

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 IPR2024-00647
Patent 11,649,287 B2

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
2006	Laurie McGinley, <i>'This is not the end': Using immunotherapy and a genetic glitch to give cancer patients hope</i> , WASH. POST (May 28, 2017), https://www.washingtonpost.com/national/health-science/this-is-not-the-end-experimental-therapy-that-targets-genes-gives-cancer-patients-hope/2017/05/28/cdce31de-365c-11e7-b373-418f6849a004_story.html
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-pd-1-therapy/
2008	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2023 Financial Results (Feb. 1, 2024) available at https://s2.q4cdn.com/584635680/files/doc_news/Merck-Announces-Fourth-Quarter-and-Full-Year-2023-Financial-Results-2024.pdf
2009-2021	RESERVED

Exhibit Number	Description
2022	Bacher et al., <i>Development of a Fluorescent Multiplex Assay for Detection of MSI-High Tumors</i> , 20(4-5) Disease Markers 237-50 (2004)
2023	Diaz et al., <i>Liquid Biopsies: Genotyping Circulating Tumor DNA</i> , 32(6) J. Clinical Oncology 579-86 (Feb. 20, 2014)
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)
2025	RESERVED
2026	Mandrekar et al., <i>All-Comers versus Enrichment Design Strategy in Phase II Trials</i> , 6(4) J. Thoracic Oncology 658-60 (Apr. 1, 2011)
2027	Freidlin et al., <i>Randomized Clinical Trials With Biomarkers: Design Issues</i> , 102(3) J. Nat'l Cancer Inst. 152-60 (Feb. 3, 2010)
2028	Malik et al., <i>Consensus Report of a Joint NCI Thoracic Malignancies Steering Committee: FDA Workshop on Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer Leading to the Inception of "Master Protocols" in Lung Cancer</i> , 9(10) J. Thoracic Oncology 1443-48 (Oct. 2014)
2029-2031	RESERVED
2032	NIH NATIONAL CANCER INSTITUTE, <i>What is Cancer?</i> (last updated Oct. 11, 2021), https://www.cancer.gov/about-cancer/understanding/what-is-cancer
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)
2035	Jenkins et al., <i>Antigen Presentation by Chemically Modified Splenocytes Induces Antigen-Specific T Cell Unresponsiveness In Vitro and In Vivo</i> , 165(2) J. Experimental Med. 302-19 (Feb. 1, 1987)
2036	Wherry et al., <i>Viral Persistence Alters CD8 T-Cell Immunodominance and Tissue Distribution and Results in Distinct</i>

Exhibit Number	Description
	<i>Stages of Functional Impairment</i> , 77(8) J. Virology 4911-27 (Apr. 2003)
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)
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)
2041	Michaud et al., <i>Regulatory B Cells in Cancer</i> , 299(1) Immunological Reviews 74-92 (Dec. 23, 2020)
2042	Nakhoda et al., <i>Addressing Recent Failures in Immuno-Oncology Trials to Guide Novel Immunotherapeutic Treatment Strategies</i> , 34 Pharmaceutical Medicine 83-91 (Mar. 10, 2020)
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)
2044	NIH NATIONAL CANCER INSTITUTE, <i>Immune Checkpoint Inhibitors</i> (last updated Apr. 7, 2022), https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors
2045	Boland et al., <i>Microsatellite Instability in Colorectal Cancer</i> , 138(6) Gastroenterology 2073-87 (May 2010)
2046	Branch et al., <i>Immune Surveillance in Colorectal Carcinoma</i> , 9 Nature Genetics 231-32 (Mar. 1995)
2047	Kloor et al., <i>Immune Evasion of Microsatellite Unstable Colorectal Cancers</i> , 127(5) Int'l J. Cancer 1001-10 (Sept. 1, 2010)
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)
2049	Thomas et al., <i>Advancing Translational Research for Colorectal Immuno-Oncology</i> , 129 British J. Cancer 1442-50 (Aug. 10, 2023)

Exhibit Number	Description
2050	Lacombe et al., <i>The Dream and Reality of Histology Agnostic Cancer Clinical Trials</i> , 8(6) Molecular Oncology 1057-63 (Sept. 12, 2014)
2051	David Shaywitz, <i>The Startling History Behind Merck's New Cancer Blockbuster</i> , FORBES (July 26, 2017)
2052-2059	RESERVED
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)
2062	News Release, Merck, Merck Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for KEYTRUDA® (pembrolizumab) in Advanced Colorectal Cancer (Nov. 2, 2015)
2063	Thomson Reuters Streetevents, Edited Transcript MRK - Q4 2018 Merck & Co Inc Earnings Call, event date Feb. 1, 2019
2064	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2022 Financial Results (Feb. 2, 2023)
2065	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2021 Financial Results (Feb. 3, 2022)
2066	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2020 Financial Results (Feb. 4, 2021)
2067	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2019 Financial Results (Feb. 5, 2020)
2068	News Release, Merck, Merck Announces Fourth-Quarter and Full-Year 2018 Financial Results (Feb. 1, 2019)
2069	Exhibit 22 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. 17-12 (D. Md. April 21, 2023)

Exhibit Number	Description
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)
2072	Declaration of Dr. Nils Lonberg
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)
2076	Jonathan Gardner, <i>Merck suffers bad week as 3 Keytruda combination trials fail</i> , BioPharma Dive (Dec. 8, 2023), https://www.biopharmadive.com/news/merck-keytruda-combination-trials-fail-patent-cliff/701975/
2077	Angus Liu, <i>Merck's Keytruda flunks pivotal studies in lung and skin cancers</i> , Fierce Pharma (Aug. 29, 2024), https://www.fiercepharma.com/pharma/mercks-keytruda-flunks-early-stage-lung-and-skin-cancer-tests
2078	Jared S. Hopkins, <i>Merck Keeps Striking Out on Expanding Its Cancer-Drug Juggernaut</i> , The Wall Street Journal (April 26, 2023), https://www.wsj.com/articles/merck-keeps-striking-out-on-expanding-its-cancer-drug-juggernaut-637c83d4
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

Exhibit Number	Description
2081	van der Bruggen et al., <i>A gene encoding an antigen recognized by 7cytolytic T lymphocytes on a human melanoma</i> , Science 254:1643-47 (Dec. 13, 1991)
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)
2083	Shigehisa Kitano et al., <i>Myeloid-derived suppressor cell quantity prior to treatment with ipilimumab at 10mg/kg to predict for overall survival in patients with metastatic melanoma</i> , J. of Clin. Oncology 30(15), 2518 (May 20, 2012)
2084	Snyder et al., <i>Genetic basis for clinical response to CTLA-4 blockade in melanoma</i> , N. Engl. J. Med. 371(23):2189-99 (Dec. 4 2014)
2085	Chan et al., <i>Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma</i> , N. Engl. J. Med. 373(20):1984 (Nov. 12, 2015)
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)
2088	RESERVED
2089	Boyiadzis et al., <i>Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease</i> , J. ImmunoTher. Cancer 6:35 (May 14, 2018)
2090	Declaration of Dr. Richard Goldberg
2091	Bray et al., <i>Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries</i> , CA Cancer J. Clin. 74:229-263 (2024)
2092	Zeineddine et al., <i>Survival improvement for patients with metastatic colorectal cancer over twenty years</i> , NPJ Precis. Oncol. 7:16 (2023)
2093	Patel et al., <i>The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection</i> , Lancet Gastroenterol Hepatol. 7: 262–74 (2022)
2094	Frank A. Sinicrope, <i>Increasing Incidence of Early-Onset Colorectal Cancer</i> , N. Engl. J. Med. 86:1547-58 (Apr. 21, 2022)

Exhibit Number	Description
2095	Frank A. Sinicrope, <i>Lynch Syndrome-Associated Colorectal Cancer</i> , N. Engl. J. Med. 379:764-73 (Aug. 23, 2018)
2096	Sargent et al., <i>Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer</i> , J. Clin. Oncol. 28:3219-3226 (July 10, 2010)
2097	Keung et al., <i>The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care</i> , Expert Rev. Anticancer Ther. 18(8):775–784 (2018)
2098	Ogunwobi et al., <i>Biomarkers in Colorectal Cancer: Current Research and Future Prospects</i> , Int. J. Mol. Sci. 21, 5311 (2020)
2099	Kong et al., <i>Prolonged surveillance of colorectal cancer patients after curative surgeries beyond five years of follow-up</i> , Ann. Transl. Med. 7(21):608 (2019)
2100	<i>Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate</i> , Advanced Colorectal Cancer Meta-Analysis Project 10:896:903 (1992)
2101	Dy et al., <i>Long-term survivors of metastatic colorectal cancer treated with systemic chemotherapy alone: a North Central Cancer Treatment Group review of 3811 patients, N0144</i> , Clin. Colorectal Cancer 8(2):88-93 (2009)
2102	Saltz et. al., <i>Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer, Irinotecan Study Group</i> , N. Engl. J. Med. 343(13):905-13 (2000)
2103	Sanoff et al., <i>Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741</i> , J. Clin. Oncol. 26:5721-5727 (2008)
2104	Hurwitz et al., <i>Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer</i> , N. Engl. J. Med. 350(23):35-42 (June 3, 2004)
2105	Saltz et al., <i>Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor</i> , J. Clin. Oncol. 22:1201-1208 (Apr. 1, 2004)

Exhibit Number	Description
2106	Van Cutsem et al., <i>Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer</i> , N. Engl. J. Med. 360(14):1408-17 (Apr. 2, 2009)
2107	Van Cutsem et al., <i>Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer</i> , J. Clin. Oncol. 25(13):1658-64 (May 1, 2007)
2108	Tabernero et al., <i>Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial</i> , Eur. J. Cancer 50:320-331 (2014)
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)
2111	Lucas et al., <i>A decade of advances in cytotoxic chemotherapy for metastatic colorectal cancer</i> , Clin. Colorectal Cancer 10(4):238-44 (Dec. 2011)
2112	Modest et al., <i>Treatment sequencing in metastatic colorectal cancer</i> , Eur. J. Cancer 109:70-83 (2019)
2113	Grothey et al., <i>Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial</i> , Lancet 381: 303–12 (Jan. 26, 2013)
2114	Mayer et al., <i>Randomized trial of TAS-102 for refractory metastatic colorectal cancer</i> , N. Engl. J. Med. 372(20):1909-19 (May 14, 2015)
2115	RESERVED
2116	Robert et al., <i>Pembrolizumab versus Ipilimumab in Advanced Melanoma</i> , N. Engl. J. Med. 372(26):2521-32 (June 25, 2015)
2117	Reck et al., <i>Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer</i> , N. Engl. J. Med. 375(19):1823-33 (Nov. 10, 2016)

Exhibit Number	Description
2118	Le et al., <i>Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade</i> , Science 357:409–413 (July 28, 2017)
2119	Ethical Guidelines, Ethics in Clinical Research, NIH Clinical Center, https://www.cc.nih.gov/recruit/ethics (last accessed Sept. 26, 2024)
2120	The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research (April 18, 1979)
2121	The Cancer Letter, Vol. 43, No. 38, Oct. 13, 2017
2122	The Cancer Letter, Vol. 48, No. 23, June 10, 2022
2123	<i>How Beth Carner went from six weeks left to live with stage 4 colon cancer to complete remission</i> , Cancer History Project (June 10, 2022), https://cancerhistoryproject.com/article/how-beth-carner-went-from-six-weeks-left-to-live-with-stage-4-colon-cancer-to-complete-remission/
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)
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

Exhibit Number	Description
	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/
2137	Declaration of Ms. Jennifer Newberger
2138	K. Dickersin, Report from the panel on the Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials, <i>Controlled Clinical Trials</i> 9:76-81 (1988)
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)
2140	International Clinical Trials Registry Platform (ICTRP), World Health Organization, https://www.who.int/clinical-trials-registry-platform (last accessed Oct. 3, 2024)
2141	The Food and Drug Administration Modernization Act of 1997, Pub. L. 105–115, Nov. 21, 1997
2142	Laine et al., <i>Update on Trials Registration: Clinical Trial Registration: Looking Back and Moving Ahead</i> , <i>ICMJE</i> (June 2007)
2143	Food and Drug Administration Amendments Act of 2007, Pub. L. 110–85, Sept. 27, 2007, 121 Stat. 823
2144	RESERVED
2145	About ClinicalTrials.gov, Nat’l Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/about-site/about-ctg

Exhibit Number	Description
2146	Krleza-Jerić et al., <i>7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials</i> , Croat. Med. J. 50:105-10 (2009)
2147	42 C.F.R. Pt. 11 (2024)
2148	42 U.S.C. § 282(j)
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
2151	21 U.S.C. § 333 - Penalties
2152	De Angelis et al., <i>Clinical trial registration: a statement from the International Committee of Medical Journal Editors</i> , Editorial, Clinical Trial Registration (2004)
2153	<i>Response</i> , The American Heritage dictionary of the English Language (5 th ed. 2011)
2154	<i>Response</i> , Collins Dictionary (10 th ed. 2009)
2155	<i>Response</i> , Oxford Dictionary of English, (3 rd ed. 2010)
2156	<i>Response</i> , The Chambers Dictionary (13 th ed. 2016)
2157	<i>Response</i> , Merriam-Webster's Collegiate Dictionary (11 th ed. 2014)
2158	<i>Response</i> , Cambridge Advanced Learner's Dictionary (4 th ed. 2013)
2159	<i>Response</i> , Webster's Third New International Dictionary of the English Language (2002)
2160	Plaintiff Merck Sharp & Dohme LLC's Opening Brief Regarding Claim Construction, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 82 (D. Md. May 1, 2024)
2161	The Johns Hopkins University's Opening Claim Construction Brief, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 81 (D. Md. May 1, 2024)
2162	Plaintiff Merck Sharp & Dohme LLC's Responsive Brief Regarding Claim Construction, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 107 (D. Md. May 1, 2024)

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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, 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
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2173	Highly Confidential Attorney Eyes Only Document 8 – Protective Order Material
2174	Highly Confidential Attorney Eyes Only Document 9 – Protective Order Material

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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)
2176	Robin Marantz Henig, Could Immunotherapy Lead the Way to Fighting Cancer?, Smithsonian Magazine (April 2018), https://www.smithsonianmag.com/innovation/immunotherapy-lead-way-fighting-cancer-180968392/
2177	Exhibit 8, The Johns Hopkins University's Infringement of U.S. Patent No. 11,649,387 by KEYTRUDA claim chart, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR
2178	Marques et al., <i>Tumor mutational burden in colorectal cancer: Implications for treatment</i> , Crit. Rev. Oncol. Hematol. (Apr. 12, 2024)
2179	Le et al., <i>Phase II Open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164</i> , J. Clin. Oncol. (38:1(1-19) (2019)
2180	Anagha Nair, High Impact Journals 2024 – Key to deciding the right journal?, Enago Academy (Feb. 19, 2024), https://www.enago.com/academy/top-high-impact-factor-journals/
2181	Highly Confidential Attorney Eyes Only Document 3 – Protective Order Material
2182	Highly Confidential Attorney Eyes Only Document 10 – Protective Order Material
2183	Email correspondence from Luis Diaz to Amy Meister and Mr. Robert Iannone dated December 27, 2012, production document Bates stamped JHU MERCK00027065
2184	Breakthroughs in Immunotherapy, Swim Across America, https://www.swimacrossamerica.org/site/SPageNavigator/Breakthroughs_35.html (last accessed Sept. 26, 2024)
2185	RESERVED
2186	Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, U.S. Dept. of HHS, FDA (May 2014)

Exhibit Number	Description
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	Segers Declaration (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)
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-

Exhibit Number	Description
	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)
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
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

Exhibit Number	Description
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
2222	RESERVED
2223	Siegel et al., <i>Cancer Statistics, 2017</i> , CA Cancer J. Clin., 67(1):7-30 (Jan-Feb 2017)
2224	Siegel et al., <i>Cancer Statistics, 2018</i> , CA Cancer J. Clin., 68(1):7-30 (Jan-Feb 2018)
2225	Siegel et al., <i>Cancer Statistics, 2019</i> , CA Cancer J. Clin., 69(1):7-34 (Jan-Feb 2019)
2226	Siegel et al., <i>Cancer Statistics, 2020</i> , CA Cancer J. Clin., 70(1):7-30 (Jan-Feb 2020)
2227	Siegel et al., <i>Cancer Statistics, 2021</i> , CA Cancer J. Clin., 71(1):7-33 (Jan-Feb 2021)
2228	Siegel et al., <i>Cancer Statistics, 2022</i> , CA Cancer J. Clin., 72(1):7-33 (Jan-Feb 2022)
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, colorectalcancer.org/treatment/types-treatment/why-biomarkers-matter/types-biomarkers/microsatellite-instability (last accessed Oct. 3, 2024)
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)
2235	Pricing Information for OPDIVO® + YERVOY®, Bristol Myers Squibb, https://www.bmspricinginformation.com/opdivo (last accessed Oct. 3, 2024)

Exhibit Number	Description
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)
2239	Merck 2016 SEC Form 10-K, dated February 28, 2017 (Excerpt)
2240	Bristol-Myers Squibb 2017 SEC Form 10-K (Excerpt)
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)
2250	Merck SEC Form 10-Q, for quarterly period ended September 30, 2023 (Excerpt)
2251-2300	RESERVED
2301	U.S. Patent No. 11,591,393
2302	Excerpts from Prosecution History of U.S. Patent No. 11,591,393
2303-2403	RESERVED
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 Motion for Pro Hac Vice Admission
2501	Declaration of Corrin N. Drakulich in support of Motion for Pro Hac Vice Admission
2502	Declaration of Dr. Christina D. Brown-Marshall in support of Motion for Pro Hac Vice Admission
2503	Declaration of Dr. Casey M. Kraning in support of Motion for Pro Hac Vice Admission
2504	Declaration of Madelyn S. McCormick in support of Motion for Pro Hac Vice Admission
2505	Declaration of Sarah E. Jack in support of Motion for Pro Hac Vice Admission

I. INTRODUCTION

Recognizing that its Petition necessarily fails based on the absence of key disclosures in the MSR, Merck engaged a new, oncology expert, Dr. Paul Oberstein, to offer opinions on Reply. But no amount of expert opinion nor attorney argument can cure the MSR's deficiencies. Merck remains unable to rebut JHU's arguments, including that: (1) the MSR does not disclose the "in response to" limitation because both MSS and MSI-H CRC patients were treated identically; (2) the MSR is an "invitation to investigate" that does not disclose any clinical results; (3) the MSR meets the Experimental Use factors; and (4) objective indicia refute Merck's obviousness position.

Rather than rebutting JHU's arguments, Merck presents disingenuous interpretations of deposition testimony and allegations of contradictory statements to FDA and the Patent Office. Review of Merck's contentions reveals their falsity and highlights Merck's inability to prove unpatentability.

II. "IN RESPONSE TO" IS A CAUSAL REQUIREMENT NOT TAUGHT BY THE MSR

Merck neither contests JHU's construction of "in response to," nor proposes its own construction. Both Merck and JHU *agree* that treating a patient "in response to determining" their MSI-H status requires a cause-and-effect relationship between determining the patient's cancer is MSI-H and administering

pembrolizumab. POR, 5-12; Reply, 9; EX1150, ¶¶25, 59-61. The words of the claims, therefore, exclude administering pembrolizumab to patients determined to be MSS. The parties agreed in district court. *See* EX2160, 30-31; EX2162, 22-23 (Merck arguing “the specification identifies a cause-and-effect relationship”). Both parties’ experts acknowledge a causal relationship is required. EX2163, 70:25-71:2; EX2072, ¶¶90-91; EX1138, 120:15-122:4; EX1136, 196:3-197:1; EX2404, 247:23-250:10.

Unable to avoid its earlier position, Merck asserts JHU’s proposed construction amounts to reading in an “unclaimed negative limitation.” Reply, 9. Unlike Merck’s case, the allegedly “unclaimed negative limitation” here is neither “unclaimed” nor “negative.” Rather, “in response to” affirmatively recites which patients should be treated and which should not. *See Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011); *DoggyPhone LLC v. Tomofun LLC*, 2024 WL4848447, at *2-3, (Fed. Cir. Nov. 21, 2024); *Fujitsu Ltd. v. Belkin Int’l, Inc.*, 2012 WL4497966, at *27-30 (N.D. Cal. Sept. 28, 2012); *Anylogic N. Amer., LLC v. THEBRAIN Techs., LP*, IPR2018-00546, Paper 10 at 10-14 (May 24, 2018).

JHU’s construction of “in response to” is also consistent with the Summary of the Invention, which describes treating only patients determined to have MSI-H

cancer while identifying MSS cancer as a “bad candidate for treatment.” EX1001, 3:36-4:4; *id.* at 6:16-18, 5:45-53, 6:52-6:2; 13:24-26. Construing “in response to determining” to include treating patients determined to have *either* MSI-H *or* MSS CRC would negate the limitation.

Merck’s cited case misses the mark. *Omega Engineering Inc. v. Raytek Corp.* is a pre-*Philips* case reversing a claim construction that violated a tenet of means-plus-function claim construction. 334 F.3d 1314, 1322 (Fed. Cir. 2003). There is no means plus function language at issue; here, the claims allow treatment only “in response to” determining the patient’s CRC is MSI-H. This is not a negative limitation excluding treatment of MSS patients. In contrast, the MSR describes giving the same treatment to every CRC patient, regardless of MSI status, and is therefore not a disclosure of treatment “in response to” an MSI-H determination. EX2072, ¶¶100-107; EX2404, 283:21-284:10.

Merck also continues to conflate the MSR with the subsequent (non-prior art) clinical study, now arguing the MSR “is the only written description support for JHU’s claims.” Reply, 1. The written description support for the claimed method of treatment is not the MSR, but the *results* of the clinical study conducted pursuant to the MSR and its many subsequent amendments. EX1001, Figs. 1-13. Indeed, in the MSR, MSI-H was *not* used as a “treatment selection marker” for

CRC as contemplated by the '287 Patent. EX1001, 13:31-33. Only after the results of the clinical study were known was pembrolizumab approved to treat MSI-H CRC tumors, and used in practice as a treatment selection marker, as described and claimed by the '287 Patent.

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

A. The Challenged Claims Are Not Expressly Anticipated by the MSR

Merck's inability to show the MSR discloses "in response to" precludes its anticipation claim. Pet., 19-21; Reply, 9-12; 37 C.F.R. §42.104(b)(4). Merck's reliance on Dr. Oberstein's opinions fails just as its reliance on Dr. Neugut's opinions failed. Like Dr. Neugut, Dr. Oberstein opines the claimed causal relationship determination and treatment is disclosed simply because the MSI-H CRC patients were treated. EX1150, ¶63; EX2404, 251:3-253:18. This opinion fails to confront the fact that the MSR discloses treating MSS CRC patients the same as MSI-H patients. The MSR did not propose treatment of CRC based on MSI-H status; rather, it proposed treatment based on *enrollment* in the study. Dr. Oberstein ignores this critical distinction. EX1150, ¶¶60-69; EX2404, 251:3-253:18.

Rather than concede the MSR's deficiency, Merck misinterprets Dr. Lonberg's testimony that scientists review literature with a critical eye as willingly

disregarding the teachings of the prior art. Reply, 3, 9-12. Merck ignores Dr. Lonberg's explanation that a scientist would approach the prior art with "a questioning attitude toward it" and "would read it carefully and try to understand whether...the assertions in the particular publication were justified." EX1138, 85:2-86:5. Dr. Oberstein agreed with Dr. Lonberg's approach, admitting, "I don't agree with everything I read," even in respected journals. EX2404, 117:9-118:14.

Next, Merck justifies the Board's construction of "in response to" as meaning "after" by claiming it was altered by the Board's single mention of a "causal relationship." Reply, 2 (citing D.I., 16), 9-10. The Board's reasoning illustrates that its mention of causality did not alter its construction, as it expressly disregards the enrollment and treatment of MSS CRC patients. *See* D.I., 16-17. In fact, the Board clarified that "[f]or the purposes of [the D.I.], we interpreted the 'in response to' limitation of claim 1 to mean that pembrolizumab is administered to a patient *after* the patient has been determined to be [MSI-H or dMMR], regardless of whether pembrolizumab is also administered to other patients."¹ *Id.*, 17 n.3. The Board applied this construction, reading out the causation requirement. *Id.*, 16-18.

¹ All emphasis added, unless otherwise indicated.

Merck's Dr. Oberstein pays lip service to causality but ultimately uses the same flawed construction and reasoning. EX2404, 250:23-253:18 (“a subject would have to have MSI-high colorectal cancer and then be treated with an effective dose of pembrolizumab *after* determining that fact.”). Thereafter, Dr. Oberstein conceded the MSR proposes treating both MSI-H and MSS CRC patients in the same way. EX2404, 283:8-284:10. If the MSR requires treating MSS CRC and MSI-H CRC patients the same way, the treatment cannot be “in response to determining that the colorectal cancer is [MSI-H]” as required by the '287 Patent. *See* §II above. Merck's anticipation argument cannot be saved by the Board's single mention of causality, which does not remedy the fact that the Board's construction of “after” expressly reads out the causation requirement Merck agrees is required. POR, 10-16; EX1150, ¶¶25, 59-61.

B. Merck's Inherency Arguments Fail on Multiple Levels

It is undisputed that the MSR does not explicitly disclose the claimed clinical outcomes or the dependent claim limitations requiring “at least one prior cancer treatment,” “prior cancer therapy drug,” “progressed subsequent to the prior treatment,” “progressed following the prior cancer therapy,” or “metastatic” CRC. POR, 17-23; Reply, 12-19. 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 later method claim where 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 the same as the patent—as JHU explained (POR, 23-27), the patent specification includes and relies critically on data **resulting** from the MSR. The MSR’s 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 key limitations including the “in response to” requirement. Because the claimed method is different from the MSR’s method, the claimed results cannot “inevitably flow” from the MSR.

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

JHU explained why the MSR was an “invitation to investigate.” POR, 23-27. [REDACTED] That the IND included a scientific rationale—as Merck argues—does not negate the MSR as an invitation to investigate, because *all* clinical trials have a rationale. EX2404, 155:3-156:12; Reply, 13-14. The language of JHU’s scientific rationale demonstrates the investigative nature of their proposed clinical trial. *See* EX1116, 18 [REDACTED]; *id.*, 19 [REDACTED] [REDACTED], 40 [REDACTED].

Contrary to Merck’s suggestion, no Federal Circuit authority requires a patentee to include a specific phrase (“abstract theory”) in its study proposal to describe its hypothesis or for FDA to question the investigator’s scientific rationale before a proposed study qualifies as an “invitation to investigate.” Reply, 13.

JHU’s arguments here are consistent with what it told FDA. The JHU inventors formed a hypothesis based on an anomalous result in a single patient in an otherwise unsuccessful study (32 patients did not respond) of a different drug and different hypothesis. *Compare* POR, 67 (the JHU inventors “hypothesi[z]ed that MSI-H cancers would respond to pembrolizumab at a rate higher than MSI-stable cancers”), *with* EX1116, 39, 40 [REDACTED]

The MSR's investigative nature is further buttressed by the MSR being the first in a long series of proposal updates leading to the invention becoming ready for patenting. POR, 28-29. Against this backdrop, Merck's interpretation of inherency, requiring JHU to file its patent application before even posting the MSR clinical trial announcement, makes no sense, particularly where "those skilled in this art would not accept anything short of such human clinical trials." *Ex Parte Balzarini*, 21 U.S.P.Q.2d 1892, at *6 (B.P.A.I. 1991); POR, 27-31.

Merck fails to make the requisite showing that the dependent claim limitations requiring prior treatment or progress after prior treatment were “necessarily present” in the MSR. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Merck’s expert admitted the MSR does not include enough information to rule out treatment of CRC patients who had not received prior therapy. EX2404, 276:7-278:10.

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patients meeting the required limitations is uncertain, then such disclosures cannot be “necessarily present” in the MSR.

Finally, with respect to the dependent claims requiring specific clinical results, the MSR does not disclose these results. And Merck’s expert agreed that one “[couldn’t] anticipate exactly” the results of the MSR study. POR, 22; *see also* §III.B.1.

C. 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 supported the ’287 Patent’s claims. JHU also provided un rebutted evidence demonstrating applicability of the experimental-use exception. POR, 27-33. 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, 7-8 (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.

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. *See* POR, 27-28. 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.”).

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).

³ This silence is unsurprising. The circumstances where an inventor must publish as part of his experimentation are limited. But the highly regulated area of human clinical studies can present exactly that circumstance.

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.

Merck next criticizes FDA expert Jennifer Newberger by claiming she did not know what ClinicalTrials.gov required in 2013. Reply, 8. Not so. As Ms. Newberger explained 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.

⁴ Merck’s footnote allegation (Reply, 8 n.14) regarding “inconsistent testimony” refers to an inconsequential inadvertent omission between declarations. *See* EX1242, 64:22-66:13.

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

D. Merck's Identified Combinations Cannot Render the Challenged Claims Obvious

As JHU 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 "in response to" limitation; (ii) Merck did not establish a reasonable expectation of success; and (iii) JHU's significant objective indicia evidence strongly supports non-obviousness. POR, 35-83.

Merck's Reply does nothing to address these deficiencies. Reply, 19-34. For example, Merck does not dispute that it relies solely on the MSR as disclosing

the “in response to” limitation. POR, 35-36. Because the MSR does not disclose this limitation, and Merck concedes none of the other references disclose it, Merck’s obviousness grounds necessarily fail. Merck also does not acknowledge, let alone rebut, its improper use of inherency to support its obviousness analysis. *Id.*

1. Merck Improperly Argues the Claimed Clinical Outcomes Are Inherently Disclosed

Merck’s prior art combinations do not explicitly disclose the clinical outcome. POR, 36-52. Again, Merck must rely on an improper and unsupported inherency argument. Reply, 19-21; POR, 35-36. But “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* §III.A)—and rehash what it alleges a POSITA would understand from the prior art. Reply, 19-21. None of this demonstrates that the clinical outcomes were “necessarily known” in any of Merck’s obviousness

combinations.⁵ Merck has not even attempted to meet that high standard; therefore, its inherent obviousness argument necessarily fails.

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

Merck has now had multiple bites at the apple, but it 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, 36-37 (citing Pet., 46, 44); EX1003, ¶¶135, 162, 167. After JHU pointed out that was the wrong standard (POR, 36-37), Merck pivoted, arguing that a POSITA would have had a RES in carrying out a generic two-step treatment method (Reply, 21-22). Merck’s generic method omits the claimed clinical outcomes, improperly lowering the bar for RES. Merck’s RES argument thus fails again.

⁵ Merck’s arguments regarding the dependent claim limitations, (Reply, 24) fail for the same reason (*see* POR, 52).

Merck argues that JHU “distorts the [RES] standard” “by requiring a certain level of success and/or a certainty of success.”⁶ Reply, 21-22. Not so. JHU applies the standard for RES laid out in the binding precedent of *OSI Pharmaceuticals v. Apotex Inc.* See POR, 34, 38-41, 47 (citing 939 F.3d 1375 (Fed. Cir. 2019)). In that case—that Merck fails to address—the Federal Circuit reversed the Board’s finding of unpatentability, 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, 38, 39.

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. Dr. Lonberg addressed each of Merck’s references and explained, “at best these

⁶ Again, Merck mischaracterizes JHU’s argument regarding the MSS cohort. POR, 36-37.

references were inviting researchers to take an outside chance on investigating additional speculative hypotheses.” POR, 45 (citing EX2072, ¶¶148-151). Merck does not rebut Dr. Lonberg’s testimony. Nor does Merck rebut JHU’s evidence teaching away from the claimed treatment. *Id.*, 45. Merck also ignores Dr. Lonberg’s testimony that JHU’s hypothesis was “not an anticipated outcome” and “does not imply any anticipation of—or any expectation of a particular result.” EX1245, 82:21-83:15; *id.*, 71:18-72:15; 80:22-85:7; 89:14-22.⁷

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

⁷ Dr. Lonberg’s testimony regarding his personal knowledge of JHU’s nonpublic work and of the nonpublic outcomes of BMS’s clinical trial are irrelevant to the knowledge or expectations of a POSITA at the time of the invention. Reply, 23.

Taken together, Merck's evidence fails to demonstrate a RES in treating MSI-H CRC under *OSI Pharms.* 939 F.3d at 1385.

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

a. Nexus

Merck provides no meaningful rebuttal to JHU's evidence that nexus should be presumed because the claims are co-extensive with Keytruda®'s label indication for treating MSI-H CRC patients. POR, 54-61. For example, Merck's Dr. Oberstein offers no opinion on nexus. *See* EX2404, 240:14-241:22. Nor does *any* Merck declarant provide an opinion identifying how treatment according to the label deviates from the claims.⁸

Instead, Merck relies on a selective reading of JHU's Dr. Goldberg's deposition testimony. Reply, 25-26. Merck's allegation that Dr. Goldberg "never used or followed the Keytruda labeling when he treated MSI-H cancer patients" (Reply, 25 n.28), is undermined by the fact that Dr. Goldberg stopped treating patients before the Keytruda® label contained the MSI-H indications (EX1243, 118:17-119:4), and thereafter he supervised physicians administering Keytruda®

⁸ Though Merck's Dr. Sheridan references nexus in his declaration, he bases his nexus opinion on a finding of anticipation. EX1151, ¶¶44-46.

“within the instructions of the KEYTRUDA label” (*id.*, 124:17-125:19). This testimony does not render the claims non-coextensive with Keytruda®’s instructed use. *See NuVasive, Inc. v. Iancu*, 752 F. App’x 985, 995-96 (Fed. Cir. 2018).

Merck’s other nexus arguments also fall short. Merck implies that a presumption of nexus can only apply when a **product** is claimed, not a method. *See Reply*, 24-25. But that is factually and legally unsound; nexus can be presumed for method claims. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020). The lone case 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...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.” *Reply*, 26. This circular argument fails because the claims are not anticipated and 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.⁹ Reply, 26-27. First, Merck misrepresents [REDACTED]
[REDACTED] *Id.* [REDACTED]
[REDACTED] EX1245, 80:17-85:7. 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] constitutes an RES, statements to FDA are ***not public*** and thus not prior art or within a POSITA's knowledge. *See Otsuka Pharm.*, 678 F.3d at 1296; *Sanofi-Aventis*, 748 F.3d at 1360.

That Merck and BMS 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, ¶133; EX2090, ¶53. EX1057, 2-3; EX2176, 22; EX2072,

⁹ Merck improperly relies on arguments in IPR2024-00240. Reply, 26, 27. If permitted, JHU asks that its IPR2024-00240 Sur-reply arguments likewise be considered.

¶133; EX2090, ¶¶52-53. The results of the BMS trial 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 argument that JHU “incorrectly conflates degree of success with unexpectedness” also fails. Reply, 27. In *Hoffmann-La Roche Inc. v. Apotex Inc.*, there was an otherwise clear showing of obviousness. 748 F.3d 1326, 1334 (Fed. Cir. 2014). Here, unexpected results are “useful to show the improved properties provided by the claimed [inventions] are much greater than would have been predicted.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quotations omitted).

c. Skepticism

Merck avoids addressing JHU’s skepticism evidence (POR, 66-69) by improperly relying on hindsight, ignoring post-Critical Date evidence, and criticizing JHU’s declarants (Reply, 27-29).

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 shows Merck was skeptical of JHU’s hypothesis and only had a change of heart once preliminary results were published. While Merck notes it provided its “expensive” drug, absent is evidence of Merck’s cost for supplying it or any explanation for why this rebuts skepticism. Reply, 28.

Nor does Merck address or rebut that even *after* JHU presented the MSI-H study results at ASCO and published them in NEJM, some researchers remained skeptical. Dr. Le recounted that at a January 2016 conference an audience member publicly criticized her because “it was too early[.]” EX2130, ¶50.

Regarding Merck’s executive’s statements, 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; EX2121, 17. Instead, Merck argued this belief was “*prior* to the Parties’ collaboration.” Reply, 28 (emphasis in original). But that is exactly the point—before JHU’s clinical trial results, Merck was skeptical.

Merck’s criticisms of JHU’s declarants fail. Merck faults Dr. Le for not remembering Merck employees’ names from a decade ago. Reply, 6. But this does not undermine Dr. Le’s testimony, which is unrebutted. As to BMS’s skepticism, JHU’s expert Dr. Lonberg testified firsthand that he thought the trial

was “very risky” and noted that, ultimately, “the skepticism among decisionmakers within [BMS] prevailed” and BMS rejected JHU’s offer to join the MSI-H study. EX2072, ¶191. Merck has not demonstrated otherwise.

d. Long-Felt, Unmet Need

Merck contends that there was no unmet need for treating MSI-H patients before the Critical Date. Reply, 29-32. But during FDA approval, [REDACTED]

[REDACTED] EX2168, 10-13, 31; EX2169, 2; *see also* POR, 72-73. Merck ignores these statements and argues that FDA approval is not required by the claims. But clearly, an unmet need existed. Reply, 29-32, n.32; *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 admitted that as of the Critical Date, “MSI-high colorectal cancer patients did qualify as a high unmet need” (*id.*, 315:19-316:8). So, ***before this dispute***, Merck recognized the unmet need for better treatments for MSI-H CRC patients. But ***now***, Merck ignores this evidence with a perfunctory footnote, (Reply, 30 n.32), obscuring that Merck now asks the Board to draw the ***opposite*** conclusion than the FDA. POR, 72-73.

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, 29-30. 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).

Merck’s reliance on FDA approval (Reply, 30), 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, ¶65. Notably, Merck did not ask Dr. Goldberg whether a long-felt need existed **more broadly** than for an FDA-approved treatment. Without that question, Merck cannot draw its desired conclusion. Here, Dr. Goldberg simply relied upon the Keytruda® label—that ultimately resulted from FDA approval—to demonstrate the complete coextensiveness between the claimed invention and how Merck instructs doctors and patients to treat MSI-H cancer—i.e., according to the ’287 Patent claims. EX2090, ¶¶73-77.

Additionally, Merck’s contention that the unmet need has no nexus to the

claims is undermined by Merck's cited cases. Reply, 30. In both cases, 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 median overall survival for metastatic CRC patients on third-line therapy was *only 7 months*.

EX2090, ¶¶45; EX2113; EX2114. Thus, clearly the 2013 MSR posting had not met this need. But treatment with the claimed method resulted in a five-year overall survival rate of 57.5%, meaning *over half* of the patients were still alive *five years* after their initial treatment—an unprecedented increase in life expectancy.

EX2090, ¶¶41. And several patients experienced full remission beyond ten years. *Id.*, ¶¶63-65.

Finally, despite Merck's insinuation (Reply, 31), long-felt unmet need does *not* require showing 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 demonstrate a failure in the industry to meet this need.¹⁰

e. Industry Praise

Merck dismisses JHU's evidence of industry praise (POR, 61-66), in one paragraph focused on nexus (Reply, 32), ignoring the direct connection between JHU's evidence and the claimed invention. Dr. Le's presentation, simultaneously published in the NEJM (EX1031), was touted for the key component of the claimed invention, i.e., "the identif[ication of] the first genomic marker—[MSI-H]—to predict the clinical benefit" of pembrolizumab. EX2135, 1. Further, Merck relied on Dr. Le's results to support the Keytruda® indication for treating MSI-H CRC. EX2129, 74 (citing KEYNOTE-016/NCT01876511). Merck ignores that FDA's press release explicitly touted the approval "based on a tumor's biomarker"—the same MSI-H biomarker claimed in the '287 Patent. POR, 64-65. Even Further, Merck relied on Dr. Le's results to support the Keytruda® indication for treating MSI-H CRC. 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, 31-32. 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 cursory acknowledgment of JHU's evidence, Merck criticizes Dr. Le's testimony regarding her plenary presentation at ASCO as a "self-referential commendation." Reply, 32 n.34. But Dr. Le's statements are just the beginning. 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, 61-66.

f. Commercial Success

Merck does not dispute that Keytruda® sales for treatment of MSI-H CRC patients grew after FDA approval for JHU's patented treatment method [REDACTED] from 2017 to 2023. POR, 80; Reply, 33-34. Instead, Merck quibbles with the timing of an inflection point in sales, and comparisons of Keytruda® sales to competitor products. See Reply, 34. Merck misses the point. Merck's Keytruda® sales *alone* are sufficient to prove commercial success. See POR, 80.

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 (internal quotations omitted); POR, 82. Second, Merck is incorrect that “others” (here, JHU) were deterred from developing the claimed method. *See* Reply, 33. Third, Merck fails to explain how any of its criticisms would impact, if at all, Keytruda®’s commercial success in the MSI-H CRC 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, 82-83.

Finally, Merck ignores that Mr. Segers evaluated Merck’s pricing and marketing, 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. *See* Reply, 34; EX2191, ¶¶24-30.

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 June 3, 2025, a complete and entire copy of this Patent Owner's Sur-Reply were provided via email, to the Petitioner by serving the email correspondence addresses of record as follows:

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