

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

IPR2024-00624
Patent 11,325,975 B2

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

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background and Summary

Merck Sharp & Dohme LLC (“Petitioner”) filed a Petition requesting *inter partes* review of claims 1–4, 6–10, and 12–15 of U.S. Patent No. 11,325,975 B2 (Ex. 1001, “the ’975 patent”). Petition (“Pet.”), Paper 1. The Johns Hopkins University (“Patent Owner”) filed a Preliminary Response. Preliminary Response (“Prelim. Resp.”), Paper 5. In addition, as authorized (Paper 7), Petitioner filed a Preliminary Reply to Patent Owner’s Preliminary Response (Paper 8) and Patent Owner filed a Preliminary Sur-reply (Paper 10).

We instituted trial on September 23, 2024. Paper 11. During trial, Patent Owner filed a Patent Owner Response to the Petition (Paper 34 (confidential Paper 31) (“PO Resp.”)), Petitioner filed a Reply (Paper 52 (confidential Paper 49) (“Pet. Reply”)), and Patent Owner filed a Sur-reply (Paper 56 (confidential Paper 53) (“PO Sur-Reply”)). The parties declined to present oral arguments in this proceeding. Paper 57.

We have jurisdiction under 35 U.S.C. § 6, and this Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during the trial. For the reasons discussed below, we determine that Petitioner has proven, by a preponderance of the evidence, that claims 1–4, 6–10, and 12–15 of the ’975 patent are unpatentable.

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 63. Patent Owner identifies The Johns Hopkins University as its real party-in-interest. Paper 3, 1 (Mandatory Notices) .

C. Related Matters

The parties indicate that the '975 patent is involved in *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), filed November 29, 2022. Pet. 63; Paper 3, 1. Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00648 against U.S. Patent No. 11,643,462; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 63; Paper 3, 1.

D. The '975 patent (Ex. 1001)

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

The '975 patent explains that

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

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

Id. at 1:49–56. According to the '975 patent, “[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types.” *Id.* at 1:67–2:3.

However, the specification describes that

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

Id. at 2:57–3:1. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '975 patent describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id.* at 3:8–14. The Specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id.* at 8:47–52. According to the '975 patent, “[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors.” *Id.* at 6:44–48.

E. The Challenged Claims

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

1. A method for treating cancer in a patient in need thereof, wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, comprising: administering an effective amount of an anti-PD-1 antibody to the patient; wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-I antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and wherein the patient has received a prior cancer therapy drug.

Ex. 1001, 25:51–66.

Representative independent claim 9 is reproduced below:

9. A method for treating cancer in a patient in need thereof, wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, the patient having received a prior cancer therapy drug to treat the tumor, the method comprising: administering an effective amount of an anti-PD-1 antibody to the patient; wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient.

Id. at 26:28–42.

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1005, MSI-H Study Record, ClinicalTrials.gov, NCT01876511, “Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C),” (June 10, 2013) available at <https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1> (“MSI-H Study Record” or “MSR”).

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

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

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

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

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

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

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

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

G. Asserted Grounds of Unpatentability

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

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

H. Claim Construction

The parties do not assert constructions of any terms recited in the challenged claims other than that their ordinary and customary meanings should apply. Pet. 11–12; PO Resp. 6.

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

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

I. Level of Ordinary Skill in the Art

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

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

Pet. 12 (citing Ex. 1003 ¶ 19). To Patent Owner, the ordinarily skilled artisan would have had a medical or graduate-level degree, or equivalent work experience, in the fields of immunology, genetics, or a related field and would have experience (i) conducting immunology research relating to oncology, (ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. PO Resp. 6 (citing Ex. 2072 ¶¶ 31–32, 86–94). Thus, Petitioner and Patent Owner characterize one of ordinary skill in the art differently.

Petitioner emphasizes medical and treatment aspects in its characterization of an ordinarily skilled artisan, whereas Patent Owner emphasizes research aspects.

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

Ex. 1005. Accordingly, the relevant field of Patent Owner's claims is treating human patients for cancer, as well as testing existing compounds for use in treatment modalities.

In light of the extent of the relevant field, we determine that the level of skill in the art relevant to the claims of the '975 patent is not limited to knowledge of and experience with conducting research relating to oncology or developing and conducting clinical trials, but includes knowledge of and experience with treating cancer patients with immunotherapy compounds, identifying the conditions these patients may have, and understanding the literature regarding clinical trials for such colorectal cancers and the associated conditions and immunotherapy.

II. ANALYSIS

A. *Legal Standards*

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

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

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

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

B. Summary of the Cited Prior Art

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

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

The MSR includes a “Brief Summary,” explaining that

[t]his study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-

tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers.

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

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

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

2. *Pernot (Ex. 1006)*

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

response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy.” *Id.* at 3741.

3. *Chapelle (Ex. 1007)*

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

4. *Benson (Ex. 1009)*

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

5. *Hamid (Ex. 1011)*

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

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

6. *Brown (Ex. 1034)*

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

7. *Duval (Ex. 1087)*

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

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

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

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

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

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

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

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

1. *Independent Claim 1*

a) *Preamble: “A method for treating cancer in a patient in need thereof, comprising:”*

To begin, Petitioner cites the teaching in the Arms and Interventions section as a method of treating cancer patients, as recited in the preamble of claim 1. Pet. 18–19 (citing Ex. 1005, 4 (Arms and Interventions); *see also id.* at 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility), Ex. 1003 ¶ 62).

Patent Owner does not raise any arguments regarding this limitation, and neither party argues that the preamble is limiting. To the extent that the

preamble is limiting, we agree with Petitioner that the MSR teaches the preamble.

b) *Element [1.1]: “wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status,”*

Petitioner argues that the MSR teaches this first element of claim 1 because the MSR discloses three study arms, including one of patients having MSI-H colorectal cancer and another of the patients having MSI-H non-colorectal cancer. Pet. 19–21 (citing Ex. 1005, 4 (Arms and Interventions)). Dr. Neugut’s testimony supports this argument. Ex. 1003 ¶¶ 60–64. In addition, Dr. Neugut testifies that the patients determined to have defective MMR (dMMR) status are biologically the same population as patients with MSI-H status. Ex. 1003 ¶ 62 (citing Ex. 1020,¹ 51 (“Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.”)).

Patent Owner does not dispute that the MSR teaches selecting a patient who has a tumor characterized as MSI-H or MMR deficient.

The arguments and evidence that Petitioner cites persuade us that the MSR teaches this element of claim 1.

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

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

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

non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 21 (citing Ex. 1005, 4.) Petitioner cites Dr. Neugut’s testimony that this teaching reads on the claim limitation “administering an effective amount of pembrolizumab to the patient,” in claim 1, because the dose taught in the MSR is identical to the dose described as being effective in the ’975 patent. *Id.* at 21–22 (citing Ex. 1003 ¶¶ 40–41, 67); Ex. 1001, 4:14–27, 8:44–50, 13:18–24, 16:1–8, 16:65–17:7, 19:40–21:18, Figs. 2, 11. Petitioner argues further that any efficacy required in the claim is inherent to that dosage because the ’975 patent shows that dosage to be effective. *Id.*

Patent Owner does not dispute that the MSR discloses an amount of pembrolizumab that is effective at achieving the therapeutic results (an improved outcome in a selected patient compared to a reference patient), as required in the ’975 patent.

d) Element [1.3]: “wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient.”

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

An affidavit executed by Andrew Pardoll, M.D., an inventor named on the '975 patent, supports Dr. Neugut's testimony and explains that

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

23. The preliminary results of this study demonstrated clinical responses at an unexpectedly high rate (>50% objective response rate) in the MSI-high (MMR deficient) arm but not in the MSS (MMR proficient) arm.

Ex. 1022 (Part 9), 2490–2491. That affidavit, submitted during prosecution of the '975 patent, supports the argument that an improved outcome of treating a patient with a tumor exhibiting an MSI-high or an MMR deficiency status with pembrolizumab compared to similarly treating a patient without an MSI-high or an MMR deficiency status, as recited in claim 1, is an inherent result because the treatment would necessarily provide the result. *Compare id.*, with Ex. 1001, 6:44–48 (“The data from the small phase 2 trial of pembrolizumab to treat tumors with and without deficiency of MMR supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors.”).

Petitioner argues that “[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. Thus, actual administration of [pembrolizumab] to patients before the critical date of the [’975 patent] is irrelevant.” Pet. 24 (citing *Schering*, 339 F.3d at 1380).

Patent Owner argues that the MSR does not disclose outcomes of the study and, therefore, does not teach that a patient administered pembrolizumab and having a tumor with MSI-H or dMMR status would exhibit an improved outcome compared to a reference patient administered pembrolizumab and not having a tumor with MSI-H or dMMR, as required in claim 1. PO Resp. 10–15. Patent Owner argues that *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012), cited by Petitioner, fails to support the assertion of inherent anticipation of the claimed method. PO Resp. 11–15; Pet. 17 (“In *In re Montgomery*, the Federal Circuit held that a document disclosing a planned clinical study inherently anticipated method of treatment claims even where the method of treatment had not yet been practiced.”). Patent Owner attempts to distinguish the facts of *Montgomery* from the facts at issue here by arguing that in *Montgomery* the disclosure of the prior art was identical to the patent itself, whereas here the MSR does not disclose treating a cancer patient with pembrolizumab when “the patient has received a prior cancer therapy drug” or “the tumor having progressed following a [cancer therapy/prior treatment].” PO Resp. 11–12; PO Sur-Reply 2. We are unpersuaded. Rather, we are persuaded by the statements in contemporaneous references citing the MSR that one of ordinary skill in the art would have understood the study to involve patients with unresectable or metastatic MSI-H cancer. Ex. 1049, 444; Ex. 1050 S4. Accordingly, we are not persuaded that the facts here differ from those in

Montgomery as much as Patent Owner argues, wherein both prior art references teach the steps recited in the challenged claims. *See Montgomery*, 677 F.3d at 1380 (“We see no error in the Board’s uncontested conclusion that HOPE discloses the administration of ramipril to patients diagnosed as in need of stroke treatment or prevention.”).

Patent Owner argues further that because the MSR is only an initial submission for an experimental trial that had not yet begun recruiting patients or obtaining experimental data, it was merely an “invitation to investigate” from which the results recited in claim 1 would not “inevitably flow.” PO Resp. 12; PO Sur-Reply 2–3. Patent Owner argues that the inventors knew that other checkpoint inhibitor drugs used to treat colorectal cancer patients were “resoundingly *unsuccessful*,” and that treatment of other types of cancer “beyond the initial success in melanoma and non-small cell lung cancer had failed.” PO Resp. 13 (citing Ex. 2090 ¶ 57). According to Patent Owner, “the MSR was a far cry from meeting *Montgomery*’s inevitability requirement for inherent anticipation” and that, in contrast to *Montgomery*, the MSR only describes a study to test the hypothesis that MSI-H might correlate with a response to treatment with pembrolizumab, rather than to secure regulatory approval. PO Resp. 13–15; Ex. 2072 ¶ 109; Ex. 2130 ¶¶ 10–13.

We do not doubt that the inventors were unaware of the results of the study described in the MSR before it was concluded. But knowledge of the results is not a component of the analysis of anticipation. *See Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (“[T]he claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [the prior art]. Newly discovered results of known processes directed to the same purpose are not

patentable because such results are inherent.”). After analysis of the full record, we are persuaded that the results recited in claim 1 would follow from the steps taught in the MSR, for the reasons and based on the evidence Petitioner cites above. For these same reasons, we are unpersuaded by Patent Owner’s argument that it was unknown whether the amount of pembrolizumab recited in claim 1 would be effective in producing an improved outcome compared to a reference patient without a tumor that was not MSI-H or dMMR, and Patent Owner does not dispute that the amount of pembrolizumab disclosed in the MSR (10 mg/kg every 14 days; *see* Ex. 1005, 4) is the same as the amount provided in the ’975 patent as being effective (10 mg/kg every 14 days; Ex. 1001, 8:48–52, 13:50–52).

Regardless of the inventors’ intent in publishing the MSR as a Stage II clinical trial on the www.clinicaltrials.gov website, as discussed above, we determine that the MSR teaches selecting a patient with a metastatic MSI-H or dMMR tumor and administering an amount of pembrolizumab that would be effective. *See, e.g.*, Ex. 1005, 4 (Arms and Interventions). The result of drug treatment inherently follows its administration. The MSR does not merely suggest that pembrolizumab may be useful in some unidentified subset of patients or suggest that some unidentified drug may be useful for MSI-H cancer patients. Instead, the MSR discloses selecting a patient with a condition recited in claim 1 and treating with the drug at the amount recited in claim 1. *Contra Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (holding that the prior art did not inherently anticipate where it failed to mention specific vitamin deficiencies, instead merely inviting further experimentation to find associations with metabolic perturbations).

Montgomery states that “even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps,” referring to a claimed method of treating or preventing stroke, which was held to be anticipated by the publication of a proposed study. 677 F.3d at 1381. Patent Owner attempts to distinguish the size and apparent surety of the study in *Montgomery* from the MSR. PO Resp. 15. But because we find that the MSR teaches performing the steps recited in claim 1 for the purpose of determining and treating MSI-H cancer, we are persuaded that the MSR inherently discloses the results of selection of patients and administration of the drug treatment recited in those steps. *See Bristol-Myers*, 246 F.3d at 1376. Whether or not the MSR could have provided results or was sufficient for full regulatory approval does not change that the MSR teaches Patent Owner’s claimed steps. We have no reason to doubt that the disclosure in the MSR of the steps recited in claim 1 produces the efficacy element required in claim 1, whether or not this efficacy was disclosed in the MSR or was known when it was published. *See Mehl/Biophile*, 192 F.3d at 1366 (“Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the article’s authors did not appreciate the results.”).

Patent Owner argues that Merck’s interpretation of inherency law cannot be correct because it would effectively preclude the patenting of unexpectedly effective methods of treating human patients. PO Resp. 15–17; PO Sur-Reply 4–5. Patent Owner asserts that if its inventors had filed a “data-less provisional application mirroring the MSR” before the MSR was published, it would have been unable to satisfy the requirements of § 101 and § 112, creating a “catch-22 scenario” wherein Patent Owner would not have been able to secure patent protection. PO Resp. 16–17. Patent Owner

cites *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1322 (Fed. Cir. 2019), *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010), and *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005), in support, asserting that these cases hold that a specification cannot provide merely prophetic examples, that it must demonstrate possession by the inventors, and that it must convey that the claimed invention benefits the public. PO Resp. 16.

Petitioner disagrees, arguing that “[i]t is well established . . . that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112.” Pet. Reply 9–10 (citing *In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (“[H]uman trials are not required for a therapeutic invention to be patentable”); *Ex parte Balzarini*, 21 USPQ2d 1892 (BPAI 1991) (holding that even in situations where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials)). Petitioner argues that “[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure.” Pet. 16–17 (citing *Schering*, 339 F.3d at 1380). According to Petitioner, actual administration of pembrolizumab to patients before the critical date of the ’975 patent is irrelevant. *Id.*

Patent Owner does not direct us to evidence that it attempted to file any patent application before the publication date of the MSR and was denied an earlier filing date. Contrary to Patent Owner’s argument that it could not file a patent application without results from the MSR, we note that the inventors filed a provisional patent application on November 13, 2014, which, although also filed more than a year after the publication of the MSR, disclosed no clinical results or data. Ex. 1001, cover; Ex. 1030, 1. After considering the parties’ arguments, we are not persuaded by Patent

Owner's assertion that the inventors could not have filed an earlier application to at least attempt to secure a priority date before the MSR was publicly available. We are not persuaded that the law prevented Patent Owner from obtaining an earlier filing date. Instead, we are persuaded by Petitioner's argument that because the MSR was published before the inventors filed an application to protect their patent rights, the MSR is prior art for the information it discloses, including the steps recited in claim 1 and any results that would inherently result from these steps.

Patent Owner argues further that the MSR discloses an experimental use that does not qualify as prior art. PO Resp. 18–25. Patent Owner argues that an inventor can be granted latitude to experiment in the public eye until her invention is ready for patenting. *Id.* at 18 (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998)). According to Patent Owner, the experimental use negation applies to the MSR under a 13-factor analysis provided in *Allen Engineering Corp. v. Bartell Industries, Inc.*, 299 F.3d 1336, 1353 (Fed. Cir. 2002). PO Resp. 19–25. For example, Patent Owner argues that to establish that treatment of MSI-H cancers was effective, the inventors had to test treatment in humans, there being no animal models, and had to publish the MSR on the government website under federal law. *Id.* at 20–22. Patent Owner argues further that the inventors had control over the MSI-H clinical study and that the field of cancer treatment was highly unpredictable, among other facts. *Id.* at 21. Patent Owner argues that “[a]t the time of the MSR’s posting, the claimed invention was not, nor could it have been, ready for patenting. The clinical study that ultimately collected the data reported in the patent specification and supporting the patent claims had not and could not have commenced before the MSR was posted.” *Id.* at 23.

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

After considering the parties’ arguments and evidence, we are persuaded that the MSR teaches the efficacy requirement of claim 1, wherein a patient with an unresectable or metastatic MSI-H tumor and administered an effective amount of pembrolizumab would have an improved outcome over a reference patient that had been also administered pembrolizumab, but whose tumor does not exhibit an MSI-H status.

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

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

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

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

Petitioner argues that “[p]atients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies.” *Id.* at 26. To that point, Dr. Neugut testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer “would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies.” Ex. 1003 ¶ 75 (citing Ex. 1020, 25; Ex. 1009, 1034; Ex. 1047, 4–7). Dr. Neugut observes that the Eligibility section of the MSR takes care to exclude patients having had prior treatment

with certain other antibodies. *Id.* ¶ 76 (“[T]he person of ordinary skill would have understood that the MSR recognizes that patients would have received prior cancer drug therapies, and because of that makes it a point to exclude those that received ‘anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies.’”). Dr. Neugut interprets this exclusion as supporting his opinion that such patients would have received a prior cancer therapy drug to treat their tumor because otherwise, the study would not have purposefully excluded these antibodies, and because if the prior therapies had worked, these patients would not have participated in the MSR. *Id.* Dr. Neugut cites to a poster presentation describing the MSR as requiring that patients have “progressive disease” and have had prior therapies. *Id.* ¶ 78.

Dr. Oberstein testifies that he agrees with Dr. Neugut. Ex. 1150 ¶¶ 64–67. Dr. Oberstein testifies that because the eligibility criteria stated in the MSR requires patients to have “measurable disease,” one of ordinary skill in the art would have expected a patient to have undergone prior cancer therapies and would have had their cancer progress after those therapies prior to enrollment. *Id.* ¶ 64. Dr. Oberstein testifies that it is reasonable to assume that patients would typically have received the two standard chemotherapy regimens before trying a novel therapeutic agent. *Id.* ¶ 65.

Patent Owner argues that the MSR is silent about whether eligible patients must have had prior, failed treatment and that Petitioner’s “assertions that a patient ‘generally’ . . . would have received a prior treatment is not enough to meet the high burden for an inherency finding.” PO Resp. 7–8.

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

Lonberg disagrees with Dr. Neugut’s interpretation of the term “measurable disease” in the MSR. Ex. 2072 ¶ 96 (“While measurable cancer refers to a cancer that has a minimum size (e.g., as determined by imaging), this has little to do with whether or not a patient’s cancer has progressed after the patient received prior therapies.”). But Dr. Lonberg fails to testify that one of ordinary skill in the art would not have understood the MSR in 2013 to teach treating patients who had received prior/different cancer therapies, wherein the patients’ cancer had progressed after the patients received the prior/different cancer therapies.

On the balance, we find Petitioner’s evidence more persuasive of what one of ordinary skill in the art would have understood from the MSR. We find Dr. Neugut’s and Dr. Oberstein’s testimony, and Dr. Lonberg’s lack of clear testimony to the contrary, persuasive as to this issue.

In light of the cited testimony, we are persuaded that Petitioner has met its burden of proving whether a skilled artisan would reasonably understand or infer that the limitation for a solid tumor that has progressed following at least one prior cancer treatment was disclosed in the MSR. Petitioner demonstrates what one of ordinary skill in the art would have understood from the MSR, not what it inherently discloses. *Contra* PO Resp. 6–9.

2. *Independent Claim 9*

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

3. *Dependent Claims 2 and 15*

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

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

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

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

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

Petitioner argues further that other prior art references citing the MSR demonstrate that physicians understood the MSR to be for patients with metastatic tumors. Pet. 30 (citing Ex. 1049, 444; Ex. 1050, S4). Specifically, one 2015 publication refers to the clinical trial number of the MSR and states: “pembrolizumab is being tested in metastatic tumors with microsatellite instability, including colorectal cancer (NCT01876511).” Ex. 1049, 444. Another 2015 publication, entitled “Novel Therapies in Development for Metastatic Colorectal Cancer,” refers to the MSR (“NCT01876511”) as a “Phase II clinical trials in development investigating immunotherapy in MSI-H mCRC,” wherein “mCRC” is defined as metastatic colorectal cancer. Ex. 1050, S2, S4.

Patent Owner argues that the MSR does not disclose treatment of metastatic colorectal cancer and that the disclosure of “measurable disease” is not a teaching of metastatic colorectal cancer because “measurable disease” is not synonymous with metastatic cancer. PO Resp. 17–18. In support, Patent Owner cites to Dr. Neugut’s testimony that “metastatic” and “measurable” are “totally different terms,” wherein metastatic tumors are not necessarily measurable. PO Resp. 18 (citing Ex. 2163:14:9–15:12).

Even if Dr. Neugut’s reasoning that the reference to “measurable” disease in the MSR would have indicated patients having metastatic cancer is flawed, we are persuaded by Petitioner’s evidence of publications referring to the MSR as a study of metastatic colorectal cancer that one of ordinary skill in the art would have understood the MSR to disclose treating

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

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

5. Dependent Claims 3, 8, and 10

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

a) Claims 3 and 10

Petitioner argues that claims 3 and 10 are anticipated by the MSR. Pet. 29–30, 33. Patent Owner presents the arguments discussed above regarding the limitations of claim 1, but does not present arguments or direct us to evidence against these challenges that are specific to the limitations of dependent claims 3 and 10.

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

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

b) Claim 8

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

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

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

6. Summary

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

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

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

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

1. Petitioner’s Contentions

a) Ground 2

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

Petitioner argues that Pernot teaches treating colorectal cancer and that, therefore, because the MSR is directed to a clinical study treating colorectal cancer patient whose cancers are MSI-H with pembrolizumab, which is an anti-PD-1 antibody, one of ordinary skill in the art knowing the teachings of the MSR would have considered the teachings of Pernot. Pet. 39. Petitioner argues that Pernot teaches that colorectal cancer patients that are MSI-H are “good candidates for immunotherapy,” such as PD-1 inhibitors. *Id.* (quoting Ex. 1006, 3741 (“[Colorectal cancer] associated with MSI could lead to a more intense immune response, but also to specific

immunoregulatory phenomena, making them good candidates for immunotherapy.”)).

Petitioner cites further to Dr. Neugut’s testimony to argue that one of ordinary skill in the art would have been motivated to combine the disclosure of Pernot with the methods taught in the MSR in order to obtain the results of the MSR’s study. Pet. 42 (citing Ex. 1003 ¶ 101).

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

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

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

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

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

In light of this evidence of the state of the art at that time, Dr. Neugut testifies that one of ordinary skill in the art would have wanted to obtain data from the MSR and would have reasonably expected success, given that pembrolizumab was already approved for another oncology indication. Ex. 1003 ¶¶ 102–105; Pet. 40–41. Dr. Neugut concludes that “[a]s a result of carrying out the methods in the MSR of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study, the person of ordinary skill would have seen the results that naturally flow from those methods.” Ex. 1003 ¶ 105.

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

Petitioner argues further that one of ordinary skill in the art would have considered it obvious that the MSR discloses treating patients with metastatic or unresectable cancer in light of the teachings of Benson. Pet. 42–45. Petitioner argues that Benson is directed to ways in which clinical studies involving colorectal cancer are conducted, which is in the same field as the MSR. *Id.* (citing Ex. 1003 ¶ 107). Benson teaches that under the standard of care, the patient population with tumors and measurable disease that would take part in a clinical study are patients having metastatic and advanced disease. Ex. 1009, 1034; Ex. 1003 ¶ 108. Dr. Neugut testifies further that the term “advanced cancer” refers to metastatic cancer or cancer

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

b) Ground 4

In Ground 4, Petitioner relies on Brown for its teaching that PD-1 inhibitors inherently had more efficacy when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 51 (citing Ex. 1034, 747). Petitioner relies on Duval for its teaching that MSI-H cancers have cells that are easy for immune cells to recognize. *Id.* (citing Ex. 1087, 5002). Dr. Neugut’s testimony supports Petitioner’s argument that Brown and Duval would have motivated a person of ordinary skill in the art to obtain the results of the MSR. Ex. 1003 ¶¶ 121–31.

2. Patent Owner’s Contentions

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

3. *Discussion*

Because “anticipation is the epitome of obviousness,” we are persuaded that the claims Petitioner challenges as being anticipated by the MSR would have been obvious over the MSR and other references, for the reasons discussed above. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002). Accordingly, the preponderance of the evidence supports Petitioner’s challenges of claims 1–3, 6–10, and 13–15 as being obvious over the MSR alone.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the patentability of the claimed methods. PO Resp. 51–86. The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. *Id.* Because we determine, as discussed above, that the method recited in claims 1–3, 6–10, and 13–15 is anticipated by the MSR, Patent Owner’s objective evidence of non-obviousness is not persuasive as to the patentability of claims 1–3, 6–10, and 13–15. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) (“[S]econdary considerations are not an element of a claim of anticipation.”).

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

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

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

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

wherein the patient has been determined to have a tumor that exhibits a MMR deficiency status when deficiency of a mismatch repair marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the mismatch repair marker is POLE, POLD1, or MYH.

Ex. 1001, claims 4 and 12.

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

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

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

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

To begin, Patent Owner argues that Petitioner applies the wrong legal standard to argue that there would have been a reasonable expectation of success in the methods recited in the independent claims. PO Resp. 32–50. For example, Patent Owner argues that neither the MSR, Pernot, any other reference cited by Petitioner, nor the state of the art provides a reasonable expectation in using MSI status as an indicator of successful treatment with pembrolizumab. *Id.* at 33–50. Because, as discussed above, we are persuaded that the steps of the methods recited in the independent claims are expressly taught in the MSR, anticipating the limitations of independent claims, we are persuaded that Petitioner has established that one of ordinary skill in the art would have had a reasonable expectation of success in achieving a method comprising these steps, with the results being inherent. *See MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) (“Where, as here, the result is a necessary consequence of what was deliberately intended, it is of no import that the articles’ authors did not appreciate the results.”). Petitioner presents persuasive evidence that one of ordinary skill in the art would have had a reasonable expectation of success in making a method that tests for MSI-H as recited in the challenged dependent claims, and Patent Owner does not argue or present evidence to the contrary. Accordingly, we are persuaded that Petitioner has met its

burden of presenting a *prima facie* case for the obviousness of the challenged claims.

Patent Owner also presents objective evidence of non-obviousness that it asserts demonstrates the non-obviousness of the claimed methods. PO Resp. 51–86. The evidence purportedly shows industry praise, skepticism, long-felt need, unexpected results, and commercial success of the claimed methods. *Id.* Because we determine, as discussed above, that the methods recited in the independent claims are anticipated by the MSR, Patent Owner’s objective evidence of non-obviousness is not persuasive of the patentability of claims 1 and 9. *See Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008) (“[S]econdary considerations are not an element of a claim of anticipation.”).

Regarding the dependent claims 4 and 12, Patent Owner must show a nexus between the claimed methods and the evidence of non-obviousness. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (“[T]o be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention. . . . Ultimately, ‘[t]he patentee bears the burden of showing that a nexus exists.’” (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988), *WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999))).

Patent Owner mentions a nexus between the Keytruda[®] (pembrolizumab) label for testing a patient’s tumor using polymerase chain reaction or immunohistochemistry, which are recited in dependent claim 5. PO Resp. 52. But Patent Owner does not direct us to evidence of a nexus to limitations recited in dependent claims 4 and 12, which recite testing that

comprises assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24. Thus, even if there is a nexus to the Patent Owner's evidence of secondary considerations, the evidence addresses the methods of independent claims 1 and 9, not the limitations of the claims 4 and 12. PO Resp. 52–62. Patent Owner directs us only to evidence regarding treating patients determined to have MSI-H colorectal cancer with pembrolizumab, which we determine to be anticipated by the MSR. *Id.* When evidence of a “secondary consideration is exclusively related to a single feature that is in the prior art,” our reviewing court has held the evidence is of no relevance to the obviousness inquiry. *See Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1363–65 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 499 (2023) (distinguishing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330–31 (Fed. Cir. 2016)); *see also Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016) (“[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.”). In *Yita*, the prior art taught close-conformance of a floor tray with the walls of a vehicle foot well, which one of ordinary skill in the art would have had reason to use in combination with other prior-art teachings to arrive at the claimed invention. *See Yita*, 69 F.4th at 1359–61. The court held that because the asserted evidence of secondary consideration related exclusively to close-conformity, the evidence was not persuasive of non-obviousness, even though the claimed floor tray was coextensive with the product that produced the evidence. *See id.* at 1364–65 (“The coextensiveness inquiry bears only on the presumption of nexus; it does not decide the overall nexus question.”).

Because Patent Owner directs us only to evidence that the methods recited in claims 1 and 9 produced evidence of secondary considerations, we

are not persuaded that this evidence is persuasive of the non-obviousness of the specific methods recited in the dependent claims.

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

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

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

III. CONCLUSION⁴

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

⁴ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

In summary:

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

IV. ORDER

In consideration of the foregoing, it is
ORDERED that claims 1-4, 6-10, and 12-15 of the '975 patent have
been shown to be unpatentable; and

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

IPR2024-00624
Patent 11,325,975 B2

FOR PETITIONER:

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

FOR PATENT OWNER:

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