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. 10,934,356

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,934,356

Halozyme EX2418
Merck v. Halozyme
PGR2025-00087

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I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC ("Petitioner" or "Merck") requests *inter partes* review of Claims 1-28 of U.S. Patent No. 10,934,356 ("the '356 patent"), which is assigned to Patent Owner The Johns Hopkins University ("JHU").

The '356 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. It was known that MSI-H tumors were more immunogenic, and would benefit from the use of an immunotherapy drug like pembrolizumab. (EX1003, ¶¶ 42-50.) In fact, the specification of the JHU patent is a clinical study ***published in the prior art more than a year*** before the '356 patent's filing, which was a collaboration by Merck and JHU (the "MSI-H Study Record").

This study was consistent with the teachings of the prior art 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.) The prior art also taught that MSI-H tumors naturally displayed those characteristics. (*Infra*, § III.C.) 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. (EX1003, ¶¶ 42-50.)

As explained in detail below and in the Declaration of Dr. Alfred I. Neugut, M.D., Ph.D., M.P.H., all claims of the '356 patent are unpatentable, as they fail to meet several statutory requirements. (*See, e.g.*, EX1003, ¶¶1-22, 51-61, 193-94.)

First, the independent claims and most dependent claims of the '356 patent are anticipated. (35 U.S.C. § 102; *infra*, §VI.B; EX1003, ¶17, §VII.A.) 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 '356 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; ¶17; *infra*, §VI.C; EX1003, ¶17, §§VI.B-G.) 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 of 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 '356 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 1-28 of the '356 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1, 6-11, 13-20, 22-24, 26-28 are unpatentable under 35 U.S.C. § 102 as being anticipated by the published MSI-H Study Record (EX1005).

Ground 2: Claims 1, 6-11, 13-20, 22-24, and 26-27 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005) in view of Pernot (EX1006) and Benson (EX1009).

Ground 3: Claims 2-5, 11-18, 20-21, 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 in view of Pernot (EX1006) and Benson (EX1009), in view of Chapelle (EX1007).

Ground 4: Claims 1, 6-11, 13-20, 22-24, 26-28 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005) in view of Brown (EX1034), Duval (EX1087), and Benson (EX1009).

Ground 5: Claims 2-5, 11-18, 20-21, and 24-25 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005) in view of Brown (EX1034), Duval (EX1087), and Benson (EX1009), further in view of Chapelle (EX1007).

Ground 6: Claim 18 is unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record in view in view of Pernot (EX1006), Benson (EX1009), and Chapelle (EX1007), in view of Hamid (EX1011).

Ground 7: Claim 18 is unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005) in view of Brown (EX1034), Duval (EX1087), Benson (EX1009), Chapelle (EX1007), further in view of Hamid (EX1011).

III. BACKGROUND OF THE '356 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, 11, 19, and 23 of the '356 patent, the patent's independent claims, are directed to identifying 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, 25:54-28:22; EX1003, ¶22.).

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, and Merck was not the only company developing anti-PD-1 therapeutics for treating cancer. (EX1011, 135; EX1057, 462; EX1053.)

The prior art disclosed how PD-1 inhibitors treat cancer. (EX1003, ¶¶30-33.) 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, ¶¶30-33.)

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. (EX1003, ¶34.)

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. (EX1003, ¶¶23-29.) MSI-H is also known throughout the literature as MSI positive, MSI-high, MSIH, or MSI+. (EX1003, ¶27.) MSI-H is caused by deficient mismatch repair ("dMMR"), also known as "Mismatch repair deficiency" or "DNA mismatch repair deficient." (EX1003, ¶28.) MSI-H and dMMR are "biologically the same" and testing for one condition was considered "equivalent" to testing for the other. (EX1003, ¶29.) By 2014, upon diagnosis of certain cancers, it was common to test tumors for MSI-H. (EX1003, ¶26.) Whether a tumor exhibited MSI-H could inform therapeutic choices, prognosis, and familiar cancer risk appraisal. (EX1003, ¶¶23-29, 42-50.) MSI-H was known to occur commonly in several different types of cancers, including colorectal, endometrial, and small bowel cancer. (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 having colorectal and non-colorectal cancers that 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"). (EX1003, ¶35.)

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. (EX1003, ¶36.)[1] The website, www.clinicaltrials.gov, publicizes clinical trials in a searchable and easy to understand manner in order to keep doctors and patients apprised of ongoing clinical trials. (EX1003, ¶37.) It was indexed by subject matter, and would have been used by the POSA to understand the state of the art. (*Id*.)

During prosecution of the '356 patent and its family members, named inventor Andrew Pardoll, M.D., Ph.D., admitted that the MSI-H Study Record published as early as June 12, 2013. (EX1002, February 4, 2020 Declaration, 7-8,

[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, ¶36.) 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, ¶37.)

¶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 '356 patent's claimed subject matter derives directly from the MSI-H Study. (*See* EX1002, February 4, 2020 Declaration, 7-8, ¶¶22-23 (connecting the '356 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, ¶¶38-41.) Indeed, all of the '356 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, 6:43-22:40, 3:13-15; Figs. 1-13; EX1005; EX1003, ¶40.) For instance, Examples 1-4 (EX1001, 7:61-16:25) are

the design of the MSI-H Study, and Examples 5-11 (EX1001, 16:26-20:8) report its results. Further, Tables 1-3 (EX1001, 20:9-22:40) and Figures 1-13 also report the MSI-H Study's results.

The Examiner considered the MSI-H Study Record during prosecution of the '356 patent, and recognized that the MSI-H Study Record disclosed treating patients having MSI-H cancer with pembrolizumab and measuring the patients' responses. (EX1002, August 26, 2020 Non-Final Rejection, 26-27.) 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. (EX1002, December 14, 2020 Notice of Allowance, 3.) 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, ¶50) 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. (EX1003, ¶¶48-50.)

Indeed, in April 2014, Pernot taught that MSI-H 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, ¶49.) 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. (EX1003, ¶¶42-47.)

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 (EX1003, ¶44) and (2) already infiltrated by many immune cells (EX1003, ¶45). And the prior art taught that MSI-H tumors naturally displayed those characteristics. (EX1003, ¶46.)

IV. CLAIM CONSTRUCTION

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). Given the correlation

between the MSI-H Study Record, the written description of the '356 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 '356 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 '356 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 '356 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"). 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). 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* EX1002, February 4, 2020 Declaration, 7-8, ¶22, June 8, 2020 Declaration, 8-9, ¶¶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]

B. Ground 1: Claims 1, 6-11, 13-20, 22-24, 26-28 of the '356 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

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[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 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 v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325-26 (Fed. Cir. 2005)).

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. 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.

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[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 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.

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) (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, 6-11, 13-20, 22-24, and 26-28 of the '356 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. Indeed, anticipation could not 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 '356 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, ¶¶38-41.)

2. Claim 1

a. [1.pre]: " A method for treating cancer in a patient in need thereof, comprising"

The Arms and Interventions section of the MSI-H Study Record discloses a method of treating cancer patients. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) This is the method set forth in the preamble. (EX1003, ¶62.)

b. [1.1]: "determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status;"

The Arms and Interventions section of the MSI-H Study Record discloses treating three study arms, one of which consists of patients having MSI positive colorectal cancer and one of which consists of patients having MSI positive non-colorectal cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) That disclosure reads on this limitation. (EX1003, ¶¶63-66.)

The prior art taught that the MSI-H Study Record's disclosure of "MSI positive" patients refers to "MSI-H" patients. (*See, e.g.*, EX1010, 1193, 1196; EX1018, 293; EX1019, 1065; EX1003, ¶64; *supra,* §III.A.) Further, named inventor Dr. Pardoll represented in a sworn declaration to the patent office that the MSI-H Study Record concerns MSI-H patients. (EX1002, February 4, 2020 Declaration, 7-8, ¶¶ 21-23.)

The MSI-H Study Record's disclosure of treating patients with "MSI positive" cancer also discloses treating patients with a mismatch repair deficiency ("dMMR"). (EX1003, ¶65.) 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, 7:61-8:28 (using MSI status to characterize patients as dMMR).) And, in his

declaration, Dr. Pardoll equated MSI-H and dMMR patients. (EX1002, February 4, 2020 Declaration, 7-8, ¶23.) Moreover, because MSI-H is caused by dMMR, all cancers that are MSI-H are dMMR. (EX1010, 1192; EX1003, ¶65; *see also* EX1001, 1:28-30.)[4]

Further, according to the MSI-H Study Record's disclosure, the MSI-H Study Record requires determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status 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 (Primary Outcome Measures), 5 (Inclusion Criteria); EX1003, ¶66.) Without such a determination, patients could not have been placed into the proper arm of the study. (EX1003, ¶66.)

[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.

c. [1.2]: "administering an effective amount of pembrolizumab to the patient;"

The Arms and Interventions section of the MSI-H Study Record discloses treating patients having MSI-H colorectal cancer and MSI-H non-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 (Primary Outcome Measures), 5 (Inclusion Criteria).) That disclosure reads on this limitation. (EX1003, ¶¶67-71.)

The MSI-H Study Record does not expressly use the phrase "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 '356 patent, and any required efficacy is thus inherent to that dosage. (EX1003, ¶68.)

Indeed, the '356 patent itself, which only describes one dosage (EX1001, 8:45-51, 13:45-52)—the same one in the MSI-H Study Record (EX1005, 4 (Arms and Interventions)—asserts that this dosage is effective. (EX1001, 4:14-27 (showing the "[c]linical benefit to pembrolizumab according to MMR status"), 16:30-35, 16:56-65, 17:26-36, 21:1-22, Figs. 2, 11; EX1003, ¶69.) "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, ¶70.)

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 patients with MSI-H cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria); *see also* EX1003, ¶¶40-41, 67-71.)

d. [1.3]: "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and"

The Secondary Outcomes section of the MSI-H Study Record discloses that one outcome is "[d]oes MSI as a marker predict treatment response." (EX1005, 4-5 (Outcome Measures).) The Primary Outcomes section of the MSI-H Study Record discloses that primary outcomes include "[i]mmune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative

colorectal adenocarcinoma using immune related response criteria (irRC)" and "[o]bjective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)." (EX1005, 4-5 (Outcome Measures); *see also id.*, 3 (Study Description), 4 (Arms and Interventions), 5 (inclusion criteria).) These disclosures read on this limitation. (EX1003, ¶¶72-74.)

In particular, these disclosures show that the MSI-H Study Record discloses actively measuring specific outcomes in patients having MSI-H cancer and cancer that is not MSI-H. (EX1005, 4-5 (Outcome Measures); *see also id.*, 3 (Study Description), 4 (Arms and Interventions), 5 (Inclusion Criteria); EX1003, ¶¶72-73.) The MSI-H Study Record even discloses determining whether MSI-H is a marker for response to therapy. (EX1005, 4-5 (Outcomes Measures); EX1003, ¶¶72-73.) Additionally, the improved outcomes are inherent to the methods of the MSI-H Study Record. (*Supra,* §VI.B.1; EX1003, ¶73.) "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. Thus, actual administration of [pembrolizumab] to patients before the critical date of the ['356 patent] is irrelevant." *Schering*, 339 F.3d at 1380.

e. [1.4]: "wherein the patient has received a prior cancer therapy drug."

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 addition, the MSI-H Study discloses treating patients with MSI-H colorectal cancer and non-colorectal cancer. (EX1005, 3 (Study description), 3-4 (Conditions), 4 (Arms and Interventions), 5 (Outcome Measures), 5 (Inclusion Criteria).) And 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, ¶75.) In the context of the MSI-H Study Record, these disclosures demonstrate that patients would have received a prior cancer therapy drug. (EX1003, ¶¶75-80.)

In particular, the prior art taught that patients having "measurable" colorectal cancer in the context of the MSI-H Study Record refers to patients having metastatic and advanced cancer. (EX1020, PDF p. 25; EX1003, ¶76.) If a patient had colorectal cancer that is curable by resection, then a practitioner would excise the tumor because surgery "is the only way to achieve a cure." (EX1020, PDF p. 7 (under the standard of care, resection is recommended if it is possible); EX1048, 230; EX1047, 4-7; EX1003, ¶76.) Thus "measurable" disease in the context of a

clinical study does not include cancer that is resectable for the purposes of a cure. (*Id.*) Further, if metastatic patients were not included, 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, ¶76.)

Patients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies. (EX1020, PDF p. 25; *see also* EX1009, 1034; EX1047, 4-7; EX1003, ¶77.)

It is in this context that 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, ¶78.) In other words, the MSI-H Study Record informs the POSA that patients would have received prior cancer drug therapies, and because of that, makes it a point to exclude those that received "anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies." (EX1003, ¶78.) 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. (*Id*.) Indeed, the POSA would have found it highly unusual for the patient population of those who

had received prior drug treatments and had their cancer progress after those treatments to not be included in the MSI-H Study Record, especially without any explicit carve-out. (*Id*.)

For all of the reasons above, the MSI-H Study Record disclosed to the POSA a method treating patients who had received prior cancer drug therapies, and the patients' cancer had progressed after the patients received the different cancer therapies. (EX1003, ¶¶75-80.) *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc*., 949 F.3d 1366, 1373 (Fed. Cir. 2020); *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).

Indeed, Petitioner's understanding of the MSI-H Study Record is confirmed by additional evidence. In particular, a poster presentation describing the same clinical study at issue in the MSI-H Study Record indicated that the study required that patients have "progressive disease," that colorectal cancer patients have "at least 2 prior therapies," and that non-colorectal cancer patients have "at least 1 prior therapy." (*See* EX1080,[5] Eligibility Criteria; EX1003, ¶79.)

[5] EX1080 is a poster that Merck and JHU presented at the American Society of Clinical Oncology that confirms how the POSA would have understood the MSI-H

3. Claim 6: "The method of claim 1, wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug."

Claim 6's additional limitation is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]. (EX1003, ¶81.)

4. Claim 7: "The method of claim 1, wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival."

The MSI-H Study Record discloses treating patients having MSI-H colorectal cancer and non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions), 3 (Study description), 3-4

Study Record. *See Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018). EX1080 is prior art. It was displayed for 3.75 hours at ASCO, which is an annual public conference that would have been attended by tens of thousands of oncologists, including world class experts. (EX1092; EX1093; EX1003, ¶79.) EX1080 indicates that one of the reasons that the poster was on display was increasing attending doctors' awareness of the ongoing MSI-H Study including to potentially expand the patient pool. (EX1080, Abstract, Methods; EX1003, ¶79.) Thus, there was no expectation of confidentiality. (EX1003, ¶79.) *See also In re Klopfenstein* 380 F.3d 1345, 1350 (Fed. Cir. 2004).

(Conditions), 5-6 (Inclusion Criteria); EX1054, 3.) The MSI-H Study Record also discloses treating patients having colorectal cancer that is not MSI-H with 10 mg/kg of pembrolizumab every 14 days. (*Id*.) Further, the MSI-H Study Record discloses measuring objective response rate, progression-free survival, and overall survival. (EX1005, 4-5 (Outcome Measures).) These disclosures read on this limitation because the improved outcomes are inherent to the methods of the MSI-H Study Record. (*Supra,* §VI.B.1; EX1001, 4:14-27, Figures 2, 11, 16:30-35, 16:56-65, 17:26-36, 21:1-22, Figs. 2, 11; EX1003, ¶¶82-84.) *See King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010).

5. Claim 8: "The method of claim 7, wherein the outcome is assessed in the patient within approximately 20 weeks after administering pembrolizumab."

The Outcomes section of the MSI-H Study Record discloses that primary outcomes include "[i]mmune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)" and "[o]bjective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)." (EX1005, 4-5 (Outcome Measures).) That disclosure reads on this limitation because it discloses measuring the relevant outcomes at 20 weeks. (EX1003, ¶85.)

6. Claim 9: "The method of claim 1, wherein the cancer is a metastatic cancer."

As discussed in the analysis for limitation [1.4], the patients in the MSI-H Study Record would have had metastatic cancer. (EX1003, ¶86.) Indeed, prior art concerning the MSI-H Study indicates that physicians understood postings on clinicaltrials.gov indicated that patients had "metastatic tumors." (EX1049, 444; *see also* EX1050, S4; EX1003, ¶86.) *See Yeda*, 906 F.3d at 1041.

7. Claim 10: "The method of claim 1, wherein the cancer is a metastatic colorectal cancer."

As discussed in the analysis for limitation [1.4], the patients in the MSI-H Study Record would have had metastatic colorectal cancer. (EX1003, ¶87.) Indeed, prior art concerning the MSI-H Study indicates that physicians understood postings on clinicaltrials.gov indicated that patients had "metastatic tumors." (EX1049, 444; *see also* EX1050, S4; EX1003, ¶87.) *See Yeda*, 906 F.3d at 1041.

8. Claim 11

a. [11.pre]: "A method for treating cancer in a patient in need thereof, the method comprising:"

This limitation is identical to limitation [1.pre], and is disclosed for the same reasons. (*Supra* §VI.B.2.a; EX1003, ¶88.)

b. [11.1]: "detecting a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status in a tumor sample from the patient;"

This limitation is disclosed for the same reasons as limitation [1.1]. (*Supra* §VI.B.2.b; EX1003, ¶89.) Indeed, both limitations concern including patients who have MSI-H cancers in the MSI-H Study Record's study.

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).) A biopsy of a patient's tumor obtains tumor tissue for testing. (EX1003, ¶90.) 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 biopsy would obtain tumor tissue to test whether the patient's cancer is MSI-H (EX1007, 3380, 3383; EX1044, 3309; EX1045, 3485; EX1046,1193; EX1003, ¶90 *see also* EX1001, 8:1-2.) 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 claim. (EX1003, ¶¶89-91.)

c. [11.2]: "wherein the tumor sample exhibits an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers;"

The Arms and Interventions section of the MSI-H Study Record discloses determining whether the patient's tumor sample is MSI-H. (*Supra*, §VI.B.2.) By

definition, exhibiting an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers is the only way for a tumor to be MSI-H. (EX1007, 3382-83; EX1003, ¶¶92-93.)

d. [11.3]: "administering an effective amount of pembrolizumab to the patient;"

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra*, §VI.B.2.c; EX1003, ¶94.)

e. [11.4]: "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers; and"

This limitation is disclosed for the same reasons as limitation [1.3]. (*Supra* §VI.B.2.d; EX1003, ¶95.) Additionally, by definition, exhibiting an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers is the only way for a tumor to be MSI-H. (EX1007, 3382-83; EX1003, ¶95.)

f. [11.5]: "wherein the patient has received a prior cancer therapy drug."

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra* §VI.B.2.e; EX1003, ¶96.)

9. Claim 13: "The method of claim 11, wherein the cancer is a metastatic cancer."

This additional limitation is identical to Claim 9 and is disclosed for the same reasons. (*Supra* §VI.B.6; EX1003, ¶97.)

10. Claim 14: "The method of claim 11, wherein the cancer is a metastatic colorectal cancer."

This additional limitation is identical to Claim 10 and is disclosed for the same reasons. (*Supra* §VI.B.7; EX1003, ¶98.)

11. Claim 15: "The method of claim 14, wherein the metastatic colorectal cancer in the patient has progressed after the patient received the prior cancer therapy drug."

Claim 15's additional limitation is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]. (*Supra* §VI.B.2.e; EX1003, ¶¶99-100.)

12. Claim 16: "The method of claim 11, wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival."

This additional limitation is identical to Claim 7 and is disclosed for the same reasons. (*Supra* §VI.B.4; EX1003, ¶101.)

13. Claim 17: "The method of claim 16, wherein the outcome is assessed in the patient at 20 weeks after administering pembrolizumab."

This additional limitation is disclosed for the same reasons as Claim 8. (*Supra* §VI.B.5; EX1003, ¶¶102-103.) As discussed in Section VI.B.5, the MSI-H

Study Record discloses measuring outcomes at 20 weeks. Thus, the MSI-H Study Record discloses Claim 17's additional limitation. (EX1003, ¶¶102-103.)

14. Claim 18: "The method of claim 11, wherein pembrolizumab is administered by intravenous infusion."

The Arms and Interventions section of the MSI-H Study Record discloses administering 10 mg/kg of pembrolizumab every 14 days. (*Supra*, §VI.B.2.) Pembrolizumab for the treatment of cancer was administered by intravenous infusion. (*E.g.* EX1011, 134; *see also* EX1055, 1; EX1054, 3; EX1003, ¶¶104-105.)

15. Claim 19

a. [19.pre]: "A method for treating cancer in a patient in need thereof comprising:"

This limitation is identical to limitation [1.pre], and is disclosed for the same reasons. (*Supra* VI.B.2.a; EX1003, ¶106.)

b. [19.1]: "selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient solid tumor,"

This limitation is disclosed for the same reasons as limitation [1.1] (which requires treating MSI-H patients) and Claim 9 (which requires metastatic disease). (*Supra* §§VI.B.2.b, VI.B.6; EX1003, ¶¶107-108.)

Further, the MSI-H Study Record discloses that patients have "tumors" and "measurable" disease. (EX1005, 2 (Study Identification), 5-6 (Eligibility).)

Measurability is a property of solid tumors. (EX1048, 228, 230-31; EX1003, ¶108.) Thus, patients had solid tumors. (EX1003, ¶¶107-108.)

c. [19.2]: "the tumor having progressed following a cancer therapy;"

This limitation is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]. (*Supra* §VI.B.2.e; EX1003, ¶109.)

d. [19.3]: "administering an effective amount of pembrolizumab to the patient; and"

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra* §VI.B.2.c; EX1003, ¶110.)

e. [19.4]: "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status."

This limitation is identical to limitation [1.3], and is disclosed for the same reasons. (*Supra* §VI.B.2.d; EX1003, ¶111.)

16. Claim 20: "The method of claim 19, wherein the solid tumor exhibits instability in a microsatellite marker."

The Arms and Interventions section of the MSI-H Study Record discloses treating cancer patients whose tumors were determined to be MSI-H. (*Supra*, §VI.B.2; EX1003, ¶112.) By definition, all tumors that are MSI-H exhibit

instability in more than one microsatellite marker. (*Supra* §VI.B.2.b; EX1003, ¶112.)

17. Claim 22: "The method of claim 19, wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival."

This additional limitation is identical to Claim 7 and is disclosed for the same reasons. (*Supra* §VI.B.4; EX1003, ¶113.)

18. Claim 23

a. [23.pre]: "A method for treating cancer in a population of cancer patients in need thereof, comprising:"

The Arms and Interventions section of the MSI-H Study Record discloses a method of treating cancer in a population of cancer patients in need thereof. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) This is the method set forth in the preamble. (EX1003, ¶114.)

b. [23.1]: "administering an effective amount of pembrolizumab to patients in the population of cancer patients,

This limitation is disclosed for the same reasons as limitation [1.2]. (*Supra*, §VI.B.2.c; EX1003, ¶115.) Limitation [23.1] and limitation [1.2] cover the same subject matter. The difference is that [23.pre] is directed to "patients in the population of cancer patients," while limitation [1.pre] is directed to "the patient."

The MSI-H Study Record's disclosure cited in the limitation [1.2] analysis discloses treating patients in a population of cancer patients, which meets both limitations. (*Supra*, §VI.B.2.c; EX1003, ¶115.)

c. [23.2] which patients have a tumor that exhibits a high micro satellite instability (MSI-high) or a mismatch repair (MMR) deficiency status,"

This limitation is disclosed for the same reasons as limitation [1.1]. (*Supra*, §VI.B.2.b; EX1003, ¶116.) As discussed in Section VI.B.2, the Arms and Interventions section discloses treating patients having tumors that exhibit MSI-H. That disclosure meets this limitation. (EX1003, ¶116.)

d. [23.3]: "said tumor having progressed following a prior treatment; and;"

This limitation is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]. (*Supra*, §VI.B.2.e; EX1003, ¶117.)

e. [23.4]: "observing an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab."

As discussed above, the MSI-H Study Record discloses treating patients having MSI-H colorectal cancer and non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (*Supra* §VI.B.2.c.) Additionally, the MSI-H Study Record discloses determining the objective response rate in patients having MSI-H colorectal cancer. (EX1005, 4-5 (Outcome Measures).)

The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (*See supra,* VI.B.1-2; EX1003, ¶¶ 118-120.)

The '356 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 (confidence interval of objective response rate for MSI-H cancers range from 12% to 96%), 16:58-65 (same), 17:20-36 (same), Table 2 (same); EX1003, ¶120; *see also* EX1031 (results also disclosed in NEJM article).)

19. Claim 24: "The method of claim 23, wherein the tumor exhibits instability of a microsatellite marker."

As discussed in Section VI.B.2.b above, the Arms and Interventions section of the MSI-H Study Record discloses determining whether the patient's tumor sample is MSI-H. By definition, exhibiting an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers is the only way for a tumor to be MSI-H. (EX1007, 3382-83; EX1003, ¶¶121-122.) Instability of one or more microsatellite markers is caused by deficiency of one or more mismatch repair markers. (EX1001, 1:28-30; EX1010, 1192; EX1003, ¶¶121-122.) Indeed, deficiency in one or more mismatch repair markers leads to instability of more than one microsatellite marker with such frequency that, "for practical purposes," the instability of one or more microsatellite markers and the deficiency of one or more mismatch repair markers are considered "equivalent."

(EX1007, 3380; EX1003, ¶¶121-122.) Thus, the MSI-H Study Record's disclosure of treating MSI-H patients meets this limitation. (EX1003, ¶¶121-122.)

20. Claim 26: "The method of claim 23, wherein the cancer is a metastatic cancer."

This additional limitation is identical to Claim 9's additional limitation, and is disclosed for the same reasons. (*Supra*, §VI.B.6; EX1003, ¶123.)

21. Claim 27: "The method of claim 23, wherein the objective response rate is assessed in the population of cancer patients at 20 weeks after administering pembrolizumab."

The MSI-H Study Record discloses determining the objective response rate at 20 weeks in patients having MSI-H colorectal cancer. (EX1005, 4-5 (Outcome Measures).) That disclosure reads on this limitation. (EX1003, ¶124.)

22. Claim 28: "The method of claim 23, wherein the cancer is not colorectal cancer."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H non-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 (Primary Outcome Measures), 5 (Inclusion Criteria); *supra*, §VI.B.2.c.) That disclosure reads on this limitation. (EX1003, ¶¶125-29.)

Further, the non-colorectal cancer patients that the POSA would treat in the MSI-H Study would have tumors having progressed following a prior treatment.

(EX1003, ¶126.) *See Acoustic Tech.*, 949 F.3d at 1373; *Genentech,* 946 F.3d at 1340; *In re Baxter*, 952 at 390. In particular, the prior art taught that patients having "measurable" cancer in the context of the MSI-H Study Record refers to patients having metastatic, advanced, and recurrent cancer. (EX1020[6], PDF p. 25; EX1003, ¶126; *see also* EX1089, PDF p. 17; EX1088, PDF. pp. 20, 29, 97.)

Patients with metastatic, advanced, and recurrent non-colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least one prior treatment, such as standard of care chemotherapy, and had their cancers progress after that prior treatment. (EX1020, PDF p. 25; *see also* EX1009, 1034; EX1047, 4-7; EX1003, ¶127.)

It is in this context that 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, ¶128.) In other words, the MSI-H Study Record recognizes that patients would have received a prior

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[6] References directed to methods for treating colorectal cancer also reflect methods for treating small bowel cancer. (*See* EX1020, PDF pp. 6-7, 37, 48-49; EX1003, ¶126.)

treatment, and because of that makes it a point to exclude those that received "anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies." (EX1003, ¶128.) Additionally, because the patients were disclosed to still have a "tumor" and "measurable disease," it would mean that the tumor had progressed following that prior treatment. (EX1003, ¶128.) Indeed, the POSA would have found it highly unusual for the patient population of those who had received prior drug treatments and had their cancer progress after those treatments to not be included in the MSI-H Study Record, especially without any explicit carve-out. (EX1003, ¶128.)

C. Grounds 2-7: Claims 1-28 of the '356 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 published on April 13, 2014. (EX1006, 3738, PDF p. 1; EX1003, ¶¶130-32.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). The Examiner did not consider Pernot.

a. Benson

Benson is a journal article published in July 2014. (EX1009, 1028; EX1003, ¶¶133-34.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). The Examiner did not consider Benson.

b. Chapelle

Chapelle is a journal article published in 2010. (EX1007, 3380; EX1003, ¶¶146-47.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). The Examiner did not consider Chapelle.

c. Brown

Brown is a journal article published in May 2014. (EX1034; EX1003, ¶¶166-67.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). The Examiner did not consider Brown.

d. Duval

Duval is a journal article published on April 6, 2004. (EX1087; EX1003, ¶¶168-69.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). The Examiner did not consider Duval.

e. Hamid

Hamid is a journal article published in July 11, 2013. (EX1011, 132; EX1003, ¶¶185-86.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). During prosecution, Hamid was not considered in the context of the combinations and arguments presented here.

3. Ground 2: Claims 1, 6-11, 13-20, 22-24, and 26-27 of the '356 Patent Are Obvious Over the MSI-H Study Record in View of Pernot and Benson

As discussed above, Claims 1, 6-11, 13-20, 22-24, and 26-27 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that Claims 1, 6-11, 13-20, 22-24, and 26-27, would at a minimum still be unpatentable for obviousness in view of Pernot, Benson, and the knowledge of the POSA (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 the POSA would not have expected such efficacy (EX1002, December 14, 2020 Notice of Allowance at 3; *see also supra* §I), (2) to the extent Limitations [1.1], [11.1], [11.2], [19.1], and [23.2] and Claims 20 and 24 are interpreted to require testing the patient for MSI-H or MMR deficiency status, and to the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose such testing, and/or (3) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach limitations [1.4], [9.1], [10.1], [11.5], [13.1], [14.1], [15.1], [19.1], [19.2], [23.3] or [26.1], which cover features relating to progressive and metastatic disease.

Improved Outcome/Efficacy

The POSA would have expected colorectal cancer patients having MSI-H tumors[7] 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

[7] The POSA also would have expected cancer patients having MSI-H tumors generally to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study. *Infra* Section VI.C.5.

treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record. (EX1003, ¶135.)

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, ¶136.) The MSI-H Study Record is directed to a clinical study treating colorectal cancer patients whose cancers are MSI-H with pembrolizumab, an anti-PD-1 antibody (*supra*, §VI.B.2; EX1003, ¶136), 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; EX1003, ¶136.) As such, Pernot further motivated the POSA to obtain the results of the MSI-H Study Record's study. (EX1003, ¶136.)

Indeed, the state of the art would have further compelled the POSA to carry out the clinical study with a reasonable expectation of success. (EX1003, ¶137.) Physicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art with PD-1 inhibitors (EX1005, at 3 (Study Description), 3-4 (Conditions), 4 (Arms and Interventions), 5-6 (Eligibility); EX1016; EX1017; EX1003, ¶137.)

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; EX1037, 2; EX1038, 7;

EX1051, e976052-6; EX1039, 243s; *see also* EX1035, 1, 8; EX1036, 1186; EX1003, ¶138.)

Additionally, the prior art taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that were 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, ¶¶43-44, 139) and (2) already infiltrated by many immune cells. (EX1034, 747; EX1037, 2; EX1003, ¶¶43, 45, 139.) And the prior art taught that MSI-H tumors naturally displayed those characteristics. (EX1085, 673-74, 677; EX1087, 5002; EX1006, 3740-41; EX1033, 2967; EX1058, 231, 236-37; EX1036, 1186-87, 1193; EX1037, 2, 6; EX1035, 4; EX1041, 9208-09; EX1039, 243s; EX1003, ¶¶46, 139.)

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 Record's study, including determining the outcome of patients. (EX1003, ¶¶135-40; *see also* MPEP 2107.03; *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc*., No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023).) Further, because the POSA would have known that pembrolizumab was already approved for another oncology indication by 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); EX1003, ¶ 177.) Thus, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H 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).

Testing

Limitations [1.1], [11.1], [11.2], [19.1], and [23.2] and Claims 20 and 24 each require a patient that has a tumor that exhibits an MSI-H or MMR deficiency status. To the extent these limitations are interpreted to require testing the patient for such status, and to the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose such testing, it would have been obvious to test 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 discloses treating having MSI-H colorectal cancer in a single arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (eligibility); EX1003, ¶141). 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, ¶141.) Testing was the way in which it was possible to determine if the patient had the MSI-H 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, ¶141.) The POSA would have expected success in carrying out such testing, because testing for MSI-H was routine in the art. (EX1003, ¶141.)

Treating Patients Having Characteristics Related to Progressive and Metastatic Disease

Limitations [1.4], [11.5], [19.2], and [23.3], and Claims 6, 9-10, 13-15, and 26 each require that the patients had received a different cancer therapy drug, the patients' cancers had progressed after the patients received the different cancer therapy drug, or the patients had metastatic cancer. The MSI-H Study Record discloses treating such patients. (*Supra*, §VI.B.2.e) To the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose treating such patients, treating such patients would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶142-145.)

The MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal cancer patients having "tumors" and "measurable disease." (EX1005, 2 (Study Identification), 4 (Arms and Interventions, Study Design), 5-6 (Eligibility); *see supra*, §VI.B.2.e.) Benson is directed to the ways in

which clinical studies involving colorectal cancer are conducted. (EX1009, 1034; EX1003, ¶142.) 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 '356 patent. (EX1003, ¶142.)

The POSA would have had motivation to combine the MSI-H Study Record and Benson. (EX1003, ¶143.) For instance, both the MSI-H Study Record and Benson discuss treating patients with colorectal cancer. (EX1003, ¶143.) 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, ¶143.) 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 drug, and the patients' cancer had progressed after the patients received the different cancer therapy drug. (EX1003, ¶143.) 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, ¶143.) 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, ¶143.) Indeed, this is precisely

how the underlying clinical study was performed. (EX1080, Eligibility Criteria; EX1003, ¶143.)

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 patients had received a different cancer therapy drug, the patients' cancer had progressed after the patient received the different cancer therapy drug, and the patients had metastatic cancer because that is the patient population that the POSA would have expected to treat with such a method. (EX1009, 1034; EX1080, Eligibility Criteria; EX1003, ¶144.)

As discussed above, the 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. As a result, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:20-22 (all patients had treatment-refractory, progressive and metastatic disease); 16:17-21 (all patients having MSI-H colorectal cancer had received two prior chemotherapy regiments); EX1003, ¶145.)

4. Ground 3: Claims 2-5, 11-18, 20-21, and 24-25 Are Obvious Over The MSI-H Study Record, or The MSI-H Study Record in View of Pernot and Benson, in View of Chapelle

a. Claim 2: "The method of claim 1, wherein the step of determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) status includes detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence."

As discussed in Section VI.B.2.b above, the MSI-H Study Record discloses determining that the patient's cancer is MSI-H. Detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶148-151.)

Chapelle is directed towards determining whether tumors are MSI-H. (EX1007, 3380, 3383; EX1003, ¶149.) 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 '356 patent. (EX1003, ¶149.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot and Benson) and Chapelle to detect in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence, in order to test whether a tumor is MSI-H. (EX1003, ¶150.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's cancer is MSI-H. (*Supra* §§VI.B.2, VI.C.3.) Chapelle teaches standard methods of testing

whether a tumor was MSI-H, including detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence. (EX1007, 3380, 3383; EX1003, ¶150.) For example, Chappelle teaches that "a standard test" to determine whether a tumor is MSI-H, which detects in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence has "stood the test of time." (EX1007, 3382, EX1003, ¶150.) 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 cancer patients having MSI-H tumors, and indeed the claimed testing was well known, as the '356 patent admits. (EX1001, 6:16-17; 6:26-29; EX1003, ¶151.)

b. Claim 3: "The method of claim 2, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24."

Carrying out the method of Claim 2, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21, or NR-24 would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶152-53.)

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, ¶¶150, 153.) Those methods include

detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence, wherein the microsatellite marker is BAT-25 or BAT-26. (EX1007, 3380-84; EX1003, ¶153.) For example, Chappelle teaches that "a standard test" using a "[p]anel consisting of . . . BAT26, BAT25" has "stood the test of time." (EX1007, 3382.) Moreover, as discussed above, the '356 patent does not suggest that the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (*Supra*, §VI.C.4.a.).

c. Claim 4: "The method of claim 1, wherein the step of determining that the patient has a tumor that exhibits a MMR deficiency status includes detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence."

Carrying out the method of Claim 1, wherein the step of determining that the patient has a tumor that exhibits a MMR deficiency status includes detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶154-56.)

As discussed above in Section VI.C.4.c, the POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶155.) Those methods include

detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence. (EX1007, 3380-84; EX1003, ¶155.) Indeed, Chappelle teaches that "a standard test" to determine whether a tumor is MSI-H, which comprises detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence, has "stood the test of time." (EX1007, 3382; EX1003, ¶155.) Further, Chapelle teaches that such a test for MSI-H determines that the patient exhibits a MMR deficiency status because Chappelle discloses that "[f]or practical purposes, MSI 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.) Thus, Chapelle teaches determining that the patient has a tumor that exhibits a MMR deficiency status by detecting in a tumor sample obtained from the patient a mismatch repair marker in a DNA sequence. (EX1003, ¶155.)

Moreover, as discussed above, the '356 Patent does not suggest the method of testing for MSI-H or dMMR changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (*Supra*, §VI.C.4.a, EX1003, ¶156.).

d. Claim 5: "The method of claim 1, wherein the MMR deficiency status of the tumor is detected by immunohistochemistry."

Carrying out the method of Claim 1, wherein the MMR deficiency status of the tumor is detected by an immunohistochemistry test have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶157-158.)

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 and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶158.) Those methods include testing with immunohistochemistry. (EX1007, 3380, 3384; EX1003, ¶158.) Moreover, as discussed above, the '356 Patent does not suggest the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (*Supra*, §VI.C.4.a.).

e. Claims 11-18: "wherein the tumor sample exhibits an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers"

As discussed, above, the MSI-H Study Record discloses all the limitations of Claims 11 and 13-18.

Regardless, Claims 11-18, which recite the above limitation through its recitation in claim 11, are obvious over the combination for the same reasons Claim 3 is obvious, which is discussed in Section VI.C.4.b. (EX1003, ¶¶159-160.)

f. Claim 12: "The method of claim 11, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21, or NR-24."

Claim 12 is additionally obvious over the combination for the same reasons Claim 3 is obvious, which is discussed in Section VI.C.4.b. (EX1003, ¶161.)

g. Claim 20: "The method of claim 19, wherein the solid tumor exhibits instability in a microsatellite marker."

Claim 20 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶162.)

h. Claim 21: "The method of claim 20, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24."

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, ¶163.)

i. Claim 24: "The method of claim 23, wherein the tumor exhibits instability of a microsatellite marker."

Claim 24 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶164.)

j. Claim 25: "The method of claim 24, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24."

Claim 25 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶165.)

5. Ground 4: Claims 1, 6-11, 13-20, 22-24, 26-28 of the '356 Patent Are Obvious Over the MSI-H Study Record in View of Brown, Duval, and Benson

As discussed above, Claims 1, 6-11, 13-20, 22-24, 26-28 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that Claims 1, 6-11, 13-20, 22-24, 26-28, would at a minimum still be unpatentable for obviousness in view of Brown, Duval, and Benson, and the knowledge of the POSA (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 the POSA would not have expected such efficacy (EX1002, December 14, 2020 Notice of Allowance at 3; *see also supra* §I), (2) to the extent Limitations [1.1], [11.1], [11.2], [19.1], and [23.2] and Claims 20 and 24 are interpreted to require testing the patient for MSI-H or MMR deficiency status, and to the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose such testing, and/or (3) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach limitations 1.4, 9.1,

10.1, 11.5, 13.1, 14.1, 15.1, 19.1, 19.2, 23.3 or 26.1, which cover progressive and metastatic disease.

Improved Outcome/Efficacy

The POSA would have expected all patients having MSI-H tumors 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 patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record. (EX1003, ¶¶170-77.)

The MSI-H Study Record is directed to a clinical study treating patients having MSI-H colorectal and MSI-H non-colorectal cancer with pembrolizumab, an anti-PD-1 antibody (*supra*, §VI.B.2; EX1003, ¶171). MSI-H was known to occur commonly in several different types of cancers, including colorectal, endometrial, and small bowel cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶ 171.) Brown is an article directed to identifying patients who are likely to respond to PD-1 inhibitors. (*See generally* EX1034.) Brown teaches that PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize (EX1034, 747; EX1003, ¶¶167, 171). Duval is an article directed to MSI-H cancers. (*See generally* EX1087.) Duval teaches that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1087, 5002; EX1003, ¶¶169, 171.) As such,

Brown and Duval would have further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶171.)

Indeed, the state of the art would have further compelled the POSA to carry out the clinical study with a reasonable expectation of success. (*Supra*, §§III.C, VI.C.3; EX1003, ¶¶172-77.) Moreover, many prior art references taught that MSI-H tumors, such as colorectal cancer and endometrial cancer, are naturally infiltrated by many immune cells. (*Supra*, §§III.C, VI.C.3; EX1090, 681 (MSI-H endometrial cancer); EX1003, ¶¶172-177.)

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, ¶¶172-177; *see also* MPEP 2107.03; *Vanda*, 2023 WL 3335538, at *4.) 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.) Thus, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H patients with pembrolizumab at the dosage that was applied in the clinical study. *See Persion Pharms.*, 945 F.3d 1184 at 1190.

Testing

Limitations [1.1], [11.1], [11.2], [19.1], and [23.2] and Claims 20 and 24 each require a patient that has a tumor that exhibits MSI-H or MMR deficiency status. To the extent these limitations are interpreted to require testing the patient for such status, and to the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose such testing, it would have been obvious to test patients for MSI-H for the same reasons as discussed above in Section VI.C.3. (*See* EX1003, ¶178.)

Treating Patients Having Characteristics Related to Progressive and Metastatic Disease

Limitations [1.4], [11.5], [19.2], and [23.3], and Claims 6, 9-10, 13-15, and 26 each require that the patients had received a different cancer therapy drug, the patients' cancers had progressed after the patients received the different cancer therapy drug, or the patients had metastatic cancer. The MSI-H Study Record discloses treating such patients. (*Supra* §VI.B.) To the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose treating such patients, treating such patients would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶179-83.)

The MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal and non-colorectal cancer patients having "tumors" and "measurable disease." (EX1005, 2 (Study Identification), 4 (Arms and

Interventions, Study Design), 5-6 (Eligibility); *see supra* §VI.B.2.e.) MSI-H was known to occur commonly in several different types of cancers, including colorectal, endometrial, and small bowel cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶179.) 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 drug, the patients' cancers had progressed after the patients received the different cancer therapy drug, and the patients had metastatic cancer, these patient characteristics would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶179-83.)

Benson is directed to the ways in which clinical studies involving colorectal and small bowel cancer are conducted. (EX1009, 1034; EX1020, PDF pp. 6-7, 48; EX1003, ¶180.) 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 '356 patent. (EX1003, ¶180.)

The POSA would have had motivation to combine the MSI-H Study Record and Benson. (EX1003, ¶181.) For instance, both the MSI-H Study Record and Benson discuss treating patients having cancer in clinical studies. (EX1003, ¶181.) 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 generally patients who have had their cancer progress after previous drug

therapies. (EX1009, 1034; EX1003, ¶181.) Indeed, based on Benson and the state of the art, patients in a clinical study such as the MSI-H Study Record's study would have received standard of care treatment, not responded to that treatment, and not be expected to respond to additional standard of care treatment. (*See* EX1009, 1034; EX1020, PDF p. 25; EX1003, ¶181; *see also* EX1089, PDF p. 17; EX1088, PDF. pp. 20, 29, 97.) 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 drug, and the patients' cancer had progressed after the patients received the different cancer therapy drug. (EX1003, ¶181.) Indeed, this is precisely how the underlying clinical study was performed. (EX1080, Eligibility Criteria; EX1003, ¶181.)

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, advanced, and recurrent disease. (EX1009, 1034; EX1003, ¶181; *see also* EX1089, PDF p. 17; EX1088, PDF. pp. 20, 29, 97.) 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 patient's cancer was metastatic. (EX1003, ¶181.)

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 patients had received a different cancer therapy drug, the patients' cancer had progressed after the patient received the different cancer therapy drug, and the patients had metastatic cancer because that is the patient population that the POSA would have expected to treat with such a method. (EX1009, 1034; EX1080, Eligibility Criteria; EX1003, ¶182; *see also* EX1089, PDF p. 17; EX1088 at PDF. pp. 20, 29, 97.)

As discussed above, the 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. As a result, that POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:20-22 (all patients had treatment-refractory, progressive and metastatic disease); 16:17-25 (all patients having MSI-H cancer had received more than one prior cancer treatment); EX1003, ¶183.)

6. Ground 5: Claims 2-5, 11-18, 20-21, and 24-25 Are Obvious Over the MSI-H Study Record in View of Brown, Duval, and Benson, Further in View of Chapelle

Claims 2-5, 11-18, 20-21, and 24-25 are obvious over the combination for the same reasons as discussed in Ground 3. (EX1003, ¶184.) The additional

limitations in these claims are directed to specific types of MSI-H testing or microsatellite markers. (EX1003, ¶184.) Chapelle discloses these limitations. (*Supra*, §VI.C.4; EX1003, ¶¶146-165, 184.) Thus, these claims are obvious over the Ground 5 combination for the same reasons as discussed in Ground 3. (EX1003, ¶184.)

7. Ground 6: Claims 18 Is Obvious Over the MSI-H Study Record, Or the MSI-H Study Record in View of Pernot, Benson, and Chapelle, in View of Hamid

Claim 18: "The method of claim 11, wherein pembrolizumab is administered by intravenous infusion."

As discussed above in Section VI.B.2, 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 11, wherein the pembrolizumab is administered by intravenous infusion would have been obvious to the POSA in view of the general knowledge in the art, such as Hamid. (EX1003, ¶¶187-191.)

Hamid is directed towards administering pembrolizumab to cancer patients. (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 '356 patent. (EX1003, ¶188.) Hamid provides for administering pembrolizumab by intravenous infusion. (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, ¶188.)

The POSA would have had motivation to combine the MSI-H Study Record Pernot, Benson, Chapelle, and Hamid. (EX1003, ¶189.) For instance, the MSI-H Study Record disclosed administering pembrolizumab. (*Supra*, §§VI.B.1, VI.B.2.c.) Hamid demonstrated success in treating patients with advanced melanoma with pembrolizumab. (EX1011, 134; EX1003, ¶189.) Thus, the POSA would have been motivated to combine the MSI-H Study Record Pernot, Benson, Chapelle, and Hamid. (EX1003, ¶189.)

At a minimum, administering pembrolizumab by intravenous infusion would have been obvious to try. Indeed, the prior art only discloses administration of pembrolizumab by intravenous infusion to treat cancer patients. (EX1011, 134; *see also* EX1055, 1; EX1003, ¶190.) *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 by intravenous infusion, given that administering pembrolizumab by intravenous infusion had been successful in the past. (EX1011, 134; EX1003, ¶191; *see also* EX1055, 1-3, 9, 15.)

8. Ground 7: Claims 18 Is Obvious Over the MSI-H Study Record in View of Brown, Duval, Benson, Chapelle, and Hamid

Claim 18 is obvious over the combination for the same reasons as discussed in Ground 6. (EX1003, ¶192.) The additional limitation in this claim is directed to administering pembrolizumab only by intravenous infusion. (EX1003, ¶192.) Hamid discloses this limitation. (*Supra*, §VI.C.7; EX1003, ¶¶185-191.) Thus, this claim is obvious over the Ground 7 combination for the same reasons as discussed in Ground 6.

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 would not begin until mid-2026—over 2 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. There will be no overlap that warrants non-institution because Merck will seek a stay in district court.

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 the '356 patent. (EX1002, August 26, 2020 Rejection, 26-32.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least two reasons.

First, 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. (EX1002, 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, the '356 patent and its family members mean that the 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*, 339 F.3d at 1379 (discussing the patent law principle "that which would literally infringe if later in time anticipates if earlier.").

Second, 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 matters. The '356 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.). Additionally, a petition for U.S. Patent No. 11,591,393, which is a continuation of the '356 patent, is pending.

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 1-28 of the ’356 patent based on the grounds specified in this petition.

Respectfully submitted,

Dated: March 4, 2024

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. 10,934,356 contains, as measured by the word-processing system used to prepare this paper, 13,931 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: March 4, 2024

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

CERTIFICATE OF SERVICE

I hereby certify that on March 4, 2024, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,934,356 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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