

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 SUR-REPLY

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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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2033	Weiss, <i>Open Questions: Knowing Who's Who in Multicellular Animals is Not Always as Simple as We Imagine</i> , 16 BMC Biology Article number: 115 (Oct. 15, 2018)
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2069	Exhibit 18 to Johns Hopkins University Corrected Answer and Counterclaims to Complaint, Merck Sharp & Dohme LLC v. The Johns Hopkins University, Case No. 1-22-cv-03059-JRR, D.I. 17-18 (D. Md. April 21, 2023)
2070	Statista, Leading drugs worldwide based on projected 2024 sales (in billion of U.S. dollars), released December 2023, available at https://www.statista.com/statistics/973523/top-drugs-by-year-on-year-sales-increase/
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2072	Declaration of Dr. Nils Lonberg
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2080	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-028/KEYNOTE-28), ClinicalTrials.gov (Oct. 10, 2023), https://clinicaltrials.gov/study/NCT02054806
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2083	Shigehisa Kitano et al., <i>Myeloid-derived suppressor cell quantity prior to treatment with ipilimumab at 10mg/kg to predict for overall survival in patients with metastatic melanoma</i> , J. of Clin. Oncology 30(15), 2518 (May 20, 2012)
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2089	Boyiadzis et al., <i>Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease</i> , J. ImmunoTher. Cancer 6:35 (May 14, 2018)
2090	Declaration of Dr. Richard Goldberg
2091	Bray et al., <i>Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries</i> , CA Cancer J. Clin. 74:229-263 (2024)
2092	Zeineddine et al., <i>Survival improvement for patients with metastatic colorectal cancer over twenty years</i> , NPJ Precis. Oncol. 7:16 (2023)
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2101	Dy et al., Long-term survivors of metastatic colorectal cancer treated with <i>systemic chemotherapy alone: a North Central Cancer Treatment Group review of 3811 patients, N0144</i> , Clin. Colorectal Cancer 8(2):88-93 (2009)
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2120	The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research (April 18, 1979)
2121	The Cancer Letter, Vol. 43, No. 38, Oct. 13, 2017
2122	The Cancer Letter, Vol. 48, No. 23, June 10, 2022
2123	<i>How Beth Carner went from six weeks left to live with stage 4 colon cancer to complete remission</i> , Cancer History Project (June 10, 2022), https://cancerhistoryproject.com/article/how-beth-carner-went-from-six-weeks-left-to-live-with-stage-4-colon-cancer-to-complete-remission/

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2124	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (May 23, 2017)
2125	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Oct. 2015)
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2129	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (June 2020)
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
2132	O’Neil et al, <i>Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma</i> , PLoS One (Dec. 28, 2017)
2133	FDA Grants Priority Review to Merck’s Supplemental Biologics License Application (sBLA) Seeking Approval for KEYTRUDA® (pembrolizumab) for New Indication in Microsatellite Instability-High Cancer. merck.com/news/fda-grants-priority-review-to-mercks-supplemental-biologics-license-application-sbla-seeking-approval-for-keytruda-pemb...
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2135	<i>ASCO 2015: Mismatch Repair Deficiency Predicts Response to Pembrolizumab Among Patients With Colorectal and Other Cancers</i> , The ASCO Post (May 29, 2015), https://ascopost.com/News/27670
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2137	Declaration of Ms. Jennifer Newberger
2138	K. Dickersin, Report from the panel on the Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials, <i>Controlled Clinical Trials</i> 9:76-81 (1988)
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2150	21 U.S.C. § 331 - Prohibited acts
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2152	De Angelis et al., <i>Clinical trial registration: a statement from the International Committee of Medical Journal Editors</i> , Editorial, Clinical Trial Registration (2004)
2153	<i>Response</i> , The American Heritage dictionary of the English Language (5 th ed. 2011)
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2160	Plaintiff Merck Sharp & Dohme LLC's Opening Brief Regarding Claim Construction, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , 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, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , 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, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 107 (D. Md. May 1, 2024)
2163	Stenographic Deposition of Alfred I. Neugut, M.D., Ph.D., MPH taken on August 8, 2024, <i>Merck Sharp & Dohme LLC, v. The Johns Hopkins University</i> , Case IPR2024-00240 (PTAB)
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2165	Record History Tab, Study of MK03475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B, and C),

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2170	Highly Confidential Attorney Eyes Only Document 5 – Protective Order Material
2171	Highly Confidential Attorney Eyes Only Document 6 – Protective Order Material
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2173	Highly Confidential Attorney Eyes Only Document 8 – Protective Order Material
2174	Highly Confidential Attorney Eyes Only Document 9 – Protective Order Material
2175	André et al., KEYNOTE-177 Investigators. <i>Pembrolizumab in Microsatellite-Unstable-High Advanced Colorectal Cancer</i> , N. Engl. J. Med., 383(23):2207-2218 (Dec. 3, 2023)
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, <i>Merck Sharp</i>

Exhibit Number	Description
	<i>& Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR
2178	Marques et al., <i>Tumor mutational burden in colorectal cancer: Implications for treatment</i> , Crit. Rev. Oncol. Hematol. (Apr. 12, 2024)
2179	Le et al., <i>Phase II Open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164</i> , 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
2182	Highly Confidential Attorney Eyes Only Document 10 – Protective Order Material
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
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

Exhibit Number	Description
2251	Siegel et al., <i>Cancer Statistics, 2015</i> , CA Cancer J. Clin., 65(1):5-29 (Jan-Feb 2017)
2252	Noone et al. (eds). <i>SEER Cancer Statistics Review, 1975-2015</i> , 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, <i>Survival statistics for small intestine cancer</i> , https://cancer.ca/en/cancer-information/cancer-types/small-intestine/prognosis-and-survival/survival-statistics
2254	American Cancer Society, <i>Survival rates for bile duct cancer</i> , https://www.cancer.org/cancer/types/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html
2255	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer</i> , Version 4.2024 (August 12, 2024)
2256	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pancreatic Adenocarcinoma</i> , Version 3.2024 (August 2, 2024)
2257	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatocellular Carcinoma</i>
2258	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Biliary Tract Cancers</i>
2259	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Small Bowel Adenocarcinoma</i> , Version 1.2025 (December 4, 2024)
2260	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ampullary Adenocarcinoma</i> , Version 2.2024 (August 2, 2024)
2261	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Anal Carcinoma</i>

Exhibit Number	Description
2262	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer</i> , Version 1.2025 (December 4, 2024)
2263	RESERVED
2264	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms</i> , Version 3.2024 (September 20, 2024)
2265	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ovarian Cancer</i> , Version 3.2024 (July 15, 2024)
2266	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Cervical Cancer</i> , Version 4.2024 (September 24, 2024)
2267	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors</i>
2268	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Thyroid Carcinoma</i>
2269	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer</i> , Version 6.2024 (November 11, 2024)
2270	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers</i> , Version 4.2024 (July 30, 2024)
2271	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Testicular Cancer</i> , Version 2.2024 (October 29, 2024)
2272	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers</i> , Version 1.2025 (November 26, 2024)
2273	Highly Confidential Attorney Eyes Only – Protective Order Material: May 9, 2013 Submission

Exhibit Number	Description
2274	Highly Confidential Attorney Eyes Only – Protective Order Material: June 11, 2013 Submission
2275	Highly Confidential Attorney Eyes Only – Protective Order Material: July 15, 2013 Submission
2276	Boland. <i>Henry T. Lynch, MD (January 4, 1928–June 2, 2019)</i> , Gastroenterol., 157(4):905-906
2277	Aaltonen et al., <i>Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients</i> , Cancer Res., 54:1645–1648 (1994)
2278	Aarnio et al., <i>Cancer risk in mutation carriers of DNA-mismatch repair genes</i> , Int. J. Cancer 81:214–218 (1999)
2279	Chen et al., <i>Small bowel adenocarcinoma</i> , 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
2281	Hsiehchen et al., <i>Mutation burden and anti-PD-1 outcomes are not universally associated with immune cell infiltration or lymphoid activation</i> , Cancer Cell 42:1985-1987 (2024)
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., <i>Landscape of Microsatellite Instability Across 39 Cancer Types</i> , American Society of Clinical Oncology ascopubs.org May 14, 2024
2304	Akagi et al. <i>Real-world data on microsatellite instability status in various unresectable or metastatic solid tumors</i> , Cancer Science (2021)
2305	FDA Approves Merck’s Keytruda® Pembrolizumab for Patients With MSI-H/dMMR Advanced Endometrial Carcinoma, Who

Exhibit Number	Description
	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
2401	Copy of EX1001, U.S. Pat. No. 10,934,356, marked at January 6 th 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 6 th Deposition of Dr. Neugut
2403	Board Email regarding Motion to Seal dated October 4, 2024
2404	Confidential_Deposition Transcript of Paul E. Oberstein, M.D., February 19, 2025
2405-2499	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

I. INTRODUCTION

Recognizing that its Petition necessarily fails based on the absence of key disclosures in the MSR¹, Merck engaged a new declarant, Dr. Paul Oberstein, to offer opinions on Reply. But no amount of expert opinion or attorney argument can cure the MSR's deficiencies. In the end, JHU's arguments stand unrebutted: (1) the MSR does not expressly or inherently disclose treating any one of the sixteen named cancers, or additional limitations related to prior therapy and metastatic cancer; (2) the MSR is an "invitation to investigate" that does not expressly or inherently disclose any clinical results; (3) the MSR meets the Experimental Use factors; and (4) objective indicia refute obviousness.

Rather than rebutting JHU's arguments, Merck mischaracterizes deposition testimony and alleges JHU made contradictory statements to FDA and the Patent Office. Most glaringly, Merck rewrites the claims and the MSR, reducing each to two generic steps that strip out critical claim limitations and other information, creating a false equivalency. Reply, 1, 25. The Board should uphold patentability of the claims.

¹ "MSR" refers to the "MSI-H Study Record," JHU's June 10, 2013 Clinicaltrials.gov initial submission announcing its clinical trial.

II. ALL GROUNDS FAIL BECAUSE THE MSR DOES NOT ANTICIPATE OR RENDER OBVIOUS THE CLAIMS

A. Merck Has Not Shown the MSR Anticipates Any Claimed MSI-H Cancer

The third arm of the MSR's inclusion criteria requires only patients with MSI-H non-CRC. It is undisputed that the MSR identifies no particular type of MSI-H non-CRC cancer. EX1005, 5. The '462 Patent's claims, on the other hand, require the treatment of one or more of 16 specific MSI-H non-CRC cancers. EX1001, cl. 1. Controlling caselaw is unambiguous—for the MSR's generic disclosure of non-CRC MSI-H cancer to anticipate, a POSITA must “at once envisage” *all* MSI-H non-CRC cancer types—*not* just one or even a subset of the claimed MSI-H non-CRC cancer types, as Merck alleges. *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (“a reference describing the genus anticipates every species within the genus” only where “the genus is so limited that a [POSITA] can ‘at once envisage each member of this limited class.’”) (citation omitted). Merck bore the burden of proving the MSR's category of MSI-H non-CRC types was a “small” group. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001). Merck failed to acknowledge, let alone carry this burden. Pet., 17-18.

Faced with JHU's dispositive caselaw, (POR, 10-14), Merck has ***no answer***. See Reply, 9-11. The best Merck can muster is *Sanofi-Synthelabo v. Apotex, Inc.*, a case even Merck concedes supports JHU, holding "the prior art did not anticipate the claimed invention because the description of the genus would not lead a POSA to a small ***recognizable*** class of species."² Reply, 10 (original emphasis, citing 550 F.3d 1075, 1084 (Fed. Cir. 2008)). While Merck attempts to characterize the facts here to support a different outcome, its own case acknowledges that, to succeed, Merck had to show that non-CRC MSI-H cancer constitutes "a small recognizable class with common properties." *Sanofi-Synthelabo*, 550 F.3d at 1084.

Merck has not made this showing. Instead, Merck again argues the group of non-CRC MSI-H cancer was known to include "***at least one of three*** claimed cancer types (endometrial, gastric, and small bowel cancer)." Reply, 10. In so arguing, Merck effectively concedes that it cannot meet its burden to show that a POSITA would at once envisage all non-CRC MSI-H types. Merck identifies no common properties of non-CRC MSI-H cancer, or any other way a POSITA would have recognized the MSR discloses those cancers. Reply, 9-11; see POR, 13.

² All emphasis added, unless otherwise noted.

Confronted with this evidentiary failure, Merck invites the Board to instead rely on cases addressing anticipation of a ***claimed genus*** through disclosure of an ***individual species*** within the genus, relying for example on the *Brown v. 3M* case. *See* Pet., 18 (citing 265 F.3d 1349, 1351 (Fed. Cir. 2001)). This argument too necessarily fails because the MSR does not disclose ***any*** species and the '462 Patent does not claim a genus.

Contrary to Merck's assertion (Reply, 10 n.15)—Merck has failed to establish that ***any*** of the claimed cancer types are anticipated by the genus of non-CRC MSI-H cancer because Merck has not shown that a POSITA would at once envisage the ***entire*** genus—meaning every one of its constituent species—based on the MSR.³

Merck also conflates the obviousness and anticipation standards. It is irrelevant for anticipation whether a POSITA knew of ***some*** common MSI-H

³ Merck's allegation that JHU would require a single patient to have "***each and every one*** of the sixteen listed cancers" is a nonsensical strawman. Reply, 10 (original emphasis); POR, 10-14.

cancers or that doctors tested certain groups for MSI-H.⁴ *See* Reply, 10-11.

Indeed, Merck’s identification of endometrial, gastric and small bowel cancer highlights Merck’s abject failure to establish that non-CRC MSI-H cancer constitutes a “small recognizable class.” *Id.*, 10. A “small *recognizable* class” by its very nature must have identifiable, recognizable characteristics. Yet, Merck admits it cannot demonstrate that a POSITA would have envisaged a small recognizable class from the MSR by arguing there is not “anything special about any particular non-CRC MSI-H cancer in [the claimed] list”. *Id.*, 11.

Nor does what was “actually done” in the clinical trial advance Merck’s anticipation position, which is based only on the MSR. Reply, 11; POR, 20-21 (explaining MSR is not the clinical trial). Put simply, anticipation requires that a POSITA would at once envisage *all* members of the genus from the alleged anticipatory disclosure, i.e., the MSR. Because Merck has not established this prerequisite, it cannot prove the MSR discloses any of the claimed MSI-H non-CRC cancers and therefore cannot demonstrate anticipation.

⁴ Thus, Merck’s reliance on Dr. Goldberg’s testimony that certain cancers had known MSI-H prevalence is irrelevant. Reply, 3, 11; *see also id.*, 10 n.15.

Because the MSR does not disclose any of the claimed MSI-H non-CRC cancers, it necessarily fails to disclose treating those cancers “in response to” determining they are MSI-H. Reply, 12-13.

B. Merck’s Inherency Arguments Fail on Multiple Levels

In addition to not disclosing the claimed cancers, it is undisputed that the MSR does not explicitly disclose the limitations requiring “prior treatment,” “progressed following...prior treatment,” “metastatic” cancer, or the claimed clinical outcomes. POR, 15-24; Reply, 13-21. Merck must resort to inherency to fill those holes.

1. The MSR Does Not Inherently Disclose The Claimed Clinical Outcomes

In *In re Montgomery*, the Federal Circuit found that a clinical trial protocol may inherently anticipate a method claim if the results “inevitably flow” from the prior art disclosure. However, in *Montgomery*, the prior art trial disclosure “[i]n all relevant respects” was “identical to the patent itself.” 677 F.3d 1375, 1383 (Fed. Cir. 2012). Here, the MSR disclosure is not remotely the same as the patent—as JHU explained, (POR, 20-24), the patent specification includes and relies critically on data *resulting* from the MSR. The prior art MSR disclosure is not “[i]n all relevant respects...identical to the patent itself,” as in *Montgomery*. And even if it were, the MSR does not disclose several claim limitations. Merck highlights these

differences by omission when it argues the MSR disclosed a generic two-step method divorced from the actual claimed methods. Reply, 1, 25. Because the claimed method is different from the MSR's method, the claimed results cannot "inevitably flow" from the MSR.

Montgomery also distinguishes clinical trials at "an advanced stage of testing designed to secure regulatory approval," which can inherently disclose a method of treatment, from "an invitation to investigate, [which] is not an inherent disclosure." *Montgomery*, 677 F.3d at 1382 (citation omitted). Contrary to Merck's assertions (Reply, 13-14), the majority opinion in *Montgomery* explicitly agreed with the dissent on this point. *Id.* ("To be sure, ***as the dissent points out***, '[a]n invitation to investigate is not an inherent disclosure.'") (citation omitted).

JHU explained why the MSR was an "invitation to investigate." POR, 20-24. [REDACTED] That the IND included a scientific rationale—as Merck argues—does not negate the MSR as an invitation to investigate, because ***all*** clinical trials have a rationale. EX2404, 155:3-156:12; Reply, 13-15. The language of JHU's scientific rationale demonstrates the investigative nature of their proposed clinical trial, particularly in non-CRC patients. See EX1116, 18 [REDACTED]

[REDACTED]

[REDACTED]

Contrary to Merck’s suggestion, no Federal Circuit authority requires a patentee to include a specific phrase (“abstract theory”) in its study proposal to describe its hypothesis or for FDA to question the investigator’s scientific rationale before a proposed study qualifies as an “invitation to investigate.” Reply, 15.

JHU’s arguments here are consistent with what it told FDA. The inventors formed a hypothesis based on an anomalous result in a single patient in an otherwise unsuccessful study (32 patients did not respond) of a different drug, a different cancer (CRC), and different hypothesis. *Compare* POR, 48 (“the JHU inventors hypothesized that the response may have been tied to the patient’s MSI-H status”), *with* EX1116, 39, 40 [REDACTED]

[REDACTED]

[REDACTED]; *see also* EX1245, 80:17-85:7 (Dr. Lonberg testifying “[T]hat is not an anticipated outcome. That is a hypothesis.”).

The MSR’s investigative nature is further buttressed by the MSR being the first in a long series of proposal updates leading to the invention becoming ready for patenting. POR, 28. Against this backdrop, Merck’s interpretation of inherency, requiring JHU to file its patent application before even posting the MSR

clinical trial announcement, makes no sense, particularly where “those skilled in this art would not accept anything short of such human clinical trials.” *Ex Parte Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (B.P.A.I. 1991); POR, 27-31.

2. The MSR Does Not Inherently Disclose “Progressed Following...Prior Treatment”

The standards for inherent anticipation are both clear and strict. To fill a gap based on inherency, the missing disclosure must be “necessarily present[.]” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Merck’s inherency arguments defy this mandate. Merck posits that a study conducted in furtherance of the MSR *might have* included patients who had received prior treatment or whose tumor progressed following prior treatment. Such speculation does not suffice for inherent anticipation. *MEHL/Biophile Int’l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (“Occasional results are not inherent.”). That the MSR discloses treating cancer patients that *could be* within the claimed subset cannot inherently anticipate results from treating *only* patients within the claimed subset.

Not only does Merck disregard the law, it disregards unhelpful facts. For example, Merck’s Dr. Oberstein conceded that a patient *could be* included in the MSR’s proposed clinical trial even without prior treatment. EX2404, 276:7-277:10; EX2163, 99:13-21 (Dr. Neugut agreeing MSR “leaves out” previous

treatment and progression). Dr. Lonberg testified the MSR provides “no general exclusion for prior therapies,” paralleling Drs. Oberstein and Neugut’s testimony. EX1245, 56:18-57:4. Because receiving prior treatment and progressing after treatment are *not necessarily present* in the MSR, the MSR cannot inherently anticipate.

3. The MSR Does Not Inherently Disclose “Metastatic” Cancer

Merck’s inherency challenge to the dependent claims requiring “metastatic” cancer fails for similar reasons. Metastatic cancer is neither expressly nor inherently disclosed by the MSR. Inclusion criteria 1-4 (EX1005, 5) identify the eligibility requirements; none *require* metastatic cancer.

Merck tries to import the word “metastatic” into the MSR by asking the Board to disregard Dr. Neugut’s testimony disavowing any equivalence between the disclosed “measurable disease” and the claimed “metastatic” cancers. EX2163, 14:3-15:12 (explaining the difference). But Merck provides no reason to do so.

Merck also points to Dr. Lonberg’s testimony that the MSR does not *exclude* patients with metastatic disease. EX1245, 58:3-10; *id.*, 49:14-51:7. Whether such patients were excluded from the proposed study is irrelevant to whether the MSR is *limited to* or *necessarily includes* metastatic cancer patients as claimed. If the MSR was so limited, the inclusion criteria would reflect this, but

they do not. *See* EX2404, 274:16-275:18. Once again, Merck relies upon “mights” and “maybes” insufficient to support inherent anticipation. “Inherency...may not be established by probabilities or possibilities.” *Montgomery*, 677 F.3d at 1380.

C. Merck Fails to Rebut Experimental-Use Negation

It is undisputed JHU was required to post the MSR to ClinicalTrials.gov before beginning the clinical trial that supported the '462 Patent's claims. JHU also provided evidence demonstrating applicability of the experimental-use exception. POR, 27-31. Merck does not rebut that analysis. It does not dispute, for example, that the MSR was required by law, necessary to establish the usefulness of the claimed methods, and done for no commercial purpose. *Id.* The MSR is thus precisely the type of activity that courts have found support experimental-use negation. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998).

Merck instead declares—without analysis or elaboration—that “the Federal Circuit has found that ClinicalTrials.gov study records, like the MSR, are Section 102 prior art.” Reply, 8 (citing *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024)). But the *Salix* panel never addressed whether a ClinicalTrials.gov posting is subject to experimental negation. Because the panel was not presented with this issue, the panel cannot have resolved it. *Cooper*

Indus., Inc. v. Aviall Servs., Inc., 543 U.S. 157, 170 (2004). Thus, JHU’s experimental-use argument is not contrary to any Federal Circuit precedent.

As JHU explained, the Supreme Court and Federal Circuit have expressly held that public uses, sales, and offers for sale can be negated as §102 prior art if those activities were for experimental purposes. POR, 26-27. Those courts have not yet specifically addressed negation of a printed publication made for experimental purposes.⁵ *But see Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 872 (3d Cir. 1977) (after prior use or sale is shown, “the burden shifts to the patentee to prove that any prior use, sale, or ***printed publication*** was for experimental, not commercial, purposes”).

The logic and policy of experimental negation in the contexts of public uses, sales, and offers to sell apply equally to printed publications. As with an invention that requires public experimentation to establish usefulness, if a publication was made for purposes of experimentation—and indeed was ***necessary*** to enable the

⁵ This silence is unsurprising. The circumstances where an inventor must publish as part of his experimentation are limited. But the highly regulated area of human clinical studies can present exactly that circumstance.

experimentation and make the invention ready to patent—that publication should be negated as prior art, just as any experimental use would be negated.

Merck next criticizes FDA expert Jennifer Newberger by claiming she did not know what ClinicalTrials.gov required in 2013. Reply, 8. Not so. As Ms. Newberger explained, the *statute*—as opposed to administrative guidance or the ClinicalTrials.gov website—*required* the MSR’s disclosures. EX1135, 242:16-243:3.⁶

Merck’s claim (Reply, 9) that §101 and §112 requirements do not preclude the MSR being prior art is also wrong. The tension between the need to experiment to place an invention in patentable condition and the strictures of §102’s prior art provisions is long recognized. *See Pfaff*, 525 U.S. at 64. Merck’s cases fall far short of showing that it is “well established” that human clinical trial data is not required to satisfy §101 and §112 for claims like these. Numerous cases have come out the other way, including Merck’s own case. *See, e.g., Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (affirming rejection for lack of utility and non-enablement due to lack of human clinical data); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598

⁶ Merck’s allegation (Reply, 9 n.14) regarding “inconsistent testimony” refers to an inconsequential inadvertent omission. EX1242, 64:22-66:13.

F.3d 1336, 1351 (Fed. Cir. 2010) (en banc); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). The uncertainty surrounding the amount of disclosure required to support patenting a method of treating human patients reinforces the importance of applying experimental-use negation where supported by the record, especially in highly unpredictable fields such as cancer treatment.

D. Merck’s Identified Combinations Cannot Render The Challenged Claims Obvious

As JHU explained, Merck’s Petition failed to meet its burden on obviousness on multiple fronts, including because (i) Merck’s prior art (even in combination) does not disclose treating the claimed sixteen cancers “in response to” a MSI-H determination, “prior treatment,” “progressed,” or “metastatic” cancer; (ii) Merck did not establish a reasonable expectation of success; and (iii) JHU’s significant objective-indicia evidence strongly supports non-obviousness. POR, 32-82. Merck’s Reply does not overcome these deficiencies.

1. Merck’s Obviousness Combinations Do Not Disclose or Render Obvious the Missing Limitations

Merck fails to meaningfully respond to JHU’s arguments regarding why the MSR does not disclose treating the claimed MSI-H non-CRC cancers “in response to” an MSI-H determination. *See* POR, 32-35. A perfunctory footnote fails to meet the high bar for inherent obviousness. Reply, 22 n.27; POR, 32-35.

Additionally, Merck relies on circular reasoning to arrive at its conclusion that the combinations in Grounds 2-4 disclose “prior treatment,” “progressed following...prior treatment,” and “metastatic” cancer. Merck alleges that Benson, Ajani, and Koh teach “clinical trials are specified as the *standard of care* after at least one prior cancer therapy (Reply, 17), but this is only true for a subset of patients who have advanced or metastatic disease. EX1009, 7; EX1096, 533, 537; EX1095, 256; POR, 17-18. Merck thereafter (1) assumes cancer patients treated by the MSR’s method have *advanced or metastatic cancer*, and (2) ignores Benson’s repeated statement that “NCCN believes that the best management of *any* cancer patient is in a clinical trial.” EX1009, 1-3.

2. Merck Fails to Show Motivation to Pursue the Claimed MSI-H Cancers

The ’462 Patent claims treating sixteen specific MSI-H cancers. Critically, it does *not* claim all cancers having an MSI-H subpopulation. Thus, Merck can only prevail if it proves a motivation specific to the claimed MSI-H non-CRC cancers. Merck made no such showing. POR, 52-54. As discussed above, Merck’s admission that there is not “anything special about any particular non-CRC MSI-H cancer in this list” shows Merck identified no common property that would motivate a POSITA to pursue any of the claimed MSI-H non-CRC cancers

from the large and growing genus of non-CRC MSI-H cancers. Reply, 11; POR, 13. Thus, Merck articulated no motivation for a POSITA to arrive at the claims.

3. Merck Failed to Establish Reasonable Expectation of Success

Merck still cannot articulate the correct standard for reasonable expectation of success (“RES”). Merck incorrectly argued that a POSITA “would have wanted to obtain the data from the MSI-H Study, including determining the outcome of patients.” POR, 36-38 (citing Pet., 42, 44); EX1003, ¶¶135-136, 140. JHU explained that was not the right standard. POR, 36-38. Yet Merck doubles down, *recommitting to the debunked standard*. Reply, 25. Merck now also argues that a POSITA would have had a RES in carrying out something other than what’s claimed—a generic two-step treatment method. *Id.* Importantly, Merck’s generic method *leaves out the specific cancer types*, improperly lowering the bar for RES. Merck’s RES argument thus fails again.

Applying the correct standard, none of Merck’s evidence provides a RES for treating the claimed MSI-H non-CRC cancers. The standard for RES is laid out in *OSI Pharmaceuticals v. Apotex Inc.* See POR, 4, 25, 38-41, 48-51 (citing 939 F.3d 1375 (Fed. Cir. 2019)). In that case—that Merck fails to address—the Federal Circuit reversed the Board’s unpatentability finding, holding that “hope that a

potentially promising drug will treat a particular cancer is ***not enough*** to create a [RES] in a highly unpredictable art such as this.” 939 F.3d at 1385.

It is undisputed that, as in *OSI Pharms.*, the MSR discloses no efficacy data. 939 F.3d at 1383. Merck’s references provide only speculation, not clinical data, which Dr. Oberstein agreed would “be taken in a different light” than if a “definitive conclusion” were reached. EX2404, 124:3-14. For example, Brown’s statement that “patients with tumors showing naturally immunogenic mutations ...are potential candidates for treatment with immune modulators” is a mere speculative invitation to investigate and does not provide a RES. EX1034, 747; POR 42-43.

Merck’s attempt to buttress its argument [REDACTED] [REDACTED] also fails. An inventor’s hypothesis does not render his invention obvious. 35 U.S.C. §103; *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) (“Patentability does not turn on how the invention was made”); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) (“The inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.”).

Notably absent from Merck’s Petition or Reply is any evidence, as of the Critical Date, that a single patient with any one of the claimed MSI-H non-CRC cancers had responded to a PD-1 inhibitor. That’s because none had. All Merck can point to is a single **CRC** patient. Reply, 14 n.19, 34 n.37. Merck does not explain—nor could it—how a POSITA would have understood from this single CRC patient, that a method of treating the claimed MSI-H non-CRC cancers was obvious. As Merck’s own expert conceded, a positive outcome in one clinical trial does not predict a positive outcome in subsequent trials. EX2163, 125:15-126:1.

Moreover, Dr. Lonberg addressed each of Merck’s references and explained “at best” these references invited “investigating additional speculative hypotheses.” EX2072, ¶156; *see also id.* ¶¶141-81. Merck does not rebut Dr. Lonberg’s testimony. Nor does Merck rebut JHU’s teaching away evidence. *See* EX2072, ¶¶115, 129, 130, 143, 160, 162. Merck also ignores Dr. Lonberg’s testimony that JHU’s hypothesis was “not an anticipated outcome” and “does not imply any

anticipation of—or any expectation of a particular result.” EX1245, 82:21-83:15; *see also id.*, 71:18-72:15; 80:22-85:7; 89:14-22.⁷

Taken together, Merck’s evidence fails to demonstrate a RES in treating any of the claimed MSI-H non-CRC cancers under *OSI Pharms. Id.* at 1385.

4. Merck Failed to Rebut Much of JHU’s Objective-Indicia Evidence

a. Nexus

Merck provides no meaningful rebuttal to JHU’s evidence demonstrating the claims are co-extensive with Keytruda®’s label indication for treating MSI-H patients. POR, 57-62. For example, Merck’s Dr. Oberstein offers no opinion on nexus. *See* EX2404, 240:14-241:22. Nor does *any* Merck declarant provide an opinion identifying how the use of the product according to the label deviates from the claims.

⁷ Dr. Lonberg’s testimony regarding his personal knowledge of JHU’s nonpublic work and of the nonpublic outcomes of BMS’s clinical trial are irrelevant to the knowledge or expectations of a POSITA at the time of the invention. Reply, 26-27.

Instead, Merck relies on a selective reading of JHU's declarant, Dr. Goldberg's deposition testimony. Reply, 28-29. Merck's allegation that Dr. Goldberg "never used or followed the Keytruda® labeling when he treated MSI-H cancer patients" (Reply, 28 n.33), is undermined by the fact that Dr. Goldberg had personally stopped treating patients before the Keytruda® label contained the MSI-H indications (EX1243, 118:17-119:4), and that thereafter he supervised physicians administering Keytruda® "within the instructions of the KEYTRUDA label" (*id.*, 124:17-125:19). This testimony does not render the claims non-coextensive with Keytruda®'s instructed use. *See NuVasive, Inc. v. Iancu*, 752 F. App'x 985, 995-96 (Fed. Cir. 2018).

Merck's other nexus arguments also fall short. Merck implies that a presumption can only apply when a **product** is claimed, not a method. *See* Reply, 28. But that is factually and legally wrong; nexus can be presumed for method claims. *See, e.g., Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004) ("[N]exus may be inferred when...the thing (**product or method**) that is commercially successful is the invention disclosed and claimed in the patent." (quotations omitted)). The lone case that Merck cites for the contrary proposition provides no support, instead finding no presumption for an "extremely broad scope of the functionally claimed antibodies" where "unclaimed

features...undisputedly materially affect” how a claimed product functions. *Teva Pharma Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1362-63 (Fed. Cir. 2021).

Neither fact is alleged or present here.

Lastly, Merck repeats that nexus cannot be presumed because the claimed features were “indisputably known in the prior art.” Reply, 29. This circular argument necessarily fails because the claims are not anticipated, and because attorney argument alone cannot rebut the presumption of nexus. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328-29 (Fed. Cir. 2016).

b. Unexpected Results

Merck’s attempt to use [REDACTED] as evidence that the results of the claimed method were expected fails for multiple reasons.⁸ Reply, 29-30. First, Merck misrepresents [REDACTED]
[REDACTED] Reply, 29. [REDACTED]
[REDACTED] EX1245, 80:17-85:7. Moreover, Dr. Le testified that while the

⁸ Merck improperly relies on arguments from IPR2024-00240 regarding unexpected results and skepticism. Reply, 29, 31. To the extent the Board permits Merck to incorporate those arguments—it should not—JHU’s responses should likewise be considered incorporated.

inventors were “hopeful,” they “certainly did not expect the outcome of [the] study to be as positive as it was.” EX2130, ¶27. Even if [REDACTED] did articulate an expectation of success, statements to FDA are **not public**—they were confidential and thus not prior art or within a POSITA’s knowledge. *See Otsuka Pharm.*, 678 F.3d at 1296; *Sanofi-Aventis*, 748 F.3d at 1360.

That Merck and BMS had initiated similar clinical trials as of the Critical Date does not render JHU’s results expected. At that time, the only MSI-H clinical data was a single CRC patient. EX1057, 2-3; EX2176, 22; EX2072, ¶178; EX2090, ¶59. The BMS trial was limited to CRC, and the results were unknown. EX1053; EX2404, 286:25-287:12. Merck’s trial is irrelevant because it was “based on the encouraging results of [JHU’s] early study.” EX2061, 2; EX2404, 287:17-293:24. Moreover, Merck contemporaneously described JHU’s results as “exciting, while early” and MSI-H as a “**potentially** clinically meaningful tool.” EX2061, 2.

Merck’s cursory argument that JHU “incorrectly conflates degree of success with unexpectedness” also fails. Reply, 30. In Merck’s *Hoffmann-La Roche Inc. v. Apotex Inc.* case, there was an otherwise clear showing of obviousness. 748 F.3d 1326, 1334 (Fed. Cir. 2014). Moreover, “unexpected results are useful to show the improved properties provided by the claimed [inventions] are much

greater than would have been predicted.” *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quotations omitted).

c. Skepticism

Merck avoids addressing JHU’s skepticism evidence by improperly relying on hindsight, ignoring post-Critical Date evidence, and criticizing JHU’s declarants.

Merck concedes it provided no funding for JHU’s MSI-H study until after it knew the preliminary results. Reply, 31; *see also* EX1246, 108:8-112:16; EX1031, 10; EX1001, 21; EX2131, 8 (“No Funding shall be provided by Merck under this [2013] agreement.”). This contemporaneous evidence shows Merck was skeptical of JHU’s hypothesis and only had a change of heart when preliminary results were published. While Merck notes it provided its “expensive” drug, notably absent is any evidence of the cost or an explanation for why this rebuts skepticism. Reply, 31.

Nor does Merck address or rebut the contemporaneous evidence showing that even *after* JHU presented the results at ASCO and published them in NEJM, some researchers remained skeptical. Dr. Le recounted her experience at a January 2016 conference, where an audience member publicly criticized her because “it

was too early for [her] to be presenting [their] data.” EX2130, ¶50. This skepticism in the field occurred well after July 10, 2015.

Regarding the statements by Merck’s executive years later, Merck does not dispute that its executive said that “the idea was, early on” that anti-PD-1 agents (like pembrolizumab) “really [weren’t] going to work” even in CRC. POR, 70-72; EX2121, 17. Instead, Merck argued this belief was “*prior* to the Parties’ collaboration[.]” Reply, 31. But that is the point—before JHU’s unexpected clinical trial results, Merck was skeptical the claimed method would work, even in CRC, where a single patient had responded, let alone non-CRC.

Merck’s criticisms of JHU’s declarants fail. Merck takes petty aim at inventor Dr. Le for not remembering names of Merck employees from a decade ago. Reply, 6. But that is irrelevant, and regardless, her testimony stands unrebutted. As to BMS’s skepticism, JHU’s expert Dr. Lonberg testified firsthand that he thought the trial was “very risky” and noted that, ultimately, “the skepticism among decisionmakers within [BMS] prevailed,” rejecting JHU’s offer to join the MSI-H study. EX2072, ¶187. Merck has not demonstrated otherwise.

d. Long-Felt, Unmet Need

Merck now contends no unmet need existed for treating MSI-H patients. See Reply, 32-34. During the approval process, however, [REDACTED]

[REDACTED]

[REDACTED] EX2173, 17; *see also* EX2170, 5 [REDACTED]

[REDACTED]; *see also* POR, 74 (citing extensive Merck testimony). Merck ignores these statements and instead argues that FDA approval is not required by the claims. But that is not the point—an unmet need clearly existed. Reply, 32-33, n.36; *see also* EX1243, 104:11-16. Even Merck’s own expert, Dr. Oberstein readily admitted that as of the Critical Date, “MSI-high colorectal cancer patients did qualify as a high unmet need.” EX2404, 315:19-316:8. Thus, *before this dispute*, Merck recognized the unmet need for treatments for MSI-H cancer patients. But Merck *now* casts this evidence aside with a perfunctory footnote (Reply, 33, n.36), obscuring Merck’s request that the Board draw the *opposite* conclusion.

In another attempt to distract from the clear unmet need here, Merck asserts that its patents “cover[] its drug and its use broadly in the treatment of cancer.” Reply, 32. This is conclusory and unsupported—neither Merck nor its experts analyze these patents’ scope or any potential blocking effect. Further, “blocking patents”—without more—do not undermine objective indicia. *See Acorda Therapeutics, Inc. v. Roxane Lab ’ys, Inc.*, 903 F.3d 1310, 1338 (Fed. Cir. 2018).

Merck’s reliance on FDA approval (Reply, 33), similarly falls flat. Far from “reveal[ing]” his view that the long-felt need was for an FDA-approved method—an opinion that appears nowhere in his declaration or in JHU’s briefing—Dr. Goldberg simply answered Merck’s question that used the words “FDA approved.” EX1243, 98:8-11; *see also* EX2090, ¶74. Notably, Merck did not ask Dr. Goldberg whether a long-felt need existed ***more broadly*** than for an FDA-approved treatment. Without that question, Merck cannot draw its desired conclusion. Here, Dr. Goldberg simply relied upon the Keytruda® label—that ultimately resulted from FDA approval—to demonstrate the complete coextensiveness between the claimed invention and how Merck instructs MSI-H cancer treatment—i.e., according to the ’462 Patent claims. EX2090, ¶¶89-92.

Additionally, Merck’s contention that the unmet need has no nexus to the claims is undermined by Merck’s cited cases. Reply, 33. In both cases⁹, the Board found no long-felt unmet need existed because petitioners showed that known therapies in the art were treating patients ***with similar efficacies*** as the claimed

⁹ *Amerigens Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 86 (P.T.A.B. Jan. 17, 2018); *Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.*, IPR2015-01780, Paper 70 (P.T.A.B. Feb. 23, 2017).

therapies. Not so here. Before Keytruda®'s approval in 2017, the 5-year overall survival rates for patients with advanced disease were generally *less than 10%*. EX2090, ¶¶36, 50; EX2113; EX2114. Clearly the 2013 MSR posting had not met this need. Treatment with the claimed method, however, resulted in a five-year overall survival rate of **50.3%** in non-CRC MSI-H patients, meaning over half of the patients were still alive *five years* after their initial treatment—an unprecedented increase in life expectancy. EX2090, ¶¶45, 50.

Finally, despite Merck's insinuation (Reply, 34), long-felt unmet need does *not* require a separate showing of failure of others. *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 & n.5 (Fed. Cir. 2017). Even so, the abysmal overall survival rates for metastatic cancer patients, including MSI-H patients, as of the Critical Date plainly demonstrate a failure to meet this need.¹⁰

¹⁰ One response in a CRC patient, amid failures in every other CRC patient, simply cannot satisfy a long-felt need for MSI-H non-CRC patients. *Cf.* Reply, 34 n.37. The reason underlying that response (i.e., MSI-H status) was unproven until JHU's clinical trial.

e. Industry Praise

Merck dismisses JHU's extensive evidence of industry praise (POR, 64-69), in a single paragraph (Reply, 35), ignoring the direct connection between JHU's evidence and the claimed invention. Dr. Le's presentation was touted for the "identifi[cation of] the first genomic marker—[MSI-H]—to predict the clinical benefit" of pembrolizumab—i.e., the claimed treatment. EX2135, 1. Dr. Le's presentation and NEJM publication (EX1031), are directly connected to the '462 Patent, which includes large portions of the article. EX1001. Further, Merck explicitly relied on Dr. Le's results to support the Keytruda® indication for MSI-H cancer. EX2129, 74. Regarding FDA's praise, Merck ignores that FDA's press release explicitly touted the approval "based on a tumor's biomarker"—i.e., the claimed MSI-H biomarker. POR, 67-68. Even Merck praised the JHU inventors' "important scientific work" in announcing that "*first-of-its-kind*, tumor-agnostic, indication." EX2060, 2.

In its only cursory rebuttal, Merck criticizes Dr. Le's testimony regarding her plenary ASCO presentation as a "self-referential commendation." Reply, 35, n.38. But Dr. Le's statements are just the tip of the iceberg. Merck identified no evidence undermining the significance of Dr. Le's presentation, let alone any of

the other independent evidence of praise from the industry, FDA, and *Merck itself*.

See POR, 64-69.

Respectfully submitted,

Date: June 3, 2025

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CERTIFICATION UNDER 37 CFR § 42.24(d)

The undersigned hereby certifies that the word count for the foregoing
Patent Owner Sur-Reply totals 5,598 which is less than the 5,600 allowed under 37
CFR § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), the undersigned certifies that on June 3, 2025, a complete and entire copy of this Patent Owner's Sur-Reply were provided via email, to the Petitioner by serving the email correspondence addresses of record as follows:

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