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Paper 56
Entered: November 17, 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.

IPR2024-00648
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]

[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:
>
> 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, 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

[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

[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

[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.

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