

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

Patent No. 11,591,393

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,591,393**

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I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC (“Petitioner” or “Merck”) requests *inter partes* review of Claims 1-42 of U.S. Patent No. 11,591,393 (“the ’393 patent”), which is assigned to Patent Owner The Johns Hopkins University (“JHU”).

The ’393 patent broadly claims the use of a prior art drug (pembrolizumab) in a treatment of a sub-population of cancer patients (patients whose cancers have a genetic instability called microsatellite instability-high (“MSI-H”)) also disclosed in the prior art. The prior art disclosed this use because it was known that MSI-H tumors were more immunogenic, and would benefit from the use of an immunotherapy drug like pembrolizumab. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶¶41-49.) In fact, the specification of the JHU patent is a clinical study *published in the prior art more than a year* before the filing of JHU’s patent applications, which was a collaboration by Merck and JHU (the “MSI-H Study Record”).

This study was consistent with the teachings of the literature that PD-1 inhibitors naturally had more efficacy when treating tumors that (1) have many mutations, and thus are comprised of cancer cells that are easy for immune cells to recognize, and (2) are already infiltrated by many immune cells, which kill the

tumor cells. (*Infra*, §§III.C, VI.C.3.) The literature also taught that MSI-H tumors naturally displayed those characteristics. (*Infra*, §§III.C, VI.C.3.) By the relevant time period, the literature had therefore taught that MSI-H tumors exhibited the characteristics that were most relevant for PD-1 efficacy, including many mutations and infiltration by lymphocytes. (*E.g.*, EX1006, 3740-41; EX1003, ¶¶41-46.)

As explained in detail below and in the Declaration of Dr. Alfred I. Neugut, all claims of the '393 patent are unpatentable, as they fail to meet several statutory requirements.

First, the independent claims and most dependent claims of the '393 patent are anticipated. (35 U.S.C. § 102; EX1003, ¶¶ 4-17, 50-104, 175-76.) More than a year prior to JHU's first provisional application, the MSI-H Study Record taught the claimed methods, and those methods inherently achieve the claimed efficacy from the treatment. JHU overcame the MSI-H Study Record on the ground that it did not expressly include the results flowing from the treatment, but under controlling precedent of the Court of Appeals for the Federal Circuit, which was not considered during prosecution or brought to the attention of the Examiner, that outcome was legal error.

Second, all of the '393 patent claims would have been obvious to the person of ordinary skill in the art ("POSA") as of the priority date, including all dependent

claims. (35 U.S.C. § 103; EX1003, ¶¶4-17, 105-76.) For example, even if JHU's rationale for overcoming the MSI-H Study Record were accepted, the prior art provided a motivation to carry out the MSI-H Study Record's protocol and a reasonable expectation of success in doing so. Further, the prior art also taught the routine methods for testing a cancer for the genetic marker of MSI-H (and the patents do not purport to have discovered any new methodology for doing so). All but one of the additional prior art references relied on in the obviousness grounds were not considered by the Examiner, and the Examiner considered none the obviousness arguments and combinations presented in this petition.

The Board should institute trial and cancel the challenged claims.

II. STANDING AND GROUNDS

Merck certifies under 37 C.F.R. § 42.104(a) that the '393 patent is available for review and Merck is not barred or estopped from requesting review on the grounds identified herein. Merck respectfully requests review of Claims 1-42 of the '393 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 are unpatentable under 35 U.S.C. § 102 as being anticipated by the published MSI-H Study Record (EX1005).

Ground 2: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 are

unpatentable under 35 U.S.C. § 103 as being obvious over the published MSI-H Study Record (EX1005) in view of Pernot (EX1006).

Ground 3: Claims 2, 8, 15, and 21 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Chapelle (EX1007).

Ground 4: Claims 3 and 16 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Steinert (EX1008).

Ground 5: Claims 7, 20, 29-30, 32, 34, and 36-42 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Benson (EX1009).

Ground 6: Claims 9, 10, 22, and 23 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Salipante (EX1010).

Ground 7: Claims 11-12 and 24-25 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Hamid (EX1011).

Ground 8: Claims 13 and 26 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study

Record (EX1005) in view of Pernot (EX1006), in view of Steinert (EX1008) and Hamid (EX1011).

III. BACKGROUND OF THE '393 PATENT

Unless otherwise noted, the following information was known to the skilled artisan more than a year before the earliest priority date.

A. The Mechanism of the Prior Art Drug at Issue

Claims 1 and 14 of the '393 patent, the patent's only independent claims, are directed to identifying colorectal cancer patients who have MSI-H and mismatch repair deficient tumors and administering Merck's immunotherapeutic drug pembrolizumab (known today by the tradename Keytruda[®]) to those patients. (EX1001, 25:39-28:29.)

An immunotherapy is a drug that helps the body fight disease by boosting the immune system. (EX1012, 459.) One particular type of immunotherapy is called a PD-1 inhibitor. (EX1033, 2965; EX1014, 253.) By the relevant time period, Merck's drug pembrolizumab was a known PD-1 inhibitor undergoing clinical development. (EX1011, 135.)

The prior art disclosed how PD-1 inhibitors treat cancer. (EX1003, ¶¶29-32.) Normally, immune cells find and kill cancer cells. In response, cancer cells put brakes on the immune system. As Dr. Neugut explains, pembrolizumab blocks

receptors that otherwise inhibit the body's immune response, thereby releasing the brakes that the cancer cells put on the immune cells. (EX1003, ¶32.)

Merck began clinically developing pembrolizumab in 2010. (EX1015, 1388.) While developing pembrolizumab, Merck treated cancer patients in clinical studies, including patients having MSI-H cancers. (EX1005, 4 (Arms and Interventions); EX1016; EX1017; EX1023 at 42; EX1003, ¶33.)

A person's cancer is considered MSI-H if the cancer cells' DNA contains small tracts of repeating DNA, called microsatellites, that are different in size than regularly occurring microsatellites. (EX1001, 1:32-34; EX1010, 1192-93; EX1003, ¶26.) MSI-H is also known throughout the literature as MSI positive, MSI-high, MSIH, or MSI+. (EX1010, 1193, 1196; EX1018, 293 (authors include named '393 patent inventors); EX1019, 1065 (authors include a named '393 patent inventor); EX1003, ¶26.) MSI-H is caused by deficient mismatch repair ("dMMR"), also known as "Mismatch repair deficiency" or "DNA mismatch repair deficient." (EX1001, 1:32-34; EX1010, 1192; EX1003, ¶27.) MSI-H and dMMR are "biologically the same" and testing for one condition was considered "equivalent" to testing for the other. (EX1020, MS-12 (PDF p. 51); EX1007, 3380; EX1001, 10:39-64 (assessing dMMR status using MSI-H testing); EX1003, ¶24, 28.) By 2014, upon diagnosis of colorectal cancer, it was common to test tumors for MSI-H. (EX1003, ¶¶24-25.) Whether a colorectal cancer tumor

exhibited MSI-H could inform therapeutic choices, prognosis, and familiar cancer risk appraisal. (EX1003, ¶25.)

B. The Prior Art MSI-H Study Record

In late 2012, JHU approached Merck about collaborating on a clinical study using pembrolizumab to treat cancer patients whose cancers were identified as being MSI-H. (EX1029, ¶¶90-93.) The Parties agreed to collaborate on the clinical study, which uses the study identifier NCT01876511 (the “MSI-H Study”). (EX1005, 3 (Collaborators); EX1003, ¶34.)

On June 10, 2013, the MSI-H Study Record detailing the parameters and protocols for that clinical study was submitted to and published on www.clinicaltrials.gov. (EX1005, 3 (Study Status); EX1003, ¶35.)¹ The website, www.clinicaltrials.gov, publicizes clinical trials in a searchable and easy to

¹ The MSI-H Study Record was periodically resubmitted (e.g., on June 12, 2013, September 20, 2013, May 21, 2014, and June 25, 2014). (EX1024; EX1025; EX1026; EX1027; EX1003, ¶35.) Those versions are substantively identical. In any event, however, all submissions remain available in view of the practice of www.clinicaltrials.gov of maintaining archived versions of each submission. (See, e.g., EX1005, 1-2; see also EX1003, ¶51.)

understand manner in order to keep doctors and patients apprised of ongoing clinical trials. (EX1021, 1-4; EX1003, ¶36.) It was indexed by subject matter, and would have been used by a POSA to understand the state of the art. (EX1003, ¶36.)

During prosecution of the '393 patent and its family members, named inventor Andrew Pardoll admitted that the MSI-H Study Record published as early as June 12, 2013. (EX1002, March 22, 2022 Affidavit, ¶22; EX1022, February 4, 2020 Affidavit, ¶22.) And more recently, in district court litigation, JHU similarly admitted that the MSI-H Study Record was published on June 10, 2013 (and on June 12, 2013). (EX1029, ¶¶22, 103.)

The MSI-H Study Record is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). *See Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01288, Paper 30 at 14-24 (PTAB Feb. 23, 2022); *Grünenthal GMBH v. Antecip Bioventures II LLC*, PGR2019-00003, Paper 22 at 17-18 (PTAB May 5, 2020).

It was not until more than one year after the MSI-H Study Record published that JHU filed the First Provisional (without Merck's knowledge). (EX1030, PDF p. 1.) Yet the '393 patent's claimed subject matter derives directly from the MSI-H Study. (*See* EX1002, March 22, 2022 Affidavit, ¶¶22-23 (connecting the '393 patent, the MSI-H Study Record, and a New England Journal of Medicine article

(EX1031) that discusses the results of the MSI-H Study); EX1005, 2 (using study identifier number NCT0187511); EX1031, 2509 (discussing the results of the MSI-H Study using study identifier number NCT0187511); EX1003, ¶¶37-40.) Indeed, all of the '393 patent's examples, tables, and figures are devoted to the design and results of the MSI-H Study, a "small phase 2 trial of pembrolizumab." (EX1001, 6:52-22:30, 3:19-21; Figs. 1-13; EX1005; EX1003, ¶39.) For instance, Examples 1-4 (EX1001, 8:7-15:67) are the design of the MSI-H Study, and Examples 5-11 (EX1001, 16:1-18:54) report its results. Further, Tables 1-3 (EX1001, 18:60-22:28) and Figures 1-13 also report the MSI-H Study's results.

The Examiner did not consider the MSI-H Study Record during prosecution of the application that matured into the '393 patent. (*See generally* EX1002.) The Examiner did consider the MSI-H Study Record during prosecution of an earlier patent family member, U.S. Patent No. 10,934,356 ("the '356 patent"), and recognized that the MSI-H Study Record disclosed 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. (EX1022, December 14, 2020 Notice of Allowance, 3.) The Examiner nonetheless allowed the '356 patent over the MSI-H Study Record on the rationale that it did not affirmatively disclose the results flowing from the disclosed treatment. (*Id.*) The Examiner's requirement for an express disclosure of an inherent result of the disclosed treatment was

incorrect as a matter of law, as shown in detail below. (*See infra*, §VI.B.1; *see also infra*, §VII.B (explaining why the Board should not exercise its discretion to deny institution under 35 U.S.C. § 325(d)).)

C. Other Prior Art Had Recognized the Utility of PD-1 Inhibitors for Treating MSI-H Cancers, Consistent With the Fact that Merck and JHU Used Merck’s PD-1 Inhibitor to Treat Such Cancer Patients in the MSI-H Study

In addition to the MSI-H Study Record, before JHU filed the First Provisional, others in the field had published on the use of PD-1 inhibitors to treat patients whose cancers were MSI-H. For example, another clinical study record (EX1053; EX1003, ¶49) and a number of publicly available articles had already recommended evaluating the treatment of patients whose cancers were MSI-H with immunotherapeutic agents like pembrolizumab. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2969; EX1034, 747; EX1035, 1, 8; EX1036, 1186; EX1037, 2; EX1038, 7; EX1039, 243s; EX1003, ¶¶47-49.)

Indeed, in April 2014, Pernot taught that MSI-H colorectal cancers are “good candidates for immunotherapy.” (EX1006, 3740-41.) Further, Champiat taught in January 2014 that “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.” (EX1032, e27817-5; EX1003, ¶48.) Those suggestions built upon the previously established knowledge

that the MSI-H condition made it easier for a patient's immune system to detect and attack the cancer. (EX1040, 2; EX1038, 5; EX1041, 9208; EX1042, 731; EX1006, 3740-41; EX1037, 2; EX1035, 4; EX1036, 1186-87, 1193; EX1003, ¶¶41-46.)

IV. CLAIM CONSTRUCTION

For IPR proceedings, the Board applies the claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). See 37 C.F.R. § 42.100(b). Under *Phillips*, claim terms are typically given their ordinary and customary meanings, as would have been understood by the POSA, at the time of the invention, having taken into consideration the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; see also *id.* at 1312-16.

The Board only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-00633, Paper 11 at 16 (PTAB. Aug. 14, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Here, given the correlation between the MSI-H Study Record, the written description of the '393 patent, and the challenged claims, the Board need not construe any terms of the challenged claims to resolve the underlying controversy, as any reasonable

construction reads on the prior art. Merck reserves all rights to raise claim construction and other arguments in other venues.

V. LEVEL OF ORDINARY SKILL IN THE ART

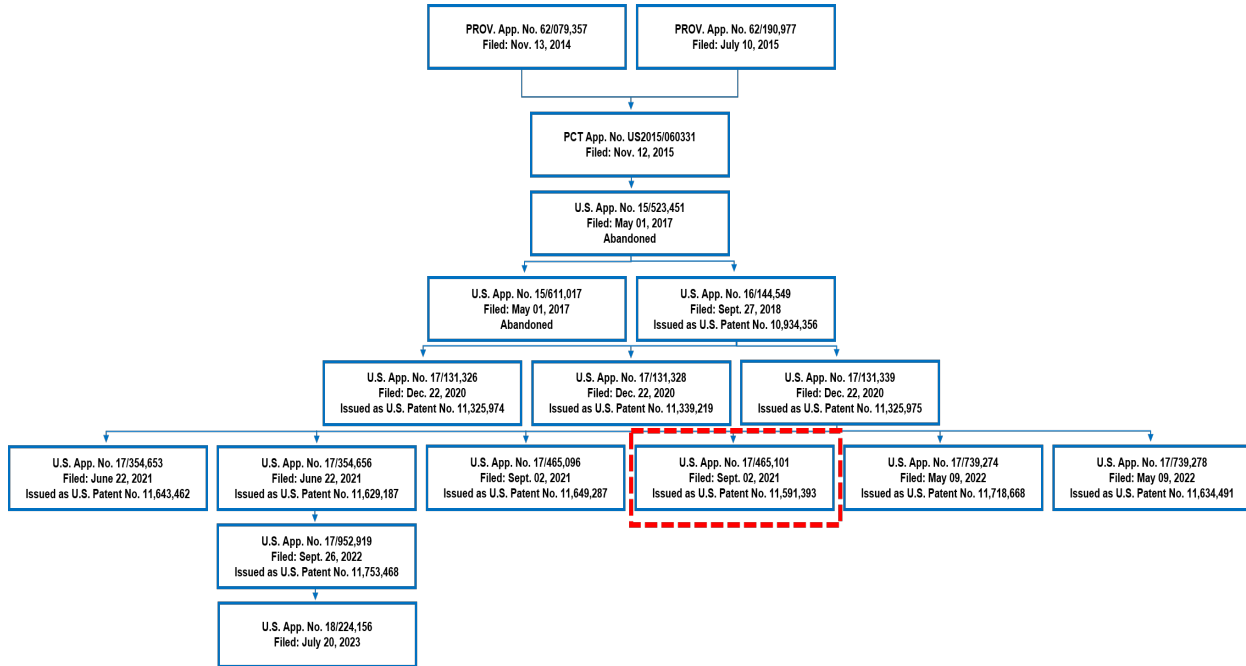
The POSA for purposes of the '393 patent would be a medical doctor or a professional in a related field with at least five years of experience with treating cancer. (EX1003, ¶19.) The POSA would also have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and a pathologist with comparable experience. (EX1003, ¶19.) The inherent anticipation and obviousness grounds discussed herein would not change due to a modestly lesser or greater level of experience.

VI. THE '393 PATENT CLAIMS ARE UNPATENTABLE

A. If JHU Is Bound to the Representations It Made During Prosecution, It Is Not Entitled to Claim Priority to the First Provisional Patent Application

On its face, the '393 patent cites two provisional patent applications: the First Provisional and U.S. Patent Application No. 62/190,977 (filed July 10, 2015) (the "Second Provisional"). The relationship of the '393 patent to those applications, as well as patents issued therefrom, is shown in the purported priority chain below:

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For a non-provisional utility application to be afforded the priority date of a provisional application, “the written description of the provisional must adequately support the claims of the non-provisional application.” *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1380 (Fed. Cir. 2017) (citations and quotations omitted) (emphasis removed). The test for adequate written description is “whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Nalpropion Pharms., Inc. v. Actavis Lab’y’s FL, Inc.*, 934 F.3d 1344, 1350 (Fed. Cir. 2019) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)) (emphasis removed). Further, the standard for what constitutes proper enablement of a prior art reference for purposes of the enablement standard

under section 112 differs from the enablement standard under section 102.

Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1326 (Fed. Cir. 2005).

Here, JHU submitted declarations during prosecution, seeking to distance the patent from the MSI-H Study, by arguing that data from the clinical study was the basis for patentability (which thus led the Examiner to a legally erroneous rationale for allowing the patent to issue). (See EX1022, February 4, 2020 Affidavit, ¶¶22, June 8, 2020 Affidavit, ¶¶27-28.) The First Provisional, however, did not include the data referred to in the declarations. Thus, even though JHU was wrong to assert that the reporting of the data from the MSI-H Study could create patentability for the treatment disclosed in the prior art), JHU must be bound to its positions – JHU cannot claim priority to the First Provisional without contradicting its sworn positions during prosecution. In other words, the First Provisional lacks the disclosure of the data (inherent in the performance of the study), which JHU nonetheless argued was necessary for patentability. As such, applying JHU’s own sworn positions, the July 10, 2015 filing date of the Second Provisional is the applicable critical date for purposes of analyzing the prior art.²

² To be clear, each ground of invalidity discussed in this Petition applies even if the First Provisional were a basis for priority. And Merck disagrees that the

B. Ground 1: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the '393 Patent are Anticipated by the MSI-H Study Record

1. Law on Anticipation

“A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, 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.” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citations omitted). “[I]f 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.” *Id.* at 1379.

In *Schering*, the Federal Circuit clarified 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.” *Schering*, 339 F.3d at 1380.

declarations are sufficient to avoid the prior art, both because the inherent efficacy of the treatment taught in the prior art cannot render the treatment itself patentable (*see infra*, §VI.B.1), and because a prior art disclosure may anticipate even if it that same disclosure could not support a claim of priority (*see Rasmusson*, 413 F.3d at 1325-26).

For example, *Schering* explained that the prior art disclosure of a method of treatment by administering loratadine, an antihistamine, inherently anticipated a later patent seeking to claim the metabolite naturally produced *in vivo*, even though, at the time of the filing of the metabolite patent, the loratadine method had not been practiced, and the metabolite was neither disclosed in the prior art or even in actual existence. *Schering*, 339 F.3d at 1378, 1380.³ It was sufficient for anticipation that, if one of skill practiced the use described in the prior art, the metabolite would be produced by the body *in vivo*. *Schering*, 339 F.3d at 1380. The Federal Circuit reaffirmed that principle as recently as April 2023. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). In *Arbutus*, the claimed morphology of a composition was inherently anticipated by following a prior art reference's formulations using that same reference's methods. *Arbutus*, 65 F.4th at 664.

³ *Schering* also brought clarity to prior precedent. *Schering*, 339 F.3d at 1377-80 (“This court recognizes that this may be a case of first impression, because the prior art supplies no express description of any part of the claimed subject matter.”). The Examiner may very well have been unfamiliar with this area of the law of anticipation.

The law established by *Schering* has specifically been applied in the context of clinical studies prior to publication of the data from the study. 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. *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012). In rejecting the argument that the claimed method must have actually been performed, the Federal Circuit explained that, “even if [the documents disclosing the 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. The Federal Circuit went on to further hold that, “even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps.” *Id.* at 1381; *see also In re Couvaras*, 70 F.4th 1374, 1380 (Fed. Cir. 2023) (“Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.”) (citing *In re Montgomery*, 677 F.3d at 1381). The Federal Circuit has also made clear that “[e]xtrinsic evidence can be used to demonstrate what is necessarily present in a prior art embodiment even if the extrinsic evidence is not itself prior art.” *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (quotations omitted).

The MSI-H Study Record inherently anticipates Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the '393 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. Indeed, anticipation could not be possibly be clearer because the treatment disclosed in the prior art MSI-H Study Record is written description support for the treatment method of the claims. For example, 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. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶¶22, 37-40.)

2. Claim 1

- a. **[1.pre]: “A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising”**

The Arms and Interventions section of the MSI-H Study Record discloses a method of treating human MSI positive colorectal cancer patients. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility).) This is the method set forth in the preamble. (EX1003, ¶¶53-57.)

As discussed above in Section VI.B.2.a, the POSA would have understood the MSI-H Study Record's disclosure of “MSI positive” patients to refer to “MSI-

H” patients. (*See, e.g.*, EX1010, 1193, 1196; EX1018, 293; EX1019, 1065; EX1003, ¶¶26-28, 54.) Indeed, named inventor Dr. Pardoll represented in a sworn declaration that the MSI-H Study Record concerns MSI-H patients. (EX1022, February 4, 2020 Affidavit, ¶¶21-23 (“Dr. Dung Le prepared a study proposal for testing anti-PD-1 antibodies . . . in . . . MSI-positive colon cancer patients The preliminary results of this study demonstrated clinical responses . . . in the MSI-H (MMR deficient) arm.”).)

The claimed method of treating patients with “DNA mismatch repair deficient” cancer reads on the MSI-H Study Record’s disclosure of a method of treating patients with “MSI positive” cancer. (EX1003, ¶¶26-28, 54.) For example, the art taught that “[p]atients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.” (EX1020, MS-12 (PDF p. 51); EX1001, 8:9-36 (using MSI status to characterize patients as dMMR).) And, in his declaration, Dr. Pardoll equated MSI-H and dMMR patients. (EX1022, February 4, 2020 Affidavit, ¶23 (“[T]he MSI-high (MMR deficient) arm.”).) Moreover, because MSI-H is caused by dMMR, all

cancers that are MSI-H are dMMR. (EX1010, 1192; EX1003, ¶¶26-28, 54; *see also* EX1001, 1:32-34.)⁴

- b. **[1.1]: “testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient’s colorectal cancer is microsatellite instability high or mismatch repair deficient;”**

The Arms and Interventions section of the MSI-H Study Record discloses three study arms, one of which consists of patients having MSI-H colorectal cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶58.)⁵

⁴ Because “[p]atients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status” (EX1020, PDF p. 51), this Petition’s use of MSI-H should be read to mean MSI-H and dMMR, unless otherwise noted.

⁵ As discussed above, “MSI positive colorectal cancer” would be understood by the POSA to mean “microsatellite instability high” and “mismatch repair deficient” colorectal cancer. (*Supra*, §VI.B.2.a.)

According to the MSI-H Study Record's disclosure, the MSI-H Study Record required testing or having tested "a biological sample obtained from a patient having colorectal cancer" in order to place the patients into the proper arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶58.) That is, to determine a patient's cancer is MSI-H is to test for specific biomarkers. (EX1003, ¶23, 58.)

- c. **[1.2]: "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."**

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶¶59-63.)

The MSI-H Study Record does not expressly use the phrase "therapeutically effective" in providing the dosage for the treatment therapy. Nonetheless, the dosage described in the MSI-H Study Record, 10 mg/kg MK-3475 (pembrolizumab), is identical to the dosage described as being "therapeutically

effective” in the ’393 patent, and any required efficacy is thus inherent to that dosage. (EX1003, ¶¶59-62.)

Indeed, the ’393 patent itself, which only describes one dosage (EX1001, 8:50-56, 13:24-30)—the same one in the MSI-H Study Record (EX1005, 4 (Arms and Interventions)—asserts that this dosage is effective. (EX1001, 4:23-36 (showing the “[c]linical benefit to pembrolizumab according to MMR status”), 16:4-8, 16:29-32, 19:40-21:15, Figs. 2, 11; EX1003, ¶61; *see also infra*, §§VI.B.22-33 (addressing the efficacy requirements of certain dependent claims).) “To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does.” *See King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010). Other sources reporting the results of the MSI-H Study similarly confirm the efficacy of the dosage used in the MSI-H Study Record. (EX1031, 2509, 2514; Table 1, Table 2, Table 3, Figure 1, Figure 2; EX1064; EX1029, ¶¶89, 105, 110, 117; EX1003, ¶62.)

The MSI-H Study Record is also enabled for the purposes of anticipation. In the context of treating cancer, “proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation,” and disclosure of the method enables the reference. *Rasmusson*, 413 F.3d at 1326. Here, as discussed above, the MSI-H Study Record discloses administering pembrolizumab 10 mg/kg every 14 days to colorectal cancer patients with MSI-H cancer. (EX1005, 4 (Arms and

Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶59.)

3. Claim 2: “The method of claim 1, wherein the biological sample is a tumor tissue from the patient.”

As discussed above in Section VI.B.2.b, the Arms and Interventions section of the MSI-H Study Record discloses determining whether the patient’s colorectal cancer is MSI-H. (*See also infra*, §VI.C.3.) Further, the Eligibility section of the MSI-H Study Record requires each patient to “[a]gree to have a biopsy of their cancer.” (EX1005, 5-6 (Eligibility).) The POSA would have understood that a biopsy of a patient’s tumor obtains tumor tissue for testing. As such, in the context of the MSI-H Study Record, where patients are separated into three separate cohorts based, in part, on whether a patient’s cancer is MSI-H, the POSA would have understood that the biopsy would obtain tumor tissue to test whether the patient’s cancer’s is MSI-H (EX1007, 3380, 3383; EX1044, 3309; EX1045, 3485; EX1046, 1193; EX1003, ¶64; *see also* EX1001, 8:13-15 (testing “[a]rchived tumor samples” or “newly obtained biopsies.”).) Therefore, the MSI-H Study Record’s disclosure of treating MSI-H patients and the MSI-H Study Record’s requirement that patients agree to have a biopsy demonstrates that the MSI-H Study Record discloses the claimed limitation. (EX1003, ¶64.)

4. **Claim 4: “The method of claim 1, wherein the patient is treated with an amount of pembrolizumab shown in a clinical trial to be effective in promoting progression-free survival in multiple human subjects whose colorectal cancer is microsatellite instability high or mismatch repair deficient.”**

The Arms and Interventions section of the MSI-H Study Record discloses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *supra*, §VI.B.2.c.) That discloses the claimed limitation because treating patients with 10 mg/kg of pembrolizumab every 14 days, as disclosed in the MSI-H Study Record, was inherently effective in promoting progression-free survival in multiple human subjects whose colorectal cancer is MSI-H. (*See supra*, §§VI.B.1, VI.B.2.c; EX1003, ¶¶40, 60-62, 65.)

5. **Claim 5: “The method of claim 1, wherein the colorectal cancer is determined to be microsatellite instability high.”**

As explained in Section VI.B.2, the Arms and Interventions section of the MSI-H Study Record discloses treating colorectal cancer patients whose tumors were determined to be MSI-H. (EX1003, ¶66.)

6. **Claim 6: “The method of claim 1, wherein the colorectal cancer is determined to be DNA mismatch repair deficient.”**

As explained in Section VI.B.2, the Arms and Interventions section of the MSI-H Study Record discloses treating colorectal cancer patients whose tumors were determined to be dMMR. (EX1003, ¶67.)

7. **Claim 7: “The method of claim 1, wherein, prior to treatment with pembrolizumab, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”**

The MSI-H Study Record’s title and Eligibility section discloses that patients in the Phase II study must have “tumors” and “measurable disease.” (EX1005, 2 (Study Identification), 4 (Study Design), 5-6 (Eligibility).) In the context of the MSI-H Study Record, that discloses that patients would have received prior drug therapies and had their cancers progress after those therapies. (EX1003, ¶¶68-72.)

Patients having “measurable” disease in the context of the MSI-H Study Record refers to patients having metastatic and advanced cancer and does not include patients whose cancer was resectable for the purposes of a cure. (EX1020, PDF p. 25; EX1003, ¶69.) If a patient had cancer that is resectable for the purposes of a cure, then a practitioner would excise the tumor because surgery “is the only way to achieve a cure;” thus the POSA would have understood “measurable” disease in the context of a clinical trial to not include cancer that is resectable for the purposes of a cure. (EX1047, 4-7; EX1020, PDF p. 7 (under the standard of care, resection is recommended if it is possible); EX1048, 230; EX1003, ¶69.)

Patients with metastatic and advanced 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. (EX1020, PDF p. 25; *see also* EX1009, 1034; EX1047, 4-7; EX1003, ¶70.) Additionally, because the patients were disclosed to still have a “tumor” and “measurable disease,” it would mean that the cancer had progressed following that prior treatment. (EX1003, ¶70.) Indeed, the POSA would have found it highly unusual for that patient population, patients who had received two prior drug treatments and had their cancer progress after those treatments, to not be included in the MSI-H Study Record, especially without any explicit carve-out. (EX1003, ¶70.)

Consistent with the above, the Eligibility section of the MSI-H Study Record excludes “[p]atients who have had prior treatment with anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies” from the clinical study. (EX1005, 5-6 (Eligibility); EX1003, ¶71.)

Therefore, the POSA would have understood that the MSI-H Study Record disclosed treating patients who had received prior/different cancer therapies, and the patients’ cancer had progressed after the patients received the different cancer therapies. (EX1003, ¶¶68-72.) *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020) (“In an anticipation analysis, the

dispositive question is whether a skilled artisan would ‘reasonably understand or infer’ from a prior art reference that every claim limitation is disclosed in that single reference”); *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1340 (Fed. Cir. 2020) (same); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (same).

8. Claim 11: “The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously.”

As discussed above in Section VI.B.2.c, the Arms and Interventions section of the MSI-H Study Record discloses administering 10 mg/kg of pembrolizumab every 14 days. A POSA would have understood that, at the time of the alleged invention, pembrolizumab for the treatment of cancer was administered intravenously. (*E.g.* EX1011, 134 (“We administered [pembrolizumab] intravenously.”); EX1054, 3; *see also* EX1055, 1 (“Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks.”); EX1003, ¶73.)

9. Claim 12: “The method of claim 2, wherein the pembrolizumab is administered to the patient intravenously.”

The additional limitation recited in Claim 12 is the same as recited in Claim 11 and disclosed for the same reasons. (*Supra*, §VI.B.8; EX1003, ¶74.)

10. Claim 14

- a. **[14.pre]: “A method of reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer, the method comprising”**

As discussed above in Section VI.B.2.c, the Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with 10 mg/kg pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Inclusion Criteria).) Thus, for all of the reasons that the MSI-H Study Record discloses all the limitations of Claim 1.pre, 1.1, and 1.2 (discussed above at §VI.B.2), the MSI-H Study Record discloses this limitation. In addition, the MSI-H Study Record discloses that outcome measures include “Immune-related progression free survival” and “Overall survival,” and as discussed above, the data inherently resulting from the MSI-H Study Record demonstrates improvements in those outcomes. (EX1005, 4-5 (Outcome Measures); *supra*, §§VI.B.1, VI.B.2.c.) For this additional reason, the MSI-H Study Record discloses “[a] method of reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer.” (EX1003, ¶75.)

- b. **[14.1]: “testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient;”**

This limitation is identical to limitation 1.1, and is disclosed for the same reasons. (*Supra*, §VI.B.2.b; EX1003, ¶76.)

- c. **[14.2]: “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.”**

This limitation is identical to limitation 1.2, and is disclosed for the same reasons. (*Supra*, §VI.B.2.c; EX1003, ¶77.)

- 11. **Claim 15: “The method of claim 14, wherein the biological sample is a tumor tissue sample from the patient.”**

The additional limitation recited in Claim 15 is the same as recited in Claim 2 and disclosed for the same reasons. (*Supra*, §VI.B.3; EX1003, ¶78.)

- 12. **Claim 17: “The method of Claim 14, wherein the patient is treated with an amount of pembrolizumab shown in a clinical trial to reduce the risk that microsatellite instability high or mismatch repair deficient colon cancer will progress.”**

The additional limitation recited in Claim 17 is the same as recited in Claim 4 and disclosed for the same reasons. (*Supra*, §VI.B.4; EX1003, ¶79.)

13. Claim 18: “The method of claim 14, wherein the colorectal cancer is determined to be microsatellite instability high.”

The additional limitation recited in Claim 18 is the same as recited in Claim 5 and disclosed for the same reasons. (*Supra*, §VI.B.5; EX1003, ¶80.)

14. Claim 19: “The method of claim 14, wherein the colorectal cancer is determined to be DNA mismatch repair deficient.”

The additional limitation recited in Claim 19 is the same as recited in Claim 6 and disclosed for the same reasons. (*Supra*, §VI.B.6; EX1003, ¶81.)

15. Claim 20: “The method of claim 14, wherein, prior to treatment with the step of selecting pembrolizumab for treating the patient’s colorectal cancer, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”

The additional limitation recited in Claim 20 is the same as recited in Claim 7 and disclosed for the same reasons. (*Supra*, §VI.B.7; EX1003, ¶82.)

16. Claim 24: “The method of claim 14, wherein the pembrolizumab is administered to the patient intravenously.”

The additional limitation recited in Claim 24 is the same as recited in Claim 11 and disclosed for the same reasons. (*Supra*, §VI.B.8; EX1003, ¶83.)

17. Claim 25: “The method of claim 15, wherein the pembrolizumab is administered to the patient intravenously.”

The additional limitation recited in Claim 25 is the same as recited in Claim 12 and disclosed for the same reasons. (*Supra*, §VI.B.9; EX1003, ¶84.)

18. Claim 27: “The method of claim 1 further comprising testing or having tested the patient for progression of the colorectal cancer after the treatment.”

The MSI-H Study Record discloses that a “primary outcome measure” is “Immune-related progression free survival (irPFS) rate at 20 weeks.” (EX1005, 4-5 (Outcome Measures).) The POSA would have understood that an “Immune-related *progression* free survival (irPFS) rate” is a test for disease progression. (EX1048, 236; EX1003, ¶85.) Thus, the MSI-H Study Record discloses this claim. (EX1003, ¶85.)

19. Claim 28: “The method of claim 14 further comprising testing or having tested the patient for progression of the colorectal cancer after the treatment.”

The additional limitation recited in Claim 28 is the same as recited in Claim 27 and disclosed for the same reasons. (*Supra*, §VI.B.18; EX1003, ¶86.)

20. Claim 29: “The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer.”

The MSI-H Study Record discloses that patients participating in the Phase II study must have “measurable disease” and “tumors.” (EX1005, 2 (Study Identification), 4 (Study Design), 5-6 (inclusion criteria); EX1003, ¶87.)⁶ In the

⁶ It also discusses that a primary endpoint was objective response rate, which refers to tumors shrinking. (EX1003, ¶68, fn. 5.)

context of the MSI-H Study Record, that discloses that patients would have metastatic and advanced cancer. (EX1003, ¶¶87-90.)

Patients having “[m]easurable” disease in the context of a study record, like the MSI-H Study Record, refers to patients having metastatic and advanced cancer,⁷ and does not include patients whose cancer was resectable for the purposes of a cure. (EX1020, PDF p. 25; *supra*, §VI.B.7; EX1003, ¶88.) The POSA would therefore understand that the MSI-H Study Record discloses treating patients with metastatic cancer and locally advanced cancer that is unresectable for purpose of a cure. (EX1003, ¶¶87-90.)

Further, if metastatic patients were not included, the POSA would have understood that would have been highly unusual, especially because the treatment in the study record was not directed to a local treatment, such as radiation or surgery. (EX1003, ¶89.)

Indeed, prior art concerning the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had “metastatic

⁷ Advanced cancer refers to metastatic cancer or cancer that is so locally advanced that it is unresectable for purposes of a cure. (EX1003, ¶69, fn. 6.)

tumors.” (EX1049, 444; *see also* EX1050, S4; EX1003, ¶90.) *See Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018).

21. Claim 30: “The method of claim 14, wherein the colorectal cancer is metastatic colorectal cancer.”

The additional limitation recited in Claim 30 is the same as recited in Claim 29 and disclosed for the same reasons. (*Supra*, §VI.B.20; EX1003, ¶91.)

22. Claim 31: “The method of claim 1, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.”

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.c.) The claimed efficacy is inherent to the MSI-H Study Record’s method of treatment. (EX1003, ¶¶40, 60-62, 92; *see supra*, §§VI.B.1, VI.B.2.c.)

The ’393 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, Fig. 11 (40% of MMR-deficient CRC patients obtained an objective response rate), 16:29-32 (same), 19:40-21:15 (same); EX1003, ¶¶40, 60-62, 92; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

- 23. Claim 32: “The method of claim 31, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation that Claim 32 recites is essentially the same as Claim 7, but further requires a cancer therapy drug. As discussed in the analysis for Claim 7, under the standard of care in the art, the MSI-H Study Record requires patients with colorectal cancer to have received at least two prior cancer therapy drugs and had their cancers progress after receiving those drugs. (*Supra*, §VI.B.7.) Thus, the additional method of Claim 32 is disclosed for the same reasons as Claim 7. (EX1003, ¶¶93-94.)

- 24. Claim 33: “The method of claim 1, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.”**

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.c.) The claimed efficacy is inherent to the MSI-H Study Record’s method of treatment. (EX1003, ¶¶40, 60-62, 95; *see supra*, §§VI.B.1, VI.B.2.c.)

The ’393 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001,

Fig. 11 (immune-related progression free survival at 20 weeks was 78% for MMR-deficient CRC), 16:4-8 (same)); EX1003, ¶¶40, 60-62, 95; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

- 25. Claim 34: “The method of claim 33, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation recited in Claim 34 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.23; EX1003, ¶96.)

- 26. Claim 35: “The method of claim 1, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.”**

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.c.) The claimed efficacy is inherent to the MSI-H Study Record’s method of treatment. (EX1003, ¶¶40, 60-62, 97; *see supra*, §§VI.B.1, VI.B.2.c.)

The ’393 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is inherent in the MSI-H Study. (EX1001, Fig. 2 (probability of progression-free survival at 9 months for MSI-H colorectal

cancer patients is at least 60%); EX1003, ¶¶40, 60-62, 97; *see also* EX1031, 2515 (results also disclosed in NEJM article).)

- 27. Claim 36: “The method of claim 35, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation recited in Claim 36 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.23; EX1003, ¶98.)

- 28. Claim 37: “The method of Claim 29, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.”**

The additional limitation recited in Claim 37 is the same as recited in Claim 31 and disclosed for the same reasons. (*Supra*, §VI.B.22; EX1003, ¶99.)

- 29. Claim 38: “The method of claim 37, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation recited in Claim 38 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.23; EX1003, ¶100.)

- 30. Claim 39: “The method of claim 29, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.”**

The additional limitation recited in Claim 39 is the same as recited in Claim 33 and disclosed for the same reasons. (*Supra*, §VI.B.24; EX1003, ¶101.)

- 31. Claim 40: “The method of claim 39, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation recited in Claim 40 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.23; EX1003, ¶102.)

- 32. Claim 41: “The method of claim 29, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.”**

The additional limitation recited in Claim 41 is the same as recited in Claim 35 and disclosed for the same reasons. (*Supra*, §VI.B.26; EX1003, ¶103.)

- 33. Claim 42: “The method of claim 41, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

The additional limitation recited in Claim 42 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.23; EX1003, ¶104.)

C. Grounds 2-8: Claims 1-42 of the '393 Patent are Obvious over the MSI-H Study Record in View of Various References

1. Law of Obviousness

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of evaluating underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and, if produced by Patent Owner, (4) so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Obviousness may be found, for example, where there was “an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. Further, claiming the inherent results of an otherwise obvious method does not make the method itself nonobvious. *Hospira*, 946 F.3d at 1329; *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

2. Overview of the Additional Prior Art

a. Pernot

Pernot is a journal article titled *Colorectal Cancer and Immunity: What We Know and Perspectives* and was published in the World Journal of

Gastroenterology on April 13, 2014. (EX1006, 3738, PDF p. 1; EX1003, ¶105.)

Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Pernot discloses and discusses how “[a]ltogether, [colorectal cancers] associated with [microsatellite instability]” are “good candidates for immunotherapy.” (EX1006, 3740-41; EX1003, ¶¶105-07.)

The Examiner did not consider Pernot.

b. Chapelle

Chapelle is a journal article titled *Clinical Relevance of Microsatellite Instability in Colorectal Cancer* and was published in the Journal of Clinical Oncology in 2010. (EX1007, 3380.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Chapelle discusses testing to determine whether a tumor is MSI-H using the tumor tissue of a patient. (EX1007, 3380, 3383.) Chapelle provides a test to measure MSI by immunohistochemistry, and discusses how, “[f]or practical purposes, [MSI-H] is equivalent to the loss of staining by immunohistochemistry (IHC) of one of the mismatch repair genes since both signify an abnormality in mismatch repair.” (EX1007, 3380; EX1003, ¶¶114-15.)

The Examiner did not consider Chapelle.

c. Steinert

Steinert is a journal article titled *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer* and was published on March 15, 2014. (EX1008, OF2) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Steinert is directed towards the testing of circulating colorectal cancer tumor cells to determine how they survive and escape the immune system, which includes determining whether a tumor is MSI-H. (EX1008, OF 1.) Steinert further discusses determining whether a tumor is MSI-H using blood samples. (EX1008, OF6; EX1003, ¶¶123-24.)

The Examiner did not consider Steinert.

d. Benson

Benson is a journal article titled *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology* and was published in the Journal of the National Comprehensive Cancer Network in July 2014. (EX1009, 1028.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Benson discloses that, under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (EX1009, 1034; EX1003, ¶¶129-30.)

The Examiner did not consider Benson.

e. Salipante

Salipante is a journal article titled *Microsatellite Instability Detection by Next Generation Sequencing* and was published in *Clinical Chemistry* in September 2014. (EX1010, PDF p. 2; EX1003, ¶151.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Salipante is directed towards tests for whether tumors are MSI-H. (EX1010.) Salipante discloses two types of tests to determine whether tumors are MSI-H: polymerase chain reaction (“PCR”) (EX1010, 1192) and next generation sequencing (EX1010, 1192). Salipante discusses that “PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use.” (EX1010, 1192.) Salipante further provides that next generation sequencing, “allows MSI status [whether tumors are MSI-H or not] to be reliably deduced at the same time that other genes of interest are sequenced, without the need for dedicated inclusion of specific markers.” (EX1010, 1193; EX1003, ¶¶151-52.)

The Examiner did not consider Salipante.

f. Hamid

Hamid is a journal article titled *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma* and was published in the *New England Journal of Medicine* on July 11, 2013. (EX1011, 132.) Therefore, it is prior art

under § 102(a) and not covered by any of the exceptions under § 102(b). Hamid reflects another name for pembrolizumab (*i.e.*, “lambrolizumab”) and discusses that pembrolizumab was administered to cancer patients intravenously. (EX1011, 134; *see* EX1054, 3 (“MK-3475 (pembrolizumab formerly lambrolizumab)”); EX1003, ¶¶163-64.)

Hamid was considered during prosecution, but not in the context of the combinations and arguments presented here.

3. Ground 2: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the '393 Patent Are Obvious Over the MSI-H Study Record in View of Pernot

As discussed above, Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that (1) even if Patent Owner (erroneously) argues that the MSI-H Study Record cannot anticipate because it did not affirmatively disclose an improved outcome or that a POSA would not have expected such efficacy (EX1022, December 14, 2020 Notice of Allowance at 3; *see also supra*, §I; *infra*, §VII.B), and/or (2) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach “testing, or having tested, a biological sample obtained from a patient” as recited in the independent claims, Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42, would at a

minimum still be unpatentable for obviousness in view of Pernot and the knowledge of a POSA.

Improved Outcome/Efficacy

The POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study, thus observing the inherent properties of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record.

(EX1003, ¶¶108-12.)

Pernot is an article directed to treating colorectal cancer. (*See generally* EX1006.) The POSA would thus have had reason to consider the teachings of Pernot. (EX1003, ¶108.) The MSI-H Study Record was directed to a clinical study treating colorectal cancer patients whose cancers were MSI-H with pembrolizumab, an anti-PD-1 antibody (*supra*, §VI.B.2), and Pernot taught that those patients are “good candidates for immunotherapy,” such as PD-1 inhibitors like pembrolizumab (EX1006, 3741; *see also* EX1029, ¶82; EX1054, 3; EX1011, 141.) As such, Pernot further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶108.)

Indeed, the state of the art would have further compelled a POSA to carry out the clinical study with a reasonable expectation of success. (EX1003, ¶¶109-12.) Physicians were treating patients with cancers that were known to have

MSI-H subpopulations in the prior art, including colorectal cancer, with PD-1 inhibitors (EX1005, 4 (Arms and Interventions); EX1016; EX1017; EX1023, 42; EX1003, ¶109.) The prior art also successfully reported treatment of a colorectal cancer patient having an MSI-H tumor with a PD-1 inhibitor. (EX1057, 463-64; EX1003, ¶109.)

Further, in addition to Pernot, several other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab. (EX1032, e27817-5; EX1033, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶110; *see also* EX1084, 1.)

Additionally, the prior art taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize (EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5; EX1003, ¶¶42-43, 111) and (2) already infiltrated by many immune cells (EX1034, 747; EX1037, 2; EX1003, ¶¶44, 111). And the prior art taught that MSI-H tumors naturally displayed those characteristics. (EX1006, 3740-41; EX1033, 2967; EX1058, 231, 236-37; EX1036, 1186-87, 1193; EX1037, 2, 6; EX1035, 4; EX1041, 9208-09; EX1039, 243s; EX1003, ¶¶45, 111.)

Given the above, the POSA would have reasonably expected patients to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study, including determining the outcome of patients. (EX1003, ¶112; *see also* MPEP 2107.03 (“[A]s a general rule ... Office personnel should presume that [an] applicant has established that the subject matter of [a human clinical] trial is reasonably predictive of having the asserted therapeutic utility.”).) Further, because the POSA would have known that pembrolizumab was already approved for another oncology indication in November 2014, the POSA would have had a higher expectation of success. (EX1055, 1-2 (pembrolizumab approved for melanoma); EX1063, 334-335 (for oncology drugs, 55% of second indications were successful if the first indication was successful, but only 9% of first indications were successful.) Thus, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1, VI.B.2.c, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. *See Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (“Inherency may supply a missing claim limitation in an obviousness analysis.”).

Testing

Based on the MSI-H Study Record, it would have been obvious to test or have tested patients for MSI-H.

As discussed directly above, the POSA would have been motivated and expected success in carrying out the MSI-H Study Record's methods. (*Supra*, §VI.C.3.) The MSI-H Study Record discusses treating colorectal cancer patients having MSI-H colorectal cancer in one arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶113). To the extent not explicitly required, this would have at least motivated the POSA to test patients for MSI-H because the POSA would need to place the patients into the proper study arm. (EX1003, ¶113.) Testing was the way in which it was possible to determine if the patient had the MSI-H colorectal cancer required for placement in that arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶113.) The POSA would have expected success in carrying out such testing, because testing for MSI-H was routine in the art. (EX1003, ¶113; *see also infra*, §§VI.C.4, VI.C.7.)

4. **Ground 3: Claims 2, 8, 15, and 21 Are Obvious Over The MSI-H Study Record, or The MSI-H Study Record in View of Pernot, in View of Chapelle**
 - a. **Claim 2: "The method of claim 1, wherein the biological sample is a tumor tissue from the patient."**

As discussed above in Section VI.B.2.b, the MSI-H Study Record discloses determining that the patient's colorectal cancer is MSI-H. (*See also supra*,

§VI.C.3.) Testing tumor tissue from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶116-18.)

Chapelle is directed towards determining whether tumors are MSI-H. (EX1007, 3380, 3383; EX1003, ¶117.) As such, the POSA would have had reason to consider Chapelle, which is in the same field as the MSI-H Study Record and the '393 patent. (EX1003, ¶117.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Chapelle to test tumor tissue from the patient, in order to test whether a tumor is MSI-H. (EX1003, ¶118.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H. (*Supra*, §§VI.B.2.b, VI.C.3.) Chapelle teaches standard methods of testing whether a tumor was MSI-H using tumor tissue. (EX1007, 3380, 3383; EX1003, ¶118.) The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not affect the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed such testing of tumor tissue was well known, as the '393 patent admits. (EX1001, 6:25-26; 6:35-38; EX1003, ¶118.)

- b. Claim 8: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample.”**

Carrying out or having carried out an immunohistochemistry test on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Chappelle. (EX1003, ¶119-20.)

As discussed above in Section VI.C.4.a, the POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) with Chappelle’s standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶¶117, 120.) Those methods include testing with immunohistochemistry. (EX1007, 3380, 3384; EX1003, ¶120.) Moreover, as discussed above, the ’393 patent does not suggest that the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. (*Supra*, §VI.C.4.a.)

- c. Claim 15: “The method of claim 14, wherein the biological sample is a tumor tissue sample from the patient.”**

Claim 15 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶121.)

- d. **Claim 21: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample.”**

Claim 21 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶122.)

5. **Ground 4: Claims 3 and 16 Are Obvious over The MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in View of Steinert**

- a. **Claim 3: “The method of claim 1, wherein the biological sample is a body fluid from the patient.”**

As discussed above in Section VI.B.2.b, the MSI-H Study Record discloses determining that the patient’s colorectal cancer is MSI-H. (*See also supra*, §VI.C.3.) Testing body fluid from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Steinert. (EX1003, ¶¶125-27.)

Steinert is directed towards determining whether a tumor is MSI-H to understand how colorectal cancer evades the immune system. (EX1008, OF1; EX1003, ¶126.) As such, the POSA would have had reason to consider Steinert, which is in the same field as the MSI-H Study Record and the ’393 patent. (EX1003, ¶126.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Steinert. (EX1003, ¶127.) The

MSI-H Study Record discloses, or at least suggests, determining that the patient’s colorectal cancer is MSI-H. (*Supra*, §§VI.B.2.b, VI.C.3.) Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. (EX1008, OF6; EX1003, ¶127.) The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed such testing of tumor tissue was well known, as the ’393 patent admits. (EX1001, 6:25-26, 6:35-38; EX1003, ¶127.)

b. Claim 16: “The method of claim 14, wherein the biological sample is a body fluid from the patient.”

Claim 16 is obvious over the combination for the same reasons Claim 3 is obvious, which are discussed in Section VI.C.5.a. (EX1003, ¶128.)

6. Ground 5: Claims 7, 20, 29-30, 32, 34, and 36-42 Are Obvious Over The MSI-H Study Record, or The MSI-H Study Record in View of Pernot, in View of Benson

a. Claim 7: “The method of claim 1, wherein, prior to treatment with pembrolizumab, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”

As discussed above, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal cancer patients with “tumors” and “measurable disease.” (EX1005, 2 (Study Identification), 4 (Arms and Interventions, Study Design), 5-6 (Eligibility); *see supra*, §§VI.B.7, VI.B.20.)

Even if the MSI-H Study Record does not explicitly teach that, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the patients' cancers had progressed after the patients received the different cancer therapy, this would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶131-35.)

Benson is directed to the ways in which clinical studies involving cancer are conducted. (EX1009, 1034; EX1003, ¶132.) As such, the POSA would have had reason to consider Benson, which is in the same field as the MSI-H Study Record and the '393 patent. (EX1003, ¶132.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Benson. (EX1003, ¶133.) For instance, both the MSI-H Study Record and Benson discuss treating patients with colorectal cancer. (EX1003, ¶133.) Further, Benson discusses that, under the standard of care, the patient population that had tumors and measurable disease that would take part in a clinical study are patients who have had their cancer progress after two previous drug therapies. (EX1009, 1034; EX1003, ¶133.) As such, the POSA would have been motivated to carry out the MSI-H Study Record's method for a clinical study, wherein, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the

patients' cancer had progressed after the patients received the different cancer therapy. (EX1003, ¶133.)

The POSA would have had a reasonable expectation of success in carrying out the MSI-H Study Record's method, wherein, prior to treatment with pembrolizumab, the patient had received a different cancer therapy, and the patient's cancer had progressed after the patient received the different cancer therapy because that is the patient population that the POSA would have expected to use for such a method. (EX1009, 1034; EX1003, ¶134.)

As discussed above, a POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to complete the study, including determining the outcome of patients. (*Supra*, §VI.C.3.) As a result, that POSA would have seen the inherent properties, discussed above in Sections VI.B.1 and VI.B.2.c, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:29-31 (all patients had treatment-refractory, progressive disease); 15:59-63 (all patients having MSI-H colorectal cancer had received two prior chemotherapy regimens); EX1003, ¶¶108-12, 135.)

- b. **Claim 20: “The method of claim 14, wherein, prior to treatment with the step of selecting pembrolizumab for treating the patient’s colorectal cancer, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”**

Claim 20 is obvious over the combination for the same reasons Claim 7 is obvious, which are discussed in Section VI.C.6.a. (EX1003, ¶136.)

- c. **Claim 29: “The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer.”**

As discussed above, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal cancer patients with “tumors” and “measurable disease.” (EX1005, 2 (Study Identification), 4 (Arms and Interventions, Study Design), 5-6 (Eligibility); *supra*, §§VI.B.7, VI.B.20, VI.C.6.a.) Treating colorectal cancer patients in the clinical study that the MSI-H Study Record discloses, wherein the colorectal cancer is metastatic colorectal cancer, would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶137-40.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Benson. (EX1003, ¶¶131-33, 138.) For instance, both the MSI-H Study Record and Benson discuss treating patients with colorectal cancer. (EX1003, ¶¶132-33.) Further, Benson discusses that, under the standard of care, the patient population with tumors and measurable

disease that would take part in a clinical study are patients with metastatic and advanced disease. (EX1009, 1034; EX1003, ¶¶133, 138.) As such, the POSA would have been motivated to carry out that the MSI-H Study Record's method for a clinical study, wherein the colorectal cancer was metastatic. (EX1003, ¶138.) Further, the POSA would have understood that the MSI-H Study Record's disclosure referred to treating patients with metastatic and advanced disease. (*Supra*, §§VI.B.7, VI.B.29.)

The POSA would have had a reasonable expectation of success in carrying out the MSI-H Study Record's method, wherein the colorectal cancer was metastatic because that is the patient population that the POSA would use for such a method. (EX1009, 1034; EX1003, ¶139.)

As discussed above, a POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to complete the study, including determining the outcome of patients. (*Supra*, §VI.C.3.) As a result, that POSA would have seen the inherent properties, discussed above in Sections VI.B.1 and VI.B.2.c, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:29-31 (all patients had metastatic disease); EX1003, ¶¶108-112, 140.)

d. Claim 30: “The method of claim 14, wherein the colorectal cancer is metastatic colorectal cancer.”

Claim 30 is obvious over the combination for the same reasons Claim 29 is obvious, which are discussed in Section VI.C.6.c. (EX1003, ¶141.)

e. Claim 32: “The method of claim 31, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”

The additional limitation that Claim 32 recites is essentially the same as Claim 7, but further requires a cancer therapy drug. As discussed in the analysis for Claim 7, under the standard of care in the art, the MSI-H Study Record requires patients with colorectal cancer to have received at least two prior cancer therapy drugs and had their cancers progress after receiving those drugs. (*Supra*, §VI.C.6.a.) Thus, the additional method of Claim 32 is disclosed for the same reasons as Claim 7. (EX1003, ¶142.)

f. Claim 34: “The method of claim 33, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”

Claim 34 is obvious over the combination for the same reasons Claim 32 is obvious, which is discussed in Section VI.C.6.e. (EX1003, ¶143.)

- g. Claim 36: “The method of claim 35, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

Claim 36 is obvious over the combination for the same reasons Claim 32 is obvious, which are discussed in Section VI.C.6.e. (EX1003, ¶144.)

- h. Claim 37: “The method of claim 29, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.”**

Claim 37 is obvious over the combination for the same reasons Claim 29 is obvious, which are discussed in Section VI.C.6.c. (EX1003, ¶145.)

- i. Claim 38: “The method of claim 37, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

Claim 38 is obvious over the combination for the same reasons Claims 29 and 32 are obvious, which are discussed in Sections VI.C.6.c and VI.C.6.e. (EX1003, ¶146.)

- j. Claim 39: “The method of claim 29, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.”**

Claim 39 is obvious over the combination for the same reasons Claim 29 is obvious, which are discussed in Section VI.C.6.c. (EX1003, ¶147.)

- k. **Claim 40: “The method of claim 39, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

Claim 40 is obvious over the combination for the same reasons Claims 29 and 32 are obvious, which are discussed in Sections VI.C.6.c and VI.C.6.e.

(EX1003, ¶148.)

- l. **Claim 41: “The method of claim 29, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.”**

Claim 41 is obvious over the combination for the same reasons Claim 29 is obvious, which are discussed in Section VI.C.6.c. (EX1003, ¶149.)

- m. **Claim 42: “The method of claim 41, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.”**

Claim 42 is obvious over the combination for the same reasons Claims 29 and 32 are obvious, which are discussed in Sections VI.C.6.c and VI.C.6.e.

(EX1003, ¶150.)

7. Ground 6: Claims 9, 10, 22, and 23 Are Obvious over The MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in View of Salipante

- a. Claim 9: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample.”**

As discussed in Section VI.B.2.b above, the MSI-H Study Record discloses determining that the patient’s colorectal cancer is MSI-H. (*See also supra*, §VI.C.3.) Carrying out or having carried out a polymerase chain reaction (“PCR”) test on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Salipante. (EX1003, ¶¶153-56.)

Salipante is directed towards determining whether a tumor is MSI-H. (EX1010.) As such, the POSA would have had reason to consider Salipante, which is in the same field as the MSI-H Study Record and the ’393 patent. (EX1003, ¶154.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Salipante. (EX1003, ¶155.) The MSI-H Study Record discloses, or at least suggests, determining that the patient’s colorectal cancer is MSI-H. (*Supra*, §§VI.B.2.b, VI.C.3.) Salipante teaches standard methods of testing whether a tumor was MSI-H using a PCR test on the sample. (EX1010, 1192 (“PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current

clinical use.”), 1192-93 (Referring to PCR testing as the “gold standard”);
EX1003, ¶155.)

The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not affect the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed such a polymerase chain reaction test was known, as the ’393 patent admits. (EX1001, 6:25-26; 8:10-15; EX1003, ¶156.)

b. Claim 10: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample.”

As discussed in Section VI.B.2.b above, the MSI-H Study Record discloses determining that the patient’s colorectal cancer is MSI-H. (*See also supra*, §VI.C.3.) Carrying out or having carried out next generation sequencing on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Salipante. (EX1003, ¶¶157-60.)

As discussed above, the POSA would have had reason to consider Salipante, which is in the same field as the MSI-H Study Record and the ’393 patent. (*Supra*, §VI.C.7.a; EX1003, ¶¶153-55, 158.) The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Salipante. (EX1003, ¶¶153-55, 158.) The MSI-H Study Record discloses, or at least suggests, determining that the patient’s colorectal cancer is MSI-H. (*Supra*,

§§VI.B.2.b, VI.C.3.) Salipante teaches methods of testing whether a tumor was MSI-H using next generation sequencing on the sample. (EX1010, 1193; EX1003, ¶159.)

The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed next generation sequencing was known, as the '393 patent admits. (EX1001, 6:25-26; 23:25-27 (citing a paper about next generation sequencing methods); EX1003, ¶160.)

- c. **Claim 22: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample.”**

Claim 22 is obvious over the combination for the same reasons Claim 9 is obvious, which are discussed in Section VI.C.7.a. (EX1003, ¶161.)

- d. **Claim 23: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample.”**

Claim 23 is obvious over the combination for the same reasons Claim 10 is obvious, which are discussed in Section VI.C.7.b. (EX1003, ¶162.)

8. Ground 7: Claims 11-12 and 24-25 Are Obvious over The MSI-H Study Record, or The MSI-H Study Record in view Pernot, in View of Hamid

a. Claim 11: “The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously.”

As discussed above in Section VI.B.1.a, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating three cohorts of human patients with “[pembrolizumab] 10 mg/kg every 14 days.” The method of Claim 1, wherein the pembrolizumab is administered to the patient intravenously would have been obvious to the POSA in view of the general knowledge in the art, such as Hamid. (EX1003, ¶¶165-69.)

Hamid is directed towards administering pembrolizumab. (EX1011.) As such, the POSA would have had reason to consider Hamid, which is in the same field as the MSI-H Study Record and the '393 patent. (EX1003, ¶166.) Hamid provides for intravenous administration of pembrolizumab. (EX1011, 134.) Hamid refers to pembrolizumab by the name “lambrolizumab”, and the POSA would have known that “lambrolizumab” was another name for pembrolizumab. (EX1011, 134; EX1054, 3; EX1003, ¶166.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Hamid. (EX1003, ¶167.) For instance, the MSI-H Study Record disclosed administering pembrolizumab.

(*Supra*, §§VI.B.2.a, VI.B.2.c.) Hamid demonstrated success in treating patients with advanced cancer with pembrolizumab. (EX1011, 134; EX1003, ¶167.) Thus, the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) with Hamid. (EX1003, ¶167.)

At a minimum, administering pembrolizumab intravenously would have been obvious to try. Indeed, the prior art only discloses intravenous administration of pembrolizumab to treat cancer patients. (EX1011, 134; *see also* EX1055, 1; EX1003, ¶168.) *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1302 (Fed. Cir. 2010); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009).

The POSA would have had a reasonable expectation of success in administering pembrolizumab intravenously, given that administering pembrolizumab intravenously had been successful in the past. (EX1011, 134; EX1003, ¶169; *see also* EX1055, 1-3, 9, 15.)

b. Claim 12: “The method of claim 2, wherein the pembrolizumab is administered to the patient intravenously.”

Claim 12 is obvious over the combination for the same reasons Claim 11 is obvious, which are discussed in Section VI.C.8.a. (EX1003, ¶170.)

- c. **Claim 24: “The method of claim 14, wherein the pembrolizumab is administered to the patient intravenously.”**

Claim 14 is obvious over the combination for the same reasons Claim 11 is obvious, which are discussed in Section VI.C.8.a. (EX1003, ¶171.)

- d. **Claim 25: “The method of claim 15, wherein the pembrolizumab is administered to the patient intravenously.”**

Claim 15 is obvious over the combination for the same reasons Claim 11 is obvious, which are discussed in Section VI.C.8.a. (EX1003, ¶172.)

9. Ground 8: Claims 13 and 26 Are Obvious over the MSI-H Study Record, or the MSI-H Study Record in view of Pernot, in view of Steinert and Hamid

- a. **Claim 13: “The method of claim 3, wherein the pembrolizumab is administered to the patient intravenously.”**

Claim 13 is obvious over the combination for the same reasons as Claims 3 and Claim 11 are obvious, which are discussed in Sections VI.C.5.a and VI.C.8.a. (EX1003, ¶173.)

- a. **Claim 26: “The method of claim 16, wherein the pembrolizumab is administered to the patient intravenously.”**

Claim 26 is obvious over the combination for the same reasons as Claims 3 and Claim 11 are obvious, which are discussed in Sections VI.C.5.a and VI.C.8.a. (EX1003, ¶174.)

VII. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. Discretionary Denial Under *Fintiv* Is Not Appropriate

The factors under *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (“*Fintiv*”) favor institution. As explained above, the merits of Merck’s arguments are compelling and the evidence in support is substantial. (*Supra*, §§VI.B-C.) That “alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*.” (EX1065 at 4-5.) But in any event, the six *Fintiv* factors do not justify denying institution.

The first *Fintiv* factor favors institution. Merck represents that it will seek a stay of the patent infringement claims in district court upon institution, if not sooner. Given the district court case between Merck and JHU is in an early stage (*see* EX1066), there is a reasonable likelihood such a stay will be granted. Even without a stay, the remaining factors support institution.

The second *Fintiv* factor favors institution. Using the average time to trial in the relevant jurisdiction, the trial will not begin until mid-2025—over 1.5 years from the filing of this petition. (EX1067.) As such, a final written decision would precede trial.

The third *Fintiv* factor also favors institution. There is still significant investment required in the district court litigation. Claim construction, discovery,

pre-trial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice, all lie in the future. (*See* EX1066.).

The fourth *Fintiv* factor favors institution. Merck has not yet presented invalidity contentions given the early stage of the litigation. There is thus no overlap that warrants non-institution.

The sixth *Fintiv* factor also favors institution. There is a significant public interest against “leaving bad patents enforceable.” *Thryv, Inc. v. Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1374 (2020). And as noted above, Merck’s arguments are compelling. And with respect to the fifth *Fintiv* factor, although the Parties are the same as in district court, that is true in nearly every case, and under the “holistic view” of whether integrity of the system and efficiency is best served, institution is favored. *Samsung Elecs. Co. Ltd. v. Dynamics Inc.*, IPR2020-00505, Paper 11 at 15 (Aug. 12, 2020).

B. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

The MSI-H Study Record was considered during prosecution of a family member of the ’393 patent that issued as U.S. Patent No. 10,934,356. (EX1022, August 26, 2020 Rejection, 26-32.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least three reasons.

First, the Examiner did not consider the MSI-H Study Record during prosecution of the '393 patent. As discussed above, the full version of the MSI-H Study Record was not even in front of the Examiner. (*Supra*, §III.B.)

Second, during prosecution of the application that issued as U.S. Patent No. 10,934,356, the Examiner failed to consider whether the MSI-H Study Record inherently anticipates under Federal Circuit precedent. Specifically, the Examiner recognized the MSI-H Study Record contemplated evaluating whether pembrolizumab results in an improved outcome for a patient whose cancer is MSI-H relative to a patient whose cancer is not MSI-H. (EX1022, December 14, 2020 Notice of Allowance, 3.) The Examiner, however, allowed the '356 patent over the MSI-H Study Record on the rationale that it did not affirmatively disclose that improved outcome and that the POSA would purportedly not have expected such efficacy. (*Id.*) That was incorrect as a matter of law, particularly given the evidence that the methods in the MSI-H Study Record were, in fact, shown to be effective, as explained above. (*See supra*, §§VI.B.1, VI.B.2.c.) Indeed, these patents mean that a POSA – who practiced the prior art MSI-H Study Record just as disclosed or using obvious techniques for carrying out that MSI-H Study Record disclosure – could be accused of infringement, which is antithetical to patent law. *Schering Corp.*, 339 F.3d at 1379 (Fed. Cir. 2003) (discussing the patent law principle “that which would literally infringe if later in time anticipates if earlier.”).

Third, the Examiner did not consider many of the other arguments and issues raised in this Petition, including the combinations of references raised in the obviousness grounds. (*Supra*, §§III.B, VI.B-C.)

VIII. MANDATORY NOTICES UNDER 37 CFR § 42.8

Real Parties-in-Interest: Pursuant to 37 C.F.R. § 42.8(b)(1), Merck identifies Merck Sharp & Dohme LLC and Merck & Co., Inc. as the real parties-in-interest.

Related Matters: Pursuant to 37 C.F.R. § 42.8(b)(2), Merck identifies the following related matter. The '393 patent is at issue in the following pending litigation: *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.).

Counsel and Service Information: Lead counsel is Naveen Modi (Reg. No. 46,224). Backup counsel are Bruce M. Wexler (Reg. No. 35,409), Preston K. Ratliff II (Reg. No. 43,034), Daniel Zeilberger (Reg. No. 65,349), David J. Feigenbaum (Reg. No. 78,139), and Mark Stewart (Reg. No. 43,936). Service information is Paul Hastings LLP, 2050 M Street NW, Washington, D.C. 20036, Tel.: 202.551.1700, Fax: 202.551.1705, email:

(1) PH-MSD-JHU-IPR@paulhastings.com; and (2) mark.stewart@merck.com.

Petitioner consents to electronic service.

IX. CONCLUSION

Merck requests institution of IPR for Claims 1-42 of the '393 patent based on the grounds specified in this petition.

Respectfully submitted,

Dated: November 30, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,591,393 contains, as measured by the word-processing system used to prepare this paper, 13,984 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: November 30, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on November 30, 2023, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,591,393 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on the USPTO's Patent Center:

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