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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]

[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

[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

[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 Cance*r, 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.

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