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 IPR2024-00648
Patent 11,643,462 B2

PATENT OWNER'S RESPONSE

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LIST OF EXHIBITS

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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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2124	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (May 23, 2017)

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2125	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Oct. 2015)
2126	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Aug. 2016)
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2130	Declaration of Dung Le, M.D.
2131	Investigator Initiated Clinical Trial Research Agreement between The Johns Hopkins University and Merck Sharp & Dohme Corp., dated August 14, 2013
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2160	Plaintiff Merck Sharp & Dohme LLC's Opening Brief Regarding Claim Construction, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, Case No. 1-22-cv-03059-JRR, D.I. 82 (D. Md. May 1, 2024)
2161	The Johns Hopkins University's Opening Claim Construction Brief, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, Case No. 1-22-cv-03059-JRR, D.I. 81 (D. Md. May 1, 2024)
2162	Plaintiff Merck Sharp & Dohme LLC's Responsive Brief Regarding Claim Construction, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, Case No. 1-22-cv-03059-JRR, D.I. 107 (D. Md. May 1, 2024)
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2167	Highly Confidential Attorney Eyes Only Document 1 – Protective Order Material
2168	Highly Confidential Attorney Eyes Only Document 2 – Protective Order Material
2169	Highly Confidential Attorney Eyes Only Document 4 – Protective Order Material
2170	Highly Confidential Attorney Eyes Only Document 5 – Protective Order Material
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2176	Robin Marantz Henig, Could Immunotherapy Lead the Way to Fighting Cancer?, Smithsonian Magazine (April 2018), https://www.smithsonianmag.com/innovation/immunotherapy-lead-way-fighting-cancer-180968392/
2177	Exhibit 6, The Johns Hopkins University's Infringement of U.S. Patent No. 11,643,462 by KEYTRUDA claim chart, *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, Case No. 1-22-cv-03059-JRR

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2178	Marques et al., *Tumor mutational burden in colorectal cancer: Implications for treatment*, Crit. Rev. Oncol. Hematol. (Apr. 12, 2024)
2179	Le et al., *Phase II Open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164*, J. Clin. Oncol. (38:1(1-19) (2019)
2180	Anagha Nair, High Impact Journals 2024 – Key to deciding the right journal?, Enago Academy (Feb. 19, 2024), https://www.enago.com/academy/top-high-impact-factor-journals/
2181	Highly Confidential Attorney Eyes Only Document 3 – Protective Order Material
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2183	Email correspondence from Luis Diaz to Amy Meister and Mr. Robert Iannone dated December 27, 2012, production document Bates stamped JHU_MERCK00027065
2184	Breakthroughs in Immunotherapy, Swim Across America, https://www.swimacrossamerica.org/site/SPageNavigator/Breakthroughs_35.html (last accessed Sept. 26, 2024)
2185	RESERVED
2186	Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, U.S. Dept. of HHS, FDA (May 2014)
2187-2188	RESERVED
2189	Email correspondence from Preston K. Ratliff to Nicholas Stephens and Casey Kraning dated August 20, 2024
2190-2204	RESERVED

Exhibit Number	Description
2205	Accelerated Approval Letter to Nahid Latif of Merck Sharp and Dohme, Corp. from Patricia Keegan of the Department of Health and Human Services dated May 23, 2017 (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125514Orig1s014ltr.pdf)
2206-2250	RESERVED
2251	Siegel et al., *Cancer Statistics, 2015*, CA Cancer J. Clin., 65(1):5-29 (Jan-Feb 2017)
2252	Noone et al. (eds). *SEER Cancer Statistics Review*, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018
2253	Canadian Cancer Society, *Survival statistics for small intestine cancer*, https://cancer.ca/en/cancer-information/cancer-types/small-intestine/prognosis-and-survival/survival-statistics
2254	American Cancer Society, *Survival rates for bile duct cancer*, https://www.cancer.org/cancer/types/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html
2255	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer*, Version 4.2024 (August 12, 2024)
2256	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pancreatic Adenocarcinoma*, Version 3.2024 (August 2, 2024)
2257	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatocellular Carcinoma*

Exhibit Number	Description
2258	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Biliary Tract Cancers*
2259	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Small Bowel Adenocarcinoma*, Version 1.2025 (December 4, 2024)
2260	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ampullary Adenocarcinoma*, Version 2.2024 (August 2, 2024)
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2263	RESERVED
2264	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms*, Version 3.2024 (September 20, 2024)
2265	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ovarian Cancer*, Version 3.2024 (July 15, 2024)
2266	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Cervical Cancer*, Version 4.2024 (September 24, 2024)
2267	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors*

Exhibit Number	Description
2268	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Thyroid Carcinoma*
2269	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer*, Version 6.2024 (November 11, 2024)
2270	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers*, Version 4.2024 (July 30, 2024)
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2272	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers*, Version 1.2025 (November 26, 2024)
2273	Highly Confidential Attorney Eyes Only – Protective Order Material: May 9, 2013 Submission
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2275	Highly Confidential Attorney Eyes Only – Protective Order Material: July 15, 2013 Submission
2276	Boland. *Henry T. Lynch, MD (January 4, 1928–June 2, 2019)*, Gastroenterol., 157(4):905-906
2277	Aaltonen et al., *Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients*, Cancer Res., 54:1645–1648 (1994)

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2278	Aarnio et al., *Cancer risk in mutation carriers of DNA-mismatch repair genes*, Int. J. Cancer 81:214–218 (1999)
2279	Chen et al., *Small bowel adenocarcinoma*, Clin. Colon Rectal. Surg. 31:267-277 (2018)
2280	Center for Drug Evaluation and Research: Manual of Policies and Procedures, Office of New Drugs, "Review Designation Policy: Priority (P) and Standard (S)," https://www.fda.gov/media/72723/download
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2282	Stenographic Deposition of Alfred I. Neugut, M.D., Ph.D., MPH taken on January 6, 2025
2283-2299	RESERVED
2300	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (March 2022)
2301	U.S. Patent No. 11,591,393
2302	Excerpts from Prosecution History of U.S. Patent No. 11,591,393
2303	Bonneville et al., *Landscape of Microsatellite Instability Across 39 Cancer Types*, American Society of Clinical Oncology ascopubs.org May 14, 2024
2304	Akagi et al. *Real-world data on microsatellite instability status in various unresectable or metastatic solid tumors*, Cancer Science (2021)
2305	FDA Approves Merck's Keytruda® Pembrolizumab for Patients With MSI-H/dMMR Advanced Endometrial Carcinoma, Who Have Disease Progression Following Prior Systemic Therapy in Any Setting and Are Not Candidates for Curative Surgery or Radiation (March 21, 2022)
2306-2400	RESERVED

Exhibit Number	Description
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
2404-2499	RESERVED
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
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 a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, the method comprising:
	[1a]	testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
	[1b]	in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.
2	[2]	The method of claim 1, wherein the biological sample is tumor tissue from the patient.
3	[3]	The method of claim 1, wherein the biological sample is a body fluid from the patient.
4	[4]	The method of claim 1, wherein the solid tumor is microsatellite instability high.
5	[5]	The method of claim 1, wherein the solid tumor is DNA mismatch repair deficient.
6	[6]	The method of claim 1, wherein the solid tumor is metastatic.
7	[7]	The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously.

Claim	Identifier	Claim Language
8	[8]	The method of claim 1, wherein the step of testing or having tested comprises assessing one or more of: BAT-25, BAT-26, MONO-27, NR-21 and NR-24.
9	[9]	The method of claim 1, wherein the solid tumor is endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer or cholangiocarcinoma.
10	[10]	The method of claim 1, wherein the solid tumor is pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer.
11	[11]	A method for prescribing a treatment for a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior cancer treatment, the method comprising:
	[11a]	testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
	[11b]	in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, prescribing treatment with a therapeutically effective amount of pembrolizumab for the patient determined to have a tumor that is microsatellite instability high or DNA mismatch repair deficient.

Claim	Identifier	Claim Language
12	[12]	The method of claim 11, wherein the biological sample is tumor tissue from the patient.
13	[13]	The method of claim 11, wherein the biological sample is a body fluid from the patient.
14	[14]	The method of claim 11, wherein the solid tumor is microsatellite instability high.
15	[15]	The method of claim 11, wherein the solid tumor is DNA mismatch repair deficient.
16	[16]	The method of claim 11, wherein the solid tumor is metastatic.
17	[17]	The method of claim 11, wherein the pembrolizumab is administered to the patient intravenously.
18	[18]	The method of claim 11, wherein the step of testing or having tested comprises assessing one or more of : BAT-25, BAT-26, MONO-27, NR-21 and NR-24.
19	[19]	The method of claim 11, wherein the solid tumor is endometrial cancer, small bowel cancer, gastric cancer, or ampullary cancer or cholangiocarcinoma.
20	[20]	The method of claim 11, wherein the solid tumor is pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer.
21	[21]	The method of claim 1, wherein the solid tumor is endometrial cancer.
22	[22]	The method of claim 21, wherein the endometrial cancer is microsatellite instability high.
23	[23]	The method of claim 21, wherein the endometrial cancer is DNA mismatch repair deficient.
24	[24]	The method of claim 21, wherein the solid tumor is metastatic endometrial cancer.

Claim	Identifier	Claim Language
25	[25]	The method of claim 1 wherein the solid tumor is gastric cancer.
26	[26]	The method of claim 25, wherein the gastric cancer is microsatellite instability high.
27	[27]	The method of claim 25, wherein the gastric cancer is DNA mismatch repair deficient.
28	[28]	The method of claim 25, wherein the solid tumor is metastatic gastric cancer.
29	[29]	The method of claim 9, wherein the solid tumor is small bowel cancer.
30	[30]	The method of claim 29, wherein the solid tumor is metastatic small bowel cancer.

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 CRC, 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 '462 Patent, which claims the first FDA-approved method of treating cancer across sixteen cancer types. 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] 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 a 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 '462 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 '462 Patent claims. For example, the MSR does not disclose the Claimed MSI-H Cancers.[2] Nor could it. At the

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

[2] The claims of the '462 Patent cover a method of treating patients having MSI-H solid tumors selected from a group of endometrial cancer, small bowel cancer,

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 "a solid tumor…that has progressed following at least one prior treatment." EX1001, claims 1, 11.

To reach just the independent claims of the '462 Patent, Merck must plug each one of these holes in the MSR. Merck tries to do this by repeatedly resorting to inherency. 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 '462 Patent.

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

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gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer. These cancers are referred to collectively herein as the "Claimed MSI-H Cancers."

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

Merck's fallback 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 in the Claimed MSI-H Cancers has changed the standard of care and saved lives.

II. '462 PATENT OVERVIEW

The '462 Patent claims a novel method of treating MSI-H or DNA mismatch repair deficient ("dMMR")[3] cancer in a patient having a Claimed MSI-H Cancer that has progressed following prior treatment (EX1001, claims 1, 11). *See* EX2072, ¶¶59-66.

The '462 Patent's priority date is July 10, 2015.[4] 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 IN THE ART("POSA")

JHU contends that a POSA on or about the claimed priority date of the '462 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, (ii) conducting genetics research relating to oncology, or (iii) developing and

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[3] 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.

[4] Contrary to Merck's convoluted assertions in §VI.A of the Petition, JHU is not attempting to claim priority to an undefined "First Provisional."

conducting clinical trials on novel cancer therapies in those fields." EX2072, ¶¶31-32, 91-99.

IV. CLAIM CONSTRUCTION

In its DI, the Board *sua sponte* construed the term "in response to" to mean "after." DI, 22. The Board's initial construction disregards the critical ***causal*** relationship between the "determining" and "treating"/"prescribing" steps in the claims. The express causal relationship between these steps establishes that ***only*** patients determined to be MSI-H are treated. This critical aspect of the claimed invention is omitted by the Board's construction.

JHU respectfully requests the Board modify its construction of "in response to" to mean "in reaction to." This construction reflects the intrinsic and extrinsic evidence, which consistently support the claimed causal relationship.

A. JHU's Proposed Construction is Supported By the Plain Meaning of the Claims and the Intrinsic Evidence

The Board's construction conflicts with the plain meaning of the claims and the intrinsic record. JHU's proposed construction reflects the causal relationship between the "determining" and "treating"/"prescribing" requirements of claims 1 and 11 made explicit by the conjunctive claim term "in response to." The claimed "treating"/"prescribing" step is performed (and only performed) in response to (as a reaction to) determining the cancer is MSI-H.

First, had the inventors intended the claimed invention to encompass treatment occurring merely "after" a determination of the patient's MSI-H status, they would have used "after" or some other word simply connoting a sequence of events. The inventors knew how to use "after" to define the scope of their invention and did so in several dependent claims of U.S. Patent No. 11,591,393 ("the '393 Patent")—a related patent in the same patent family. *See* EX2301, claims 7, 20, 27 (claiming the cancer "had progressed after" the patient received a different cancer therapy). These claims each depend from claims reciting "in response to." EX2301, claims 1, 14. Thus, within the'462 Patent's family, the word "after" appears in some of the same claims as "in response to." Different words in the same claim are presumed to have different meanings. *Chicago Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC*, 677 F.3d 1361, 1369 (Fed. Cir. 2012). Construing "in response to" to mean "after" conflicts with both the term's plain meaning and this fundamental claim construction tenet.

Second, the '462 Patent's specification is consistent with the plain meaning of "in response to." The '462 Patent explains that when "[m]icrosatellite ***instability*** is determined in the sample," "[t]he tumor is identified as a ***good*** candidate for treatment with an immune checkpoint inhibitory antibody." EX1001, 3:57-60. The specification also explains that when "[m]icrosatellite ***stability*** in the sample is determined," "[t]he tumor is identified as a ***bad*** candidate for treatment

with an immune checkpoint inhibitory antibody." *Id.*, 3:64-67. A POSA would have understood from the words of the claims and from the '462 Patent's teaching regarding good/bad candidates that "in response to" describes administering the claimed treatment only as ***a reaction*** to the determination that the patient's cancer is MSI-H. The contrary view advanced by the Board improperly renders meaningless the "in response to" step of the claim. As initially constructed by the Board, the claims would cover treatment administered to MSI-H patients for any reason or no reason at all—even accidental treatment would be covered. That reading is inconsistent with the specification.

Third, the Board's initial construction is inconsistent with the meaning applied to the "in response to" term by the Examiner. Less than a week after allowing '462 Patent's claims (EX1002, 22), the Examiner allowed the claims of the '393 Patent. EX2302, 1. In allowing the '393 Patent's claims, the Examiner used the shorthand "based on" to express the plain meaning of "in response to." *See* EX2302, 8. "Based on" does not mean "after." It requires the claimed causal relationship. The Examiner understood "in response to" as requiring this causal relationship, and there is no evidence that the Examiner treated the term "in response to" differently during the prosecution of the related '393 and '462 Patents.

B. Extrinsic Evidence Supports JHU's Proposed Construction

The extrinsic evidence also shows the plain meaning of "in response to" is "in reaction to." To begin, the causal relationship between the "determining" and "treating"/"prescribing" limitations is so clearly expressed by the words of the claims that Merck did not propose "in response to" be construed. Pet., 10-11. The Parties, in fact, shared the view before the District Court that the claim required a causal relationship between the "determining" and "treating"/"prescribing" limitations. Both JHU and Merck relied on the words of the claims, and the Examiner's statement during prosecution, to support their proposed causal constructions before the District Court. *See* EX2161, 19; EX2162, 22-23. Merck's only dispute was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." EX2160, 30.

As further support, contemporaneous dictionaries define the non-technical word "response" to mean "a reaction to something," "the act of responding; reply or reaction." EX2154, 4; EX2155, 3; *see also* EX2153, 4; EX2156, 4-5; EX2157, 4; EX2158, 8; EX2159, 5. Thus, the claimed treating/prescribing step can only occur in reaction to determining that the patient is MSI-H.

The experts here also agree that "in response to" requires causality. Merck's expert, Dr. Neugut, understood that "in response to" means what it says. Indeed, it

"[n]ever entered [his] mind that the phrase 'in response to' would have a meaning different than what it says." EX2163, 70:25-71:2. JHU's expert likewise agrees. According to Dr. Lonberg, the plain meaning of treating/prescribing "in response to" is treating/prescribing "in reaction to" a determination that the patient's tumor is MSI-H. EX2072, ¶¶100-101.

Finally, the Federal Circuit has adopted JHU's plain meaning construction of "in response to" in another case. *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011) ("'In response to' connotes that the second event occur ***in reaction to*** the first event."). Nothing about the facts or context of *American Calcar* suggests the construction of the plain English phrase "in response to" should mean something different here.

V. CLAIMS 1-30 ARE PATENTABLE OVER ANTICIPATION GROUND 1

A. The MSR Cannot Anticipate Because It Does Not Expressly or Inherently Disclose the Claimed MSI-H Cancers

The MSR describes three experimental arms. EX1005, 4. Two arms are for CRC patients. *Id.* The third arm states it is for "MSI Positive Non-Colorectal Cancer." *Id.* Other than specifying the participant's cancer must be non-colorectal, the MSR provides no details or guidance about cancer types to be included in that third arm. EX2130, ¶12. It does not list *any* of the Claimed MSI-H Cancers, whether the few cherrypicked by Merck in its petition (endometrial,

small bowel cancer, and gastric cancer (e.g., Pet. 17)) or the other thirteen cancers claimed in the ’462 Patent. Other than colorectal, the MSR lists no particular cancer types at all. *See* 2282, 85:11-87:1. By its plain terms, the third arm was open to all-comers with any MSI-H cancer other than CRC. It was meant to explore the inventors’ hypothesis that MSI-H as a biomarker could predict efficacy of anti-PD-1 therapy across cancer types. EX2130, ¶¶10-11.

The MSR’s third arm—directed to the genus of MSI positive non-CRC—thus does not anticipate any of the sixteen individual species that make up the Claimed MSI-H Cancers. “It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *see also Metabolite Lab’ys, Inc. v. Lab’y Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (“A prior art reference that discloses a genus…does not inherently disclose all species within that broad category.”). A genus only anticipates in the limited circumstance where the genus is so small that a POSA would immediately recognize all its species. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008) (no anticipation “when the description of the genus would not lead a person of ordinary skill to a small recognizable class with common properties” (cleaned up)); *VirnetX Inc. v. Apple Inc.*, 665 F. App’x 880, 887 (Fed. Cir. 2016).

Whether a genus is small enough for disclosure of the genus to disclose the specific species within that genus is a factual prerequisite to finding anticipation. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001) (vacating summary judgment and remanding for further factual development regarding the size of the genus disclosed in the prior art). The Petition does not address this prerequisite question. *See generally* Pet. 17-18. It proffers no evidence of the number of species that comprise the genus of "MSI Positive Non-Colorectal Cancers" and does not contend that a POSA would immediately appreciate the genus's full scope. Instead, the Petition addresses a separate, irrelevant question: whether MSI-H was known to occur in Merck's hand-picked set of cancers. *See* Pet. 17 (discussing just three of the sixteen Claimed MSI-H Cancers: endometrial, small bowel, and gastric). In doing so, the Petition also overlooks the substantial majority of Claimed MSI-H Cancers and ignores unclaimed non-CRC MSI-H cancers. EX2072, ¶103. The Petition also overstates the extent of a POSA's understanding of MSI-H in those cancers. Of the three cancer types addressed by the petition, only *one* (endometrial cancer) was tested for MSI-H as a part of standard care at the time of the invention—and it was only tested to identify familial susceptibility (not in relationship to treatment). EX2090, ¶79. In fact, Dr. Le had a hard time recruiting MSI-H patients for the non-CRC arm of the clinical trial because MSI-H testing was not routinely done in

cancers other than colorectal cancer. EX2130, ¶12. This failure of proof should be dispositive of Merck's anticipation argument in Ground 1.

Merck's failure of proof on this gateway question is unsurprising. As Dr. Lonberg explains, "MSI Positive Non-Colorectal Cancers" is a genus of unknown size, comprising at least 29 species and likely many more. EX2072, ¶53; EX2303, 1; EX2304, 1108; *see also* Pet. 17 (agreeing MSI-H was known to occur in several cancer types); EX1003, ¶25 (same); EX2273, 37 (same). Because it is a large—and growing—genus, there is no support for a conclusion that "a person of ordinary skill in the art can at once envisage each member." *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (cleaned up).

In its effort to obscure this major deficiency in its anticipation theory, Merck disregards the applicable caselaw concerning genus/species anticipation and instead relies on cases addressing factual scenarios inapplicable here. *E.g.*, Pet. 17-18. For example, the Federal Circuit has held that where a reference discloses a limited universe of potential combinations, such disclosure may be anticipatory if a POSA would immediately envisage the claimed combination. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381-83 (Fed. Cir. 2015). That line of cases is inapplicable here. The MSR discloses no list of options, and certainly no limited list. *See* EX1005, 3-5.

Merck further cites (*e.g.*, Pet. 18, 22), without explanation, caselaw addressing anticipation in the context of overlapping numerical ranges. *See Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1339 (Fed. Cir. 2020). This caselaw is also inapplicable here. There is no parallel between a POSA's understanding derived from disclosures of numerical ranges and, as here, the disclosure of a genus.

Merck also cites a case addressing ***anticipation of a claimed genus*** through ***disclosure of an individual species*** within the genus. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). This is yet another inapplicable factual circumstance. Disclosure of an individual species is the ***opposite*** of the present situation, where the claims are directed not to a genus but to individual species. While disclosure of a species may anticipate a genus, the disclosure of a genus anticipates individual claimed species only in limited circumstances that do not apply here.

Merck's attempt to patch quotes together from disparate and inapplicable cases does not cure the fundamental flaw in its anticipation case: "MSI Positive Non-Colorectal Cancer" is a large genus comprising a large, and unknown, number of species. A POSA would not envisage all its species, let alone the claimed subset of those species, based on the bare disclosure in the MSR. Because a POSA would not envisage all species, there is no anticipation of Claimed MSI-H Cancers as a matter of law.

B. The MSR Does Not Anticipate Because It Does Not Disclose Treating the Claimed MSI-H Cancers "In Response To" Those Cancers Being Determined To Be MSI-H

As just shown, the MSR does not describe or disclose any of the sixteen cancers specifically claimed in claims 1 and 11 of the '462 Patent. Likewise, the MSR does not describe or disclose treating any of those sixteen cancers "in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient." EX1001, claims 1, 11. The MSR does not disclose, for example, treating "breast cancer" "in response to" an MSI-H determination or, as another example, treating "testicular cancer" "in response to" an MSI-H determination. Nothing in the MSR instructs a POSA to identify any of the claimed cancer types as having the MSI-H biomarker and, in response to that determination, treating/prescribing treatment with pembrolizumab. The MSR's lack of disclosure of treating the Claimed MSI-H Cancers in response to a determination that the tumor is MSI-H is another, independent reason the challenged claims are not anticipated. EX2072, ¶104.

C. The MSR Also Cannot Anticipate Because It Does Not Expressly or Inherently Disclose "a Solid Tumor…That Has Progressed Following At Least One Prior Treatment."

As with the Petition's analysis of the cancers claimed in the '462 Patent, the Petition continues its misapplication of anticipation caselaw when addressing the requirement that the Claimed MSI-H Cancer "has progressed following at least one

prior treatment." Pet. 19-22. This is a second, independent basis for finding no anticipation.

Independent claims 1 and 11 each require that, prior to receiving treatment according to the claimed method, the patient's cancer must have progressed following a prior cancer treatment. The MSR, however, is silent on whether eligible patients must have had a prior treatment, let alone a prior treatment that failed. *See* EX1005, 5-6. Merck's expert, Dr. Neugut, agrees. *See* EX2163, 99:13-21 ("[I]t 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."). No amount of attorney argument or expert testimony can satisfy the requirement to demonstrate express anticipation. The MSR itself must disclose treatment occurring only after the prerequisite that the cancer "has progressed following at least one prior treatment" has been satisfied. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (caselaw "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, *4 (Fed. Cir. 2023).

Merck's assertions that a patient "generally" (Pet. 20; EX1003, ¶51) 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 an inherency

finding. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[U]nless 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"). Merck's cited cases (Pet., 21-22) show its position to be wrong. The cases on which Merck relies each involve a prior art reference containing what a POSA would have understood to necessarily disclose the contested limitation. *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373-74 (Fed. Cir. 2020) (finding the reference disclosed claimed technology despite using different words); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991) (finding the primary reference's identification of commercially available product was sufficient to disclose undisputed property of that product); *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1337-40 (Fed. Cir. 2020) (affirming anticipation finding where prior art temperature range overlapped the claimed range). Merck's resort to "additional evidence" tacitly concede that its primary arguments are based on generalities rather than actual disclosure.

Not only does Merck fail to satisfy its burden to show express anticipation, Merck also cannot meet its heavy burden to prove inherent anticipation because the "prior treatment" limitation is not inherent. Merck's own reference, Ajani, advises that certain Stage IV gastric cancer patients proceed directly to clinical trials ***without prior treatment***. *See* EX1096, 533, 537; EX2072, ¶106. Additionally,

Merck's Benson reference (Grounds 2-4), 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; EX2072, ¶106.

Merck's inherent anticipation argument fails as a factual as well as a legal matter. The MSR does not disclose a method of treatment following cancer progression after prior cancer treatment. The MSR does not refer to tumor progression whatsoever. The ***only*** reference in the MSR to prior treatment is the ***exclusion*** of individuals who had received certain prior treatments. EX2072, ¶105. This is ***the opposite of*** a prior treatment requirement. *Id.* Moreover, JHU added an express requirement for a prior treatment to the ClinicalTrials.gov study record in January 2016—three years ***after*** the MSR's publication. *Compare* EX1005, 5-6 with EX2165, 8; EX2166, 8. If a disclosure of prior treatment was "necessarily present" to a POSA reading the original MSR in 2013 (EX1005), JHU would not have needed to amend the study record to add such a requirement. EX2072, ¶107.

Merck's reliance on the 2014 ASCO poster as confirming that the 2013 MSR included criteria for MSI-H CRC patients of "at least 2 prior therapies" and for MSI-H non-CRC patients of "at least 1 prior therapy" also necessarily fails. Pet., 22; EX1080. The ASCO poster is a separate reference from the MSR, created well after the MSR was posted—it is not an anticipatory reference. 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.

Because the MSR provides no express or inherent disclosure of the "progressed following at least one prior cancer treatment," the MSR cannot anticipate the claims of the '462 Patent.

D. The MSR Cannot Anticipate Certain Dependent Claims Because It Does Not Disclose Treating "Metastatic" Cancer

Claims 6, 16, 24, 28, and 30 each require that the cancer treated according to the claimed method is "metastatic." "Metastatic" cancer is cancer that spreads from its origin site to another part of the body. EX2072, ¶108. Merck's anticipation argument for these claims necessarily fails because the MSR does not disclose treatment of metastatic cancer.

Rather than address the challenged claims' "metastatic cancer" requirement, the Petition and Merck's expert, Dr. Neugut, point to the MSR's requirement that patients have "measurable disease." Pet., 19-20; EX1003, ¶68. "Measurable disease" is very different from "metastatic cancer." EX1048, 230-31; EX1020, 82. "Measurable disease" in the cancer context 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 as required by claims 6, 16, 24, 28, and 30. EX2072, ¶¶108-112.

E. The MSR Does Not Inherently Anticipate the Challenged Claims.

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., 15), 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 patient with the Claimed MSI-H Cancers with pembrolizumab nor does it disclose treating "a solid tumor…that has progressed following at least one prior treatment" or treating a patient having "metastatic" cancer. One or more of these limitations must be met for each of the challenged claims, but the MSR is silent as to each of them. 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 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 '462 Patent. 677 F.3d at 1382. Certainly, without any data, the method of treatment 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 "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 conducting a Phase II trial to investigate the efficacy in CRC or any tumor type." EX2090, ¶57. Moreover, treatment of

other cancer types 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.*, at 1380.

The MSR was a classic "invitation to investigate"—an "abstract theory" in a highly unpredictable field having no supporting data. EX2072, ¶118. It 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 F.3d 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 a biomarker independent of cancer type. *Id.*

Quite unlike the MSR, the prior art study in *Montgomery* had 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.[5] The Board and Federal

[5] 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., 15. Additionally, *Schering Corp. v. Geneva Pharmaceuticals* is inapposite because the issue was whether the claimed compound "necessarily and inevitably

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.

F. Merck's Interpretation of Inherency Is Legally Incorrect

Merck's interpretation of inherency law cannot be correct because it effectively precludes patenting 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 could not have satisfied 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) (patent application must "reasonably convey[] to those skilled in the art that the inventor had possession of

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

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.

G. 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 ’462 Patent.

(1) Necessity. The ’462 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, ¶119. 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, ¶¶113-18; 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 '462 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, ¶¶33-58, 114; *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, ¶114; 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, ¶114. 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 explained in §VII.B, *infra*. EX2072, ¶¶63, 183-186; 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. Even in recent years, pembrolizumab has failed in numerous clinical trials. EX2072, ¶¶114, 132-134, 181; 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 rather than 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, ¶¶55-56, 116-117, 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 '462 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 '462 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 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 '462 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 '462 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 '462 Patent. Because the MSR does not qualify as prior art to the '462 Patent, Merck's Grounds 1-7 necessarily fail.

VI. CLAIMS 1-30 ARE PATENTABLE OVER GROUNDS 2-7

A. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating Any Claimed MSI-H Cancer "In Response To" Determining that a Patient is MSI-H

As shown above, the MSR does not anticipate the claims of the '462 Patent at least because it does not disclose the Claimed MSI-H Cancers or discuss treating the Claimed MSI-H Cancers. To fill this hole in the MSR's disclosure, the Petition presents a two-stage argument contending, first, that it was obvious to treat ***all*** MSI-H cancers according to the claimed methods and, second, assuming the first to be true, that it was obvious to treat at least a few of the Claimed MSI-H Cancers. *See* Pet., 42-45. Because, as explained below, a POSA would not have reasonably expected the claimed methods to work in ***all*** MSI-H cancers (and therefore would

not have treated them as claimed), the first stage of Merck's argument fails. The second stage of Merck's argument, built upon the first, then necessarily collapses due to the lack of disclosure of *any* Claimed MSI-H Cancer in the MSR. EX2072, ¶120.

In addition to not showing it would have been obvious to treat the claimed MSI-H cancers at all, Merck's six different obviousness combinations based on eight additional prior art references (Pet., 41-61) fail for a second reason: like the MSR, none of the added references teach or disclose treating any patient having the Claimed MSI-H Cancers "in response to" a determination that they are MSI-H. That is, none of these references teach a causal connection between treatment—much less treatment with pembrolizumab—and an MSI-H determination. EX2072, ¶121.

The Petition concedes this point. The obviousness grounds purporting to address independent claims 1 and 11 are Grounds 2-4, which combine the MSR with Brown, Duval, and Benson, and additionally with Koh (Ground 3) or Ajani (Ground 4). The Petition does not rely on these references as disclosing the claimed requirement that the specifically Claimed MSI-H Cancers be treated in response to an MSI-H determination. *See* Pet., 47-48. Instead, Merck relies on Brown and Duval as disclosing "Improved Outcome/Efficacy," (Pet., 42-45), and Merck relies on Benson, Koh, and Ajani as disclosing progressive or metastatic

disease (*id*., 48-54). None of these references discloses testing patients who have one of the Claimed MSI-H Cancers for MSI-H status and, in response to determining the patient is MSI-H, treating the patient with pembrolizumab. EX2072, ¶¶72-85, 141-151. Beyond failing to disclose the claimed limitations, none of the references presented in Grounds 2-7 provides a POSA with reasonable expectation of success or a motivation for accomplishing the claimed invention. *See* EX2072, ¶¶67-90, 139-173. For at least this reason, all of Merck's obviousness challenges fail.

While Merck purports to use inherency to fill the holes in its obviousness analysis (*see* Pet., 42, 43, 45, 51), Merck has not attempted to meet, let alone met, the heightened burden imposed for inherent disclosure in the obviousness context for this limitation. 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***[.]" *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). Because the

genus of MSI positive non-colorectal cancer is larger than the subset listed in the claims, Merck cannot—and does not—meet this high standard.

B. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating a Patient Whose Cancer Has Progressed Following Prior Treatment/Has Metastatic Cancer

Merck's six different obviousness combinations based on eight additional prior art references also do not supply the missing "progressed following at least one prior treatment" limitation required by the independent claims. They also fail to disclose the "metastatic" limitation of dependent claims 6, 16, 24, 28, and 30.

In Grounds 2, 3, and 4, Merck relies on Benson, Koh, and Ajani as disclosing what the Petition describes as "Treating Patients Having Characteristics Related to Progressive and Metastatic Disease." Pet., 48-51, 52-54 . This argument fails to identify with particularity how the cited references disclose any specific claim limitation. Benson, Koh, and Ajani, 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, Koh, and Ajani allow for clinical trials as first-line therapy. Benson explains that "when appropriate, patients should ***preferentially*** be included in a clinical trial over standard or accepted therapy." EX1009, 2. Benson, Koh, and Ajani each 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."

EX1009, 1; EX1095, 1; EX1096, 3. Even if Benson, Koh, and Ajani disclose that in ***some*** scenarios, it may make sense to recruit patients whose tumors had progressed after prior therapy and who have metastatic cancer, Merck has not provided any rationale for why a POSA would have selectively handpicked these characteristics from Benson, Koh, and Ajani —while ignoring Benson, Koh, and Ajani'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 generally patients who have had their cancer progress after previous drug therapies***" is unsupported. Pet., 49; EX1003, ¶146; EX2072, ¶122. The same is true of Merck's related contention that, by participating in a clinical trial, a cancer patient must have advanced or metastatic disease. Pet., 49-50.

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

Turning from the shortcomings of the references and combinations themselves to 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., 44[6] ; *see also id.*, 42. 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,

[6] Merck's citation to MPEP §2107.03, (Pet., 44), is irrelevant; this subsection relates to whether there is a lack of ***utility***, not ***reasonable expectation of success***.

¶¶124-127. Merck's fundamental misapplication of law precludes Merck from meeting its burden to show the'462 Patent claims were obvious to a POSA. *Eli Lilly*, 8 F.4th 1331 at 1344.

2. None of Merck's References Provides a Reasonable Expectation of Success in the Claimed MSI-H Cancers[7]

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 treating 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…

[7] 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.

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 treating NSCLC with erlotinib. *Id*. at 1383-86. 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 merely an experiment designed to test a hypothesis. EX1002, 166-67. As discussed in §V.G, certain clinical trials are experiments designed to test hypotheses. EX2163, 37:17-38:1, 136:18-23, 145:9-13; EX2072, ¶¶57-58, 68-69, 113-119, 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.[8] 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, ¶¶67-71, 139-140.

That these results were unexpected is further supported by approval of the 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 Institutional Review Board ("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 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

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

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; 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 published, 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, ¶¶55-56, 116-117, 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. Secondary References

Merck's secondary references—Brown and Duval—do not establish a reasonable expectation of success in any MSI-H cancer, let alone in all MSI-H cancers or in each Claimed MSI-H Cancers. Pet. 42. Contrary to the Petition's characterization, Brown is not about "identifying patients who are likely to respond to PD-1 inhibitors" and does not teach "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. 42. Instead, Brown describes a meta-analysis of missense mutation data wherein researchers explored potential correlations between tumors with high rates of such mutations and survival rate. EX1034,743-745. As one of Brown's many conclusions, it posits that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are ***potential candidates*** for treatment with ***immune modulators such as CTLA4- or PDCD1-targeted antibodies***." *Id.*, 747. Brown does not suggest that such candidates are "likely" to respond to PD-1 inhibitors. At best, Brown provides an "invitation to investigate," that falls well short of creating an expectation that the claimed method would in fact "***achieve success in the treatment***." *Eli Lilly*, 8 F.4th at 1344.

Brown's observation that one of the studies' "interesting" findings was that "colorectal tumors, many of which had very high mutational loads, showed the

strongest association between predicted immunogenic mutation counts and CD8A expression" also does not create an expectation of success for the claimed methods. *Id.*, 747. Once again, Brown provided only an "invitation to investigate," observing that "[u]nfortunately…the number of subjects varied widely among cancer types" and advised that "comprehensive evaluation of immunogenic mutations specific to ***individual cancer types*** remains an important topic for future study." *Id.* Thus, far from standing for the sweeping propositions that Merck proclaims, Brown at best suggests potential avenues for future research in individual non-colorectal cancer types. *See Montgomery*, 677 F.3d at 1382.

The Petition also mischaracterizes Duval in contending that it provides a reasonable expectation of success. Duval is not "an article directed to MSI-H cancers" and does not teach that "MSI-H cancers have cancer cells that are easy for immune cells to recognize." Pet. 42. Instead, Duval is an article about detecting MSI-H in one cancer type: lymphomas. EX1087, 5002. Lymphomas are non-tumor cancers and are not among the Claimed MSI-H Cancers, so are not implicated by the '462 Patent. EX2072, ¶77; EX2282, 82:5-19.

In its background discussion, Duval notes that MSI-H is a feature of certain tumors and explains that MSI-H is a factor associated with survival advantages in gastric cancer and CRC. EX1087, 5002. Duval, however, discloses no connection between MSI-H and a cancer being "easy for immune cells to recognize." Pet. 42.

Instead, consistent with the prevailing understanding at the time, Duval discusses MSI-H with reference to cancer type and seeks to identify this characteristic in lymphoma. EX1087, 5002. Duval—which is not about cancer *treatment* at all—says nothing that would lead a POSA to reasonably expect that a treatment, particularly a treatment based on checkpoint inhibition, based on the MSI-H characteristic would be effective in the Claimed MSI-H Cancers.

A POSA would also not have had a reasonable expectation of success in treating the Claimed MSI-H cancers based on "prior art beyond Brown and Duval." Pet. 43-44. The Petition and Dr. Neugut contend that additional references show that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize." Pet. 43; EX1003, ¶138. The Petition and Dr. Neugut repeat the same proposition, citing the same seven references, while providing no specific citation, elaboration or explanation. *See id*. The cited articles do not support the Petition's contention. Instead, the articles disparately discuss MSI-H in general (EX1085), hypotheses for anti-PD-1/PD-L1 therapies (EX1038; EX1032), and cancer-specific considerations (EX1040 (breast cancer); EX1041 (CRC); EX1042 (osteosarcoma)). Far from supporting Merck's assertion, these articles show the art's highly unpredictable nature. *E.g.*, EX1038, 9 ("meticulous artistry in clinical

trial design is essential to carve out the clinical benefits [of anti-PD-1/PD-L1 antibodies] for carefully selected patients"); EX1040, 2 (distinguishing triple negative breast cancer from carcinogen-induced solid cancer types). As these references confirm, at the time of the invention, the prevailing approach was to treat cancers individually by type. EX2072, ¶¶154-173. Even if a POSA would have expected the claimed method to succeed in CRC (they would not), a POSA would not have had a reasonable expectation of success in treating a particular non-CRC cancer, let alone the Claimed MSI-H Cancers, based on references discussing CRC treatment. Pet. 44 (citing EX1006, EX1032, EX1033, EX1036, EX1037, EX1038, EX1051, EX1039).

Similarly, a POSA would not have had a reasonable expectation of success in treating the Claimed cancers based on the possibility that the patients might have Lynch Syndrome. The Petition implies that an expectation of success would derive from a connection between Lynch Syndrome and MSI-H. *See* Pet., 47-48. This argument, however, presumes a connection between MSI-H and responsiveness to checkpoint inhibition, which was unknown in the art. The Petition then presumes that the POSA knowing the (unknown) connection between MSI-H and responsiveness to checkpoint inhibition would expect this relationship to extend across multiple cancer types. *Id.* Yet, what was known in the art, was that success in treating one cancer type did not create a reasonable expectation of success in

treating another. EX2072, ¶158; EX2282, 75:21-76:7. In fact, Keytruda has been shown to work in some cancer types but not in others. *See infra* § VI.C.3.b.

The Petition's scattershot approach—citing nearly two dozen references largely without explanation—to demonstrate a reasonable expectation of success, shows that there was no such expectation. The Petition demonstrates why it is improper to use the claimed invention as a roadmap for picking and choosing disclosures from the prior art to support invalidity. Only based on hindsight reconstruction (and misinterpretation of references) does Merck contend the methods claimed by the '462 Patent were obvious at the time of invention. In fact, the Petition fails to establish the premise that a "POSA would have expected all patients having MSI-H tumors to respond" to pembrolizumab. Pet. 42. The Petition also fails to explain why any of the individually Claimed MSI-H Cancers, let alone all of them, would be reasonably expected to respond to the claimed method of treatment.

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., 43. 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, ¶¶33-58, 114. 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, ¶¶55-56, 116-117, 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., 43. 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. Those studies' records 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 patients are in fact MSI-H does not support Merck's reasonable expectation of success claim. EX2072, ¶¶174-177.

To the contrary, the evidence available at the time of the MSR establishes that 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 other thirty-two CRC patients in BMS's nivolumab studies did not respond to the therapy, making this one patient's response a "statistically meaningless" result. EX1002, 166; EX1057, 2-3; EX2176, 22; EX2072, ¶178; EX2090, ¶57. In other words, it was known to the POSA that the BMS PD-1 inhibitor had shown a ***97% failure rate*** in 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 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 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 this anomalous result. *See* EX2163, 132:5-9; EX1002, 164-66; 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, including in the Claimed MSI-H Cancers. 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 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 '462 Patent's

priority date) 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 tumor location, 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 Claimed MSI-H Cancers 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 own expert agrees. 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, ¶179.

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., 44-45. 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 the Claimed MSI-H Cancers. EX2072, ¶179. 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, ¶180.

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. By 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 clinical failures make 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. The Petition Identifies No Motivation to Treat the Claimed MSI-H Cancers in the Claimed Way, and There Was None

Beyond failing to establish any reasonable expectation of success, *see* EX2072, ¶¶123-181, the Petition does not establish any motivation to pursue the claimed treatment for the Claimed MSI-H Cancers, as opposed to other MSI-H

Cancers. *See* EX2303, 1 (identifying MSI-H in 27 cancers including, among others, renal cancer, thymoma, and thyroid carcinoma); EX2304, 1108 (identifying MSI-H in 29 non-CRC cancers); EX2072, ¶53. That endometrial, small bowel, and gastric cancers (the cancers cherrypicked by Merck from the sixteen Claimed MSI-H Cancers) are a few among dozens of potential MSI-H cancers is not a motivation to select those cancers—or any others—for treatment by the claimed method. Nor does the association of the few cancers identified by Merck with Lynch syndrome provide motivation to select the Claimed MSI-H Cancers and not others. *See* EX2282, 47:17-49:6. Yet that is all the Petition says about motivation to pursue those cancers. Pet. 47-48.

The Petition's discussion of generalized motivation to pursue different treatments in some MSI-H cancers does not remedy Merck's failure to articulate a specific motivation to pursue the claimed method for each Claimed MSI-H Cancer. *See* Pet. 42-43. Treating some of those cancers in some other way is unrelated to whether there was a motivation to treat all of the claimed cancers specifically in the claimed way. Moreover, even to the extent the Petition's statement—in a different section—that "the POSA would have been motivated to treat patients having common types of MSI-H cancers," Pet. 42-43, can be understood as articulating a motivation, that contention (like the rest of the Petition) finds support only in the say so of Merck's expert (EX1003, ¶136)—support that should be

afforded little weight. *See Xerox Corp. v. Bytemark, Inc.*, No. IPR2022-00624, Paper 12, 5 (PTAB Feb. 10, 2023).

E. Inherency Does Not Cure the Missing Limitations

It was not obvious to use the claimed method in treating the Claimed MSI-H Cancers. Because the method was not obvious, inherency plays no role in the analysis. *See Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) ("[I]nherency renders a claimed limitation obvious only if the limitation is necessarily present, or is the natural result of the combination of elements explicitly disclosed by the prior art." (cleaned up)); *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) ("limitation…necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art"). Merck's inherency arguments regarding "Improved Outcome/Efficacy," Pet., 42-45, thus have no place in the obviousness analysis.

That the study performed ***after*** the MSR was posted and which ultimately yielded data showing the hypothesized connection between MSI-H status and responsiveness to pembrolizumab was correct, cannot be used to show the claimed method of treating the Claimed MSI-H Cancers was obvious. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("That which may be inherent is not necessarily

known. Obviousness cannot be predicated on what is unknown."); *In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977).

VII. OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS FURTHER PROVE 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 provides an array of strong objective evidence of non-obviousness, including industry praise, skepticism, long-felt unmet need, and unexpected results. JHU is an academic institution that designed and ran a clinical trial whose outcome led to a novel, patented method of treatment using Merck's drug, pembrolizumab. Merck sells pembrolizumab under the brand name Keytruda® and labels its drug specifically to treat MSI-H cancer patients 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…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. ITC*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (cleaned up).

A. Nexus

The surprising results of JHU's study ultimately led to FDA approval of pembrolizumab for MSI-H cancer treatment—including the Claimed MSI-H Cancers—resulting in actual treatment of patients with the Claimed MSI-H Cancers. Here, a clear nexus exists between 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 v. Brunswick Corp.*, 81 F.4th 1202, 1211 (Fed. Cir. 2023).

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 '462 Patent. The objective indicia here are narrowly tailored to the claimed method of treatment— the indications[9] that were ultimately tested and approved, ***not*** to pembrolizumab generally. EX2175. Every step of the claimed treatment method is set forth in Merck's Keytruda® label for indication "1.8 Microsatellite Instability-High or

[9] "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.

Mismatch Repair Deficient Cancer" and indication "1.15 Endometrial Carcinoma," added in March 2022. EX2129; EX2207; EX2090, ¶92; *see also* EX2177. 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, ¶¶82-93):

1[pre]. A method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, the method comprising:
The Keytruda® label instructs physicians to select patients having a solid tumor that has progressed following prior treatment for treatment with Keytruda according to Indication 1.8 and Indication 1.15, added in March 2022: **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.

1.15 Endometrial Carcinoma

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

EX2300, 6.

The Claimed MSI-H Cancers are each solid tumors that a physician would treat under Indications 1.8 and/or 1.15. EX2090, ¶92.

1[a]. testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and

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 Indications 1.8 and 1.15. 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.

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; *see also* EX2300, 7 (referring to sections 14.7 and 14.8).

Further, the Dosage and Administration section refers physicians to Clinical Studies section 14.8 that instructs physicians to test or have tested the patient tumor's MSI-H/dMMR status:

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; *see also* EX2300, 89-90 (section 14.7).

The Clinical Studies section 14.15 also instructs physicians to test or have tested the patient tumor's MSI-H/dMMR status in endometrial cancer:

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR 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.

EX2300, 114.

1[b]. in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.

The Recommended Dosage section of the Keytruda® label provides the recommended dosages of Keytruda® administered in response to determining that the solid tumor is MSI-H/dMMR, as well as the duration/timing of treatment based on the indication, wherein the indication is directed to cancers confirmed to be MSI-H/dMMR, including the Claimed MSI-H Cancers:

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* EX2300, 8.

The Keytruda® label includes clinical trial results showing that the recommended dosages of Keytruda® are therapeutically effective among cancer patients with MSI-H/dMMR solid tumors, including Claimed MSI-H Cancers, relevant to Indications 1.8 and 1.15:

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+)
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, 73-75.

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K who received at least one dose of KEYTRUDA. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR 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.

Table 80: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158

Endpoint	KEYTRUDA n=90*
Objective Response Rate	
ORR (95% CI)	46% (35, 56)
Complete response rate	12%
Partial response rate	33%
Duration of Response	n=41
Median in months (range)	NR (2.9, 55.7+)
% with duration ≥12 months	68%
% with duration ≥24 months	44%

* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)
\+ Denotes ongoing response
NR = not reached

EX2300, 114-115.

Claim 11 of the'462 Patent includes similar requirements. EX2090, ¶91.

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 presume a 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) (cleaned up) (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 '462 Claims

Even absent a 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***. JHU's objective evidence relates directly and specifically to the merits of the claimed method of treating patients determined to have a Claimed 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 patients with the Claimed MSI-H Cancers satisfied a long-felt, unmet need, saving the lives and futures of patients otherwise likely lost. EX2090, ¶¶28-50, 63-65; 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, ¶¶43-45; EX2005, 1-3; EX2006, 1; EX2089, 2, 5; EX2004, 1; EX2060, 2. Thus, the specific objective indicia here (and explained below) are both legally and factually connected to the method claimed in the '462 Patent, and nexus finding is appropriate. *See Volvo*, 81 F.4th at 1212.

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 the Claimed MSI-H Cancers. 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 nexus showing 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 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—including the Claimed MSI-H Cancers— 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 JHU's Results

JHU's clinical study results were nothing short of revolutionary. JHU presented its results—including positive results in patients with the Claimed MSI-H Cancers—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 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, ¶¶62, 183; EX2130, ¶47; EX2180, 3-4. Later results of JHU's study were published in Science. EX2118.

After FDA approved pembrolizumab for the MSI-H tumor agnostic indication (including approval for treatment of the Claimed MSI-H Cancers), 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. 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.").

FDA's approval of pembrolizumab to treat MSI-H cancer—including the Claimed MSI-H Cancers—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 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…." 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, including the Claimed 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. 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.*, 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, 166-67; 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 then 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 or the Claimed MSI-H Cancers specifically. *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.*

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

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 oncologists 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 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 invented 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 such as the Claimed MSI-H Cancers. EX2090, ¶¶28-50.

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.

The New York Times highlighted the successful treatment of MSI-H cancer patients, including patients with the Claimed MSI-H Cancers. EX2005, 1; EX2090, 73. The article tells the story of Adrienne Skinner, a patient suffering from ampullary cancer[11] which is an "extraordinarily rare and deadly cancer…that arises at the end of the bile duct." *Id.*, 3. It was "cancer so rare there were no tested treatments." *Id.*, 1. She had 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 pembrolizumab dose, 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 the Claimed MSI-H Cancers with pembrolizumab, Adrienne and many, many

[11] One of the Claimed MSI-H Cancers.

others suffering with the Claimed MSI-H Cancers 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; s*ee also* EX2170, 5 ("[redacted] [c[redacted]"). During its approval process, Merck also explained to FDA that [redacted] EX2171, 18. In seeking a breakthrough therapy designation for MSI-H cancers, Merck asserted that [redacted] EX2172, 15; *see also* 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—including the Claimed 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 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). 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. To expedite MSI-H cancer patients' access to pembrolizumab, FDA granted Keytruda® breakthrough therapy designation, priority review, and accelerated approval." EX2182, 2; *see also* EX2062; EX2133; EX2205. 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 oncologist treated their patients. EX2090, ¶¶75-81. Before the 2017 approval, clinical oncologists rarely ordered MSI-H testing for their patients because it was not a biomarker that was known to be useful for determining treatment choices in patients with advanced cancers. EX2090, ¶75; EX2282, 46:9-49:6, 100:22-105:23; EX2130, ¶12. MSI-H testing was generally only used in limited circumstances, such as determining whether 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, including several Claimed MSI-H Cancers. EX2090, ¶¶79-80. GI oncologists, for example, went from testing MSI-H in only certain CRC patients to routinely testing patients in all 11 cancer types they manage (including esophageal, gastric, pancreatic, and small bowel) 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) (cleaned up). 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.

Cancer treatment is inherently unpredictable. The unexpectedness of JHU's clinical study results 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 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 '462 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, 71% of MMR-deficient (MSI-H) non-CRC patients showed either a partial response or stable disease at week 12. *Id*. Likewise, 67% of MMR-deficient non-CRC patients had progression free survival (PFS) at 20 weeks. In fact, 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, 4:33-36.

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. Here, the median follow-up time for non-CRC MMR-deficient patients[12] 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 non-CRC MMR-deficient patients had their tumors progress yet—***after 9 months***—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 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. The 5-year overall survival for MSI-H non-CRC patients in the JHU study turned out to be an astounding ***50.3%***. EX2090, ¶50; EX2130, ¶30.

[12] This cohort consisted of patients having Claimed MSI-H Cancers: ampullary or cholangiocarcinoma, endometrial, small bowel, and gastric. EX1031, 3.

The JHU's clinical trial results 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, before 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 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 FDA submission. *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 different patient population independent of cancer type—MSI-H cancer patients—Merck is wrong, for the reasons discussed in §VI.C, *supra.*

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

VIII. CONCLUSION

For these reasons, JHU respectfully requests a final written decision confirming the challenged claims' patentability.

Respectfully submitted,

Dated: January 23, 2025

/Nicholas W. Stephens/

Nicholas Stephens, Reg. No. 74,320
Grace J. Kim, Reg. No. 71,977
Todd G. Miller, Reg. No. 42,003
Matthew L. Chun, Reg. No. 77,763
Frank E. Scherkenbach, *Pro Hac Vice*
Corrin N. Drakulich, *Pro Hac Vice*
Christina D. Brown-Marshall, *Pro Hac Vice*
Casey M. Kraning, *Pro Hac Vice*
Madelyn S. McCormick, *Pro Hac Vice*
Sarah E. Jack, *Pro Hac Vice*
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402

Attorneys for Patent Owner

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

The undersigned hereby certifies that the word count for the foregoing Patent Owner Response totals 17,484, which is less than the 17,500 authorized by the Board in Paper 12 dated December 9, 2024.

Respectfully submitted,

Dated: January 23, 2025

/Nicholas W. Stephens/

Nicholas Stephens, Reg. No. 74,320
Grace J. Kim, Reg. No. 71,977
Todd G. Miller, Reg. No. 42,003
Matthew L. Chun, Reg. No. 77,763
Frank E. Scherkenbach, *Pro Hac Vice*
Corrin N. Drakulich, *Pro Hac Vice*
Christina D. Brown-Marshall, *Pro Hac Vice*
Casey M. Kraning, *Pro Hac Vice*
Madelyn S. McCormick, *Pro Hac Vice*
Sarah E. Jack, *Pro Hac Vice*
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402

Attorneys for Patent Owner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4), the undersigned certifies that on January 23, 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:

Naveen Modi (Reg. No. 46,224)
Bruce M. Wexler (Reg. No. 35,409)
Preston K. Ratliff II (Reg. No. 43,034)
Daniel Zeilberger (Reg. No. 65,349)
David J. Feigenbaum (Reg. No. 78,139)
Mark Stewart (Reg. No. 43,936)
Paul Hastings LLP
PH-MSD-JHU-IPR@paulhastings.com
mark.stewart@merck.com

/Crena Pacheco/
Crena Pacheco
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
pacheco@fr.com