

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 IPR2024-00624
Patent 11,325,975

PATENT OWNER'S SUR-REPLY

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LIST OF EXHIBITS

Exhibit Number	Description
2001	RESERVED
2002	Curriculum Vitae of Dr. Nils Lonberg
2003	Dung T. Le, Sidney Kimmel Comprehensive Cancer Center, PD-1 Blockade in Tumors with Mismatch Repair Deficiency, Presentation at 2015 ASCO Annual Meeting (May 30, 2015) (abstract available at https://meetings.asco.org/abstracts-presentations/109904)
2004	FDA News Release, FDA, FDA Approves First Cancer Treatment for Any Solid Tumor with a Specific Genetic Feature (May 23, 2017) available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature
2005	Gina Kolata, <i>Cancer Drug Proves to Be Effective Against Multiple Tumors</i> , N.Y. TIMES (June 8, 2017), https://www.nytimes.com/2017/06/08/health/cancer-drug-keytruda-tumors.html
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2007	News Release, Merck, Merck Receives Accelerated Approval of KEYTRUDA® (Pembrolizumab), the First FDA-Approved Anti-PD-1 Therapy (Sept. 4, 2014) available at https://www.merck.com/news/merck-receives-accelerated-approval-of-keytruda-pembrolizumab-the-first-fda-approved-anti-

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2009	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: Mar. 6, 2022) retrieved from File History of U.S. Patent No. 11,325,974 (U.S. Patent Application No. 17/131,326)
2010	RESERVED
2011	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: Mar. 6, 2022) retrieved from File History of U.S. Patent No. 11,339,219 (U.S. Patent Application No. 17/131,328)
2012	RESERVED
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2014	RESERVED
2015	Information Disclosure Statement Signed by Examiner Lisa V. Cook (Date Considered: Dec. 17, 2021) retrieved from File History of U.S. Patent No. 11,649,287 (U.S. Patent Application No. 17/465,096)
2016	RESERVED
2017	RESERVED
2018	Office Action (Nov. 29, 2017) retrieved from File History of U.S. Patent Application No. 15/611,017

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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
2020	Information Disclosure Statement Signed by Examiner Mark Halvorson (Date Considered: Oct. 6, 2019) retrieved from File History of U.S. Patent Application No. 15/523,451
2021	Sidney Kimmel Comprehensive Cancer Center (Clinical Trial Announcement NCT01876511) (June 12, 2013) (updated Oct. 6, 2017)
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2024	Brahmer et al., <i>Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates</i> , 28(19) J. Clinical Oncology 3167-75 (July 1, 2010)
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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)
2034	Mumphrey et al., <i>Distinct Mutational Processes Shape Selection of MHC Class I and Class II Mutations Across Primary and Metastatic Tumors</i> , 42(8) Cell Reports 112965 1-20 (Aug. 29, 2023)
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2037	Lotze et al., <i>Lysis of Fresh and Cultured Autologous Tumor by Human Lymphocytes Cultured in T-Cell Growth Factor</i> , 41 Cancer Research 4420-25 (Nov. 1981)

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2038	Briukhovetska et al., <i>Interleukins in Cancer: From Biology to Therapy</i> , 21 Nature Reviews Cancer 481-99 (June 3, 2021)
2039	Bod et al., <i>B-Cell-Specific Checkpoint Molecules That Regulate Anti-Tumour Immunity</i> , 619 Nature 348-56 (June 21, 2023)
2040	Wang et al., <i>CD19⁺CD24^{hi}CD38^{hi}Bregs Involved in Downregulate Helper T Cells and Upregulate Regulatory T Cells in Gastric Cancer</i> , 6(32) Oncotarget 33486-99 (Sept. 10, 2015)
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2043	Korman et al., <i>The Foundations of Immune Checkpoint Blockade and the Ipilimumab Approval Decennial</i> , 21 Nature Reviews Drug Discovery 509-28 (July 2022)
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2048	Zhong et al., <i>Comparison of the Molecular and Cellular Phenotypes of Common Mouse Syngeneic Models with Human Tumors</i> , 21 BMC Genomics Article number: 2 (Jan. 2, 2020)

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2052	IPR2024-00240, Paper No. 1 (PTAB, Nov. 30, 2023)
2053	<i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , 1:22-cv-03059-JRR, ECF 67, Claim Construction Order
2054	Information Disclosure Statement Signed by Examiner Mark Halvorson (Date Considered: Dec. 17, 2021) retrieved from File History of U.S. Patent Application No. 17/465,101
2055	Maryland, U.S. District Court – Judicial Caseload Profile, updated Dec. 2023, available at https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distprofile1231.2023.pdf
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2060	News Release, Merck, FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors (May 25, 2017)
2061	News Release, Merck, First Study Evaluating DNA Mismatch Repair as Genetic Guide for Immunotherapy Treatment with Merck's KEYTRUDA® (pembrolizumab) Presented at 2015 ASCO Annual Meeting and Published in the New England Journal of Medicine (May 29, 2015)

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2069	Exhibit 15 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. 17-15 (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/
2071	Letter to Magistrate Judge Aslan from The Johns Hopkins University, Merck Sharp & Dohme LLC v. The Johns Hopkins University, Case No. 1-22-cv-03059-JRR, D.I. 100 (D. Md. May 14, 2024)

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2073	Connolly et al., <i>Novel Mouse Models for Cancer Immunology</i> , Annual Review of Cancer Biology 6:269-91 (2022)
2074	Sun et al., <i>Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends</i> , Signal Transduction Targeted Therapy, 8:320 (2023)
2075	Dobosz et al., <i>Challenges of the Immunotherapy: Perspectives and Limitations of the Immune Checkpoint Inhibitor Treatment</i> Int. J. Mol. Sci., 23, 2847:1-17 (2022)
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2079	<i>Merck's trial of Keytruda regimen fails to meet primary endpoint</i> , Clinical Trials Arena (May 10, 2024), https://www.clinicaltrialsarena.com/news/merck-trial-keytruda-regimen/?cf-view
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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2082	Lawrence et al., <i>Mutational heterogeneity in cancer and the search for new cancer-associated genes</i> , Nature 499:214-18 (July 11, 2013)
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2086	McGranahan et al., <i>Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade</i> , Science 351(6280):1463-69 (Mar. 25, 2016)
2087	Hellmann et al., <i>Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer</i> , Cancer Cell 33, 853-861 (May 14, 2018)
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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)

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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)
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2102	Saltz et. al., <i>Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer, Irinotecan Study Group, N. Engl. J. Med. 343(13):905-13 (2000)</i>
2103	Sanoff et al., <i>Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741, J. Clin. Oncol. 26:5721-5727 (2008)</i>
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2105	Saltz et al., <i>Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor, J. Clin. Oncol. 22:1201-1208 (Apr. 1, 2004)</i>
2106	Van Cutsem et al., <i>Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer, N. Engl. J. Med. 360(14):1408-17 (Apr. 2, 2009)</i>
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2109	Venook et al., <i>Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial</i> , JAMA 317(23):2392-2401 (2017)
2110	McRee et al., <i>Optimal management of metastatic colorectal cancer: current status</i> , Drugs 71(7):869-884 (2011)
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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/
2124	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (May 23, 2017)
2125	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Oct. 2015)
2126	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Aug. 2016)
2127	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (Mar. 2017)
2128	Merck & Co., Inc. KEYTRUDA® (pembrolizumab), Full Prescribing Information (May 18, 2017)

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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...
2134	News Release, <i>Merck Makes \$3 Million Charitable Donation to Support Swim Across America</i> , Merck (Oct. 10, 2017), https://www.merck.com/news/merck-makes-3-million-charitable-donation-to-support-swim-across-america/
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
2136	Video interview, Dung T. Le, MD, and Axel Grothey, MD, on PD-1 Blockade in Tumors With Mismatch Repair Deficiency, 2015 ASCO Annual Meeting, recorded on May 31, 2015, https://ascopost.com/archive/meetings/2015-asco-annual-meeting/dung-t-le-md-and-axel-grothey-md-on-pd-1-blockade-in-tumors-with-mismatch-repair-deficiency/

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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)
2139	D. Moher, <i>Clinical-trial registration: a call for its implementation in Canada</i> , <i>CMAJ</i> 149(11):1657-58 (Dec. 1, 1993)
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2144	RESERVED
2145	About ClinicalTrials.gov, Nat’l Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/about-site/about-ctg
2146	Krleza-Jerić et al., <i>7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials</i> , <i>Croat. Med. J.</i> 50:105-10 (2009)
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2149	Protocol Registration Data Element Definitions for Interventional and Observational Studies, Nat'l Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/policy/protocol-definitions
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)
2153-2162	RESERVED
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)
2164	EX1096 from '187 proceeding, IPR2024-00649, Ajani et al., <i>National Comprehensive Cancer Network. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines</i> , J. Natl Compr. Canc. Netw., 11(5):531-46 (May 1, 2013)
2165	Record History Tab, Study of MK03475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B, and C), National Library of Medicine, ClinicalTrials.gov (Jan. 4, 2016), https://clinicaltrials.gov/study/NCT01876511?tab=history&a=12#version-content-panel
2166	Record History Tab, Study of MK03475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B, and C), National Library of Medicine, ClinicalTrials.gov, Compare between June 10, 2013 and Jan. 4, 2016,

Exhibit Number	Description
	https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1&b=12#version-content-panel
2167	Highly Confidential Attorney Eyes Only Document 1 – Protective Order Material
2168	Highly Confidential Attorney Eyes Only Document 2 – Protective Order Material
2169	Highly Confidential Attorney Eyes Only Document 4 – Protective Order Material
2170	Highly Confidential Attorney Eyes Only Document 5 – Protective Order Material
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
2174	Highly Confidential Attorney Eyes Only Document 9 – Protective Order Material
2175	André et al., KEYNOTE-177 Investigators. <i>Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer</i> , N. Engl. J. Med., 383(23):2207-2218 (Dec. 3, 2023)
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2177	Exhibit 3, The Johns Hopkins University's Infringement of U.S. Patent No. 11,325,975 by KEYTRUDA claim chart, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR
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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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2186	Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, U.S. Dept. of HHS, FDA (May 2014)

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2187	Highly Confidential Attorney Eyes Only Document 11 – Protective Order Material
2188	Highly Confidential Attorney Eyes Only Document 12 – Protective Order Material
2189	Email correspondence from Preston K. Ratliff to Nicholas Stephens and Casey Kraning dated August 20, 2024
2190	RESERVED
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
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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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2199	Is KEYTRUDA® Right for You?, KEYTRUDA, https://www.keytruda.com/msi-h/treatment-options (last accessed Oct. 3, 2024)
2200	Lorenzi et al., <i>Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review</i> , Hindawi Journal of Oncology (2020)
2201	Boland et al., <i>Microsatellite Instability in Colorectal Cancer</i> Boland, Gastroenterology Volume 138, Issue 6, 2073 - 2087.e3 (2010)
2202	Siegel et al., <i>Cancer statistics, 2024</i> , 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, <i>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</i> , Merck (March 29, 2023)

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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
2211	Merck & Co., Inc., Q1 2019 Earnings Call, dated April 30, 2019
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
2215	Bristol-Myers Squibb Company, Q1 2019 Earnings Call, dated April 25, 2019
2216	Merck & Co., Inc. 2017 SEC Form 10-K, dated February 27, 2018
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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., <i>Cancer Statistics, 2017</i> , CA Cancer J. Clin., 67(1):7-30 (Jan-Feb 2017)
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2229	Siegel et al., <i>Cancer Statistics, 2023</i> , CA Cancer J. Clin., 73(1):17-48 (2023)
2230	Microsatellite Instability Biomarker (MSI-H), Colorectal Cancer Alliance, colorectalcaner.org/treatment/types-treatment/why-biomarkers-matter/types-biomarkers/microsatellite-instability (last accessed Oct. 3, 2024)

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2231	Merck Q2 2017 Earnings Call, dated July 28, 2017
2232	Abel et al., <i>Cancer-Related Direct-to-Consumer Advertising: Awareness, Perceptions, and Reported Impact Among Patients Undergoing Active Cancer Treatment</i> , J. Clin. Oncol., 27(25):4182-7 (Sept. 1, 2009)
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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2236	Bristol Myers Squibb. YERVOY® (ipilimumab) Full Prescribing Information. February 2024
2237	Alex Watt, <i>Keytruda and Opdivo: a decade review</i> , Pharmaceutical Technology (Sept. 30, 2024), https://www.pharmaceutical-technology.com/analyst-comment/keytruda-opdivo-decade-review/
2238	Merck 2015 SEC Form 10-K, dated February 26, 2016 (Excerpt)
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2240	Bristol-Myers Squibb 2017 SEC Form 10-K (Excerpt)

Exhibit Number	Description
2241	Bristol-Myers Squibb 2018 SEC Form 10-K (Excerpt)
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)
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)
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2251	Siegel et al., <i>Cancer Statistics, 2015</i> , CA Cancer J. Clin., 65(1):5-29 (Jan-Feb 2017)
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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>

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2262	National Comprehensive Cancer Network, <i>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer</i> , Version 1.2025 (December 4, 2024)
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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>
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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
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2276	Boland. <i>Henry T. Lynch, MD (January 4, 1928–June 2, 2019)</i> , <i>Gastroenterol.</i> , 157(4):905-906
2277	Aaltonen et al., <i>Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients</i> , <i>Cancer Res.</i> , 54:1645–1648 (1994)
2278	Aarnio et al., <i>Cancer risk in mutation carriers of DNA-mismatch repair genes</i> , <i>Int. J. Cancer</i> 81:214–218 (1999)
2279	Chen et al., <i>Small bowel adenocarcinoma</i> , <i>Clin. Colon Rectal. Surg.</i> 31:267-277 (2018)
2280	Center for Drug Evaluation and Research: Manual of Policies and Procedures, Office of New Drugs, “Review Designation Policy: Priority (P) and Standard (S),” https://www.fda.gov/media/72723/download
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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
2286	“Jemperli Prices, Coupons, Copay Cards & Patient Assistance,” Drugs.com, available at https://www.drugs.com/price-guide/jemperli
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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	Press Release, Bristol Myers Squibb, Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the

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	U.S. Food and Drug Administration (Dec. 22, 2014)
2292	Bristol Myers Squibb - Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration, December 22, 2014
2293-2400	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
2405-2410	RESERVED
2411	Confidential_Deposition Transcript of Sean D. Sheridan, Ph.D., February 14, 2025
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

Exhibit Number	Description
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, 22-24. 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 limitations requiring “prior cancer therapy drug,” “progressed after...the prior cancer therapy drug,” “metastatic” cancer, or the claimed clinical outcomes. POR, 6-15, 25-31; Reply, 10-17. 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, 11-12), 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 the 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 '975 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, 10-11), 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]

[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]
[REDACTED]
[REDACTED]

¹ All emphasis added herein unless otherwise noted.

[REDACTED]

[REDACTED]

[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, 10-11.

JHU’s arguments here are consistent with what it told FDA in the IND. Reply, 10-11. 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, 46 (“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 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, 18-25). 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, 16-17.

2. The MSR Does Not Inherently Disclose "a Prior Cancer Therapy Drug" or "Progressed After...the Prior Cancer Therapy Drug"

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 who had received a prior cancer therapy drug or who progressed after receiving the prior drug. 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.

Not only does Merck disregard the applicable law, it disregards unhelpful facts. For example, Merck’s Dr. Oberstein conceded that a patient *could be* included in the clinical trial proposed by the MSR even if she had not received a prior cancer therapy drug. EX2404, 276:7-25; *see also id.*, 277:2-10; EX2163, 99:13-21 (Dr. Neugut agreeing MSR “leaves out” previous treatment and progression). JHU’s Dr. Lonberg agreed, testifying the MSR “does not require treatment of only patients who have received at least one prior cancer therapy.” EX1245, 57:10-14. Dr. Lonberg testified the MSR provides “no general exclusion for prior therapies,” paralleling Drs. Oberstein and Neugut’s testimony. *Id.*, 56:18-57:4; EX2404, 277:2-10; EX2163, 99:13-21. Because the claimed requirement that the patient receive a prior cancer therapy drug is *not necessarily present* in the MSR, the MSR cannot inherently anticipate this limitation.

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

Merck’s inherency challenge to dependent claims 6-7 and 13-14, which require the cancer to be “metastatic,” fails for similar reasons. 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 ’975 Patent’s claims. JHU also provided unrebutted evidence demonstrating applicability of the

experimental-use exception. POR, 18-25. 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. *See 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.

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, 18-19. 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.

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, 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, 9-10) 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

⁴ Merck’s footnote allegation (Reply, 9 n.15) 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 “prior therapy,” “progressed,” “metastatic” 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, 25-86. Merck’s Reply does not overcome these deficiencies.

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

Merck relies on circular reasoning to arrive at its conclusion that the combinations in Grounds 2 and 4 disclose the limitations requiring “prior cancer therapy drug,” “progressed...after the prior cancer therapy drug,” and “metastatic” cancer. Merck alleges that Benson teaches “clinical trials are only specified in the *standard of care* as therapy ‘after second progression’” (Reply, 14, 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, 25-27.

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, and 9-10. POR, 27-31. Again, Merck must rely on an improper and unsupported inherency argument. Reply, 19-22; POR, 31. 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] and the prior art. Reply, 19-22. 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, 32-33 (citing Pet., 38, 40, 52-53); EX1003, ¶¶100-101, 105, 124-125, 131. After JHU pointed out that was the wrong standard (POR, 32-33), Merck pivoted, arguing that a POSITA would have had a RES in carrying out a generic two-step treatment method (Reply, 22-24). Critically, Merck’s generic method *leaves out the claimed clinical outcomes*, improperly lowering the bar for RES. Merck’s RES argument thus fails again.

Merck argues that JHU “misconstrues the [RES] standard by requiring a certain level of success and/or a certainty of success.”⁵ Reply, 23. Not true. JHU

⁵ Again, Merck mischaracterizes JHU’s argument regarding the MSS cohort. POR, 34-36.

applies the standard for RES laid out in the binding precedent of *OSI Pharmaceuticals v. Apotex Inc.* POR, 4, 16-17, 33-34, 36-39, 45-46, 48 (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, 33-35.

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., 39; Reply, 5, 24. 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, 42-43 (citing EX2072,

¶¶154-157). Dr. Lonberg’s testimony stands unrebutted. As does JHU’s evidence teaching away from the claimed treatment. *Id.*, 43. Merck’s contention that Dr. Lonberg and Dr. Goldberg “acknowledged” that “multiple prior art references suggested there were expected positive results for treating MSI-H tumors with PD-1 inhibitors” is flat wrong. Reply, 24. 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. *See* 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, 52-60. 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 in part on a selective reading of JHU's declarant, Dr. Goldberg's deposition testimony.⁶ Reply, 25-26. The claims require a comparison between the outcome of a MSI-H cancer patient and the outcome of a "reference patient," i.e., a MSS cancer patient. EX1001, cls. 1, 9. Merck claims "there is no legal or factual support to establish a presumption of nexus here based on the label." Reply, 26. But in doing so 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, ¶¶92-93. And relying on the Keytruda® label is an appropriate way to

⁶ Merck's allegation that Dr. Goldberg "never used or followed the Keytruda® labeling when he treated MSI-H cancer patients," (Reply, 25 n.29), 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).

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).

Merck's other nexus arguments also fall short. Merck implies that a presumption of nexus can only apply when a **product** is claimed, arguing that the '975 Patent is not a product patent. Reply, 25. But that is factually and legally unsound, as Federal Circuit precedent establishes that 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)); *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, let alone 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, 26. 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, 27. First, it misrepresents [REDACTED]

[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.

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, ¶¶45-46.

That Merck and BMS had initiated similar clinical trials as of the Critical Date does not render JHU's results expected. As of the Critical Date, 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, because it was "based on the encouraging results of [JHU's] early study." EX2061, 1; EX2404, 287:17-293:10. 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, 28. 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

Merck concedes it provided no funding for JHU's MSI-H study until after it knew the preliminary results. Reply, 28-29; *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, 28-29.

⁸ Merck improperly relies on arguments it made in IPR2024-00240. Reply, 27, 28. 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.

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, 67-68; EX2121, 17. Instead, Merck argued this belief was “*prior* to the Parties’ collaboration[.]” Reply, 28-29. 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, 7. 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, ¶187. 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, 30-32. During the approval process, however, [REDACTED]
[REDACTED] EX2173, 17;
see also EX2170, 5 [REDACTED]
[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, 30-32, n.33; *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, 30, n.33), obscuring the fact that Merck now asks the Board to 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, 30. This is conclusory and unsupported—neither Merck nor its experts analyze what these patents cover or any potential blocking effect. 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 “an FDA-approved method” argument (Reply, 30-31), 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 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 ’975 Patent claims. EX2090, ¶¶89-93.

Additionally, Merck's contention that the unmet need has no nexus to the claims is undermined by Merck's cited cases. Reply, 30-31. 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 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. 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, 31-32), long-felt unmet need does *not* require a separate showing of failure of others. *Millennium Pharms., Inc.*

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).

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

e. Industry Praise

Merck dismisses JHU's extensive evidence of industry praise (*see* POR, 62-67) in a single paragraph focused on nexus (Reply, 32-33), 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 an anti-PD1 antibody (pembrolizumab). EX2135, 1. Dr. Le's presentation, simultaneously published in the NEJM (EX1031), is directly connected to the '975 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).

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. Reply, 32 n.34. The reason for that complete response was unknown until JHU conducted its clinical trial.

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, 32 n.35. 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, 62-67.

f. Commercial Success

Merck does not dispute that Keytruda® sales for the non-first line treatment of MSI-H patients grew after FDA approval for JHU’s patented treatment method [REDACTED] billion from 2017 to 2023. POR, 83-84; Reply, 33-35. Instead, Merck quibbles with the timing of an inflection point in sales, and comparisons of Keytruda® sales to competitor products. Reply, 34. Merck misses the point. Merck’s estimated [REDACTED] in Keytruda® sales for non-first line treatment MSI-H patients *alone* is sufficient to prove commercial success. POR, 84-85.

Merck’s other criticisms also fail. First, no Merck declarant provided any analysis of the “other patents” covering Keytruda® or their economic impact. Reply, 33-34; 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, 86. Second, Merck is not an inventor on the ’975 Patent, so Merck is incorrect that “others” (here, JHU) were deterred from developing the claimed method. Reply, 33-34. Third, 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, 85-86.

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, 34-35; 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 5,596 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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