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Paper 52
Date: September 19, 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.

IPR2024-00650
Patent 11,634,491 B2

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

KATZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner, Merck Sharp & Dohme LLC, filed a Petition to institute an *inter partes* review of all claims, namely claims 1–38 of U.S. Patent No. 11,634,491 B2 (Ex. 1001, "the '491 patent") pursuant to 35 U.S.C. § 311(a). (Paper 1 ("Pet.") 1, 3–4.) Patent Owner, The Johns Hopkins University, did not file a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). We granted the Petition and instituted an *inter partes* review. (Paper 6 ("Decision").)

During the review, Patent Owner filed a Patent Owner Response to the Petition (Paper 28 (confidential Paper 24) ("PO Resp.")), Petitioner filed a Reply (Paper 45 (confidential Paper 42) ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 50 (confidential Paper 47) ("PO Sur-Reply")).

The parties declined to present oral arguments in this proceeding. (*See* Paper 49.) We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial.[1] For the reasons discussed below, we

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

determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–38 of the '491 patent are unpatentable.

A. Real Parties in Interest

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

B. Related Matters

Both Petitioner and Patent Owner report that the litigation *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), is a related matter. (*See* Pet. 64; Paper 3, 1.)

In addition, several other inter partes reviews are related to this proceeding, including IPR 2024-00622, challenging the claims of U.S. Patent No. 10,934,356; IPR2024-00623, challenging claims of U.S. Patent No. 11,325,974 B2; IPR2024-00624, challenging the claims of U.S. Patent No. 11,325,975 B2; IPR2024-00625, challenging claims of U.S. Patent No. 11,339,219 B2; IPR2024-00647, challenging claims of U.S. Patent No. 11,649,287 B2; IPR2024-00648, challenging claims of U.S. Patent No. 11,643,462 B2; IPR2024-00649, challenging claims of U.S. Patent No. 11,629,187 B2.

IPR2024-00240 is also related. Claims 1–42 of U.S. Patent No. 11,591,393 B2 were held to be unpatentable in that proceeding. (*See Merck Sharp & Dohme, LLC v. The Johns Hopkins Univ.,* IPR2024-00240, Paper 90 (PTAB June 9, 2025), Final Written Decision.) Patent Owner's request for Director Review of that decision was denied. (*Id.,* Paper 93.)

C. The '491 Patent

The application that became the '491 patent was filed on May 9, 2022, claiming priority to a number of continuation applications and also to provisional application 62/190,977, which was filed July 10, 2015. (*See* Ex. 1001, codes (22), (60).) The '491 patent cites another provisional application, filed November 13, 2014, but Patent Owner claims priority only to July 10, 2015. (*See* PO Resp. 5 n.4; Ex. 1001, code (60).)

The '491 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor, in cancer patients. (*See* Ex. 1001, Abstract.) More specifically, the '491 patent is directed to treating cancer patients with high mutational burdens, such as found in microsatellite instable (MSI) cancer, with anti-PD-1 antibodies. (*Id.* at 3:39–43.) The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in a clinical trial. (*Id.* at 8:54–58.)

Claim 1 of the '491 patent recites:

> A method of treating cancer in a human patient, the method comprising:
>
> testing or having tested a biological sample obtained from a patient having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer, thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab.

(*Id.* at 25:36–52.) Independent claim 16, the only other independent claim, is similar and recites the same steps of "testing" and "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating . . . ." (*Id.* at 26:24–41.)

The parties refer to the term "microsatellite instability high" as "MSI-H" and the term "mismatch repair deficient" as "dMMR." The parties agree that testing for either MSI-H or dMMR is considered the equivalent of testing for the other condition, and refer most often to MSI-H as the identified condition. (*See* Pet. 6; PO Resp. 5 n.3.)

D. Evidence

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

Name	**Reference**	**Exhibit**
MSR (MSI-H Study Record)	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1	1005
Chapelle	Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)	1007
Steinert	Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014)	1008
Benson	Benson et al., *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014)	1009
Salipante	Salipante et al., *Microsatellite Instability*	1010

	Detection by Next Generation Sequencing, 60(9) Clinical Chemistry 1192 (2014)	
Hamid	Hamid et al., *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New Eng. J. Medicine 134 (July 2013)	1011
Brown	Brown et al., *Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival*, 24 Genome Res. 743 (May 2014)	1034
Duval	Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) Proc. Nat'l Acad. Sci. 5002 (April 2004)	1087
Koh	Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. Nat'l Comprehensive Cancer Network 248 (February 2014)	1095

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–38 are unpatentable on the following grounds:

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1, 2, 4–7, 11–17, 19–22, 26–38	102	MSR
2	1, 2, 4–7, 11–17, 19–22, 26–38	103	MSR, Brown, Duval, Benson
3	1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	103	MSR, Brown, Duval, Benson, Koh

[2] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013, before the filing of the applications to which the '393 patent claims priority. Therefore, we apply the AIA versions of Sections 102 and 103.

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
4	2, 8, 17, 23	103	MSR, Brown, Duval, Benson, Koh, Chapelle
5	3, 18	103	MSR, Brown, Duval, Benson, Koh, Steinert
6	9, 10, 24, 25	103	MSR, Brown, Duval, Benson, Koh, Salipante
7	11, 26	103	MSR, Brown, Duval, Benson, Koh, Hamid

II. ANALYSIS

A. Legal Standards

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

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

> if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have

> been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.

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

B. Level of Ordinary Skill in the Art and Declarants

The parties rely on the testimony of witnesses for their opinions on what one of ordinary skill in the art would have known and understood at the relevant time. Specifically, Petitioner relies on the testimony of Alfred L. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2072) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be a medical doctor, or a professional in a related field, with experience treating cancer or access to those with experience in clinical studies of therapeutics and to a pathologist with this experience. (*See* Pet. 11 (citing Ex. 1003 ¶ 19).) To Patent Owner, the ordinarily skilled artisan would have had a medical or graduate-level degree, or equivalent work experience, in the fields of immunology, genetics, or a related field and would have experience (i) conducting immunology research relating to oncology, (ii) conducting

genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. (*See* PO Resp. 5–6 (citing Ex. 2072 ¶¶ 31–32, 91–99).) Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

The '491 patent claims a method of treating a human patient with cancer having certain characteristics using pembrolizumab and the main prior art reference cited by Petitioner discloses testing pembrolizumab to treat human patients. (*See* Ex. 1001, 25:36–52, 26:24–41, Ex. 1005; *see* Decision 8–9.) Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds.

In light of the extent of the relevant field, we determine that the level of skill in the art relevant to the claims of the '491 patent is not limited to knowledge of and experience with conducting research relating to oncology or developing and conducting clinical trials, but includes knowledge of and experience with treating cancer patients with immunotherapy compounds, identifying the conditions these patients may have, and understanding the literature regarding clinical trials for such colorectal cancers and the associated conditions and immunotherapy.

C. Claim Construction

We construe claims "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b) (2020).

Claims 1 and 16 require treating the patient with a therapeutically effective amount of pembrolizumab "in response to determining that the

colorectal cancer is microsatellite instability high or DNA mismatch repair deficient . . . ." (Ex. 1001, 25:47–49, 26:36–38.) Petitioner argues that the discussion in the MSR of treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days reads on this limitation of claim 1. (*See* Pet. 21–22 (citing Ex. 1005, 2–6.)) For the purposes of our decision whether to institute review, we agreed and stated that Petitioner had shown

> a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of non-colorectal cancer patients and the determination of their MSI status, wherein non-colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were placed into a study arm and then treated with pembrolizumab. (*See* Ex. 1005, Ex. 1003 ¶¶ 60–73.) Because treatment of the patients was performed only after MSI-H status was determined, the MSI-H Study Record teaches treating the patients "in response to" determining their MSI-H status.
>
> The MSI-H Study Record describes other patients being enrolled and treated with pembrolizumab, including colorectal cancer patients determined to be MSI-H and colorectal cancer patients determined not to be MSI-H. At this point in the proceeding, we interpret the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients. Patent Owner has not directed us to evidence that one of ordinary skill in the art would have understood treating a patient "in response to" the determination that the patient has a condition to exclude the same treatment of other patients, such as the treatment of control patients not having the condition.

(Decision 14–15.)

Patent Owner argues, in regard to the Final Decision in IPR2024-00240, that the Board's construction "disregards the critical ***causal***

relationship between the 'determining' and 'treating' steps in the claims. The express causal relationship between these steps establishes that ***only*** patients determined to be MSI-H are treated." (PO Resp. 6.) According to Patent Owner, the claim term "in response to" is properly construed as "in reaction to" because "[t]he claimed 'treating' step is performed (and only performed) in response to (as a reaction to) determining the cancer is MSI-H." (*Id.* at 6–7.) Patent Owner disagrees that the claim term "in response to" means only "after." (*See id.*)

Patent Owner argues further that the Specification of the '491 patent is consistent with the asserted "plain meaning" of the claim term "in response to" as meaning a causal relationship, wherein the "treating" step is only performed as a reaction to determining the patient's cancer is MSI-H. (*See id.* at 7–8.) Specifically, Patent Owner cites the disclosure in the '491 patent for the determination that MSI-H indicates a tumor is a "good candidate" for treatment with an immune checkpoint inhibitory antibody and that MSI-stable indicates the tumor is a "bad candidate" for treatment with an immune checkpoint inhibitory antibody. (Ex. 1001, 3:57–67.) According to Patent Owner, one of ordinary skill in the art would have understood from the characterization of good/bad candidates in the '491 patent that administering the claimed treatment would be only as a reaction to the determination of MSI-H. (*See* PO Resp. 8.) According to Patent Owner, a "purely sequential construction" would render meaningless the "in response to" step of the claim because if "in response to" meant merely "after," the claims would cover treatment "for any reason or no reason at all—even accidental treatment would be covered." (*Id.*)

We agree with Patent Owner that the phrase "in response to" in claims 1 and 16 requires a causal relationship, wherein the patient must be tested for MSI-H and, if he or she is determined to be MSI-H or dMMR, then the patient is treated with 10 mg/kg of pembrolizumab every 14 days. In claims 1 and 16, a biological sample from the patient must be tested to determine if the cancer is MSI-H and, if so, the patient is treated with a therapeutically effective amount of pembrolizumab. For this reason, if the prior art teaches the limitations of 1) testing a biological sample obtained from a patient having non-colorectal cancer to determine that the patient's cancer is MSI-H or dMMR, and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, the art anticipates claims 1 and 16. We are not persuaded that claim 1 or 16 requires or excludes anything else because nothing else is recited in the claim.

Patent Owner argues that the inventors used the term "after" in several dependent claims of the related U.S. patent 11,591,393. (*See* PO Resp. 7 (citing Ex. 2301, claims 7, 20, 27).) For example, claim 7 of U.S. patent 11,591,393 ("the '393 patent"), which depends on an independent claim reciting the "in response to" limitation, requires that the cancer "had progressed after" the patient received a different cancer therapy. (Ex. 2301, 25:64–67, 26:41–46; *see also id.* at 26:62–64.) Patent Owner argues that "within the '491 Patent's family," the word "after" appears in some of the same claims as "in response to," indicating that terms have different meanings. (PO Resp. 7.)

Patent Owner does not explain why the meaning of terms not found in claims of the '491 patent is relevant to the claims of the '491 patent, but to

the extent those claims are relevant, they do not persuade us that the '491 patent claims require anything other than 1) testing a biological sample and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, as discussed above. The relationship between testing and treating in claims 1 and 16 of the '491 patent is different from than the relationship of the term "after" in claims 7, 20, and 27 of the '393 patent, wherein patients must have been first treated with a different cancer therapy and the cancer had later progressed. (Ex. 2301, 25:66–67, 26:44–46, 26:63–64.) As discussed above, we do not disagree that the phrase "in response to" in claims 1 and 16 requires a causal relationship, but we are not persuaded that the prior art must teach anything other than testing a biological sample to determine that the patient's cancer is MSI-H or dMMR, and, if so, treating the patient with a therapeutically effective amount of pembrolizumab. We are not persuaded that anything else is required in claim 1 or 16 of the '491 patent.

Patent Owner argues that the "in response to" limitation of claim 1 describes administering the claimed treatment *only* to patients determined to have an MSI-H tumor. (*See* PO Resp. 6.) But neither claim 1 nor claim 16 includes a limitation excluding the treatment of any patient, such as specifically excluding treatment of any patient who has a tumor that is not MSI-H or dMMR. Neither claim 1 nor claim 16 recites any language differentiating between patients or identifying a patient population to be excluded from treatment. Instead, claims 1 and 16 provide that if the colorectal cancer patient is tested and the cancer is determined to be MSI-H or dMMR, the patient is treated with a therapeutically effective amount of pembrolizumab.

We note that the methods of claims 1 and 16 use the open-ended transitional phrase "comprising" that is generally interpreted to not exclude additional, unrecited elements. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claim."). The use of the open-ended transitional phrase "comprising" in claims 1 and 16 further suggests to us that any additional steps taken in conjunction with expressly recited method steps, such as the treatment of patients who are not MSI-H or dMMR, are not excluded from the scope of the claim.

Patent Owner argues that the Examiner used a construction of the term "in response to" that is consistent with Patent Owner's position during prosecution. (*See* PO Resp. 8.) Patent Owner asserts that the Examiner "used the shorthand 'based on' to express the plain meaning of 'in response to,'" and that "based on" requires a causal relationship. (*Id.* (citing Ex. 2302, 8 ("Lipson does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed.").) According to Patent Owner, the term "based on" does not mean "after," but requires a causal relationship. (*See id.*) Again, we do not disagree with Patent Owner that claim 1 recites a causal relationship. But we are not persuaded that either claim 1 or claim 16 requires anything other than testing a cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of

pembrolizumab. The Examiner's reasoning does not indicate that the claims of the '491 patent exclude treating any patient other than the one tested.

Similarly, we are not persuaded that Petitioner argued for a claim construction in District Court that would exclude treatment of any patient other than the one determined to be MSI-H or dMMR, as Patent Owner implies. (*See* PO Resp. 9–10.) Patent Owner argues that "Merck's only dispute [in District Court] was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." (*Id.* at 9 (citing Ex. 2160, 24[3]).) But Patent Owner does not point to a specific argument in which Petitioner argued that claim 1 or 16 requires anything other than 1) testing a biological sample and 2) treating the patient with a therapeutically effective amount of pembrolizumab if the patient's cancer is determined to be MSI-H or dMMR, as discussed above. Before the District Court, Petitioner argued the claim language "requires that 'treating' occur 'in response to' some form of 'determining'" and that a "response" is "a ***reaction***, as that of an organism to any of its parts, to a ***specific*** stimulus." (Ex. 2160, 24–25.) This construction does not limit the scope of claim 1 or 16 to contemplating the treatment of any patients other than the one tested and determined to be MSI-H or dMMR. Although Petitioner argued for a claim construction before the District Court, it did not argue for the construction Patent Owner asserts now. (*Id.* at 25 ("[Patent Owner]'s proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it

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

means, invites legal error and jury confusion about what behavior the claims cover.").)

Patent Owner argues further that Petitioner's witness, Dr. Neugut, agrees that "in response to" should be given its plain meaning and that Patent Owner's witness, Dr. Lonberg, testifies that "in response to" means "in reaction to" a determination that the patient's tumor is MSI-H. (*See* PO Resp. 9–10 (citing Ex. 2163, 70:25–71:2; Ex. 2072 ¶¶ 84–85).) Neither of these statements persuades us that claim 1 or 16 requires anything other than testing a colorectal cancer patient and, if determined to be MSI-H or dMMR, treating that patient with a therapeutically effective amount of pembrolizumab. Neither Dr. Neugut's nor Dr. Lonberg's testimony persuades us that the scope of claim 1 or 16 excludes treating any patient other than the one tested and confirmed to be MSI-H.

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

claim term "in response to" requires a causal relationship between a first action and a second action, but we disagree that the court's reasoning in *Am. Calcar* is relevant to the claims before us. The issue presented by claims 1 and 16 is whether treatment of patients not meeting the recited limitation (MSI-H) is excluded by the claim language, not whether treating patients "in response to" a determination of MSI-H incurs further action by a care provider. The reasoning of *Am. Calcar* does not persuade us that exclusion is required because *Am. Calcar* does not address the phrase "in response to" in the context of excluding one condition over another.

After considering the parties' arguments and the evidence presented, we construe claims 1 and 16 to require testing a biological sample obtained from a cancer patient having cancer to determine that the patient's tumor is MSI-H or dMMR and treating the patient with a therapeutically effective amount of pembrolizumab if the patient's tumor is determined to be MSI-H or dMMR. We are not persuaded that either claim 1 or 16 requires or excludes other patients or steps because neither claim 1 nor claim 16 recites any other steps or contain negative limitations.

D. Ground 1: Anticipation over the MSR

Petitioner argues that claims 1, 2, 4–7, 11–17, 19–22, and 26–38 are anticipated under 35 U.S.C. § 102. (*See* Pet. 13–36.)

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

The MSR reports a "Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors." (Ex. 1005, 2.) The parties' witnesses agree that MK-3475 is pembrolizumab, the compound recited in claim 1. (*See* Ex. 1003 ¶ 38; *see* Ex. 2072 ¶ 69.) Patent Owner does not dispute Petitioner's assertion that the MSR was published on a government

web site on June 10, 2013, more than two years before the priority date of the '393 patent on July 10, 2015. (*See* Pet. 6–7 (citing Ex. 1005, 3, Ex. 1003 ¶ 35).)

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

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

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

(*Id.* at 4.) The chart above identifies three patient populations, including "MSI Positive Colorectal Cancer," "MSI Negative Colorectal Cancer," and

[4] Petitioner relies on the testimony of Dr. Neugut and several prior art references to assert that the terms "MSI positive," "MSI-high," "MSIH," and "MSI+" were used to mean "MSI-H" by those in the art at the time. (*See* Pet. 6 (citing, e.g., Ex. 1018, 293 ("MSIH (MSI high) was considered MSI positive and MSS (MS stable)")); Ex. 1003 ¶ 26).) Patent Owner does not contest the identifications.

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

Petitioner cites the teaching in the Arms and Interventions section as a method of treating human MSI positive colorectal cancer patients, as recited in the preamble of claim 1. (*See* Pet. 16 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility)).) Petitioner argues that the claimed methods are anticipated by the MSR even if the recited steps had not been performed yet because any efficacy requirement in the claims would be inherent to the steps. (*Id.* at 21–22.) Petitioner argues that the challenged claims are directed to the methods disclosed in the MSR. (*See id.* at 18.)

2. Claim 1

a) Preamble "A method of treating cancer in a human patient, the method comprising"

Petitioner argues that the MSR teaches "[a] method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient," as recited in the preamble of claim 1. (Pet. 16 (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 60–61).)

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

b) Element 1.1: "testing or having tested a biological sample obtained from a patient"

Petitioner argues that the MSR teaches testing or having tested a biological sample from a patient in order to place the patient into the proper arm of the study. (*See* Pet. 18 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 64–66).)

Patent Owner does not argue to the contrary.

In light of the evidence of record, we are persuaded that the MSR teaches this limitation.

c) Element 1.2: "having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer,"

Petitioner argues that the Arms and Interventions section of the MSR teaches treating patients having non-colorectal MSI-H cancer. (*See* Pet. 19 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) Petitioner argues that MSI-H was known to occur in several different types of cancers, including endometrial, small bowel, and gastric cancer, along with colorectal cancer, and that these types of cancers were known to occur in Lynch syndrome, which was known to be closely associated with MSI-H tumors. (*See id.* (citing Ex. 1085,[5] 673–75; Ex.

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

1086,[6] 14; Ex. 1003 ¶¶ 25, 67).) Petitioner relies on Dr. Neugut's testimony that endometrial, small bowel cancer, and gastric cancer are "common in Lynch syndrome, which was known at the time to be closely related to MSI-H." (Ex. 1003 ¶ 67 (citing Ex. 1085, 673 ("DNA mismatch repair (MMR) deficiency results in a strong mutator phenotype and high-frequency microsatellite instability (MSI-H), which are the hallmarks of tumors arising within Lynch syndrome.")); *see also* Ex. 1085, 673 ("Tumors of the Lynch syndrome . . . and some sporadic gastrointestinal and endometrial cancers belong to the MSI pathway.").) Thus, "the person of ordinary skill would have immediately pictured treating [patients with endometrial, small bowel, and gastric cancer] with the MSI-H Study Record's methods" and that "the person of ordinary skill would have concluded that the limitation [listing recited types of cancer] was found in the MSI-H Study Record." (Ex. 1003 ¶¶ 67–68.)

Patent Owner argues the MSR does not expressly or inherently disclose the claimed MSI-H cancers. (*See* PO Resp. 10–14.) As Patent Owner argues, "[o]ther than specifying the participant's cancer must be non-colorectal, the MSR provides no details or guidance about cancer types to be included in that third arm" and does not list any of the claimed MSI-H cancers. (*Id.* at 10.) Patent Owner acknowledges that the MSR discloses the "third arm" disclosed in the MSR "was open to all-comers with any MSI-H cancer other than CRC," but argues that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of the genus. (*See id.* at 11 (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d

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

991, 999 (Fed. Cir. 2006) and *Metabolite Lab'ys, Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004).)

Next, Patent Owner argues that the Petition did not provide evidence of the number of species in the genus described in the MSR and does not contend that one of ordinary skill would have immediately appreciated the full scope of the genus, which includes at least twenty-nine species. (*See id.* at 12–13 (citing Ex. 2072 ¶ 53).) According to Patent Owner, the issue of whether MSI-H was known to occur in Petitioner's "hand-picked set of cancers" (endometrial, gastric, and small bowel cancer) is irrelevant because it overlooks the other MSI-H cancers recited in claim 1 and ignores the "unclaimed non-[colorectal] MSI-H cancers." (*See id.* at 12.) According to Patent Owner, the size of the non-colorectal cancers included in the MSR is large and there is no support for a conclusion that a person of ordinary skill in the art could have at once envisaged each member. (*See id.* at 13.)

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

In contrast, the testimony of Patent Owner's witness, Dr. Goldberg, supports Petitioner's argument of the knowledge in the art at the time, wherein Dr. Goldberg testifies that "[w]hile many clinical oncologists were aware that patients with Lynch Syndrome had a defect in DNA mismatch repair, they associated MSI testing with young onset colorectal and endometrial cancer and patients with a family history of colorectal and/or endometrial cancer." (Ex. 2090 ¶ 79.) Similarly, during his deposition Dr. Goldberg also agreed that endometrial, gastric, and small-bowel cancers would come to mind when he saw a reference to MSI-high non-colorectal cancer. (*See* Ex. 1243, 115:5–116:22 (Q. And so does endometrial cancer come to mind when you see reference to MSI-high non-colorectal cancers? . . . A. Yes. Q. As a person -- a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does gastric cancer come to mind?. . . A. I believe it was listed among the items that I stated when you asked me what comes to mind. So the answer is yes. Q. As a person of skill in the field, when you see reference to MSI-high non-colorectal cancers, does small bowel cancer come to mind? . . . A. Yes.").) Patent Owner does not direct us to other evidence contradicting Petitioner's argument that MSI-H was known to occur in endometrial, small bowel, and gastric cancer. (*See* Pet. 19.)

Patent Owner argues that the Petition does not consider the breadth of the genus disclosed in the MSR and does not argue or provide evidence to show that one of ordinary skill in the art could have envisaged each species within that genus. (*See* PO Resp. 11–14.) We are not persuaded that either the size of the genus in the MSR or whether one of ordinary skill in the art would have been able to envisage every species within it is dispositive of

whether the MSR anticipates claim 1, where one or ordinary skill in the art would have known that specific cancers recited in claim 1 would be included in the MSR. As Petitioner argues, claim 1 requires that "a patient having" one of the listed cancers is tested and treated. (*See* Ex. 1001, 25:38–39; *see* Pet. Reply 10.) Claim 1 does not require that the patient have each and every one of the sixteen listed cancers. (*See id.*) Rather, claim 1 requires testing a sample from "a patient" with one of the recited types of cancer and treating the patient. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.").

Patent Owner argues further that *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009), supports its position, requiring that one of ordinary skill in the art must at once envisage all MSI-H non-colorectal cancer types included in the MSR, not just one or even a subset of the claimed cancer types, in order for the MSR to anticipate claim 1. (*See* PO Sur-Reply 2.) *Gleave* states:

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

> circumstance, a reference describing the genus anticipates every species within the genus. *See Perricone*, 432 F.3d at 1377.

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

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

Patent Owner attempts to distinguish *Brown* by arguing that its holding is limited to anticipation of a claimed genus through disclosure of individual species, whereas the facts of this case involve the disclosure of a genus. (*See* PO Resp. 14.) Because the facts before us, including the testimony of Patent Owner's witness, indicate that one of ordinary skill in the art would have immediately understood that the third arm of the study described in the MSR includes patients with cancers recited in claim 1, including endometrial, gastric, and small-bowel cancers, we are persuaded that one of ordinary skill in the art would have understood that the MSR

discloses species that fall within the scope of claim 1. (*See* Ex. 2090 ¶ 79; Ex. 1243, 115:5–116:22; Ex. 1085, 673–75; Ex. 1086, 14; Ex. 1003 ¶¶ 25, 67; Ex. 1005, 4.) We are not persuaded that where species falling within the scope of claim 1 were previously known and disclosed in MSR, that claim 1 is patentable over the MSR. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage'" the claimed arrangement or combination." (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

After considering the parties' arguments and the evidence presented, we are persuaded that the MSR teaches "testing or having tested a biological sample obtained from a patient" having endometrial, small bowel, or gastric cancer and, thus teaches the corresponding limitation of claim 1.

d) Element [1.3]: "thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient;"

Petitioner argues that the MSR teaches testing or having tested a biological sample from a patient. (*See* Pet. 20 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 62–66, 69, 70).)

We are persuaded that this testing would result in determining that a patient's cancer is MSI-H or dMMR, as recited in claim 1. Patent Owner does not argue to the contrary.

e) Element [1.4]: "and in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or

DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab."

Petitioner argues that the disclosure in the MSR of treating MSI-H non-colorectal patients with 10 mg/kg of pembrolizumab every 14 days teaches the limitation of treating a patient with a therapeutically effective amount of pembrolizumab in response to determining that the patient's cancer is MSI-H or dMMR. (*See* Pet. 21 (citing Ex. 1005, 4 (Arms and Interventions); 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); Ex. 1003 ¶¶ 35, 50, 71–74.) Petitioner argues that although the MSR does not use the phrase "therapeutically effective amount," it teaches administering 10 mg/kg of MK-3457 (pembrolizumab), which is the same dosage of pembrolizumab the '491 patent describes as being therapeutically effective. (*See id.* (citing Ex. 1001, 8:50–56, 13:24–30, 16:4–8, 16:29–32, 19:40–21:15, Figs. 2, 11; Ex. 1003 ¶¶ 72–73).)

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

As explained above, we are persuaded by Petitioner's arguments and the cited evidence that one of ordinary skill in the art would have understood and envisaged the MSR to include patients with at least endometrial, small bowel, or gastric cancers. We are further persuaded that the MSR teaches treating these patients in response to the determination that these patient's tumors were MSI-H in the third arm of the study described. Patent Owner's

arguments about the failure of the MSR to expressly identify any of the cancers recited in claim 1 do not persuade us otherwise. Instead, we are persuaded that one of ordinary skill in the art would have understood that the MSR teaches testing a patient with a non-colorectal cancer, such as endometrial, small bowel, or gastric cancers, to determine if the patient has an MSI-H tumor and, if the tumor is determined to be MSI-H, treating the patient with amount of pembrolizumab described as being therapeutically effective in the '491 patent.

Accordingly, we are persuaded that the MSR teaches this limitation of claim 1.

f) Patent Owner's Other Arguments

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

Patent Owner argues that Petitioner inappropriately relies on *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), to support the assertion of inherent anticipation of the claimed method. (*See id.* at 20–24; Pet. 15 ("In *In re Montgomery*, the Federal Circuit held that a document disclosing a planned clinical study inherently anticipated method of treatment claims even where the method of treatment had not yet been practiced.").) Patent Owner argues that because the MSR is only an initial submission for an experimental trial that had not yet begun recruiting patients or obtaining experimental data, it was merely an "invitation to investigate" from which the results claimed by the '393 Patent did not

"inevitably flow." (PO Resp. 20–21.) Patent Owner cites the testimony of inventor Le to argue that at the time the MSR was posted, the inventors had only a hypothesis based on a single patient's response to a different drug, lacking even preliminary animal data. (*See id.* at 21 (citing Ex. 2130 ¶¶ 10, 22).) Patent Owner argues further that the inventors only knew the drug had been unsuccessful in other studies and that the outcome of the MSR was not assured. (*See id.* at 21–22 (citing Ex. 2090 ¶ 57; Ex. 2024;[7] Ex. 1013[8]).) According to Patent Owner, "the MSR was a far cry from meeting *Montgomery*'s inevitability requirement for inherent anticipation," being design only to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. (*Id.* at 22–24; *see* Ex. 2072 ¶ 118.)

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded, but we are not persuaded the MSR is so vague that it does not teach the steps expressly recited in claim 1. Regardless of the inventors' intent in publishing the MSR as a Stage II clinical trial on the www.clinicaltrials.gov website, as discussed above, we determine that one of ordinary skill in the art would have known that the MSR teaches testing a biological sample from a patient having either endometrial, small bowel, or gastric cancer to determine if the patient's cancer is MSI-H or dMMR and, if so, treating the patient with a

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[7] Brahmer et al., *Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*, 28(19) J. CLINICAL ONCOLOGY 3167 (July 1, 2010).
[8] Topalian et al., Safety, *Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer*, 366(26) NEW ENG. J. MED. 2443 (June 28, 2012).

therapeutically effective amount of pembrolizumab. (*See*, *e.g.*, Ex. 1005, 4 (Arms and Interventions).) The result of drug treatment inherently follows its administration. The MSR does not merely suggest that pembrolizumab may be useful in some unidentified subset of cancer patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the MSR discloses testing patients with cancers known to be associated with MSI-H, as recited in claim 1, and treating with the drug recited in claim 1 if the cancer was determined to be MSI-H. *See Metabolite Labs.*, 370 F.3d at 1367 (holding that the prior art did not inherently anticipate where it failed to mention specific vitamin deficiencies, instead merely inviting further experimentation to find associations with metabolic perturbations).)

Montgomery states that "even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps," referring to a claimed method of treating or preventing stroke, which was held to be anticipated by the publication of a proposed study. 677 F.3d at 1381. Patent Owner attempts to distinguish the size and apparent surety of the study in *Montgomery* from the MSR. (*See* PO Resp. 23–24.) But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by Kris. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent."). Whether or not the MSR could have provided results or was sufficient for

full regulatory approval does not change that the MSR teaches Patent Owner's claimed steps.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. (*See* PO Resp. 26–32.) Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. (*See id.* at 26 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998).) According to Patent Owner, the experimental use negation applies to the MSR under a 13-factor analysis provided in *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002). (*See id.* at 27–31.) For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test the treatment in humans, there being no animal models, and had to publish the MSR on the government website under federal law. (*See id.* at 27–28.) Patent Owner argues further that the inventors had control over the MSI-H clinical study and that the field of cancer treatment was highly unpredictable, among other facts. (*See id.* at 28–31.) Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." (*Id.* at 34.)

Petitioner disagrees, arguing that "[i]t is well established . . . that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112." (Pet. Reply 9 (citing *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"); *Ex parte Balzarini*, 21 U.S.P.Q.2d 1892 (BPAI 1991) (holding that even in situations

where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials.)).)

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support patenting a method of treating human patients reinforces the importance of applying experimental-use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment." (PO Sur-Reply 13.) But Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSR and was denied an earlier filing date. We note that Patent Owner filed a provisional patent application on November 13, 2014, which, although also filed more than a year after the publication of the MSR, disclosed no clinical results or data. (*See* Ex. 1001, cover; Ex. 1030, 1).) Patent Owner does not attempt to rely on this provisional application for a prior filing date in the current proceeding, but does not direct us to evidence that the earlier date would have been denied. (*See* PO Resp. 5 n.4.) We are not persuaded by Patent Owner's assertion that "there can be no question" that Patent Owner could not have filed an earlier application to secure a priority date before the MSR was publicly available.

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

Elizabeth v. Am. Nicholson Pavement Co., 97 U.S. 126, 137 (1877). Be*cause we are not persuaded that Patent Owner* could not have filed an earlier application, we are not persuaded that the experimental use doctrine is properly applied in this case, particularly given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir.), *cert. denied*, 145 S. Ct. 567 (2024), and *cert. denied*, 145 S. Ct. 983 (2024).

g) Summary for claim 1

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of claim 1. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claim 1 is anticipated by the MSR.

3. Independent Claim 16

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

4. Dependent claims

a) Claims 13, 28, 32, and 36

Petitioner argues that claims 13, 28, 32, and 36 are anticipated by the MSR. (*See* Pet. 25–29, 33–35.) These claims each require the patient to have received a "prior cancer therapy," and the patient's cancer to have progressed "after the patient was treated with the prior cancer therapy." (Ex. 1001, 26:15–18, 27:3–6, 27:14–17, 28:8–11.) Petitioner argues that because the MSR discloses that patients eligible for the study must have "tumors"

and "measurable disease," one of ordinary skill in the art would have known that the patients would have received prior drug therapies and that their cancers would have progressed after these therapies. (*See* Pet. 25–29 (citing Ex. 1005, 2 (Study Identification), 4 (Study Design), 5–6 (Eligibility); Ex. 1003 ¶¶ 89–93).)

Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have known the reference to "measurable cancer" in the MSR would include patients with metastatic and advanced cancer, not resectable cancer, because patients whose tumors are resectable can be cured by surgery. (*See id.* at 26 (citing Ex. 1003 ¶ 90).) Petitioner argues further, relying again on Dr. Neugut's testimony, that patients with metastatic and advanced cancer who would participate in a clinical study would generally have received at least one prior drug therapy, such as standard care chemotherapy, and would have had their cancer progress after these therapies. (*See id.* at 27 (citing Ex. 1003 ¶ 91; Ex. 1089, 17; Ex. 1020, 25; Ex. 1094, 12, 15; Ex. 1009, 1034; Ex. 1047, 4–7).)

Petitioner argues further that because the eligibility section of the MSR excludes patients who have had specific prior treatment, providing a list of those specific treatments (anti PD-1, anti PD-L1, anti PD-L2, anti CD137, anti OX-40, anti CD40 or anti CTLA-4 antibodies), patients who have previously been treated, in general, and had their cancer progress after the prior treatment were included in the study. (*See id.* at 25–26 (citing Ex. 1003 ¶ 92).) As confirmation of this understanding, Petitioner cites a 2014 poster presentation discussing the clinical study described in the MSR being

for eligible patients with "progressive disease" and non-colorectal cancer who had "at least 1 prior therapy." (Ex. 1080[9]; *see* Pet. 28.)

Patent Owner argues that the MSR is silent on whether eligible patients must have been previously treated with a prior cancer drug and that the cancer had progressed following the prior treatment. (*See* PO Resp. 16–18.) According to Patent Owner, "[n]o amount of attorney argument or expert testimony can satisfy the requirement to demonstrate express anticipation" and the MSR itself must disclose the limitation. (*Id.* at 16.) Patent Owner argues that Petitioner fails to meet the burden to show inherent anticipation of the limitations of these dependent claims. (*See id.* at 19–22.)

Patent Owner argues that the only reference to prior treatment in the MSR is the reference to excluded prior treatments, which is the opposite of inclusion of patients with prior treatment, as required in the challenged claims. (*See id.* at 18 (citing Ex. 2072 ¶ 105).) Patent Owner argues further that three years after the MSR was published, an express requirement for prior treatment was added to the ClinicalTrials.gov record, indicating that such a requirement was not present in 2013 when the MSR was originally available. (*See id.* (citing Ex. 2165, 8 ("Patients with other [non-colon] cancer types must have received at least one prior cancer therapy"); Ex. 2166, 8 ("Patients with other [non-colon] cancer types must have received at least one prior cancer therapy"); Ex. 2072 ¶ 107).) Patent Owner argues that Petitioner's reliance on the poster presentation that included a requirement for a prior treatment fails because the poster is separate from the MSR and is

[9] Poster presented at ASCO, Le et al., *Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors* (Jun. 1, 2014).

not prior art, having been publicly available only later. (*See id.* at 18–19 (citing Ex. 1080).)

In addition, Patent Owner disputes Petitioner's evidence about what was generally understood at the time of the MSR, arguing that it was advised that some Stage IV gastric cancer patients proceed directly to clinical trials without prior treatment. (*See id.* at 17–18 (citing Ex. 1096, 533; Ex. 2072 ¶ 106).) Patent Owner also cites published guidelines on treating colon cancer that state: "Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." (Ex. 1009, 1029; PO Resp. 18.)

Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression" and that three years later it was updated with a statement requiring prior cancer treatment, but he fails to testify that one of ordinary skill in the art would not have understood the MSR in 2013 to teach treating patients who had received a prior cancer therapy drug, wherein the patients' cancer had progressed after receiving the prior drug. (*See* Ex. 2072 ¶¶ 105–107.) Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. (*See* Ex. 2072 ¶ 107 ("While ***measurable cancer*** refers to a cancer that has a minimum size (e.g., as determined by imaging), this has little to do with whether or not a patient's cancer has ***progressed*** after the patient received prior therapies.").) But Dr. Lonberg fails to testify that one of ordinary skill in the art would not have understood the MSR in 2013 to teach treating patients who had received a prior cancer therapy and had a subsequent progression in the cancer, contradicting Petitioner's evidence.

On the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. Both parties cite generalized guidelines about cancer treatment, which do not shed much light on what one of ordinary skill in the art would have understood from the MSR, specifically. The parties disagree about the reason for the 2016 update of the MSR to include a limitation for only patients with non-colon cancer who had previously received at least one prior cancer therapy, but the reason for the change is still unclear. Does the update indicate a change to the study or merely a clarification? We are not persuaded that the update by itself is dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients who had received a prior cancer therapy and the patient's cancer to have subsequently progressed.

There is a difference, though, in the testimony of the parties' witnesses. Dr. Neugut, Petitioner's witness, testifies that "the person of ordinary skill would have found it highly unusual for the patient population of those who had received prior drug treatments and had their cancer progress after those treatments to not be included in the MSI-H Study Record, especially without any explicit carve-out." (*See* Ex. 1003 ¶ 92.) Dr. Oberstein, Petitioner's other witness concurs, testifying that because the MSR describes a study of a new immunotherapy drug, one of ordinary skill in the art would have understood that metastatic and advanced cancer patients who would participate would have received prior drug therapies, but that their cancer would have progressed. (*See* Ex. 1150 ¶ 69.) Dr. Oberstein testifies further that if the study was intended only for patients who had not been previously treated, a one of ordinary skill would have expected an

explicit carve out excluding all patients who had been previously treated. (*See id.*) As Dr. Oberstein notes, the MSR does not include a blanket exclusion for patients who had received any prior treatment – it only includes exclusions for some specific prior drug treatments. (*See id.*; Ex. 1005, 6.)

Dr. Lonberg, Patent Owner's witness, does not dispute any of Dr. Neugut's or Dr. Oberstein's testimony, but asserts only that Dr. Neugut's testimony relies only on what was generally done, not on what is expressly disclosed in the MSR. (*See* Ex. 2072 ¶¶ 105–107.) On cross-examination, Dr. Lonberg agreed with Dr. Oberstein that patients who had received prior cancer therapy were not excluded from the study described in the MSR. (*See* Ex. 1245, 57:5–58:2, 40:5–14, 49:2–12.)

Thus, after considering the evidence cited by each party, we find Dr. Neugut's and Dr. Oberstein's testimony to be the most directly relevant and persuasive about what one of ordinary skill in the art would have understood from the MSR itself. We are also persuaded by the lack of a specific contradiction regarding the understanding of one of ordinarily skill in the art by Dr. Lonberg. Even if some patients who had been previously treated with specific drugs were excluded from the study described in the MSR, we are persuaded that one of ordinary skill in the art would have understood the MSR as including other patients who have been treated with a prior cancer therapy drug. We are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitations of claims 13, 28, 32, and 36 were disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have

understood from the MSR, not what it inherently discloses. (*Contra* PO Resp. 19–22.)

Accordingly, we are persuaded that claims 13, 28, 32, and 36 are anticipated by the MSR.

b) Claims 15, 30, 34, and 38

Petitioner argues that claims 15, 30, 34, and 38 are anticipated by the MSR. (*See* Pet. 30, 34, 35, 36.) Claims 15, 30, 34, and 38 require that the colorectal cancer recited in claim 1 or claim 16, respectively, be metastatic cancer. (*See* Ex. 1001, 26:22–23, 27:11–12, 28:4–5, 28:15–16.) Petitioner argues that the prior art referencing the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov to mean patients with "metastatic tumors." (*See* Pet. 30 (citing Ex. 1049,[10] 444; Ex. 1050,[11] S4; Ex. 1003 ¶¶ 97–98, 113, 118, 122).) Specifically, one 2015 publication refers to the clinical trial number of the MSR and states: "pembrolizumab is being tested in metastatic tumors with microsatellite instability, including colorectal cancer (NCT01876511)." (Ex. 1049, 444.) Another 2015 publication, entitled "Novel Therapies in Development for Metastatic Colorectal Cancer," refers to the MSR ("NCT01876511") as a "Phase II clinical trials in development investigating immunotherapy in MSI-H mCRC," wherein "mCRC" is defined as metastatic colorectal cancer. (Ex. 1050, S2, S4.)

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

Patent Owner argues that the MSR does not disclose treatment of metastatic colorectal cancer and that the disclosure of "measurable disease" is not a teaching of metastatic colorectal cancer because "measurable disease" is not synonymous with metastatic cancer. (*See* PO Resp. 19–20 (citing Ex. 2072 ¶¶ 108–112).) In support, Patent Owner cites to Dr. Neugut's testimony that "metastatic" and "measurable" are "totally different terms," wherein metastatic tumors are not necessarily measurable. (*See id.* (citing Ex. 2163, 14:9–15:12).)

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

We are persuaded by Petitioner's evidence that claims 15, 30, 34, and 38 are anticipated by the MSR.

c) Claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37

Petitioner argues that claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37 are also anticipated by the MSR. (*See* Pet. 22–35.) Aside from arguments pertaining to independent claims 1 and 16, which we have discussed above, Patent Owner does not raise any arguments specific to these dependent claims.

Briefly, Petitioner argues that claims 2 and 17, which require the biological sample to be a tumor tissue from the patient, are anticipated by the MSR because the Eligibility Criteria section of the MSR requires each patient to "[a]gree to have a biopsy of their cancer" and Dr. Neugut testifies

that one of ordinary skill in the art would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. (*See id.* at 22, 32 (citing, *inter alia*, Ex. 1005, 5–6; Ex. 1003 ¶¶ 75–76).)

Petitioner argues that claims 6, 7, 21, and 22, which require that the colorectal cancer be microsatellite high or DNA mismatch repair deficient is anticipated by the MSR because the MSR teaches treating colorectal cancer patients whose tumors are determined to be MSI-H. (*See id.* at 24, 33 (citing Ex. 1003 ¶¶ 81–84, 107, 108); Ex. 1001, 25:64–67, 26:53–56.)

Petitioner argues that claims 11 and 26, which require the pembrolizumab to be administered to the patient intravenously is anticipated by the MSR because one of ordinary skill in the art would have understood at the time that pembrolizumab for the treatment of cancer was administered intravenously. (*See id.* at 24–25, 33 (citing Ex. 1011, 134 ("We administered [pembrolizumab] intravenously."); Ex. 1054,[12] 3; Ex. 1055,[13] 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); Ex. 1003 ¶¶ 85–86, 109).)

Petitioner argues that claims 14, 29, 33, and 37, which recite "further comprising testing or having tested the patient for progression of the cancer after the treatment" were anticipated by the MSR because one of ordinary skill in the art would have understood that an "[i]mmune-related ***progression*** free survival (irPFS) rate," as disclosed in the Primary Outcome Measures

[12] Ascierto et al., *Future Perspectives in Melanoma Research: Meeting Report from the "Melanoma Bridge", Napoli, December 5th-8th 2013*, 12 J. TRANSLATIONAL MEDICINE 277 (October 2024)
[13] September 4, 2014 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

section of the MSR, is a test for disease progression. (*See* Pet. 29–30, 34 (citing Ex. 1005, 4–5, Ex. 1003 ¶¶ 95, 96, 112); Ex. 1001, 26:19–21, 27:7–9, 28:1–3, 28:12–14.)

Claims 4, 5, 12, 19, 20, 27, 31, and 35 recite specific cancers from the list recited in claims 1 and 16. For example, claims 4 and 19 recite "wherein the cancer is endometrial cancer, small bowel cancer, gastric cancer," as well as other cancers. (Ex. 1001, 25:57–59, 26:46–48.) Claims 12 and 27 recite "wherein the cancer is small bowel cancer." (*Id.* at 26:12–13, 27:1–2.) And claims 31 and 35 recite "wherein the cancer is endometrial cancer." (*Id.* at 27:12–13, 28:6–7.) Petitioner argues that one of ordinary skill in the art would have at once envisaged the MSR to include treating patients with endometrial, small bowel, and gastric cancers, for the reasons discussed above in regard to claim 1. (*See* Pet. 23, 25, 34–35 (citing Ex. 1003 ¶¶ 67–69, 77–78, 87–88).) As discussed above, after considering the record cited by both parties, we are persuaded by Petitioner's arguments.

Claims 5 and 20 recite "wherein the cancer is . . . uterine cancer," as well as other cancers. (Ex. 1001, 25:60–63, 26:49–52.) Petitioner argues that endometrial cancer is a type of uterine cancer and that one of ordinary skill in the art would have at once envisaged the MSR to include treating patients with uterine cancer as well. (*See* Pet. 24, 32 (citing Ex. 1003 ¶¶ 79–80).) Patent Owner does not argue to the contrary.

We are persuaded by Petitioner's uncontested evidence that each of claims 2, 4–7, 11, 12, 14, 17, 19–22, 26, 27, 29, 31, 33, 35, and 37 are anticipated by the MSR.

5. Summary

The preponderance of the evidence supports Petitioner's argument that the MSR teaches each and every element of the claims challenged in Ground 1. We are not persuaded otherwise by Patent Owner's arguments. Accordingly, we determine that claims 1, 2, 4–7, 11–17, 19–22, 26–38 are anticipated by the MSR.

E. Grounds 2–7: Obviousness over the MSR and Other References

Petitioner asserts six grounds of challenge against each of claims 1–38 of the '491 patent based on obviousness over the MSR and other cited references. (*See* Pet. 40–64.)

1. Claims 1, 2, 4–7, 11–17, 19–22, and 26–38

In Ground 2, Petitioner argues that the claims 1, 2, 4–7, 11–17, 19–22, 26–38, the same claims challenged under Ground 1 as being anticipated by the MSR, would also have been obvious over the MSR, Brown, Duval, and Benson. (*See* Pet. 40–51.) In Ground 3, Petitioner argues that claims 1–2, 4–7, 11, 13–17, 19–22, 26, and 28–38, claims which were also challenged under Ground 1 as being anticipated by the MSR, would have been obvious over the MSR, Brown, Duval, Benson, and Koh. (*See id.* at 51–52.) Petitioner presents Ground 2 as being an alternative to Ground 1 and Ground 3 as being an alternative to Ground 2. (*See id.* at 40, 51.) In addition, Petitioner asserts Ground 7, challenging claims 11 and 26, which were included in Ground 1, as being obvious over MSR, Brown, Duval, Benson, Koh, Hamid. (*See id.* at 59–61.)

Patent Owner argues that these challenges fail because none of the cited references discloses any of the specific MSI-H cancers recited in the claims and because none of the cited references disclose treating any patient

having the claimed MSI-H cancers "in response to" a determination that they are MSI-H. (*See* PO Resp. 32–34.) Patent Owner also argues that none of the cited references disclose previous treatment and progression after treatment, as required by dependent claims 13, 28, 32, and 36. (*See id.* at 35–36.)

As discussed above, we are persuaded that one of ordinary skill in the art would have understood that the MSR discloses treating patients with at least one of the MSI-H cancers recited in the challenged claims, "in response to" the determination that the tumor is MSI-H. As also discussed above, we are persuaded that one of ordinary skill in the art would have understood that the MSR discloses treating patients who had been treated with a prior cancer therapy drug and whose cancer had progressed after treatment with the prior drug. Accordingly, we are not persuaded that challenged claims would not have been obvious because one of ordinary skill in the art would have considered these elements to not be taught in the MSR.

Patent Owner argues further that Petitioner fails to show that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the methods recited in the challenged claims because Petitioner relies on the wrong standard and because the state of the art did not create a reasonable expectation of success. (*See* PO Resp. 36–52.) Patent Owner also argues that the Petition fails to establish a motivation to pursue the claimed treatments for the claimed MSI-H cancers, as opposed to other MSI-H cancers. (*See id.* at 52–54.)

As discussed above, we are persuaded the MSR anticipates the methods recited in claims 1, 2, 4–7, 11–17, 19–22, and 26–38, teaching each and every element of the recited methods. Patent Owner's arguments fail to

persuade us that the methods would not have been obvious, as well. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("anticipation is the epitome of obviousness"). Accordingly, the preponderance of the evidence supports Petitioner's challenges of claims 1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 as being obvious over the MSR alone or with other references and support Petitioner's challenges under Grounds 2, 3, and 7.

2. Claims 8 and 23

In Ground 4, Petitioner challenges the claims 2, 8, 17, and 23 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Chapelle. (*See* Pet. 52–54.) As discussed above, we are persuaded that claims 2 and 17 are anticipated by the MSR and, thus, would have been obvious over the MSR and other references. Accordingly, we focus on the challenge to claims 8 and 23, which were not included in Petitioner's anticipation grounds of challenge.

Claims 8 and 23 recite the method of claim 1 or 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample." (Ex. 1001, 26:1–3, 26:57–59.)

Petitioner argues that one of ordinary skill in the art "would have had motivation to combine the [MSR] (whether alone or combined with Brown, Duval, and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so." (Pet. 53–54 (citing Ex. 1003 ¶ 156).) Petitioner cites Chapelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claims 8 and 23. (*See id.* at 54 (citing Ex. 1007, 3380, 3384; Ex. 1003 ¶ 156).) Petitioner argues further that the '491 patent does not suggest that the

method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (*See id.* (citing Ex. 1003 ¶ 157); *see* Ex. 1001, 6:25–26 ("Testing of MSI can be accomplished by any means known in the art").)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 155–157, 159.)

Patent Owner does not present specific arguments against Petitioner's challenge to claim 8 or 23 regarding the teachings of the MSR and Chapelle or Dr. Neugut's testimony.

3. Claims 3 and 18

In Ground 5, Petitioner challenges claims 3 and 18 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Steinert. (*See* Pet. 54–56.) Claims 3 and 18 recite the method of claim 1 or 16, respectively, "wherein the biological sample is a body fluid from the patient." (Ex. 1001, 25:55–56, 26:44–45.)

Petitioner argues that the methods of claims 3 and 18 would have been obvious to one of ordinary skill in the art in view of the general knowledge in the art, such as Steinert, which teaches determining whether a tumor is MSI-H to understand how cancer evades the immune system. (*See* Pet. 54–55 (citing Ex. 1008, OF1; Ex. 1003 ¶¶ 161, 163).) Specifically, Petitioner argues that Steinert teaches methods of testing whether a tumor was MSI-H using body fluid, specifically blood samples. (*See id.* at 55 (citing Ex. 1008, OF6; Ex. 1003 ¶¶ 161, 164).) Petitioner argues that one of ordinary skill in the art "would have had motivation to combine the MSI-H Study Record

(whether alone or combined with Brown, Duval, and Benson) and Steinert." (*Id.* (citing Ex. 1003 ¶ 164).)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 160–165.)

Patent Owner does not present specific arguments against Petitioner's challenge to claim 3 or 18 regarding the teachings of the MSR and Steinert or Dr. Neugut's testimony.

4. Claims 9, 10, 24, and 25

In Ground 6, Petitioner challenges claims 9, 10, 24, and 25 as being obvious over the MSR, Brown, Duval, Benson, Koh, and Salipante. (*See* Pet. 56–59.) Claims 9 and 24 recite the methods of claims 1 and 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample." (Ex. 1001, 26:4–6, 26:60–61.) Claims 10 and 25 recite the methods of claims 1 and 16, respectively, "wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample." (*Id.* at 26:7–9, 26:63–65.) Petitioner cites the teaching in Salipante of testing a tumor for microsatellite instability high using a PCR test or next generation sequencing on a sample. (*See* Pet. 56–60 (citing Ex. 1010, 1192 ("PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use."), 1193 ("Here we describe an approach for determination of MSI by [next generation DNA sequencing] (mSINGS) based on microsatellite markers which are incidentally included in targeted gene capture sequencing data."); Ex. 1003 ¶¶ 167–174).) Petitioner argues that one of ordinary skill

in the art "would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Salipante." (*See* Pet. 56, 58 (citing Ex. 1003 ¶¶ 170, 174).)

We find that Dr. Neugut's testimony and the cited references as recounted above support Petitioner's arguments. (*See* Ex. 1003 ¶¶ 167–174.)

Patent Owner does not present specific arguments against Petitioner's challenge to claims 9, 10, 24, and 25 regarding the teachings of the MSR and Salipante or Dr. Neugut's testimony.

5. Patent Owner's Arguments

Patent Owner does not raise specific arguments against any of the challenges to claims 3, 8–10, 18, and 23–25 as being obvious. Rather, as discussed above, Patent Owner argues that one of ordinary skill in the art would not have reasonably expected the claimed method to work in all of the recited MSI-H cancers and would not have treated patients with all of the recited MSI-H cancers. (*See* PO Resp. 32–33; PO Sur-Reply 15–18.) Patent Owner also argues that none of the references cited in addition to the MSR teach or disclose treating a patient with the recited cancers "in response to" a determination of MSI-H and that none of the cited references would have provided one of ordinary skill in the art with a reasonable expectation of success or motivation for accomplishing the claimed methods. (*See* PO Resp. 33–34.)

Patent Owner argues that the cited references do not "supply the missing previous treatment and progression after treatment," required in claims 13, 15, 28, 30, 32, 34, 36, and 38, but does not present any other arguments about the limitations of individual dependent claims. (*Id.* at 35.)

For example, Patent Owner argues that Benson and Koh do not require prior treatment, progression on a prior therapy, or metastatic disease before a patient is enrolled in clinical trials, but Patent Owner does not address the grounds of challenge based on Chapelle, Steinert, or Salipante individually. (*See id.* at 35–54.)

Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, we are persuaded that Petitioner has established that one of ordinary skill in the art would have had a reasonable expectation of success in achieving a method comprising these steps, with the results being inherent. *See MEHL/Biophile*, 192 F.3d at 1366 ("Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the articles' authors did not appreciate the results."). Petitioner presents persuasive evidence that one of ordinary skill in the art would have had a reasonable expectation of success in making a method that tests for MSI-H with immunohistochemistry, polymerase chain reaction, or next generation sequencing, that uses a bodily fluid, as recited in the challenged dependent claims, and Patent Owner does not argue or present evidence to the contrary. Accordingly, we are persuaded that Petitioner has met its burden of presenting a *prima facie* case for the obviousness of the challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. (*See* PO Resp. 55–84.) The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. (*See id.*) Because we determine, as discussed above,

that the methods recited in the independent claims are anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 16. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("secondary considerations are not an element of a claim of anticipation."). Similarly, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of dependent claims 1, 2, 4–7, 11–17, 19–22, 26–38, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8–10, 18, and 23–25), Patent Owner must show a nexus between the claimed methods and the evidence of non-obviousness. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("to be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a 'nexus' to the claims, *i.e.*, there must be 'a legally and factually sufficient connection' between the evidence and the patented invention. . . . Ultimately, '[t]he patentee bears the burden of showing that a nexus exists.'" (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988), *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999)).

Patent Owner highlights portions of the Keytruda® (pembrolizumab) label that discuss testing a patient's tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claims 8, 9, 23, and 24. (*See* PO Resp. 59–60; PO Sur-Reply 18–20.) But Patent Owner does not direct us to evidence of a nexus to limitations recited in the dependent claims, for example to claims 3 and 18, which recite testing a

biological sample that is a bodily fluid, or claims 10 and 25, which recite testing that comprises carrying out next generation sequencing.

Furthermore, Patent Owner's arguments address the methods of independent claims 1 and 16, not the limitations of the claims Petitioner challenges as being obvious. (*See* PO Resp. 66–84.) Patent Owner directs us only to evidence regarding treating patients determined to have MSI-H cancers with pembrolizumab, which we determine to be anticipated by the MSR. When evidence of a "secondary consideration is exclusively related to a single feature that is in the prior art," our reviewing court has held the evidence is of no relevance to the obviousness inquiry. *See Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1363–65 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 499 (2023) (distinguishing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330–31 (Fed. Cir. 2016)); *see also Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."). In *Yita*, the prior art taught close-conformance of a floor tray with the walls of a vehicle foot well, which one of ordinary skill in the art would have had reason to use in combination with other prior-art teachings to arrive at the claimed invention. *See Yita*, 69 F.4th at 1359–61. The court held that because the asserted evidence of secondary consideration related exclusively to close-conformity, the evidence was not persuasive of non-obviousness, even though the claimed floor tray was coextensive with the product that produced the evidence. *See id.* at 1364–65 ("The coextensiveness inquiry bears only on the presumption of nexus; it does not decide the overall nexus question.").

Because Patent Owner directs us only to evidence that the methods recited in claims 1 and 16 produced evidence of secondary considerations, we are not persuaded that this evidence is persuasive of the non-obviousness of the specific methods recited in the dependent claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claims 3 and 18, or wherein the testing comprises immunohistochemistry, polymerase chain reaction or next generation sequencing, as in claims 8–10 and 23–25, demonstrated unexpected results or commercial success.

Following a review of the evidence, including Patent Owner's evidence of secondary considerations with regard to the subject matter of claim 1, we conclude that Petitioner has demonstrated by a preponderance of the evidence that the methods of claims 3, 8–10, 18, and 23–25 would have been obvious.

6. Summary

The preponderance of the evidence supports Petitioner's argument that the challenged claims would have been obvious over the MSR and the other references Petitioner cites. Patent Owner does not persuade us otherwise. Accordingly, we determine that claims 1–38 are rendered obvious by the MSR and the other cited references.

III. CONCLUSION[14]

Based on the fully developed trial record, Petitioner has demonstrated by a preponderance of the evidence that claims 1–38 of the '491 patent are unpatentable.

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 4–7, 11–17, 19–22, 26–38	102	MSR	1, 2, 4–7, 11–17, 19–22, 26–38	
1, 2, 4–7, 11–17, 19–22, 26–38	103	MSR, Brown, Duval, Benson	1, 2, 4–7, 11–17, 19–22, 26–38	
1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	103	MSR, Brown, Duval, Benson, Koh	1–2, 4–7, 11, 13–17, 19–22, 26, 28–38	
2, 8, 17, 23	103	MSR, Brown, Duval, Benson, Koh, Chapelle	2, 8, 17, 23	
3, 18	103	MSR, Brown, Duval, Benson, Koh, Steinert	3, 18	

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

9, 10, 24, 25	103	MSR, Brown, Duval, Benson, Koh, Salipante	9, 10, 24, 25	
11, 26	103	MSR, Brown, Duval, Benson, Koh, Hamid	11, 26	
Overall Outcome			1–38	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–38 of the '491 patent have been shown to be unpatentable; and

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

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