other than the one tested and confirmed to be MSI-H.

Patent Owner cites *Am. Calcar, Inc. v. American Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011), in support of the claim construction that the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H, but not when the patient is MSI-stable. PO Resp. 10. In that case, the Federal Circuit determined that, in claims directed to systems for identifying a service provided when a vehicle needs service, the term "the processing element identifying one of the plurality of providers *in response to* the vehicle condition" means "that the second event occur in reaction to the first event." *Am. Calcar*, 651 F.3d at 1324, 1340. The court continued, by explaining that "[t]he language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction." *Id.* at 1340. We note that, as explained above, we agree the claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claim 1 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required

because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claim 1 to require testing a biological sample obtained from a patient having cancer to determine that the patient's cancer is microsatellite instability high or mismatch repair deficient, and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be microsatellite instability high or DNA mismatch repair deficient. We are not persuaded that claim 1 either requires or excludes other patients or steps because claim 1 does not recite any other steps or contain negative limitations.

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 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) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be "a medical doctor or a professional in a related field with at least five years of experience with treating cancer" and "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." Pet. 11 (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. PO Resp. 5–6 (citing Ex. 2072 ¶¶ 31–32, 89–97). Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '187 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, 25:5–27; Ex. 1005. Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds.

In the Decision to institute trial, we adopted Petitioner's uncontested proposal defining that the level of skill in the art, presented above. Inst. Dec. 7. Neither party directs us to evidence of the level of skill in the art beyond what we considered for institution of trial. Having considered Patent Owner's positions and evidence of record, however, we determine that the level of skill also 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 cancers and the associated conditions and immunotherapy.

II. ANALYSIS

A. Introduction

"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, 1368–69 (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) (alterations in original))).

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. Summary of the Cited Prior Art

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

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

[3] Ascierto et al., *Future Perspectives in Melanoma Research: Meeting Report from the "Melanoma Bridge", Napoli, December 5th-8th 2013*, 12 J. TRANSLATIONAL MEDICINE 277 (October 2024)

melanoma."); *see also* Ex. 1069 (titled "ANTITUMOR ACTIVITY OF PEMBROLIZUMAB (PEMBRO; MK-3475) . . . .")).

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

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

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" *Id.* at 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

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

2. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with

deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.* at 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.* at 3380, 3384.

3. Steinert (Ex. 1008)

Steinert is an article titled "Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer." Ex. 1008, OF1. Steinert discloses a detailed genomic and phenotypic analyses of single colorectal cancer–derived circulating tumor cells (CTC). *Id.* Steinert describes that "[a]mplified gDNA of CTC and tumor tissue samples was tested for microsatellite instability (MSI) using the markers NR21, NR24, and BAT 25." *Id.* at OF2. Steinert describes that the analyses of single cancer-derived CTC found disparities in key mutations, including MSI, in comparison to the primary tumor. *Id.* at OF4. "MSI at one or more markers . . . was detected in CTC from 2 patients (of 25 with complete MSI data sets; 7.7%, Fig. 2C). In 1 patient, two of 11 tested CTC were MSI despite a microsatellite stable (MSS) tumor (Table 1)." *Id.* In one patient, "[t]hree single CTC were classified as MSI-high level (MSI-H) and showed a mutation in the coding region of the *ELAVL* gene." *Id.* at OF6.

4. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing

metastatic CRC, focusing mainly on systemic therapy." *Id.* at 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.* at 1034.

5. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.* at 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic mutations have . . . elevated expression of *CTLA4* and *PDCD1*," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.* at 747–748.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes

that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.* (emphasis omitted).

8. Koh (Ex. 1095)

Koh is an article titled "Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology." Ex. 1095, 248. Koh describes that "[t]he NCCN Guidelines for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management." *Id.* at Abstract. Koh discloses that patients having endometrial cancer who were enrolled in a clinical study would generally have had a tumor that had progressed after at least one prior cancer treatment and metastatic cancer. *Id.* at 256.

C. Ground 1: Anticipation of Claims 1, 2, 4–7, 9–12, 14–17, and 19–28 by the MSI-H Study Record

1. Petitioner's Contentions

Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, and 19–28 are anticipated by the MSI-H Study Record. Pet. 13–38. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how

each element of claims 1–2, 4–7, 9–12, 14–17, and 19–28 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 50–127.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 13–14. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 16. Relying on those cases, Petitioner contends that "[t]he MSI-H Study Record inherently anticipates [c]laims 1–2, 4–7, 9–12, 14–17, [and] 19–28 of the '187 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." *Id.*

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '187 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "[i]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 14.

a) Independent Claim 1

Like the parties, our analysis focuses on independent claim 1. *See, e.g.*, Pet. 32–34 (relying substantially on analysis of claim 1 for independent

claim 11). We analyze the parties' contentions with regard to the elements of claim 1 below.

> (1) *[1.pre]: "A method for reducing the risk of progression of a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment in a patient, the method comprising:"*

Petitioner argues that, in general, the MSI-H Study Record anticipates claim 1 of the '187 patent because it "teaches the claimed drug, given at the only therapeutically effective dosage described in the '187 patent, and given to the claimed patient population." Pet. 16–17. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating patients having non-colorectal MSI-H cancer, as recited in the preamble of claim 1. *Id.* at 18 (citing Ex. 1003 ¶¶ 38–41, 59–63; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)).

Petitioner contends that the MSI-H Study Record concerns the treatment of solid tumor and further contends that "MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel cancer, and gastric cancer." *Id.* at 17–18 (citing Ex. 1005, 2 (Study Identification), 5–6 (Eligibility); Ex. 1048, 228, 230–3; Ex. 1085,[4]

[4] Imai et al., *Carcinogenesis and Microsatellite Instability: The Interrelationship Between Genetics and Epigenetics*, 29(4) CARCINOGENESIS 673 (2008).

673, 675; Ex. 1086,[5] 14; Ex. 1003 ¶¶ 25, 60–61, 63). Petitioner relies on Dr. Neugut's testimony that endometrial, small bowel cancer, and gastric cancer are "common in Lynch syndrome, which was known at the time to be closely related to MSI-H." Ex. 1003 ¶ 63 (citing Ex. 1085, 673–74 ("DNA mismatch repair (MMR) deficiency results in a strong mutator phenotype and high-frequency microsatellite instability (MSI-H), which are the hallmarks of tumors arising within Lynch syndrome.")); *see also* Ex. 1085, 673 ("Tumors of the Lynch syndrome . . . and some sporadic gastrointestinal and endometrial cancers belong to the MSI pathway."). Thus, "the person of ordinary skill would have immediately pictured treating [patients with endometrial, small bowel, and gastric cancer] with the MSI-H Study Record's methods" and that "the person of ordinary skill would have concluded that the limitation [listing recited types of cancer] was found in the MSI-H Study Record." Ex. 1003 ¶¶ 63–64.

To begin, Patent Owner argues that the MSR cannot anticipate because it does not expressly or inherently disclose the claimed MSI-H cancers. PO Resp. 10–14. Patent Owner contends that the MSR provides no details or guidance about cancer types to be included in the third arm of patients, but only describes its third arm as "MSI Positive Non-Colorectal Cancer." *Id.* at 10 (citing 1005, 4); *see also id.* ("Other than specifying the participant's cancer must be noncolorectal, the MSR provides no details or guidance about cancer types to be included in that third arm."). Patent Owner further contends that "MSI Positive Non-Colorectal Cancer" is a large genus "comprising a large, and unknown, number of species" such that

[5] Cheung et al., *Current Advance in Small Bowel Tumors*, 44(1) CLINICAL ENDOSCOPY 13 (2011).

a person of ordinary skill in the art "would not envisage all its species, let alone the claimed subset of those species, based on the bare disclosure in the MSR." PO Resp. at 14; *see also* PO Sur-Reply 3 (Petitioner "identifies no common properties of non-CRC MSI-H cancer, or any other way a POSITA would have recognized the MSR discloses those cancers."); *Id.* at 4 (Petitioner "has not shown that a POSITA would at once envisage the ***entire*** genus—meaning every one of its constituent species—based on the MSR."). Patent Owner acknowledges that the MSR discloses the "third arm" disclosed in the MSR "was open to all-comers with any MSI-H cancer other than CRC," but argues that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of the genus. PO Resp. 10–11 (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006), *Metabolite Lab'ys, Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)).

Next, Patent Owner argues that the Petition did not provide evidence of the number of species in the genus described in the MSR and does not contend that one of ordinary skill would immediately appreciate the full scope of the genus, which includes at least twenty-nine species. PO Resp. 13 (citing Ex. 2072 ¶ 53). According to Patent Owner, the issue of whether MSI-H was known to occur in Petitioner's "hand-picked set of cancers" (endometrial, gastric, and small bowel cancer) is irrelevant because it overlooks the other MSI-H cancers recited in claim 1 and ignores the "unclaimed non-[colorectal] MSI-H cancers." *Id.* at 12. According to Patent Owner, the size of the non-colorectal cancers included in the MSR is large and there is no support for a conclusion that a person of ordinary skill in the art could have at once envisaged each member. *Id.* at 13.

Patent Owner argues that the Petition overstates the understanding one of ordinary skill in the art would have of MSI-H cancers. PO Resp. at 12 (citing Ex. 2072 ¶ 102). According to Patent Owner, only endometrial cancer "was tested for MSI-H as a part of standard care at the time of the invention—and it was only tested to identify familial susceptibility (not in relationship to treatment)." *Id.* (citing Ex. 2090 ¶ 79). Patent Owner further cites inventor Le's testimony that the MSR investigators had difficulty recruiting MSI-H patients for the non-colorectal cancer arm of the study because such testing was not routinely done in non-colorectal cancers. *Id.* (citing Ex. 2130 ¶ 12). This evidence, though, does not persuade us of what one of ordinary skill in the art would have understood from the disclosure of the MSR.

In contrast, the testimony of Patent Owner's witness, Dr. Goldberg, supports Petitioner's argument of the knowledge in the art at the time, wherein Dr. Goldberg testifies that "[w]hile many clinical oncologists were aware that patients with Lynch Syndrome had a defect in DNA mismatch repair, they associated MSI testing with young onset colorectal and endometrial cancer and patients with a family history of colorectal and/or endometrial cancer." Ex. 2090 ¶ 79. Similarly, during his deposition Dr. Goldberg also agreed that endometrial, gastric, and small-bowel cancers would come to mind when he saw a reference to MSI-high non-colorectal cancer. (*See* Ex. 1243, 115:5–116:22 (Q. And so does endometrial cancer come to mind when you see reference to MSI-high non-colorectal cancers? . . . A. Yes. Q. As . . . a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does gastric cancer come to mind? . . . A. I believe it was listed among the items that I stated when you asked me what comes to mind. So the answer is yes. Q. As a person of skill in the

field, when you see reference to MSI-high non-colorectal cancers, does small bowel cancer come to mind? . . . A. Yes.").) Patent Owner does not direct us to other evidence contradicting Petitioner's argument that MSI-H was known to occur in endometrial, small bowel, and gastric cancer. Pet. 18.

Patent Owner argues that the Petition does not consider the breadth of the genus disclosed in the MSR and does not argue or provide evidence to show that one of ordinary skill in the art could have envisaged each species within that genus. PO Resp. 11–14. We are not persuaded that either the size of the genus in the MSR or whether one of ordinary skill in the art would have been able to envisage every species within it is dispositive of whether the MSR anticipates claim 1, where one or ordinary skill in the art would have known that specific cancers recited in claim 1 would be included in the MSR. As Petitioner argues, claim 1 requires that "a patient having" one of the listed cancers is tested and treated. Pet. Reply 10. Claim 1 does not require that the patient have each and every one of the sixteen listed cancers. *Id.* Rather, claim 1 requires testing a sample from "a patient" with one of the recited types of cancer and treating the patient. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.").

Patent Owner argues further that *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009), supports its position, requiring that one of ordinary skill in the art must at once envisage all MSI-H non-colorectal cancer types included in the MSR, not just one or even a subset of the claimed cancer types, in order for the MSR to anticipate claim 1. PO Sur-Reply 2. *Gleave* states:

> For the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law. *Compare Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) (rejecting "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list") with *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). This distinction collapses when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can "at once envisage each member of this limited class." *Eli Lilly*, 471 F.3d at 1376. In that limited circumstance, a reference describing the genus anticipates every species within the genus. *See Perricone*, 432 F.3d at 1377.

In re Gleave, 560 F.3d at 1337–38. This portion of *Gleave*, cited by Patent Owner, does not hold that a reference anticipates *only* when all species either disclosed in the reference or recited in the challenged claim can be envisioned, but rather that when each species of the prior art genus could be envisaged, the genus is anticipatory.

Nothing in *Gleave* or any other reference cited by Patent Owner refutes the patent law concept that a claim encompassing a species is anticipated if a prior art disclosure leads to a genus small enough that a person of ordinary skill in the art would at once envisage the claimed species. *See Brown*, 265 F.3d at 1351; *In re Slayter*, 276 F.2d 408, 411 (CCPA 1960) ("[A] generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus."); *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989) (holding that a claim reciting a genus of twenty-one specific chemical species in a Markush group is anticipated by prior art that discloses two of the chemical species).

Patent Owner attempts to distinguish *Brown* by arguing that its holding is limited to anticipation of a claimed genus through disclosure of individual species, whereas the facts of this case involve the disclosure of a genus. PO Resp. 14. Because the facts before us, including the testimony of Patent Owner's witness, indicate that one of ordinary skill in the art would have immediately understood that the third arm of the study described in the MSR includes patients with cancers recited in claim 1, including endometrial, gastric, and small-bowel cancers, we are persuaded that one of ordinary skill in the art would have understood that the MSR discloses species that fall within the scope of claim 1. Ex. 2090 ¶ 79; Ex. 1243, 115:5–116:22; Ex. 1085, 673–75; Ex. 1086, 14; Ex. 1003 ¶¶ 25, 63; Ex. 1005, 4. We are not persuaded that where species falling within the scope of claim 1 were previously known and disclosed in MSR, that claim 1 is patentable over the MSR. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage'" the claimed arrangement or combination." (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

After considering the parties' arguments and the evidence presented, we are persuaded that the MSR teaches "testing or having tested a biological sample obtained from a patient" having endometrial, small bowel, or gastric cancer and, thus teaches the corresponding limitation of claim 1.[6]

[6] We need not decide whether the preamble is limiting as we find that the MSI-H Study Record discloses the preamble.

(2) [1.1]: "in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating a patient"

Petitioner argues that the MSI-H Study Record anticipates this limitation in claim 1 because the Arms and Interventions section treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 19–21; *see also* Ex. 1003 ¶¶ 65–67 ("The MSI-H Study Record's discussion of treating patients with 'MSI positive' cancer also concerns treating patients with a mismatch repair deficiency ('dMMR')").

Patent Owner argues that the MSR does not disclose treating any of the 16 cancers recited in claim 1 "in response to determining that the patient's cancer is [MSI-H]" because nothing in the MSR teaches identifying any of the claimed cancer types as having the MSI-H biomarker and, in response to that determination, treating with pembrolizumab. PO Resp. 15 (citing Ex. 2072 ¶ 103).

As explained above, we are persuaded by Petitioner's arguments and the cited evidence that one of ordinary skill in the art would have understood and envisaged the MSR to include patients with at least endometrial, small bowel, or gastric cancers. We are further persuaded that the MSR teaches treating these patients in response to the determination that these patient's tumors were MSI-H in the third arm of the study described. Patent Owner's arguments about the failure of the MSR to expressly identify any of the cancers recited in claim 1 do not persuade us otherwise. Instead, we are persuaded that one of ordinary skill in the art would have understood that the MSR teaches testing a patient with a non-colorectal cancer, such as endometrial, small bowel, or gastric cancers, to determine if the patient has

an MSI-H tumor and, if the tumor is determined to be MSI-H, treating the patient with amount of pembrolizumab described as being therapeutically effective in the '187 patent.

Accordingly, we are persuaded that the MSR teaches this limitation of claim 1.

(3) [1.2]: "having a solid tumor"

This limitation is identical to limitation [1.pre], discussed above, and met for the same reasons. Pet. 21.

(4) [1.3]: "selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer"

This limitation is identical to limitation [1.pre], discussed above, and met for the same reasons. Pet. 21.

(5) [1.4]: "with a therapeutically effective amount of pembrolizumab"

Petitioner relies on Dr. Neugut's testimony to assert that the dosage described in the MSI-H Study Record is the same as the dosage described as being effective in the '187 patent. *Compare* Pet. 21–22 (citing Ex. 1003 ¶¶ 70–73; Ex. 1005, 2 (Study Identification), 3 (Study Description), 4 (Arms and Interventions), 4–5 (Outcome Measures), 5–6 (Eligibility)) *with* Ex. 1001 4:23–36, 8:51–58, 13:30–37.

In view of the above, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation. Patent Owner does not argue to the contrary.

(6) [1.5]: "based on a determination that the solid tumor has progressed following at least one prior cancer treatment"

Petitioner alleges that the MSI-H Study Record discloses the above limitation, because the MSI-H Study Record requires the enrolled patients to have "tumors" and "measurable disease," which Dr. Neugut testifies would include metastatic and advanced non-colorectal cancers in the context of the MSI-H Study Record. Pet. 23 (citing Ex. 1005, 2–6 (Study Identification, Study Design, Eligibility); Ex. 1020, 25; Ex. 1003 ¶¶ 74–75). According to Dr. Neugut, the MSI-H Study Record indicated that, "before receiving treatment based on the MSI-H Study Record, patients would have generally received a prior cancer therapy drug and had their solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 74.

Dr. Neugut testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer "would have generally received at least one prior drug therapy, such as standard of care chemotherapy, and had their cancers progress after that drug therapy." *Id.* ¶ 76 (citing Ex. 1089 at PDF p. 17 (endometrial); Ex. 1020, 25 (small bowel)). Dr. Neugut observes that the Eligibility section of the MSI-H Study Record takes care to exclude patients having had prior treatment with certain antibodies. *Id.* at ¶ 74. 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.* ¶ 79.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 68–71. Dr. Oberstein testifies that because the eligibility criteria stated in the MSR 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.* at ¶ 68. 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.* at ¶ 69.

Patent Owner argues that the MSR is silent about whether eligible patients must have had prior, failed treatment and that Petitioner's "assertions that a patient 'generally' . . . would have received a prior treatment is not enough to meet the high burden for an inherency finding." PO Resp. 16–17.

Patent Owner cites evidence to show that, instead, it was known that some cancer patients can proceed directly to clinical trials even without prior treatment. *Id.* at 17–19. First, Patent Owner cites published guidelines for the management of patients with gastric cancer. *Id.* at 18 (citing Ex. 1096, 533, 537; Ex. 2072 ¶ 105). But Patent Owner fails to explain the flow diagrams in the cited pages of this publication and, although there is mention of "clinical trial" for "Unresectable locally advanced, locally recurrent or metastatic disease," it is not clear that this is recommended in the absence of different or prior cancer therapy. Ex. 1096, 533, 537. Second, Patent Owner cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." Ex. 1009, 1029.

Patent Owner's evidence is directed to the general knowledge in the field, not to the specific understandings of one of ordinary skill in the art when reviewing the MSR, such as the testimony of a witness regarding the content of the MSR. Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about . . . cancer progression." Ex. 2072 ¶ 104; PO Resp. 18. Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. Ex. 2072 ¶ 106 ("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 MSR 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 MSR. As Patent Owner argues, the MSR was updated in 2016 to add the "express requirement for a prior treatment." PO Resp. 18. We have considered this argument but find that this update alone does not indicate that the MSR as it appeared in 2013 was not within the scope of the challenged claims. *See* Ex. 1150 ¶ 69 (Dr. Oberstein testifying that "it is reasonable to assume that patients would typically receive [the two standard chemotherapy regimens (FOLFOX and FOLFIRI) for colorectal cancer] before trying a novel therapeutic agent."). It is also not clear why the MSR was updated – was it a change to the study or merely a clarification? The update by itself is not dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients

who had received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." 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 light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitation for a solid tumor that has progressed following at least one prior cancer treatment was disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. *Contra* PO Resp. 16–19.

> *(7) [1.6]: "and further based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency."*

Petitioner contends that the Arms and Interventions section of the MSI-H Study Record teaches this limitation in claim 1. Pet. 27–28. Specifically, Petitioner contends that "the MSI-H Study Record discloses treating three study arms, one of which consists of patients having MSI positive non-colorectal cancer—that is non-colorectal cancer that exhibits an instability of more than one microsatellite marker and a deficiency of one or more mismatch repair markers." *Id.* (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); Ex. 1007, 3382–3383; Ex. 1003 ¶ 80). Petitioner also relies on Dr. Neugut's testimony that, in order to place the patients into the proper arm, the MSI-H Study Record required a biological sample from the patient that had previously

been tested to determine whether the cancer is microsatellite instability high or DNA mismatch repair deficient. *Id.* at 28; Ex. 1003 ¶ 81.

In view of the above, and after review of the entire record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation. Patent Owner does not argue to the contrary.

(8) Patent Owner's Remaining Arguments

In addition to arguing that the MSR does not teach specific elements recited in claim 1, Patent Owner argues that the MSR cannot anticipate claim 1 because it does not inherently disclose the clinical results of the study described in the MSR and because the MSR proposed an experimental use disqualifying it as prior art. PO Resp. 20–32.

Patent Owner argues that Petitioner inappropriately relies on *In re Montgomery*, 677 F.3d at 1381, 1385, to support the assertion of inherent anticipation of the claimed method. PO Resp. 20–24; Pet. 15 ("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 argues 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 claimed by the '187 Patent did not "inevitably flow." PO Resp. 21. Patent Owner cites the testimony of inventor Le to argue that, at the time the MSR was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. *Id.* (citing Ex. 2130 ¶¶ 10, 22). Patent Owner argues further that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the

MSR was not assured. *Id.* at 21–22 (citing Ex. 2090 ¶ 57; Ex. 2024;[7] Ex. 1013[8]). According to Patent Owner, "the MSR was a far cry from meeting *Montgomery*'s inevitability requirement for inherent anticipation," being design only to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. *Id.* at 22–24; Ex. 2072 ¶ 118.

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded, but we are not persuaded that the MSR is so vague it does not teach the steps expressly recited in claim 1. 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 one of ordinary skill in the art would have known that the MSR teaches testing a biological sample from a patient having either endometrial, small bowel, or gastric cancer to determine if the patient's cancer is MSI-H or dMMR and, if so, treating the patient with a therapeutically effective amount of pembrolizumab. *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 cancer patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the

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[7] Brahmer et al., *Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*, 28(19) J. CLIN. ONCOLOGY 3167 (July 1, 2010).

[8] Topalian et al., Safety, *Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer*, 366(26) NEW ENG. J. MED. 2443 (June 28, 2012).

MSR discloses testing patients with cancers known to be associated with MSI-H, as recited in claim 1, and treating with the drug recited in claim 1 if the cancer was determined to be MSI-H. *See Metabolite Labs.*, 370 F.3d at 1367 (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. 23–24. But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *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."). 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.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. PO Resp. 26–32. 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 26 (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 id.* at 27–31. For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test the treatment in humans, there being no animal models, and had to publish the MSR on the government website under federal law. *Id.* at 27–30. 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 28. Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." *Id.* at 30.

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 U.S.P.Q.2d 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.)).)

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support patenting a method of treating human patients reinforces the importance of applying experimental-use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment." PO Sur-Reply 14. But 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. We note that Patent Owner 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. Patent Owner does not attempt to rely on this provisional application for a prior filing date in the current proceeding, but does not direct us to evidence that the earlier date would have been denied. PO Resp. 5 n.4. We are not persuaded by Patent Owner's assertion that "there can be no question" that Patent Owner could not have filed an earlier application to secure a priority date before the MSR was publicly available.

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, particularly given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024), *cert. denied*, 145 S. Ct. 567 (2024), and *cert. denied*, 145 S. Ct. 983 (2024).

g. Summary for claim 1

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

2. Independent Claim 11

Patent Owner does not present separate arguments against Petitioner's challenge to claim 11 as being anticipated by the MSR. *See*, *e.g.*, PO Resp. 15, 16 (referring to claims 1 and 11 together). For the reasons discussed above regarding claim 1, we are persuaded that claim 11 is anticipated by the MSR.

3. Dependent Claims

a) Claims 6, 16, 24, and 28

Petitioner argues that claims 6, 16, 24, and 28 are anticipated by the MSR. Pet. 30, 35, 37, 38. Claims 6, 16, 24 and 28 each require that the cancer treated according to the claimed method is "metastatic." As discussed above, the MSI-H Study Record indicated that, "before receiving treatment based on the MSI-H Study Record, patients would have generally received a prior cancer therapy drug and had their solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 74; *see also id.* ¶ 89 ("the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had 'metastatic tumors.'") (citing

Ex. 1049,[9] 444; Ex. 1050,[10] S4). 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 the MSR does not disclose treatment of metastatic colorectal cancer and that the disclosure of "measurable disease" is not a teaching of metastatic cancer because "measurable disease" is not synonymous with metastatic cancer. PO Resp. 19–20. 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. *Id.* (citing Ex. 1003 ¶ 77; Ex. 2163, 14:9–15:12).

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 that one of ordinary skill in the art would have understood the MSR to disclose treating

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[9] Matikas et al., *The Place of Targeted Agents in the Treatment of Elderly Patients with Metastatic Colorectal Cancer*, 7(1) CANCERS 439 (March 13, 2015).
[10] Lee et al., *Novel Therapies in Development for Metastatic Colorectal Cancer*, 7(4 Supp. 1) GASTROINTESTINAL CANCER RESEARCH S2 (September 2015).

patients with metastatic colorectal cancer. *See* Ex. 1049, 444; Ex. 1050, S4. Patent Owner does not address this evidence.

We are persuaded by Petitioner's evidence that claims 6, 16, 24, and 28 are anticipated by the MSR.

b) Claims 2, 4, 5, 7, 9, 10, 12, 14, 15, 17, 19–23, and 25–27

Petitioner argues that claims 2, 4, 5, 7, 12, 14, 15, 17, 22, 23, and 25–27 are also anticipated by the MSR. Pet. 23–24, 29–31. Patent Owner does not argue these claims separately.

Briefly, Petitioner argues that claims 2 and 12, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSR because the Eligibility Criteria section of the MSR requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies that one of ordinary skill in the art would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. Ex. 1005, 5–6; Ex. 1003 ¶ 70.

Petitioner argues that claims 4, 5, 14, 15, 22, 23, 26, and 27 which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient is anticipated by the MSR because the MSR teaches treating colorectal cancer patients whose tumors are determined to be MSI-H or dMMR. Pet. 24, 30 (citing Ex. 1003 ¶¶ 72–75).

Petitioner argues that claims 7 and 17, which require the pembrolizumab to be administered to the patient intravenously is anticipated by the MSR because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. Pet. 29, 31 (citing Ex. 1011, 134 ("We administered

[pembrolizumab] intravenously."); Ex. 1054, 3; Ex. 1055,[11] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003 ¶¶ 87–88).

Petitioner argues that claims 9, 10, 19, 20, 21, and 25, which require the solid tumor to be, *inter alia*, endometrial cancer, small bowel, and gastric cancer, where endometrial cancer is a type of uterine cancer. *See* Pet. 31, 36 (citing Ex. 1089, 39; Ex. 1003 ¶ 95).

In view of the above, we are persuaded by Petitioner's evidence that each of claims 2, 4, 5, 7, 9, 10, 12, 14, 15, 17, 19–23, and 25–27 are anticipated by the MSR.

4. Conclusion

For the foregoing reasons, we determine that the preponderance of the evidence supports Petitioner's argument that the MSI-H Study Record teaches each and every element of the challenged dependent claims. We are not persuaded otherwise by Patent Owner's arguments pertaining to these claims. Accordingly, we determine that claims 1, 2, 4–7, 9–12, 14–17, and 19–28 are anticipated by the MSI-H Study Record.

D. Ground 2: Obviousness of Claims 1, 2, 4–7, 9–12, 14–17, and 19–28 over MSI-H Study Record, Brown, Duval, and Benson

Petitioner presents a challenge to claims 1, 2, 4–7, 9–12, 14–17, and 19–28 of the '187 patent under 35 U.S.C. § 103, as an alternative to the challenge under 35 U.S.C. § 102, to address certain arguments by Patent Owner. Pet. 41–42. Because "anticipation is the epitome of obviousness," we are persuaded that the claims Petitioner challenges as being anticipated

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

by the MSR would have been obvious over the MSR 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, 2, 4–7, 9–12, 14–17, and 19–28 as being obvious over the MSR alone.

A. Grounds 3–6: Obviousness of Claim 1–28 Based on the MSI-H Study Record, Brown, Duval, Benson, Koh, Steinert, and Hamid

Petitioner argues that certain dependent claims of the '187 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle, Steinert, Benson, and Hamid. Pet. 48–62. Because, as discussed above, we determined that claims 1, 2, 4–7, 9–12, 14–17, and 19–28 are anticipated by the MSR, they also would have been obvious over MSR alone in each of Grounds 3–6 for the reasons discussed above. *In re McDaniel*, 293 F.3d at 1385. In the discussion that follows, we review Petitioner's obviousness challenges for the claims not addressed in Ground 1—that is, claims 3, 8, 13, and 18.

1. Claims 8 and 18: Obviousness over the MSR, Brown, Duval, Benson, Koh, Chapelle

Claims 8 and 18 recite the methods of claims 1 and 11, respectively, "wherein the previous testing comprised assessing one or more of BAT-25, BAT-26, MONO-27, NR-21 and NR-24." Petitioner cites Chapelle for its teaching of Chappelle's standard methods for testing for MSI-H, including a test for MSI-H that has "stood the test of time" comprises testing for "two mononucleotide repeats (BAT26, BAT25)." Pet. 56–57 (citing Ex. 1003 ¶ 164; Ex. 1007, 3382). Petitioner contends that "[a] method wherein the biological sample was tested by a method comprising assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-

27, NR-21 and NR-24 would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. *Id.* (citing Ex. 1003 ¶¶ 162–164).

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

2. Claims 3 and 13: Obviousness over the MSR, Brown, Duval, Benson, Koh, and Steinert

Claims 3 and 13 recite the method of claim 1 or 11, respectively, "wherein the biological sample is a body fluid from the patient." Petitioner cites Steinert for its teaching of testing body fluid to determine whether a tumor is microsatellite instability high. Pet. 58–59 (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 168, 170).

Petitioner argues that one of ordinary skill in the art would have been motivated to combine the MSR (alone or combined with Pernot) and Steinert because the MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H and Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. *Id.* (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 168, 170). Petitioner argues, citing Dr. Neugut's testimony, that one of ordinary skill in the art would have had a reasonable expectation of success given that the method of testing for MSI-H would not have been expected to change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. *Id.* at 59 (citing Ex. 1001, 6:25–26 ("Testing of MSI can be accomplished by any means known in the art"), 6:35–38; Ex. 1003 ¶ 171).

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

3. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 8, 13, and 18 as being obvious. *See generally* PO Resp. That is, Patent Owner argues against all of the obviousness challenges together, without arguing that any of the limitations recited in the dependent claims renders the method of claim 1 or 11 non-obvious.

Patent Owner presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 55–83. 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 MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 11. *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, 4–7, 9, 10, 12, 14–17, and 19–28, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8, 13, 18), Patent Owner must show a nexus between the claimed methods 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 the dependent claims, for example to claims 3 and 13, which recite testing a biological sample that is a bodily fluid, claims 8 and 18, which recite 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.

Even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 11, not the limitations of the claims Petitioner challenges as being obvious. PO Resp. 55–83. Patent Owner directs us only to evidence regarding treating patients determined to have certain MSI-H cancers with pembrolizumab, which we determine to be anticipated by the MSR. *Id.* at 58. 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 methods recited in claims 1 and 11 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claim 3, or "wherein the at least one marker comprises BAT-25, BAT-26, MONO-27, NR-21 or NR-24," as recited in claim 8, demonstrated unexpected results or commercial success.

Accordingly, having considered the evidence of record as a whole, we determine that Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 3, 8, 13, and 18 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 MSR and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 3, 8, 13, and 18 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[12]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–36 of the '287 patent are unpatentable. In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–7, 9–12, 14–17, 19–28	102	MSR	1, 2, 4–7, 9–12, 14–17, 19–28	
1, 2, 4–7, 9–12, 14–17, 19–28	103	MSR, Brown, Duval, Benson	1, 2, 4–7, 9–12, 14–17, 19–28	
1, 2, 4–7, 9–12, 14–17, 19–28	103	MSR, Brown, Duval, Benson, Koh	1, 2, 4–7, 9–12, 14–17, 19–28	
2, 8, 12, 18	103	MSR, Brown, Duval, Benson, Koh, Chapelle	2, 8, 12, 18	
3, 13	103	MSR, Brown, Duval, Benson, Koh, Steinert	3, 13	
7, 17	103	MSR, Brown, Duval, Benson, Koh, Hamid	7, 17	
Overall Outcome			1–28	

[12] 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).

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–28 of the '187 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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd Miller
Matthew Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com

Trials@uspto.gov
571-272-7822

Paper 52
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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.

IPR2024-00650
Patent 11,634,491 B2

Before DEBORAH KATZ, SHERIDAN K. SNEDDEN, 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 1–38 of U.S. Patent No. 11,634,491 B2 (Ex. 1001, "the '491 patent") pursuant to 35 U.S.C. § 311(a). (Paper 1 ("Pet.") 1, 3–4.) Patent Owner, The Johns Hopkins University, did not file a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). We granted the Petition and instituted an *inter partes* review. (Paper 6 ("Decision").)

During the review, Patent Owner filed a Patent Owner Response to the Petition (Paper 28 (confidential Paper 24) ("PO Resp.")), Petitioner filed a Reply (Paper 45 (confidential Paper 42) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 50 (confidential Paper 47) ("PO Sur-Reply")).

The parties declined to present oral arguments in this proceeding. (*See* Paper 49.) 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 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.

determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–38 of the '491 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. 64.) 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. 64; Paper 3, 1.)

In addition, several other inter partes reviews are related to this proceeding, including IPR 2024-00622, 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; IPR2024-00625, challenging claims of U.S. Patent No. 11,339,219 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.

IPR2024-00240 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 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 '491 Patent

The application that became the '491 patent was filed on May 9, 2022, 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 '491 patent cites another provisional application, filed November 13, 2014, but Patent Owner claims priority only to July 10, 2015. (*See* PO Resp. 5 n.4; Ex. 1001, code (60).)

The '491 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor, in cancer patients. (*See* Ex. 1001, Abstract.) More specifically, the '491 patent is directed to treating cancer patients with high mutational burdens, such as found in microsatellite instable (MSI) cancer, with anti-PD-1 antibodies. (*Id.* at 3:39–43.) 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 8:54–58.)

Claim 1 of the '491 patent recites:

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

(*Id.* at 25:36–52.) Independent claim 16, the only other independent claim, is similar and recites the same steps of "testing" and "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating . . . ." (*Id.* at 26:24–41.)

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 for 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.3.)

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
Chapelle	Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)	1007
Steinert	Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014)	1008
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
Salipante	Salipante et al., *Microsatellite Instability*	1010

	Detection by Next Generation Sequencing, 60(9) Clinical Chemistry 1192 (2014)	
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 Res. 743 (May 2014)	1034
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
Koh	Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. Nat'l Comprehensive Cancer Network 248 (February 2014)	1095

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–38 are unpatentable on the following grounds:

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1, 2, 4–7, 11–17, 19–22, 26–38	102	MSR
2	1, 2, 4–7, 11–17, 19–22, 26–38	103	MSR, Brown, Duval, Benson
3	1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	103	MSR, Brown, Duval, Benson, Koh

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

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
4	2, 8, 17, 23	103	MSR, Brown, Duval, Benson, Koh, Chapelle
5	3, 18	103	MSR, Brown, Duval, Benson, Koh, Steinert
6	9, 10, 24, 25	103	MSR, Brown, Duval, Benson, Koh, Salipante
7	11, 26	103	MSR, Brown, Duval, Benson, Koh, Hamid

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) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be 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. 11 (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, 91–99).) Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '491 patent claims a method of treating a human patient with 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, 25:36–52, 26:24–41, Ex. 1005; *see* Decision 8–9.) Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds.

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 '491 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

We construe claims "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." 37 C.F.R. § 42.100(b) (2020).

Claims 1 and 16 require treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the

colorectal cancer is microsatellite instability high or DNA mismatch repair deficient . . . ." (Ex. 1001, 25:47–49, 26:36–38.) Petitioner argues that the discussion in the MSR of treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. (*See* Pet. 21–22 (citing Ex. 1005, 2–6.)) For the purposes of our decision whether to institute review, we agreed and stated that Petitioner had shown

> a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of non-colorectal cancer patients and the determination of their MSI status, wherein non-colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were placed into a study arm and then treated with pembrolizumab. (*See* Ex. 1005, Ex. 1003 ¶¶ 60–73.) Because treatment of the patients was performed only after MSI-H status was determined, the MSI-H Study Record teaches treating the patients "in response to" determining their MSI-H status.
>
> The MSI-H Study Record describes other patients being enrolled and treated with pembrolizumab, including colorectal cancer patients determined to be MSI-H and colorectal cancer patients determined not to be MSI-H. At this point in the proceeding, we interpret the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients. Patent Owner has not directed us to evidence that one of ordinary skill in the art would have understood treating a patient "in response to" the determination that the patient has a condition to exclude the same treatment of other patients, such as the treatment of control patients not having the condition.

(Decision 14–15.)

Patent Owner argues, in regard to the Final Decision in IPR2024-00240, that the Board's construction "disregards the critical ***causal***

relationship between the 'determining' and 'treating' steps in the claims. The express causal relationship between these steps establishes that ***only*** patients determined to be MSI-H are treated." (PO Resp. 6.) According to Patent Owner, the claim term "in response to" is properly construed as "in reaction to" because "[t]he claimed 'treating' step is performed (and only performed) in response to (as a reaction to) determining the cancer is MSI-H." (*Id.* at 6–7.) Patent Owner disagrees that the claim term "in response to" means only "after." (*See id.*)

Patent Owner argues further that the Specification of the '491 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is only performed as a reaction to determining the patient's cancer is MSI-H. (*See id.* at 7–8.) Specifically, Patent Owner cites the disclosure in the '491 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. (Ex. 1001, 3:57–67.) According to Patent Owner, one of ordinary skill in the art would have understood from the characterization of good/bad candidates in the '491 patent that administering the claimed treatment would be only as a reaction to the determination of MSI-H. (*See* PO Resp. 8.) According to Patent Owner, a "purely sequential construction" would render meaningless the "in response to" step of the claim because if "in response to" meant merely "after," the claims would cover treatment "for any reason or no reason at all—even accidental treatment would be covered." (*Id.*)

We agree with Patent Owner that the phrase "in response to" in claims 1 and 16 requires a causal relationship, wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is treated with 10 mg/kg of pembrolizumab every 14 days. In claims 1 and 16, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having non-colorectal cancer to determine that the patient's cancer is MSI-H or dMMR, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, the art anticipates claims 1 and 16. We are not persuaded that claim 1 or 16 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the inventors used the term "after" in several dependent claims of the related U.S. patent 11,591,393. (*See* PO Resp. 7 (citing Ex. 2301, claims 7, 20, 27).) For example, claim 7 of U.S. patent 11,591,393 ("the '393 patent"), which depends on an independent claim reciting the "in response to" limitation, requires that the cancer "had progressed after" the patient received a different cancer therapy. (Ex. 2301, 25:64–67, 26:41–46; *see also id.* at 26:62–64.) Patent Owner argues that "within the '491 Patent's family," the word "after" appears in some of the same claims as "in response to," indicating that terms have different meanings. (PO Resp. 7.)

Patent Owner does not explain why the meaning of terms not found in claims of the '491 patent is relevant to the claims of the '491 patent, but to

the extent those claims are relevant, they do not persuade us that the '491 patent claims require anything other than 1) testing a biological sample and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, as discussed above. The relationship between testing and treating in claims 1 and 16 of the '491 patent is different from than the relationship of the term "after" in claims 7, 20, and 27 of the '393 patent, wherein patients must have been first treated with a different cancer therapy and the cancer had later progressed. (Ex. 2301, 25:66–67, 26:44–46, 26:63–64.) As discussed above, we do not disagree that the phrase "in response to" in claims 1 and 16 requires a causal relationship, but we are not persuaded that the prior art must teach anything other than testing a biological sample to determine that the patient's cancer is MSI-H or dMMR, and, if so, treating the patient with a therapeutically effective amount of pembrolizumab. We are not persuaded that anything else is required in claim 1 or 16 of the '491 patent.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment *only* to patients determined to have an MSI-H tumor. (*See* PO Resp. 6.) But neither claim 1 nor claim 16 includes a limitation excluding the treatment of any patient, such as specifically excluding treatment of any patient who has a tumor that is not MSI-H or dMMR. Neither claim 1 nor claim 16 recites any language differentiating between patients or identifying a patient population to be excluded from treatment. Instead, claims 1 and 16 provide that if the colorectal cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab.

We note that the methods of claims 1 and 16 use the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim."). The use of the open-ended transitional phrase "comprising" in claims 1 and 16 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner argues that the Examiner used a construction of the term "in response to" that is consistent with Patent Owner's position during prosecution. (*See* PO Resp. 8.) Patent Owner asserts that the Examiner "used the shorthand 'based on' to express the plain meaning of 'in response to,'" and that "based on" requires a causal relationship. (*Id.* (citing Ex. 2302, 8 ("Lipson does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed.").) According to Patent Owner, the term "based on" does not mean "after," but requires a causal relationship. (*See id.*) Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that either claim 1 or claim 16 requires anything other than testing a cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of

pembrolizumab. The Examiner's reasoning does not indicate that the claims of the '491 patent exclude treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one determined to be MSI-H or dMMR, as Patent Owner implies. (*See* PO Resp. 9–10.) Patent Owner argues that "Merck's only dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." (*Id.* at 9 (citing Ex. 2160, 24[3]).) But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 or 16 requires anything other than 1) testing a biological sample and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, as discussed above. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a ***reaction***, as that of an organism to any of its parts, to a ***specific*** stimulus." (Ex. 2160, 24–25.) This construction does not limit the scope of claim 1 or 16 to contemplating the treatment of any patients other than the one tested and determined to be MSI-H or dMMR. Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now. (*Id.* at 25 ("[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it

[3] Patent Owner cites to page 30 of Exhibit 2160, which is page 24 of the underlying document.

means, invites legal error and jury confusion about what behavior the claims cover.").)

Patent Owner argues further that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that Patent Owner's witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a determination that the patient's tumor is MSI-H. (*See* PO Resp. 9–10 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 84–85).) Neither of these statements persuades us that claim 1 or 16 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of claim 1 or 16 excludes treating any patient other than the one tested and confirmed to be MSI-H.

Patent Owner cites *Am. Calcar, Inc. v. American Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011), in support of the claim construction that the "treating" step is *only* performed as a reaction to determining the patient's cancer is MSI-H, but not when the patient is MSI-stable. (*See* PO Resp. 10.) In that case, the Federal Circuit determined that, in claims directed to systems for identifying a service provided when a vehicle needs service, the term "the processing element identifying one of the plurality of providers *in response to* the vehicle condition" means "that the second event occur in reaction to the first event." *Am. Calcar*, 651 F.3d at 1324, 1340. The court continued, by explaining that "[t]he language of the claim itself suggests that when a vehicle condition is detected, the processing element identifies a provider automatically as opposed to requiring further user interaction." *Id.* at 1340. We note that, as explained above, we agree the

claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claims 1 and 16 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claims 1 and 16 to require testing a biological sample obtained from a cancer patient having cancer to determine that the patient's tumor is MSI-H or dMMR and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's tumor is determined to be MSI-H or dMMR. We are not persuaded that either claim 1 or 16 requires or excludes other patients or steps because neither claim 1 nor claim 16 recites any other steps or contain negative limitations.

D. Ground 1: Anticipation over the MSR

Petitioner argues that claims 1, 2, 4–7, 11–17, 19–22, and 26–38 are anticipated under 35 U.S.C. § 102. (*See* Pet. 13–36.)

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, 2.) The parties' witnesses agree that MK-3475 is pembrolizumab, the compound recited in claim 1. (*See* Ex. 1003 ¶ 38; *see* Ex. 2072 ¶ 69.) 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 '393 patent on July 10, 2015. (*See* Pet. 6–7 (citing Ex. 1005, 3, Ex. 1003 ¶ 35).)

> 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[?]" (*Id.* at 4–5.) The MSR provides "Arms and Interventions" as follows[4]:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

(*Id.* at 4.) The chart above identifies three patient populations, including "MSI Positive Colorectal Cancer," "MSI Negative Colorectal Cancer," and

[4] 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)")); Ex. 1003 ¶ 26).) Patent Owner does not contest the identifications.

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

Petitioner cites the teaching in the Arms and Interventions section as a method of treating human MSI positive colorectal cancer patients, as recited in the preamble of claim 1. (*See* Pet. 16 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility)).) Petitioner argues that the claimed methods are anticipated by the MSR even if the recited steps had not been performed yet because any efficacy requirement in the claims would be inherent to the steps. (*Id.* at 21–22.) Petitioner argues that the challenged claims are directed to the methods disclosed in the MSR. (*See id.* at 18.)

2. Claim 1

a) Preamble "A method of treating cancer in a human patient, the method comprising"

Petitioner argues that the MSR teaches "[a] method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient," as recited in the preamble of claim 1. (Pet. 16 (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 60–61).)

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 this limitation.

b) Element 1.1: "testing or having tested a biological sample obtained from a patient"

Petitioner argues that the MSR teaches testing or having tested a biological sample from a patient in order to place the patient into the proper arm of the study. (*See* Pet. 18 (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 ¶¶ 64–66).)

Patent Owner does not argue to the contrary.

In light of the evidence of record, we are persuaded that the MSR teaches this limitation.

c) Element 1.2: "having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer,"

Petitioner argues that the Arms and Interventions section of the MSR teaches treating patients having non-colorectal MSI-H cancer. (*See* Pet. 19 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) Petitioner argues that MSI-H was known to occur in several different types of cancers, including endometrial, small bowel, and gastric cancer, along with colorectal cancer, and that these types of cancers were known to occur in Lynch syndrome, which was known to be closely associated with MSI-H tumors. (*See id.* (citing Ex. 1085,[5] 673–75; Ex.

[5] Imai et al., *Carcinogenesis and Microsatellite Instability: The Interrelationship Between Genetics and Epigenetics*, 29(4) CARCINOGENESIS 673 (2008).

1086,[6] 14; Ex. 1003 ¶¶ 25, 67).) Petitioner relies on Dr. Neugut's testimony that endometrial, small bowel cancer, and gastric cancer are "common in Lynch syndrome, which was known at the time to be closely related to MSI-H." (Ex. 1003 ¶ 67 (citing Ex. 1085, 673 ("DNA mismatch repair (MMR) deficiency results in a strong mutator phenotype and high-frequency microsatellite instability (MSI-H), which are the hallmarks of tumors arising within Lynch syndrome.")); *see also* Ex. 1085, 673 ("Tumors of the Lynch syndrome . . . and some sporadic gastrointestinal and endometrial cancers belong to the MSI pathway.").) Thus, "the person of ordinary skill would have immediately pictured treating [patients with endometrial, small bowel, and gastric cancer] with the MSI-H Study Record's methods" and that "the person of ordinary skill would have concluded that the limitation [listing recited types of cancer] was found in the MSI-H Study Record." (Ex. 1003 ¶¶ 67–68.)

Patent Owner argues the MSR does not expressly or inherently disclose the claimed MSI-H cancers. (*See* PO Resp. 10–14.) As Patent Owner argues, "[o]ther than specifying the participant's cancer must be non-colorectal, the MSR provides no details or guidance about cancer types to be included in that third arm" and does not list any of the claimed MSI-H cancers. (*Id.* at 10.) Patent Owner acknowledges that the MSR discloses the "third arm" disclosed in the MSR "was open to all-comers with any MSI-H cancer other than CRC," but argues that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of the genus. (*See id.* at 11 (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d

[6] Cheung et al., *Current Advance in Small Bowel Tumors*, 44(1) CLINICAL ENDOSCOPY 13 (2011).

991, 999 (Fed. Cir. 2006) and *Metabolite Lab'ys, Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004).)

Next, Patent Owner argues that the Petition did not provide evidence of the number of species in the genus described in the MSR and does not contend that one of ordinary skill would have immediately appreciated the full scope of the genus, which includes at least twenty-nine species. (*See id.* at 12–13 (citing Ex. 2072 ¶ 53).) According to Patent Owner, the issue of whether MSI-H was known to occur in Petitioner's "hand-picked set of cancers" (endometrial, gastric, and small bowel cancer) is irrelevant because it overlooks the other MSI-H cancers recited in claim 1 and ignores the "unclaimed non-[colorectal] MSI-H cancers." (*See id.* at 12.) According to Patent Owner, the size of the non-colorectal cancers included in the MSR is large and there is no support for a conclusion that a person of ordinary skill in the art could have at once envisaged each member. (*See id.* at 13.)

Patent Owner argues that the Petition overstates the understanding one of ordinary skill in the art would have of MSI-H cancers. (*See id.* at 12 (citing Ex. 2072 ¶ 103).) According to Patent Owner, only endometrial cancer "was tested for MSI-H as a part of standard care at the time of the invention—and it was only tested to identify familial susceptibility (not in relationship to treatment)." (*Id.* (citing Ex. 2090 ¶ 79).) Patent Owner further cites inventor Le's testimony that the MSR investigators had difficulty recruiting MSI-H patients for the non-colorectal cancer arm of the study because such testing was not routinely done in non-colorectal cancers. (*See id.* (citing Ex. 2130 ¶ 12).) This evidence, though, does not persuade us of what one of ordinary skill in the art would have understood from the disclosure of the MSR.

In contrast, the testimony of Patent Owner's witness, Dr. Goldberg, supports Petitioner's argument of the knowledge in the art at the time, wherein Dr. Goldberg testifies that "[w]hile many clinical oncologists were aware that patients with Lynch Syndrome had a defect in DNA mismatch repair, they associated MSI testing with young onset colorectal and endometrial cancer and patients with a family history of colorectal and/or endometrial cancer." (Ex. 2090 ¶ 79.) Similarly, during his deposition Dr. Goldberg also agreed that endometrial, gastric, and small-bowel cancers would come to mind when he saw a reference to MSI-high non-colorectal cancer. (*See* Ex. 1243, 115:5–116:22 (Q. And so does endometrial cancer come to mind when you see reference to MSI-high non-colorectal cancers? . . . A. Yes. Q. As a person -- a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does gastric cancer come to mind?. . . A. I believe it was listed among the items that I stated when you asked me what comes to mind. So the answer is yes. Q. As a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does small bowel cancer come to mind? . . . A. Yes.").) Patent Owner does not direct us to other evidence contradicting Petitioner's argument that MSI-H was known to occur in endometrial, small bowel, and gastric cancer. (*See* Pet. 19.)

Patent Owner argues that the Petition does not consider the breadth of the genus disclosed in the MSR and does not argue or provide evidence to show that one of ordinary skill in the art could have envisaged each species within that genus. (*See* PO Resp. 11–14.) We are not persuaded that either the size of the genus in the MSR or whether one of ordinary skill in the art would have been able to envisage every species within it is dispositive of

whether the MSR anticipates claim 1, where one or ordinary skill in the art would have known that specific cancers recited in claim 1 would be included in the MSR. As Petitioner argues, claim 1 requires that "a patient having" one of the listed cancers is tested and treated. (*See* Ex. 1001, 25:38–39; *see* Pet. Reply 10.) Claim 1 does not require that the patient have each and every one of the sixteen listed cancers. (*See id.*) Rather, claim 1 requires testing a sample from "a patient" with one of the recited types of cancer and treating the patient. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.").

Patent Owner argues further that *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009), supports its position, requiring that one of ordinary skill in the art must at once envisage all MSI-H non-colorectal cancer types included in the MSR, not just one or even a subset of the claimed cancer types, in order for the MSR to anticipate claim 1. (*See* PO Sur-Reply 2.) *Gleave* states:

> For the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law. *Compare Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) *(rejecting "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list") with Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) *("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.").* This distinction collapses when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can "at once envisage each member of this limited class." *Eli Lilly*, 471 F.3d at 1376. In that limited

> circumstance, a reference describing the genus anticipates every species within the genus. *See Perricone*, 432 F.3d at 1377.

In re Gleave, 560 F.3d at 1337–38. This portion of *Gleave*, cited by Patent Owner, does not hold that a reference anticipates *only* when all species either disclosed in the reference or recited in the challenged claim can be envisioned, but rather that when each species of the prior art genus could be envisaged, the genus is anticipatory.

Nothing in *Gleave* or any other reference cited by Patent Owner refutes the patent law concept that a claim encompassing a species is anticipated if a prior art disclosure leads to a genus small enough that a person of ordinary skill in the art would at once envisage the claimed species. *See Brown*, 265 F.3d at 1351; *In re Slayter*, 276 F.2d 408, 411 (CCPA 1960) ("[A] generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus."); *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989) (holding that a claim reciting a genus of twenty-one specific chemical species in a Markush group is anticipated by prior art that discloses two of the chemical species).

Patent Owner attempts to distinguish *Brown* by arguing that its holding is limited to anticipation of a claimed genus through disclosure of individual species, whereas the facts of this case involve the disclosure of a genus. (*See* PO Resp. 14.) Because the facts before us, including the testimony of Patent Owner's witness, indicate that one of ordinary skill in the art would have immediately understood that the third arm of the study described in the MSR includes patients with cancers recited in claim 1, including endometrial, gastric, and small-bowel cancers, we are persuaded that one of ordinary skill in the art would have understood that the MSR

discloses species that fall within the scope of claim 1. (*See* Ex. 2090 ¶ 79; Ex. 1243, 115:5–116:22; Ex. 1085, 673–75; Ex. 1086, 14; Ex. 1003 ¶¶ 25, 67; Ex. 1005, 4.) We are not persuaded that where species falling within the scope of claim 1 were previously known and disclosed in MSR, that claim 1 is patentable over the MSR. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage'" the claimed arrangement or combination." (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

After considering the parties' arguments and the evidence presented, we are persuaded that the MSR teaches "testing or having tested a biological sample obtained from a patient" having endometrial, small bowel, or gastric cancer and, thus teaches the corresponding limitation of claim 1.

d) Element [1.3]: "thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient;"

Petitioner argues that the MSR teaches testing or having tested a biological sample from a patient. (*See* Pet. 20 (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 ¶¶ 62–66, 69, 70).)

We are persuaded that this testing would result in determining that a patient's cancer is MSI-H or dMMR, as recited in claim 1. Patent Owner does not argue to the contrary.

e) Element [1.4]: "and in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or

DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab."

Petitioner argues that the disclosure in the MSR of treating MSI-H non-colorectal patients with 10 mg/kg of pembrolizumab every 14 days teaches the limitation of treating a patient with a therapeutically effective amount of pembrolizumab in response to determining that the patient's cancer is MSI-H or dMMR. (*See* Pet. 21 (citing Ex. 1005, 4 (Arms and Interventions); 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 35, 50, 71–74.) Petitioner argues that although the MSR does not use the phrase "therapeutically effective amount," it teaches administering 10 mg/kg of MK-3457 (pembrolizumab), which is the same dosage of pembrolizumab the '491 patent describes as being therapeutically effective. (*See id.* (citing Ex. 1001, 8:50–56, 13:24–30, 16:4–8, 16:29–32, 19:40–21:15, Figs. 2, 11; Ex. 1003 ¶¶ 72–73).)

Patent Owner argues that the MSR does not disclose treating any of the 16 cancers recited in claim 1 "in response to determining that the patient's cancer is [MSI-H]" because nothing in the MSR teaches identifying any of the claimed cancer types as having the MSI-H biomarker and, in response to that determination, treating with pembrolizumab. (*See* PO Resp. 15 (citing Ex. 2072 ¶ 104).)

As explained above, we are persuaded by Petitioner's arguments and the cited evidence that one of ordinary skill in the art would have understood and envisaged the MSR to include patients with at least endometrial, small bowel, or gastric cancers. We are further persuaded that the MSR teaches treating these patients in response to the determination that these patient's tumors were MSI-H in the third arm of the study described. Patent Owner's

arguments about the failure of the MSR to expressly identify any of the cancers recited in claim 1 do not persuade us otherwise. Instead, we are persuaded that one of ordinary skill in the art would have understood that the MSR teaches testing a patient with a non-colorectal cancer, such as endometrial, small bowel, or gastric cancers, to determine if the patient has an MSI-H tumor and, if the tumor is determined to be MSI-H, treating the patient with amount of pembrolizumab described as being therapeutically effective in the '491 patent.

Accordingly, we are persuaded that the MSR teaches this limitation of claim 1.

f) Patent Owner's Other Arguments

In addition to arguing that the MSR does not teach specific elements recited in claim 1, Patent Owner argues that the MSR cannot anticipate claim 1 because it does not inherently disclose the clinical results of the study described in the MSR and because the MSR proposed an experimental use disqualifying it as prior art. (*See* PO Resp. 20–32.)

Patent Owner argues that Petitioner inappropriately relies on *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), to support the assertion of inherent anticipation of the claimed method. (*See id.* at 20–24; Pet. 15 ("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 argues 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 claimed by the '393 Patent did not

"inevitably flow." (PO Resp. 20–21.) Patent Owner cites the testimony of inventor Le to argue that at the time the MSR was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. (*See id.* at 21 (citing Ex. 2130 ¶¶ 10, 22).) Patent Owner argues further that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the MSR was not assured. (*See id.* at 21–22 (citing Ex. 2090 ¶ 57; Ex. 2024;[7] Ex. 1013[8]).) According to Patent Owner, "the MSR was a far cry from meeting *Montgomery*'s inevitability requirement for inherent anticipation," being design only to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. (*Id.* at 22–24; *see* Ex. 2072 ¶ 118.)

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded, but we are not persuaded the MSR is so vague that it does not teach the steps expressly recited in claim 1. 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 one of ordinary skill in the art would have known that the MSR teaches testing a biological sample from a patient having either endometrial, small bowel, or gastric cancer to determine if the patient's cancer is MSI-H or dMMR and, if so, treating the patient with a

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[7] Brahmer et al., *Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*, 28(19) J. CLINICAL ONCOLOGY 3167 (July 1, 2010).
[8] Topalian et al., Safety, *Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer*, 366(26) NEW ENG. J. MED. 2443 (June 28, 2012).

therapeutically effective amount of pembrolizumab. (*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 cancer patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the MSR discloses testing patients with cancers known to be associated with MSI-H, as recited in claim 1, and treating with the drug recited in claim 1 if the cancer was determined to be MSI-H. *See Metabolite Labs.*, 370 F.3d at 1367 (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. 23–24.) But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *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."). 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.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. (*See* PO Resp. 26–32.) 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 26 (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 id.* at 27–31.) For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test the treatment in humans, there being no animal models, and had to publish the MSR on the government website under federal law. (*See id.* at 27–28.) 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 28–31.) Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." (*Id.* at 34.)

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 U.S.P.Q.2d 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.)).)

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support patenting a method of treating human patients reinforces the importance of applying experimental-use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment." (PO Sur-Reply 13.) But 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. We note that Patent Owner 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).) Patent Owner does not attempt to rely on this provisional application for a prior filing date in the current proceeding, but does not direct us to evidence that the earlier date would have been denied. (*See* PO Resp. 5 n.4.) We are not persuaded by Patent Owner's assertion that "there can be no question" that Patent Owner could not have filed an earlier application to secure a priority date before the MSR was publicly available.

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). Be*cause 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, particularly given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See 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).

g) Summary for claim 1

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. Independent Claim 16

Patent Owner does not present separate arguments against Petitioner's challenge to claim 16 as being anticipated by the MSR. (*See, e.g.* PO Resp. 15 (referring to claims 1 and 16 together).) For the reasons discussed above regarding claim 1, we are persuaded that claim 16 is anticipated by the MSR.

4. Dependent claims

a) Claims 13, 28, 32, and 36

Petitioner argues that claims 13, 28, 32, and 36 are anticipated by the MSR. (*See* Pet. 25–29, 33–35.) These claims each require the patient to have received a "prior cancer therapy," and the patient's cancer to have progressed "after the patient was treated with the prior cancer therapy." (Ex. 1001, 26:15–18, 27:3–6, 27:14–17, 28:8–11.) Petitioner argues that because the MSR discloses that patients eligible for the study must have "tumors"

and "measurable disease," one of ordinary skill in the art would have known that the patients would have received prior drug therapies and that their cancers would have progressed after these therapies. (*See* Pet. 25–29 (citing Ex. 1005, 2 (Study Identification), 4 (Study Design), 5–6 (Eligibility); Ex. 1003 ¶¶ 89–93).)

Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have known the reference to "measurable cancer" in the MSR would include patients with metastatic and advanced cancer, not resectable cancer, because patients whose tumors are resectable can be cured by surgery. (*See id.* at 26 (citing Ex. 1003 ¶ 90).) Petitioner argues further, relying again on Dr. Neugut's testimony, that patients with metastatic and advanced cancer who would participate in a clinical study would generally have received at least one prior drug therapy, such as standard care chemotherapy, and would have had their cancer progress after these therapies. (*See id.* at 27 (citing Ex. 1003 ¶ 91; Ex. 1089, 17; Ex. 1020, 25; Ex. 1094, 12, 15; Ex. 1009, 1034; Ex. 1047, 4–7).)

Petitioner argues further that because the eligibility section of the MSR excludes patients who have had specific prior treatment, providing a list of those specific treatments (anti PD-1, anti PD-L1, anti PD-L2, anti CD137, anti OX-40, anti CD40 or anti CTLA-4 antibodies), patients who have previously been treated, in general, and had their cancer progress after the prior treatment were included in the study. (*See id.* at 25–26 (citing Ex. 1003 ¶ 92).) As confirmation of this understanding, Petitioner cites a 2014 poster presentation discussing the clinical study described in the MSR being

for eligible patients with "progressive disease" and non-colorectal cancer who had "at least 1 prior therapy." (Ex. 1080[9]; *see* Pet. 28.)

Patent Owner argues that the MSR is silent on whether eligible patients must have been previously treated with a prior cancer drug and that the cancer had progressed following the prior treatment. (*See* PO Resp. 16–18.) According to Patent Owner, "[n]o amount of attorney argument or expert testimony can satisfy the requirement to demonstrate express anticipation" and the MSR itself must disclose the limitation. (*Id.* at 16.) Patent Owner argues that Petitioner fails to meet the burden to show inherent anticipation of the limitations of these dependent claims. (*See id.* at 19–22.)

Patent Owner argues that the only reference to prior treatment in the MSR is the reference to excluded prior treatments, which is the opposite of inclusion of patients with prior treatment, as required in the challenged claims. (*See id.* at 18 (citing Ex. 2072 ¶ 105).) Patent Owner argues further that three years after the MSR was published, an express requirement for prior treatment was added to the ClinicalTrials.gov record, indicating that such a requirement was not present in 2013 when the MSR was originally available. (*See id.* (citing Ex. 2165, 8 ("Patients with other [non-colon] cancer types must have received at least one prior cancer therapy"); Ex. 2166, 8 ("Patients with other [non-colon] cancer types must have received at least one prior cancer therapy"); Ex. 2072 ¶ 107).) Patent Owner argues that Petitioner's reliance on the poster presentation that included a requirement for a prior treatment fails because the poster is separate from the MSR and is

[9] Poster presented at ASCO, Le et al., *Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors* (Jun. 1, 2014).

not prior art, having been publicly available only later. (*See id.* at 18–19 (citing Ex. 1080).)

In addition, Patent Owner disputes Petitioner's evidence about what was generally understood at the time of the MSR, arguing that it was advised that some Stage IV gastric cancer patients proceed directly to clinical trials without prior treatment. (*See id.* at 17–18 (citing Ex. 1096, 533; Ex. 2072 ¶ 106).) Patent Owner also cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." (Ex. 1009, 1029; PO Resp. 18.)

Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression" and that three years later it was updated with a statement requiring prior cancer treatment, but he fails to testify that one of ordinary skill in the art would not have understood the MSR in 2013 to teach treating patients who had received a prior cancer therapy drug, wherein the patients' cancer had progressed after receiving the prior drug. (*See* Ex. 2072 ¶¶ 105–107.) Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. (*See* Ex. 2072 ¶ 107 ("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 MSR in 2013 to teach treating patients who had received a prior cancer therapy and had a subsequent progression in the cancer, contradicting Petitioner's evidence.

On the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. Both parties cite generalized guidelines about cancer treatment, which do not shed much light on what one of ordinary skill in the art would have understood from the MSR, specifically. The parties disagree about the reason for the 2016 update of the MSR to include a limitation for only patients with non-colon cancer who had previously received at least one prior cancer therapy, but the reason for the change is still unclear. Does the update indicate a change to the study or merely a clarification? We are not persuaded that the update by itself is dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients who had received a prior cancer therapy and the patient's cancer to have subsequently progressed.

There is a difference, though, in the testimony of the parties' witnesses. Dr. Neugut, Petitioner's witness, testifies that "the person of ordinary skill would have found it highly unusual for the patient population of those who had received prior drug treatments and had their cancer progress after those treatments to not be included in the MSI-H Study Record, especially without any explicit carve-out." (*See* Ex. 1003 ¶ 92.) Dr. Oberstein, Petitioner's other witness concurs, testifying that because the MSR describes a study of a new immunotherapy drug, one of ordinary skill in the art would have understood that metastatic and advanced cancer patients who would participate would have received prior drug therapies, but that their cancer would have progressed. (*See* Ex. 1150 ¶ 69.) Dr. Oberstein testifies further that if the study was intended only for patients who had not been previously treated, a one of ordinary skill would have expected an

explicit carve out excluding all patients who had been previously treated. (*See id.*) As Dr. Oberstein notes, the MSR does not include a blanket exclusion for patients who had received any prior treatment – it only includes exclusions for some specific prior drug treatments. (*See id.*; Ex. 1005, 6.)

Dr. Lonberg, Patent Owner's witness, does not dispute any of Dr. Neugut's or Dr. Oberstein's testimony, but asserts only that Dr. Neugut's testimony relies only on what was generally done, not on what is expressly disclosed in the MSR. (*See* Ex. 2072 ¶¶ 105–107.) On cross-examination, Dr. Lonberg agreed with Dr. Oberstein that patients who had received prior cancer therapy were not excluded from the study described in the MSR. (*See* Ex. 1245, 57:5–58:2, 40:5–14, 49:2–12.)

Thus, after considering the evidence cited by each party, we find Dr. Neugut's and Dr. Oberstein's testimony to be the most directly relevant and persuasive about what one of ordinary skill in the art would have understood from the MSR itself. We are also persuaded by the lack of a specific contradiction regarding the understanding of one of ordinarily skill in the art by Dr. Lonberg. Even if some patients who had been previously treated with specific drugs were excluded from the study described in the MSR, we are persuaded that one of ordinary skill in the art would have understood the MSR as including other patients who have been treated with a prior cancer therapy drug. We are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitations of claims 13, 28, 32, and 36 were disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have

understood from the MSR, not what it inherently discloses. (*Contra* PO Resp. 19–22.)

Accordingly, we are persuaded that claims 13, 28, 32, and 36 are anticipated by the MSR.

b) Claims 15, 30, 34, and 38

Petitioner argues that claims 15, 30, 34, and 38 are anticipated by the MSR. (*See* Pet. 30, 34, 35, 36.) Claims 15, 30, 34, and 38 require that the colorectal cancer recited in claim 1 or claim 16, respectively, be metastatic cancer. (*See* Ex. 1001, 26:22–23, 27:11–12, 28:4–5, 28:15–16.) Petitioner argues that the prior art referencing the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov to mean patients with "metastatic tumors." (*See* Pet. 30 (citing Ex. 1049,[10] 444; Ex. 1050,[11] S4; Ex. 1003 ¶¶ 97–98, 113, 118, 122).) 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.)

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[10] Matikas et al., *The Place of Targeted Agents in the Treatment of Elderly Patients with Metastatic Colorectal Cancer*, 7(1) CANCERS 439 (March 13, 2015).

[11] Lee et al., *Novel Therapies in Development for Metastatic Colorectal Cance*r, 7(4 Supp. 1) GASTROINTESTINAL CANCER RESEARCH S2 (September 2015).

Patent Owner argues that the MSR 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. (*See* PO Resp. 19–20 (citing Ex. 2072 ¶¶ 108–112).) 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. (*See id.* (citing Ex. 2163, 14:9–15:12).)

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

We are persuaded by Petitioner's evidence that claims 15, 30, 34, and 38 are anticipated by the MSR.

c) Claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37

Petitioner argues that claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37 are also anticipated by the MSR. (*See* Pet. 22–35.) Aside from arguments pertaining to independent claims 1 and 16, which we have discussed above, Patent Owner does not raise any arguments specific to these dependent claims.

Briefly, Petitioner argues that claims 2 and 17, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSR because the Eligibility Criteria section of the MSR requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies

that one of ordinary skill in the art would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. (*See id.* at 22, 32 (citing, *inter alia*, Ex. 1005, 5–6; Ex. 1003 ¶¶ 75–76).)

Petitioner argues that claims 6, 7, 21, and 22, which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient is anticipated by the MSR because the MSR teaches treating colorectal cancer patients whose tumors are determined to be MSI-H. (*See id.* at 24, 33 (citing Ex. 1003 ¶¶ 81–84, 107, 108); Ex. 1001, 25:64–67, 26:53–56.)

Petitioner argues that claims 11 and 26, which require the pembrolizumab to be administered to the patient intravenously is anticipated by the MSR because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. (*See id.* at 24–25, 33 (citing Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1054,[12] 3; Ex. 1055,[13] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003 ¶¶ 85–86, 109).)

Petitioner argues that claims 14, 29, 33, and 37, which recite "further comprising testing or having tested the patient for progression of the cancer after the treatment" were anticipated by the MSR because one of ordinary skill in the art would have understood that an "[i]mmune-related ***progression*** free survival (irPFS) rate," as disclosed in the Primary Outcome Measures

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[12] Ascierto et al., *Future Perspectives in Melanoma Research: Meeting Report from the "Melanoma Bridge", Napoli, December 5th-8th 2013*, 12 J. TRANSLATIONAL MEDICINE 277 (October 2024)
[13] September 4, 2014 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

section of the MSR, is a test for disease progression. (*See* Pet. 29–30, 34 (citing Ex. 1005, 4–5, Ex. 1003 ¶¶ 95, 96, 112); Ex. 1001, 26:19–21, 27:7–9, 28:1–3, 28:12–14.)

Claims 4, 5, 12, 19, 20, 27, 31, and 35 recite specific cancers from the list recited in claims 1 and 16. For example, claims 4 and 19 recite "wherein the cancer is endometrial cancer, small bowel cancer, gastric cancer," as well as other cancers. (Ex. 1001, 25:57–59, 26:46–48.) Claims 12 and 27 recite "wherein the cancer is small bowel cancer." (*Id.* at 26:12–13, 27:1–2.) And claims 31 and 35 recite "wherein the cancer is endometrial cancer." (*Id.* at 27:12–13, 28:6–7.) Petitioner argues that one of ordinary skill in the art would have at once envisaged the MSR to include treating patients with endometrial, small bowel, and gastric cancers, for the reasons discussed above in regard to claim 1. (*See* Pet. 23, 25, 34–35 (citing Ex. 1003 ¶¶ 67–69, 77–78, 87–88).) As discussed above, after considering the record cited by both parties, we are persuaded by Petitioner's arguments.

Claims 5 and 20 recite "wherein the cancer is . . . uterine cancer," as well as other cancers. (Ex. 1001, 25:60–63, 26:49–52.) Petitioner argues that endometrial cancer is a type of uterine cancer and that one of ordinary skill in the art would have at once envisaged the MSR to include treating patients with uterine cancer as well. (*See* Pet. 24, 32 (citing Ex. 1003 ¶¶ 79–80).) Patent Owner does not argue to the contrary.

We are persuaded by Petitioner's uncontested evidence that each of claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37 are anticipated by the MSR.

5. Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of the claims challenged in Ground 1. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claims 1, 2, 4–7, 11–17, 19–22, 26–38 are anticipated by the MSR.

E. Grounds 2–7: Obviousness over the MSR and Other References

Petitioner asserts six grounds of challenge against each of claims 1–38 of the '491 patent based on obviousness over the MSR and other cited references. (*See* Pet. 40–64.)

1. Claims 1, 2, 4–7, 11–17, 19–22, and 26–38

In Ground 2, Petitioner argues that the claims 1, 2, 4–7, 11–17, 19–22, 26–38, the same claims challenged under Ground 1 as being anticipated by the MSR, would also have been obvious over the MSR, Brown, Duval, and Benson. (*See* Pet. 40–51.) In Ground 3, Petitioner argues that claims 1–2, 4–7, 11, 13–17, 19–22, 26, and 28–38, claims which were also challenged under Ground 1 as being anticipated by the MSR, would have been obvious over the MSR, Brown, Duval, Benson, and Koh. (*See id.* at 51–52.) Petitioner presents Ground 2 as being an alternative to Ground 1 and Ground 3 as being an alternative to Ground 2. (*See id.* at 40, 51.) In addition, Petitioner asserts Ground 7, challenging claims 11 and 26, which were included in Ground 1, as being obvious over MSR, Brown, Duval, Benson, Koh, Hamid. (*See id.* at 59–61.)

Patent Owner argues that these challenges fail because none of the cited references discloses any of the specific MSI-H cancers recited in the claims and because none of the cited references disclose treating any patient

having the claimed MSI-H cancers "in response to" a determination that they are MSI-H. (*See* PO Resp. 32–34.) Patent Owner also argues that none of the cited references disclose previous treatment and progression after treatment, as required by dependent claims 13, 28, 32, and 36. (*See id.* at 35–36.)

As discussed above, we are persuaded that one of ordinary skill in the art would have understood that the MSR discloses treating patients with at least one of the MSI-H cancers recited in the challenged claims, "in response to" the determination that the tumor is MSI-H. As also discussed above, we are persuaded that one of ordinary skill in the art would have understood that the MSR discloses treating patients who had been treated with a prior cancer therapy drug and whose cancer had progressed after treatment with the prior drug. Accordingly, we are not persuaded that challenged claims would not have been obvious because one of ordinary skill in the art would have considered these elements to not be taught in the MSR.

Patent Owner argues further that Petitioner fails to show that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the methods recited in the challenged claims because Petitioner relies on the wrong standard and because the state of the art did not create a reasonable expectation of success. (*See* PO Resp. 36–52.) Patent Owner also argues that the Petition fails to establish a motivation to pursue the claimed treatments for the claimed MSI-H cancers, as opposed to other MSI-H cancers. (*See id.* at 52–54.)

As discussed above, we are persuaded the MSR anticipates the methods recited in claims 1, 2, 4–7, 11–17, 19–22, and 26–38, teaching each and every element of the recited methods. Patent Owner's arguments fail to

persuade us that the methods would not have been obvious, as well. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("anticipation is the epitome of obviousness"). Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 as being obvious over the MSR alone or with other references and support Petitioner's challenges under Grounds 2, 3, and 7.

2. Claims 8 and 23

In Ground 4, Petitioner challenges the claims 2, 8, 17, and 23 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Chapelle. (*See* Pet. 52–54.) As discussed above, we are persuaded that claims 2 and 17 are anticipated by the MSR and, thus, would have been obvious over the MSR and other references. Accordingly, we focus on the challenge to claims 8 and 23, which were not included in Petitioner's anticipation grounds of challenge.

Claims 8 and 23 recite the method of claim 1 or 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample." (Ex. 1001, 26:1–3, 26:57–59.)

Petitioner argues that one of ordinary skill in the art "would have had motivation to combine the [MSR] (whether alone or combined with Brown, Duval, and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so." (Pet. 53–54 (citing Ex. 1003 ¶ 156).) Petitioner cites Chapelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claims 8 and 23. (*See id.* at 54 (citing Ex. 1007, 3380, 3384; Ex. 1003 ¶ 156).) Petitioner argues further that the '491 patent does not suggest that the

method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (*See id.* (citing Ex. 1003 ¶ 157); *see* Ex. 1001, 6:25–26 ("Testing of MSI can be accomplished by any means known in the art").)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 155–157, 159.)

Patent Owner does not present specific arguments against Petitioner's challenge to claim 8 or 23 regarding the teachings of the MSR and Chapelle or Dr. Neugut's testimony.

3. Claims 3 and 18

In Ground 5, Petitioner challenges claims 3 and 18 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Steinert. (*See* Pet. 54–56.) Claims 3 and 18 recite the method of claim 1 or 16, respectively, "wherein the biological sample is a body fluid from the patient." (Ex. 1001, 25:55–56, 26:44–45.)

Petitioner argues that the methods of claims 3 and 18 would have been obvious to one of ordinary skill in the art in view of the general knowledge in the art, such as Steinert, which teaches determining whether a tumor is MSI-H to understand how cancer evades the immune system. (*See* Pet. 54–55 (citing Ex. 1008, OF1; Ex. 1003 ¶¶ 161, 163).) Specifically, Petitioner argues that Steinert teaches methods of testing whether a tumor was MSI-H using body fluid, specifically blood samples. (*See id.* at 55 (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 161, 164).) Petitioner argues that one of ordinary skill in the art "would have had motivation to combine the MSI-H Study Record

(whether alone or combined with Brown, Duval, and Benson) and Steinert." (*Id.* (citing Ex. 1003 ¶ 164).)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 160–165.)

Patent Owner does not present specific arguments against Petitioner's challenge to claim 3 or 18 regarding the teachings of the MSR and Steinert or Dr. Neugut's testimony.

4. Claims 9, 10, 24, and 25

In Ground 6, Petitioner challenges claims 9, 10, 24, and 25 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Salipante. (*See* Pet. 56–59.) Claims 9 and 24 recite the methods of claims 1 and 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample." (Ex. 1001, 26:4–6, 26:60–61.) Claims 10 and 25 recite the methods of claims 1 and 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample." (*Id.* at 26:7–9, 26:63–65.) Petitioner cites the teaching in Salipante of testing a tumor for microsatellite instability high using a PCR test or next generation sequencing on a sample. (*See* Pet. 56–60 (citing Ex. 1010, 1192 ("PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use."), 1193 ("Here we describe an approach for determination of MSI by [next generation DNA sequencing] (mSINGS) based on microsatellite markers which are incidentally included in targeted gene capture sequencing data."); Ex. 1003 ¶¶ 167–174).) Petitioner argues that one of ordinary skill

in the art "would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Salipante." (*See* Pet. 56, 58 (citing Ex. 1003 ¶¶ 170, 174).)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 167–174.)

Patent Owner does not present specific arguments against Petitioner's challenge to claims 9, 10, 24, and 25 regarding the teachings of the MSR and Salipante or Dr. Neugut's testimony.

5. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 8–10, 18, and 23–25 as being obvious. Rather, as discussed above, Patent Owner argues that one of ordinary skill in the art would not have reasonably expected the claimed method to work in all of the recited MSI-H cancers and would not have treated patients with all of the recited MSI-H cancers. (*See* PO Resp. 32–33; PO Sur-Reply 15–18.) Patent Owner also argues that none of the references cited in addition to the MSR teach or disclose treating a patient with the recited cancers "in response to" a determination of MSI-H and that none of the cited references would have provided one of ordinary skill in the art with a reasonable expectation of success or motivation for accomplishing the claimed methods. (*See* PO Resp. 33–34.)

Patent Owner argues that the cited references do not "supply the missing previous treatment and progression after treatment," required in claims 13, 15, 28, 30, 32, 34, 36, and 38, but does not present any other arguments about the limitations of individual dependent claims. (*Id.* at 35.)

For example, Patent Owner argues that Benson and Koh do not require prior treatment, progression on a prior therapy, or metastatic disease before a patient is enrolled in clinical trials, but Patent Owner does not address the grounds of challenge based on Chapelle, Steinert, or Salipante individually. (*See id.* at 35–54.)

Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, 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."). 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 for MSI-H with immunohistochemistry, polymerase chain reaction, or next generation sequencing, that uses a bodily fluid, as recited in the challenged dependent claims, and 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 challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. (*See* PO Resp. 55–84.) 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 methods recited in the independent claims are anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 16. *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 1, 2, 4–7, 11–17, 19–22, 26–38, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8–10, 18, and 23–25), Patent Owner must show a nexus between the claimed methods 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 highlights portions of the Keytruda® (pembrolizumab) label that discuss testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claims 8, 9, 23, and 24. (*See* PO Resp. 59–60; PO Sur-Reply 18–20.) But Patent Owner does not direct us to evidence of a nexus to limitations recited in the dependent claims, for example to claims 3 and 18, which recite testing a

biological sample that is a bodily fluid, or claims 10 and 25, which recite testing that comprises carrying out next generation sequencing.

Furthermore, Patent Owner's arguments address the methods of independent claims 1 and 16, not the limitations of the claims Petitioner challenges as being obvious. (*See* PO Resp. 66–84.) Patent Owner directs us only to evidence regarding treating patients determined to have MSI-H cancers with pembrolizumab, which we determine to be anticipated by the MSR. 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 methods recited in claims 1 and 16 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 claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claims 3 and 18, or wherein the testing comprises immunohistochemistry, polymerase chain reaction or next generation sequencing, as in claims 8–10 and 23–25, 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 methods of claims 3, 8–10, 18, and 23–25 would have been obvious.

6. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSR and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 1–38 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[14]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–38 of the '491 patent are unpatentable.

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–7, 11–17, 19–22, 26–38	102	MSR	1, 2, 4–7, 11–17, 19–22, 26–38	
1, 2, 4–7, 11–17, 19–22, 26–38	103	MSR, Brown, Duval, Benson	1, 2, 4–7, 11–17, 19–22, 26–38	
1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	103	MSR, Brown, Duval, Benson, Koh	1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	
2, 8, 17, 23	103	MSR, Brown, Duval, Benson, Koh, Chapelle	2, 8, 17, 23	
3, 18	103	MSR, Brown, Duval, Benson, Koh, Steinert	3, 18	

[14] 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).

9, 10, 24, 25	103	MSR, Brown, Duval, Benson, Koh, Salipante	9, 10, 24, 25	
11, 26	103	MSR, Brown, Duval, Benson, Koh, Hamid	11, 26	
Overall Outcome			1–38	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–38 of the '491 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.

FOR PETITIONER:

Naveen Modi
Bruce Wexler
Preston Ratliff
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
brucewexler@paulhastings.com
prestonratliff@paulhatings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Todd G. Miller
Matthew L. Chun
Kristi Sawert
FISH & RICHARDSON P.C.
nstephens@fr.com
gkim@fr.com
miller@fr.com
mchun@fr.com
sawert@fr.com