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Paper 90
Date: June 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

IPR2024-00240
Patent 11,591,393 B2

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

KATZ, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner, Merck Sharp & Dohme LLC, filed a Petition to institute an *inter partes* review of all claims, namely claims 1–42, of U.S. Patent No. 11,591,393 B2 ("the '393 patent") pursuant to 35 U.S.C. § 311(a). (Paper 1 ("Pet.") 1, 3–5.) Patent Owner, The Johns Hopkins University, filed a Preliminary Response pursuant to 37 C.F.R. § 42.107(b). (Paper 5 ("Prelim. Resp.").) In addition, as authorized (*see* Ex. 3001), Petitioner filed Petitioner's Reply to Patent Owner's Preliminary Response (Paper 8) and Patent Owner filed Patent Owner's Sur-Reply (Paper 9). We granted the Petition and instituted an *inter partes* review. (Paper 10 ("Decision" or "Dec.").)

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

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

We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial.[1] For the reasons discussed below, we

[1] To the extent this Final Written Decision includes portions of the record that are presently sealed, the parties may meet and confer concerning whether any portions of this Decision should be redacted before it is made available to the public. If any party maintains that redactions to the Final Written Decision should be made, that party may, within seven (7) days of entry of the Final Written Decision, submit a proposed redacted and publicly-available version of the Final Written Decision along with a motion to seal explaining why the redactions are necessary and outweigh any public

determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–42 of the '393 patent are unpatentable.

A. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. (*See* Pet. 67.) Patent Owner identifies The Johns Hopkins University as its real party-in-interest. (*See* Paper 4, 1.)

B. Related Matters

Both Petitioner and Patent Owner report that the litigation *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), is a related matter. (*See* Pet. 67; Paper 4, 1.)

In addition, several other inter partes reviews are related to this proceeding, including IPR 2024-00622, challenging the claims of U.S. Patent No. 10,934,356; IPR2024-00623, challenging claims of U.S. Patent No. 11,325,974 B2; IPR2024-00624, challenging the claims of U.S. Patent No. 11,325,975 B2; IPR2024-00625, challenging claims of U.S. Patent No. 11,339,219 B2; IPR2024-00647, challenging claims of U.S. Patent No. 11,649,287 B2; IPR2024-00648, challenging claims of U.S. Patent No. 11,643,462 B2; IPR2024-00649, challenging claims of U.S. Patent No. 11,629,187 B2; IPR2024-00650, challenging claims of U.S. Patent No. 11,634,491 B2.

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interest in the redacted information. Any opposition to such motion must be filed within ten (10) days after the motion is filed. If no motion is filed within the timeline set forth above or if the parties otherwise inform the Board (via email to trials@uspto.gov) that no redactions are necessary, the Final Written Decision will be made available to the public in unredacted form.

C. The '393 Patent

The application that became the '393 patent was filed on September 2, 2021, claiming priority to a number of continuation applications and also to provisional application 62/190,977, which was filed July 10, 2015. (*See* Ex. 1001, codes (22), (60).) The '393 patent cites another provisional application, filed November 13, 2014, but Patent Owner claims priority only to July 10, 2015. (*See* PO Resp. 4, n.2.)

The '393 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor, in colorectal cancer ("CRC") patients. (*See* Ex. 1001, Abstract.) More specifically, the '393 patent is directed to treating cancer patients with high mutational burdens, such as found in microsatellite instable (MSI) cancer, with anti-PD-1 antibodies. (*Id.* at 3:40–53.) The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in a clinical trial. (*Id.* at 8:52–56.)

Claim 1 of the '393 patent recites:

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

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

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

The parties refer to the term "microsatellite instability high" as "MSI-H" and the term "mismatch repair deficient" as "dMMR." The parties agree that testing for either MSI-H or dMMR is considered the equivalent of testing for the other condition, and refer most often to MSI-H as the identified condition. (*See* Pet. 6; PO Resp. 4, n.1.)

D. Evidence

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

Name	**Reference**	**Exhibit**
MSR (MSI-H Study Record)	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1	1005
Pernot	Pernot et al., Colorectal Cancer and Immunity: What We Know and Perspectives, 20(14) World J. Gastroenterology 3738 (April 2014)	1006
Chapelle	Chapelle et al., Clinical Relevance of Microsatellite Instability in Colorectal Cancer, 28(20) J. Clinical Oncology 3380 (2010)	1007
Steinert	Steinert et al., Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer, 74(6) Cancer Research OF1 (March 2014)	1008
Benson	Benson et al., Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014)	1009
Salipante	Salipante et al., Microsatellite Instability Detection by Next Generation Sequencing, 60(9)	1010

	Clinical Chemistry 1192 (2014)	
Hamid	Hamid et al., Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma, 369(2) New Eng. J. Medicine 134 (July 2013)	1011

E. Prior Art and Asserted Grounds

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

	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42	102	MSR
2	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24–25, 27–42	103	MSR, Pernot
3	2, 8, 15, 21	103	MSR, or MSR, Pernot, Chapelle
4	3, 16	103	MSR, or MSR, Pernot, Steiner
5	7, 20, 29, 30, 32, 34, 36–42	103	MSR, or MSR, Pernot, Benson
6	9, 10, 22, 23	103	MSR, or MSR, Pernot, Salipante
7	11, 12, 24, 25	103	MSR, or MSR, Pernot, Hamid
8	13, 26	103	MSR, or MSR, Pernot, Steinert, Hamid

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

II. ANALYSIS

A. Legal Standards

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

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

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

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

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

B. Level of Ordinary Skill in the Art and Declarants

The parties rely on the testimony of witnesses for their opinions on what one of ordinary skill in the art would have known and understood at the relevant time. Specifically, Petitioner relies on the testimony of Alfred L. Neugut, M.D., Ph.D., M.P.H.[3] (Ex. 1003) and Paul E. Oberstein, M.D. (Ex. 1150). Patent Owner relies on the testimony of Nils Lonberg, Ph.D. (Ex. 2001) and Richard Goldberg, M.D. (Ex. 2090).

Petitioner and Patent Owner characterize one of ordinary skill in the art differently. To Petitioner, the ordinarily skilled artisan would be a medical doctor, or a professional in a related field, with experience treating cancer or access to those with experience in clinical studies of therapeutics

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

and to a pathologist with this experience. (*See* Pet. 12 (citing Ex. 1003 ¶ 19).) To Patent Owner, the ordinarily skilled artisan would have had a medical or graduate-level degree, or equivalent work experience, in the fields of immunology, genetics, or a related field and would have experience (i) conducting immunology research relating to oncology, (ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. (*See* PO Resp. 5 (citing Ex. 2072 ¶¶ 31–32, 83).) Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

As we discussed in the Decision to institute trial, the '393 patent claims a method of treating a human patient with colorectal cancer having certain characteristics using pembrolizumab and the main prior art reference cited by Petitioner discloses testing pembrolizumab to treat human patients. (*See* Ex. 1001, 25:40–50, Ex. 1005; *see* Decision 8–9.) Accordingly, the relevant field of Patent Owner's claims is treating human patients, as well as testing existing compounds. Neither party directs us to evidence of the level of skill in the art beyond what we considered for institution of trial.

In the Decision to institute trial, we determined that the level of skill in the art relevant to the claims of the '393 patent is not limited to knowledge of and experience with conducting research relating to oncology or developing and conducting clinical trials. (*See* Dec. 8–9.) We determined that the level of skill also includes knowledge of and experience with treating colorectal cancer patients with immunotherapy compounds, identifying the conditions these patients may have, and understanding the literature regarding clinical trials for such colorectal cancers and the

associated conditions and immunotherapy. (*See id.*) Because the parties do not present additional evidence or argument, we maintain that determination.

C. Claim Construction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

D. Ground 1: Anticipation over the MSR

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

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

The MSR reports a "Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors." (Ex. 1005, 2.) The parties' witnesses agree that MK-3475 is pembrolizumab, the compound recited in claim 1. (*See* Neugut Decl., Ex. 1003 ¶ 37; *see* Lonberg Decl., Ex. 2001, ¶ 65.) Patent Owner does not dispute Petitioner's assertion that the MSR was published on a government web site on June 10, 2013, more than two years before the priority date of the '393 patent on July 10, 2015. (*See* Pet. 7 (citing Ex. 1005, 3, Ex. 1003 ¶ 35).)

The MSR includes a "Brief Summary," explaining that

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

(Ex. 1005, 3.) Two of the outcome measures reported in the MSR are "[i]mmune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" (Ex. 1005, 4–5.) The MSR provides "Arms and Interventions" as follows[6]:

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

(Ex. 1005, 4.) The chart above identifies three patient populations, including "MSI Positive Colorectal Cancer," "MSI Negative Colorectal Cancer," and "MSI Positive Non-Colorectal Cancer," and the same therapeutic intervention for each of the populations: "MK-3475 10 mg/kg every 14 days." (*Id.*)

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

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

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

2. Claim 1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Patent Owner next disputes Petitioner's reliance on *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), to support the assertion of inherent anticipation of the claimed method. (*See* PO Resp. 25–29; Pet. 17 ("In *In re Montgomery*, the Federal Circuit held that a document disclosing a planned clinical study inherently anticipated method of treatment claims even where the method of treatment had not yet been practiced.").) Patent Owner argues that because the MSR is only an initial submission for an experimental trial that had not yet begun recruiting patients or obtaining experimental data, it was merely an "invitation to investigate" from which the results claimed by the '393 Patent did not "inevitably flow." (PO Resp. 25.)

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

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

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded, but we are not persuaded the MSR is so vague it does not teach the steps expressly recited in claim 1. Regardless of the inventors' intent in publishing the MSR as a Stage II clinical trial on the www.clinicaltrials.gov website, as discussed above, we determine that the MSR teaches testing a biological sample from a colorectal cancer patient to determine if the cancer is MSI-H or dMMR and treating patients with MSI-H or dMMR colorectal cancer with a therapeutically effective amount of pembrolizumab in response to the determination the cancer is MSI-H or dMMR. (*See*, *e.g.*, Ex. 1005, 4 (Arms and Interventions).) The result of drug treatment inherently follows its administration. The MSR does not merely suggest that pembrolizumab may be useful in some unidentified subset of colorectal cancer patients or suggest that some unidentified drug may be useful for MSI-H colorectal cancer patients. Instead, the MSR discloses testing for the condition recited in claim 1 and treating with the drug recited in claim 1 if the condition is met. *See Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (holding that the prior art did not inherently anticipate where it failed to mention specific vitamin deficiencies, instead merely inviting further experimentation to find associations with metabolic pertubations).)

Montgomery states that "even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps," referring to a claimed method of treating or preventing stroke, which was held to be

anticipated by the publication of a proposed study. 677 F.3d at 1381. Patent Owner attempts to distinguish the size and apparent surety of the study in *Montgomery* from the MSR. (*See* PO Resp. 28.) But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H colorectal cancer, we are persuaded that the MSR anticipates the results of administration of the drug treatment recited in those steps. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by Kris. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent."). Whether or not the MSR could have provided results or was sufficient for full regulatory approval does not change that the MSR teaches Patent Owner's claimed steps.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. (*See* PO Resp. 29–36.) Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. (*See id.* at 29 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998).) According to Patent Owner, the experimental use negation applies to the MSR under a 13-factor analysis provided in *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002). (*See* PO Resp. 31–36.) For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test treatment in humans, there being no animal models, and had to publish the MSR on the government website under federal law. (*See* PO Resp. 30–32.) Patent Owner argues further that the inventors had control

over the MSI-H clinical study and that the field of cancer treatment was highly unpredictable, among other facts. (*See id.* at 32–36.) Patent Owner argues that "[a]t that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun." (*Id.* at 34.)

Petitioner disagrees, arguing that "[i]t is well established that there is no requirement under §101 or §112 that evidence from human clinical trials must be provided for patentability." (Pet. Reply 19 (citing *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"); *Ex parte Balzarini*, 21 USPQ2d 1892 (BPAI 1991) (holding that even in situations where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials.)).) Petitioner notes that Patent Owner filed a provisional patent application on November 13, 2014, which, although also filed more than a year after the publication of the MSR, disclosed no clinical results or data. (Pet. Reply 19–20 (citing Ex. 1001, cover; Ex. 1030, 1).)

Patent Owner disputes Petitioner's assertions about the requirements for patentability, arguing that "[t]he uncertainty surrounding the amount of disclosure required to support a patent reinforces the importance of experimental use negation, especially in highly unpredictable fields such as cancer treatment." (PO Sur-Reply 13–14 (footnote omitted).) But Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSR and was denied an earlier filing date. We are not persuaded by Patent Owner's assertion that "there

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

The Supreme Court was concerned that "[i]t is sometimes said that an inventor acquires an undue advantage over the public by delaying to take out a patent, inasmuch as he thereby preserves the monopoly to himself for a longer period than is allowed by the policy of the law," but held that "when the delay is occasioned by a *bona fide* effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended," the experiment use exception can preserve the inventor's rights. *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 137 (1877). Because we are not persuaded that Patent Owner could not have filed an earlier application, we are not persuaded that the experimental use doctrine is properly applied in this case, particularly given that clinical trial protocols published on the ClinicalTrials.gov website have been successfully asserted as prior art in other cases. *See Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir.), *cert. denied*, 145 S. Ct. 567 (2024), and *cert. denied*, 145 S. Ct. 983 (2024).

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

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

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

3. Independent Claim 14

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

4. Dependent claims

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

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

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

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

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

"In an anticipation analysis, the dispositive question is whether a skilled artisan would 'reasonably understand or infer' from a prior art reference that every claim limitation is disclosed in that single reference." *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020). Extrinsic evidence, such as declarations and depositions may be considered when it is used to explain, but not expand, the meaning of a reference. *See In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991) (holding that the depositions and declarations of skilled workers were properly used to show what those skilled in the art would have known about the prior art). We credit Dr. Neugut's and Dr. Oberstein's testimony about what one of ordinary skill in the art would have understood after reviewing the MSR.

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

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

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

Patent Owner's evidence is directed to the general knowledge in the field, not to the specific understandings of one of ordinary skill in the art when reviewing the MSR, such as the testimony of a witness regarding the content of the MSR. Patent Owner cites Dr. Lonberg's testimony that the MSR "says ***nothing*** about cancer progression" and that three years later it was updated with a statement requiring prior cancer treatment, but he does not directly contradict Dr. Neugut's or Dr. Oberstein's testimony about the MSR as it was published in 2013. (*See* Ex. 2072 ¶ 102 (citing Ex. 2165); *see* PO Resp. 21–22.) Dr. Lonberg disagrees with Dr. Neugut's interpretation of the term "measurable disease" in the MSR. (*See* Ex. 2072 ¶ 102 ("While ***measurable cancer*** refers to a cancer that has a minimum size (e.g., as determined by imaging), this has little to do with whether or not a patient's cancer has ***progressed*** after the patient received prior therapies.").) But Dr. Lonberg fails to testify that one of ordinary skill in the art would not have understood the MSR in 2013 to teach treating patients who had received prior/different cancer therapies, wherein the patients' cancer had progressed after the patients received the prior/different cancer therapies.

On the balance, we find Petitioner's evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. As Patent Owner argues, the MSR was updated in 2016, wherein "[p]atients

with colon cancer must have received at least two prior cancer therapy regimens," but the claims of the cited claims of the '393 patent encompass only one prior therapy. Therefore, the update does not by itself indicate the MSR as it appeared in 2013 was not within the scope of the challenged claims. (*See* Ex. 1150 ¶ 77.) It is also not clear why the MSR was updated – was it a change to the study or merely a clarification? The update by itself is not dispositive of whether one of ordinary skill in the art would have understood the 2013 version of the MSR cited by Petitioner to teach treating patients who had received a "different cancer therapy" or "prior cancer therapy," and the patient's cancer to have progressed "after the patient received the different cancer therapy" or "following the prior cancer therapy." We find Dr. Neugut's and Dr. Oberstein's testimony, and Dr. Lonberg's lack of clear testimony to the contrary, persuasive as to this issue.

In light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would "reasonably understand or infer" that the limitations of claims 7, 20, 32, 34, 36, 38, 40, and 42 were disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. (*Contra* PO Resp. 19–22.)

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

b) Claims 29 and 30

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

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

Petitioner argues further that other prior art, referring to the MSR indicates that physicians understood the MSR to be for patients with metastatic tumors. (*See* Pet. 32–33 (citing (Ex. 1049, 444; *see also* Ex. 1050, S4; Ex. 1003 ¶ 90.) Specifically, one 2015 publication refers to the clinical trial number of the MSR and states: "pembrolizumab is being tested in metastatic tumors with microsatellite instability, including colorectal cancer (NCT01876511)." (Ex. 1049, 444.) Another 2015 publication, entitled "Novel Therapies in Development for Metastatic Colorectal Cancer," refers to the MSR ("NCT01876511") as a "Phase II clinical trials

in development investigating immunotherapy in MSI-H mCRC," wherein "mCRC" is defined as metastatic colorectal cancer. (Ex. 1050, S2, S4.)

Patent Owner argues that the MSR does not disclose treatment of metastatic colorectal cancer and that the disclosure of "measurable disease" is not a teaching of metastatic colorectal cancer because "measurable disease" is not synonymous with metastatic cancer. (*See* PO Resp. 22.) In support, Patent Owner cites to Dr. Neugut's testimony that "metastatic" and "measurable" are "totally different terms," wherein metastatic tumors are not necessarily measurable. (*See* PO Resp. 23 (citing Ex. 2163:14:9–15:12).)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

e) Summary

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

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

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

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

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

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

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

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

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

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

Petitioner cites Pernot as teaching that colorectal cancer patients are good candidates for immunotherapy, such as the PD-1 inhibitor pembrolizumab, to address the expectation of success in the method of claim 1. (*See* Pet. 43 (citing Ex. 1006, 3741).) Pernot states "[colorectal cancers] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy." (Ex. 1006, 3740–41; *see* Pet. 10.) Petitioner argues, citing Dr. Neugut's testimony, that Pernot would have motivated one of ordinary skill in the art to obtain the results of the MSI-H Study Record. (*See* Pet. 43 (citing Ex. 1003 ¶ 108).)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Petitioner cites Hamid for its teaching of administering pembrolizumab (called "lambrolizumab") intravenously. (Pet. 61–63 (citing Ex. 1011, 134; Neugut Decl., Ex. 1003 ¶ 166).) Petitioner relies on Dr. Neugut's testimony to argue that one of ordinary skill in the art would have had a motivation to combine the MSR (alone or combined with Pernot) and Hamid because the MSR discloses administering pembrolizumab, Hamid demonstrates success in treating patients with advanced cancer with pembrolizumab, and the prior art only discloses intravenous administration of pembrolizumab to treat cancer patients. (*See* Pet. 61–62 (citing Ex. 1011, 134; *see also* Ex. 1055, 1, Ex. 1003 ¶¶ 168–169).) Petitioner argues that one of ordinary skill in the art would have had a reasonable expectation of success in administering pembrolizumab intravenously, given that administering pembrolizumab intravenously had been successful in the past. (*See id.*)

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

5. Patent Owner's Arguments

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

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

Patent Owner argues only that Petitioner applies the wrong legal standard to argue that there would have been a reasonable expectation of success in the methods recited in independent claims 1 and 14. (*See* PO Resp. 39–55.) For example, Patent Owner argues that neither the MSR, Pernot, any other reference cited by Petitioner, nor the state of the art provides a reasonable expectation in using MSI status as an indicator of successful treatment with pembrolizumab. (*See id.* at 41–55.) Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, we are persuaded that Petitioner has established that one of ordinary skill in the art would have had a reasonable expectation of success in achieving a method comprising these steps, with the results being inherent. *See Mehl/Biophile*, 192 F.3d at 1366 ("Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the articles' authors did not appreciate the results."). Petitioner presents persuasive evidence that one of ordinary skill in the art would had a reasonable expectation of success in making a method that tests for MSI-H with immunohistochemistry, polymerase chain reaction, or next generation sequencing, that uses a bodily fluid, or that uses

intravenous administration of pembrolizumab, as recited in the challenged dependent claims, and Patent Owner does not argue or present evidence to the contrary. Accordingly, we are persuaded that Petitioner has met its burden of presenting a *prima facie* case for the obviousness of the challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. (*See* PO Resp. 57–91.) The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. (*See id.*) Because we determine, as discussed above, that the methods recited in the independent claims are anticipated by the MSR, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 14. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) ("secondary considerations are not an element of a claim of anticipation."). Similarly, Patent Owner's objective evidence of non-obviousness is not persuasive of the patentability of dependent claims 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42, which we determine are anticipated by the MSR.

Regarding the dependent claims that Petitioner challenges only on obviousness grounds (claims 3, 8, 9, 10, 13, 16, 21, 22, 23, 26), Patent Owner must show a nexus between the claimed methods and the evidence of non-obviousness. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("to be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a 'nexus' to the claims, *i.e.*, there must be 'a legally and factually sufficient connection' between the evidence and the patented invention. . . .

Ultimately, '[t]he patentee bears the burden of showing that a nexus exists.'" (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988), *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999)).

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

Even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 14, not the limitations of the claims Petitioner challenges as being obvious. (*See* PO Resp. 68–91.) Patent Owner directs us only to evidence regarding treating patients determined to have MSI-H colorectal cancer with pembrolizumab, which we determine to be anticipated by the MSR. When evidence of a "secondary consideration is exclusively related to a single feature that is in the prior art," our reviewing court has held the evidence is of no relevance to the obviousness inquiry. *See Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1363–65 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 499 (2023) (distinguishing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330–31 (Fed. Cir. 2016)); *see also Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) ("[I]f the feature that creates the

commercial success was known in the prior art, the success is not pertinent."). In *Yita*, the prior art taught close-conformance of a floor tray with the walls of a vehicle foot well, which one of ordinary skill in the art would have had reason to use in combination with other prior-art teachings to arrive at the claimed invention. *See Yita*, 69 F.4th at 1359–61. The court held that because the asserted evidence of secondary consideration related exclusively to close-conformity, the evidence was not persuasive of non-obviousness, even though the claimed floor tray was coextensive with the product that produced the evidence. *See id.* at 1364–65 ("The coextensiveness inquiry bears only on the presumption of nexus; it does not decide the overall nexus question.").

Because Patent Owner directs us only to evidence that the methods recited in claims 1 and 14 produced evidence of secondary considerations, we are not persuaded that this evidence is persuasive of the non-obviousness of the specific methods recited in the dependent claims. For example, Patent Owner fails to direct us to evidence that a method of treating MSI-H colorectal cancer in a patient "wherein the biological sample is a body fluid from the patient," as recited in claim 3, or "wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample," as recited in claim 10, demonstrated unexpected results or commercial success.

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

6. Summary

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

III. CONCLUSION[7]

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

In summary:

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

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

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
14, 15, 17–20, 24, 25, 27–42			17–20, 24, 25, 27–42	
2, 8, 15, 21	103	MSR, or MSR, Pernot, Chapelle	2, 8, 15, 21	
3, 16	103	MSR, or MSR, Pernot, Steiner	3, 16	
7, 20, 29, 30, 32, 34, 36–42	103	MSR, or MSR, Pernot, Benson	7, 20, 29, 30, 32, 34, 36–42	
9, 10, 22, 23	103	MSR, or MSR, Pernot, Salipante	9, 10, 22, 23	
11, 12, 24, 25	103	MSR, or MSR, Pernot, Hamid	11, 12, 24, 25	
13, 26	103	MSR, or MSR, Pernot, Steinert, Hamid	13, 26	
Overall Outcome			1–42	

IV. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1–42 of the '393 patent have been shown to be unpatentable; and

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

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