PUBLIC VERSION

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

Case IPR2024-00623
Patent 11,325,974 B2

PATENT OWNER'S RESPONSE

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LIST OF EXHIBITS

Exhibit Number	Description
2001	RESERVED
2002	Curriculum Vitae of Dr. Nils Lonberg
2003	Dung T. Le, Sidney Kimmel Comprehensive Cancer Center, PD-1 Blockade in Tumors with Mismatch Repair Deficiency, Presentation at 2015 ASCO Annual Meeting (May 30, 2015) (abstract available at https://meetings.asco.org/abstracts-presentations/109904)
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2169	Highly Confidential Attorney Eyes Only Document 4 – Protective Order Material
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2171	Highly Confidential Attorney Eyes Only Document 6 – Protective Order Material
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2290	GSK 2023 Annual Report
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2292-2400	RESERVED
2401	Copy of EX1001, U.S. Pat. No. 10,934,356, marked at January 6th Deposition of Dr. Neugut
2402	Copy of EX1005, ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013), marked at January 6th Deposition of Dr. Neugut
2403	Board Email regarding Motion to Seal dated October 4, 2024
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2500	Declaration of Frank E. Scherkenbach in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2501	Declaration of Corrin N. Drakulich in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2502	Declaration of Christina D. Brown-Marshall in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2503	Declaration of Casey M. Kraning in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney

Exhibit Number	Description
2504	Declaration of Madelyn S. McCormick in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney
2505	Declaration of Sarah E. Jack in Support of Notice of Intent to Designate a Provisionally Recognized PTAB Attorney

LISTING OF CHALLENGED CLAIMS

Claim	Identifier	Claim Language
1	[1pre]	A method for treating cancer in a patient in need thereof,
	[1a]	wherein a tumor sample obtained from the patient has been determined to exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers,
	[1b]	the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:
	[1c]	administering an effective amount of pembrolizumab to the patient;
	[1d]	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 pembrolizumab, wherein the reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers.
2	[2]	The method of claim 1, wherein the cancer in the patient has progressed after the patient received the prior cancer therapy drug.
3	[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 (OS).
4	[4]	The method of claim 1, wherein 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, or wherein the tumor sample from the patient

Claim	Identifier	Claim Language
		exhibits a deficiency of one or more mismatch repair markers, wherein the mismatch repair marker is POLE, POLD1, or MYH.
5	[5]	The method of claim 1, wherein the cancer is a metastatic cancer.
6	[6]	The method of claim 1, wherein the cancer is a metastatic colorectal cancer.
7	[7]	The method of claim 1, wherein pembrolizumab is administered by intravenous infusion.

I. INTRODUCTION

Armed only with a hypothesis based on a single colorectal cancer (CRC) patient, the JHU inventors designed a small clinical trial to test whether a tumor's microsatellite instability status (MSI-H or MS-stable) indicated responsiveness to Merck's pembrolizumab, not only in colorectal cancer, but across cancer types. The answer—a resounding, and unexpected, yes—shocked the cancer community. This identification of MSI-H as a predictive biomarker led to JHU's '974 Patent, which claims the first FDA-approved method of treating cancer independent of the tumor's location in the patient's body. Merck lauded JHU's "exciting results" that "open the door for research with KEYTRUDA in colorectal cancer and other tumor types with this potentially clinically meaningful tool." EX2061, 2.

Merck used the results of JHU's clinical trial to seek FDA approval for treating MSI-H solid tumors with pembrolizumab independent of cancer type. During the FDA approval process, Merck emphasized the urgent need for these treatments, telling FDA that [redacted] EX2173, 17. Once approved, Merck touted "FDA's approval of this ***first-of-its-kind***, tumor-agnostic, indication" and praised JHU's role in securing that approval by stating, "[t]his is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and

clinicians at Johns Hopkins University ***for their important scientific work***[.]"[1] *Id.*; EX2060, 2.

Hoping to avoid paying JHU a reasonable royalty for the multi-billion dollar windfall it received from JHU's pioneering invention, without which Merck would not have obtained FDA approval for using Keytruda® to treat MSI-H cancers, Merck stands before the Office singing an entirely different tune. Ignoring its own praise of the JHU inventors' work and the importance of FDA's groundbreaking approval, Merck argues that JHU's invention was nothing special and that it is anticipated and rendered obvious by the prior art.

Merck asks the Board to find the '974 Patent claims unpatentable over the very regulatory posting JHU was required to make before conducting the human clinical trial necessary to test its hypothesis. This bare-bones clinical trial announcement posting, which Merck calls the "MSI-H Study Record" (hereafter, "MSR"), fails to teach multiple limitations of the '974 Patent claims—as Merck's own expert admitted. *See infra* Sections V.A-C. For example, the MSR does not disclose "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 a tumor that does not exhibit an instability of the one or more microsatellite markers

[1] Unless otherwise indicated, all emphasis is added.

or a deficiency of the one or more mismatch repair markers." EX1001, claim 1. Nor could it. At the time of that posting, the JHU inventors had only a hypothesis. They had no patients enrolled or tested—reference or otherwise—let alone any data showing the claimed outcome. Similarly, the MSR does not disclose "the patient having received a prior cancer therapy drug to treat the tumor," "the cancer in the patient has progressed after the patient received the prior cancer therapy drug," or where "the cancer is a metastatic cancer[.]" EX1001, claims 1, 2, 5.

To reach just the independent claims of the '974 Patent, Merck must plug numerous holes in the MSR. Merck tries to do this by resorting to inherency over and over again. Those inherency arguments fail as a matter of law because the MSR says nothing about these claim limitations. Merck cannot meet the high burden imposed by Federal Circuit precedent to show that the MSR ***necessarily includes*** each of these limitations. *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). Because no amount of attorney argument or expert opinion can convert the MSR's silence into disclosure of the claimed teachings, the MSR cannot expressly or inherently anticipate the claims of the '974 Patent.

Merck's Petition also fails because the MSR itself should not be afforded prior art status. The MSR is indisputably a statutorily required prerequisite to

conducting a clinical trial. That clinical trial was indisputably conducted to test the inventors' hypothesis that MSI-H might be predictive of pembrolizumab efficacy in treating cancer patients. This is the epitome of an experimental use that does not qualify as prior art.

Merck's fall-back obviousness arguments also fail, because Merck cannot show that a person of ordinary skill in the art would have reasonably expected the claimed method of treatment to succeed. "[H]ope that a potentially promising drug will treat a particular cancer is ***not enough*** to create a reasonable expectation of success in a highly unpredictable art such as this." *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). Overwhelming evidence, unrebutted by Merck, demonstrates the results of the JHU study were wholly unexpected by the relevant community of clinicians and researchers. Indeed, JHU's discovery ushered in a paradigm shift in cancer therapy. Overwhelming objective indicia evidence also highlights the failings of Merck's obviousness arguments. When the MSR was posted, the prognosis for MSI-H cancer patients was bleak. JHU's experimental results, presented with great fanfare to oncologists at major conferences and in leading scientific publications, brought hope to these patients. Despite its current financial motivations to argue otherwise, Merck's own words and deeds at the relevant time evidence the truth—using MSI-H as a biomarker to

predict efficacy of anti-PD-1 therapy has changed the standard of care and saved the lives of thousands of cancer patients.

II. OVERVIEW OF THE '974 PATENT

The '974 Patent claims a novel method of treating MSI-H or DNA mismatch repair deficient ("dMMR")[2] cancer in a patient (EX1001, claim 1). *See* EX2072, ¶¶58-65.

The priority date of the '974 Patent is July 10, 2015.[3] Independent claim 1 is representative for purposes of this proceeding and is recited in the list of challenged claims, *supra*.

III. PERSON OF ORDINARY SKILL ("POSA") IN THE ART

JHU contends that a POSA on or about the claimed priority date of the '974 Patent would have had a M.D. or graduate-level degree (or equivalent work experience) in the fields of immunology, genetics, or a related field and at least five years of experience (i) conducting immunology research relating to oncology,

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[2] MSI-H and dMMR are related, and testing for one condition is considered equivalent to testing for the other. Pet., 6. Here, JHU will refer to MSI-H only.

[3] Contrary to Merck's assertions in §VI.A of the Petition, JHU is not attempting to claim priority to an undefined "First Provisional," or to U.S. Provisional Application No. 62/079,357 (EX1030 (mislabeled in Merck's List of Exhibits)).

(ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. EX2072, ¶¶31-32, 86-94.

IV. CLAIM CONSTRUCTION

JHU does not formally construe any claim terms at this time because the deficiencies in the Petition highlighted in this POR do not turn on claim construction.

V. CLAIMS 1-3 AND 5-7 OF THE '974 PATENT ARE PATENTABLE OVER ANTICIPATION GROUND 1

A. The MSR Cannot Anticipate Because It Does Not Expressly or Inherently Disclose "The Patient Having Received a Prior Cancer Therapy Drug"/The Cancer "Progressed After the Patient Received the Prior Cancer Therapy Drug"

Independent claim 1 requires that, prior to receiving treatment according to the claimed method, the patient must have received a prior cancer therapy drug, and dependent claim 2 adds that the patient's cancer must have progressed after receiving that prior cancer therapy drug. The MSR, however, is silent on whether eligible patients ***must*** have had a prior treatment and have progressed after receiving that prior treatment. *See* EX1005, 5-6. Merck's expert, Dr. Neugut, agrees. *See* EX2163, 99:13-21 ("it leaves out…that the patients had to have previous treatment and progressed on the previous treatment before being allowed to be put on an experimental drug"). Neither the Board nor attorney argument can

replace the missing disclosure of these limitations. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (case law "does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them."); *VirnetX Inc. v. Apple Inc.*, 2023 WL 6933812, at *4 (Fed. Cir. Oct. 20, 2023).

Merck's assertions that a patient "generally" (Pet., 24; EX1003, ¶69) would have received at least one other prior treatment, and would have had their cancers progress after those drug therapies, fails to meet the high burden for a finding of inherency. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("unless a reference discloses within the four corners…all of the limitations arranged or combined in the same way as recited in the claim, it…cannot anticipate"). In addition, and independently, Merck also cannot meet its inherent anticipation burden because the claim limitation is not, in fact, inherent. Indeed, the Benson reference on which Merck relies (Grounds 2-7), emphasizes that, although cancer treatment generally follows guidelines, "when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." EX1009, 2. Benson goes on to explain that "NCCN [provider of the guidelines] believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." *Id.*, 1.

Another reference that Merck relies on in a parallel proceeding, advises that certain Stage IV cancer patients should proceed directly to clinical trials ***without prior treatment***. *See* EX2164, 533, 537.

Case law relied upon by Merck (Pet., 25) also does not support its view that a prior art reference can anticipate, despite missing a limitation, so long as a POSA would understand the limitation to be "generally" present. Instead, each of Merck's cases relates to the scenario where the express disclosure establishes that a POSA would understand the limitation was ***necessarily*** present. *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373-74 (Fed. Cir. 2020) (reference disclosed claimed technology despite using different words); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991) (primary reference's identification of commercially available product sufficient to disclose undisputed property of that product for purposes of anticipation); *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1337-40 (Fed. Cir. 2020) (affirming anticipation finding where prior art temperature range overlapped with the claimed range). In each of these cases, a POSA would have understood the reference to ***necessarily*** disclose the apparently missing limitation. Here, even Merck acknowledges its conclusions are based on generalities and not necessary disclosure. By its own admission, Merck's inherency argument fails.

Simply put, the MSR does not refer to prior treatment or tumor progression whatsoever. Indeed, the only reference in the MSR to prior treatment is the ***exclusion*** of individuals who had received certain prior treatments. EX2072, ¶96. This is ***the opposite of*** a requirement of prior treatment. *Id.* And a requirement of prior treatment was ***added*** to the ClinicalTrials.gov record in January 2016—three years ***after*** the publication of the MSR. *Compare* EX1005, 5-6 with EX2165, 8; EX2166, 8. Were such a requirement "necessarily present" to a POSA reading the original MSR (EX1005), there would have been no need for JHU to amend the MSR to add this requirement. EX2072, ¶96. Similarly, the 2014 ASCO poster—relied upon by Merck as allegedly confirming its understanding of the disclosure of the MSR—explicitly requires in the inclusion criteria that MSI-H CRC patients have "at least 2 prior therapies" and MSI-H non-CRC patients have "at least 1 prior therapy." Pet., 25-26; EX1080. The ASCO poster is a separate reference from the MSR, created well after the MSR was posted. Again, if a POSA shared Merck's understanding of the MSR, it would have been unnecessary for the ASCO poster to list these inclusion criteria.

B. The MSR Cannot Anticipate Because It Does Not Disclose the Claimed Clinical Results

Independent Claim 1 also requires knowledge of the outcome of the study initiated by the MSR. This claim requires "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 pembrolizumab," where the reference patient's tumor is not MSI-H, dMMR or demonstrate an instability of a marker for either. Similarly, dependent claim 3 specifies that "the outcome that is improved is an improved objective response rate (ORR), and improved progression-free survival (PFS), or an improved overall survival (OS)."

1. The MSR Does Not Expressly Disclose the Claimed Clinical Results

Of course, the MSR does not disclose any of the results of the study proposed. EX2072, ¶¶97-98; EX2163, 147:18-148:2; EX2282, 77:2-5. The purpose of the MSR was to initiate a study that would obtain data that could be assessed for whether the hypothesis under consideration was valid. A POSA reading the MSR would not and could not have known the outcome of the proposed study before the study had commenced. EX2072, ¶98. In particular, a POSA would have had no way of knowing: (1) whether the amount of pembrolizumab used would be effective in MSI-H/dMMR patients; (2) whether the MSI-H/dMMR patients would fare better than a reference patient; or (3) the objective response rate/progression-free survival/overall survival of the MSI-H/dMMR patient population after administration of pembrolizumab. EX2072, ¶¶97-98. Because the claimed outcome was impossible to know, Merck concedes

the point in its obviousness analysis, arguing that "the POSA would have wanted to complete the study, ***including determining the outcome*** of patients." Pet., 44; *see also id.*, 54.

2. The MSR Does Not Inherently Disclose the Claimed Clinical Results

The MSR also fails to inherently disclose the clinical results of JHU's study. As such, Merck's reliance on *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012) (*see* Pet., 17-18), necessarily fails.

First, as explained above, the MSR did not disclose the claimed but unperformed method, as was the case in *Montgomery*, so Merck's inherency argument necessarily fails. As shown above, the MSR does not disclose treating a cancer patient with pembrolizumab with "the patient having received a prior cancer therapy drug[.]" This limitation must be met for each of the challenged claims, but the MSR is silent on this point. In *Montgomery*, the prior art trial disclosure "[i]n all relevant respects" was "identical to the patent itself." 677 F.3d at 1383. Not so here. Neither the MSR nor any portion of its disclosure is cited in or appears in the patent's specification. Written description support for the claimed method comes from information later obtained and included in the patent specification, including preliminary results from the clinical trial, that is entirely missing from the MSR.

Second, the MSR was an initial submission for an experimental trial that had

not even begun recruiting patients. This "invitation to investigate," which at the time of its posting had obtained no supporting experimental data, could not and did not provide the results claimed by the '974 Patent. 677 F.3d at 1382. Certainly, without any data, the claimed results could not be said to "inevitably flow" from the proposed clinical trial as was the case in *Montgomery*. *Id.* at 1381.

As explained further below, *Montgomery* distinguished the very type of "invitation to investigate" at issue here—a potential association between MSI-H cancer and response to treatment with pembrolizumab, the results of which were far from inevitable. *Montgomery*, 677 F.3d at 1382. At the time of the MSR's posting, the inventors did not have any data on how MSI-H cancers would respond to treatment with PD-1 inhibitors or even animal data to preliminarily support their hypothesis. EX2130, ¶¶10, 22. What the inventors did know was that prior studies of another checkpoint inhibitor used to treat CRC were resoundingly ***unsuccessful***, with 32 of 33 patients not responding to the therapy. EX2024; EX1013. As Dr. Goldberg explained, a single responding patient out of thirty-three CRC patients "would generally be regarded as too low to justify a Phase II trial to investigate the efficacy in CRC or any tumor type." EX2090, ¶57. Moreover, treatment of other types of cancers beyond the initial success in melanoma and non-small cell lung cancer had failed. EX2024; EX2090, ¶57.

As an untested proposal to conduct further study, a positive outcome was far from assured. Tellingly, when given the chance to sponsor JHU's clinical trial to assess whether JHU's hypothesis was valid, Merck (and Bristol-Myers Squibb (BMS)) declined, *see* §VII.C, *infra*. These facts further demonstrate the MSR was a far cry from meeting *Montgomery's* inevitability requirement for inherent anticipation. 677 F.3d at 1381 ("a result is only inherent if it inevitably flows from the prior art disclosure."); *see also* §VI.C, *infra* (discussing unpredictable nature of cancer treatment). *Montgomery* distinguishes clinical trials that are at "an advanced stage of testing designed to secure regulatory approval," which have the potential to inherently disclose a claimed method of treatment, from the situation here, "an invitation to investigate, [which] is not an inherent disclosure." *Id.* at 1382 (quoting *Metabolite Lab'ys, Inc. v. Lab'y Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)). As the *Montgomery* dissent explains, and as directly relevant here, "[w]ere inevitability not required for inherency, a mere proposal for further experimentation could anticipate a claimed invention. That is not the law, however. There is nothing inevitable about a proposal." *Id.* at 1384 (Lourie, J., dissenting). This aligns with the majority's requirement that "[t]he inherent result must inevitably result from the disclosed steps." *Id.*, 1380.

The MSR was a classic "invitation to investigate"—an "abstract theory" in a

highly unpredictable field having no supporting data. EX2072, ¶109. It most certainly was not at "an advanced stage of testing designed to secure regulatory approval." *Montgomery*, 677 F.3d at 1382. The MSR instead describes a study intended to test the hypothesis that MSI-H might correlate with response to treatment with pembrolizumab. As an invitation to engage in "further experimentation to find such associations." (*Metabolite Lab'ys, Inc.*, 370 at 1367), the MSR proposal included both MSI-H and MSI-stable CRC patients rather than presuming the correlation and only testing MSI-H patients. EX2130, ¶¶10-13. It also included MSI-H non-CRC patients to test if MSI-H could be used as a biomarker independent of cancer type. *Id*.

Quite unlike the MSR, the prior art study in *Montgomery* had enrolled and begun treatment of 9,541 patients. 677 F.3d at 1378. There was no question that the drug being tested prevented stroke as claimed. *Id.* at 1381.[4] The Board and

[4] Unlike *In re Couvaras*, 70 F.4th 1374 (Fed. Cir. 2023), also relied on by Merck, at the time the MSR was posted, there were no known treatments for MSI-H cancer. Pet., 17-18. Additionally, *Schering Corp. v. Geneva Pharmaceuticals* is inapposite because the issue was whether the claimed compound "necessarily and inevitably

Federal Circuit thus had little difficulty concluding the prior art reference was "far from an abstract theory" and instead was "an advanced stage of testing designed to secure regulatory approval." *Id.* at 1382. And again, critically, the prior art reference's disclosure "[i]n all relevant respects" was "identical to the patent itself." *Id.* at 1383. That is not even arguably the case here. The MSR's disclosure does not meet the *Montgomery* standard, and the Board should find that Merck has failed to carry its heavy burden to show inherent anticipation.

3. Merck's Interpretation of Inherency Is Legally Incorrect

Merck's interpretation of inherency law cannot be correct because it effectively precludes the patenting of unexpectedly effective methods of treating human patients. If, on the one hand, JHU had filed a data-less provisional application mirroring the MSR before the MSR was posted (and before any clinical study had begun), it would have been unable to satisfy the requirements of §101 and §112. *Cf. Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1322 (Fed. Cir. 2019) (absent supporting data, mere prophetic examples are inadequate); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (a patent application must "reasonably convey[] to those skilled in the art that the inventor

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forms," not whether steps of a method claim are necessarily ***performed***. 339 F.3d 1373, 1378 (Fed. Cir. 2003).

had possession of the claimed subject matter as of the filing date"); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) (§101 requires "that [the] claimed invention has a significant and presently available benefit to the public"). If, on the other hand, JHU waited—as it did—until it had data to submit in a patent application, in Merck's view any resulting patents would be invalid as inherently anticipated by the data-less MSR. Merck takes this position even though the study results were obtained entirely after the MSR was posted and were unexpectedly positive. Merck maintains this position even though the disclosure of the MSR does not support a reasonable expectation of success in achieving the claimed method for purposes of obviousness. *See infra* §VI.C.2.a (discussing *OSI Pharms.*, 939 F.3d 1375).

The catch-22 scenario that Merck advances cannot be correct. The requirements for receiving patent claims (sufficient data to satisfy §101 and §112) cannot be more rigorous than the requirements for the enablement of prior art (a description of proposed testing of a hypothesis without supporting data) such that JHU would be precluded from securing patent protection over its breakthrough discovery. Yet, Merck would have the Board impose these requirements so that Merck might avoid liability for using JHU's pioneering inventions.

C. The MSR Cannot Anticipate Dependent Claims 5-6 Because It Does Not Disclose Treating "Metastatic Cancer" or "Metastatic Colorectal Cancer" as Claimed

Claim 5 requires that the cancer treated according to the claimed method be a "metastatic cancer," while claim 6 specifies that the cancer treated be a "metastatic colorectal cancer." "Metastatic cancer" is cancer that has spread from its site of origin to another part of the body. EX2072, ¶99. Merck's anticipation argument with respect to these claims necessarily fails because the MSR does not disclose treatment of metastatic cancer or metastatic colorectal cancer.

Rather than address the "metastatic cancer" requirement of the challenged claims, the Petition and Merck's expert, Dr. Neugut, point to the MSR's requirement that patients have "measurable disease." Pet., 23-26; EX1003, ¶68. "Measurable disease" is very different from "metastatic cancer." EX1048, 230-31 (discussing definition of "measurable"); EX1020, 82 (discussing "measurable metastatic disease"). "Measurable disease" in the context of cancer means only that the cancer has a minimum size—i.e., a size that is measurable—***not*** that the cancer is metastatic. EX1048, 230-31. Merck's expert, Dr. Neugut, conceded this distinction during deposition. There, he testified that, contrary to the opinions he expressed through declaration, "metastatic" and "measurable" are "total different terms," and metastatic tumors "would not necessarily be measurable[.]" EX2163, 14:9-15:12. Given Dr. Neugut's concession, there is no evidence that the MSR

discloses treating "metastatic cancer" or "metastatic colorectal cancer" as required by claims 5 and 6. EX2072, ¶¶99-103.

D. The MSR, Which Proposed an Experimental Use, Does Not Qualify as Prior Art

Grounds 1-7 also fail because the MSR, as a disclosure of a proposed experimental use, does not qualify as prior art. Experimental use balances the "public's right to retain knowledge already in the public domain and the inventor's right to control whether and when he may patent his invention." *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 65 (1998). It does this by granting an inventor latitude to experiment—even in the public eye—until his invention is ready for patenting. *Id.* at 64 ("[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye."). Consistent with these policies, the Supreme Court and Federal Circuit have held that public experimental activities can be negated as §102 prior art if those activities were for experimental purposes. *See, e.g., City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 133-36 (1877) (discussing experimental negation of a public use); *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352-55 (Fed. Cir. 2002) (discussing experimental negation of sales and offers for sale); *cf. Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 872 (3d Cir. 1977) ("Once the party asserting invalidity has convincingly

proven the prior use or sale…the burden shifts to the patentee to prove that any prior use, sale, or ***printed publication*** was for experimental, not commercial, purposes.”).

Experimental use negation applies to the MSR as a matter of fact under the Federal Circuit’s multi-factor analysis, which considers: (1) necessity; (2) control; (3) nature of the invention; (4) length of time; (5) payment; (6) secrecy obligations; (7) recordkeeping; (8) who conducted the experiment; (9) commercial exploitation; (10) necessity of testing under conditions of use; (11) whether testing was systematic; (12) monitoring of the experiment, and (13) nature of contacts with potential customers. *Allen Eng’g Corp.*, 299 F.3d at 1353; *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380-81 (Fed. Cir. 2006). As explained below, each of these factors supports finding the MSR should not be considered as prior art to the ’974 Patent.

(1) Necessity. The ’974 Patent inventors could not have run the groundbreaking clinical study that ultimately provided support for their patent claims without first submitting the required information on ClinicalTrials.gov. *See* 42 U.S.C. §282(j) (EX2148); EX2137, ¶¶8-52; EX2163, 138:15-21, 141:13-18, 143:14-145:1; *cf.* 42 C.F.R. §§11.2-11.66 (EX2147); EX2130, ¶17. Indeed, Merck required JHU to register NCT01876511 on the ClinicalTrials.gov website before

shipping pembrolizumab for use in the study. EX2131, §9.F; EX2130, ¶17. Federal regulations require that ClinicalTrials.gov postings include certain details about any planned human clinical study, including a description of the study design, study outcomes to be measured, and study eligibility. EX2137, ¶¶33-47; EX2130, ¶¶18-19. Researchers must publish these details before undertaking any human clinical study, and the posting must be regularly updated until the study is complete. EX2137, ¶¶37, 47-48; EX2130, ¶19; EX2072, ¶110. No U.S. clinical study can lawfully proceed without complying with these obligations. EX2137, ¶¶39-42. And, without obtaining the actual study results, the inventors could not know (or reasonably expect) that their claimed methods work. EX2072, ¶¶104-109; EX2130, ¶¶21-27; *see also* EX2163, 25:13-19, 136:11-23. Thus, the submission of the MSR was a necessary step to rendering the claims ready for patenting. *See Barry*, 914 at 1322 (citation omitted) ("readiness for patenting" requires that the invention had been reduced to practice, which requires that "the inventor (1) constructed an embodiment or performed a process that met all the limitations and (2) determined that the invention would work for its intended purpose.").

(2) Control. The '974 Patent inventors maintained control over the underlying study, overseeing it from patient recruitment through the publication of

results. EX2130, ¶33. The inventors also retained control over the ClinialTrials.gov posting throughout the MSI-H clinical study. EX2130, ¶33. They updated the posting 28 times over 7 years. EX2130, ¶19; EX1005, 1-2.

(3) Nature of the Invention and (10) Necessity of Testing Under Conditions of Use. Cancer treatment is a highly unpredictable art. *See* §VI.C.2.a; EX2072, ¶¶33-57, 105; *see also* EX2163, 181:15-25. At the time that the inventors were developing the MSI-H clinical study protocol, pembrolizumab had not yet been approved by FDA for any treatment of any cancer. EX2072, ¶105; EX2130, ¶8; EX2163, 177:24-178:3. And, at the time of the invention, no cancer-type-agnostic treatment had ever been approved by FDA. EX2072, ¶105. Pembrolizumab's subsequent approval for MSI-H, tissue-agnostic treatment—based in large part on the results of the study initiated by the MSR—was heralded as a breakthrough in the industry, as discussed in more detail in §VII.B, *infra*. EX2072, ¶¶62, 182-186; EX2090, ¶¶64-65, 74; EX2130, ¶¶36-53.

Even if pembrolizumab had been approved for another indication, Merck's expert admitted that a positive outcome in one clinical trial does not portend a positive outcome in subsequent trials. EX2163, 125:15-126:1. Indeed, even in recent years, pembrolizumab has failed in numerous clinical trials. EX2072, ¶¶105, 132-134, 179; EX2130, ¶¶24-26. Given the nascent nature of

pembrolizumab treatment at the time of the MSR and the lack of support for treating cancers based on a biomarker, as opposed to tissue type, experimentation was necessary to establish that the claimed methods would work as hypothesized.

Testing in humans under the conditions described in the MSR was also necessary. At the time of the MSR, there were no reliable models of MSI-H in animals. Even today, there are no animal models that represent the human body's response to checkpoint inhibitors. EX2072, ¶¶54-55, 107-108, 140, 189; EX2130, ¶¶21-22; *see also* EX2163, 148:3-6. To establish that treatment of MSI-H cancers was effective, the inventors ***had*** to test in humans, and thus ***had*** to post the MSR on ClinicalTrials.gov.

(4) Length of Time. The '974 Patent inventors posted to ClinicalTrials.gov shortly before activating the clinical trial, to allow for patient recruitment. EX2130, ¶23; *see also* EX2163, 187:5-11, 192:14-193:11. At the time of the MSR's posting, the claimed invention was not, nor could it have been, ready for patenting. The clinical study that ultimately collected the data reported in the patent specification and supporting the patent claims had not and could not have commenced before the MSR was posted.

(5) Payment, (9) Commercial Exploitation, and (13) Nature of Contacts with Potential Customers. The '974 Patent inventors were not paid to submit the MSR.

EX2130, ¶20. The FDA does not pay for submissions to ClinicalTrials.gov. EX2137, ¶23; *see also* EX2163, 189:3-11. The inventors also were not paid by participants in the clinical study itself. EX2130, ¶20; *see also* EX2163, 188:13-189:2. Treatment was provided to patients without charge, so there was no commercial exploitation by the inventors in the conduct of the study. EX2130, ¶20. There were certainly no contacts by the inventors with potential customers, because, as an academic research institution, JHU ***does not sell pembrolizumab***. *Id.* To the extent individuals involved with the study might later seek out pembrolizumab treatment, the product would not come from JHU. *Id.*

(6) Secrecy Obligations and (7) Recordkeeping. The ’974 Patent inventors were powerless to impose secrecy obligations over the ClinicalTrials.gov posting itself, because such postings are controlled by the government and are required to be made public. EX2137, ¶30; EX2163, 144:13-145:1. The inventors did, however, maintain the records from the study under strict confidentiality. EX2130, ¶34; *see also* EX2163, 190:16-23.

(8) Who Conducted the Experiment, (11) Whether Testing Was Systematic, and (12) Monitoring of the Experiment. The ’974 Patent inventors were highly involved in conducting the MSI-H clinical study, from drafting the protocol and posting on ClinicalTrials.gov to treatment of patients to publication of results.

EX2130, ¶¶14-19. Inventor Dung Le was the principal investigator overseeing every aspect of the study. EX2130, ¶16. The MSI-H study was done systematically in accordance with best practices for running human clinical trials. EX2130, ¶¶14-19; *see also* EX2163, 37:17-38:1, 136:11-23, 145:9-13.

In sum, the MSR was submitted as a threshold and required step in the inventors' experimentation to test a scientific hypothesis. The inventors received no financial benefit from the submission and carefully maintained the ClinicalTrials.gov posting while also diligently completing the underlying clinical study—all to obtain data necessary to assess their theory and later support the patentability of their groundbreaking invention. Under these circumstances, the Board should find that the MSR does not qualify as prior art to the '974 Patent. Because the MSR does not qualify as prior art to the '974 Patent, Merck's Grounds 1-7 necessarily fail.

VI. CLAIMS 1-7 ARE PATENTABLE OVER THE OBVIOUSNESS GROUNDS 2-7

A. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating a Cancer Patient Who Has Received a Prior Cancer Therapy Drug/Progressed After Receiving the Prior Cancer Therapy Drug /Has Metastatic Cancer

Because the MSR does not anticipate the challenged claims, Merck cobbles together seven different obviousness combinations based on six additional prior art references to try to reach JHU's claims. Pet., 36-57. These grounds combine the

MSR with Pernot and Benson (Ground 2) and Brown, Duval, and Benson (Ground 4). But neither of these combinations supplies the missing "prior cancer therapy"/"progressed after receiving the prior cancer therapy" limitations required by independent claim 1. They also fail to disclose the "metastatic" limitation of dependent claims 5 and 6. Moreover, none of Pernot, Benson, Brown, Duval nor any other references presented in Grounds 2-7 provides a POSA with a reasonable expectation of success. *See* EX2072, ¶¶123-171. For at least these reasons, Merck's obviousness challenges necessarily fail.

In both Grounds 2 and 4, Merck relies on Benson as disclosing what the Petition describes as "Treating Patients Having Characteristics Related to Progressive and Metastatic Disease." Pet., 42-45, 51-54. This argument fails to identify with particularity how the cited reference discloses any specific claim limitation. Benson, however, did not require prior treatment, progression on a prior therapy, or metastatic disease before a patient is enrolled in clinical trials. In fact, Benson allows for clinical trials as first-line therapy, explaining that "when appropriate, patients should ***preferentially*** be included in a clinical trial over standard or accepted therapy." EX1009, 2. Benson goes on to explain that "NCCN [provider of the guidelines] believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is

especially encouraged." *Id.*, 1. Even if Benson discloses that in ***some*** scenarios, it may make sense to recruit patients whose tumors had progressed after prior therapy and who have metastatic cancer/colorectal cancer, Merck has not provided any rationale for why a POSA would have selectively handpicked these characteristics from Benson—while ignoring Benson's encouragement of clinical trials as first-line therapy—to use as inclusion criteria for carrying out the study described in the MSI-H Study Record. Thus, Merck's contention 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 [prior] therapies***" is unsupported. Pet., 43; EX1003, ¶105; EX2072, ¶115. The same is true of Merck's related contention that, by virtue of participating in a clinical trial, a cancer patient must have advanced or metastatic disease. *Id.*

B. Merck's Obviousness Combinations Do Not Disclose or Render Obvious The Claimed Clinical Outcomes

Independent claim 1 requires knowledge of the outcome of the study initiated by the MSR but not yet performed by the JHU researchers. These claims recite "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 pembrolizumab, wherein the reference patient has a tumor that [is

non MSI-H/dMMR]." Claim 3 specifies that the improved outcome is an "improved objective response rate (ORR), an improved progression-free survival (PFS), or an improved overall survival (OS)." These claimed outcomes were unknown in the prior art and would not have been obvious in view of the prior art. A contrary conclusion presumes those of skill in the art could know the outcome of the clinical study described in the MSR before that study was conducted. EX2072, ¶¶116-122. Because even the named inventors did not know what those results would be and were surprised by the results they obtained, the MSR could not and did not disclose the clinical outcomes claimed (*see* §V.B. above).

Merck's reliance on Pernot (Ground 2) and Brown/Duval (Ground 4) as showing "Improved Outcome/Efficacy" also fails, as these references fall far short of disclosing the claimed outcomes in the claimed patient cohort, after treatment with the claimed method. Pet., 37-40, 47-50.

Specifically, in Ground 2, Merck alleges that Pernot teaches MSI-H colorectal cancer patients are "good candidates for immunotherapy" (Pet., 37). However, Pernot says nothing about treating MSI-H patients with pembrolizumab (or any other PD-1 inhibitor). As such, Pernot does not disclose or suggest the results of JHU's trial or any similar trial. Next, Merck contends that Pernot is "directed to treating colorectal cancer." *Id.* Of course, that says nothing about

treating MSI-H cancer or whether ***other types of MSI-H cancer*** would be good candidates for PD-1 checkpoint inhibitors. EX1006. Pernot also fails to provide a reasonable expectation of success in using the claimed method to treat MSI-H CRC cancer, let alone all other types of MSI-H cancer as claimed. *See* EX2072, ¶¶119, 141-143. This lack of reasonable expectation of success is confirmed by the unexpected results of the JHU clinical trial. *See* §VII.E below.

In Ground 4, Merck contends that "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." Pet., 48. This argument too fails, because Brown discloses no connection between the efficacy of PD-1 inhibitors and the patient's MSI-H status. Brown mentions MSI-H status just once—in the context of Lynch syndrome in CRC patients—concluding only that "a mutator tumor phenotype may, in general, enhance immunoreactivity." EX1034, 5. "Immunoreactivity" is a broad term that is not equivalent to response to immunotherapy, let alone response to anti-PD-1 therapy specifically. EX2072, ¶120. Also, unlike the claims of the '974 Patent, Brown's analysis focuses on ***specific cancer types*** and proposes future investigation, noting that "[a] comprehensive evaluation of immunogenic mutations ***specific to individual cancer types*** remains an important topic for future study." EX1034, 5; EX2282, 75:13-

76:7 (Merck's expert agreeing that "[t]umor biology is different across different organs"); *see also* EX2281. This is not a teaching of the claimed outcomes or even a suggestion of how to achieve them as Brown does ***not*** address the inherent efficacy of PD-1 inhibitors, let alone the efficacy of those inhibitors for MSI-H cancers in general. Pet., 48; EX2072, ¶120.

In combination with Brown, Merck relies on Duval as teaching that "MSI- H cancers have cancer cells that are easy for immune cells to recognize." Pet., 48. But Duval describes a study focused on only one very specific cancer type—non-Hodgkin lymphomas (NHL), a cancer that is not representative of MSI-H cancers generally, as it is "of a whole other world" from MSI-H solid tumors such as CRC. EX2282, 78:14-79:2, 80:25-82:19. Duval found that only 2% of these patients studied were MSI-H. EX1087. Rather than pointing to MSI-H as a marker for successful treatment with anti-PD-1 therapy, Duval suggests that MSI-H tumors may emerge in immunodeficient NHL patients because of "a decrease in the capacity of the host to recognize and eliminate such highly immunogenic MSI-H lymphoid clones." EX1087, 5; EX2072, ¶121. Duval also observes that, unlike MSI-H solid tumors, MSI-H immunodeficient NHL is not associated with a type of mutation that makes MSI-H solid tumors ***harder*** for the immune system to recognize. EX1087, 5; EX2072, ¶121. Overall, Duval supports the 1995

hypothesis of Branch et al. (EX2046) that MSI-H tumors are ***non-immunogenic*** and that these patients are ***poor candidates*** for immunotherapy. EX2072, ¶121. In other words, the combination of Brown and Duval does not disclose or suggest the success of achieving the claimed outcomes.

Pernot (Ground 2) and Brown/Duval (Ground 4) also say nothing about treating MSI-H cancer patients with pembrolizumab (or any other PD-1 inhibitor) and certainly do not disclose the results of the JHU trial (or any similar trial). As noted above, the experts agree the claimed response rates were ***impossible*** to predict. EX2163, 114:22-24; 111:20-24, 116:6-7; EX2072, ¶¶116-122. Merck itself admits that "the POSA would have wanted to complete the study, ***including determining the outcome*** of patients." Pet., 44, 54. Of course, without knowing the patient outcomes, a POSA would not have been able to know that MSI-H patients had improved outcomes as compared to reference MSI-stable patients. EX2072, ¶¶116-122.

While Merck argues that inherency can cure the many failings of its obviousness analysis (*see* Pet., 32-33, 37-40, 44, 47-50, 54), Merck cannot meet the heightened burden imposed for inherent disclosure in the obviousness context. The Federal Circuit has cautioned that "the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of

obviousness." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). To rely on inherency in an obviousness analysis, Merck must meet a "high standard," specifically that "the limitation…***necessarily must be present***" in the prior art reference. *Id.* at 1195-96. Inherency "may not be established by probabilities or possibilities" and "[t]he mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Id*. at 1196 (citation omitted).

C. Merck Fails to Show That a POSA Would Have Had a Reasonable Expectation of Achieving the Claimed Invention

1. Merck Applies the Wrong Standard for Reasonable Expectation of Success

Merck's reliance on various references as providing a reasonable expectation of success necessarily fails, because Merck applies the ***wrong legal standard***. Federal Circuit precedent makes clear that for method of treatment claims, it is "not enough for the [patent challenger] to have shown that a skilled artisan would have pursued the claimed method as a treatment option," but rather the challenger "also had to show that the skilled artisan would have ***reasonably expected to achieve success in the treatment***." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021). Merck instead argues an incorrect standard of whether a 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." Pet., 39, 49-50[5]; *see also id.*, 49. That is not the law, and Merck cites no case saying so. That a POSA may have wanted to "obtain the data" or "obtain the results" is ***not*** an expectation that the claimed method of treatment would in fact "***achieve success in the treatment***." *Eli Lilly*, 8 F.4th at 1344.

Indeed, a POSA will always want to obtain data from a clinical study; that is the entire reason for incurring the significant expense and burden of conducting clinical trials. EX2072, ¶125. Yet, wanting to obtain data is ***not*** the same as expecting a proposed treatment to work in a specific patient population. EX2072, ¶¶124-127. Merck's fundamental misapplication of law precludes Merck from meeting its burden to show the claims of the '974 Patent were obvious to a POSA. *Eli Lilly*, 8 F.4th at 1344.

2. None of Merck's References Provides a Reasonable Expectation of Success[6]

[5] Merck's citation to MPEP §2107.03, (Pet., 39, 50), is irrelevant; this subsection relates to whether there is a lack of ***utility***, not ***reasonable expectation of success***.

[6] Tellingly, Merck's expert admitted at his deposition that "[m]ost of [the prior art references] were chosen by the attorneys" and he did not look for any references as part of preparing his opinions for this case. EX2282, 59:4-22.

a. MSR

Merck has failed to show that the MSR itself provides a reasonable expectation of success in performing the claimed method for the same reasons identified by Federal Circuit precedent. For example, in *OSI Pharmaceuticals*, the Federal Circuit reversed the Board, holding that evidence disclosing a "hope that a potentially promising drug will treat a particular cancer" did not support a reasonable expectation of success. 939 F.3d at 1385. Those claims related to a method for the treatment of non-small cell lung cancer ("NSCLC") with erlotinib. *Id*. at 1378. The Board found the claims obvious over an article that noted that erlotinib, among other drugs, was currently in clinical trials, observing that "these compounds appear to have good anti-cancer activity in preclinical models… particularly in patients with [NSCLC]." *Id*. at 1383. The Federal Circuit reversed the Board's obviousness finding, holding that none of petitioner's cited references disclosed the treatment of NSCLC with erlotinib. *Id*. at 1383-86. Indeed, there was "no data or other promising information regarding erlotinib's efficacy in treating NSCLC," which was "significant because of the highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II." *Id*. at 1384. The Federal Circuit also rejected the Board's reliance on preclinical efficacy data. *Id*. at 1385. Noting that "[c]ancer treatment is highly unpredictable," the Federal Circuit found that the prior art

"provide[d] no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this." *Id*. at 1377-78, 1385.

Merck's arguments should be rejected for the same reasons. The MSR was a submission to obtain approval to ***begin*** enrollment for a clinical trial. It discloses nothing more than an experiment designed to test a hypothesis. EX1002, 270-71. As discussed in §V.D, certain clinical trials are experiments designed to test hypotheses. EX2163, 37:17-38:1, 136:18-23, 145:9-13; EX2072, ¶¶56-57, 68, 104-110, 139-140. At the time the MSR was published, no patient with an identified MSI-H tumor had been enrolled or treated with pembrolizumab per the trial protocol.[7] EX2163, 136:24-137:6; EX2072, ¶140. Both parties' experts agree that ***nothing*** in the MSR itself teaches or suggests to a POSA that the protocol would result in a finding that MSI-H status is a powerful indicator of successful treatment with pembrolizumab. EX2163, 137:19-23; EX2072, ¶¶66-70, 98, 139-140.

That these results were unexpected is further supported by approval of the

[7] The one MSI-H CRC patient who responded to treatment in the previous study was treated with a different anti-PD-1 therapy (nivolumab).

clinical investigation's inclusion of ***both*** MSI-stable and MSI-H patients. For JHU's study to move forward, it had to be approved by an IRB. EX2090, ¶68. If a POSA would have known or expected that treatment of MSI-stable cancer patients with pembrolizumab would ***fail***, the clinical trial ***would not have been approved*** by the clinical investigators or the Institutional Review Boards ("IRBs") governing the study. *Id.*, ¶¶68-70. The IRB's role is to ensure that a clinical trial treats patients ethically. *Id.* In one arm of JHU's clinical trial design, patients with CRC tumors that were ***not*** MSI-H—that were instead MSI-***stable***—were to be treated with pembrolizumab. If it were obvious that pembrolizumab was ***not*** effective in treating MSI-stable CRC tumors, then it would have been unethical to construct the trial protocol with that arm, let alone enroll and treat those patients. EX2090, ¶70. Doctors would not have prescribed it, and patients would not have wanted to take it. *Id.* But until JHU's clinical trial was performed, no one knew that pembrolizumab would be ***effective*** in treating MSI-H tumors but ***ineffective*** in treating MSI-stable tumors.

Consistent with *OSI Pharmaceuticals*, it is undisputed that the MSR "do[es] not disclose *any* data or other information about [pembrolizumab's] efficacy in treating [MSI-H cancer]," nor does the MSR "contain any clinical (human) data or preclinical (animal) data," or even "*in vitro* (test tube) data regarding

[pembrolizumab's] effect on [MSI-H cancer]." 939 F.3d at 1383 (emphasis in original); EX2163, 147:18-148:2; EX2072, ¶140; *see also Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 640-42 (Fed. Cir. 2017) (affirming no reasonable expectation of success even after two full clinical trials using a "promising new…compound" had been completed and a "post hoc analysis" suggested the claimed outcome later confirmed in a third clinical trial). At the time the MSR was submitted, FDA had not approved pembrolizumab for any indication. EX2072, ¶140. And no preclinical or animal model for testing efficacy on human tumors, let alone MSI-H tumors, existed. EX2163, 148:3-6; EX2072, ¶¶54-55, 107-108, 140, 189. On these facts, even Merck's expert agreed that the MSR provided no expectation of success. EX2163, 137:19-23 ("Q. Is there anything in the [MSR] that tells a POSA that the protocol will be successful or have a positive outcome? A. No.").

b. Pernot

Pernot also cannot provide a reasonable expectation of success. Merck incorrectly contends "Pernot taught that those patients [whose colorectal cancers were MSI-H] are 'good candidates for immunotherapy,' such as PD-1 inhibitors like pembrolizumab." Pet., 37 (quoting EX1006, 3741). Pernot, however, does not disclose pembrolizumab or anti-PD-1 therapies—a fact confirmed by Merck's own expert:

Q. Pernot does not disclose anti-PD-1 therapies; right?

A. No, correct.

Q. Pernot does not disclose that MSI high CRC patients would be promising candidates for PD-1 checkpoint blockade therapy; correct?

A. No, he does not.

Q. And Pernot does not disclose *any relationship* between MSI high CRC patients and their likelihood of responding to PD-1 checkpoint blockade therapy; right?

A. No, he doesn't make reference to it.

EX2163, 152:12-153:6. Because Pernot discloses nothing about the likelihood of a MSI-H CRC patient, let alone MSI-H cancers in general, responding to a PD-1 checkpoint inhibitor (like pembrolizumab), Pernot provides no expectation of success whatsoever in using the claimed method to treat MSI-H cancer patients. *OSI Pharms.*, 939 F.3d at 1383; *see also* EX2072, ¶¶141-143.

Merck's focus on a single speculative sentence in Pernot—"***CRC*** associated with MSI ***could*** lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good ***candidates*** for immunotherapy"—is also misplaced. EX1006, 5; *see also* Pet., 37. When describing "Immunotherapy in CRC," Pernot lists 27 different ongoing clinical trials of immunotherapy involving six types of immunotherapy strategies—***none*** of which included anti-PD-1 therapies, let alone pembrolizumab, and none of which demonstrated clinical efficacy. EX1006, 10 (Table 1); EX2072, ¶143; *see also* EX2282, 90:19-21, 92:4-93:8, 95:21-96:18. And where Pernot does mention anti-

PD-1 therapies, it is in passing and only in the context of ***melanoma***—not CRC, let alone MSI-H CRC or other MSI-H tumors. EX1006, 6. Additionally, contrary to the Board's reading, Pernot does not teach that "colorectal cancer patients" are "good candidates for immunotherapy." DI, 25. In fact, Pernot teaches that "escape mechanisms to antitumor immune response" in CRC are "a ***major obstacle***…to the use of immunotherapy" in CRC. EX1006, 2; *see also* EX2072, ¶¶51-52, 106, 130-131, 148-149. Thus, Pernot does not disclose or even suggest that pembrolizumab would work in MSI-H CRC patients, let alone MSI-H cancer patients in general. EX2072, ¶¶71-73, 141-143.

Indeed, Pernot postulates that "immunotherapeutic approaches is a seducing ***alternative to try*** to improve the prognosis of these [CRC] patients in the future." EX1006, 9. But Pernot does not point to, nor were there any, "identified, predictable solutions" at this time. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Pernot's suggestion for possible future study is insufficient to support a reasonable expectation of success. "[H]ope that a potentially promising drug will treat a particular cancer is ***not enough*** to create a reasonable expectation of success in a highly unpredictable art such as this." *OSI Pharms.*, 939 F.3d at 1385; *see also Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) ("speculative and tentative disclosure of what 'might' or 'may' [explain the

cause of a desired effect] does not sufficiently direct or instruct one of skill in this art"); *Alza Corp. v. Mylan Lab'ys, Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) ("[L]egal determinations of obviousness…should be based on evidence rather than on mere speculation or conjecture.").

c. Benson

Benson also does not provide a reasonable expectation of success for the claimed invention. Benson describes clinical practice guidelines for colon cancer. EX1009, 1; EX2072, ¶¶74-75, 144. Merck primarily relies on Benson as disclosing that patients taking part in clinical trials are generally patients with advanced, metastatic disease, who would also would have had their cancer progress after two previous drug therapies. Pet., 43; *see also id.*, 24, 42-45, 51-54. Benson, however, does not disclose or suggest that MSI-H CRC patients—let alone MSI-H cancer patients of any type—would be particularly promising candidates for PD-1 checkpoint blockade therapy. EX2072, ¶144.

d. Brown

While Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated TIL are ***potential*** candidates for treatment with immune modulator such as CTLA4- or PDCD1-targeted antibodies." (EX1034, 5), Brown does not provide a reasonable expectation of success for the claimed invention, (EX2072, ¶¶78-82, 145-150). Brown is a tumor genome meta-

analysis that speculates about a connection between "the abundance of predicted immunogenic mutations" (not MSI-H) and benefit from immunotherapies (not PD-1 inhibitors). EX1034, 1. Brown does not discuss the many features of MSI-H tumors, known at the time of the invention, that taught away from MSI-H patients being good candidates for immunotherapy and especially for checkpoint blockade therapy. EX2072, ¶¶147-150. For example, MSI-H tumors have low HLA expression, which indicated that those tumors are ***non-immunogenic*** and these patients would be poor candidates for immunotherapy. *Id.*; EX1006, 5-6; EX2046, 2. While Brown discusses MSI-H in the context of Lynch syndrome and CRC, concluding that "a mutator tumor phenotype ***may***, in general, enhance immuno-reactivity," Brown does not connect the broad concept of immunoreactivity to response to PD-1 inhibitors. EX1034, 5; EX2072, ¶150. Consequently, Brown does not disclose any connection between MSI-H and response to PD-1 inhibitors in CRC, let alone cancers generally.

e. Duval

Duval also fails to provide a reasonable expectation of success. Duval reports the results of a study on the occurrence of MSI-H tumors in Non-Hodgkin lymphomas (NHL), a cancer that is not representative of MSI-H cancers generally, as it is "of a whole other world" from MSI-H solid tumors such as CRC. EX2282, 82:5-19. The authors observed that MSI-H lymphomas are extremely rare,

"occur[ring] significantly only in immunodeficiency-related lymphomas." . EX1087, 1; EX2072, ¶¶83-84, 151-153. While the authors suggest a "clinical relationship between the emergence of the tumoral mutator phenotype and host immunodeficiency ***in a particular subset of tumors*** represented by human lymphomas" (EX1087, 5), they also found "the target gene mutation profile associated with MSI-H [immunodeficiency-related lymphomas] ***is specific for this tumor subtype***, when compared to other MSI-H cancers such as gastrointestinal and endometrial tumors." *Id.*, 4; EX2072, ¶153. The study does not address MSI-H tumors in non-immunodeficient patients or MSI-H in any cancer types other than NHL. *Id.* Drawing conclusions about a reasonable expectation of success in all MSI-H tumors based on immunodeficient MSI-H NHL would be illogical. *See* EX2282, 82:5-19. As such, Duval provides no expectation of success for the claimed invention.

f. Merck's Additional References

Merck also relies on ***thirteen*** additional references in Ground 2 in its failed effort to support three blanket statements about what was purportedly known in the art:

- "[S]everal other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab";
- "[T]he 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 and (2) already infiltrated by many immune cells";

- "[T]he prior art taught that MSI-H tumors naturally displayed those characteristics."

Pet., 38-39 (citing EX1006, EX1032-1042, EX1051, EX1058, EX1085, EX1087). Merck's Petition fails to identify any specific disclosures within these references to support any of these points. Instead, Merck relies on Dr. Neugut's explanation of the alleged support. *See* Pet., 38-39 (citing EX1003, ¶¶43-46, 99-100). Just as with Pernot, however, what these references say and what Merck and Dr. Neugut claim they say are worlds apart. As Dr. Lonberg explains, at best these references were inviting researchers to investigate additional speculative hypotheses. EX2072, ¶¶154-157.

Merck also disregards evidence in these ***very references*** that taught ***away*** from the treatment method of the '974 Patent. *See, e.g.*, EX1032, Table 1 (showing a ***0% response rate*** for anti-PD1 agents and anti-PD-L1 agents among colorectal cancer patients); EX1033, 2969 (describing disparities in findings of PD-L1 expression in MSI-stable and MSI-H colon cancer with previous studies); EX1035, 2 ("there may ***not*** be a single biomarker that will prove sufficient information for predicting treatment response and patient outcome"). Merck also ignores the many trials of anti-PD-1/PD-L1 inhibitors that ultimately failed, with

the reasons remaining poorly understood even to the present day and certainly as of the Critical Date of the ’974 Patent. EX2074, 18; EX2075, 1; EX2072, ¶¶132-134. These references demonstrate that there was no reasonable expectation of success for the method of treatment claimed in the ’974 Patent. EX2072, ¶¶154-171.

Collectively, Merck’s references fail to demonstrate a reasonable expectation of success. At best, they provide only speculation about how MSI-H cancer might be candidates for immunotherapy generally, while ignoring evidence that MSI-H cancers would not respond to immunotherapy. *Id.*, ¶171. Moreover, evolving research has since clarified significant gaps in the understanding of what makes tumors responsive to immunotherapy, undermining Merck’s interpretation of the prior art. *Id.*

3. The State of the Art Does Not Create a Reasonable Expectation of Success

a. PD-1 Inhibitors Were In Their Infancy

Merck’s argument that “the state of the art” compelled a reasonable expectation of success also fails. Pet., 38, 48. At the time of the MSR, pembrolizumab had not been approved for ***any*** indication. *See* EX1055, 1 (Keytruda® label, “Initial U.S. Approval: 2014”). Other anti-PD-1 antibodies were “still in development” and had only “shown promising clinical results…for tumors classically considered to be immunogenic such as melanoma and renal cell

carcinoma (RCC)" and also "for common epithelial malignancies such as [NSCLC], historically resistant to immunotherapy." EX1057, 1.

The state of the art then, as now, is that cancer therapy is inherently and notoriously unpredictable. EX2072, ¶¶33-57, 105. Compounding the challenge, no animal models of MSI-H cancer existed, precluding the inventors from generating even initial preclinical data suggestive of eventual success. EX2163, 148:3-6; EX2072, ¶¶54-55, 106-107, 140, 189; EX2073, 271-272. As Dr. Le explained: the "clinic is the experiment." EX2130, ¶21.

Merck's claim that "[p]hysicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art with PD-1 inhibitors," is, at best, misleading. Pet., 38, 48. At the time, MSI-H and MSI-stable patients were treated the same way. EX2090, ¶37. Any patients with MSI-H tumors treated in the clinical trials cited by Merck were only ***retrospectively*** identified as being MSI-H. The records of those studies do not even mention MSI/MMR testing. EX1016, 6-7; EX1017, 5-6. Treating patients with cancer types that ***may*** have MSI-H subpopulations without appreciating the relevance of MSI-H status or even knowing that any of those patients are in fact MSI-H does not support Merck's claim of a reasonable expectation of success. EX2072, ¶¶172-175.

To the contrary, the evidence available at the time of the MSR establishes

that the results of JHU's clinical results were unpredictable and unexpected. Attempts to use anti-PD-1 inhibitors to treat cancers other than melanoma and NSCLC had failed to elicit responses. *See, e.g.*, EX2024. For example, only one CRC patient had been identified as responding to treatment with a different PD-1 inhibitor (BMS's nivolumab). EX1057. Notably, the thirty-two other CRC patients in the BMS studies of nivolumab did not respond to the therapy, making this one patient's response a "statistically meaningless" result. EX1002, 270; EX1057, 2-3; EX2176, 22; EX2072, ¶176; EX2090, ¶57. In other words, it was known to the POSA that the BMS PD-1 inhibitor had shown a ***97% failure rate*** in the treatment of CRC. To the extent this result was relevant to pembrolizumab, "the only reasonable expectation at the time of the invention was ***failure***, not success." *OSI Pharms.*, 939 F.3d at 1385 (finding no reasonable expectation of success given "a 99.5% failure rate and no efficacy data or any other reliable indicator of success").

Importantly, at the time of the BMS study, the reason why the single CRC patient responded and the others did not was unknown. While the JHU inventors hypothesized that the response may have been tied to the patient's MSI-H status, which was which was unknown prior to treatment, at the time the hypothesis was mere conjecture. *See* EX2163, 131:5-132:9 (publication "makes no reference to

it"). The patient's MSI status was determined later, as part of the inventors' efforts to explain his anomalous result. *See* EX2163, 132:5-9; EX1002, 268-70; EX2176, 22-23; EX2090, ¶¶59-60. The MSR was proposed in furtherance of a desire to generate data that ***might*** explain why this patient responded when so many other patients did not. *Sanofi*, 875 F.3d at 647.

While the inventors had one retrospective data point for MSI-H CRC, they had ***no*** data to support their hypothesis that MSI might also be a useful biomarker for identifying patients responsive to PD-1 inhibitors regardless of cancer type. The inclusion of an [redacted] was intended to test the outer limits of the inventors' hypothesis. EX2273, 37.

The inventors' hypothesis, even limited to CRC patients, was certainly not accepted at the time by interested companies. In fact, BMS's investigators speculated that the single positive CRC response could be due to ***PD-L1***, a different biomarker, which they thought might predict response to anti-PD-1 therapy. EX1057, 3. Merck had the same hypothesis, and launched its own study testing pembrolizumab in CRC patients with ***PD-L1*** positive tumors, six months after JHU's trial began. EX2080. That study too was a failure, with only one CRC patient out of twenty-three (23) responding—***a 96% failure rate***—and that patient was later (after the priority date of the '974 Patent) found to be MSI-H. EX2132,

11. Merck concluded from its study that pembrolizumab had "limited antitumor activity in patients with heavily pretreated PD-L1-positive advanced CRC." *Id.*

Further demonstrating that JHU's invention was unexpected, both Merck and BMS ***rejected*** JHU's request to fund the inventors' clinical trial. EX2072, ¶¶126, 140, 187; EX2090, ¶61. Instead, the JHU researchers were forced to secure philanthropic funding to test their hypothesis. EX2121, 6. The idea that pembrolizumab (or nivolumab)—drugs that had not been approved for ***any*** indication at this time—could be used to treat cancer based on a specific genetic marker, rather than the location of the tumor, was both unexpected and groundbreaking. EX2090, ¶¶62-67.

b. Pembrolizumab's Other Approvals Do Not Predict Success

Merck's argument that pembrolizumab's approvals after the MSR submission but prior to the Critical Date would have led a POSA to have a higher expectation of success for the MSI-H cancer indication is inconsistent with the realities of cancer treatment and Federal Circuit precedent. As the court found in *OSI Pharmaceuticals*, "it is undisputed that a drug's success in treating one type of cancer does not necessarily translate to success in treating a different type of cancer, which underscores the unpredictability in cancer treatment generally." 939 F.3d at 1384. Merck's expert agrees:

> Q. A skilled artisan would understand that just because a therapy resulted in a positive outcome in one clinical trial, does not mean it will result in a positive outcome in subsequent trials; right?
>
> **A. That is true.**

EX2163, 125:15-126:1. Even Merck's chief medical officer recognized this, saying recently "it's still always going to be a game of chance," as "[e]very cancer is different, and every setting within the cancer can be different." EX2078, 2. In particular here, where FDA had never before approved a cancer therapy based on a biomarker alone ***independent of cancer type***, no precedent existed for a POSA to reasonably believe such a method of treatment would succeed. EX2072, ¶177.

Merck's reliance on the statistic that "for oncology drugs, 55% of second indications were successful if the first indication was successful" is similarly misplaced. Pet., 37-40, 47-50. When the MSR was posted, pembrolizumab had not been approved for any indication. Moreover, the FDA had not approved any tissue agnostic, biomarker-based cancer therapies, so even if there were previous approvals for pembrolizumab, they would have been irrelevant to the expectation of success for all MSI-H cancers. EX2072, ¶177. Additionally, Merck's statistic ***excludes*** drug trials that were sponsored "exclusively by academic, government, or non-profit organizations." *See* EX1063, 1. As Dr. Lonberg explains, studies run by these three institution types—like JHU here—are far more likely than pharmaceutical company trials to be high risk, experimental studies, and more

likely to fail. Omitting this data misleadingly inflates the success rate Merck relies upon. EX2072, ¶178.

Even so, Merck's robust history of its own clinical trial failures provides far more meaningful insight on whether a POSA would have reasonably expected success than the misleading statistic on which Merck relies. A Merck-sponsored trial of Keytruda® (pembrolizumab) in CRC patients who were positive for PD-L1, another biomarker thought to be associated with antitumor immune responses, failed in all but one patient. That single responding patient was later identified as MSI-H. EX2132, 1-2; EX2130, ¶¶9-10, 25. This was not Merck's only clinical failure with pembrolizumab. As of April 2023, Keytruda had "failed as a combination therapy in ***21 late-stage studies*** spanning nine different partner drug technologies," and "[r]esearchers also didn't advance at least ***66 combination studies*** after early or midstage trials." EX2078, 1; *id*. ("The track record has been horrible."); *see also* EX2076; EX2077; EX2079. As Merck's own history of clinical failures makes clear, even if pembrolizumab had been approved for one indication at the time of the MSR—which it had not—that prior approval does not supply the reasonable expectation of success for other indications.

D. Merck Has Not Shown Any of Claims 1-7 Would Have Been Obvious Over the Prior Art in Grounds 3, 5-7

The prior art in Grounds 3 and 5-7 does nothing to fill the Petition's

deficiencies regarding either the "received a prior cancer therapy drug" (claim 1), "progressed after the patient received the prior cancer therapy drug" (claim 2) or the "outcome that is improved" (claims 1, 3) limitations, or the requirement that a POSA "would have reasonably expected to achieve success in the treatment" claimed by the '974 Patent. *Eli Lilly*, 8 F.4th at 1344. In fact, Merck does not allege it does. Instead, as the DI acknowledges, Merck relies on Chapelle and Hamid for other claimed steps relating to determining MSI-H status (claim 4) or claims requiring that pembrolizumab be administered by intravenous infusion (claim 7). DI, 25-27, 30-33. EX2072, ¶¶76-77, 85, 180-181.

VII. OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS FURTHER PROVES THE CHALLENGED CLAIMS ARE PATENTABLE

The relationship between Merck and JHU is not the typical Petitioner-Patent Owner relationship that the Board sees in post-grant proceedings. Instead, the parties' prior relationship is the source of an array of strong objective evidence of non-obviousness, including industry praise, skepticism, long-felt unmet need, unexpected results, and commercial success. JHU is an academic institution that designed and ran a clinical trial, the outcome of which led to a novel, patented method of treatment using Merck's drug, pembrolizumab. Merck markets and sells pembrolizumab under the brand name Keytruda® and labels its drug specifically to treat cancer patients determined to have MSI-H tumors pursuant to

JHU's patented method. In doing so, Merck infringes JHU's patents and benefits richly from this willful infringement.

JHU's objective evidence of non-obviousness confirms the validity of each challenged claim. "[O]bjective considerations of non-obviousness must be considered in *every* case," *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (emphasis in original), and "can be the ***most probative evidence of non-obviousness in the record***," enabling the court "to ***avert the trap of hindsight***." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (quotation marks omitted).

A. Nexus

The surprising results of JHU's study ultimately led to FDA approval of pembrolizumab for the treatment of MSI-H cancer, resulting in actual treatment of patients with MSI-H tumors and concomitant sales of pembrolizumab to treat those patients. Here, a clear nexus exists between the development and commercialization of Merck's pembrolizumab product, Keytruda®, and the patented method of treatment. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). There is a presumption of nexus when a "product embodies the invention and is coextensive with it." *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1211 (Fed. Cir. 2023). In the absence of a presumption, a patent owner can provide evidence to support a nexus

to individual objective indicia. *See id.*

1. JHU is Entitled to a Presumption of Nexus

Here, JHU's objective evidence is tied to the method of using pembrolizumab to treat cancer patients determined to have MSI-H or MMR-deficient tumors as disclosed and claimed in the '974 Patent. The objective indicia here are narrowly tailored to the claimed method of treatment, i.e., the indications[8] that were ultimately tested and approved, ***not*** to pembrolizumab generally. EX2175; EX2179. Every step of the claimed treatment method is set forth in Merck's Keytruda® label for indication "1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer."[9] EX2129; EX2177; EX2179. Independent claim 1 is representative, and each claimed step is identified in the Keytruda® label as shown below and as described by Dr. Goldberg, (EX2090, ¶¶82-92):

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[8] "Indication" refers to the FDA approved use of a drug for a specific disease or condition, as indicated on the drug label. EX2090, ¶27, n.3.

[9] Treatment with Keytruda according to Indication 1.15 (Endometrial Carcinoma) added to the March 2022 label also practices the claimed method. EX2090, ¶92.

1[pre]. A method for treating cancer in a patient in need thereof,
1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. EX2129, 5.
1[a]. wherein a tumor sample obtained from the patient has been determined to exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers, the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:
The Keytruda® label instructs physicians to select patients from whom a tumor sample has been determined to exhibit an instability of one or more microsatellite markers or a deficiency of one or more mismatch repair markers, i.e. MSI-H/dMMR, and have received a prior cancer therapy drug to treat the tumor for treatment with Keytruda according to Indications 1.8: **1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer** KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. EX2129, 5. The Dosage and Administration section (Section 2) of the Keytruda Label instructs physicians to select patients having a cancer that is either MSI-H or

dMMR for treatment with Keytruda according to Indication 1.8. That section further refers physicians to Clinical Studies section 14.8 that instructs physicians to test or have tested the patient tumor's MSI H/dMMR status via local polymerase chain reaction (PCR) or immunohistochemistry (IHC).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, or TMB-H Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)]*.
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.4)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.7)]*.
- metastatic gastric cancer *[see Clinical Studies (14.10)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- metastatic esophageal cancer *[see Clinical Studies (14.11)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.12)]*.

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.8, 14.9)]*.

EX2129, 7.

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

EX2129, 73-74.

1[b]. administering an effective amount of pembrolizumab to the patient;

The Recommended Dosage section of the Keytruda Label provides the

recommended dosages of Keytruda, as well as the duration/timing of treatment based on the indication, wherein the indication is directed to cancer confirmed to be MSI-H or dMMR and the patient has received a prior cancer therapy drug to treat the tumor.

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months

* 30-minute intravenous infusion

EX2129, 7-8; *see also id.*, 5.

The Clinical Studies section 14.8 instructs physicians to treat MSI-H/dMMR cancer patients who have progressed on a prior therapy with Keytruda according to indication 1.8. The Clinical Studies section 14.8 also includes clinical trial results showing that the recommended dosages of Keytruda are a therapeutically effective amount among patients with MSI-H/dMRR solid tumors (1.8).

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

Table 51: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)

EX2129, 73-75.

1[c]. 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 pembrolizumab, wherein the reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers.
The Keytruda Label instructs physicians to use Keytruda (pembrolizumab) to treat cancer in a patient, wherein treatment in accordance with the Label results in an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient whose tumor is not MSI-H/dMMR. For example, Clinical Studies Section 14.8 of the Keytruda Label demonstrates that the recommended dosages of Keytruda are therapeutically effective among patients with MSI-H or dMMR solid tumors relevant to Indication 1.8 who have received a prior cancer therapy drug to treat the tumor. **14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer** The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR. EX2129, 73. The Clinical Studies section includes KEYNOTE-016 (NCT01876511), which demonstrated that the efficacy of Keytruda in patients with MSI-H CRC (Arm A) and MSI-H non-CRC (Arm C) as compared to patients with MS-stable CRC (Arm B), who represent a reference patient.

Table 49: MSI-H Trials

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

EX2129, 74.

Table 50: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	KEYTRUDA n=149
Objective Response Rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Duration of Response	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 51: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

EX2129, 75.

Keytruda®'s label dictates the uses for which it may be prescribed by doctors and marketed by Merck, who may only market Keytruda® for its FDA-approved indications. EX2090, ¶¶82-93; EX2072, ¶191. Thus, the method of determining MSI-H status and then using Keytruda® to treat MSI-H cancer patients is coextensive with the claims, and the Board should apply a presumption of nexus.

Merck cannot rebut the presumption of nexus "with argument alone—it ***must*** present evidence." *WBIP*, 829 F.3d at 1329; *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988) (quotation marks omitted) (patent challenger must "adduce evidence" showing objective

indicia "due to extraneous factors other than the patented invention…argument and conjecture are insufficient."). To date, Merck has presented no such evidence.

2. Even Absent a Presumption, JHU's Objective Indicia Has a Nexus to the '974 Claims

In addition to the presumption, there is a "legally and factually sufficient connection" between JHU's objective evidence and the patented invention. *Henny Penny*, 938 F.3d at 1332 (quoting *Demaco*, 851 F.2d at 1392); *Volvo*, 81 F.4th at 1211.

Here, a nexus exists "between the evidence and the merits of the claimed invention." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). The merits of the claimed method of treatment relate to the claims ***as a whole***. Specifically, JHU's objective evidence relates directly and specifically to the merits of the claimed method of treating patients determined to have MSI-H cancer with pembrolizumab. For example, key industry players, including Merck, were skeptical that the claimed method would work. EX2121, 17; EX2183; EX2131; EX2184, 3; EX2072, ¶187; EX2130, ¶50. When JHU revealed the dramatic results of its clinical trial, those results were unexpected and surprising to those in the field. EX2130, ¶¶29-32; EX2121, 6; EX1031, 1, 5. The finding that pembrolizumab worked to treat MSI-H cancer patients satisfied a long-felt, unmet need, saving the lives and futures of patients otherwise likely lost. EX2090,

¶¶28-50, 71-74; EX2121, 7; EX2006. The industry praise for the discovery that the treatment of MSI-H cancer patients with pembrolizumab worked was immediate and overwhelming. EX2130, ¶¶43-46; EX2005, 1-3; EX2006, 1; EX2089, 2, 5; EX2004, 1; EX2060, 2. Finally, as a result, Merck's commercialization of the claimed invention by selling Keytruda® to treat MSI-H cancer patients is a commercial success. EX2191, ¶¶23-44; EX2187; EX2188. Thus, the specific objective indicia here (and discussed in more detail below) are both legally and factually connected to the method claimed in the '974 Patent, and a finding of nexus is appropriate. *See Volvo*, 81 F.4th at 1212.

Critically, the objective evidence here ***cannot*** be tied to the MSR, because, as Merck's expert agreed, nothing in the MSR suggests that the method of treatment would ***work*** to treat MSI-H cancer patients. EX2163, 137:19-23; *see also* EX2072, ¶¶139-140. Therefore, until JHU conducted the clinical trial proposed by the MSR, the results showing that it worked—the results underlying each and every objective indicia—simply were "***not*** known in the prior art." *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017).

Thus, overwhelming evidence demonstrates that even if Merck somehow rebuts JHU's presumption of nexus, each category of objective evidence on its own has a sufficient nexus to the claimed invention. The stronger the showing of

nexus, the greater the weight accorded the objective evidence of non-obviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985). Here, given the strong showing of coextensiveness between the claimed method and the narrowly tailored objective evidence, the Board should afford determinative weight to JHU's objective evidence.

B. Industry Praise

The method of using pembrolizumab (Keytruda®) to treat patients with MSI-H tumors has received overwhelming praise from the oncology community, FDA, and Merck itself. Such industry praise tends to show the invention was not obvious. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc).

1. The Oncology Community Lauded the Results of JHU's Research

The results of JHU's clinical study were nothing short of revolutionary. JHU presented its results at the American Society of Clinical Oncology ("ASCO") 2015 meeting. ASCO "is considered the super bowl of the cancer world," according to Merck's expert, and is "attended by tens of thousands of oncologists and others each year." EX1003, ¶36, n.1; *see also* EX2163, 104:13-105:3 (ASCO is "where everyone is…to hear what's new and exciting"). ASCO selected JHU's abstract as a "late breaking" abstract, even though JHU did not submit it as such.

EX2130, ¶¶43-46. Dr. Le explains that "late breaking" abstracts are "typically reserved for presentations concerning the bigger Phase 3 drug trials that tend to include practice changing data," rather than data from a small trial, like JHU's. EX2130, ¶44. Dr. Le also explained that ASCO does not release late breaking abstracts before the meeting, but rather "treats these presentations somewhat like movie premieres, with fanfare and press conferences the day before the conference to build excitement about the discoveries that will be announced." EX2130, ¶45; EX2135.

Not only did ASCO select JHU's abstract from the thousands of other submitted abstracts, it also selected Dr. Le to give a featured ***presentation*** at the meeting. EX2130, ¶43. As Merck's own expert testified, to be selected to give a presentation like this "would be because of the several thousand papers [it] would be considered one of the main—***one of the most important discoveries of the year*** among all the abstracts that were submitted." EX2163, 107:4-12; *see also id.*, 106:4-107:3. Dr. Le describes how she "delivered [her] presentation to a standing room only crowd of [her] fellow clinicians in a huge conference hall at ASCO" and how when she "revealed [the] data to the audience, you could hear a pin drop in this huge room." EX2130, ¶43.

On the same day as Dr. Le's ASCO presentation, the New England Journal

of Medicine ("NEJM") published the initial results from JHU's clinical trial. EX1031. NEJM is "considered ***the most prestigious journal***," according to Merck's own expert, with "the most prominent papers that are published in medicine." EX2163, 109:12-110:4; *see also* EX2282, 53:5-18; EX2072, ¶¶61, 183; EX2130, ¶47. Indeed, it has the third-highest impact factor of any scientific journal. EX2180, 3-4. Later results of JHU's study were published in Science—another prestigious scientific journal. EX2118.

After FDA's approval of pembrolizumab for the MSI-H tumor agnostic indication, JHU's research supporting its claimed invention received tremendous praise from others in the oncology community. For example, Dr. Jose Baselga, a chief physician at Memorial Sloan Kettering Cancer Center, referred to JHU's study as "absolutely brilliant," and described the durability of the patients' treatment response as "insane." EX2005, 1, 3. The results were widely reported as a "breakthrough" and heralded as a "new frontier in cancer treatment." EX2006, 1. Indeed, researchers from the NIH in 2018 noted that this approval "marks the first tissue-agnostic approval of any drug and thus represents a ***paradigm shift***" in treating cancer patients. EX2089, 2; *see also id.*, 5 (describing approval as "a ***tipping point*** for disease reclassification based on tumor-specific factors," "propel[ling] oncology further toward the goal of precision medicine.").

The approval of pembrolizumab to treat MSI-H cancer completely changed the standard of care for those patients. EX2090, ¶¶75-81. Tellingly, Merck's own expert, Dr. Neugut, changed his standard of care for MSI-H patients because of the "obvious efficacy of the drug in that context." EX2163, 82:21-83:11; *see also* EX2282, 50:4-16. (describing treatment with PD-1 inhibitor as "major boon" for MSI-H patients).

2. FDA Recognized the Impact of JHU's Invention

FDA also recognized the special nature of JHU's invention. Once FDA approved cancer type-agnostic treatment with Keytruda® in response to the presence of the MSI-H biomarker, it issued a press release. In that release, FDA's Oncology Center of Excellence highlighted the groundbreaking nature of JHU's invention: "This is ***an important first*** for the cancer community…Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location." EX2004, 1.

FDA also recognized that it was charting new territory while navigating the approval process because no precedent existed for the tumor-agnostic indication Merck sought based on JHU's work. As Merck's Vice President of Global Clinical Oncology explained, "[w]hen they saw these data, [FDA] were really

helping us to figure out what exactly we would provide for them to be able to sign off on a tissue-agnostic approval, and so it really was a collaborative effort once the data started to come in, and once we had the breakthrough status from them." EX2121, 17. It was a unique "collaboration of academia, FDA, and industry." *Id*.

3. Merck Praised JHU's Innovation

Merck's own sentiments echoed those of the industry and FDA. In concert with Dr. Le's keynote address at ASCO and NEJM's publication of the results, Merck issued a press release highlighting the powerful initial results of JHU's research. Dr. Roger Dansey, Merck's senior vice president of oncology late-stage development, commented that "[t]hese ***exciting results***, while early, suggest that evidence of DNA mismatch repair deficiency may be an important way of identifying tumors that are responsive to checkpoint blockade," and that "these results ***open the door*** for research with KEYTRUDA in colorectal cancer and other tumor types with this potentially clinically meaningful tool." EX2061, 2.

When FDA later approved Merck's application for using Keytruda® to treat MSI-H cancers, Merck similarly celebrated the approval and acknowledged its groundbreaking nature. The President of Merck Research Laboratories, Dr. Roger Perlmutter, stated, "FDA's approval of this ***first-of-its-kind***, tumor-agnostic, indication is further evidence of Merck's commitment to helping people with difficult-to-treat cancers, and to advancing the use of biomarkers to guide clinical

decision-making." EX2060, 2. And Merck openly acknowledged and praised JHU's role in securing that approval. Indeed, Dr. Perlmutter publicly thanked JHU for its inventive work by stating, "[t]his is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and clinicians at Johns Hopkins University ***for their important scientific work***[.]" *Id*.

This widespread praise for JHU's claimed method of treatment from the industry at large, FDA, and Merck is strong evidence of non-obviousness. *See Apple*, 839 F.3d at 1053.

C. Skepticism

"Expressions of disbelief by experts constitute strong evidence of nonobviousness." *Env't Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-98 (Fed. Cir. 1983). Here, neither the industry nor Merck believed in the inventors' hypothesis that MSI-H cancers would respond to pembrolizumab at a rate higher than MSI-stable cancers. EX1002, 270-71; EX2072, ¶187; EX2090, ¶61.

After FDA approval, Merck admitted that the prevailing belief had been that pembrolizumab would ***not*** work even in CRC patients, that it was "very interesting," and that "there have been prior small numbers of colon cancer patients who'd been treated with anti-PD-1 agents, and the responses were pretty much

zero, and so the idea was, early on, that ***it really wasn't going to work*** in colon cancer, as a monotherapy." EX2121, 17. In fact, while Merck agreed to provide pembrolizumab for JHU to run the study, it declined to provide any initial funding for the study. *See* EX2183, 1; EX2131. Merck's unwillingness to fund JHU's limited clinical trial contrasts sharply with Merck's approach to funding other pembrolizumab clinical trials. For tissue-specific cancers, Merck effectively gave its scientists a blank check. EX2051, 15-16. But for JHU's hypothesis about MSI-H cancers, Merck only jumped on the bandwagon to fund follow-on studies after seeing the positive results starting to flow from JHU's initial study. *See* EX2080.

Nor was Merck the only company skeptical of JHU's proposed clinical study and hypothesis. As Dr. Lonberg explains, when he was Senior Vice President, Oncology Discovery Biology at BMS, JHU approached BMS about using BMS's PD-1 checkpoint inhibitor nivolumab and funding JHU's study. EX2072, ¶187. Dr. Lonberg believed at the time that JHU's study was high-risk because there was no reason to expect it would work in ***CRC patients*** when PD-1 inhibitors had failed repeatedly in that population, let alone in MSI-H cancers in general. *Id.* BMS therefore declined to provide either its drug or funding. When the preliminary results of JHU's clinical trial were announced, however, BMS

regretted missing such an opportunity. *Id.*, ¶¶184, 190.

Without funding from either Merck or BMS, JHU ultimately funded its study through Swim Across America, a charity that stages swim meets to fund cancer research.[10] Swim Across America's CEO, Rob Butcher, explained that the organization "like[s] doing high-risk, high-reward projects, the ones where there is a potential for a breakthrough, but where there is just no funding for it. We seek those out." EX2121, 6. As inventor Dr. Diaz explained later, "I had applied for funding to an endless number of organizations," but "I was denied by all of them." EX2184, 3. "Merck finally agreed to give us a sample of Keytruda…but I had to come up with funding for the clinical trials. Enter Swim Across America[.]" *Id*. While the pharmaceutical companies had closed their doors to JHU, a charity took a chance. And the results were "unbelievable!" EX2121, 6.

Even ***after*** JHU had presented its results at ASCO and in NEJM, some members of the oncology community continued to question whether these remarkable results could really be true. For example, when Dr. Le presented the results again, one colleague questioned her data as premature during the public

[10] Notably, just after the FDA approved Keytruda® for the MSI-H indication, Merck gave Swim Across America a $3 million dollar donation. EX2134.

question-and-answer session, arguing Dr. Le needed more data before associating MSI-H status with responsiveness to pembrolizumab. EX2130, ¶50.

This skepticism from Merck, the industry at large, and clinicians further supports the non-obviousness of the claimed method of treatment. *See Env't Designs*, 713 F.2d at 697-98.

D. Long-Felt Need

"Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple*, 839 F.3d at 1056. Before JHU's invention of the claimed treatment method, there was a long-felt but unmet need for therapies that could treat cancer, and in particular, treat advanced or metastatic cancer as well as cancers in patients with MSI-H tumors. EX2090, ¶¶28-50.

For example, before the priority date of the '974 Patent in 2015, the five-year survival rate of patients diagnosed with unresectable metastatic CRC was roughly 9.8%, meaning that after 5 years, ***only 9.8% of patients were still alive***. These patients had a median overall survival (OS) of between 15 and 20 months—***less than 2 years***. EX2090, ¶42. In patients who had failed their first and second line of therapies, the outlook was even worse, with a median survival of only 6-7 months. EX2090, ¶¶47-49. Comparatively, the median survival in patients treated

with best supportive care—i.e., "comfort care"—was 4.5 months. *Id*., ¶49; *see also* EX2130, ¶28. Thus, in patients who had failed two prior therapies, the ***best*** therapies available before the invention only increased life expectancy by ***1-2 months***, often with the harsh side effects of chemotherapy. EX2090, ¶49. Yet even these meager gains were significant to the oncology community, and these chemotherapeutics were "quickly adopted into practice." *Id.*

As these numbers suggest, with the ***best*** five-year overall survival rate less than 10%, being diagnosed with advanced CRC was akin to a death sentence in 2015. EX2090, ¶¶42, 45. As Merck's expert, Dr. Neugut, testified, "[c]uring a patient with a metastatic solid tumor, it's a very rare phenomenon." EX2163, 181:15-25. Prior to 2015, survival expectancy for other types of advanced cancer was also grim, with many cancers having Stage IV five-year survival rates of 2-10%. EX2090, ¶36.

But statistics show only one facet of long-felt, unmet need; the cancer patients suffering and in desperate need of new therapies show the true human face of this unmet need. The journeys of some of these patients before being treated with the claimed method have been documented. For example, Dr. Goldberg has told of meeting his 26-year-old patient, Beth Carner, who was dying of advanced colorectal cancer when they met. EX2121, 7; EX2090, ¶71. After treating Beth

with pembrolizumab, Dr. Goldberg described "[l]iterally, I saw for the first time in my career, the Lazarus effect," continuing, "I treated her, and within a couple of months she was completely normal…and she went back to dancing—from dead to dancing." EX2121, 7; EX2090, ¶71; *see also* EX2006 (describing response of CRC patient Stefanie Joho treated in the JHU clinical trial)

The New York Times highlighted the successful treatment of MSI-H non-CRC patients with pembrolizumab, describing how "[t]he 86 cancer patients were a disparate group, with tumors of the pancreas, prostate, uterus or bone." EX2005, 1; EX2090, ¶73. "One woman had a cancer so rare there were no tested treatments." EX2005, 1. That patient was Adrienne Skinner, who "had an extraordinarily rare and deadly cancer, ampullary cancer, that arises at the end of the bile duct," with a "dire" prognosis. *Id.*, 3. After being scheduled for a surgery to remove part of her pancreas, small intestine, and gall bladder, her tumor was discovered to be MSI-H, and she was treated in JHU's clinical study instead of surgery. Three months after her first dose of pembrolizumab, Adrienne's tumor was gone. *Id.*, 4. Her treatment was so successful Adrienne's doctor told her, "[i]f someone hadn't told me you have ampullary cancer, I would not have known." *Id.*

Without JHU's claimed method of determining MSI-H status and treating MSI-H cancer patients with pembrolizumab, Beth, Stefanie, Adrienne, and many,

many others suffering with MSI-H cancer would have succumbed to their illness. EX2090, ¶74.

During the approval process, Merck repeatedly told FDA that MSI-H cancers suffered from an unmet medical need for effective treatments. For example, Merck told FDA that [redacted] EX2173, 17; *see also* EX2170, 5 [redacted] During its approval process, Merck also explained to FDA that [redacted] EX2171, 18. Further, there was [redacted] *Id.* In seeking a breakthrough therapy designation for MSI-H cancers, Merck asserted that [redacted]

[redacted] EX2172, 15; *see also* EX2170, 5; EX2171, 11, 18-20, 30, 32, 36-37; EX2172, 29; EX2167, 8-9; EX2173, 17; EX2174, 4-5. As the foregoing makes clear, before this dispute, Merck recognized and understood the long felt unmet medical need to find better treatments for MSI-H cancers but is now telling the Board a different story.

The Board should not allow Merck to do an about-face regarding what it previously told FDA about treating MSI-H patients in order to achieve expedited approval. *See, e.g.*, 87 Fed. Reg. 45764 (July 29, 2022) (requiring disclosure of inconsistent statements to PTO and FDA regardless of timing). This post-priority evidence of Merck's statements can "be used to show the state of the art existing on the date of the application in question." *In re Koller*, 613 F.2d 819, 824 (C.C.P.A. 1980); *see also Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017) (citing *In re Koller*). And because the FDA submission with Merck's statement was outside the context of a disputed proceeding, it necessarily has a stronger hallmark of truth than its self-serving attorney arguments in this proceeding. *Cf. Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005).

Based on Merck's representations, FDA recognized the long-felt, unmet need in the MSI-H cancer population. FDA has several programs "intended to

facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition," including breakthrough therapy designation, priority review, and accelerated approval. EX2186, 5. These programs "are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks." *Id.*; EX2090, ¶¶65-67. FDA specifically defines "unmet medical need" as "a condition whose treatment or diagnosis is not addressed adequately by available therapy." EX2186, 8. Recognizing the unmet need, to expedite MSI-H cancer patients' access to pembrolizumab, FDA granted Keytruda® breakthrough therapy designation, priority review, and accelerated approval because [redacted] EX2182, 2; *see also* EX2062; EX2133; EX2205. This was in addition to finding that [redacted] EX2181, 2. Merck's expert, Dr. Neugut, explained that, under a normal FDA approval timeline, "the number of patients who are not going

to be treated and suffer during that time is certainly in the hundreds," and for a drug like pembrolizumab, "which has such a dramatic benefit, would really be unethical to – or it would be detrimental to not fast track it and do something more rapidly." EX2163, 183:19-184:8. In fact, "[i]t's not done except in such dramatic circumstances." *Id*., 184:8-9.

FDA approval of Keytruda's MSI-H tumor agnostic indication led to dramatic change in the way oncologists treated their patients. EX2090, ¶¶75-81. Prior to the 2017 approval, clinical oncologists rarely ordered MSI-H testing for their patients because it was not a biomarker that was known to be of use for determining treatment choices in patients with advanced cancers. EX2090, ¶75; EX2282, 46:9-49:6, 100:22-105:23. MSI-H testing was generally only used in limited circumstances, such as determining if a patient had Lynch syndrome, an inherited defect in DNA mismatch repair, or assessing prognosis for chemotherapy in Stage II colon cancer. EX2090, ¶¶75-78; EX2282, 45:5-24, 48:19-49:6, 60:9-61:7, 105:8-23. After the 2017 tumor agnostic approval, the National Comprehensive Cancer Network (NCCN) added the recommendation to test for MSI-H to multiple cancer guidelines. EX2090, ¶¶79-80. GI oncologists, for example, went from testing MSI-H in only certain CRC patients to routinely testing patients in all 11 types of cancer they manage based on the prospect of

complete and potentially long-term responses in MSI-H patients treated with pembrolizumab. EX2090, ¶81; EX2282, 40:2-14 ("No patient gets by me without having their MSI tested"); *id.*, 62:18-63:9.

The significant evidence of long-felt, unmet need here weighs in favor of non-obviousness of the claimed method of treatment. *Apple*, 839 F.3d at 1056; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1082-83 (Fed. Cir. 2012).

E. Unexpected Results

"Unexpected results are useful to show the improved properties provided by the claimed [inventions] are much greater than would have been predicted." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quotation marks omitted). No one expected JHU's method of treatment embodied in the claimed invention to succeed. Rather, "[t]he indication—and the trial—resulted from a hunch." EX2121, 4; *see also id.*, 5.

Cancer treatment is inherently unpredictable. The unexpectedness of the results of JHU's clinical study highlight this unpredictability. Indeed, the only studies that had tested pembrolizumab or other PD-1 inhibitors in CRC patients had failed resoundingly, with ***97% and 95% failure rates***. *See supra* §VI.C.3.a. Moreover, before JHU's clinical study, no studies indicated that treatment of other types of MSI-H cancers with PD-1 inhibitors would be successful or that MSI-H

would be a useful biomarker for identifying patients who would respond to treatment with pembrolizumab regardless of cancer type. EX2090, ¶¶52-58.

Even JHU's investigators were skeptical at first. Dr. Pardoll told his co-inventor "that checkpoint inhibitors [like pembrolizumab] didn't seem to be working in colorectal cancer." EX2121, 6. The results therefore surpassed any expectation even the inventors themselves had. EX2130, ¶¶29-32. As co-inventor Dr. Diaz explained, "we start[ed] enrolling patients, and these patients are doing miraculously well"; their "tumors are melting away." EX2121, 6. Put simply, in oncology, "[t]hings don't work a lot," and "[w]hen something works, it's unbelievable!" *Id.*

The powerful results from JHU's research supporting its claimed invention were not just anecdotal; they were borne out by robust and surprising data. The preliminary results reported in the NEJM and in the specification of the '974 Patent showed significant promise in MSI-H (i.e., MMR-deficient) patients:

	MMR-deficient[18] CRC (n = 10)	**MMR-proficient CRC (n = 18)**	**MMR-deficient non-CRC (n = 7)**
Complete Response (%)	0 (0)	0 (0)	1 (14)
Partial Response (%)	4 (40)	0 (0)	4 (57)
Stable Disease (Week 12) (%)	5 (50)	2 (11)	0 (0)
Progressive Disease (%)	1 (10)	11 (61)	2 (29)
Not Evaluable (%)	0 (0)	5 (28)	0 (0)
[redacted]			
Immune-related objective response rate (irORR) (95% CI)	40 (12-74)	0 (0-19)	71 (29-96)
Immune-related disease control rate (95% CI)	90 (55-100)	11 (1-35)	71 (29-96)
Immune-related PFS at 20 weeks (95% CI)	78 (40-97)	11 (1-35)	67 (22-96)

EX1001, Fig. 11 (cleaned up); *see also* EX1031, 1, 5. Notably, 90% of MMR-deficient (MSI-H) CRC patients and 71% of MMR-deficient (MSI-H) non-CRC patients showed either a partial response or stable disease at week 12, while only 11% of MMR-proficient CRC patients had stable disease at week 12; the rest of the patients' tumors had progressed. *Id.* Likewise, 78% of MMR-deficient CRC patients and 67% of MMR-deficient non-CRC patients had progression free survival (PFS) at 20 weeks, compared to only 11% of MMR-proficient CRC patients. In fact, the MMR-deficient CRC patients had not even reached the median progression-free survival or overall survival at the time of this analysis.

EX1001, Figs. 2A-B. Similarly, the MMR-deficient non-CRC patients did not reach median progression-free survival until 6 months and had not reached median overall survival at 12 months. *Id.*, Figs. 2C-D. In contrast, the MMR-proficient CRC patients, had a progression free survival of only 2.2 months, and a median overall survival of 5.0 months. EX1001, 4:29-32.

For perspective, as described above, in 2015 an increased life expectancy of only ***1-2 months*** had been significant enough in patients who had failed two prior therapies to be "quickly adopted into practice." EX2090, ¶49; *see* §VII.D, *supra*. Here, the median follow-up time for the MMR-deficient CRC patients was 36 weeks—9 months—and still median progression free survival had not been met, in a patient population confirmed to have failed at least two prior therapies. Put differently, not enough patients had their tumors progress yet—***after 9 months***—to be able to calculate a median. EX1031, 1, 5; *see also* EX2130, ¶¶29-31; EX2090, ¶62. Even after JHU published the full results of its study in Science, median progression-free survival and overall survival had ***still*** not been reached in both CRC and non-CRC MMR-deficient patients, after a median follow-up time of ***12.5 months***. EX2118, 2. As even Merck's expert, Dr. Neugut, admits—"the survival benefit is impressive[.]" EX2163, 182:25-183:9; *see also id.*, 181:17-25 (comparing curing 7 patients over a 40-year career treating thousands of patients to

curing "another seven in the last five years" with Keytruda® in MSI-H CRC patients); *id.*, 178:4-7. Indeed, the 5-year overall survival for MSI-H CRC patients in the JHU study turned out to be an astounding ***57.5%***, and the 5-year overall survival for MSI-H non-CRC patients was an equally astounding ***50.3%***. EX2090, ¶45; EX2130, ¶30.

The results of JHU's clinical trial were so unbelievable and unexpected that they caught Merck off guard. Surely, if Merck had anticipated the success of JHU's clinical trial, or truly believed the results were going to be obvious, then Merck would have either sponsored JHU's clinical trial, or initiated its own clinical trial sooner, so that Merck could take the quickest path to FDA approval. It is common sense that the faster FDA approves an indication, the sooner a company can profit from sales under that indication. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005) ("the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art."). Indeed, prior to the JHU study, Merck rushed to get as many tissue-specific indications approved as quickly as possible. *See* EX2051, 15-16 ("Former Merck executive Reicin recalls presenting [Merck research chief] Perlmutter with a prioritized list of potential Keytruda clinical studies and asking him, based on resources, where to draw the

line. 'There is no line,' Perlmutter reportedly responded. 'Do them all.'").

But Merck ***declined*** to do a MSI-H cancer study. Instead, JHU conducted its study as an Investigator-Initiated Clinical Trial ("IICT"), meaning that it was investigators at JHU, an academic institution, and ***not*** Merck, running the trial. EX2130, ¶¶20, 37. It is quite uncommon for IICTs to be used to support FDA submissions. EX2130, ¶37. Typically, if an IICT yields promising results, the pharmaceutical company will run its own follow-up trial, so that the data is collected in a format suitable for submission to FDA. *Id.* Here, Merck was in such a rush to get approval after seeing JHU's data that, instead of completing its own follow-on trial first, Merck collaborated with JHU to collect JHU's data and format it for FDA submission—a non-trivial task. EX2130, ¶¶35-38; EX2169, 3.

Finally, to the extent Merck argues that the fact that FDA had approved pembrolizumab for treating one other specific cancer prior to the Critical Date means a POSA would have expected pembrolizumab to work in a completely different patient population independent of cancer type—MSI-H cancer patients—Merck is wrong, for the reasons discussed in §VI.C.2, *supra*.

The extensive evidence of unexpected results further supports the non-obviousness of the claimed method of treatment. *Leo Pharm.*, 726 F.3d at 1358. *See also* EX2072, ¶¶188-190.

F. Commercial Success

The Federal Circuit has repeatedly recognized commercial success as highly relevant objective evidence of non-obviousness. *See Merck*, 395 F.3d at 1376. "[A] patentee can demonstrate commercial success" with "significant sales in a relevant market," *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021) (quotation marks omitted), and by growth in the number of users of the patented product, including increase in sales and annual growth rate in the relevant industry, *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000). "[S]ales figures alone are also evidence of commercial success." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999). Under these and other metrics, Keytruda®'s use in MSI-H cancers has been and is a commercial success. EX2191, ¶¶8-46.

Since its approval for treatment in MSI-H or dMMR patients, Keytruda® sales have been large and consistently growing. EX2191, ¶¶23-30. To start, Keytruda® overall sales grew significantly from [redacted] in 2015 to [redacted] in 2023, totaling over [redacted]:

[redacted]

EX2191, Appendix 2. Additionally, the timing of Merck's approval for Keytruda®'s use in MSI-H patients in May 2017 coincided with an apparent inflection point in Keytruda® sales trajectory. EX2191, ¶¶24-26.

As an example, sales of Keytruda® for the non-first-line treatment of MSI-H cancer[11] also experienced consistent and rapid growth since FDA approval for

[11] After 2020, MSI-H CRC could be treated as both a first- and non-first-line therapy, the latter being covered by the method claimed in the '974 Patent and the former by the method claimed in JHU's '393, '287, and '291 Patents. *See* IPR2024-00240; IPR2024-00647.

JHU's patented method of use, [redacted] from 2017 to 2023:

[redacted]

Id., Appendix 5; *see also id.*, ¶¶27-32. This growth is strong compared to competitor products in the market. *Id*., ¶¶33-34. These sales and growth show the commercial success of JHU's claimed invention. *See Ruiz*, 234 F.3d at 668; *Tec Air*, 192 F.3d at 1361.

Keytruda® sales for treatment of MSI-H cancer indications could not have been made ***but for*** JHU's invention of the claimed method. EX2090, ¶¶82-93; *see also* EX2191, ¶¶35-44. That is because FDA oversees the marketing Merck is permitted to do in the United States by governing what Merck puts on the Keytruda® label (EX2191, ¶39), and Merck was only able to get FDA approval to put this indication on its label by relying on JHU's clinical study data. Indeed,

earlier versions of Keytruda®'s label do not contain an indication for MSI-H cancers, and so Merck was not previously permitted to market Keytruda® for JHU's patented treatment. EX2090, ¶¶82-83; EX1055; EX2125; EX2128.

Moreover, even if other factors contributed in some way to the sales for treating MSI-H cancer patients, "[i]t is not necessary…that the patented invention be ***solely*** responsible for the commercial success," for nexus to exist; rather, it can "be given weight appropriate to the evidence, along with other pertinent factors." *Cont'l Can Co. USA*, 948 F.2d at 1273; *see also Fox Factory, Inc. v. SRAM, LLC*, 813 F. App'x 539, 543 (Fed. Cir. 2020). Thus, the Federal Circuit authorizes the Board to credit Keytruda®'s commercial success in MSI-H cancer patients, even if it finds the patented method not "solely responsible" for it.

VIII. CONCLUSION

For these reasons, JHU respectfully requests a final written decision confirming patentability of the Challenged Claims.

Respectfully submitted,

Dated: January 13, 2025

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CERTIFICATION UNDER 37 CFR § 42.24(d)

The undersigned hereby certifies that the word count for the foregoing Patent Owner Response totals 17,440, which is less than the 17,500 authorized by the Board in Paper 19 dated December 9, 2024.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4), the undersigned certifies that on January 13, 2025, a complete and entire copy of this Patent Owner's Response was provided by email to the Petitioner by serving the correspondence address of record as follows:

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