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. 11,325,975

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,325,975

Halozyme EX2420
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 1-4, 6-10, and 12-15 of U.S. Patent No. 11,325,975 ("the '975 patent"), which is assigned to Patent Owner The Johns Hopkins University ("JHU").

The '975 patent broadly claims the use of anti-PD-1 antibodies 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 an anti-PD-1 antibody. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; 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 filing of JHU's patent applications, which was a collaboration by Merck and JHU (the "MSI-H Study Record").

This study was consistent with the teachings of the literature that PD-1 inhibitors, for example anti-PD-1 antibodies, 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 literature 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. (*E.g.*, EX1006, 3740-41; EX1003, ¶¶42-50.)

As explained in detail below and in the Declaration of Dr. Alfred I. Neugut, all claims of the ’975 patent are unpatentable, as they fail to meet several statutory requirements. (*See, e.g.*, EX1003, ¶¶1-22, 51-58, 147-148.)

First, the independent claim and most dependent claims of the ’975 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 ’975 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 '975 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 1-4, 6-10, and 12-15 of the '975 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1-3, 6-10, and 13-15 are unpatentable under 35 U.S.C. § 102 as being anticipated by the published MSI-H Study Record (EX1005).

Ground 2: Claims 1-3, 6-10, and 13-15 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 4 and 12 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006) and Benson (EX1009), in view of Chapelle (EX1007).

Ground 4: Claims 1-3, 6-10, and 13-15 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 4 and 12 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 8 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 of Pernot (EX1006), Benson (EX1009), and Chapelle (EX1007), in view of Hamid (EX1011).

Ground 7: Claim 8 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), and Chapelle (EX1007), further in view of Hamid (EX1011).

III. BACKGROUND OF THE ’975 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 9 of the ’975 patent, the patent’s only independent claims, are directed to identifying cancer patients who have MSI-H and mismatch repair deficient tumors and administering an anti-PD-1 antibody, such as Merck’s immunotherapeutic drug pembrolizumab (known today by the tradename Keytruda®) to those patients. (EX1001, 25:50-26:65.)

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 an anti-PD-1 antibody. (EX1033, 2965; EX1014, 253.) By the relevant time period, Merck’s drug pembrolizumab was a known anti-PD-1 antibody 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 antibodies 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. (EX1005, 4 (Arms and Interventions); EX1016; EX1017; EX1023, 42; 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. (EX1001, 1:26-28; EX1010, 1192-93; EX1003, ¶¶23-29.) MSI-H is also known throughout the literature as MSI positive, MSI-high, MSIH, or MSI+. (EX1010, 1193, 1196; EX1018, 293 (authors include named '975 patent inventors); EX1019, 1065 (authors include a named '975 patent inventor); EX1003, ¶27.) MSI-H is caused by deficient mismatch repair ("dMMR"), also known as "Mismatch repair deficiency" or "DNA mismatch repair deficient." (EX1001, 1:26-28; EX1010, 1192; EX1003, ¶28.) MSI-H and dMMR are "biologically the same" and testing for one condition was considered "equivalent" to testing for the other. (EX1020, MS-12 (PDF p. 51); EX1007, 3380; EX1001, 10:32-56 (assessing dMMR status using MSI-H testing); 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. (EX1085, 673, 675; EX1086, 14; 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"). (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. (EX1005, 3 (Study Status); EX1003, ¶36.)[1] The website, www.clinicaltrials.gov, publicizes clinical trials in a searchable and easy to

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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, ¶37.)

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 '975 patent's family members, named inventor Andrew Pardoll admitted that the MSI-H Study Record published as early as June 12, 2013. (EX1022, February 4, 2020 Affidavit, 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.)

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 '975 patent's claimed subject matter derives directly from the MSI-H Study. (*See* EX1022, February 4, 2020 Affidavit, 7-8, ¶¶22-23 (connecting the '975 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 ’975 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, 6:44-18:55, 3:12-14; 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, 16:1-18:55) report its results. Further, Tables 1-3 (EX1001, 18:56-22:35) 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 ’975 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 (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. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2969; EX1034, 747; EX1035, 1, 8; EX1036, 1186; EX1037, 2; EX1038, 7; EX1039, 243s; 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. (EX1040, 2; EX1038, 5; EX1041, 9208; EX1042, 731;

EX1006, 3740-41; EX1037, 2; EX1035, 4; EX1036, 1186-87, 1193; EX1003, ¶¶42-47.)

Additionally, the prior art taught that PD-1 inhibitors, such as anti-PD-1 antibodies, inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize (EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5; EX1003, ¶44) and (2) already infiltrated by many immune cells (EX1034, 747; EX1037, 2; EX1003, ¶45). 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; EX1090, 681; EX1003, ¶46.)

IV. CLAIM CONSTRUCTION

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

The Board only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-00633, Paper 11 at 16 (PTAB. Aug. 14, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Here, given the correlation between the MSI-H Study Record, the written description of the '975 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.

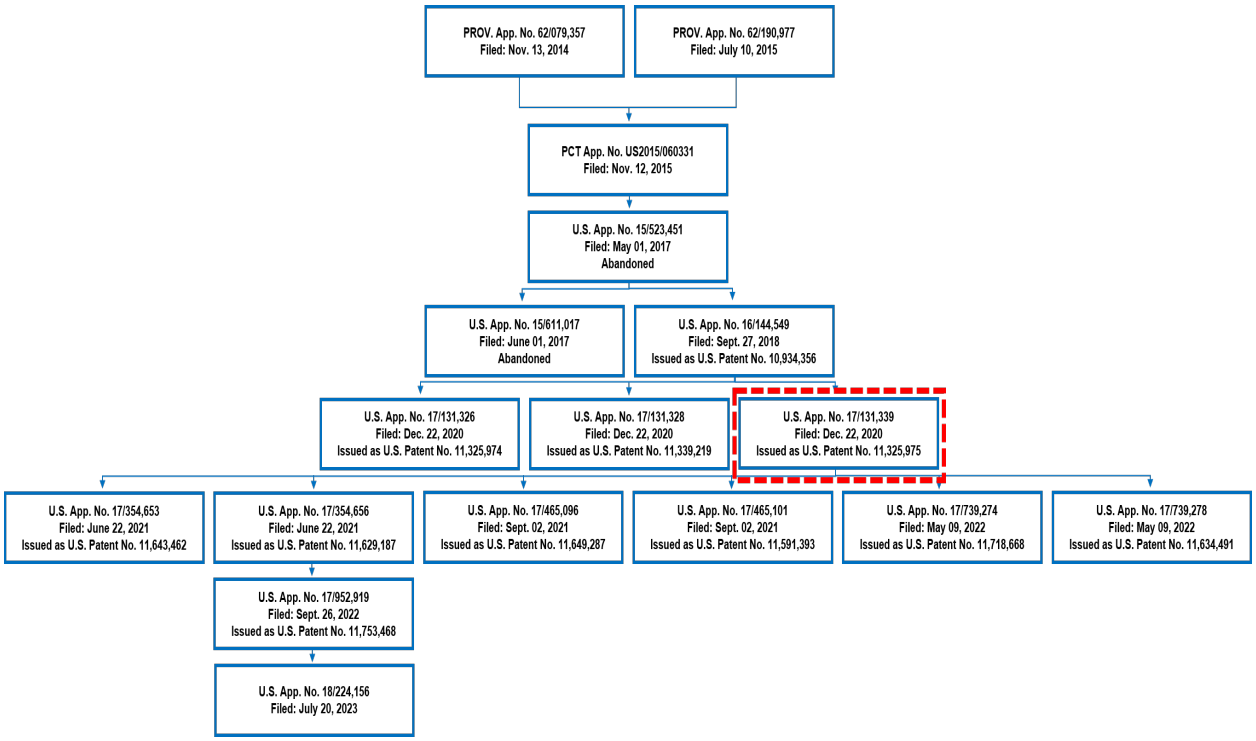
V. LEVEL OF ORDINARY SKILL IN THE ART

The POSA for purposes of the '975 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 '975 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 '975 patent cites two provisional patent applications: the First Provisional and U.S. Patent Application No. 62/190,977 (filed July 10, 2015) (the "Second Provisional"). The relationship of the '975 patent to those applications, as well as patents issued therefrom, is shown in the purported priority chain below:



For a non-provisional utility application to be afforded the priority date of a provisional application, "the written description of the provisional must adequately support the claims of the non-provisional application." *Amgen Inc. v. Sanofi*, 872

F.3d 1367, 1380 (Fed. Cir. 2017) (citations and quotations omitted) (emphasis removed). The test for adequate written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Nalpropion Pharms., Inc. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344, 1350 (Fed. Cir. 2019) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)) (emphasis removed). Further, the standard for what constitutes proper enablement of a prior art reference for purposes of the enablement standard under section 112 differs from the enablement standard under section 102. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

Here, during prosecution of the 75 patent's family members, JHU submitted declarations during prosecution, seeking to distance the patent from the MSI-H Study, by arguing that data from the clinical study was the basis for patentability (which thus led the Examiner to a legally erroneous rationale for allowing the patent to issue). (*See* EX1022, February 4, 2020 Affidavit, 7-8, ¶22, June 8, 2020 Affidavit, ¶¶27-28.) The First Provisional, however, did not include the data referred to in the declarations. Thus, even though JHU was wrong to assert that the reporting of the data from the MSI-H Study could create patentability for the treatment disclosed in the prior art), JHU must be bound to its positions – JHU cannot claim priority to the First Provisional without contradicting its sworn

positions during prosecution. In other words, the First Provisional lacks the disclosure of the data (inherent in the performance of the study), which JHU nonetheless argued was necessary for patentability. As such, applying JHU's own sworn positions, the July 10, 2015 filing date of the Second Provisional is the applicable critical date for purposes of analyzing the prior art.[2]

B. Ground 1: Claims 1-3, 6-10, and 13-15 of the '975 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

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

reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citations omitted d). "[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." *Id.* at 1379.

In *Schering*, the Federal Circuit clarified that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering*, 339 F.3d at 1380. 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

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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.

anticipation that, if one of skill practiced the use described in the prior art, the metabolite would be produced by the body *in vivo*. *Schering*, 339 F.3d at 1380. The Federal Circuit reaffirmed that principle as recently as April 2023. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). In *Arbutus*, the claimed morphology of a composition was inherently anticipated by following a prior art reference's formulations using that same reference's methods. *Arbutus*, 65 F.4th at 664.

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 1-3, 6-10, and 13-15 of the '975 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. Indeed, anticipation could not be possibly be clearer because the treatment disclosed in the prior art MSI-H Study Record is written description support for the treatment method of the claims. For example, the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '975 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,"

The Arms and Interventions section of the MSI-H Study Record discloses a method for treating cancer in patient 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, ¶59.)

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

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); *supra*, §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶¶60-64.)

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, ¶61; *see also supra* §III.A.) Further, named inventor Dr. Pardoll represented in a sworn declaration during prosecution of one of the '975 patent's family members that the MSI-H Study Record concerns MSI-H patients. (EX1022, February 4, 2020 Affidavit, 7-8, ¶¶23-23 ("Dr. Dung Le prepared a study proposal for testing anti-PD-1 antibodies . . . in . . .

MSI-positive colon cancer patients . . . . The preliminary results of this study demonstrated clinical responses. . . . in the MSI-H (MMR deficient) arm.”).)

The MSI-H Study Record’s disclosure of treating patients with “MSI positive” cancer also discloses treating patients with a mismatch repair deficiency (“dMMR”). (EX1003, ¶62.) For example, the art taught that “[p]atients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.” (EX1020, MS-12 (PDF p. 51); EX1001, 8:1-30 (using MSI status to characterize patients as dMMR).) And, in his declaration, Dr. Pardoll equated MSI-H and dMMR patients. (EX1022, February 4, 2020 Affidavit, 7-8, ¶23 (“[T]he MSI-high (MMR deficient) arm.”).) Moreover, because MSI-H is caused by dMMR, all cancers that are MSI-H are dMMR. (EX1010, 1192; EX1003, ¶62; *see also* EX1001, 1:26-28.)[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

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[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.

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, ¶63.) Without such a determination, patients could not have been placed into the proper arm of the study. (EX1003, ¶63.)

Thus, the MSI-H Study Record teaches a method wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status. (EX1003, ¶64.)

c. [1.2]: "administering an effective amount of an anti-PD-1 antibody to the patient;"

The Arms and Interventions section of the MSI-H Study Record discusses 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); *supra* §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶¶65-69.)

Pembrolizumab is an anti-PD-1 antibody. (EX1011, 134-35; EX1003, ¶66.)

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 ’975 patent, and any required efficacy is thus inherent to that dosage. (EX1003, ¶66.)

Indeed, the ’975 patent itself, which only describes one dosage (EX1001, 8:44-50, 13:18-24)—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”), 16:1-8, 16:65-17:7, 19:40-21:18, Figs. 2, 11; EX1003, ¶¶40-41, 67.) “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, ¶68.)

Thus, the MSI-H Study Record discloses a method comprising administering an effective amount of an anti-PD-1 antibody to the patient. (EX1003, ¶69.)

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, 65-69.)

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

This limitation is disclosed for the same reason as limitation [1.2] because it recites obtaining the inherent results of the MSI-H Study Record's method of treatment. (*Supra*, §VI.B.2.c; EX1003, ¶¶65-72.)

Moreover, 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 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, ¶71.) The MSI-H Study Record even discloses determining whether MSI-H is a marker for response to therapy. (EX1005, 4-5 (Outcomes Measures); EX1003, ¶71.) Additionally, the improved outcomes are inherent to the methods of the MSI-H Study Record. (*Supra* §VI.B.1; EX1003, ¶¶40-41, 71.) "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 ['975 patent] is irrelevant." *Schering*, 339 F.3d at 1380.

Thus, the MSI-H Study Record discloses a method wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status. (EX1003, ¶72.)

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, ¶73.) In the context of the MSI-H Study Record, these disclosures demonstrate that patients would have received a prior cancer therapy drug. (EX1003, ¶¶73-78.)

In particular, and as an initial matter, 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, ¶74.) 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, ¶74.) 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, ¶74.)

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, ¶75.)

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, ¶76.) In other words, the MSI-H Study Record recognizes that patients would have received prior cancer drug therapies, and because of that makes it a point to exclude those that received "anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies." (EX1003, ¶76.) 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 treating patients who had received prior cancer drug therapies, and the patients' cancer had progressed after the patients received the different cancer therapies. (EX1003, ¶¶73-77.) *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc*., 949 F.3d 1366, 1373 (Fed. Cir. 2020) ("In an anticipation analysis, the dispositive question is whether a skilled artisan would 'reasonably understand or infer' from a prior art reference that every claim limitation is disclosed in that single reference"); *Genentech, Inc. v. Hospira, Inc*., 946 F.3d 1333, 1340 (Fed. Cir. 2020) (same); *In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991) (same).

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, ¶78.)

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[5] EX1080 is a poster that Merck and JHU presented at the American Society of

Thus, the MSI-H Study disclosed a method wherein the patient has received a prior cancer therapy drug. (EX1003, ¶77.)

3. Claim 2: "The method of claim 1, wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug."

Claim 2 modifies limitation [1.4] by further requiring the patient's cancer to have progressed after the patient received the prior cancer drug therapy. This

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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, ¶78.) 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, ¶78.) Thus, there was no expectation of confidentiality. (EX1003, ¶78.) *See also In re Klopfenstein* 380 F.3d 1345, 1350 (Fed. Cir. 2004).

additional limitation is addressed in, and disclosed for the reasons provided in the discussion of, limitation [1.4]. (*Supra*, §VI.B.2.e; EX1003, ¶79.)

4. Claim 3: "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."

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.) 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 (showing the "[c]linical benefit to pembrolizumab according to MMR status" and discussing figure 2), Figures 2 (showing overall survival for the three cohorts), 11 (showing objective response rates and progression free survival for the three cohorts), 16:1-8 (discussing objective response rate and progression free survival), 16:65-17:7 (discussing overall survival and progression-free survival) 19:45-21:18; EX1003, ¶80.) *See King Pharms*, 616 F.3d at 1276.

Thus, the MSI-H Study Record discloses a method wherein the outcome that is improved is an improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival. (EX1003, ¶81.)

5. Claim 6: "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. (*Supra,* §VI.B.2.e; EX1003, ¶82.) 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, ¶82.) *See Yeda*, 906 F.3d at 1041.

Thus, the MSI-H Study Record discloses a method wherein the method of claim 1, wherein the cancer is a metastatic cancer. (EX1003, ¶82.)

6. Claim 7: "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. (*Supra,* §VI.B.2.e; EX1003, ¶83.) 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, ¶83.) *See Yeda*, 906 F.3d at 1041.

Thus, the MSI-H Study Record discloses a method wherein the method of claim 1, wherein the cancer is a metastatic colorectal cancer. (EX1003, ¶83.)

7. Claim 8: "The method of claim 1, wherein the anti-PD-1 antibody is administered by intravenous infusion."

As discussed in Section VI.B.2, the Arms and Interventions section of the MSI-H Study Record discloses administering 10 mg/kg of pembrolizumab every 14 days. The prior art taught that, at the time of the alleged invention, pembrolizumab for the treatment of cancer was administered by intravenous infusion. (*E.g.* EX1011, 134 ("We administered [pembrolizumab] intravenously."); EX1054, 3; *see also* EX1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); EX1003, ¶¶84-85.)

8. Claim 9

a. [9.pre]: " A method for treating cancer in a patient in need thereof,"

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. (*Supra*, §VI.B.2.a; EX1003, ¶86.)

b. [9.1]: "wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status,"

This limitation is identical to limitation [1.1], and is disclosed for the same reasons. (*Supra*, §VI.B.2.b; EX1003, ¶87.)

c. [9.2]: "the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:"

As discussed in the analysis for Limitation [1.4], the MSI-H Study Record discloses a method wherein patients had received a prior cancer therapy drug. (*Supra* §VI.B.2.e; EX1003, ¶88.)

d. [9.3]: "administering an effective amount of an anti-PD-1 antibody to the patient;"

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra*, §VI.B.2.c; EX1003, ¶89.)

e. [9.4]: "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient."

This limitation is identical to limitation [1.3], and is disclosed for the same reasons. (*Supra*, §VI.B.2.d; EX1003, ¶90.)

9. Claim 10: "The method of claim 9, 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 additional limitation recited in Claim 10 is the same as recited in Claim 3 and disclosed for the same reasons. (*Supra*, §VI.B.4; EX1003, ¶91.)

10. Claim 13: "The method of claim 10, wherein the cancer is a metastatic cancer."

The additional limitation recited in Claim 13 is the same as recited in Claim 6 and disclosed for the same reasons. (*Supra*, §VI.B.5; EX1003, ¶92.)

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

The additional limitation recited in Claim 14 is the same as recited in Claim 7 and disclosed for the same reasons. (*Supra*, §VI.B.6; EX1003, ¶93.)

12. Claim 15: "The method of claim 10, wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug."

The additional limitation recited in Claim 15 is the same as recited in Claim 2 and disclosed for the same reasons. (*Supra*, §VI.B.3; EX1003, ¶94.)

C. Grounds 2-7: Claims 1-4, 6-10, and 13-15 of the '975 Patent are Obvious over the MSI-H Study Record in View of Various References

1. Law of Obviousness

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a

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

2. Overview of the Additional Prior Art

a. Pernot

Pernot is a journal article titled *Colorectal Cancer and Immunity: What We Know and Perspectives* and was published in the World Journal of Gastroenterology on April 13, 2014. (EX1006, 3738, PDF p. 1; EX1003, ¶95.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Pernot discloses and discusses how "[a]ltogether, [colorectal

cancers] associated with [microsatellite instability]" are "good candidates for immunotherapy." (EX1006, 3740-41; EX1003, ¶¶96-97.)

The Examiner did not consider Pernot during prosecution of the '975 patent.

a. 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; EX1003, ¶98.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Benson discloses that, under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (EX1009, 1034; EX1003, ¶¶98-99.)

The Examiner did not consider Benson.

b. Chapelle

Chapelle is a journal article titled *Clinical Relevance of Microsatellite Instability in Colorectal Cancer* and was published in the Journal of Clinical Oncology in 2010. (EX1007, 3380; EX1003, ¶111.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Chapelle discusses testing to determine whether a tumor is MSI-H using the tumor tissue of a patient. (EX1007, 3380, 3383.) Chapelle provides a test to measure MSI by immunohistochemistry, and discusses how, "[f]or practical purposes, [MSI-H] is

equivalent to the loss of staining by immunohistochemistry (IHC) of one of the mismatch repair genes since both signify an abnormality in mismatch repair." (EX1007, 3380; EX1003, ¶¶111-112.)

The Examiner did not consider Chapelle during prosecution of the '975 patent.

c. 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, ¶120.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

Brown teaches 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, and (2) already infiltrated by many immune cells. (EX1034, 747; EX1003, ¶121).

The Examiner did not consider Brown during prosecution of the '975 patent.

d. 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, ¶122.)

Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b).

Duval teaches that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1087, 5002; EX1003, ¶123.)

The Examiner did not consider Duval during prosecution of the ’975 patent.

e. 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, ¶139.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Hamid reflects another name for pembrolizumab (*i.e.*, “lambrolizumab”) and discusses that pembrolizumab was administered to cancer patients intravenously. (EX1011, 134; *see* EX1054, 3 (“MK-3475 (pembrolizumab formerly lambrolizumab)”); EX1003, ¶140.)

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

3. Ground 2: Claims 1-3, 6-10, and 13-15 of the ’975 Patent Are Obvious Over the MSI-H Study Record in View of Pernot and Benson

As discussed above, Claims 1-3, 6-10, and 13-15 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to

demonstrate that Claims 1-3, 6-10, and 13-15 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 (EX1022, December 14, 2020 Notice of Allowance at 3; *see also supra* §I), (2) to the extent limitations [1.1] and [9.1] 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] and [9.2] and claims 2, 6-7, and 13-15, which cover features relating to progressive and metastatic disease.

Improved Outcome/Efficacy

The POSA would have expected colorectal cancer patients having MSI-H tumors[6] to respond to a sufficient degree that the POSA would have wanted to

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[6] 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 IV.C.5.

obtain the data from the MSI-H Study, thus observing the inherent properties of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record. (EX1003, ¶¶100-105.)

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, ¶101.) 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), and Pernot taught that those patients are "good candidates for immunotherapy," such as PD-1 inhibitors like pembrolizumab (EX1006, 3741; *see also* EX1029, ¶ 82; EX1054, 3; EX1011, 141.) As such, Pernot further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶101.)

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, ¶102.) 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, ¶102.) The prior art also successfully reported treatment of a colorectal cancer patient having an MSI-H tumor with a PD-1 inhibitor. (EX1057, 463-64; EX1003, ¶102.)

Further, in addition to Pernot, several other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab. (EX1032, e27817-5; EX1033, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶103; *see also* EX1035 at 1, 8.)

Additionally, the prior art taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize (EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5; EX1003, ¶¶43-44, 104) and (2) already infiltrated by many immune cells. (EX1034, 747; EX1037, 2; EX1003, ¶¶43, 45, 104.) 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; EX1087, 5002; EX1039, 243s; EX1003, ¶¶46, 104.)

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, ¶105; *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 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.) 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) (“Inherency may supply a missing claim limitation in an obviousness analysis.”).

Testing

Limitations [1.1] and [9.1] each require a patient that has been determined to have a tumor that exhibits an MSI-H or dMMR 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; EX1003, ¶¶100-105.) The MSI-H Study Record discloses treating patients 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, ¶106.) 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, ¶106.) 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, ¶106.) The POSA would have expected success in carrying out such testing, because testing for MSI-H was routine in the art. (EX1003, ¶106.)

Treating Patients Having Characteristics Related to Progressive and Metastatic Disease

Limitation [1.4] and [9.2] and claims 2, 6-7, and 13-15 each require that the patients had received a different cancer therapy drug to treat their tumors, a different cancer therapy drug to treat their tumors, 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, ¶¶107-110.)

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, ¶107.) 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 '975 patent. (EX1003, ¶107.)

The POSA would have had motivation to combine the MSI-H Study Record and Benson. (EX1003, ¶108.) For instance, both the MSI-H Study Record and Benson discuss treating patients with colorectal cancer. (EX1003, ¶108.) 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 to treat their

tumors. (EX1009, 1034; EX1003, ¶108.) 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 to treat their tumors, and the patients' cancer had progressed after the patients received the different cancer therapy drug. (EX1003, ¶108.) 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 having metastatic and advanced disease. (EX1009, 1034; EX1003, ¶108.) 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, ¶108.) 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, ¶108.)

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 to treat their tumors, 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, ¶109.)

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 colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:23-30 (all patients had treatment-refractory, progressive and metastatic disease); 15:59-62 (all patients having MSI-H colorectal cancer had received two prior chemotherapy regiments); EX1003, ¶110.)

4. Ground 3: Claims 4 and 12 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 4: "The method of claim 1, wherein the patient has been determined to have a tumor that exhibits a MSI-high status when instability of a microsatellite marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24; or wherein the patient has been determined to have a tumor that exhibits a MMR deficiency status when deficiency of a mismatch repair marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the mismatch repair marker is POLE, POLD1, or MYH.."

As discussed in Section VI.B.2.b above, the MSI-H Study Record discloses determining that the patient's cancer is MSI-H. The method of Claim 1, wherein the patient has been determined to have a tumor that exhibits a MSI-high status when instability of a microsatellite marker in a DNA sequence has been detected in a tumor sample obtained from the patient, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24 would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶113-117.)

Chapelle is directed towards determining whether tumors are MSI-H. (EX1007, 3380, 3383; EX1003, ¶¶112, 114.) 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 '975 patent. (EX1003, ¶114.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot and Benson) and Chapelle to determine whether the tumor sample from the patient exhibits an instability of one or more microsatellite markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24. (EX1003, ¶115.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's cancer is MSI-H when instability of a microsatellite marker in a DNA sequence has been detected in a tumor sample obtained from the patient. (*Supra,* §§VI.B.2, VI.C.3.) Indeed, 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 prior art taught that a biopsy of a patient's tumor obtains tumor tissue for testing. (EX1044, 3309; EX1045, 3485; EX1046, 1193; EX1003, ¶115.) 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 are 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, ¶115; *see also* EX1001, 8:7-8 (testing "[a]rchived tumor samples" or "newly obtained biopsies.").)

Moreover, Chapelle teaches standard methods of testing whether a tumor was MSI-H, including detecting in a tumor sample obtained from the patient an instability of one or more microsatellite markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24. (EX1007, 3380, 3383; EX1003, ¶¶112, 116.) For example, Chappelle teaches that "a standard test" using a "[p]anel consisting of . . . BAT26, BAT25" has "stood the test of time." (EX1007, 3382.)

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 '975 patent admits. (EX1001, 6:17-18; 6:27-30; EX1003, ¶117.)

b. Claim 12: "The method of claim 10, wherein the tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status exhibits instability in a microsatellite marker, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, or wherein the tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status exhibits a deficiency of a mismatch repair marker, wherein the mismatch repair marker is POLE, POLD1, or MYH."

Carrying out the method of Claim 10, wherein the tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status

exhibits instability in a microsatellite marker, 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, ¶118.) As discussed above in Section VI.C.3, 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, ¶119.) 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, ¶119.) 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 '975 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).

5. Ground 4: Claims 1-3, 6-10, and 13-15 of the '975 Patent Are Obvious Over the MSI-H Study Record in View of Brown, Duval, and Benson

As discussed above, Claims 1-3, 6-10, and 13-15 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that Claims 1-3, 6-10, and 13-15, 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 (EX1022, December 14, 2020 Notice of Allowance at 3; *see also supra* §I), (2) to the extent limitations [1.1] and [9.1] 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] and [9.2] and claims 2, 6-7, and 13-15, which cover features relating to 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, ¶¶124-131.)

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, ¶125). 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, ¶25, 125.) 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, ¶¶121, 125). 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, ¶¶123, 125.) As such, Brown and Duval would have further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶125.)

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, ¶126.) 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, ¶126.)

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 colorectal , small bowel, and endometrial cancer, and had cancer cells that are easy for immune cells to recognize. (EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5; EX1085, 673-74; EX1006, 3740-41; EX1058, 231, 236-37; EX1036, 1186-87, 1193; EX1037, 2, 6; EX1035, 4; EX1039, 243s; EX1003, ¶127). 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 cells. (EX1034, 747; EX1037, 2; EX1003, ¶128.) Moreover, many prior art references taught that MSI-H tumors, such as colorectal cancer and endometrial cancer tumors, are naturally infiltrated by many immune cells. (EX1006, 3740-41 (MSI-H colorectal cancer); EX1033, 2967 (same); EX1058, 231, 236-37 (same); EX1036, 1186-87, 1193 (same); EX1037, 2, 6 (same); EX1035, 4; EX1041, 9208-09 (same); EX1039, 243s (same); EX1090, 681 (MSI-H endometrial cancer); EX1003, ¶129.)

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, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶130.)

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,

¶131; *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*, 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 (for oncology drugs, 55% of second indications were successful if the first indication was successful, but only 9% of first indications were successful.) Thus, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H patients with pembrolizumab at the dosage that was applied in the clinical study. *See Persion*, 945 F.3d at 1190 ("Inherency may supply a missing claim limitation in an obviousness analysis.").

Testing

Limitations [1.1] and [9.1] each require a patient that has been determined to have a tumors that exhibits an MSI-H or dMMR 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.B.2. (EX1003, ¶132.)

Treating Patients Having Characteristics Related to Progressive and Metastatic Disease

Limitation [1.4] and [9.2] and claims 2, 6-7, and 13-15 each require that the patients had received a different cancer therapy drug, a different cancer therapy drug to treat their tumors, 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. 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, ¶¶133-137.)

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.) 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 to treat their tumors, 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, ¶133.)

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, 37, 48-49; EX1003, ¶134.) 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 '975 patent. (EX1003, ¶134.)

The POSA would have had motivation to combine the MSI-H Study Record and Benson. (EX1003, ¶135.) For instance, both the MSI-H Study Record and Benson discuss treating patients having cancer. (*Id*.) 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 to treat their tumors. (EX1009, 1034; EX1003, ¶135; *see also see also* EX1088 at PDF. pp. 20, 29, 97.) 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 to treat their tumors, 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, ¶135; *see also* EX1089, PDF p. 17; EX1088 at 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 to

treat their tumors, and the patients' cancer had progressed after the patients received the different cancer therapy drug. (EX1003, ¶135.) 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 having metastatic, advanced, and recurrent disease. (EX1009, 1034; *see also* EX1089, PDF p. 17; EX1088, PDF. pp. 20, 29, 97; EX1003, ¶135.) 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 cancer was metastatic. (EX1003, ¶135.) 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, ¶135.)

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 to treat their tumors, 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, ¶136; *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, 8:23-25 (all patients had treatment-refractory, progressive and metastatic disease); 15:58-67 (all patients having MSI-H cancer had received more than one prior cancer treatment); EX1003, ¶137.)

6. Ground 5: Claims 4 and 12 Are Obvious Over the MSI-H Study Record in View of Brown, Duval, and Benson, Further in View of Chapelle

Claims 4 and 12 are obvious over the combination for the same reasons as discussed in Ground 3. (EX1003, ¶138.) The additional limitation in these claims are directed to a specific type of MSI-H testing. (*Id.*) Chapelle discloses these limitations. (*Supra*, §VI.C.4; EX1003, ¶¶111-119, 138.) Thus, these claims are obvious over the Ground 5 combination for the same reasons as discussed in Ground 3. (EX1003, ¶138.)

7. Ground 6: Claim 8 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 8: "The method of claim 1, wherein the anti-PD-1 antibody 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 1, wherein the anti-PD-1 antibody 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, ¶¶141-145.)

Hamid is directed towards administering pembrolizumab. (EX1011, 1033-34; EX1003, ¶¶140-141.) As such, the POSA would have had reason to consider Hamid, which is in the same field as the MSI-H Study Record and the '393 patent. (EX1003, ¶141.) Hamid provides for administering pembrolizumab, which is an anti-PD-1 antibody by intravenous infusion. (EX1011, 133-134; EX1003, ¶¶140, 142.). 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, ¶¶140, 142.)

The POSA would have had motivation to combine the MSI-H Study Record Pernot, Benson, Chapelle, and Hamid. (EX1003, ¶143.) For instance, the MSI-H Study Record disclosed administering pembrolizumab. (*Supra*, §§VI.B.1, VI.B.2.) Hamid demonstrated success in treating patients having advanced cancer with pembrolizumab. (EX1011, 134; EX1003, ¶¶140, 143.) Thus, the POSA would have been motivated to combine the MSI-H Study Record Pernot, Benson, Chapelle, and Hamid. (EX1003, ¶143.)

At a minimum, administering pembrolizumab, the anti-PD-1 antibody, 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, ¶144.) *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, the anti-PD-1 antibody, by intravenous infusion, given that administering pembrolizumab by intravenous infusion had been successful in the past. (EX1011, 134; EX1003, ¶145; *see also* EX1055, 1-3, 9, 15.)

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

Claim 8 is obvious over the combination for the same reasons as discussed in Ground 6. (EX1003, ¶146.) The additional limitation in this claim is directed to administering an anti-PD-1 antibody, such as pembrolizumab, by intravenous infusion. (*Id*.) Hamid discloses this limitation. (*Supra*, §VI.C.7; EX1003, ¶¶139-146.) 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 will 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 ’975 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 ’975 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.) 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*, 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 '975 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 family member of the '975 patent, is pending.

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IX. CONCLUSION

Merck requests institution of IPR for Claims 1-4, 6-10, and 12-15 of the ’975 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. 11,325,975 contains, as measured by the word-processing system used to prepare this paper, 13,367 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/
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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. 11,325,975 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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