UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner

v.

The Johns Hopkins University,
Patent Owner

Patent No. 11,634,491

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,634,491

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I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC ("Petitioner" or "Merck") requests *inter partes* review of Claims 1-38 of U.S. Patent No. 11,634,491 ("the '491 patent"), which is assigned to Patent Owner The Johns Hopkins University ("JHU").

The '491 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, ¶¶42-49.) In fact, the specification of the JHU patent is a clinical study ***published in the prior art more than a year*** before the '491 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, ¶¶42-49.)

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 '491 patent are unpatentable, as they fail to meet several statutory requirements. (EX1003, ¶¶1-22, 50-58, 186-187.)

First, the independent claims and most dependent claims of the '491 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 any 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 '491 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; *infra,* §VI.C; EX1003, ¶17, §§VII.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 '491 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 1-38 of the '491 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1-2, 4-7, 11-17, 19-22, and 26-38 are unpatentable under 35 U.S.C. § 102 as being anticipated by the published MSI-H Study Record (EX1005).

Ground 2: Claims 1-2, 4-7, 11-17, 19-22, and 26-38 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 3: Claims 1-2, 4-7, 11, 13-17, 19-22, 26, and 28-38 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), Benson (EX1009), and Koh (EX1095).

Ground 4: Claims 2, 8, 17, and 23 are unpatentable under 35 U.S.C. § 103 as being obvious over the references discussed in Grounds 1, 2, or 3, and further in view of Chapelle (EX1007).

Ground 5: Claims 3 and 18 are unpatentable under 35 U.S.C. § 103 as being obvious over the references discussed in Grounds 1, 2, or 3, and further in view of Steinert (EX1008).

Ground 6: Claims 9-10 and 24-25 are unpatentable under 35 U.S.C. § 103 as being obvious over the references discussed in Grounds 1, 2, or 3, and further in view of Salipante (EX1010).

Ground 7: Claims 11 and 26 are unpatentable under 35 U.S.C. § 103 as being obvious over the references discussed in Grounds 1, 2, or 3, and further in view of Hamid (EX1011).

III. BACKGROUND OF THE '491 PATENT

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

A. The Mechanism of the Prior Art Drug at Issue

Claims 1 and 16 of the '491 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, 25:35-28:16; EX1003, ¶22.)

An immunotherapy is a drug that helps the body fight disease by boosting the immune system. (EX1003, ¶¶30-33.) One particular type of immunotherapy is called a PD-1 inhibitor. (EX1003, ¶30.) 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. (EX1003, ¶30.)

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, ¶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, ¶¶24-29.) 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, ¶¶24-26.) Whether a tumor exhibited MSI-H could inform therapeutic choices, prognosis, and familiar cancer risk appraisal. (EX1003, ¶¶24, 42-9.) MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel, and gastric cancer. (EX1003, ¶¶25-26.) Those tumor types, as well as colorectal, are also common in Lynch syndrome, which was known at the time to be closely associated with MSI-H. (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 cancers that were identified as being MSI-H. (EX1029, ¶¶90-93; EX1003, ¶35.) The Parties agreed to collaborate on the clinical study, which uses the study identifier NCT01876511 (the "MSI-H Study"). (EX1005, 3 (Collaborators); 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. (EX1021, 1-4; EX1003, ¶37.) It was indexed by subject matter, and would have been used by the POSA to understand the state of the art. (EX1003, ¶37.)

During prosecution of the '491 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, August 29, 2022 Declaration, 7-8, ¶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.)

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[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, ¶36.)

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 '491 patent's claimed subject matter derives directly from the MSI-H Study. (*See* EX1002, August 29, 2022 Declaration, 7-8, ¶¶22-23 (connecting the '491 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 '491 patent's examples, tables, and figures are devoted to the design and results of the MSI-H Study, a "small phase 2 trial of pembrolizumab." (EX1001, 6:52-22:21, 3:20-22; Figs. 1-13; EX1005; EX1003, ¶40.) For instance, Examples 1-4 (EX1001, 8:6-16:6) are the design of the MSI-H Study, and Examples 5-11 (EX1001, 16:9-18:67) report its results. Further, Tables 1-3 (EX1001, 19:1-22:21) and Figures 1-13 also report the MSI-H Study's results.

The Examiner considered the MSI-H Study Record during prosecution of a family member of the '491 patent, U.S. Patent No. 10,934,356 (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. (EX1022, 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. (EX1022, 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 (EX1003, ¶47) 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, ¶¶42-49.)

Indeed, in April 2014, Pernot taught that MSI-H cancers are "good candidates for immunotherapy." (EX1006, 3740-41; EX1003, ¶46.) 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 . . . ." (EX1032, e27817-5; EX1003, ¶44.) 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, ¶46.)

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, ¶¶43-44) and (2) already infiltrated by many immune cells (EX1034, 747; EX1037, 2; EX1003, ¶¶43, 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 '491 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 '491 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 '491 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 '491 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 of the '491 patent's family, seeking to distance the patent from the MSI-H Study, by arguing that data from the clinical study was the basis for patentability (which thus led the Examiner to a legally erroneous rationale for allowing the patent to issue). (*See* EX1022, February 4, 2020 Declaration, 7-8, ¶22; *see also* 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]

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[2] To be clear, each ground of invalidity discussed in this Petition applies even if the

B. Ground 1: Claims 1-2, 4-7, 11-17, 19-22, 26-38 of the '491 Patent are Anticipated by the MSI-H Study Record

1. Law on Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citations omitted). "[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." *Id.* at 1379.

In *Schering*, the Federal Circuit clarified that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter;

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*, 413 F.3d at 1325-26).

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. 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

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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.

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) ("Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.") (citing *In re Montgomery*, 677 F.3d at 1381). The Federal Circuit has also made clear that "[e]xtrinsic evidence can be used to demonstrate what is necessarily present in a prior art embodiment even if the

extrinsic evidence is not itself prior art." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (quotations omitted).

The MSI-H Study Record inherently anticipates Claims 1-2, 4-7, 11-17, 19-22, 26-38 of the '491 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 '491 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 of treating cancer in a human patient, the method comprising:"

The Arms and Interventions section of the MSI-H Study Record discloses a method of treating cancer in a human patient. (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 claim. (EX1003, ¶¶60-61.)

b. [1.1]: "testing or having tested a biological sample obtained from a patient"

The Arms and Interventions section of the MSI-H Study Record discloses three study arms, one of which consists of patients having MSI-H non-colorectal cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶62.) That disclosure reads on this limitation. (EX1003, ¶¶62-66.)[4]

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, ¶¶27, 63; *see also 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, June 28, 2022 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, ¶64.) For example, the art taught that "[p]atients

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[4] As discussed above, "MSI positive non-colorectal cancer" would be understood by the POSA to mean "microsatellite instability high" and "mismatch repair deficient" non-colorectal cancer. (*Supra*, §III.A.)

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, June 28, 2022 Declaration, 7-8, ¶23.) Moreover, because MSI-H is caused by dMMR, all cancers that are MSI-H are dMMR. (EX1010, 1192; EX1003, ¶64; *see also* EX1001, 1:28-30.)[5]

According to the MSI-H Study Record's disclosure, the MSI-H Study Record required testing or having tested "a biological sample obtained from a patient" in order to place the patients into the proper arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶65.) That is, to determine a patient's cancer is MSI-H is to test for specific biomarkers. (EX1003, ¶¶64-66.)

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[5] 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]: "having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer,"

The Arms and Interventions section of the MSI-H Study Record discloses treating patients having non-colorectal MSI-H cancer. (EX1005, 4 (Arms and Interventions); *see also id*., 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel cancer, and gastric cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶¶25, 67.) Those tumor types, as well as colorectal, are also common in Lynch syndrome, which was known at the time to be closely associated with MSI-H. (EX1085, 673-74; EX1003, ¶¶25, 67.) Thus, the POSA would have at once envisaged treating patients having endometrial, small bowel, and gastric cancer with the MSI-H Study Record's methods. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("A reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination.") (quoting *In re Petering*, 49 CCPA 993, 301 F.2d 676, 681 (1962)); *VirnetX Inc. v. Apple Inc*., 665 F. App'x 880, 888 (Fed. Cir. 2016) ("Substantial evidence supports

the PTAB's finding that Wesinger's disclosure of the genus 'computer' encompasses the 'notebook computer' species"); *see also Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1340 (Fed. Cir. 2020) ("Anticipation is established when one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim limitation was disclosed in that single reference.") (citations, quotations, and brackets omitted). Indeed, the specification did not differentiate between different non-colorectal cancers when analyzing the efficacy of the method. (EX1001, Fig. 11, Example 7, Tables 1-2; EX1003, ¶67.)

Thus the MSI-H Study Record discloses this limitation. (EX1003, ¶68.) *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.").

d. [1.3]: "thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient;"

As discussed in the analysis for limitation [1.1], the MSI-H Study Record discloses testing or having tested a biological sample obtained from a patient and thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient. (*Supra*, §VI.B.2.a; EX1003, ¶¶62-66, 69-70.)

e. [1.4]: "and in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab."

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), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶¶35, 50, 71.) That disclosure reads on this limitation. (EX1003, ¶¶71-74.)

The MSI-H Study Record does not expressly use the phrase "therapeutically effective" in providing the dosage for the treatment therapy. Nonetheless, the dosage described in the MSI-H Study Record, 10 mg/kg MK-3475 (pembrolizumab), is identical to the dosage described as being "therapeutically effective" in the '491 patent, and any required efficacy is thus inherent to that dosage. (EX1003, ¶72.)

Indeed, the '491 patent itself, which only describes one dosage (EX1001, 8:50-56, 13:24-30)—the same one in the MSI-H Study Record (EX1005, 4 (Arms and Interventions)—asserts that this dosage is effective. (EX1001, 4:23-36, 16:4-8, 16:29-32, 19:40-21:15, Figs. 2, 11; EX1003, ¶73.) "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, ¶73.)

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 cancer patients having MSI-H non-colorectal cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶¶35, 50, 71.)

3. Claim 2: "The method of claim 1, wherein the biological sample is tumor tissue."

As discussed above in Section VI.B.2.b, the Arms and Interventions section of the MSI-H Study Record discloses determining whether the patient's cancer is MSI-H. (*See also infra*, §VI.C.5.) Further, the Eligibility section of the MSI-H Study Record requires each patient to "[a]gree to have a biopsy of their cancer." (EX1005, 5-6 (Eligibility).) The POSA would have understood that a biopsy of a patient's tumor obtains tumor tissue for testing. As such, in the context of the

MSI-H Study Record, where patients are separated into three separate cohorts based, in part, on whether a patient's cancer is MSI-H, the POSA would have understood that the biopsy would obtain tumor tissue to test whether the patient's cancer's is MSI-H (EX1007, 3380, 3383; EX1044, 3309; EX1045, 3485; EX1046,1193; EX1003, ¶75; *see also* EX1001, 8:14-15 (testing "[a]rchived tumor samples" or "newly obtained biopsies.").) Therefore, the MSI-H Study Record's disclosure of treating MSI-H patients and the MSI-H Study Record's requirement that patients agree to have a biopsy demonstrates that the MSI-H Study Record discloses the claimed limitation. (EX1003, ¶¶75-76.)

4. Claim 4: "The method of claim 1, wherein the cancer is endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer or choloangiocarcinoma."

As discussed above in Section VI.B.2.c, based on the MSI-H Study Record's disclosure, the POSA would have at once envisaged treating endometrial cancer, small bowel, and gastric cancer. *See Kennametal*, 780 F.3d at 1381; *VirnetX*, 665 at 888; *see also Genentech*, 946 F.3d at 1340. Thus, the MSI-H Study Record anticipates Claim 4's additional limitation. (EX1003, ¶¶77-78.) *See Brown*, 265 F.3d at 1351.

5. Claim 5: "The method of claim 1, wherein the cancer is pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer."

As discussed above in Section VI.B.2.c, the POSA would have at once envisaged treating endometrial cancer. Endometrial cancer is a type of uterine cancer. (EX1089, PDF p. 39.) Thus, the MSI-H Study Record anticipates Claim 5's additional limitation. (EX1003, ¶¶79-80.) *See Brown*, 265 F.3d at 1351.

6. Claim 6: "The method of claim 1, wherein the cancer is determined to be microsatellite instability high."

As explained in Sections VI.B.2.b and VI.B.2.d-e, the Arms and Interventions section of the MSI-H Study Record discloses treating cancer patients whose tumors were determined to be MSI-H. (EX1003, ¶¶81-82.)

7. Claim 7: "The method of claim 1, wherein the cancer is determined to be mismatch repair deficient."

As explained in Sections VI.B.2.b and VI.B.2.d-e, the Arms and Interventions section of the MSI-H Study Record discloses treating cancer patients whose tumors were determined to be dMMR. (EX1003, ¶¶83-84.)

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

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.e.)

Pembrolizumab for the treatment of cancer was administered by intravenous infusion. (*E.g.* EX1011, 134; *see also* EX1055, 1; EX1054, 3; EX1003, ¶¶85-86.)

9. Claim 12: "The method of claim 1, wherein the cancer is small bowel cancer."

As discussed above in Section VI.B.2.c, based on the MSI-H Study Record, the POSA would have at once envisaged treating small bowel cancer. (*See also* EX1003, ¶¶87-88.) Thus, the MSI-H Study Record discloses this limitation. *See Kennametal*, 780 F.3d at 1381; *VirnetX*, 665 at 888; *see also Genentech*, 946 F.3d at 1340.

10. Claim 13: "The method of claim 1, wherein the patient had previously been treated with a prior cancer therapy drug and the patient's cancer had progressed after the patient was treated with the prior cancer therapy drug."

The MSI-H Study Record's title and Eligibility section disclose 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 non-colorectal cancer in a Phase II clinical study. (EX1005, 3 (Study description), 3-4 (Conditions), 4 (Study Design, 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, ¶89.) In the context of the MSI-H Study Record, these disclosures demonstrate that, the patients in that the MSI-H Study Record refers to had previously been treated with a prior cancer therapy drug and the patients' cancers had progressed after the patients were treated with the prior cancer therapy drug. (EX1003, ¶89.)

As discussed above, the POSA would have at once envisaged treating endometrial, small bowel, and gastric cancer in the MSI-H Study. (*Supra*, §VI.B.2.c.) The prior art taught that patients having "measurable" endometrial, small bowel, and gastric cancer in the context of a clinical study treating patients having tumors, like the MSI-H Study Record, refers to patients having metastatic, advanced, and recurrent cancer. (EX1089, PDF p. 17 (endometrial); EX1020,[6] PDF p. 25 (small bowel); EX1094, PDF p. 15; EX1003, ¶90.) 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, ¶90.)

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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, ¶90.)

Patients with metastatic and advanced endometrial, small bowel, and gastric cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least one prior drug therapy, such as standard of care chemotherapy, and had their cancers progress after that drug therapy. (EX1089, PDF p. 17 (endometrial); EX1020, PDF p. 25 (small bowel); EX1094, PDF p. 12, 15 (gastric cancer patients would generally receive a standard first line therapy, unless diagnosis was late stage); *see also* EX1009, 1034; EX1047, 4-7; EX1003, ¶91.) And indeed, the POSA would have expected that all of the patients selected for a clinical study would have been similarly situated with respect to prior drug therapies. (*See* EX1005, 3 (Study Description), 4 (Study Design, Arms and Interventions), EX1003, ¶91.)

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, ¶92.) 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, ¶92.) Additionally, because the patients were disclosed to still have a "tumor" and "measurable disease," it would mean

that the cancer had progressed following that prior treatment. (EX1003, ¶92.) 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, ¶92.)

For all of the reasons above, the MSI-H Study Record disclosed to the POSA that patients had previously been treated with a prior cancer therapy drug and the patients' cancer had progressed after the patients were treated with the prior cancer therapy drug. (EX1001, 9:56-59 (patients with non-colorectal cancer must have "had at least 1 prior cancer therapy"); EX1003, ¶¶89-93.) *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020) ("In an anticipation analysis, the dispositive question is whether a skilled artisan would 'reasonably understand or infer' from a prior art reference that every claim limitation is disclosed in that single reference"); *Genentech*, 946 F.3d at 1340 (same); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (same).

Indeed, additional evidence confirms this understanding of the MSI-H Study Record. In particular, a poster presentation discussing 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[7] at Eligibility Criteria.)

11. Claim 14: "The method of claim 1 further comprising testing or having tested the patient for progression of the cancer after the treatment."

The MSI-H Study Record discloses that a "primary outcome measure" is "Immune-related progression free survival (irPFS) rate" at 20 weeks. (EX1005, 4-5 (Outcome Measures).) The POSA would have understood that an "Immune-related ***progression*** free survival (irPFS) rate" is a test for disease

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[7] 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 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, ¶94.) 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, ¶94.) Thus, there was no expectation of confidentiality. (EX1003, ¶94.) *See also In re Klopfenstein* 380 F.3d 1345, 1350 (Fed. Cir. 2004).

progression. (EX1048, 236; EX1003, ¶95.) Thus, the MSI-H Study Record discloses Claim 14's additional limitation. (EX1003, ¶96.)

12. Claim 15: "The method of claim 1, wherein the cancer is metastatic."

As discussed in the analysis for Claim 13, the patients in the MSI-H Study Record would have had metastatic cancer. (EX1003, ¶¶97-98.) Indeed, prior art concerning the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had "metastatic tumors." (EX1049, 444; *see also* EX1050, S4; EX1003, ¶97.) *See* Yeda, 906 F.3d at 1041.

13. Claim 16

a. [16.pre]: "A method of reducing the risk of cancer progression or increasing overall survival in a human patient, the method comprising:"

As discussed above in Sections VI.B.2.b and VI.B.2.d-e, the Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H non-colorectal cancer with 10 mg/kg pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Inclusion Criteria).) Thus, for all of the reasons that the MSI-H Study Record discloses all the limitations of Claim 1 (discussed above at §VI.B.2), the MSI-H Study Record discloses this limitation. In addition, the MSI-H Study Record discloses that outcome measures include "Immune-related progression free survival" and "Overall survival," and as

discussed above, the data inherently resulting from the MSI-H Study Record demonstrates improvements in those outcomes. (EX1005, 4-5 (Outcome Measures); *supra*, §VI.B.2.) For this additional reason, the MSI-H Study Record discloses "[a] method of reducing the risk of cancer progression or increasing overall survival in a human patient." (EX1003, ¶99.)

b. [16.1]: "testing, or having tested, a biological sample obtained from a patient"

This limitation is identical to limitation [1.1], and is disclosed for the same reasons. (*Supra*, §VI.B.2.b; EX1003, ¶¶62-66, 100.)

c. [16.2]: "having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer,"

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra*, §VI.B.2.c; EX1003, ¶¶67-68, 101.)

d. [16.3]: "thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient;"

This limitation is identical to limitation [1.3], and is disclosed for the same reasons. (*Supra*, §VI.B.2.d; EX1003, ¶¶69-70, 102.)

e. [16.4]: "and in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab."

This limitation is identical to limitation [1.4], and is disclosed for the same reasons. (*Supra*, §VI.B.2.e; EX1003, ¶¶71-74, 103.)

14. Claim 17: "The method of claim 16, wherein the biological sample is a tumor tissue sample from the patient."

The additional limitation in Claim 17 is the same as recited in Claim 2 and disclosed for the same reasons. (*Supra*, §VI.B.3; EX1003, ¶¶75-76, 104.)

15. Claim 19: "The method of claim 16, wherein the cancer is endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer or choloangiocarcinoma."

The additional limitation in Claim 19 is the same as recited in Claim 4 and disclosed for the same reasons. (*Supra*, §VI.B.4; EX1003, ¶¶77-78, 105.)

16. Claim 20: "The method of claim 16, wherein the cancer is pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer."

The additional limitation in Claim 20 is the same as recited in Claim 5 and disclosed for the same reasons. (*Supra*, §VI.B.5; EX1003, ¶¶79-80, 106.)

17. Claim 21: "The method of claim 16, wherein the cancer is determined to be microsatellite instability high."

The additional limitation in Claim 21 is the same as recited in Claim 6 and disclosed for the same reasons. (*Supra*, §VI.B.6; EX1003, ¶¶81-82, 107.)

18. Claim 22: "The method of claim 16, wherein the cancer is determined to be mismatch repair deficient."

The additional limitation in Claim 22 is the same as recited in Claim 7 and disclosed for the same reasons. (*Supra*, §VI.B.7; EX1003, ¶¶83-84, 108.)

19. Claim 26: "The method of claim 16, wherein the pembrolizumab is administered to the patient intravenously."

The additional limitation in Claim 26 is the same as recited in Claim 11 and disclosed for the same reasons. (*Supra*, §VI.B.8; EX1003, ¶¶85-86, 109.)

20. Claim 27: "The method of claim 16, wherein the cancer is small bowel cancer."

The additional limitation in Claim 27 is the same as recited in Claim 12 and disclosed for the same reasons. (*Supra*, §VI.B.9; EX1003, ¶¶87-88, 110.)

21. Claim 28: "The method of claim 16, wherein the patient had previously been treated with a prior cancer therapy drug and the patient's cancer had progressed after the patient was treated with the prior cancer therapy drug."

The additional limitation in Claim 28 is the same as recited in Claim 13 and disclosed for the same reasons. (*Supra*, §VI.B.10; EX1003, ¶¶89-94, 111.)

22. Claim 29: "The method of claim 17 further comprising testing or having tested the patient for progression of the cancer after the treatment."

The additional limitation in Claim 29 is the same as recited in Claim 14 and disclosed for the same reasons. (*Supra*, §VI.B.11; EX1003, ¶¶95-96, 112.)

23. Claim 30: "The method of claim 16, wherein the cancer is metastatic cancer."

The additional limitation in Claim 30 is the same as recited in Claim 15 and disclosed for the same reasons. (*Supra*, §VI.B.12; EX1003, ¶¶97-98, 113.)

24. Claim 31: "The method of claim 1, wherein the cancer is endometrial cancer."

As discussed above in Sections VI.B.2.c and VI.B.4-5 based on the MSI-H Study Record, the POSA would have at once envisaged treating endometrial cancer. (*See also* EX1003, ¶¶67-69, 77-80, 114-115.) Thus, the MSI-H Study Record discloses this limitation. *See Kennametal*, 780 F.3d at 1381; *VirnetX*, 665 at 888; *see also Genentech*, 946 F.3d at 1340.

25. Claim 32: "The method of claim 31, wherein the patient had previously been treated with a prior cancer therapy drug and the patient's cancer had progressed after the patient was treated with the prior cancer therapy drug."

The additional limitation in Claim 32 is the same as recited in Claim 13 and disclosed for the same reasons. (*Supra*, §VI.B.10; EX1003, ¶¶89-94, 116.)

26. Claim 33: "The method of claim 31 further comprising testing or having tested the patient for progression of the cancer after the treatment."

The additional limitation in Claim 33 is the same as recited in Claim 14 and disclosed for the same reasons. (*Supra*, §VI.B.11; EX1003, ¶¶95-96, 117.)

27. Claim 34: "The method of claim 31, wherein the cancer is metastatic."

The additional limitation in Claim 34 is the same as recited in Claim 15 and disclosed for the same reasons. (*Supra*, §VI.B.12; EX1003, ¶¶97-98, 118.)

28. Claim 35: "The method of claim 16, wherein the cancer is endometrial cancer."

The additional limitation in Claim 35 is the same as recited in Claim 31 and disclosed for the same reasons. (*Supra*, §VI.B.24; EX1003, ¶¶114-115, 119.)

29. Claim 36: "The method of claim 35, wherein the patient had previously been treated with a prior cancer therapy drug and the patient's cancer had progressed after the patient was treated with the prior cancer therapy drug."

The additional limitation in Claim 36 is the same as recited in Claim 32 and disclosed for the same reasons. (*Supra*, §VI.B.25; EX1003, ¶¶116, 120.)

30. Claim 37: "The method of claim 35 further comprising testing or having tested the patient for progression of the cancer after the treatment."

The additional limitation in Claim 37 is the same as recited in Claim 33 and disclosed for the same reasons. (*Supra*, §VI.B.26; EX1003, ¶¶117, 121.)

31. Claim 38: "The method of claim 35, wherein the cancer is metastatic."

The additional limitation in Claim 38 is the same as recited in Claim 34 and disclosed for the same reasons. (*Supra*, §VI.B.27; EX1003, ¶¶118, 122.)

C. Grounds 2-7: Claims 1-38 of the '491 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. Brown

Brown is a journal article titled *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival* and was published online in Genome Research in May 2014. (EX1034; EX1003, ¶123.) 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 during prosecution of the ’491 patent.

b. Duval

Duval is a journal article titled *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas* and was published in the Proceedings of the National Academy of Sciences on April 6, 2004. (EX1087; EX1003, ¶125.) 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 during prosecution of the ’491 patent.

c. Benson

Benson is a journal article titled *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology* and was published in the Journal of the National Comprehensive Cancer Network in July 2014. (EX1009, 1028, 1028; EX1003, ¶127.) 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 during prosecution of the ’491 patent.

d. Koh

Koh is a journal article titled *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology* and was published in in the Journal of the National Comprehensive Cancer Network in February 2014. (EX1095, 248; EX1003, ¶144.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

The Examiner did not consider Koh during prosecution of the ’491 patent.

e. Chapelle

Chapelle is a journal article titled *Clinical Relevance of Microsatellite Instability in Colorectal Cancer* and was published in the Journal of Clinical Oncology in 2010. (EX1007, 3380; EX1003, ¶150.) 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 during prosecution of the ’491 patent.

f. Steinert

Steinert is a journal article titled *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer* and was published on March 15,

2014. (EX1008, OF2; EX1003, ¶160.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

The Examiner did not consider Steinert during prosecution of the ’491 patent.

g. Salipante

Salipante is a journal article titled *Microsatellite Instability Detection by Next Generation Sequencing* and was published in Clinical Chemistry in September 2014. (EX1010, PDF p. 2; EX1003, ¶166.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

The Examiner did not consider Salipante during prosecution of the ’491 patent.

h. Hamid

Hamid is a journal article titled *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma* and was published in the New England Journal of Medicine on July 11, 2013. (EX1011, 134; EX1003, ¶178.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

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

3. Ground 2: Claims 1-2, 4-7, 11-17, 19-22, 26-38 of the '491 Patent Are Obvious Over the MSI-H Study Record in View of Brown, Duval, and Benson

As discussed above, Claims 1-2, 4-7, 11-17, 19-22, 26-38 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that Claims 1-2, 4-7, 11-17, 19-22, 26-38, 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], [1.3], [16.1], and [16.3] 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, (3) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach Limitations [1.2] and [16.2] and Claims 4-5, 12, 19-20, 27, and 30-38, which require specific types of cancer, and/or (4) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach Claims 13, 15, 28, 30, 32, 34, 36, and 38, 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, ¶¶129-134.)

The MSI-H Study Record is directed to a clinical study treating patients having MSI-H non-colorectal cancer with pembrolizumab, an anti-PD-1 antibody. (*Supra,* §§III.B, VI.B; EX1003, ¶130.). MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel, and gastric cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶¶25, 130.) 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, ¶¶124, 130). 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, ¶¶126, 130.) As such, Brown and Duval would have further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶130.) Specifically, the POSA would have been motivated to treat

patients having common types of MSI-H cancers, including endometrial, small bowel, and gastric cancer in the MSI-H Study. (EX1003, ¶130.)

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, ¶131.) Physicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art with PD-1 inhibitors ((EX1005, 3 (Study Description), 3-4 (Conditions), 4 (Arms and Interventions), 5-6 (Eligibility); EX1016; EX1017; EX1003, ¶131.)

Additionally, prior art beyond Brown and Duval taught 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, and that all MSI-H cancer, such as endometrial, small bowel, and gastric cancer, have cancer cells that are easy for immune cells to recognize. (EX1085, 673-74, 677; EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5.)[8]. Further, Brown and other prior art also taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are already infiltrated by many immune

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[8] This was also true for MSI-H colorectal cancer. (EX1006, 3740-41; EX1058, 231, 236-37; EX1036, 1186-87, 1193; EX1037, 2, 6; EX1035, 4; EX1039, 243s.)

cells. (EX1034, 747; EX1037, 2; EX1003, ¶¶124, 132.) Moreover, many prior art references taught that MSI-H tumors, such as endometrial cancer tumors, are naturally infiltrated by many immune cells. (EX1090, 681 (MSI-H endometrial cancer); EX1091, 28, 30, 31; EX1003, ¶132.)

Further several sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 1968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶133.) While these disclosures are in the context of MSI-H colorectal cancer, the POSA would have understood their teachings to be applicable to other MSI-H cancers, especially in light of the fact that small bowel cancer is often treated similarly to colorectal cancer. (*See* EX1020, PDF pp. 6-7, 37, 48-49; EX1003, ¶133.)

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, ¶134; *see also* MPEP 2107.03 ("[A]s a general rule . . . Office personnel should presume that [an] applicant has established that the subject matter of [a human clinical] trial is reasonably predictive of having the asserted therapeutic utility."); *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc.*, No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023) ("There is no error in the district court's

use of the then-ongoing clinical trial as one piece of evidence, combined with other prior art references, to support an obviousness determination.”).) Further, because the POSA would have known that pembrolizumab was already approved for another oncology indication in November 2014, the POSA would have had a higher expectation of success. (EX1055, 1-2 (pembrolizumab approved for melanoma); EX1063, 334-335 (for oncology drugs, 55% of second indications were successful if the first indication was successful, but only 9% of first indications were successful.) Thus, the POSA would have seen the inherent properties, discussed above in Section VI.B, of treating MSI-H endometrial, small bowel, and gastric cancer patients with pembrolizumab at the dosage that was applied in the clinical study. *See Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (“Inherency may supply a missing claim limitation in an obviousness analysis.”).

Testing

Limitations [1.1], [1.3], [16.1], and [16.3] “require testing or having tested a biological sample obtained from a patient” and “thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient.” 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 based on the MSI-H Study Record.

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; EX1003, ¶¶129-134.) The MSI-H Study Record discloses treating having MSI-H non-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, ¶135). To the extent not explicitly required, this would have at least motivated the POSA to test or have tested a biological sample obtained from a patient in order to thereby determine that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient because the POSA would need to place the patients into the proper study arm. (EX1003, ¶135.) Previous testing of a biological sample obtained from a patient 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, ¶135.) The POSA would have expected success in carrying out the claimed testing, because testing a biological sample obtained from a patient for MSI-H was routine in the art. (EX1003, ¶135; *see also infra*, §VI.C.5.)

Treating Specific Types of MSI-H Cancers

Limitations [1.2] and [16.2] and Claims 4-5, 12, 19-20, 27, and 30-38 each require specific types of cancer, such as endometrial, small bowel, and uterine cancer. The MSI-H Study Record discloses treating patients having those cancers. (*Supra,* §VI.B.) To the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose treating patients having those cancers, treating them would have been obvious to the POSA in view of the general knowledge in the art. (EX1003, ¶¶136-137.)

The Arms and Interventions section of the MSI-H Study Record discloses treating patients having non-colorectal MSI-H cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel, and gastric cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶¶25, 136.) Endometrial cancer is a type of uterine cancer. (EX1089, PDF p. 39; EX1003, ¶136.) Those tumor types, as well as colorectal, are also common in Lynch syndrome, which was known at the time to be closely associated with MSI-H. (EX1085, 673-74; EX1003, ¶¶25, 136.)

As discussed above, the POSA would have been motivated and expected success in carrying out the MSI-H Study Record's methods, including treating

patients having MSI-H non-colorectal cancer. (*Supra*, §VI.C.3; EX1003, ¶¶129-134.) To the extent not explicitly required, this would have at least motivated the POSA to treat patients having MSI-H endometrial, small bowel, and gastric cancer. (EX1003, ¶137.) The POSA would have expected success in treating patients having those cancers, because those are common types of MSI-H non-colorectal cancer. (EX1003, ¶137.)

Treating Patients Having Characteristics Related to Progressive and Metastatic Disease

Claims 13, 15, 28, 30, 32, 34, 36, and 38 each require treating patients who had previously been treated with a prior cancer therapy drug and whose cancers had progressed after the patients were treated with the prior cancer therapy drug or who had metastatic cancer. To the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose a method comprising treating patients having those characteristics, these limitations would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶138-143.)

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.10, VI.B.12, VI.B.21, VI.B.23, VI.B.25, VI.B.27, VI.B.29, VI.B.21.) MSI-H was known to

occur commonly in several different types of cancers, including endometrial, small bowel, and gastric cancer. (EX1085, 673, 675; EX1086, 14; EX1003, ¶¶25, 138.) Even if the MSI-H Study Record does not explicitly teach treating patients who had previously been treated with a prior cancer therapy drug and whose cancers had progressed after the patients were treated with the prior cancer therapy drug or who had metastatic cancer, treating these patients would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶138.)

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, ¶¶128, 139.) 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 '491 patent. (EX1003, ¶139.)

The POSA would have had motivation to combine the MSI-H Study Record and Benson. (EX1003, ¶140.) For instance, both the MSI-H Study Record and Benson discuss treating patients having cancer in clinical studies. (EX1003, ¶140.) 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, ¶140.) 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; EX1089, PDF p. 17 (endometrial); EX1020, PDF p. 25 (small bowel); EX1094, PDF p. 12, 15 (gastric cancer patients would receive a standard first line therapy, unless diagnosis was late stage); *see also* EX1047, 4-7; EX1003, ¶140.) 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, ¶140.) Further, the POSA would have expected that all of the patients selected for a clinical study would have been similarly situated with respect to prior drug therapies. (*See* EX1005, 3 (Study Description), 4 (Study Design, Arms and Interventions), EX1003, ¶140.) Indeed, this is precisely how the underlying clinical study was performed. (EX1080, Eligibility Criteria (The MSI-H 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"); EX1003, ¶140.)

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. (EX1089, PDF p.17 (endometrial); EX1094, PDF p. 15 (gastric); EX1020, PDF p. 25 (small bowel); EX1003, ¶141.) 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, ¶141.)

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; EX1003, ¶142; EX1080, eligibility criteria *see also* EX1089, PDF p. 17; EX1088, 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 patients having MSI-H cancer with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:31-33 (all patients had treatment-refractory, progressive and metastatic disease); 15:66-16:6 (all patients

having MSI-H cancer had received more than one prior cancer treatment); EX1003, ¶143.)

4. Ground 3: Claims 1-2, 4-7, 11, 13-17, 19-22, 26, and 28-38 of the '491 Patent Are Obvious Over the MSI-H Study Record in View of Brown, Duval, Benson, and Koh

As discussed above, Claims 1-2, 4-7, 11, 13-17, 19-22, 26, and 28-38 would have been obvious based on Brown, Duval, and Benson. (*Supra*, §VI.C.3.) However, to the extent that Patent Owner argues that the teachings in Benson relating to patients receiving prior treatment and having progressive and metastatic disease, do not apply to Claims 1-2, 4-7, 11, 13-17, 19-22, 26, and 28-38 to the extent that those claims are directed towards uterine cancer and endometrial cancer (which is a form of uterine cancer), these claims at minimum would have been obvious further in view of Koh.

Koh is directed to the ways in which clinical studies involving endometrial cancer are conducted. (EX1095, 256; EX1089, PDF p. 17; EX1003, ¶¶145, 147.) As such, the POSA would have had reason to consider Koh, which is in the same field as the MSI-H Study Record and the '491 patent. (EX1003, ¶147.)

The POSA would have had motivation to combine the MSI-H Study Record and Koh. (EX1003, ¶148.) For instance, both the MSI-H Study Record and Koh discuss treating patients having cancer in clinical studies. (EX1003, ¶148.) Koh discusses that the patients having endometrial cancer that would participate in a

clinical study generally would have had a tumor that has progressed following at least one prior cancer treatment and metastatic cancer. (EX1095, 256; EX1089, PDF p. 17; EX1003, ¶128; *see also* EX1080, Eligibility Criteria.) Thus, the POSA would have been motivated to treat such patients in a clinical study. (EX1003, ¶148.)

The POSA would have expected success in treating such patients in the MSI-H Study's clinical study because those are the types of patients that are normally treated in such a clinical study. (EX1003, ¶156.)

Thus, Claims 1-2, 4-7, 11, 13-17, 19-22, 26, and 28-38 would have been obvious to the POSA over the MSI-H Study Record in View of Brown, Duval, Benson, and Koh.

5. Ground 4: Claims 2, 8, 17 and 23 Are Obvious Over The References Discussed in Grounds 1, 2, or 3, and Further in View of Chapelle

a. Claim 2: "The method of claim 1, wherein the biological sample is tumor tissue."

As discussed above in Section VI.B, the MSI-H Study Record discloses determining that the patient's cancer is MSI-H. (*See also supra*, §VI.C.3.) Testing tumor tissue from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶152-154.)

Chapelle is directed towards determining whether tumors are MSI-H. (EX1007, 3380, 3383; EX1003, ¶¶151, 153.) 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 '491 patent. (EX1003, ¶153.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Chapelle to test tumor tissue from the patient, in order to test whether a tumor is MSI-H. (EX1003, ¶154.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's cancer is MSI-H. (*Supra*, §§VI.B, VI.C.3.) Chapelle teaches standard methods of testing whether a tumor was MSI-H using tumor tissue. (EX1007, 3380, 3383; EX1003, ¶¶151, 154.) 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 such testing of tumor tissue was well known, as the '491 patent admits. (EX1001, 6:25-26; 6:35-38; EX1003, ¶154.)

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

Carrying out or having carried out an immunohistochemistry test on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶155.)

As discussed above in Section VI.C.5.a, the POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with

Brown, Duval, and Benson) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶156.) Those methods include testing with immunohistochemistry. (EX1007, 3380, 3384; ¶156.) Moreover, as discussed above, the '491 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.3; EX1003, ¶157.)

c. Claim 17: "The method of claim 16, wherein the biological sample is a tumor tissue sample from the patient."

Claim 17 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.5.a. (EX1003, ¶¶152-154, 158.)

d. Claim 23: "The method of claim 16, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample."

Claim 23 is obvious over the combination for the same reasons Claim 8 is obvious, which are discussed in Section VI.C.5.b. (EX1003, ¶¶155-157, 159.)

6. Ground 5: Claims 3 and 18 Are Obvious Over The References Discussed in Grounds 1, 2, or 3, and Further in View of Steinert

a. Claim 3: "The method of claim 1, wherein the biological sample is a body fluid."

As discussed above in Section VI.C.5, the MSI-H Study Record discloses testing or having tested a biological sample obtained from the patient to determine

whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient. (*See also supra*, §VI.B.) That method wherein the biological sample is a body fluid from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Steinert. (EX1003, ¶¶162-164.)

Steinert is directed towards determining whether a tumor is MSI-H to understand how cancer evades the immune system. (EX1008, OF1; EX1003, ¶¶161, 163.) As such, the POSA would have had reason to consider Steinert, which is in the same field as the MSI-H Study Record and the '491 patent. (EX1003, ¶163.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Steinert. (EX1003, ¶164.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's cancer is MSI-H. (*Supra*, §§VI.B, VI.C.5.) Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. (EX1008, OF6; EX1003, ¶¶161, 164.) The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not change the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors, and indeed such testing of tumor tissue was well known, as the '491 patent admits. (EX1001, 6:25-26, 6:35-38; EX1003, ¶164.)

b. Claim 18: "The method of claim 16, wherein the biological sample is a body fluid from the patient."

Claim 18 is obvious over the combination for the same reasons Claim 3 is obvious, which are discussed in Section §VI.C.6.a. (EX1003, ¶¶162-165.)

7. Ground 6: Claim 9-10 and 24-25 Are Obvious Over The References Discussed in Grounds 1, 2, or 3, and Further in View of Salipante

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

As discussed in Section VI.B, the MSI-H Study Record discloses determining that the patient's cancer is MSI-H. (*See also supra*, §VI.C.5.) Carrying out or having carried out a polymerase chain reaction ("PCR") test on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Salipante. (EX1003, ¶168.)

Salipante is directed towards determining whether a tumor is MSI-H. (EX1010; EX1003, ¶¶167, 169.) As such, the POSA would have had reason to consider Salipante, which is in the same field as the MSI-H Study Record and the '491 patent. (EX1003, ¶169.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Salipante. (EX1003, ¶170.) The MSI-H Study Record discloses, or at least suggests,

determining that the patient's cancer is MSI-H. (*Supra*, §§VI.B, VI.C.5.) Salipante teaches standard methods of testing whether a tumor was MSI-H using a PCR test on the sample. (EX1010, 1192 ("PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use."), 1192-93 (Referring to PCR testing as the "gold standard"); EX1003, ¶170.)

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 such a polymerase chain reaction test was known, as the '491 patent admits. (EX1001, 6:25-26; 8:11-16; EX1003, ¶171.)

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

As discussed in Section VI.B above, the MSI-H Study Record discloses determining that the patient's cancer is MSI-H. (*See also supra*, §VI.C.5.) Carrying out or having carried out next generation sequencing on the sample would have been obvious to the POSA in view of the general knowledge in the art, such as Salipante. (EX1003, ¶173.)

As discussed above, the POSA would have had reason to consider Salipante, which is in the same field as the MSI-H Study Record and the '491 patent. (*Supra*,

§VI.C.7.a; EX1003, ¶174.) The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Brown, Duval, and Benson) and Salipante. (EX1003, ¶174.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's cancer is MSI-H. (*Supra*, §§VI.B, VI.C.5.) Salipante teaches methods of testing whether a tumor was MSI-H using next generation sequencing on the sample. (EX1010, 1193; EX1003, ¶¶167, 174.)

The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not change the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors, and indeed next generation sequencing was known, as the '491 patent admits. (EX1001, 6:25-26; 23:20-23 (citing a paper about next generation sequencing methods); EX1003, ¶175.)

c. Claim 24: "The method of claim 16, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction on the sample."

Claim 24 is obvious over the combination for the same reasons Claim 9 is obvious, which are discussed in Section VI.C.7.a. (EX1003, ¶¶168-171, 176.)

d. Claim 25: "The method of claim 16, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample."

Claim 25 is obvious over the combination for the same reasons Claim 10 is obvious, which are discussed in Section VI.C.7.b. (EX1003, ¶¶172-175, 177.)

8. Ground 7: Claims 11 and 26 Are Obvious Over The References Discussed in Grounds 1, 2, or 3, and Further in View of Hamid

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

As discussed above in Section VI.B, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating three cohorts of human patients with "[pembrolizumab] 10 mg/kg every 14 days." The method of Claim 1, wherein the pembrolizumab is administered to the patient intravenously would have been obvious to the POSA in view of the general knowledge in the art, such as Hamid. (EX1003, ¶¶180-184.)

Hamid is directed towards administering pembrolizumab to cancer patients. (EX1011; EX1003, ¶¶179, 181.) 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 '491 patent. (EX1003, ¶181.) Hamid provides for a method wherein the pembrolizumab is administered to the patient intravenously. (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, ¶¶179, 181.)

The POSA would have had motivation to combine the MSI-H Study Record, Brown, Duval, Benson, and Hamid. (EX1003, ¶182.) For instance, the MSI-H Study Record disclosed administering pembrolizumab to the patient. (*Supra*, §§III.B, VI.B.) Hamid demonstrated success in treating patients with advanced melanoma with pembrolizumab. (EX1011, 134; EX1003, ¶182.)

At a minimum, a method wherein the pembrolizumab is administered to the patient intravenously would have been obvious to try. Indeed, the prior art only discloses administering the pembrolizumab to the patient intravenously to treat cancer patients. (EX1011, 134; *see also* EX1055, 1; EX1003, ¶183.) *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 of administering pembrolizumab to the patient intravenously, given that administering pembrolizumab by intravenous infusion had been successful in the past. (EX1011, 134; EX1003, ¶184; *see also* EX1055, 1-3, 9, 15.)

b. Claim 26: "The method of claim 16, wherein the pembrolizumab is administered to the patient intravenously."

Claim 26 is obvious over the combination for the same reasons Claim 11 is obvious, which are discussed in Section VI.C.8.a. (EX1003, ¶¶180-185.)

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, 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 a family member of the '491 patent that issued as U.S. Patent No. 10,934,356. (EX1022,

August 26, 2020 Rejection, 26-32.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least three reasons.

First, the Examiner did not consider the MSI-H Study Record during prosecution of the '491 patent. As discussed above, the full version of the MSI-H Study Record was not even in front of the Examiner. (*Supra*, §III.B.)

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

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

VIII. MANDATORY NOTICES UNDER 37 CFR § 42.8

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

Related Matters: Pursuant to 37 C.F.R. § 42.8(b)(2), Merck identifies the following related matters. The '491 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, petitions for U.S. Patent Nos. 11,591,393 (IPR2024-00240), 10,934,356 (IPR2024-00622), 11,325,974 (IPR2024-00623), 11,325,975 (IPR2024-00624), and 11,339,219 (IPR2024-00625), which are family members of the '491 patent, are pending.

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Petitioner consents to electronic service.

IX. CONCLUSION

Merck requests institution of IPR for Claims 1-38 of the ’491 patent based on the grounds specified in this petition.

Respectfully submitted,

Dated: March 13, 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. 11,634,491 contains, as measured by the word-processing system used to prepare this paper, 13,786 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 13, 2024

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

CERTIFICATE OF SERVICE

I hereby certify that on March 13, 2024, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,634,491 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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