Trials@uspto.gov
Tel: 571-272-7822

Paper 10
Entered June 13, 2024

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, ROBERT A. POLLOCK, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–42 of U.S. Patent No. 11,591,393 B2 (Ex. 1001, "the '393 patent"). (Petition ("Pet."), Paper 1.) The Johns Hopkins University ("Patent Owner") filed a Preliminary Response identifying itself as the owner of the '393 patent. (Preliminary Response ("Prelim. Resp."), Paper 5.) 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).

The Director may not authorize an *inter partes* review "unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). We determine whether to institute a post grant review on behalf of the Director. *See* 37 C.F.R. § 42.4(a).

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner.

Upon considering the Petition, the Preliminary Response, and the evidence of record, we determine that Petitioner has demonstrated there is a reasonable likelihood that the petition would prevail in showing that at least one challenged is unpatentable. Accordingly, we institute *inter partes* review of all challenged claims on all asserted grounds. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a).

A. Related Matters and Real Parties-in-Interest

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; *see* Paper 4, 1.)

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

B. The '393 Patent and Challenged Claims

The '393 patent is directed to anti-cancer therapies that block immune system checkpoints, including the PD-1 receptor. (*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. (*See* Ex. 1001, 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. (*See* Ex. 1001, 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 microsatsellite 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.

(Ex. 1001, 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 . . . ."

(Ex. 1001, 26:17–28.)

C. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–42 are unpatentable based on the following grounds (*see* Pet. 3–5):

	Claims Challenged	Statutory Basis - 35 U.S.C.[1]	References
1	1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, 27–42	§ 102	MSI-H Study Record[2] (Ex. 1005)
2	1, 2, 4–7, 11–12, 14, 15, 17–20, 24–25, 27–42	§ 103	MSI-H Study Record (Ex. 1005), Pernot[3] (EX1006)
3	2, 8, 15, 21	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (Ex. 1006), and Chapelle[4] (Ex. 1007)

[1] 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.

[2] ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1 ("MSI-H Study Record"); also available at Merck Sharp & Dohme LLC v. The Johns Hopkins University, 1:22-cv-03059-BPG, ECF 1, Complaint, Exhibit B (11/29/22) (Ex. 1005).

[3] Pernot et al, *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) World J. Gastroenterology 3738 (April 2014) (Ex. 1006).

[4] Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010) (Ex. 1007).

	Claims Challenged	Statutory Basis - 35 U.S.C.[1]	References
4	3, 16	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (EX1006), Steinert[5] (Ex. 1008)
5	7, 20, 29–30, 32, 34, 36–42	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (Ex. 1006), and Benson[6] (Ex. 1009)
6	9, 10, 22, 23	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (Ex. 1006), and Salipante[7] (Ex. 1010)
7	11–12, 24–25	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (Ex. 1006), and Hamid[8] (Ex. 1011)
8	13, 26	§ 103	MSI-H Study Record (Ex. 1005), or the MSI-H Study Record (Ex. 1005), Pernot (EX1006), Steinert (Ex. 1008), and Hamid (Ex. 1011)

[5] Steinert et al, *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014) (Ex. 1008).
[6] Benson et al, *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014) (Ex. 1009).
[7] Salipante et al, *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) Clinical Chemistry 1192 (June 2014) (Ex. 1010).
[8] Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New Eng. J. Medicine 134 (July 2013) (Ex. 1011).

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. Level of Skill and Declarants

Petitioner argues that one of ordinary skill in the art relevant to the challenged claims would be a medical doctor or a professional in a related field with at least five years of experience treating cancer. (Pet. 12 (citing Neugut Decl., Ex. 1003, ¶19).) Petitioner argues further that one of ordinary skill in the art would have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and to a pathologist with comparable experience. (*See id.*)

Patent Owner puts forth a different definition, wherein one of ordinary skill in the art of the challenged claims

> would have a M.D. or graduate-level degree (or equivalent work experience) in the fields of immunology, genetics, or a related field and at least five years of 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.

(Prelim. Resp. 47.) Patent Owner argues that clinical experience treating cancer patients with "already approved drugs/therapeutics" is not a necessary characteristic for one of ordinary skill in the art because, as of the filing date of the '393 patent, such treatments were not known. (*See* Prelim. Resp. 47.) Instead, Patent Owner argues that one of ordinary skill in the art would have had the skills to develop such methods, including "experience conducting immunology or genetics research relating to oncology (e.g., developing and conducting clinical trials to test novel hypotheses relating to investigational cancer therapeutic products and/or methods of cancer treatment in immunology and genetics)." (Prelim. Resp. 47–48.)

Patent Owner argues that doctors and other professionals with experience treating cancer would not have had the knowledge, training, or experience necessary to develop such methods for treating cancer before they are approved. (*See* Prelim. Resp. 48 (citing Lonsberg Decl., Ex. 2001, ¶ 88).) Patent Owner cites *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007), in support, arguing that it holds that, although a doctor may have knowledge about treating an ear infection and prescribing medications, doctors would not have had the training or knowledge to develop new antibiotic compounds absent specialty training such as engaging in "developing pharmaceutical formulations and treatment methods for the ear . . . ." (Prelim. Resp. 49 (citing *Daiichi*, 501 F.3d at 1256–57.)) But *Daiichi* explains that "the problem the invention of the '741 patent was trying to solve was to create a topical antibiotic compound to treat ear infections (otopathy) that did not have damage to the ear as a side effect" and that "most of the written description details the inventors' testing ofloxacin on guinea pigs . . . ." (*See Daiichi*, 501 F.3d at 1257.)

The '393 patent claims a method of treating a human patient with colorectal cancer having certain characteristics using an existing compound – pembrolizumab. (*See* Ex. 1001, 25:40–50.) Similarly, the prior art cited by Petitioner discloses testing of an existing compound for a new use in human patients. (*See* MSI-H Study Record, Ex. 1005, 3 ("Brief Summary: This 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."). Accordingly, the relevant art involves treating human patients, as well as testing existing compounds.

Based on the totality of the record before us, 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 immunology or genetics research relating to oncology or developing and conducting clinical trials to test novel hypotheses relating to investigational cancer therapeutic products, but 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.

Petitioner presents the testimony of Alfred I. Neugut, M.D., Ph.D., M.P.H., for opinion testimony regarding what one of ordinary skill in the art would have understood at the time of filing. (*See* Ex. 1003.) Dr. Neugut testifies that he is a medical oncologist with a particular focus on gastrointestinal tract cancers, including colorectal cancers, and is Professor of Medicine and Epidemiology at Columbia University. (*See* Ex. 1003 ¶ 4.) Dr. Neugut testifies further that he is the Director of the Center for Pharmacoepidemiology and Health Outcomes Research in Columbia's Department of Epidemiology and Director of Global Oncology Research for Columbia's Herbert Irving Comprehensive Cancer Center. (*See* Ex. 1003 ¶ 5.) Dr. Neugut testifies that he sees approximately 30 patients per week to treat gastrointestinal cancers, including colorectal cancer. (*See id.*)

Patent Owner argues that Dr. Neugut is not one of ordinary skill in the relevant art and is not qualified to testify about the subject matter at issue because he is a "treating oncologist with research experience in epidemiology and oncology" with "no relevant experience in immunology or genetics research or developing and conducting clinical trials." (Prelim. Resp. 53.)

Because Dr. Neugut has experience treating cancer and has knowledge of clinical studies for therapeutics and how they work, based on the record discussed above regarding the level of skill in the relevant art, at this time we consider him to

be qualified to provide opinion testimony about the subject matter of the '393 patent and the prior art.

Patent Owner argues further that Dr. Neugut makes certain factual mistakes in his testimony because of his lack of qualifications. (*See* Prelim. Resp. 54–60.) These arguments address the merits of Dr. Neugut's testimony regarding the obviousness of the challenged claims. For example, Patent Owner argues that Dr. Neugut testifies incorrectly about the nature of the invention and prior art and that his interpretation of the term "measurable disease" is unreliable. (*See id.*) We are not persuaded that Dr. Neugut's testimony should be discounted entirely, even if some of his testimony is unsupported. Rather, we weigh the merits of his specific opinions based on the support he cites and evidence to the contrary cited by Patent Owner in the analysis below.

Patent Owner presents the testimony of Dr. Nils Lonberg. (*See* Declaration of Dr. Nils Lonberg ("Lonberg Decl."), Ex. 2001.) Dr. Lonberg testifies that he has a Ph.D. in Biochemistry and Molecular Biology and has worked in biotechnology/pharmaceutical industry since 1990. (*See* Ex. 2001 ¶¶ 2–4.) Dr. Lonberg testifies that he has experience developing antibody therapies that target and modulate immune-attenuating pathways to active patient immune responses to cancer cells. (*See id.* at ¶¶ 3–4.) At this point in the proceeding, we weigh the merits of Dr. Lonberg's specific opinions based on the support he cites and evidence to the contrary cited by Petitioner in the analysis below.

C. Claim Construction

Petitioner argues that we need not construe any terms of the challenged claims to resolve the issues presented in the Petition. (*See* Pet. 11–12.) Patent Owner argues that the deficiencies in the Petition do not turn on claim construction. (*See* Pet. 11–12; *see* Prelim. Resp. 18.) To the extent we deem it

necessary to construe the terms of the challenged claims at this point in the proceeding, we do so in the analysis below. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The Board is required to construe 'only those 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))).

D. Ground 1 — Anticipation Based on the MSI-H Study Record

The parties agree that the MSI-H Study Record was published by June 12, 2013. (*See* Pet. 7; *see* Prelim. Resp. 12 ("JHU submitted the MSI-H Study Record on June 10, 2013, and it was posted on clinicaltrials.gov on approximately June 12, 2013").) At this point in the proceeding, JHU does not contest Merck's assertion that the MSI-H Study Record is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). (*See* Pet. 8.)

The title of the MSI-H Study Record is "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. (*See* Neugut Decl., Ex. 1003, ¶ 37; *see* Lonberg Decl., Ex. 2001, ¶ 65.)

The MSI-H Study Record includes a "Brief Summary," explaining that

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

(Ex. 1005, 3.) Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria

(irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" (Ex. 1005, 4–5.) The MSI-H Study Record provides "Arms and Interventions" as follows[9]:

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 and the therapeutic intervention to be provided.

Petitioner argues that, in general, the MSI-H Study Record anticipates claim 1 of the '393 patent because it "teaches the claimed drug, given at the only therapeutically effective dosage described in the '393 patent, and given to the claimed patient population." (Pet. 18.) Specifically, Petitioner cites to the teaching in the Arms and Interventions section of 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.*, 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility)).)

Petitioner argues further that the Arms and Interventions section of the MSI-H Study Record teaches the limitation in claim 1 of "testing, or having tested, a

[9] 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 in its Preliminary Response.

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." (*See* Pet. 20.) Petitioner relies on Dr. Neugut's testimony that the study required testing or that a patient had been tested in order to put them into the proper arm 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; *see* Pet. 21.)

Petitioner argues that the MSI-H Study Record anticipates the limitation in claim 1 of treating with a therapeutically effective amount of pembrolizumab "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient" 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.) Petitioner relies on Dr. Neugut's testimony to assert that the dosage described in the MSI-H Study Record is the same as the dosage described as being effective in the '393 patent. (*See* Pet. 21–22 (citing Ex. 1003 ¶¶ 59–62); *see* Ex. 1001 4:23–36, 8:52–56, 13:28–30.)

In support of its challenge to claim 1 as being anticipated by the MSI-H Study Record, Petitioner cites to 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." *Id.* at 1382. According to Petitioner, the MSI-H Study Record inherently anticipates

the method of claim 1 because the claims are directed to the methods disclosed in the MSI-H Study Record. (*See* Pet. 18.)

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the method of claim 1 because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '393 patent, and given to the claimed patient population. (*See* Pet. 18.) 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. 15.)

Patent Owner contests Petitioner's challenge to the claims as being anticipated by the MSI-H Study Record, arguing that claim 1 requires the treating step be "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient," but that the MSH-I Study Record reports treating all accepted patients, whether or not the patient has MSH-I cancer. (Prelim. Resp. 38–45 (citing Lonberg Decl., Ex. 2001, ¶¶ 99–111).) Patent Owner argues that Petitioner fails to carry its burden because the "in response to" claim limitation is not addressed, despite the emphasis on it during prosecution. (*See* Prelim. Resp. 39–40.)

Patent Owner argues that the MSI-H Study Record does not indicate there was any restriction in recruiting or enrolling colorectal cancer patients and that patients could be recruited and enrolled without any prior knowledge that their cancer was MSI-H. (*See* Prelim. Resp. 41 (citing Lonberg Decl., Ex. 2001 ¶¶ 104–106).) Patent Owner argues that "[c]ontrary to Merck's assumptions, the CRC patient's tumors would be biopsied ***after*** enrollment, to determine the patient's MSI status for the purpose of assigning the patient to an appropriate arm of the

study. (*See* EX1005, 5 ('Inclusion Criteria: . . . Agree to have a biopsy of their cancer').)" (Prelim. Resp. 41.) Patent Owner argues further that the MSI-H Study Record describes an "all-comers" study, which allowed patients to meet the eligibility requirements regardless of their MSI-H status. (*See* Prelim Resp. 41.) According to Patent Owner, this feature of the MSI-H Study Record indicates that patients were not treated "in response to determining" that they were MSI-H or DNA mismatch repair deficient.

Patent Owner's argument focuses on the design of the MSI-H study, rather than on what the MSI-H Study Record discloses about the treatment steps for colorectal cancer in a human patient. Patent Owner argues that "[w]hile the MSI-H Study Record may teach administering the claimed drug at a therapeutically effective amount, it teaches doing the ***very same thing*** for a population that is not claimed." (Prelim. Resp. 42.) Thus, Patent Owner does not dispute that the MSI-H Study Record teaches treating colorectal cancer patients having an MSI-H status with a therapeutically effective amount of pembrolizumab, but argues, instead, that claim 1 is not anticipated because other patients are treated as well.

Patent Owner argues that there is no causal relationship described in the MSI-H Study Record between treating of colorectal cancer patients and determining their MSI status because all patients were treated with pembrolizumab and MSI status was only described after enrollment in order to assign a patient to a cohort. (*See* Prelim. Resp. 42–43.) Again, Patent Owner focuses on the design of the study, not what the study describes as the actual treatment of microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient.

At this point in the proceeding, contrary to Patent Owner's argument, Petitioner has sufficiently shown that there is a reasonable likelihood that the MSI-

H Study Record teaches treating colorectal cancer patients after they were determined to be microsatellite instability high or DNA mismatch repair deficient with pembrolizumab. (*See* MSI-H Study Record, Ex, 1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4–5 (Outcome Measures), 5–6 (Eligibility); *see* Neugut Decl., Ex. 1003, ¶¶ 58–62.) At this point in the proceeding, Petitioner has sufficiently shown that there is a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of colorectal cancer patients and the determination of their MSI status — all colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were treated. Whether or not other patients were treated or enrolled in the study does not detract from this teaching.

Patent Owner's witness, Dr. Lonberg, testifies that the MSI-H Study Record indicates colorectal cancer patients could be "enrolled in the trial ***before*** their MSI status is even known" and that "[t]he determination of the CRC patient's MSI status has no bearing on treatment, and therefore, the treatment is in no way 'in response' to the determination." (Ex. 2001, ¶¶ 102, 106.) But Dr. Lonberg does not dispute that treatment is provided to colorectal cancer patients after their status as MSI-H positive has been determined. (Ex. 2001 ¶ 106.) Dr. Lonberg testifies that "the MSI-H Study Record allows for a CRC patient who meets all other eligibility criteria to be entered into the study for treatment without ***any*** knowledge of their MSI-H status," but he does not point to any disclosure in the MSI-H Study Record that indicates determining a patient's status as MSI-H was done after a patient was treated with pembrolizumab. (Ex. 2001 ¶ 106.) Thus, because treatment of the patient was performed only after MSI-H status was determined, the evidence of record favors Petitioner.

Dr. Lonberg's testimony, like Patent Owner's arguments, focuses on the design of the MSI-H study, specifically the recruitment and enrollment of patients. (*See* Ex. 2001, ¶¶ 102, 104, 109 ("However, even for patients in the MSI-H CRC study arm, the MSI-H Study Record does not disclose recruiting the study subjects into the trial based on a determination that they are MSI-H CRC patients.").) Dr. Lonberg summarizes:

> In my opinion, the treatment described by the MSI-H Study Record might be considered given in response to a study subject's ***enrollment*** in the clinical trial. But this is clearly not the same as treating a patient with pembrolizumab in response to a determination that the patient's colorectal cancer is microsatellite instability high or DNA mismatch repair deficient—especially when the enrollment is also not dependent on determining the patient's MSI status.

(Ex. 2001 ¶ 109.) His testimony does not persuade us, at this point in the proceeding, that one of ordinary skill in the art would not have understood the MSI-H Study Record to teach testing a biological sample to determine if a patient's colorectal cancer is MSI-H followed by treating the patient with pembrolizumab.

According to Patent Owner's argument, testing and determining that a patient is MSI-H after enrollment in a study in which pembrolizumab is to be administered is not within the scope of the claim step "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." At this point in the proceeding, though, we do not interpret the claim step as meaning anything other than the treatment of colorectal cancer patients after they have been determined to be microsatellite instability high or DNA mismatch repair deficient. Although the term "in response to" in claim 1 requires that treatment of the patient occur after the determination that the colorectal cancer is MSI-H, we do not interpret the term to mean that other patients

are not treated or that the recruitment and enrollment of patients for a clinical trial has any bearing on the steps recited in claim 1.

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim "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." *Id.* Patent Owner has not directed us to evidence that one of ordinary skill in the art would have understood treating a patient "in response to" the determination that the patient has a condition excludes treatment of other patients without the condition, although it does require that treatment of the patient occur after the determination that the colorectal cancer is MSI-H. The language of claim 1 refers only to patients that are determined to have microsatellite instability high or DNA mismatch repair deficient colorectal cancer, not to other patients. (*See* Ex. 1001, 25:40–50.) At this point in the proceeding, the record does not indicate that the treatment of patients determined not to be MSI-H is be factored into whether the teaching of treating patients determined to be MSI-H anticipates the method of claim 1. At this point in the proceeding, we construe the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients.

Patent Owner argues that Petitioner fails to provide an analysis of how the MSI-H Study Record discloses treating patients "in response to" determining their MSI status and that institution of a trial could be denied based solely on this deficiency in the Petition. (*See* Prelim. Resp. 39–40.) Patent Owner's argument is

unavailing on this record because the Petition addresses the limitation by showing that the MSI-H Study Record teaches administering pembrolizumab 10 mg/kg to colorectal cancer patients after the patient has been determined to be MSI-H. (*See* Pet. 21–23.)

Accordingly, the evidence of record sufficiently shows that there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Ground 1 in the Petition.

Because we determine that Ground 1 warrants institution on the basis of independent claim 1 and Patent Owner addresses the challenged claims together, we do not address any other claims included in Ground 1. Nevertheless, the other claims included in Ground 1 (claims 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42) are included in the instituted review. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1358 (2018) ("The statute hinges inter partes review on the filing of a petition challenging specific patent claims; it makes the petition the centerpiece of the proceeding both before and after institution; and it requires the Board's final written decision to address every claim the petitioner presents for review."); *see* 37 C.F.R. § 42.108(a).

E. Ground 2 — Obviousness Based on the MSI-H Study Record and Pernot

Petitioner presents a challenge to claims 1, 2, 4–7, 11, 12, 14, 15, 17–20, 24, 25, and 27–42 of the '393 patent under 35 U.S.C. § 103, as an alternative to the challenge under 35 U.S.C. § 102, reportedly to address potential arguments by Patent Owner. (*See* Pet. 42–43.) Petitioner expects Patent Owner's arguments to be that the MSI-H Study Record cannot anticipate because it does not disclose an improved outcome and does not teach "testing, or having tested, a biological sample obtained from a patient," as required in claim 1, because these points were

noted in the Notice of Allowance for a related patent. (*See* Pet. 42–43 (citing December 14, 2020, Notice of Allowance in application 16/144,549, Ex. 1022 (part 11), 3073).) In response, Petitioner cites references that teach an improved outcome with a PD-1 inhibitor and that teach testing a biological sample from a patient to determine microsatellite instability status.

For example, 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 Neugut Decl., EX1003, ¶108).)

Petitioner also 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. (*See* Pet. 43–45 (citing Ex. 1003, ¶¶ 109–112).) Specifically, Petitioner refers to Lipson[10] for its reporting of the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor, albeit different from pembrolizumab:

> A 71-year-old male with [colorectal cancer] underwent a right hemicolectomy in October 2003, revealing a moderately differentiated adenocarcinoma with metastases to 4 of 16 pericolonic lymph nodes

[10] Lipson et al, *Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody*, 19(2) Clinical Cancer Research 462 (January 2015).

> and vascular and perineural invasion [G_2, pT3N2; *microsatellite instability (MSI)-high genotype]*. He received adjuvant 5-fluorouracil (5-FU) and leucovorin; however, a CT scan the following year revealed metastatic disease. Over the subsequent 3 years, the patient received multiple chemotherapeutic regimens with temporary response but then progression at multiple lymph node sites (gastrohepatic, portacaval, and peripancreatic); therapies included FOLFOX, irinotecan, bevacizumab, and cetuximab. Chemotherapy was last administered in April 2007. The patient began therapy with anti-PD-1 at 3 mg/kg per dose in July 2007 after documentation of disease progression, and received 5 doses over the next 9 months. *CT scans conducted 8 and 12 weeks after a single dose of anti-PD-1 showed a partial response (Fig. 1A). A [complete remission] was achieved in January 2008, and periodic CT and PET scans have revealed no evidence of recurrence since then.* The patient was most recently evaluated in April 2011, at which time he had not received any antineoplastic therapy for 3 years and had no evidence of disease recurrence.

(Ex. 1057, 463-64 (emphasis added).) We note that the Examiner considered Lipson during prosecution, but found it "does not treat the patient based on a determination of microsatellite instability high or DNA mismatch repair deficient as claimed." (*See* Application 17/465,101, Notice of Allowance issued January 10, 2023, Ex. 1002 (part 2) 544.)

Petitioner cites to other references as "independently urg[ing] the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab." (Pet. 44 (citing Neugut Decl., Ex. 1003, ¶ 110).) For example, Petitioner cites to Champiot,[11] 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

[11] Champiat et al, *Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy*, 3(1) OncoImmunology e27817-1(January 2014).

> 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.) As with Lipson, the Examiner cited Champiat, but allowed the claims because administration of pembrolizumab as the anti PD-1 agent was not taught. (*See* Notice of Allowance in application 16/144,549. Ex. 1022 (part 11), 3072.)

Petitioner argues further that the MSI-H Study Record itself would have rendered it obvious to test patients for MSI-H because one of ordinary skill in the art would have been motivated to and would have expected success in carrying out the methods taught in the MSI-H Study Record. (*See* Pet. 45–46.) Petitioner argues that the MSI-H Study Record discusses treating colorectal cancer patients having MSI-H colorectal cancer in one arm, which would have at least motivated one of ordinary skill in the art to test for MSI-H because it would have been necessary to place the patients into the correct arm of the study. (*See* Pet. 46.) Petitioner argues further that one of ordinary skill in the art would have expected success testing MSI-H positive patients because it was routine in the art. (*See id.* (citing Neugut Decl., Ex. 1003, ¶ 113).)

Patent Owner argues only that Petitioner's challenge based on obviousness over the MSI-H Study Record and Pernot fails because Pernot does not cure the deficiency of the MSI-H Study Record not teaching the limitation of treating "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient." (*See* Prelim. Resp. 45.)

As explained above in regard to Ground 1, on this record we determine that sufficient evidence exists to institute on the anticipation ground. For the same reasons, we determine the evidence is sufficient to proceed on Ground 2. "It is

well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (citation omitted).

Furthermore, to the extent the MSI-H Study Record does not disclose the limitation of "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," the record before us supports this limitation being rendered obvious by Pernot and the MSI-H Study Record. Specifically, because Pernot teaches that colorectal cancer patients are good candidates for immunotherapy, the evidence of the current record shows that one of ordinary skill in the art would have had a reason to use to PD-1 inhibitors to treat colorectal cancers. (*See* Ex. 1006, 3741.) Additionally, the focus in the MSI-H Study Record on a clinical study treating colorectal cancer patients who had been determined to be MSI-H with prembrolizumab indicates that it would have been obvious to test for this condition before treatment.

The additional references discussed by Petitioner contribute further to a reasonable likelihood that Petitioner will prevail. For example, Libson reports the successful treatment of a colorectal cancer patient having MSI-H status with a PD-1 inhibitor (*see* Ex. 1057, 463-64) and Champiat discusses evaluating the clinical activity of PD-1 agents in DNA mismatch repair, such as MSI+, colorectal cancer (*see* Ex. 1032, e27817-5). (*See* Pet. 44.) Thus, based on the entire record before us, Petitioner presents a reasonable likelihood that the method of claim 1 would have been considered obvious by one of ordinary skill in the art.

Accordingly, we are persuaded that there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Ground 2 in the Petition.

F. Grounds 3–8 — Obviousness Based on the MSI-H Study Record, Pernot, and Additional References

Petitioner argues that certain of the dependent claims of the '393 patent are unpatentable because they are obvious over the MSI-H Study Record, Pernot, and other cited references, including Chapelle, Steinert, Benson, Salipante, and Hamid. (*See* Pet. 46–63.) In regard to Ground 3, Petitioner cites Chapelle for its teaching of testing tumor tissue from a patient to determine microsatellite instability in colorectal cancer, as recited in claims 2, 15, and 21. (*See* Pet. 46–47 (citing Ex. 1007, 3380, 3383; Neugut Decl., Ex. 1003 ¶ 118.) Petitioner also cites Chappelle as teaching immunohistochemistry techniques to test for microsatellite instability status, as recited in claim 8. (*See* Pet. 48 (citing Ex. 1007, 3380, 3384; Neugut Decl., Ex. 1003 ¶¶ 117, 120.)

In regard to Ground 4, Petitioner cites Steinert for its teaching of testing body fluid to determine whether a tumor is microsatellite instability high, as recited in claims 3 and 16. (*See* Pet. 49–50 (citing Ex. 1008, OF6; Neugut Decl., Ex. 1003, ¶ 127.)

In regard to Ground 5, Petitioner cites to Benson for its teaching of a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer, as recited in claims 7, 20, 29, 30, 32, 34, and 36–42. (*See* Pet. 51–57 (citing Ex. 1009, 1034; Neugut Decl., Ex. 1003, ¶¶ 133, 138.)

In regard to Ground 6, Petitioner cites to Salipante for its teaching to test a tumor for microsatellite instability high using a PCR test or next generation sequencing on a sample, as recited in claims 9, 10, 22, and 23. (*See* Pet. 58–60 (citing Ex. 1010, 1192–1193; Neugut Decl., Ex. 1003, ¶¶ 155, 159.))

In regard to Grounds 7 and 8, Petitioner cites to Hamid for its teaching of administering pembrolizumab intravenously, as recited in claims 11–13, and 24–26. (Pet. 61–63 (citing Ex. 1011, 134; Neugut Decl., Ex. 1003, ¶ 166.))

In the Preliminary Response, Patent Owner argues only that the additional references do not cure the deficiency of the MSI-H Study Record in failing to teach the "in response to" limitation. (*See* Prelim. Resp. 46.) As explained above, at this point in the proceeding, the record indicates that there is a reasonable likelihood that the MSI-H Study Record anticipates the claims of the '393 patent, including the "in response to" limitation. Patent Owner's arguments do not indicate contrary evidence in the record.

Accordingly, there is a reasonable likelihood that Petitioner will prevail with respect to at least one claim challenged under Grounds 3–8 in the Petition.

G. Discretionary Denial

a. 35 U.S.C. § 325(d)

Under 35 U.S.C. § 325(d):

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

Thus, we have the discretion to deny institution when the prior art cited in Petitioner's challenges was previously presented to the Office. To determine if art or arguments are the same or substantially the same as those presented to the Office during prosecution, we look to the parties' evidence of

> (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for

> rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph). We apply a two-part test to analyze these factors, as articulated in *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential), wherein we ask

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

(*Id.* at 8.)

Petitioner argues that discretionary denial is inappropriate under the facts of the ’393 patent because of how the Examiner considered the information in the MSI-H Study Record. (*See* Pet. 65–67.) First, Petitioner argues that the Examiner did not consider the MSI-H Study Record during prosecution that led to the issuance of the ’393 patent. (*See* Pet. 9.) Petitioner acknowledges that the Examiner did consider the MSI-H Study Record during prosecution of application 16/144,549 (“the ’549 application”), which issued as U.S. Patent No. 10,934,356 (“the ’356 patent”) and is in the chain of priority for the ’393 patent. (*See id.* (citing Exs. 1002, 1022.)

Petitioner argues further that, during prosecution of the '549 application, the Examiner recognized that the MSI-H Study Record discloses a mechanism for how pembrolizumab works in a patient whose cancer was MSI-H or dMMR relative to a patient without MSI-H or dMMR cancer, but erroneously allowed the prior, related '356 patent, a related patent to with the '549 application claims priority, anyway, reasoning that the MSI-H Study Record did not affirmatively disclose the results flowing from treatment with pembrolizumab. (*See* Pet. 9–10 (citing EX1022, December 14, 2020 Notice of Allowability, 3 (Part 11, 281)).) The Examiner stated:

> Clinical Trial Announcement NCT01876511 does not teach the mental step of determining that the patient with a MSI-high or MMR deficiency status who has been treated with pembrolizumab exhibits an improved outcome compared to a patient who has been treated with pembrolizumab but does not have such a status. The announcement contemplates evaluating this parameter as primary and secondary outcome measures of the proposed clinical trial. (Page 3/8.) On its own, however, the announcement does not establish why the person of ordinary skill in the art would have reasonably expected the claimed outcome. In particular, the announcement does not establish a reasonable expectation of observing claim 41's objective response rate of about 12%-96% in MSI-high or MMR-deficiency patients treated with pembrolizumab.

(December 14, 2020, Notice of Allowability, EX1022 (part 11), 3073.)

Petitioner argues that the Examiner's "requirement for an express disclosure of an inherent result of the disclosed treatment was incorrect as a matter of law . . . ." (Pet. 9–10.) Specifically, Petitioner argues that the Examiner allowed the claims of the '356 patent over the MSI-H Study Record on the rationale that it did not affirmatively disclose an improved outcome and that the POSA would purportedly not have expected such efficacy. (*See* Pet. 66.) Petitioner argues that, more importantly, one carrying out the techniques reported in the MSI-H Study

Record (administering pembrolizumab to MSI-H positive colorectal cancer patients) could be accused of infringement. (*See* Pet. 66 (citing *Schering Corp.*, 339 F.3d at 1379 ("that which would literally infringe if later in time anticipates if earlier.")).) Petitioner argues that the Examiner did not consider whether the MSI-H Study Record inherently anticipates the methods claimed in the '393 patent and, thus, discretionary denial is inappropriate for the challenges presented in the Petition. (*See* Pet. 66.)

Patent Owner responds by arguing that we should exercise discretion to deny instituting a trial under 35 U.S.C. § 325(d) because the examiner repeatedly considered the MSI-H Study Record and updates to it during prosecution of the '393 patent and at least nine other related applications examined before the '393 patent was allowed, as indicated at least by signatures on Information Disclosure Statements. (*See* Prelim. Resp. 20–22 (citing Ex. 1002 (part 1), 123, 162; Ex 2009, 1; Ex. 2010, 1; Ex. 2011, 1; Ex. 2012, 1; Ex. 2013, 3; Ex. 2014, 1; Ex. 2015, 1; Ex. 2016, 3; Ex. 2017, 3).) Patent Owner points specifically to the Examiner's consideration of the MSI-H Study Record in the prosecution of related applications 15/611,017 and 16/144,549 prior to allowance of the claims in the '393 patent. (*See* Prelim. Resp. 23–24.)

Patent Owner argues further that in regard to Grounds 2–8 in the Petition, Pernot does not cure the deficiency of the MSI-H Study Record, because it does not disclose the "in response to" element, but rather is cumulative to the MSI-H Study Record and the other references the Examiner cites. (*See* Prelim. Resp. 26–29.)

Turning to the *Becton, Dickinson* factors, even if we consider the MSI-H Study Record to have been fully considered during prosecution of the application that became the '393 patent and even if we consider that it would have been the

basis for a rejection had it not been discounted in the prosecution of prior applications (factors (a) through (c)), we are persuaded that these considerations do not indicate we should deny institution in this case. As discussed above, at this point in the proceeding, we agree with Petitioner that the MSI-H Study Record teaches the steps of at least claim 1 of the '393 patent — testing a biological sample from a patient with colorectal cancer for microsatellite instability high status and in response to determining that the colorectal cancer is MSI-H, treating the patient with a therapeutically effective dose of pembrolizumab. Thus, at this point, we agree with Petitioner that the Examiner erred in allowing the claims over the MSI-H Study Record on the rationale that the art did not affirmatively disclose an improved outcome or that one or ordinary skill would not have expected such efficacy. (*See* Pet. 9–10.) We are persuaded that a reference need not show the efficacy of treatment if the steps were taught in the prior art. *See Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("MEHL/Biohile does not dispute on appeal that the laser operating parameters disclosed in the article substantially coincide with those disclosed in the patent. Accordingly, to the extent that the embodiment in the patent achieves hair depilation, so does the Polla method. 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.").

Because we conclude the Examiner erred in not rejecting at least claim 1 as being anticipated by the MSI-H Study Record, we also disagree with Patent Owner that institution of a trial based on Grounds 3–8, challenging dependent claims under 35 U.S.C. § 103, should be denied under 35 U.S.C. § 325(d). (*See* Prelim. Resp. 29–34.) We disagree with Patent Owner that the MSI-H Study Record

presents deficiencies indicating that the Examiner did not err in allowing the claims.

b. 35 U.S.C. § 314(a)

Patent Owner argues that the timing of the parallel district court litigation indicates we should exercise our discretion to deny institution of an inter partes review. (*See* Prelim. Resp. 60– 67 (citing *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.); *see also* Patent Owner's Pre-Institution Sur-Reply ("PO Sur-Reply"), Paper 9.) Petitioner opposes Patent Owner's assertions. (*See* Pet. 64–65; *see also* Petitioner's Reply to Patent Owner's Preliminary Response ("Pet. Reply"), Paper 8.)

We look to the following factors in evaluating whether to do so:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
> 3. investment in the parallel proceeding by the court and the parties;
> 4. overlap between issues raised in the petition and in the parallel proceeding;
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Apple Inc. v. Fintiv, Inc., IPR2020-00019, Paper 11 at 5-6 (PTAB Mar. 20, 2020) (precedential). We are also guided by the Director's Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation, issued on June 21, 2022 ("Memorandum") (Ex. 1065).

In regard to the first factor identified in *Fintiv*, Patent Owner argues that a stay of the district court litigation is unlikely, even though Petitioner asserts that it will seek one and that the early stage of the proceeding portends a reasonable

likelihood of granting a stay. (*See* Prelim. Resp. 62; *see* Pet. 64.) According to Patent Owner, because Petitioner has filed other IPR petitions challenging eight other patents asserted in the district court litigation and the decisions on institution are due after the district court activities "will be significantly advanced," there is no evidence to suggest a stay will be granted. (Prelim. Resp. 61–62.) Patent Owner also argues that the district court litigation involves contract claims that cannot be resolved by the Board, making a stay unlikely. (*See* PO Sur-Reply 4.)

Given that no request for a stay has been made at this time, it is unclear if the Court will entertain a stay. Accordingly, *Fintiv* factor 1 neither indicates nor does not indicate discretionary denial.

The parties dispute the facts of the second *Fintiv* factor — proximity of the court's trial date to the Board's deadline for a final written decision. Patent Owner argues that the district court has entered a Scheduling Order under which pre-trial motions are due by February 3, 2025. (*See* Prelim. Resp. 62–63.) Patent Owner asserts that the expected trial date is April or May of 2025, which is before the estimated date of our final decision — mid-June 2025. (*See* Prelim. Resp. 62–63.) Petitioner disputes Patent Owner's assertion of a trial date, arguing that no actual expected trial date has been set and that, in light of the average time to trial in the District of Maryland being over 40 months, a trial would be expected in mid-2026, a year later than Patent Owner asserts.[12] (*See* Pet. Reply 1–2 (citing U.S. District Court — Judicial Caseload Profile, Ex. 1067).) Patent Owner argues in sur-reply that the schedule for the district court litigation requires dispositive motions be fully briefed by February 3, 2025, and that anticipating the Court "would let the

[12] In the Petition, Petitioner argues that the trial date would be "the trial will not begin until mid-2025—over 1.5 years from the filing of this petition" (Pet. 64), but in the Sur-reply, Petitioner refers to this as an "obvious typo given the context and the time-to-trial statistics." (Pet. Reply 1–2.)

case languish for 15 months thereafter without trial, as Merck contends, is inconsistent with the pace set by the Scheduling Order." (PO Sur-Reply 5 (citing Scheduling Order, Ex. 1066, 6.))

The Director has stated that *scheduled* trial dates are unreliable and often change, making them not a good indicator of whether a district court trial would occur before the statutory deadline for a final written decision. (*See* Memorandum, Ex. 1065, 8.) Because the Court's scheduling order does not yet include a trial date, indicating the trial has currently not been scheduled, we are not persuaded that a trial will occur when Patent Owner contends. Instead, it seems likely that a trial will occur considerably later and after our Final Written Decision must be issued in mid-June 2025, particularly in light of the statistics Petitioner presents. Accordingly, the second *Fintiv* factor weighs in favor of not exercising our discretion to deny institution of a trial.

Patent Owner argues that in regard to the third *Fintiv* factor, investment in the parallel proceeding by the court and the parties, the District Court litigation has been pending for over 15 months and the parties have already "engaged in considerable discovery." (Prelim. Resp. 63–64.) Patent Owner argues that other activities, such as claim construction, fact and expert discovery, and a trial will occur, although after we would institute a trial. (*See id.*) According to Patent Owner, "[t]his is a situation of [Petitioner's] making" because Petitioner filed suit against Patent Owner and, thus, had a chance to challenge Patent Owner's patents before filing its Petition. (PO Sur-Reply 5.)

Patent Owner cites to no investment in the district court proceeding by either the parties or the court beyond the usual effort in beginning a litigation. Because the district court case is in its early stages, with no substantive orders specific to the facts or circumstance of the case, we are not persuaded that *Fintiv* factor 3

weighs in favor of denying institution of a trial. (*See Fintiv.* IPR2020-00019, Paper 11 at 9–10.) Patent Owner asserts that Petitioner delayed in filing this Petition, but given the timeline, wherein the complaint in the district court litigation was filed before the '393 patent issued on February 28, 2023, (Ex. 1001) and the Petition was filed November 30, 2023, we do not discern a long delay. (*See* PO Sur-Reply 5; *see* Prelim. Resp. 63 (asserting that the district court proceeding had been pending for over 15 months in light of the Preliminary Response filed March 14, 2024, Patent Owner discloses that the district court case began before the '393 patent issued).) *See Fintiv,* IPR2020-00019, Paper 11 at 11 ("As a matter of petition timing, notwithstanding that a defendant has one year to file a petition, it may impose unfair costs to a patent owner if the petitioner, faced with the prospect of a looming trial date, waits until the district court trial has progressed significantly before filing a petition at the Office."). Accordingly, the third *Fintiv* factor does not indicate we should deny institution.

Fintiv factors 4 and 5 weigh in favor of denying institution because Petitioner does not deny that the same claims, the same prior art, and the same parties are involved in the district court proceeding. (*See* Prelim. Resp. 64–65; *see* Pet. Reply 2–3.)

In regard to *Fintiv* factor 6, though, we are guided by the Director's June 21, 2022 Memorandum, which states that "to benefit the patent system and the public good, the PTAB will not rely on the *Fintiv* factors to discretionarily deny institution in view of parallel district court litigation where a petition presents compelling evidence of unpatentability." (Memorandum 2, *see id.* at 3–5.) As explained in detail above, at this point in the proceeding, we are persuaded that the merits of Petitioner's challenges are compelling. Thus, the interest of efficiency and integrity in the overall patent system may be served by instituting a trial and

allowing the proceeding to continue in the event the parallel proceeding settles or fails to resolve the patentability question presented in this proceeding. (*See Finitv.* IPR2020-00019, Paper 11 at 5–6.) The sixth *Fintiv* factor weighs heavily in favor of not exercising our discretion to deny institution.

In summary, we find that although the overlap of the issues and identity of the parties (factors 4 and 5) tend to indicate we should exercise our discretion to deny institution, the proximity of a trial date (factor 2), investment of the parties and the Court (factor 3), and, particularly, the merits of Petitioner's challenge (factor 6), tend to indicate we should institute an *inter partes* review. Accordingly, we decline to exercise discretion to deny institution of a trial under 35 U.S.C. § 314(a).

III. CONCLUSION

After reviewing the merits of the Petition and Patent Owner's arguments in opposition, we are persuaded that Petitioner has met the burden to show a reasonable likelihood of prevailing on at least one challenge to claim 1. *See* 35 U.S.C. § 314(a). We are not persuaded that there is a reason to exercise the discretion provided by either 35 U.S.C. § 314(a) or § 325(d) to deny institution of trial. Accordingly, we institute trial on all grounds of challenge presented in the Petition.

We have not made a final determination as to the patentability of any challenged claim or as to the construction of any claim term. Any final determination will be based on the record developed during trial.

IV. ORDER

It is hereby

ORDERED that, pursuant to 35 U.S.C. § 314(a), a post-grant review of claims 1–42 of U.S. Patent 11,591,393 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter-partes* review of the '393 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

FOR PETITIONER:

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

FOR PATENT OWNER:

Nicholas Stephens
Grace Kim
Anita Meiklejohn
Matthew Chun
Todd Miller
nstephens@fr.com
gkim@fr.com
meiklejohn@fr.com
mchun@fr.com
miller@fr.com