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 IPR2024-00625
Patent 11,339,219

PATENT OWNER'S SUR-REPLY

TABLE OF CONTENTS

I. INTRODUCTION 1

II. ALL GROUNDS FAIL BECAUSE THE MSR DOES NOT ANTICIPATE OR RENDER OBVIOUS THE CHALLENGED CLAIMS 1

A. Merck's Inherency Arguments Fail on Multiple Levels 1

1. The MSR Does Not Inherently Disclose The Claimed Clinical Outcomes 2

2. The MSR Does Not Inherently Disclose Treating "Unresectable or Metastatic Cancer" 5

B. Merck Fails to Rebut Experimental-Use Negation 6

C. Merck's Identified Combinations Cannot Render The Challenged Claims Obvious 10

1. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating a Cancer Patient Who Has Unresectable or Metastatic Cancer 10

2. Merck Improperly Argues The Claimed Clinical Outcomes Are Inherently Disclosed 11

3. Merck Failed to Establish Reasonable Expectation that the Claimed Method of Treatment Would Succeed 12

4. Merck Failed to Rebut Much of JHU's Objective-Indicia Evidence and Argument 14

a. Nexus 14

b. Unexpected Results 17

c. Skepticism 19

d. Long Felt Unmet Need 21

e. Industry Praise 25

f. Commercial Success 26

II. CONCLUSION 28

LIST OF EXHIBITS

Exhibit Number	Description
2001	RESERVED
2002	Curriculum Vitae of Dr. Nils Lonberg
2003	Dung T. Le, Sidney Kimmel Comprehensive Cancer Center, PD-1 Blockade in Tumors with Mismatch Repair Deficiency, Presentation at 2015 ASCO Annual Meeting (May 30, 2015) (abstract available at https://meetings.asco.org/abstracts-presentations/109904)
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2019	Reply to Action of November 29, 2017 (May 29, 2018) retrieved from File History of U.S. Patent Application No. 15/611,017
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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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Exhibit Number	Description
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Exhibit Number	Description
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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

Exhibit Number	Description
2169	Highly Confidential Attorney Eyes Only Document 4 – Protective Order Material
2170	Highly Confidential Attorney Eyes Only Document 5 – Protective Order Material
2171	Highly Confidential Attorney Eyes Only Document 6 – Protective Order Material
2172	Highly Confidential Attorney Eyes Only Document 7 – Protective Order Material
2173	Highly Confidential Attorney Eyes Only Document 8 – Protective Order Material
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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
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2189	Email correspondence from Preston K. Ratliff to Nicholas Stephens and Casey Kraning dated August 20, 2024
2190	RESERVED

Exhibit Number	Description
2191	Declaration of Mr. Brian Segers (Highly Confidential Attorney Eyes Only – Protective Order Material)
2192	How Does KEYTRUDA® Work?, KEYTRUDA, https://www.keytruda.com/how-does-keytruda-work/#how-keytruda-works (last accessed Oct. 2, 2024)
2193	Merck & Co., Inc. 2014 SEC Form 10-K, dated February 27, 2015
2194	Merck & Co., Inc. 2023 SEC Form 10-K, dated February 26, 2024
2195	Merck Sharp & Dohme LLC Private Company Profile at S&P Capital IQ
2196	Johns Hopkins University Educational Institution Profile at S&P Capital IQ
2197	Research & Faculty, Johns Hopkins University, https://www.jhu.edu/research/ (last accessed Oct. 3, 2024)
2198	Nobel Prize Winners, Johns Hopkins University, https://www.jhu.edu/research/milestones/nobel-prize-winners/ (last accessed Oct. 3, 2024)
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2200	Lorenzi et al., *Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review*, Hindawi Journal of Oncology (2020)
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2202	Siegel et al., *Cancer statistics, 2024*, CA Cancer J. Clin., 74(1):12-49 (2024)
2203	Immune Checkpoint Inhibitors and Their Side Effects, American Cancer Society, https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html (last accessed Oct. 3, 2024)
2204	How KEYTRUDA® is Given, KEYTRUDA, https://www.keytruda.com/taking-keytruda/ (last accessed Oct. 3, 2024)
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	News Release, *FDA Converts to Full Approval Indication for KEYTRUDA® (pembrolizumab) for Certain Adult and Pediatric Patients With Advanced Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors*, Merck (March 29, 2023)
2207	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information. August 2024
2208	Merck & Co., Inc., Q2 2018 Earnings Call, dated July 27, 2018
2209	Merck & Co., Inc., Q3 2018 Earnings Call, dated October 25, 2018
2210	Merck & Co., Inc., Q4 2018 Earnings Call, dated February 01, 2019
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2212	List of Targeted Therapy Drugs Approved for Specific Types of Cancer, National Cancer Institute, https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list (last accessed Oct. 3, 2024)
2213	Bristol-Myers Squibb Company, Q2 2018 Earnings Call, dated July 26, 2018
2214	Bristol-Myers Squibb Company, Q3 2018 Earnings Call, dated October 25, 2018
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2216	Merck & Co., Inc. 2017 SEC Form 10-K, dated February 27, 2018
2217	Merck & Co., Inc. 2018 SEC Form 10-K, dated February 27, 2019
2218	Merck & Co., Inc. 2019 SEC Form 10-K, dated February 26, 2020
2219	Merck & Co., Inc. 2020 SEC Form 10-K, dated February 25, 2021
2220	Merck & Co., Inc. 2021 SEC Form 10-K, dated February 25, 2022
2221	Merck & Co., Inc. 2022 SEC Form 10-K, dated February 24, 2023
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2223	Siegel et al., *Cancer Statistics, 2017*, CA Cancer J. Clin., 67(1):7-30 (Jan-Feb 2017)

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2225	Siegel et al., *Cancer Statistics, 2019*, CA Cancer J. Clin., 69(1):7-34 (Jan-Feb 2019)
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2233	Cost Information and Financial Help, KEYTRUDA (pembrolizumab), https://www.keytruda.com/financial-support/ (last accessed Oct. 3, 2024)
2234	Pricing Information for OPDIVO®, Bristol Myers Squibb, https://www.bmspricinginformation.com/opdivo (last accessed Oct. 3, 2024)

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2235	Pricing Information for OPDIVO® + YERVOY®, Bristol Myers Squibb, https://www.bmspricinginformation.com/opdivo (last accessed Oct. 3, 2024)
2236	Bristol Myers Squibb. YERVOY® (ipilimumab) Full Prescribing Information. February 2024
2237	Alex Watt, *Keytruda and Opdivo: a decade review,* Pharmaceutical Technology (Sept. 30, 2024), https://www.pharmaceutical-technology.com/analyst-comment/keytruda-opdivo-decade-review/
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2240	Bristol-Myers Squibb 2017 SEC Form 10-K (Excerpt)
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2242	Bristol-Myers Squibb 2019 SEC Form 10-K (Excerpt)
2243	Bristol-Myers Squibb 2020 SEC Form 10-K (Excerpt)
2244	Bristol-Myers Squibb 2021 SEC Form 10-K (Excerpt)
2245	Bristol-Myers Squibb 2022 SEC Form 10-K (Excerpt)
2246	Bristol-Myers Squibb 2023 SEC Form 10-K (Excerpt)

Exhibit Number	Description
2247	Merck SEC Form 10-Q, for quarterly period ended March 31, 2018 (Excerpt)
2248	Merck SEC Form 10-Q, for quarterly period ended March 31, 2023 (Excerpt)
2249	Merck SEC Form 10-Q, for quarterly period ended June 30, 2023 (Excerpt)
2250	Merck SEC Form 10-Q, for quarterly period ended September 30, 2023 (Excerpt)
2251	Siegel et al., *Cancer Statistics, 2015*, CA Cancer J. Clin., 65(1):5-29 (Jan-Feb 2017)
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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
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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)

Exhibit Number	Description
2257	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatocellular Carcinoma*
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)
2261	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Anal Carcinoma*
2262	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer*, Version 1.2025 (December 4, 2024)
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)

Exhibit Number	Description
2267	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors*
2268	National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Thyroid Carcinoma*
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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

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2277	Aaltonen et al., *Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients*, Cancer Res., 54:1645–1648 (1994)
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
2281	Hsiehchen et al., *Mutation burden and anti-PD-1 outtcomes are not universally associated with immune cell infiltration or lymphoid activation*, Cancer Cell 42:1985-1987 (2024)
2282	Stenographic Deposition of Alfred I. Neugut, M.D., Ph.D., MPH taken on January 6, 2025
2283	FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors," FDA, August 17, 2021, available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors
2284	Prescription Drug Advertising | Questions and Answers," U.S. Food & Drug Administration, available at https://www.fda.gov/drugs/prescription-drug-advertising/prescription-drug-advertising-questions-and-answers
2285	JEMPERLI U.S. Prescribing Information, available at https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Jemperli/pdf/JEMPERLI-PI-MG.PDF

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2286	"Jemperli Prices, Coupons, Copay Cards & Patient Assistance," Drugs.com, available at https://www.drugs.com/price-guide/jemperli
2287	Support & Resources | JEMPERLI (dostarlimab-gxly), available at https://jemperli.com/endometrial-cancer/support-resources/
2288	GSK 2021 Annual Report
2289	GSK 2022 Annual Report
2290	GSK 2023 Annual Report
2291	Yearly average currency exchange rates, Internal Revenue Service
2292	RESERVED
2293	Segers Declaration in IPR2024-00240 (Highly Confidential Attorney Eyes Only – Protective Order Material)
2294-2400	RESERVED
2401	Copy of EX1001, U.S. Pat. No. 10,934,356, marked at January 6th Deposition of Dr. Neugut
2402	Copy of EX1005, ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013), marked at January 6th Deposition of Dr. Neugut
2403	Board Email regarding Motion to Seal dated October 4, 2024
2404	Confidential_Deposition Transcript of Paul E. Oberstein, M.D., February 19, 2025
2405-2410	RESERVED
2411	Confidential_Deposition Transcript of Sean D. Sheridan, Ph.D., February 14, 2025

Exhibit Number	Description
2412-2499	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 MSR, Merck engaged a new, Merck-sponsored declarant (EX2404, 229:21-24), 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 multiple 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 presents the Board with mischaracterizations of deposition testimony and allegations of 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, to create a false equivalency. Reply, 1, 19-21. The Board should uphold patentability of the claims.

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

A. Merck's Inherency Arguments Fail on Multiple Levels

It is undisputed that the MSR does not explicitly disclose the limitation requiring "unresectable or metastatic" cancer, or the claimed clinical outcomes.

POR, 6-15, 23-29; Reply, 9-15. Therefore, 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 "in 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, 11), 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 it was in *Montgomery.* And even if it were, the MSR does not disclose several claim limitations. Merck highlights these differences by omission when it argues that MSR disclosed a generic two-step method divorced from the actual claimed methods. Reply, 1-2. Because the claimed method is different from the method disclosed by the MSR, the results claimed by the '219 Patent cannot "inevitably flow" from the MSR.

Montgomery also distinguishes clinical trials that are at "an advanced stage of testing designed to secure regulatory approval," which can inherently disclose a method of treatment, from what we have here, i.e., "an invitation to investigate,

[which] is not an inherent disclosure." *Id.*, 1382 (citation omitted). Contrary to Merck's assertions (Reply, 10), 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.'").[1]

JHU previously explained why the MSR was an "invitation to investigate." POR, 11-15. [redacted] That the IND included a scientific rationale—as Merck argues—does not negate that the MSR was an invitation to investigate because ***all*** clinical trials have a rationale. EX2404, 155:3-156:12; Reply, 10-12. The language of JHU's scientific rationale demonstrates the investigative nature of their proposed clinical trial:

[redacted]

[1] All emphasis added herein unless otherwise noted.

[redacted]

Contrary to Merck's suggestion, no Federal Circuit authority requires a patent owner to include a specific phrase ("abstract theory") in its study proposal to describe its hypothesis or for the FDA to question the investigator's scientific rationale before a proposed study qualifies as an "invitation to investigate." Reply, 11-12.

JHU's arguments here are consistent with what it told FDA in the IND. Reply, 11-12. The JHU inventors formed a hypothesis based on an anomalous result seen in a single patient in an otherwise unsuccessful study (32 other patients did not respond) of a different drug and different hypothesis. *Compare* POR, 44 ("the JHU inventors hypothesized that the response may have been tied to the patient's MSI-H status"), *with* EX1116, 39-40 [redacted] *see also* EX1245, 80:17-85:7 (Dr. Lonberg testifying "[T]hat is not an anticipated outcome. That is a hypothesis.").

The investigative nature of the MSR is further buttressed by JHU's showing that the MSR was the first in a long series of proposal updates leading to the invention becoming ready for patenting (POR, 16-24). Against this backdrop, Merck's interpretation of inherency, which would require 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, 15-16.

2. The MSR Does Not Inherently Disclose Treating "Unresectable or Metastatic Cancer"

The standards for inherent anticipation are both clear and strict. To fill a gap based on inherency, the missing disclosure must be "necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Merck's inherency arguments defy this mandate. In short, Merck posits that a study conducted in furtherance of the MSR ***might have*** included patients with unresectable or metastatic cancer. Such speculation does not suffice for inherent anticipation. In *MEHL/Biophile Int'l. Corp. v. Milgraum*, the Federal Circuit explained that the possibility a reference ***might disclose*** a claim limitation "does not legally suffice to show anticipation" because "[o]ccasional results are not inherent." 192 F.3d 1362, 1365 (Fed. Cir. 1999). That the MSR discloses treating cancer patients ***that could*** be within the claimed subset cannot inherently anticipate results later obtained by treating ***only*** patients within the claimed subset.

Metastatic cancer is neither expressly nor inherently disclosed by the MSR. Inclusion criteria 1-4 (EX1005, 5) identify the types of cancers the patients in the proposed trial must have; none ***require*** metastatic cancer. Merck tries to import the word "metastatic" into the MSR by asking the Board to disregard Dr. Neugut's deposition testimony disavowing any equivalence between the disclosed "measurable disease" and the claimed "metastatic" cancers. EX2163, 14:3-12, 14:13-15:12 (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; *see also id.*, 49:14-51:7. Whether such patients were excluded from the proposed study is a far cry from evidence of the MSR being ***limited to*** or necessarily including 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 the "mights" and "maybes" which are insufficient to support an inherent anticipation claim. "Inherency…may not be established by probabilities or possibilities." *Montgomery*, 677 F.3d at 1380.

B. Merck Fails to Rebut Experimental-Use Negation

It is undisputed that JHU was required to post the MSR to ClinicalTrials.gov before beginning the clinical trial that yielded data supporting the '219 Patent's claims. JHU also provided unrebutted evidence demonstrating applicability of the

experimental-use exception. POR, 16-23. Merck does not respond to 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)). That is true but irrelevant—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).[2] Thus, JHU's experimental-use argument is not contrary to any Federal Circuit precedent.

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[2] The same is true for *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, IPR2022-00578, Paper 78 at 24-28 (P.T.A.B. Aug. 29, 2023).

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, 16-17. Those courts have not yet had the opportunity to specifically address negation of a printed publication made for experimental purposes.[3] *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 experimentation and to make the invention ready to patent—that publication should be negated as prior art, just as any experimental use would be negated.

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[3] This silence is unsurprising. The factual 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.

Merck next criticizes FDA expert Jennifer Newberger by claiming she did not know what ClinicalTrials.gov required in 2013. Reply, 8-9. Not so. As Ms. Newberger explained immediately after Merck's quote, the *statute*—as opposed to administrative guidance or the ClinicalTrials.gov website—*requires* the pertinent disclosures made in the MSR. EX1135, 242:16-243:3.[4]

Merck's claim (Reply, 9) that the requirements of §101 and §112 do not preclude finding the MSR to be 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 64-65. Merck's cases fall far short of showing that it is "well established" that there is no requirement for human clinical trial data to meet the requirements of §101 and §112 for claims like these. Numerous cases have come out the other way, including one cited by Merck. *See, e.g.*, *Balzarini*¸ 21 U.S.P.Q.2d 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 F.3d 1336, 1351 (Fed. Cir. 2010) (en

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[4] Merck's footnote allegation (Reply, 9 n.13) regarding "inconsistent testimony" refers to an inconsequential, inadvertent omission between declarations. *See* EX1242, 64:22-66:13.

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.

C. Merck's Identified Combinations Cannot Render The Challenged Claims Obvious

As JHU previously 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 the "unresectable or metastatic cancer" or clinical outcomes limitations; (ii) Merck did not establish a reasonable expectation of success; and (iii) JHU's significant objective-indicia evidence strongly supports non-obviousness. POR, 23-87. Merck's Reply does not overcome these deficiencies.

1. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating a Cancer Patient Who Has Unresectable or Metastatic Cancer

Merck relies on circular reasoning to arrive at its conclusion that the combinations in Grounds 2 and 4 disclose the limitations requiring "unresectable or metastatic" MSI cancer limitation required by the independent claim. Merck alleges that Benson teaches "clinical trials are only specified as ***standard of care*** for 'advanced or metastatic disease' 'after second progression'" (Reply, 14-15,

original emphasis), but this is only true for a subset of CRC patients who have advanced or metastatic disease (EX1009, 7). Merck thereafter (1) assumes cancer patients treated by the claimed method have ***advanced or metastatic CRC***, which is ***not*** disclosed in the MSR and (2) ignores Benson's repeated statement that "NCCN believes that the best management of ***any*** cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged." EX1009, 1-3; *see* POR, 23-24.

2. Merck Improperly Argues The Claimed Clinical Outcomes Are Inherently Disclosed

Merck's prior art combinations do not explicitly disclose the clinical outcome limitations in Claims 1-3. POR, 25-29. Again, Merck must rely on an improper and unsupported inherency argument. Reply, 16-19; POR, 28-29. But "the use of inherency in the context of obviousness must be carefully circumscribed because that which may be inherent is not necessarily known and that which is unknown cannot be obvious." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (quotation omitted). Yet here, Merck does nothing more than cite its failed inherency argument—where the clinical results did not "inevitably flow" from the MSR (*supra* §II.A)—and rehash what it alleges a POSITA would understand from [redacted] the prior art. Reply, 16-19. Nothing demonstrates that the clinical outcome limitations were

"necessarily known" in any of Merck's obviousness combinations. Merck has not even attempted to meet that high standard; therefore, its inherent obviousness argument necessarily fails.

3. Merck Failed to Establish Reasonable Expectation that the Claimed Method of Treatment Would Succeed

Merck has now had multiple bites at the apple, but still cannot articulate the correct standard for reasonable expectation of success ("RES"). First, 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, 29-30 (citing Pet., 35, 37); EX1003, ¶¶92-93, 97, 113-114, 120. After JHU pointed out that was the wrong standard, (POR, 29-30), Merck pivoted, arguing that a POSITA would have had a RES in carrying out a generic two-step treatment method (Reply, 19-21). Critically, Merck's generic method ***leaves out the claimed clinical outcomes***, improperly lowering the bar for RES. Merck's success argument thus fails again.

Merck argues JHU allegedly "misconstrues the [RES] standard by requiring a certain level of success and/or a certainty of success."[5] Reply, 19-21. Not true. JHU applies the standard for RES laid out in the binding precedent of *OSI*

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[5] Again, Merck mischaracterizes JHU's argument regarding the MSS cohort. POR, 33-34.

Pharmaceuticals v. Apotex Inc. POR, 4, 15-16, 31-35, 37, 43-44, 46 (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; *see* POR, 31-32.

Applying the correct standard, none of Merck's evidence provides a RES for the claimed treatment method. It is undisputed that, as in *OSI Pharma*, the MSR does not disclose any efficacy data in humans or animals, or even any *in vitro* data. 939 F.3d at 1383. Each of Merck's references provides only speculative statements, 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, Pernot's statement that MSI-H CRC patients could be "good candidates for immunotherapy," is facially speculative and limited to CRC. EX1006, 5; Pet., 36; Reply, 5, 21. As Dr. Oberstein testified, "immunotherapy" is a "very broad term" that could even include ***exercise***. EX2404, 204:25-206:4.

Dr. Lonberg addressed each of Merck's references and explained, "at best these references were inviting researchers to take an outside chance on investigating additional speculative hypotheses." POR, 40 (citing EX2072, ¶¶153-156). Dr. Lonberg's testimony stands unrebutted. As does JHU's evidence

teaching away from the claimed treatment. *Id*., 41. Merck's contention that Dr. Lonberg and Dr. Goldberg "acknowledged" that "multiple prior art references suggested that there were expected positive results for treating MSI-H tumors with PD-1 inhibitors" is flat wrong. Reply, 21. Merck 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. At best, Dr. Lonberg and Dr. Goldberg acknowledged (1) the public statements about BMS's trial and (2) the scientific rationale included in the IND, which is not prior art.

Taken together, Merck's evidence fails to demonstrate a RES in treating MSI-H CRC under *OSI Pharma*, let alone ***all types*** of MSI-H cancer, as required by the claims. 939 F.3d at 1385.

4. Merck Failed to Rebut Much of JHU's Objective-Indicia Evidence and Argument

a. Nexus

Merck provides no meaningful rebuttal to JHU's evidence demonstrating that nexus should be presumed because the claims are co-extensive with Keytruda®'s label indication for treating MSI-H patients. POR, 50-61. For example, Merck's Dr. Oberstein offers no opinion on nexus. 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.

Instead, Merck relies on a selective reading of JHU's declarant, Dr. Goldberg's deposition testimony.[6] Reply, 22-23. The claims require a comparison between the outcome of a MSI-H cancer patient and the outcome of a MSS cancer patient. EX1001, cl. 1. Merck ignores Dr. Goldberg's testimony on redirect where he expressly revised his earlier testimony and agreed, upon further review, that the Keytruda® label instructs a physician to make the claimed comparison, consistent with his declaration. *See* EX1243, 128:18-130:19; EX2090, ¶¶91-92. And relying on the Keytruda® label is an appropriate way to connect the claimed method of treatment to the use of Keytruda®. *See, e.g.*, *NuVasive, Inc. v. Iancu*, 752 F. App'x 985, 987 (Fed. Cir. 2018) (concluding Board erred in finding no nexus between claimed method and its commercial technique).

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[6] Merck's allegation that Dr. Goldberg "never used or followed the Keytruda labeling when he treated MSI-H cancer patients" (Reply, 23 n. 26), 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 who were administering Keytruda® "within the instructions of the KEYTRUDA label" (*id*., 124:17-125:19).

Merck's other nexus arguments also fall short. Merck implies that a presumption of nexus can only apply when a ***product*** is claimed, not a method of treatment. Reply, 22-23. But that is factually and legally unsound; nexus can also 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)); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020). The lone case that Merck cites for the contrary proposition provides no support, instead holding that nexus could not be presumed where there was an "extremely broad scope of the functionally claimed antibodies" as well as "unclaimed features that 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 falls back on its argument that nexus cannot be presumed because the claimed features were "indisputably known in the prior art."[7] Reply, 24. 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 at least two reasons. Reply, 24. First, it misrepresents [redacted] Moreover, Dr. Le testified that while the 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.

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[7] While Merck's rebuttal economics expert, Dr. Sheridan, references nexus in his declaration, he also bases his nexus opinion on a finding of anticipation. EX1151, ¶¶46-47.

Merck also contends that JHU "disregards" certain events before the priority date. Reply, 24. Not so. To start, "[t]o be particularly probative," evidence of unexpected results must have been unexpected to a POSITA "***at the time of the invention***." *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 693 (Fed. Cir. 2023) (internal citation omitted). The results of JHU's clinical trial were announced by Dr. Le on May 29, 2015. EX2135; EX2061. These results were based on an analysis conducted as of May 8, 2015. EX2061, 2. The unexpectedness of JHU's results should therefore be assessed as of May 8, 2015, when the invention was reduced to practice. Even if unexpectedness should be assessed as of July 10, 2015, the only non-anecdotal results available were the JHU inventors' own results.

That Merck and BMS had initiated similar clinical trials as of the Critical Date does not render JHU's results expected. As of July 10, 2015, the only clinical data on treatment of MSI-H cancers was a single CRC patient. EX1057, 2-3; EX2176, 22; EX2072, ¶176; 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; it was not even initiated until May 29, 2015. This is only logical, as Merck's trial was "based on the encouraging results of [JHU's] early study." EX2061, 1; EX2404, 287:17-293:24. Moreover, Merck contemporaneously

described JHU's results as "exciting, while early" and dMMR/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, 25. 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," as is the case here. *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.[8]

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[8] Merck improperly relies on arguments it made in IPR2024-00240. Reply, 24, 25. To the extent the Board permits Merck to incorporate those arguments—it should not—JHU's response to those arguments in its IPR2024-00240 Sur-reply should likewise be considered incorporated here.

Merck concedes that it provided no funding for JHU's MSI-H study until after it knew the preliminary results. Reply, 26; *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 that Merck was skeptical of JHU's hypothesis and only had a change of heart when preliminary results were published. This is telling evidence of nonobviousness. While Merck notes it provided its "expensive" drug, notably absent is any evidence of Merck's cost for supplying it or any explanation for why this rebuts skepticism. Reply, 26.

Nor does Merck address or rebut the contemporaneous evidence that shows that even ***after*** JHU presented the MSI-H study 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 a Merck 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" in CRC. POR, 68-69; EX2121, 17. Instead, Merck argued this belief was "***prior*** to the Parties' collaboration[.]" Reply, 26. But that is exactly the point—before JHU's

unexpected clinical trial results, Merck was skeptical the claimed method would work.

Merck's criticisms of JHU's declarants fail. Merck takes aim at inventor Dr. Le for not remembering names of Merck employees from a decade ago. Reply, 6. But this minor point does not undermine Dr. Le's testimony, and in any event, Merck provides no evidence rebutting Dr. Le's testimony. 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" regarding BMS's rejection of JHU's offer to join the MSI-H study. EX2072, ¶186. Merck has not demonstrated otherwise.

d. Long Felt Unmet Need

Before the Board, Merck contends that there was no unmet need for treating MSI-H patients before the Critical Date. Reply, 27-29. During the approval process, however, [redacted] EX2173, 17; *see also* EX2170, 5[redacted]; *see also* EX2170, 5; EX2171, 11,15, 18-20, 30, 32, 36-37; EX2172, 29; EX2167, 8-9; EX2173, 17; EX2174, 4-5. Merck ignores these statements and instead argues that FDA approval is not required by the claims. But that does not diminish the point—an unmet need clearly existed. Reply, 27-29, n.30; *see also*

EX1243, 104:11-16. To make matters worse, Merck withheld its statements from its own expert, Dr. Oberstein (EX2404, 84:3-86:5), who readily admitted that as of the Critical Date, "MSI-high colorectal cancer patients did qualify as a high unmet need" (*id*., 315:19-316:8). In other words, ***before this dispute***, Merck recognized and understood the unmet medical need for better treatments for MSI-H cancer patients. But Merck ***now*** casts this evidence aside with a perfunctory footnote (Reply, 28, n.30), obscuring the fact that Merck now asks the Board to draw the ***opposite*** conclusion than the one proffered to FDA.

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, 27. This is conclusory and unsupported—neither Merck nor its experts analyze what Merck's other patents cover or who would have been blocked from doing what. Further, so-called "blocking patents"—without more—do not undermine objective indicia of non-obviousness. *See Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1338 (Fed. Cir. 2018). Moreover, Merck itself was certainly not blocked from solving the unmet need of treatments for MSI-H patients, yet it did not.

Merck's "long felt need for FDA-approved method" argument (Reply, 27-28), 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, and perhaps intentionally, Merck did not ask Dr. Goldberg whether a long-felt need existed ***more broadly*** than just 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 doctors and patients to treat MSI-H cancer—i.e., according to the '219 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, 27-28. In both cases[9], 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 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***

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[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).

10%. EX2090, ¶¶36, 50; EX2113; EX2114. Thus, 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 and ***57.5%*** in 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. And several patients experienced full remission beyond ten years. *Id*., ¶¶71-74.

Finally, despite Merck's insinuation (Reply, 29), 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 in the industry to meet this need.[10]

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[10] Observing a complete response in a single CRC patient who was later identified as MSI-H, amid failures in every other CRC patient, does not satisfy a long-felt need. *See* Reply, 29 n.31. The reason for that complete response was unknown until JHU conducted its clinical trial.

e. Industry Praise

Merck dismisses JHU's extensive evidence of industry praise (POR, 63-68), in a single paragraph focused on nexus (Reply, 29-30), ignoring the direct connection between JHU's evidence and the claimed invention. Dr. Le's presentation was touted for the key component of the claimed invention, i.e. "the identification of the first genomic marker [MSI-H]" to "predict the clinical benefit" of pembrolizumab. EX2135, 1. Dr. Le's presentation, simultaneously published in the NEJM (EX1031), is directly connected to the '219 Patent, which includes large portions of the article. EX1001. Further, Merck explicitly relied on Dr. Le's results to support the Keytruda® indication for treating MSI-H cancer. EX2129, 74 (citing KEYNOTE-016/NCT01876511). Merck praised the JHU inventors' "important scientific work" in the context of announcing that "***first-of-its-kind***, tumor-agnostic, indication." EX2060, 2.

In the only cursory acknowledgement of JHU's evidence, Merck criticizes Dr. Le's testimony regarding her plenary presentation at ASCO as a "self-referential commendation." Reply, 29-30, n.32. But Dr. Le's statements are not in a vacuum—they are just the tip of the iceberg. Merck identified no evidence undermining the significance of Dr. Le's ASCO presentation, let alone any of the other independent evidence of praise from the industry, FDA, and ***Merck itself***. *See* POR, 63-68.

f. Commercial Success

Merck does not dispute that Keytruda® sales for MSI-H patients grew after FDA approval for JHU's patented treatment method [redacted] from 2017 to 2023. POR, 84-85; Reply, 30-32. Instead, Merck quibbles with the timing of an inflection point in sales, and comparisons of Keytruda® sales to competitor products. Reply, 31-32. Merck misses the point. Merck's estimated [redacted] in Keytruda® sales for MSI-H patients ***alone*** is sufficient to prove commercial success. POR, 85-86.

Merck's other criticisms also fail. First, no Merck declarant provided any analysis of the "other patents" covering Keytruda® or their economic impact. Reply, 31; EX1151, ¶¶31-34; EX2411, 23:4-11. "[T]he mere existence or sheer number of blocking patents does not, without more, necessarily detract from evidence of commercial success of a product or process," *Acorda*, 903 F.3d at 1338 (quotations omitted). Even so, "[i]t is not necessary…that the patented invention be solely responsible for the commercial success." POR, 87. Second, Merck is not an inventor on the '219 Patent, so Merck is incorrect that "others" (here, JHU) were deterred from developing the claimed method. Reply, 31. Third, Merck provides no data to support its argument that Dr. Segers' analysis "fail[s] to account for off-label use and the approval of another tumor-agnostic indication in 2020," or to show by how much. Reply, 32. Presumably Merck, as the company

making those sales and the corresponding profit, could have provided such data, but it declined to do so. It was therefore reasonable for JHU's economic expert Mr. Segers to conclude those sales were negligible. Finally, and perhaps most importantly, Merck fails to explain how any of its criticisms would impact, if at all, Keytruda®'s commercial success in the MSI-H population. *See, e.g.*, EX2411, 53:21-54:3, 81:1-6; EX2191, 24-30. Instead, Merck continues to make significant sales that would not have been made ***but for*** JHU's invention. *See* POR, 86-87.

Finally, Merck ignores that Mr. Segers evaluated Merck's pricing and marketing—common economic factors that might affect commercial performance—to which Merck's expert had no response. *See* EX2191, ¶¶38-44; EX2411, 53:21-54:3. Moreover, Merck failed to explain or quantify how any "brand recognition" would undermine Mr. Segers' conclusion. Reply, 32; EX2191, ¶¶24-30.

II. CONCLUSION

For these reasons, JHU respectfully requests the Board find the Challenged Claims patentable.

Respectfully submitted,

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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 5,599 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 May 29, 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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