

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 RESPONSE

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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

Exhibit Number	Description
	https://s2.q4cdn.com/584635680/files/doc_news/Merck-Announces-Fourth-Quarter-and-Full-Year-2023-Financial-Results-2024.pdf
2009-2021	RESERVED
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

Exhibit Number	Description
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 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)

Exhibit Number	Description
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)
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

Exhibit Number	Description
	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)
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/

Exhibit Number	Description
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

Exhibit Number	Description
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
2081	van der Bruggen et al., <i>A gene encoding an antigen recognized by cytolytic 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

Exhibit Number	Description
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)
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)

Exhibit Number	Description
2101	Dy et al., Long-term survivors of metastatic colorectal cancer treated with systemic chemotherapy alone: a North Central Cancer Treatment Group review of 3811 patients, N0144, Clin. Colorectal Cancer 8(2):88-93 (2009)
2102	Saltz et. al., Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer, Irinotecan Study Group, N. Engl. J. Med. 343(13):905-13 (2000)
2103	Sanoff et al., Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741, J. Clin. Oncol. 26:5721-5727 (2008)
2104	Hurwitz et al., Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer, N. Engl. J. Med. 350(23):35-42 (June 3, 2004)
2105	Saltz et al., 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)
2106	Van Cutsem et al., Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer, N. Engl. J. Med. 360(14):1408-17 (Apr. 2, 2009)
2107	Van Cutsem et al., 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, J. Clin. Oncol. 25(13):1658-64 (May 1, 2007)
2108	Tabernero et al., Afibercept 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, Eur. J. Cancer 50:320-331 (2014)
2109	Venook et al., Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With

Exhibit Number	Description
	<i>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)
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)

Exhibit Number	Description
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®

Exhibit Number	Description
	(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	ASCO 2015: Mismatch Repair Deficiency Predicts Response to Pembrolizumab Among Patients With Colorectal and Other Cancers, 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

Exhibit Number	Description
2142	Laine et al., <i>Update on Trials Registration: Clinical Trial Registration: Looking Back and Moving Ahead</i> , ICMJE (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
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)

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2157	<i>Response, Merriam-Webster’s Collegiate Dictionary (11th ed. 2014)</i>
2158	<i>Response, Cambridge Advanced Learner’s Dictionary (4th ed. 2013)</i>
2159	<i>Response, Webster’s Third New International Dictionary of the English Language (2002)</i>
2160	Plaintiff Merck Sharp & Dohme LLC’s Opening Brief Regarding Claim Construction, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 82 (D. Md. May 1, 2024)
2161	The Johns Hopkins University’s Opening Claim Construction Brief, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 81 (D. Md. May 1, 2024)
2162	Plaintiff Merck Sharp & Dohme LLC’s Responsive Brief Regarding Claim Construction, <i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR, D.I. 107 (D. Md. May 1, 2024)
2163	Stenographic Deposition of Alfred I. Neugut, M.D., Ph.D., MPH taken on August 8, 2024, <i>Merck Sharp & Dohme LLC, v. The Johns Hopkins University</i> , Case IPR2024-00240 (PTAB)
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

Exhibit Number	Description
	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
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)
2176	Robin Marantz Henig, Could Immunotherapy Lead the Way to Fighting Cancer?, <i>Smithsonian Magazine</i> (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 &</i>

Exhibit Number	Description
	<i>Dohme LLC v. The Johns Hopkins University</i> , Case No. 1-22-cv-03059-JRR
2178	Marques et al., <i>Tumor mutational burden in colorectal cancer: Implications for treatment</i> , Crit. Rev. Oncol. Hematol. (Apr. 12, 2024)
2179	Le et al., <i>Phase II Open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164</i> , J. Clin. Oncol. (38:1(1-19) (2019)
2180	Anagha Nair, High Impact Journals 2024 – Key to deciding the right journal?, Enago Academy (Feb. 19, 2024), https://www.enago.com/academy/top-high-impact-factor-journals/
2181	Highly Confidential Attorney Eyes Only Document 3 – Protective Order Material
2182	Highly Confidential Attorney Eyes Only Document 10 – Protective Order Material
2183	Email correspondence from Luis Diaz to Amy Meister and Mr. Robert Iannone dated December 27, 2012, production document Bates stamped JHU_MERCK00027065
2184	Breakthroughs in Immunotherapy, Swim Across America, https://www.swimacrossamerica.org/site/SPageNavigator/Breakthroughs_35.html (last accessed Sept. 26, 2024)
2185	RESERVED
2186	Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, U.S. Dept. of HHS, FDA (May 2014)
2187	Highly Confidential Attorney Eyes Only Document 11 – Protective Order Material

Exhibit Number	Description
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)

Exhibit Number	Description
2201	Boland et al., <i>Microsatellite Instability in Colorectal Cancer Boland</i> , 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)
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-

Exhibit Number	Description
	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
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)

Exhibit Number	Description
2228	Siegel et al., <i>Cancer Statistics</i> , 2022, CA Cancer J. Clin., 72(1):7-33 (Jan-Feb 2022)
2229	Siegel et al., <i>Cancer Statistics</i> , 2023, 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)
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)

Exhibit Number	Description
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
2303-2499	RESERVED
2500	Declaration of Frank E. Scherkenbach in support of Motion for Pro Hac Vice Admission

Exhibit Number	Description
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

LISTING OF CHALLENGED CLAIMS

Claim	Identifier	Claim Language
1	[1pre]	A method for treating colorectal cancer in a human patient, the method comprising:
	[1a]	in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,
	[1b]	wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.
2	[2]	The method of claim 1, wherein the biological sample is tumor tissue from the patient.
3	[3]	The method of claim 1, wherein the biological sample is a body fluid from the patient.
4	[4]	The method of claim 1, wherein the colorectal cancer is microsatellite instability high.
5	[5]	The method of claim 1, wherein the colorectal cancer is DNA mismatch repair deficient.
6	[6]	The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer.
7	[7]	The method of claim 1, wherein the patient had received at least one prior cancer treatment and the cancer had progressed subsequent to the prior treatment.
8	[8]	The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously.
9	[9]	The method of claim 4, wherein the biological sample was tested by a method comprising

Claim	Identifier	Claim Language
		immunohistochemistry testing, next generation sequencing or PCR testing.
10	[10]	The method of claim 1, wherein the biological sample was tested by a method comprising assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24.
11	[11pre]	A method for reducing the risk of progression of colorectal cancer in a human patient, the method comprising:
	[11a]	in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab,
	[11b]	wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.
12	[12]	The method of claim 11, wherein the biological sample is tumor tissue from the patient.
13	[13]	The method of claim 11, wherein the biological sample is a body fluid from the patient.
14	[14]	The method of claim 11, wherein the colorectal cancer is microsatellite instability high.
15	[15]	The method of claim 11, wherein the colorectal cancer is DNA mismatch repair deficient.
16	[16]	The method of claim 11, wherein the colorectal cancer is metastatic colorectal cancer.
17	[17]	The method of claim 11, wherein the patient had received at least one prior cancer treatment and the cancer had progressed subsequent to the prior treatment.

Claim	Identifier	Claim Language
18	[18]	The method of claim 11, wherein the pembrolizumab is administered to the patient intravenously.
19	[19]	The method of claim 14, wherein the biological sample was tested by a method comprising immunohistochemistry testing, next generation sequencing or PCR testing.
20	[20]	The method of claim 11, wherein the biological sample was tested by a method comprising assessing one or more markers selected from the group consisting of BAT-25, BAT-26, MONO-27, NR-21 and NR-24.
21	[21]	The method of claim 1, wherein the treatment increases the median progression free survival of patients having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient compared to the median progression free survival of patients having colorectal cancer that is not microsatellite instability high or DNA mismatch repair deficient.
22	[22]	The method of claim 1, wherein the treatment increases the median overall survival of patients having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient compared to the median overall survival of patients having colorectal cancer that is not microsatellite instability high or DNA mismatch repair deficient.
23	[23]	The method of claim 11 wherein the treatment increases the median progression free survival of patients having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient compared to the median progression free survival of patients having colorectal cancer that is not

Claim	Identifier	Claim Language
		microsatellite instability high or DNA mismatch repair deficient.
24	[24]	The method of claim 11, wherein the treatment increases the median overall survival of patients having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient compared to the median overall survival of patients having colorectal cancer that is not microsatellite instability high or DNA mismatch repair deficient.
25	[25]	The method of claim 1, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.
26	[26]	The method of claim 25, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.
27	[27]	The method of claim 1, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.
28	[28]	The method of claim 27, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.
29	[29]	The method of claim 1, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.

Claim	Identifier	Claim Language
30	[30]	The method of claim 29, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.
31	[31]	The method of claim 6, wherein the method results in an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients.
32	[32]	The method of claim 31, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.
33	[33]	The method of claim 6, wherein the method results in a probability of progression-free survival at 20 weeks for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 78%.
34	[34]	The method of claim 33, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer therapy drug and the cancer had progressed following the prior cancer therapy.
35	[35]	The method of claim 6, wherein the method results in a probability of progression-free survival at 9 months for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients is at least 60%.
36	[36]	The method of claim 35, wherein the microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients have received a prior cancer

Claim	Identifier	Claim Language
		therapy drug and the cancer had progressed following the prior cancer therapy.

I. INTRODUCTION

Merck's challenge to the claims of the '287 Patent fails on all fronts because its primary reference does not disclose the key causal relationship between the "determining" and "treating" language contained in all of the challenged claims. The inventors determined, based on their clinical trial, that MSI-H status could distinguish patients likely to benefit from pembrolizumab therapy (MSI-H patients) from those unlikely to benefit (MSI-stable patients). As such, the challenged claims are directed to a method of using MSI-H as a predictive biomarker such that pembrolizumab therapy is provided to patients "*in response to*" determining the patient's colorectal cancer (CRC) is MSI-H.

The use of MSI-H as a predictive biomarker is not disclosed by the reference Merck refers to as the "MSI-H Study Record," (hereafter, "MSR") because at the time of posting the MSR by the Hopkins researchers, these inventors had only a hypothesis, but no data to support the existence of this relationship. Thus, the MSR, unlike the challenged claims, discloses treating all enrolled CRC patients—both MSI-H and MSI-stable patients—with pembrolizumab. No patient was treated "in response to" a determination that the patient was MSI-H. Because the MSR does not describe the claimed causal relationship between determining MSI-H status and deciding whether the CRC patients will be treated with

pembrolizumab, the MSR cannot inherently anticipate any of the challenged claims.

Only after reaching an initial construction of the claim term “in response to” as meaning “after”—erasing the causal relationship at the heart of the claims—could the Board institute. That construction is incorrect and led to a misunderstanding of the scope of the challenged claims. The words of the claims, the intrinsic evidence, and the extrinsic evidence each consistently demonstrate that “in response to” means “in reaction to.” This definition is expressed by the structure of the claims—“treating” only in response/reaction to “determining” MSI-H status. It is also the plain meaning of “response,” it is apparent from the patent’s specification, and it is aligned with the Examiner’s understanding of the term as expressed during prosecution. Likewise, the extrinsic evidence, including Merck’s claim construction position before the District Court and the opinion of its expert in these proceedings, confirms the causal relationship compelled by the term “in response to.” Even the Federal Circuit, in another case involving the term “in response to,” affirmed the district court’s construction of “in reaction to.”

Once “in response to” is correctly construed, all of Merck’s challenges necessarily fail. The MSR does not teach the limitation nor render the challenged dependent claims obvious. The secondary and tertiary references relied on by Merck also fail to fill the void in the MSR’s disclosure. Without a teaching of “in

response to” the MSR also cannot inherently anticipate any challenged claim under *In re Montgomery*, as argued by Merck.

Merck’s Petition also fails because the MSR itself should not be afforded prior art status. The clinical trial conducted pursuant to the MSR was plainly a non-prior art experimental use to test the inventors’ hypothesis that MSI-H was predictive of treatment efficacy in CRC patients. The MSR was a statutorily required prerequisite to conducting the experimental human clinical trial.

Finally, Merck’s obviousness arguments fail because Merck cannot show a reasonable expectation of success; the results of the JHU study were wholly unexpected and introduced a paradigm shift in cancer treatment. Moreover, overwhelming objective indicia evidence disproves Merck’s obviousness arguments. When the MSR was posted, the prognosis for CRC patients was bleak. JHU’s clinical trial results changed that. The presentations and publications describing JHU’s invention were heralded with fanfare and celebration. At the relevant time, even Merck itself lauded what a breakthrough JHU’s discovery was. Simply put, using MSI-H as a biomarker to predict efficacy of anti-PD-1 therapy has changed the standard of care and saved the lives of thousands of cancer patients.

II. OVERVIEW OF THE '287 PATENT

The '287 Patent claims (1) a novel method for treating MSI-H or DNA mismatch repair deficient (“dMMR”)¹ CRC in a human patient ***in response to*** a determination the patient’s CRC cancer is MSI-H (EX1001, claim 1), and (2) a novel method for reducing the risk of CRC progression in a human patient ***in response to*** determining the patient’s CRC cancer is MSI-H (*id.*, claim 11). See EX2072, ¶¶58-65.

The priority date of the '287 Patent is July 10, 2015.² Independent claim 1 is representative for purposes of this proceeding and is recited in the list of challenged claims, *supra*.

III. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

JHU contends that a POSA on or about the claimed priority date of the '287 Patent would have had a M.D. or graduate-level degree (or equivalent work experience) in the fields of immunology, genetics, or a related field and at least five years of experience (i) conducting immunology research relating to oncology,

¹ MSI-H and dMMR are related; testing for one condition is equivalent to testing for the other. Pet., 6. Here, JHU will refer to MSI-H only.

² Contrary to Merck’s assertions in Petition §VI.A, JHU is not attempting to claim priority to an undefined “First Provisional.”

(ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields. EX2072, ¶¶31-32, 81-89. A higher level of education may compensate for less work experience, and vice versa. *Id.*

IV. CLAIM CONSTRUCTION

In its DI, the Board *sua sponte* construed the term “in response to” to mean “after.” DI, 17 n.3. The Board’s initial construction disregards the critical **causal** relationship between the “determining” and “treating” requirements expressed by the claims. The express causal relationship between these requirements establishes that **only** CRC patients determined to be MSI-H are treated. This critical aspect of the claimed invention is omitted by the Board’s construction.

JHU respectfully requests the Board modify its construction of “in response to” to mean “in reaction to.” This construction correctly reflects the intrinsic and extrinsic evidence, all of which consistently supports the claimed causal relationship. The correct construction of “in response to” is not a semantic distinction. Under the correct construction of the term, each of Merck’s patentability challenges necessarily fails.

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

The Board’s construction conflicts with the plain meaning of the words of the claims and the intrinsic record. JHU’s proposed construction reflects the causal

relationship between the “determining” and “treating” requirements of claims 1 and 11 made explicit by the conjunctive claim term “in response to.” The claimed “treating” step is performed (and only performed) in response to (i.e., as a reaction to) determining the patient’s CRC is MSI-H.

First, had the inventors intended the claimed invention to encompass treatment occurring merely “after” a determination of the patient’s MSI-H status, as the Board’s initial construction requires, they would have used “after” in their claims. The inventors knew how to use “after” to define the scope of their invention and did so in several dependent claims of U.S. Patent No. 11,591,393 (“the ’393 Patent”)—a related patent in the same patent family. *See* EX2301, claims 7, 20, 27 (claiming the cancer “had progressed **after**”³ the patient received a different cancer therapy). These claims each depend from claims reciting “in response to.” Thus, within the patent family of the ’287 Patent, the word “after” appears in some of the same claims as “in response to.” Different words in the same claim are presumed to have different meanings. *Chic. Bd. Options Exch., Inc. v. Int’l Sec. Exch., LLC*, 677 F.3d 1361, 1369 (Fed. Cir. 2012). Construing “in response to” to mean “after” conflicts with both the plain meaning of the term and this fundamental tenet of claim construction.

³ Emphases added unless otherwise noted.

Second, the '287 Patent's specification is consistent with the plain meaning of "in response to." The '287 Patent explains that when "[m]icrosatellite ***instability*** is determined," "[t]he tumor is identified as a ***good*** candidate for treatment with an immune checkpoint inhibitory antibody." EX1001, 3:58-60. The specification also explains that when "[m]icrosatellite ***stability***...is determined," "[t]he tumor is identified as a ***bad*** candidate for" such treatment. *Id.*, 3:64-67. A POSA would have understood from the words of the claims and from the '287 Patent's teaching of which patients are good or bad treatment candidates that "in response to" describes administering the claimed treatment only as ***a reaction*** to the determination that the patient's CRC is MSI-H. The contrary view advanced by the Board improperly renders meaningless the "in response to" step of the claim. As initially constructed by the Board, the claims would cover treatment administered to MSI-H patients for any reason or no reason at all—even accidental treatment would be covered. Such a reading is entirely inconsistent with the teaching of the specification.

Third, the Board's initial construction is inconsistent with the meaning applied to the "in response to" term by the Examiner during prosecution. When JHU amended current claim 1 (then, claim 2) during prosecution of the '287 Patent to add "in response to," the Examiner understood the term imposed a causal relationship. Just three months prior to allowing the claims of the '287 Patent

(EX1002, 7-8), the Examiner allowed the claims of the '393 Patent—a related patent in the same patent family which also used the term “in response to.” EX2301, claims 1, 14. In allowing the claims of the '393 Patent, the Examiner used the shorthand “based on” to express this plain meaning. *See* EX2302, 8 (explaining that the prior art “does not treat the patient ***based on*** a determination of microsatellite instability high or DNA mismatch repair deficient as claimed.”). “Based on” does not mean “after.” It requires the claimed causal relationship as expressed by JHU’s proposed construction. The Examiner understood “in response to” as requiring this causal relationship, and there is no evidence that the Examiner treated the term “in response to” differently during the prosecution of the related '393 and '287 Patents.

B. JHU’s Proposed Construction is Also Supported By the Extrinsic Evidence

The extrinsic evidence also shows the plain meaning of “in response to” is “in reaction to.” To begin, the causal relationship between the “determining” and “treating” limitations is so clearly expressed by the words of the claims that neither Party proposed “in response to” be construed by the Board. *Pet.*, 11. The Parties, in fact, shared the view before the District Court that the claim required a causal relationship between the “determining” and “treating” limitations. Both JHU and Merck relied on the words of the claims, and the Examiner’s statements during

prosecution, to support their proposed causal constructions before the District Court. *See* EX2161, 13; EX2162, 17-18. Merck's only dispute was over the breadth of that causal relationship, with Merck proposing that the term be construed even more narrowly to mean "as the reaction specifically to." EX2160, 24.

As further support, contemporaneous dictionaries define the non-technical word "response" to mean "a reaction to something," "reply or reaction." EX2153, 4; EX2154, 3; EX2155, 3; EX2156, 4; EX2157, 4; EX2158, 7-8; EX2159, 5. Thus, the claimed treating step can only occur in reaction to determining that the patient's CRC is MSI-H.

The experts here also agree that "in response to" requires causality. Merck's expert, Dr. Neugut, said it "[n]ever entered [his] mind that the phrase 'in response to' would have a meaning different than what it says." EX2163, 70:25-71:2. JHU's expert likewise agrees that the plain meaning of treating "in response to" is treating "in reaction to" a determination that the patient's tumor is MSI-H. EX2072, ¶¶90-91.

Finally, the Federal Circuit has adopted JHU's plain meaning construction of "in response to" in another case. *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1340 (Fed. Cir. 2011) ("In response to' connotes that the second event occur **in reaction to** the first event."); *id.* (affirming "in response to" construction

requiring a “cause-and-effect relationship”). Nothing about the facts or context of *American Calcar* suggests the construction of the plain English phrase “in response to” should mean something different here.

V. THE CHALLENGED CLAIMS OF THE '287 PATENT ARE PATENTABLE OVER ANTICIPATION GROUND 1

A. The MSR Does Not Disclose Treating a CRC Patient “In Response To” a Determination that the Patient is MSI-H, So It Does Not Anticipate the Challenged Claims

Merck does not allege that any of the challenged claims are expressly anticipated. Instead, Merck’s challenge relies on an improper inherent anticipation theory to fill in limitations not disclosed by the reference on which it relies. The Federal Circuit has made clear, “[a]nticipation by inherent disclosure is appropriate only when the single prior art reference discloses prior art that must *necessarily* include the unstated limitation.” *U.S. Water Servs., Inc. v. Novozymes A/S*, 843 F.3d 1345, 1350 (Fed. Cir. 2016) (cleaned up); *see also id.* (“Inherency...may not be established by probabilities or possibilities.”) (citation omitted). Here, the prior art does not disclose that the patient’s MSI-H status is the reason they will be treated with pembrolizumab, and certainly does meet the exacting requirements for a finding of inherent anticipation.

1. The MSR Is Silent With Respect to Determining That a Patient's CRC is MSI-H Before Treating With Pembrolizumab

Claims 1 and 11 require determining whether a patient's CRC is MSI-H based on a previously tested biological sample and “in response to determining that the [CRC] is [MSI-H], treating [the patient] with a therapeutically effective amount of pembrolizumab.” As discussed, both parties agree that “in response to” requires a causal relationship between the determination that the CRC is MSI-H and the treatment with a therapeutically effective amount of pembrolizumab. *Supra* §IV. This is consistent with the purpose of the claimed method of treatment, which is to identify those patients who are likely to respond to treatment with pembrolizumab and treat them. *See supra* §IV.A (discussing EX1001, 3:57-67). The MSR does not disclose this causal relationship between determining the patients' MSI-H status and treating the patient with pembrolizumab because the MSR is silent with respect to when testing for MSI-H occurs.

The MSR does not disclose the claimed causal relationship between determining that a patient's CRC is MSI-H and treating ***in response to*** that determination. This causal relationship requires one to look at ***why*** the decision to treat is made. EX2072, ¶102. The MSR discloses recruiting subjects for two CRC-related arms (MSI-H CRC and MSI-stable CRC), and then administering pembrolizumab to ***all*** of the enrolled CRC patients, including CRC patients who

were ultimately determined to be **MSI-stable**. See EX1005, 4-5. The decision to administer pembrolizumab to a CRC patient according to the MSR is not **in response to** the determination of their MSI status because the CRC patient will receive pembrolizumab treatment regardless of the ultimate result of their MSI test. EX2072, ¶¶100-107. Put differently, the CRC patient would **not** be treated in reaction to her positive MSI-H status—she would receive the drug simply because she was enrolled in the study. Thus, contrary to the Board’s initial understanding, the recruitment and enrollment of CRC patients in the clinical trial demonstrate that the MSR provides no disclosure of the causal relationship between the determining and treatment steps recited in Claim 1. See DI, 16-17.

Because the decision to treat a CRC patient with pembrolizumab is made at the time of enrollment according to the MSR, Merck would need to show that the MSR teaches that the patient’s cancer is determined to be MSI-H before enrollment. It does not. The MSR neither explicitly discloses nor inherently teaches that patients have their MSI status determined before the treatment decision is made or that the treatment decision is based on that determination. The MSR allows for recruitment and enrollment of patients without any prior knowledge of whether their cancer is MSI-H. EX1005, 3-6. In fact, the MSR does not even require that the patient’s cancer be tested **at all**, only that the patient “[a]gree to have a biopsy.” *Id.*, 5 (Inclusion Criteria).

In the DI, the Board relied in part on Merck's expert's Declaration as providing support for its initial determination that the MSR "teaches treating [CRC] patients after they were determined to be" MSI-H. DI, 16. But Dr. Neugut, Merck's expert, admitted that there was **no disclosure** in the MSR that a patient's MSI status would need to be determined before enrollment. EX2163, 102:20-103:1. Thus, within its four corners, the MSR fails to disclose that treatment is provided in response to an MSI-H determination. In fact, the CRC patient's tumor need not even be biopsied until **after** enrollment, and enrollment ensures the patient will receive pembrolizumab therapy. See EX1005, 5 ("Inclusion Criteria: ...Agree to have a biopsy of their cancer"). Accordingly, the MSR allowed patients to meet the eligibility requirements regardless of their MSI-H status, consistent with well-known clinical trial designs. EX2026, 1 ("[A]ll patients meeting the eligibility criteria (**regardless of a particular biomarker status**) are entered..."); see also EX2027, 2 ("All patients are randomly assigned regardless of biomarker status..."); EX2028, 2 (treatment effect assessed in both the biomarker-positive and biomarker-negative patient populations in all-comers design); EX2072, ¶¶98-107. This, of course, was the entire point of the study: give the drug to those both with and without the MSI-H marker to assess whether treatment would be more effective when the marker is present.

When the correct claim construction is applied, the question at issue is not whether JHU can show that the MSR discloses determining a patient's MSI-H status after the patient was already treated with pembrolizumab.⁴ Instead, the correct inquiry is whether Merck has shown the MSR teaches treating a CRC patient “in response to determining that the [CRC] is [MSI-H].” Merck has failed to show that MSR discloses this limitation and thus has failed to demonstrate that any of the challenged claims are inherently anticipated.

2. The MSR Does Not Disclose a Causal Relationship Between Determining a Patient's CRC is MSI-H and Treating With Pembrolizumab

Even if the MSR did disclose determining a patient's CRC is MSI-H before the treatment decision—it does not—the method it discloses does not describe treating a CRC patient “in response to determining that the [CRC] is [MSI-H].” For a causal relationship to exist between the MSI-H determination and the treatment step, the results of the MSI testing must drive the treatment decision. EX2072, ¶100. Here, as Dr. Neugut acknowledges, the MSR describes using MSI-H testing results merely to “place patients in the correct arm” (EX1003, ¶50), as

⁴ Even under the Board's initial construction of “in response to,” this would improperly shift the burden to JHU to prove a negative. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016).

both MSI-H and MSI-stable patients are treated regardless of the outcome of their MSI test. Thus, an accusation of infringement could not be made for carrying out the MSR method. *Cf.* Pet., 64-65.

Because nothing in the MSR teaches a causal relationship between the determination that a patient's CRC is MSI-H and treatment with pembrolizumab, the Petition simply ignores the "in response to" limitation. Indeed, review of the Petition reveals the "in response to" limitation is mentioned just twice—both in Ground 1—and each time, Merck provides ***no analysis whatsoever*** about how the MSR discloses treating patients "in response to" determining their MSI status. Pet., 19-21, 30; EX2072, ¶¶92-96. This fact alone highlights Merck's complete failure to carry its burden in this IPR. 37 C.F.R. §42.104(b)(4) ("The Petition must specify where each element of the claim is found in the prior art...relied upon").

The Petition cites Dr. Neugut's declaration for support. But Dr. Neugut likewise does not explain how the MSR or any other reference that the Petition relies on discloses treating patients "in response to" determining their MSI status. Instead, Dr. Neugut parrots the claim language without analysis. EX1003, ¶¶61-66, 91; *see also* EX2072, ¶97. Dr. Neugut's conclusory testimony does not address the "in response to" claim language. Nor does he attempt to show that the MSR teaches a causal relationship between the determination that a patient's CRC is MSI-H and treatment with pembrolizumab, disregarding the MSI-stable CRC

patients who are also administered pembrolizumab. His declaration opinions are thus entitled to “little or no weight.” 37 C.F.R. §42.65(a); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential). And Dr. Neugut has now conceded that there is no requirement in the MSR for testing before enrollment, which is a prerequisite for the claimed causal relationship. EX2163, 102:20-103:1.

As discussed earlier (§IV.B, *supra*), the Board’s DI also failed to account for the required causal relationship in its analysis of the “in response to” limitation. In the DI, the Board applied an incorrect construction of “in response to,” noting that it “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 microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients.” DI, 17 n.3. Treating all the CRC patients—both MSI-H and MSI-stable—after testing simply does not practice the method of treating “in response to determining the [CRC] is [MSI-H]” recited in claims 1 and 11. Once the correct construction of this limitation is applied, the failings of the Petition are manifest.

Because the Petition fails to show that the MSR discloses the “in response to” limitation, the Board should find that Merck has failed to carry its burden to prove anticipation by a preponderance of the evidence.

B. The MSR Does Not Disclose The Dependent Claims

1. The MSR Does Not Disclose “Received [At Least One Prior Cancer Treatment/A Prior Cancer Therapy Drug]” or “Progressed [Subsequent To/Following] The Prior [Treatment/Cancer Therapy]”

Claims 7, 17, 26, 28, 30, 32, 34, and 36 each require that, prior to receiving treatment according to the claimed method, the patient must have received a different cancer treatment/therapy and the patient’s cancer must have progressed following that treatment/therapy. The MSR, however, is silent on whether eligible patients *must* have had prior, failed treatment or therapy. See EX1005, 5-6. Merck’s expert, Dr. Neugut, agrees. See EX2163, 99:13-21 (“it leaves out...that the patients had to have previous treatment and progressed on the previous treatment”). Treatment after a patient has “received [at least one prior cancer treatment/a prior cancer therapy drug]” and the patient’s cancer has progressed is thus not disclosed by the MSR. See *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (caselaw “does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them.”); *VirnetX Inc. v. Apple Inc.*, 2023 WL 6933812, at *4 (Fed. Cir. Oct. 20, 2023). Merck’s assertions that a patient “generally” (Pet., 26-27; EX1003, ¶83) would have received a prior treatment is not enough to meet the high burden for a finding of inherency. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (“unless a reference

discloses within the four corners...all of the limitations arranged or combined in the same way as recited in the claim, it...cannot anticipate”). Indeed, Merck’s own reference cited in a parallel proceeding advises that certain Stage IV cancer patients *in fact* proceed directly to clinical trials without prior treatment. See EX2164, 533, 537. Additionally, Merck’s Benson reference (Ground 5), emphasizes that, although CRC treatment generally follows guidelines, “when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.” EX1009, 2.

Merck’s cited case law (Pet., 27) does not support its apparent view that a prior art reference can anticipate, despite missing a limitation, so long as a POSA would understand the limitation to be “generally” present. Instead, each of Merck’s cases relates to the scenario where the express disclosure in a reference establishes that a POSA would understand the limitation was, in fact, necessarily present. See *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373-74 (Fed. Cir. 2020) (reference disclosed claimed technology despite using different words); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991) (POSA would understand the reference disclosed features of the commercially available product); *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1337-40 (Fed. Cir. 2020) (affirming anticipation finding where prior art temperature range overlapped with the claimed range). In each case, the prior art

reference contained disclosures that pointed to one conclusion: a POSA would have understood the reference to ***necessarily*** disclose the apparently missing limitation. Here, however, even Merck acknowledges its conclusions are based on generalities versus actual disclosure.

As the Petition tacitly acknowledges through its deficient inherency analysis, the MSR does not disclose a method of treatment following cancer progression after prior cancer treatment. The MSR does not refer to tumor progression whatsoever. And, the only reference in the MSR to prior treatment is the *exclusion* of individuals who had received certain prior treatments. EX2072, ¶108. This is ***the opposite of*** a requirement of prior treatment. *Id.* Further supporting that a POSA would not understand these limitations were necessarily present in the MSR, the express requirement of prior treatment was ***added*** to the ClinicalTrials.gov record in January 2016—three years after the publication of the MSR. *Compare* EX1005, 5 with EX2165, 8; EX2166, 8. If such a requirement were “necessarily present” to a POSA reading the original MSR (EX1005), there would have been no need for an amendment to add such a requirement. EX2072, ¶108. Thus, there can be no finding of anticipation of the “received [at least one prior cancer treatment/a prior cancer therapy drug]” and “progressed [subsequent to/following] the prior [treatment/cancer therapy]” limitations on this record.

2. The MSR Does Not Disclose Treating “Metastatic” CRC

Claims 6 and 16 each require that the CRC treated according to the claimed method is “metastatic” CRC. “Metastatic cancer” is cancer that spreads from its site of origin to another part of the body. EX2072, ¶110. The Petition offers no evidence that the MSR discloses treatment of metastatic CRC. Instead, the Petition and Dr. Neugut point to the MSR’s requirement that patients have “measurable disease.” Pet., 24-25; EX1003, ¶¶54, 76-80. But “measurable disease” is not synonymous with “metastatic cancer.” EX1048, 230-31. “Measurable disease” in the context of cancer means only that the cancer has a minimum, measurable size not that the cancer is metastatic. *Id.* Consistent with this independent evidence, Merck’s expert, Dr. Neugut, testified that, contrary to the representation he made in his declaration, “metastatic” and “measurable” are “total different terms,” and metastatic tumors “would not necessarily be measurable[.]” EX2163, 14:9-15:12.

Moreover, Dr. Neugut’s argument that it would have been “highly unusual” to not include patients having metastatic cancer, is immaterial. EX1003, ¶78. Whether or not it would have been **unusual** to exclude patients with metastatic cancer is irrelevant to whether the MSI-H Study Record **discloses** patients with metastatic cancer—either explicitly or inherently. As Dr. Lonberg explains, the MSI-H Study Record is silent with respect to this limitation. EX2072, ¶¶109-113.

Finally, Dr. Neugut relies on two publications (EX1049 and EX1050) to argue that the words “measurable” and “metastatic” are equivalent. (EX1003, ¶79.) Each of these publications points out or suggest that the clinical trial announced in the MSI-H Study Record included metastatic patients. EX1049, 6; EX1050, 3. But, as Dr. Lonberg explains, neither of these publications cites the MSI-H Study Record as the basis for this statement—much less the MSI-H Study Record’s use of the term “measurable disease.” EX2072, ¶¶109-113. Instead, these publications appear to be relying on the clinical trial itself. *Id.* The fact that the clinical trial announced in the MSI-H Study Record **ultimately** included metastatic CRC patients does not imply any equivalence between metastatic cancer and the term “measurable disease” as used in the trial announcement—especially given that the accepted meaning of these terms are so different. *Id.*

3. The MSR Does Not Disclose the Claimed Results

Several dependent claims additionally require knowing the outcome of the study disclosed in the MSR. None of these claims are disclosed by the MSR:

- Claims 21-24 require that the treatment **increases** the “median progression free survival” or “median overall survival” of MSI-H CRC patients compared to those of MSI-stable CRC patients.
- Claims 25, 27, 29, 31, 33, and 35 require that the method “**results in**” either “an objective response rate of 40% or higher,” “a

probability of progression-free survival at 20 weeks” of “at least 78%,” or “a probability of progression-free survival at 9 months” of “at least 60%.”

It is undisputed that the MSR does not disclose any of these results of JHU’s study. EX2072, ¶¶114-117; EX2163, 147:18-148:2; EX2282, 77:2-5. Once again, the point of the study was to get and assess results. Indeed, the MSR preceded the study and its outcome. Therefore, a POSA reading the MSR could not have known the study outcome. EX2072, ¶117. Thus, a POSA could not have known whether the treatment, would in fact, “increase[] the median progression free survival” or “increase[] the median overall survival” of MSI-H CRC patients compared to MSI-stable CRC patients, let alone what the objective response rate, or progression-free survival rates would end up being. These rates were **impossible** to predict, as both Merck and JHU’s experts agree. EX2163, 114:22-24 (“Again, what the exact number would have been...you can’t anticipate exactly”); *see also id.*, 111:20-112:2, 115:25-116:7; EX2282, 77:2-13, 94:5-19; EX2072, ¶¶117, 178-179. Merck effectively admits this in its obviousness analysis by arguing that “the POSA would have wanted to complete the study, **including determining the outcome** of patients.” Pet., 54; *see also id.*, 56. To anticipate these dependent claims through inherency, Merck must “make clear that the missing descriptive matter is

necessarily present in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill.***” *Cont’l Can Co. USA*, 948 F.2d at 1268.

By Merck’s expert’s own admission, a POSA could not have recognized the specific claimed outcomes based on the MSR. The MSR therefore cannot anticipate these dependent claims.

C. The MSR Cannot Inherently Anticipate the Challenged Claims.

Both Merck and the DI rely on *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012), as supporting the inherent anticipation of claims 1 and 11 by the MSR. *See* Pet., 17-18; DI, 13-17. Merck cannot carry its burden under *Montgomery* for two reasons. First, as explained above, the MSR does not disclose the claimed method of treatment “in response to” determining that the patient’s CRC is MSI-H and therefore cannot inherently anticipate any challenged claim. Second, the MSR—an initial submission for an experimental trial that had not yet begun recruiting patients, let alone obtaining experimental data—was merely an “invitation to investigate” from which the results claimed by the ’287 Patent did not “inevitably flow.” Even crediting Merck’s recitation of facts, Merck cannot meet the *Montgomery* standard.

Merck relies on *Montgomery* for two propositions: (1) disclosure of a planned clinical study proposing a method of treatment anticipates, even if the study is not performed, and (2) efficacy is inherent in carrying out the claimed

steps of a method. Pet, 17. Merck’s arguments both miss the mark because they are predicated on the MSR in fact disclosing the claimed method of treatment, which it does not do. The MSR does not disclose treating a CRC patient with pembrolizumab **in response to** determining the patient’s CRC is MSI-H, as required by the claims. In *Montgomery*, the prior art trial disclosure “in all relevant respects” was “identical to the patent itself.” 677 F.3d at 1383. In contrast, neither the MSR nor any portion of its disclosure is cited in or appears in the patent’s specification so it cannot provide written description support for the claimed method, as alleged by Merck. Pet., 18.

Even if the MSR disclosed the claimed method—which it does not—it still cannot inherently anticipate the challenged claims because it was merely an “invitation to investigate” a potential association between MSI-H CRC and response to treatment with pembrolizumab. *Montgomery*, 677 F.3d at 1382. At the time of the MSR’s posting, the inventors had a mere hypothesis based on a single patient’s response to a different drug. The inventors did not even have animal data to preliminarily support their hypothesis. EX2130, ¶21. What the inventors did know is that prior studies of other checkpoint inhibitors to treat CRC were unsuccessful. EX2024; EX1013. As Dr. Goldberg explained, a single responder out of thirty-three CRC patients “would generally be regarded as too low to justify a Phase II trial to investigate the efficacy in CRC or any tumor

type.” EX2090, ¶52. As an untested proposal to conduct further study, a positive outcome was far from assured. In fact, when given the chance to sponsor JHU’s clinical trial to obtain the needed data, Merck (and BMS) declined, *see* §VII.C, *infra*, evidencing that the MSR was a far cry from meeting *Montgomery*’s inevitability requirement for inherent anticipation. 677 F.3d at 1381.

Montgomery 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.” *Id.* at 1382 (quoting *Metabolite Lab ’ys, Inc. v. Lab ’y Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)). As the *Montgomery* dissent highlights, and as directly relevant here, “[w]ere inevitability not required for inherency, a mere proposal for further experimentation could anticipate a claimed invention. That is not the law, however. There is nothing inevitable about a proposal.” *Id.* at 1384 (Lourie, J., dissenting). The MSR was a classic “invitation to investigate”—an “abstract theory” in a highly unpredictable field having no supporting data. EX2072, ¶123. It was not “an advanced stage of testing designed to secure regulatory approval.” *Montgomery*, 677 F.3d at 1382. The MSR instead describes a study to test the hypothesis that MSI-H might correlate with response to treatment with pembrolizumab. As a test of a hypothesis, the MSR proposal included both MSI-H and MSI-stable CRC patients rather than presuming

the correlation and only testing MSI-H patients. EX2130, ¶¶10-13. The MSR was an invitation to engage in “further experimentation to find such associations.”

Metabolite Labs., Inc., 370 at 1367.

In contrast, the prior art study in *Montgomery* had enrolled and begun treatment of 9,541 patients. 677 F.3d at 1378. There was no question that the drug being tested prevented stroke as claimed. *Id.* at 1381.⁵ The Board and Federal Circuit thus had little difficulty concluding the prior art reference was “far from an abstract theory” and instead was “an advanced stage or testing designed to secure regulatory approval.” *Id.* at 1382. Importantly, the prior art reference’s disclosure “in all relevant respects” was “identical to the patent itself.” *Id.*

“A result is only inherent if it inevitably flows from the prior art disclosure.” *Id.* at 1381. Because the MSR did not disclose the claimed method, and the results to be obtained through testing based on the MSR were unknown and unpredictable,

⁵ Unlike *In re Couvaras*, 70 F.4th 1374 (Fed. Cir. 2023), also relied on by Merck, at the time the MSR was posted, there were no known treatments for MSI-H CRC. Pet. at 17. Additionally, *Schering Corp. v. Geneva Pharmaceuticals* is inapposite because the issue was whether the claimed compound “necessarily and inevitably forms,” not whether steps of a method claim are necessarily *performed*. 339 F.3d 1373, 1378 (Fed. Cir. 2003).

inherency could not flow from the MSR's disclosure. Thus, the method of treatment disclosed by the MSR cannot meet the *Montgomery* standard and the Board should find Merck has failed to carry its burden to demonstrate inherent anticipation.

D. The MSR Is Not Prior Art Because It Proposes An Experimental Use

Grounds 1-6 also fail because the MSR is an experimental use that does not qualify as prior art. Experimental use balances the “public’s right to retain knowledge already in the public domain and the inventor’s right to control whether and when he may patent his invention.” *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 65 (1998). It does this by granting an inventor latitude to experiment—even in the public eye—until his invention is ready for patenting. *Id.* at 64 (“[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye.”). Consistent with these policies, the Supreme Court and Federal Circuit have held that public experimental activities can be negated as §102 prior art if those activities were for experimental purposes. *See, e.g., City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 133-36 (1877) (discussing experimental negation of a public use); *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1352-55 (Fed. Cir. 2002) (discussing experimental negation of

sales and offers for sale); *cf. Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 872 (3d Cir. 1977) (“Once the party asserting invalidity has convincingly proven the prior use or sale...the burden shifts to the patentee to prove that any prior use, sale, or **printed publication** was for experimental, not commercial, purposes.”).

Experimental use negation applies to the MSR as a matter of fact under the Federal Circuit’s multi-factor analysis, which considers: (1) necessity; (2) control; (3) nature of the invention; (4) length of time; (5) payment; (6) secrecy obligations; (7) recordkeeping; (8) who conducted the experiment; (9) commercial exploitation; (10) necessity of testing under conditions of use; (11) whether testing was systematic; (12) monitoring of the experiment, and (13) nature of contacts with potential customers. *Allen Eng’g Corp.*, 299 F.3d at 1353; *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380-81 (Fed. Cir. 2006). As explained below, each of these factors—alone and in combination—supports that the MSR should not be considered as applicable prior art to the ’287 Patent.

(1) *Necessity*. The ’287 Patent inventors could not have run the groundbreaking clinical study that supports their patent claims without first publishing on ClinicalTrials.gov. *See* 42 U.S.C. §282(j) (EX2148); EX2137, ¶¶8-52; EX2163, 138:15-21, 141:13-17, 143:14-145:1; *cf.* 42 C.F.R. §§11.2-11.66 (EX2147). Indeed, Merck itself required JHU to register NCT01876511 on the ClinicalTrials.gov website before shipment of pembrolizumab for use in the study.

EX2131, §9.F; EX2130, ¶17. Federal regulations require that ClinicalTrials.gov postings include significant details about a planned clinical study, including a description of the study design, study outcomes to be measured, and study eligibility. EX2137, ¶¶33-47; EX2130, ¶¶18-19. Researchers must publish these details before undertaking any clinical study and the posting must be regularly updated until the study is complete. EX2137, ¶¶37, 47-48; EX2130, ¶19; EX2072, ¶124. No U.S. clinical study can lawfully proceed without complying with these obligations. EX2137, ¶¶39-42. JHU's study of MSI-H cancer patients could not have proceeded without the MSR first publishing on ClinicalTrials.gov. EX2137, ¶¶39-42; EX2130, ¶17. Further, without the study results, the inventors could not know (or even reasonably expect) that the claimed methods work. EX2072, ¶¶118-123; EX2130, ¶¶21-27; *see also* EX2163, 25:13-19, 136:11-23. Thus, the submission of the MSR was a necessary step to rendering the claims ready for patenting. *See Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1322 (Fed. Cir. 2019) (“readiness for patenting” requires that the invention had been reduced to practice, which requires that “the inventor (1) constructed an embodiment or performed a process that met all the limitations and (2) determined that the invention would work for its intended purpose.”) (citation omitted).

(2) *Control*. The '287 Patent inventors retained control over the ClinicalTrials.gov posting throughout the MSI-H clinical study. EX2130, ¶33.

They updated the posting 28 times over 7 years. EX2130, ¶19; EX1005, 1-2. The inventors also maintained control over the underlying study itself, overseeing it from recruitment through publication. EX2130, ¶33.

(3) Nature of the Invention and (10) Necessity of Testing Under Conditions of Use. Cancer treatment is a highly unpredictable art. See §VI(B)(2)(a); EX2072, ¶¶33-57, 119; *see also* EX2163, 181:15-25. At the time that the inventors were developing the MSI-H clinical study protocol, pembrolizumab had not yet been approved by FDA for any treatment of any cancer. EX2072, ¶119; EX2130, ¶8; EX2163, 177:24-178:3. And, at the time of the invention, no cancer-type-agnostic treatment had ever been approved by FDA. EX2072, ¶119. Pembrolizumab's subsequent approval for MSI-H, tissue-agnostic treatment—based in large part on the results of the study outlined in the MSR—was heralded as a breakthrough in the industry, as detailed in §VII.B, *infra*. EX2072, ¶¶62, 187-191; EX2090, ¶¶57-58, 65; EX2130, ¶¶36-53. Further, even if pembrolizumab had been approved for another indication, Merck's expert admitted that a positive outcome in one clinical trial does not portend a positive outcome result in subsequent trials. EX2163, 125:15-126:1. Indeed, pembrolizumab has subsequently failed numerous clinical trials. EX2072, ¶¶119, 136-138, 176; EX2130, ¶¶24-26. Given the nascent nature of pembrolizumab treatment at the time of the MSR and the lack of support for

treating cancers by biomarker, rather than by tissue type, experimentation was necessary to establish that the claimed methods work.

Testing was also necessary in humans under the conditions described in the MSR. There are no reliable models of MSI-H in animals and there are no animal models that represent the human body's response to checkpoint inhibitors.

EX2072, ¶¶54-55, 121-122, 144, 193; EX2130, ¶¶21-22; *see also* EX2163, 148:3-6. To establish that treatment of MSI-H cancers was effective, the inventors **had** to test in humans, and thus **had** to publish on ClinicalTrials.gov.

(4) Length of Time. The '287 Patent inventors posted to ClinicalTrials.gov shortly before activating the clinical trial to allow patient recruitment. EX2130, ¶23; *see also* EX2163, 187:5-11, 192:20-193:11. At that time, there can be no question that the claimed invention was not ready for patenting. The clinical study supporting the data in the patent had not yet begun.

(5) Payment, (9) Commercial Exploitation, and (13) Nature of Contacts with Potential Customers. The '287 Patent inventors were not paid to submit the MSR. EX2130, ¶20. The FDA does not pay for submissions to ClinicalTrials.gov. EX2137, ¶23; *see also* EX2163, 189:3-11. The inventors also were not paid by participants in the clinical study itself. EX2130, ¶20; *see also* EX2163, 188:13-189:2. Treatment was provided to patients for free, so there was no commercial exploitation. EX2130, ¶20. And there were no contacts with potential

customers. JHU is an academic research institution that ***does not sell a commercial product***. *Id.* To the extent individuals involved with the study may later seek out pembrolizumab treatment, the product would not come from JHU. *Id.*

(6) *Secrecy Obligations and (7) Recordkeeping.* The '287 Patent inventors were powerless to impose secrecy obligations over the ClinicalTrials.gov posting because such postings are controlled by the government and are required to be public. EX2137, ¶30; EX2163, 144:13-145:1. But the inventors maintained the records from the study under strict confidentiality. EX2130, ¶34; *see also* EX2163, 190:16-23. .

(8) *Who Conducted the Experiment, (11) Whether Testing Was Systematic, and (12) Monitoring of the Experiment.* The '287 Patent inventors were highly involved in conducting the MSI-H clinical study, from drafting the protocol and posting on ClinicalTrials.gov to treatment of patients to publication of results. EX2130, ¶¶14-19. Dr. Le served as the principal investigator overseeing every aspect of the study. EX2130, ¶16. The MSI-H study was done systematically in accordance with best practices for running human clinical trials. EX2130, ¶¶14-19; *see also* EX2163, 37:17-38:1, 136:11-23, 145:9-13.

In sum, the MSR was submitted as part of the inventors' experimentation. The inventors received no financial benefit from the submission and carefully

maintained the ClinicalTrials.gov posting while also diligently completing the underlying clinical study—all to obtain data necessary to support the patentability of their groundbreaking study and invention. Under these circumstances, the Board should find that the MSR does not qualify as prior art to the '287 Patent. As a result, Merck's Grounds 1-6, all of which rely on the MSR, necessarily fail.

E. Policy Warrants Rejecting Merck's Interpretation of Inherency

As a matter of policy, Merck's interpretation of inherency law cannot be correct because it makes patenting a surprisingly effective method of treatment impossible. If, on the one hand, JHU had filed a dataless provisional application mirroring the MSR before the MSR was published (before any clinical study had begun), it could not have satisfied the requirements of §101 and §112. As explained, no animal models existed for *in vitro* testing of the claimed method, and the inventors had just one human data point—a patient identified retrospectively and treated with a different drug. *See infra* §VI.B.3.a. In those circumstances, mere prophetic examples are inadequate. *Cf. Barry*, 914 F.3d at 1322. Even if all the process steps had been disclosed in the MSR—the “in response to” step was not—the claimed method would not have met the requirements of §101 and §112 because a POSA reading the MSR would not have recognized that the inventors had possession of the claimed invention nor believed that the claimed invention

had utility. *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).

If, on the other hand, JHU waited—as it did—until it had data to submit in an application, Merck’s interpretation is that the claims are nevertheless inherently anticipated by the dataless MSR. This is even though the results of the study were unexpected and surprising. And even though the MSR cannot even show a *reasonable expectation of success* in achieving the claimed method for purposes of obviousness. *See infra* §VI.B.2.a (discussing *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019)).

The catch-22 Merck advances cannot be correct. It cannot be that the requirements for receiving patent claims are so much more rigorous than the requirements for enablement of prior art that JHU is functionally precluded from securing patent protection over its breakthrough discovery. It cannot be that JHU’s only options were either (1) pursuing unsupported claims that would likely be unpatentable under §101 or invalid under §112 or (2) pursuing claims with data but have those claims found invalid as anticipated by a dataless clinical study announcement that JHU was statutorily required to post as a prerequisite for conducting a clinical trial to obtain data. Yet, Merck would have the Board interpret *Montgomery* and/or experimental use law to require such a conclusion.

**VI. THE CHALLENGED CLAIMS ARE PATENTABLE OVER
OBVIOUSNESS GROUNDS 2-6**

**A. Merck’s Obviousness Combinations Do Not Disclose or Render
Obvious Treating a CRC Patient “In Response To” Determining
that the Patient is MSI-H**

Because the MSR does not anticipate the challenged claims, Merck cobbles together five different obviousness combinations based on five additional prior art references to try to reach the claims. Pet., 40-62. The only obviousness ground purporting to address the independent claims is Ground 2, which combines the MSR with Pernot. Merck relies on Pernot for two requirements: “Improved Outcome/Efficacy” and “Testing.” Pet., 43-48. Merck does *not* rely on Pernot to supply the missing “in response to” limitation. See EX2163, 150:2-7, 151:2-9. Nor could Pernot supply it, because Pernot does not disclose testing patients for MSI-H status or treating them with pembrolizumab. EX2072, ¶¶71-73, 145-147; *see also* EX2163, 152:12-153:6. Moreover, neither Pernot nor any of the other references presented in Grounds 2-6 provides a POSA with a reasonable expectation of success. See EX2072, ¶¶125-168. For at least that reason, all of Merck’s obviousness challenges fail.

Despite Merck’s cursory nods toward using inherency in its obviousness analysis (*see* Pet., 40, 44-47, 54, 56-57), Merck has not attempted, let alone met, the heightened burden imposed for inherent disclosure in the obviousness context. The Federal Circuit has cautioned that “the use of inherency...must be carefully

circumscribed in the context of obviousness.” *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). To rely on inherency in an obviousness analysis, Merck must meet a “high standard:” “the limitation...***necessarily must be present***[.]” *Id.* at 1195-96. Inherency “may not be established by probabilities or possibilities” and “[t]he mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient.” *Id.* at 1196 (citation omitted).

B. Merck Cannot Show a Reasonable Expectation of Success

1. Merck Applies the Wrong Standard for Reasonable Expectation of Success

Merck’s attempts to rely on various references as allegedly providing a reasonable expectation of success necessarily fail, as Merck applied the ***wrong legal standard***. Federal Circuit precedent is clear that for method of treatment claims, it is “not enough for the [patent challenger] to have shown that a skilled artisan would have pursued the claimed method as a treatment option,” but rather the challenger “also had to show that the skilled artisan would have ***reasonably expected to achieve success in the treatment***.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021). Instead, Merck improperly twists the analysis into whether a POSA “would have reasonably expected patients to respond to a sufficient degree that the POSA would have wanted to ***obtain the data*** from the MSI-H Study, including determining the outcome of patients.”

Pet., 46; *see also id.*, 44.⁶ The expectation that patients would have responded enough that a POSA would have wanted to “obtain the data” or “obtain the results” is ***not*** an expectation that the claimed method of treatment would in fact “***achieve success in the treatment.***” *Eli Lilly*, 8 F.4th at 1344.

Indeed, a POSA will always want to obtain data from a clinical study; that is the entire reason for investing in the significant expense and burden of conducting clinical trials. EX2072, ¶129. Put simply, wanting to obtain the data is ***not*** the same as expecting treatment in response to a determination of MSI-H status to work. EX2072, ¶¶128-131. Merck’s fundamental misapplication of law precludes Merck from meeting its burden to show the claims of the ’287 Patent were obvious to a POSA. *Eli Lilly*, 8 F.4th 1331 at 1344.

⁶ Merck’s citation to MPEP §2107.03, (Pet., 46), is irrelevant; this subsection relates to lack of ***utility***, not ***reasonable expectation of success***.

2. None of Merck's References Provide a Reasonable Expectation of Success⁷

a. MSR

Applying the correct standard, Merck has failed to show that the MSR provides a reasonable expectation of success in performing the claimed method. Nor could Merck make such a showing, as confirmed by binding Federal Circuit precedent. For example, in *OSI Pharmaceuticals*, the Federal Circuit reversed a Board finding and held that similar evidence disclosing a “hope that a potentially promising drug will treat a particular cancer” did not support a reasonable expectation of success. 939 F.3d at 1385. The claims related to a method for the treatment of non-small cell lung cancer (“NSCLC”) with erlotinib. *Id.* at 1378. The Board found the claims obvious over a review article that noted that erlotinib, among other drugs, was currently in clinical trials, and stated that “these compounds appear to have good anti-cancer activity in preclinical models... particularly in patients with [NSCLC].” *Id.* at 1383. The Federal Circuit reversed the Board’s obviousness finding, holding that none of petitioner’s cited references disclosed the treatment of NSCLC with erlotinib. *Id.* at 1383-86. Indeed, there

⁷ Tellingly, Merck’s expert admitted at his deposition that “[m]ost of [the prior art references] were chosen by the attorneys;” he did not look for any references as part of preparing his opinions for this case. EX2282, 59:4-22.

was “no data or other promising information regarding erlotinib’s efficacy in treating NSCLC,” which was “significant because of the highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II.” *Id.* at 1384. The Federal Circuit also rejected the Board’s reliance on preclinical efficacy data. *Id.* at 1385. Noting that “[c]ancer treatment is highly unpredictable,” the Federal Circuit found that the prior art “provide[d] no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this.” *Id.* at 1377-78, 1385.

Similar facts warrant the same outcome here. The MSR is a **submission to obtain approval** to begin enrollment for a clinical trial. It discloses merely an experiment designed to test a hypothesis, specifically, whether MSI-H patients “would exhibit an improved response when treated with [pembrolizumab], compared with the more common MSS or MMR proficient colon cancers.” EX1002, 213. As discussed above in §V.D, certain clinical trials are experiments designed to test hypotheses. EX2163, 37:17-38:1, 136:18-23, 145:9-13; EX2072, ¶¶56-57, 68, 118-124, 143-144. At the time the MSR was published, no patient with an MSI-H tumor had been either enrolled or treated with pembrolizumab. EX2163, 136:24-137:6; EX2072, ¶144. And both parties’ experts agree that **nothing** in the MSR itself tells a POSA that the protocol would result in a finding

that MSI-H status is a powerful indicator of successful treatment with pembrolizumab. EX2163, 137:19-23; EX2072, ¶¶66-70, 117, 143-144, 179.

Moreover, if a POSA would have known or expected the outcome of the trial disclosed in the MSR—that treatment with pembrolizumab in patients with MSI-stable CRC cancer would **fail**—the clinical trial **would not have been approved** by either the clinical investigators or the Institutional Review Boards (“IRBs”) governing the study. EX2090, ¶¶60-62. For JHU’s study to move forward, it had to be approved by an IRB. *Id.*, ¶60. The IRB’s role is to ensure that a clinical trial treats patients ethically. *Id.* In one arm of JHU’s clinical trial design, patients with CRC tumors that were **not** MSI-H—that were instead MSI-**stable**—were set to be treated with pembrolizumab. If the results of JHU’s study had in fact been obvious in showing that pembrolizumab was **not** effective in treating MSI-stable CRC tumors, then it would have been unethical to construct the trial protocol with that arm, let alone actually enroll and treat those patients. EX2090, ¶62. Put simply, it would have been unethical to treat a cancer patient with a therapy **expected** not to work on the patient’s cancer. *Id.* Doctors would not have prescribed it, and patients would not have wanted to take it. *Id.* But until JHU’s clinical trial was performed, no one knew that pembrolizumab would be effective in treating MSI-H CRC tumors and ineffective in treating MSI-stable CRC tumors. These results were unexpected, (*see infra* §VII.E), and there was

therefore no reasonable expectation of success for a POSA in performing the '287 Patent's claimed method of treatment.

Here it is undisputed that, just like in *OSI Pharmaceuticals*, the MSR “do[es] not disclose *any* data or other information about [pembrolizumab's] efficacy in treating [MSI-H CRC],” nor does the record “contain any clinical (human) data or preclinical (animal) data,” or even “*in vitro* (test tube) data regarding [pembrolizumab's] effect on [MSI-H CRC].” 939 F.3d at 1383 (emphasis in original); EX2163, 147:18-148:2; EX2072, ¶144; *see also Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 640-42 (Fed. Cir. 2017) (affirming no reasonable expectation of success even after two full clinical trials using a “promising new...compound” had been completed and a “post hoc analysis” suggested the claimed outcome later confirmed in a third clinical trial). At the time the MSR was published, FDA had not approved pembrolizumab. EX2072, ¶144. And no preclinical or animal model for testing efficacy on human, let alone MSI-H, tumors existed. EX2163, 148:3-6; EX2072, ¶¶54-55, 121-122, 144, 193.

Thus, nothing in the MSR provided a POSA with a reasonable expectation of success, as Merck's expert conceded. EX2163, 137:19-23 (“Q. Is there anything in the [MSR] that tells a POSA that the protocol will be successful or have a positive outcome? A. No.”).

b. Pernot

Pernot also cannot provide a reasonable expectation of success. For starters, Merck's representations about Pernot conflict with Pernot's actual disclosures. For instance, Merck contends that "Pernot taught that those patients [whose CRCs were MSI-H] are 'good candidates for immunotherapy,' such as PD-1 inhibitors like pembrolizumab." Pet., 44 (quoting EX1006, 3741). Pernot, however, does not disclose pembrolizumab. And Merck's expert, Dr. Neugut, testified that Pernot lacks key disclosures about anti-PD-1 therapies:

Q. Pernot does not disclose anti-PD-1 therapies; right?

A. No, correct.

Q. Pernot does not disclose that MSI high CRC patients would be promising candidates for PD-1 checkpoint blockade therapy; correct?

A. No, he does not.

Q. And Pernot does not disclose any relationship between MSI high CRC patients and their likelihood of responding to PD-1 checkpoint blockade therapy; right?

A. No, he doesn't make reference to it.

EX2163, 152:12-153:6. Because Pernot discloses nothing about the likelihood of an MSI-H CRC patient responding to a PD-1 checkpoint inhibitor (like pembrolizumab), Pernot provides no expectation of success whatsoever in using the claimed method to treat MSI-H CRC patients. *OSI Pharms.*, 939 F.3d at 1383; *see also* EX2072, ¶¶145-147.

Undeterred, Merck focuses on a single sentence: “CRC associated with MSI **could** lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good **candidates** for immunotherapy.” EX1006, 5; Pet., 44. But when describing “Immunotherapy in CRC,” Pernot lists 27 different ongoing clinical trials of immunotherapy involving six types of immunotherapy strategies—**none** of which included anti-PD-1 therapies, let alone pembrolizumab. EX1006, 10 (Table 1); *see also* EX2282, 90:19-21, 92:4-93:8, 95:21-96:18. And where Pernot does mention anti-PD-1 therapies, it is in passing and only in the context of **melanoma**—not CRC, let alone MSI-H CRC or other MSI-H tumors. *Id.*, 6. Additionally, contrary to the Board’s reading, Pernot does not teach that “[CRC] patients are good candidates for immunotherapy.” DI, 21. In fact, Pernot teaches that “escape mechanisms to antitumor immune response” in CRC are “a **major obstacle**...to the use of immunotherapy” in CRC. EX1006, 2; *see also* EX2072, ¶¶51-52, 120, 134-135, 155-156. Thus, Pernot does not disclose or even suggest that pembrolizumab would work in MSI-H CRC patients. EX2072, ¶¶71-73, 145-147.

Indeed, Pernot concludes that “immunotherapeutic approaches is a seducing **alternative to try** to improve the prognosis of these patients in the future.” EX1006, 9. But there were no “identified, predictable solutions” at this time. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Pernot’s forward-looking

statements are mere hypotheses insufficient to support a reasonable expectation of success. “[H]ope that a potentially promising drug will treat a particular cancer is **not enough** to create a reasonable expectation of success in a highly unpredictable art such as this.” *OSI Pharms.*, 939 F.3d at 1385; *see also Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) (“speculative and tentative disclosure of what ‘might’ or ‘may’ [explain the cause of a desired effect] does not sufficiently direct or instruct one of skill in this art”); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006).

c. Merck’s Tertiary References

Merck also relies on **fifteen** additional references in Ground 2 in its failed effort to support three blanket statements about what was known in the art:

- “[S]everal other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab”;
- “[T]he prior art taught that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that were easy for immune cells to recognize and (2) already infiltrated by many immune cells”;
- “[T]he prior art taught that MSI-H tumors naturally displayed those characteristics.”

Pet., 45-46 (citing EX1006, EX1032-1042, EX1051, EX1058, EX1085, EX1087).

Merck’s Petition fails to identify any specific disclosures within these references to support these points. Instead, Merck relies on Dr. Neugut to identify and explain

the alleged support. *See* Pet., 45-46 (citing EX1003, ¶¶42-45, 133-134). Just as with Pernot, however, what these references say and what Merck and Dr. Neugut claim they say are worlds apart. As Dr. Lonberg explains, at best these references were inviting researchers to take an outside chance on investigating additional speculative hypotheses. EX2072, ¶¶148-151 (citing EX1032, e27818-5; EX1038, 9; EX1041, 9208; EX1042, 732; EX1051, e976052-6; EX1084, 1; EX1033, 2969).

Moreover, Merck ignores evidence in these **very same sources** that taught **away** from the treatment method of the '287 Patent. *See, e.g.*, EX1032, Table 1 (showing a **0% response rate** for anti-PD1 agents and anti-PD-L1 agents among CRC patients); EX1033, 2969 (describing disparities of findings of PD-L1 expression in MSS and MSI-H colon cancer with previous studies); EX1035, 2 (“there may **not** be a single biomarker that will prove sufficient information for predicting treatment response and patient outcome”). Merck additionally ignores that many trials of anti-PD-1/PD-L1 inhibitors ultimately failed, with the reasons remaining poorly understood even well after the Critical Date of the '287 Patent. EX2074, 18; EX2075, 1; EX2072, ¶¶136-138. As the evidence shows, and as Dr. Lonberg explains, the notion that the prior art provided a reasonable expectation of success for the method of treatment claimed in the '287 Patent is simply wrong. EX2072, ¶¶148-168 (citing EX1032-1042, EX1051, EX1058, EX1085, EX1087).

3. The State of the Art Does Not Create a Reasonable Expectation of Success

a. PD-1 Inhibitors Were In Their Infancy

Merck's argument that "the state of the art" compelled a reasonable expectation of success similarly falls short. At the time of the MSR, anti-PD-1 antibodies were "still in development" and had only "shown promising clinical results...for tumors classically considered to be immunogenic such as melanoma and renal cell carcinoma (RCC)" and also "for common epithelial malignancies such as [NSCLC], historically resistant to immunotherapy." EX1057, 1.

But cancer therapy is inherently and notoriously unpredictable. EX2072, ¶¶33-57, 119. Here, no animal models of MSI-H cancer existed, so there was no way for the inventors to generate even initial preclinical data that would have suggested eventual success. EX2163, 148:3-6; EX2072, ¶¶54-55, 121-122, 144, 193; EX2073, 271-272. As Dr. Le explained: the "clinic is the experiment." EX2130, ¶21.

While Merck alleges that "[p]hysicians were treating patients having cancers that were known to have MSI-H subpopulations in the prior art, including CRC, with PD-1 inhibitors," this is misleading. Pet., 45. No PD-1 inhibitor had been approved for any indication before JHU's filing of the MSR to enroll patients on June 10, 2013. EX2072, ¶¶119, 144. At the time, MSI-H and MSI-stable patients were treated the same way. EX2090, ¶33. The patients with MSI-H tumors treated

in the other clinical trials cited by Merck were only **retrospectively** identified as being MSI-H, as the study records do not mention MSI testing. EX1023; EX1016, 6-7; EX1017, 5-6. Treating cancer types that **may** have MSI-H subpopulations without awareness that any of those patients are in fact MSI-H does not provide a reasonable expectation of success. EX2072, ¶¶169-172.

Nor does Merck's reliance on the treatment of a single CRC patient with a different PD-1 inhibitor create a reasonable expectation of success. See Pet., 45 (citing EX1057). On the contrary, this evidence supports the unpredictability and unexpectedness of JHU's clinical results. Only **one** patient out of thirty-three CRC patients responded in the BMS study to which Merck cites—a “statistically meaningless” result.⁸ EX1002, 225; EX1057, 2-3; EX2176, 22; EX2072, ¶173; EX2090, ¶52. In other words, at that time a different PD-1 inhibitor—not pembrolizumab—had shown a **97% failure rate**. To the extent this result reflects the effect of pembrolizumab at all, “the only reasonable expectation at the time of the invention was **failure**, not success.” *OSI Pharms.*, 939 F.3d at 1385 (finding

⁸ Because this patient's MSI-H tumor status was only discovered after treatment occurred, treatment was not “in response to” the determination of MSI-H status as required by the claimed method.

no reasonable expectation of success given “a 99.5% failure rate and no efficacy data or any other reliable indicator of success”).

Additionally, at that time, it was not known that the single CRC patient responded **because** his tumor was MSI-H. See EX2163, 131:5-132:9 (publication “makes no reference to it”). That status was determined only after observing the complete response and investigating why it happened. See EX2163, 132:5-9; EX1002, 210-212, 225; EX2176, 22-23; EX2090, ¶¶53-54. The MSR therefore represented a “mere ‘hypothesis’” to generate the data that **might** explain why the patient responded. *Sanofi*, 875 F.3d at 647.

The inventors’ hypothesis was not accepted at the time by interested companies. In fact, BMS’s investigators speculated that its single positive CRC response could be due to **PD-L1**, a different biomarker thought to predict response to anti-PD-1 therapy. EX1057, 3. Merck had the same hypothesis, and launched its own study testing pembrolizumab in CRC patients with **PD-L1** positive tumors, six months after JHU’s trial began. EX2080. But yet again, only one CRC patient out of twenty-three (23) responded—a **96% failure rate**—and that patient was later (after the priority date of the ’287 Patent) found to be MSI-H. EX2132, 11. Merck concluded from its study that pembrolizumab had “limited antitumor activity in patients with heavily pretreated PD-L1-positive advanced CRC.” *Id.*, 11.

Further, both Merck and Bristol Myers Squibb **rejected** JHU's request to fund the inventor's clinical trial. EX2072, ¶¶130, 144, 191; EX2090, ¶55. Instead, the JHU researchers were forced to find philanthropic funding. EX2121, 6. The idea that pembrolizumab (or nivolumab)—drugs that had not been approved for **any** indication at this time—could be used to treat cancer based on a specific genetic marker, rather than the location of the tumor, was unexpected and groundbreaking. EX2090, ¶¶56-59.

b. Pembrolizumab's Other Approvals Do Not Predict Success

Merck's argument that pembrolizumab's previous approvals would have led a POSA to have a higher expectation of success for the MSI-H CRC indication is inconsistent with the realities of cancer treatment and Federal Circuit precedent. As the court found in *OSI Pharmaceuticals*, "it is undisputed that a drug's success in treating one type of cancer does not necessarily translate to success in treating a different type of cancer, which underscores the unpredictability in cancer treatment generally." 939 F.3d at 1384. Merck's own expert agrees. EX2163, 125:15-126:1. Even Merck's chief medical officer recognized this, saying recently "it's still always going to be a game of chance," as "[e]very cancer is different, and every setting within the cancer can be different." EX2078, 2. In particular here, where FDA had never before approved a cancer therapy based on a biomarker

alone, no precedent existed for a POSA to reasonably believe such a method of treatment would succeed. EX2072, ¶174.

For that reason, Merck’s reliance on the statistic that “for oncology drugs, 55% of second indications were successful if the first indication was successful” is similarly misplaced. Pet., 46. Never before had the proposed second or follow-on indication been for a tissue agnostic, biomarker-based therapy. Additionally, Merck’s statistic **excluded** drugs that were sponsored “exclusively by academic, government, or non-profit organizations.” See EX1063, 1. As Dr. Lonberg explains, studies run by these three institution types are far more likely than pharmaceutical companies to be high risk, experimental studies, more likely to fail, and therefore **drive down** the success rate Merck relies upon. EX2072, ¶175.

More telling than a blanket statistic is pembrolizumab’s own history. Keytruda®, Merck’s pembrolizumab product, has repeatedly failed in clinical trials, even today. A Merck-sponsored trial of Keytruda in CRC patients who were positive for a PD-L1, another biomarker thought to be associated with antitumor immune responses, failed in all but one patient, who later was identified as MSI-H. EX2132, 1-2; EX2130, ¶¶9-10, 25. As of April 2023, Keytruda had “failed as a combination therapy in **21 late-stage studies** spanning nine different partner drug technologies,” and “[r]esearchers also didn’t advance at least **66 combination studies** after early or midstage trials.” EX2078, 1; *id.* (“The track record has been

horrible.”); *see also* EX2076; EX2077; EX2079. Therefore, the fact that pembrolizumab had been approved once simply does not supply the reasonable expectation of success.

C. Merck Has Not Shown the Dependent Claims Would Have Been Obvious Over the Prior Art in Ground 2

As noted above, under Ground 2 Merck does not address any specific dependent claim, and thus has not met its burden with respect to the obviousness of any dependent claim, particularly the two groups of claims that are independently patentable over Ground 2, as identified in §V(B)(3), *supra*.

As discussed above, showing that each of these groups of claims either existed in the prior art or would have been obvious over the prior art, **requires knowing the results** of the clinical study described in the MSR. EX2072, ¶¶177-179. Pernot published in April 2014 and is silent regarding treating MSI-H patients with pembrolizumab (or any other PD-1 inhibitor) and does not disclose the results of the JHU trial (or similar trial). Thus, a POSA would have had no way of knowing whether the amount of pembrolizumab used was, in fact, “effective in promoting progression-free survival” or “reduce[d] the risk” of cancer progression, let alone what the precise objective response rate, or progression-free survival rates would end up being. As noted above, the experts agree these rates were **impossible** to predict. EX2163, 114:22-24; 111:20-24, 116:6-7; EX2072,

¶179. Merck admits as much here by arguing that “the POSA would have wanted to obtain the data from the MSI-H Study, ***including determining the outcome*** of patients.” Pet., 46; *see also id.*, 54, 56. Without obtaining patient outcomes, a POSA would not have been able to show that these narrow and specific dependent claims were obvious over the prior art.⁹ EX2072, ¶179.

D. Merck Has Not Shown the Dependent Claims Would Have Been Obvious Over the Prior Art in Grounds 3-6

The prior art in Grounds 3-6 does nothing to fill the Petition’s deficiencies regarding either the “in response to” claim limitation or the requirement that a POSA “would have reasonably expected to achieve success in the treatment” claimed in the ’287 Patent. *Eli Lilly*, 8 F.4th at 1344. Merck does not allege it does. Instead, as the DI acknowledges, Merck relies on Chapelle, Steinert, Benson, and Hamid for discrete limitations unrelated to either issue. DI, 22-23. None renders the dependent claims unpatentable. EX2072, ¶¶74-80, 180-185.

⁹ Merck relies on Benson for disclosure of the specific outcomes, but that argument also fails as Merck cites nothing in Benson for claims 31 and 33-35. Pet., 58-59. Merck points back to claim 6 but claim 6 requires only that the CRC be metastatic. EX2072, ¶184; Pet., 53-54.

**VII. OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS FURTHER
PROVE THE CHALLENGED CLAIMS ARE PATENTABLE**

The relationship between Merck and JHU is far from the typical Petitioner-Patent Owner relationship that the Board sees in post-grant proceedings. Instead, the parties' prior relationship is the source of an array of strong objective evidence of non-obviousness, including industry praise, skepticism, long-felt unmet need, unexpected results, and commercial success. JHU is an academic institution that designed and ran a clinical trial whose outcome led to a novel, patented method of treatment using the drug pembrolizumab. Merck markets and sells pembrolizumab under the brand name Keytruda® and labels its drug specifically to treat CRC patients determined to have MSI-H tumors pursuant to JHU's patented method. In doing so, Merck infringes JHU's patents and benefits richly from this willful infringement.

JHU's objective evidence of non-obviousness, coupled with Merck's failure to show a reasonable expectation of success, confirms the validity of each challenged claim. "[O]bjective considerations of non-obviousness must be considered in *every* case," *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (emphasis in original), and "can be the ***most probative evidence of non-obviousness in the record***," enabling the court "to ***avert the trap of hindsight***."

Crocs, Inc. v. Int’l Trade Comm’n, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (cleaned up).

A. Nexus

The surprising results of JHU’s study ultimately led to FDA approval of pembrolizumab for the treatment of MSI-H CRC, thereafter resulting in actual treatment of patients with MSI-H CRC tumors, and concomitant sales of pembrolizumab under the brand name Keytruda® to treat those patients. Here, a clear nexus exists between the development and commercialization of Merck’s pembrolizumab product, Keytruda®, and the patented method of treatment. See *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). There is a presumption of nexus when a “product embodies the invention and is coextensive with it.” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1211 (Fed. Cir. 2023).

1. JHU is Entitled to a Presumption of Nexus

Here, JHU’s objective evidence is tied to the method of using pembrolizumab to treat CRC patients determined to have MSI-H tumors as disclosed and claimed in the ’287 Patent. Put another way, the objective indicia

here are narrowly tailored to the claimed method of treatment, i.e., the indications¹⁰ that were ultimately tested and approved, **not** to pembrolizumab generally.

EX2175; EX2179. For example, every step of the claimed treatment method is set forth in Merck’s Keytruda® label for indications “1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer” and “1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer.” EX2129, 5; EX2177; EX2179. Independent claim 1 is representative, and each claimed step is identified in the Keytruda® label as shown in the below table and as described by Dr. Goldberg, (EX2090, ¶¶66-77):

1[pre]. A method for treating colorectal cancer in a human patient, the method comprising:	
1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer	KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumor response rate and durability of response [see <i>Clinical Studies</i> (14.8)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. <u>Limitations of Use:</u> The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.
1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer	KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

EX2129, 5.

¹⁰ “Indication” refers to the FDA approved use of a drug for a specific disease or condition, as indicated on the drug label. EX2090, ¶27, n.3.

1[a]. in response to determining that the colorectal cancer is [MSI-H/dMMR], treating a human patient having colorectal cancer that is [MSI-H/dMMR] with a therapeutically effective amount of pembrolizumab,

The Recommended Dosage section of the Keytruda® label provides the recommended dosages of Keytruda®, as well as the duration/timing of treatment based on the indication, wherein the indication is directed to CRC confirmed to be MSI-H or dMMR:

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months

* 30-minute intravenous infusion

EX2129, 7-8.

The Keytruda® label includes clinical trial results showing that the recommended dosages of Keytruda® are therapeutically effective among CRC patients with MSI-H or dMMR solid tumors relevant to Indication 1.8 and 1.9:

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR) solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

Table 51: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)

EX2129, 73-75.

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Table 52: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-1

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
Objective Response Rate‡		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Duration of Response‡,§		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 months¶	75%	37%
% with duration ≥24 months¶	43%	18%

* Based on Cox regression model

† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)

‡ Based on confirmed response by BICR review

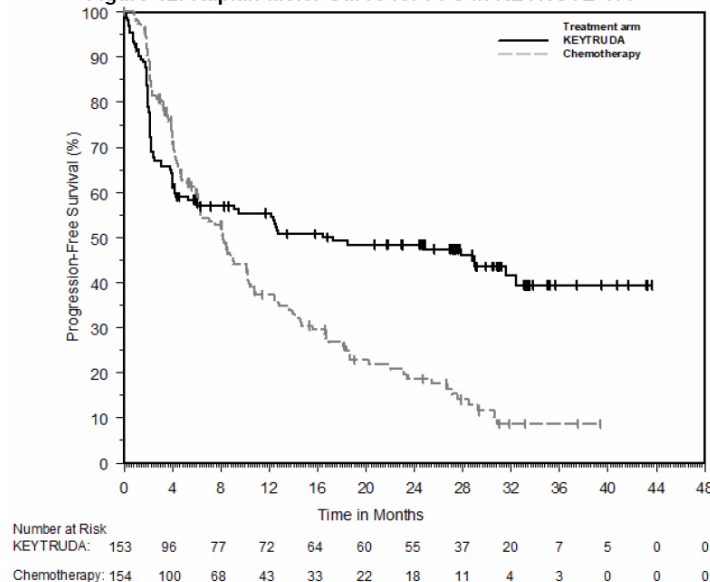
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm

¶ Based on observed duration of response

+ Denotes ongoing response

NR = not reached

Figure 12: Kaplan-Meier Curve for PFS in KEYNOTE-177



EX2129, 75-77.

1[b]. wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is [MSI-H or dMMR].

The Dosage and Administration section (Section 2) of the Keytruda® label instructs physicians to select patients having a cancer that is either MSI-H or dMMR for treatment with Keytruda according to Indications 1.8 and 1.9:

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, or TMB-H Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation [see *Clinical Studies (14.2)*].
- metastatic NSCLC [see *Clinical Studies (14.2)*].
- first-line treatment of metastatic or unresectable, recurrent HNSCC [see *Clinical Studies (14.4)*].
- metastatic urothelial carcinoma [see *Clinical Studies (14.7)*].
- metastatic gastric cancer [see *Clinical Studies (14.10)*]. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- metastatic esophageal cancer [see *Clinical Studies (14.11)*].
- recurrent or metastatic cervical cancer [see *Clinical Studies (14.12)*].

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens [see *Clinical Studies (14.8, 14.9)*].

EX2129, 7.

Further, the Dosage and Administration section refers physicians to Clinical Studies sections 14.8 and 14.9 that instructs physicians to test or have tested the patient tumor's MSI-H/dMMR status via local polymerase chain reaction (PCR) or immunohistochemistry (IHC):

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR) solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 4 were identified using both tests.

EX2129, 73-74.

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

EX2129, 75.

As shown above, Keytruda®’s label dictates the uses for which Keytruda® may be prescribed by doctors and marketed by Merck. EX2090, ¶¶66-77; EX2072, ¶195. Thus, the method of determining MSI-H status and then using Keytruda® to treat MSI-H CRC patients is coextensive with the claims, and the Board should apply a presumption of nexus.

Merck cannot rebut the presumption of nexus “with argument alone—it *must* present evidence.” *WBIP*, 829 F.3d at 1329; *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988) (patent challenger must “adduce evidence” showing objective indicia “due to extraneous factors other than the patented invention...argument and conjecture are insufficient.”) (cleaned up). To date, Merck has presented no such evidence.

2. Even Absent a Presumption, JHU’s Objective Indicia Has A Nexus to the ’287 Claims

Even without the presumption, JHU can show that there is a “legally and factually sufficient connection” between JHU’s objective evidence and the patented invention. *Henny Penny*, 938 F.3d at 1332 (quoting *Demaco*, 851 F.2d at 1392); *Volvo*, 81 F.4th at 1211.

Here, a nexus exists “between the evidence and the merits of the claimed invention.” *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). The merits of the claimed method of treatment relate to the claims **as a whole**. JHU’s objective evidence relates directly and specifically to the merits of the claimed method of treating patients determined to have MSI-H CRC with pembrolizumab. For example, key industry players, including Merck, were skeptical that the claimed method would work. EX2121, 17; EX2183; EX2131; EX2184, 3; EX2072, ¶191; EX2130, ¶50. When JHU revealed the dramatic results of its clinical trial, those results were unexpected and surprising to those in the field. EX2130, ¶¶29-32; EX2121, 6; EX1031, 1, 5. The finding that pembrolizumab worked to treat MSI-H CRC patients satisfied a long-felt, unmet need, saving the lives and futures of patients otherwise likely lost. EX2090, ¶¶28-45, 63-65; EX2121, 7; EX2006. The industry praise for the discovery that the treatment of MSI-H CRC patients with pembrolizumab worked was immediate and overwhelming. EX2130, ¶¶43-46; EX2005, 1-3; EX2006, 1; EX2089, 2, 5; EX2004, 1; EX2060, 2. Finally, as a result, Merck’s commercialization of the claimed invention by selling Keytruda® to treat MSI-H CRC patients is a commercial success. EX2191, ¶¶23-44; EX2187; EX2188. Thus, the specific objective indicia asserted here (and detailed below) are both legally and factually

connected to the specific method claimed in the '287 Patent, and a finding of nexus in fact is appropriate. *See Volvo*, 81 F.4th at 1212.

The objective evidence here **cannot** be tied to the MSR alone, because, as Merck's expert agreed, nothing in the MSR suggests that the method of treatment would **work** to treat MSI-H CRC patients. EX2163, 137:19-23; *see also* EX2072, ¶¶143-144. Therefore, until the clinical trial proposed by the MSR was conducted, the results showing that it worked—the results underlying each and every objective indicia—simply were “**not** known in the prior art.” *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017).

Thus, overwhelming evidence demonstrates that even if Merck somehow rebuts JHU's presumption of nexus, each category of objective evidence on its own has a sufficient nexus to the claimed invention. The stronger the showing of nexus, the greater the weight accorded the objective evidence of non-obviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985). Here, given the strong showing of coextensiveness between the claimed method and the narrowly tailored objective evidence, the Board should afford significant, if not determinative, weight to JHU's objective evidence.

B. Industry Praise

The method of using pembrolizumab (Keytruda®) to treat patients with MSI-H tumors has received overwhelming praise from the oncology community,

FDA, and Merck itself. Such industry praise tends to show the invention was not obvious. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc).

1. The Oncology Community Lauded the Results of JHU's Research

The results of JHU's clinical study were nothing short of revolutionary. JHU submitted its results with an abstract to the American Society of Clinical Oncology ("ASCO") 2015 meeting. ASCO "is considered the super bowl of the cancer world," according to Merck's expert, and is "attended by tens of thousands of oncologists and others each year." EX1003, ¶35, n.1; *see also* EX2163, 104:13-105:3 (ASCO is "where everyone is...to hear what's new and exciting"). ASCO selected JHU's abstract as a "late breaking" abstract, even though JHU did not submit it as such. EX2130, ¶¶43-46. Dr. Le explains that "late breaking" abstracts are "typically reserved for presentations concerning the bigger phase 3 drug trials that tend to include practice changing data," rather than data from a small trial, like JHU's. EX2130, ¶44. Dr. Le also explained that ASCO does not release late breaking abstracts before the meeting, but rather "treats these presentations somewhat like movie premieres, with fanfare and press conferences the day before the conference to build excitement about the discoveries that will be announced." EX2130, ¶45; EX2135.

Not only did ASCO select JHU's abstract from the thousands of other submitted abstracts, it also selected JHU inventor Dr. Le to give a featured ***oral presentation*** at the meeting. EX2130, ¶43. As Merck's own expert testified, to be selected to give a presentation like this "would be because of the several thousand papers [it] would be considered one of the main – ***one of the most important discoveries of the year*** among all the abstracts that were submitted." EX2163, 107:4-12; *see also id.*, 106:4-107:3. Dr. Le describes how she "delivered [her] presentation to a standing room only crowd of [her] fellow clinicians in a huge conference hall at ASCO" and how when she "revealed [the] data to the audience, you could hear a pin drop in this huge room." EX2130, ¶43.

On the same day as Dr. Le's ASCO presentation, the New England Journal of Medicine ("NEJM") published the initial results from JHU's clinical trial. EX1031. NEJM is "considered ***the most prestigious journal***," according to Merck's expert, with "the most prominent papers that are published in medicine." EX2163, 109:12-110:4; *see also* EX2282, 53:5-18; EX2072, ¶¶61, 187; EX2130, ¶47. Indeed, it has the third-highest impact factor of any scientific journal. EX2180, 3-4. Later results of JHU's study were published in another prestigious scientific journal—Science. EX2118.

After FDA's approval of pembrolizumab for the MSI-H tumor agnostic indication and the MSI-H CRC second line therapy indication, JHU's research

supporting its claimed invention received tremendous praise from others in the oncology community. For example, Dr. Jose Baselga, a chief physician at Memorial Sloan Kettering Cancer Center, referred to JHU's study as "absolutely brilliant," and described the durability of the patients' treatment response as "insane." EX2005, 1, 3. The results were widely reported as a "breakthrough" and heralded as a "new frontier in cancer treatment." EX2006, 1. Indeed, researchers from the NIH in 2018 noted that this approval "marks the first tissue-agnostic approval of any drug and thus represents a *paradigm shift*" in treating cancer patients. EX2089, 2; *see also id.*, 5 (describing approval as "a *tipping point* for disease reclassification based on tumor-specific factors," "propel[ling] oncology further toward the goal of precision medicine.").

The approval of pembrolizumab to treat MSI-H CRC changed the standard of care for those patients. EX2090, ¶72. Even Merck's expert, Dr. Neugut, changed his standard of care because of the "obvious efficacy of the drug in that context." EX2163, 82:21-83:11; *see also* EX2282, 50:4-16 (describing treatment with PD-1 inhibitors as "major boon" for MSI-H patients).

2. FDA Recognized the Impact of JHU's Invention

FDA also recognized the special nature of JHU's invention. When FDA approved location-agnostic treatment with Keytruda® in response to the presence of the MSI-H biomarker, it issued a press release. In it, FDA's Oncology Center of

Excellence highlighted the groundbreaking nature of JHU’s invention: “This is ***an important first*** for the cancer community...Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor’s biomarker without regard to the tumor’s original location.” EX2004, 1.

FDA also recognized that it was charting new territory while navigating the approval process, since no precedent existed for the nature of the indication Merck sought based on JHU’s work. As Merck’s Vice President of Global Clinical Oncology explained, “[w]hen they saw these data, [FDA] were really helping us to figure out what exactly we would provide for them to be able to sign off on a tissue-agnostic approval, and so it really was a collaborative effort once the data started to come in...” EX2121, 17. It was a unique “collaboration of academia, FDA, and industry.” *Id.*

3. Merck Praised JHU’s Innovation

Merck’s own sentiments echoed those of the industry and FDA. In concert with Dr. Le’s keynote address at ASCO and NEJM’s publication of the results, Merck released a press release highlighting the powerful initial results of JHU’s research. Dr. Roger Dansey, Merck’s senior vice president of oncology late-stage development, commented that “[t]hese ***exciting results***, while early, suggest that evidence of DNA mismatch repair deficiency may be an important way of

identifying tumors that are responsive to checkpoint blockade,” and that “these results ***open the door*** for research with KEYTRUDA in CRC and other tumor types with this potentially clinically meaningful tool.” EX2061, 2.

When FDA later approved Merck’s application for using Keytruda® to treat MSI-H cancers, Merck similarly celebrated the approval and acknowledged its groundbreaking nature. The President of Merck Research Laboratories, Dr. Roger Perlmutter, stated, “FDA’s approval of this ***first-of-its-kind***, tumor-agnostic, indication is further evidence of Merck’s commitment to helping people with difficult-to-treat cancers, and to advancing the use of biomarkers to guide clinical decision-making.” EX2060, 2. And Merck openly acknowledged and praised JHU’s role in securing that approval. Indeed, Dr. Perlmutter publicly thanked JHU for its inventive work, stating, “[t]his is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and clinicians at Johns Hopkins University ***for their important scientific work***[.]” *Id.*

This widespread praise for JHU’s claimed method of treatment from the industry at large, FDA, and Merck is strong evidence of non-obviousness. *Apple*, 839 F.3d at 1053.

C. Skepticism

“Expressions of disbelief by experts constitute strong evidence of nonobviousness.” *Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693,

697-98 (Fed. Cir. 1983). Neither the industry nor Merck believed in the inventors' hypothesis that MSI-H cancers would respond to pembrolizumab at a rate higher than MSI-stable cancers. EX1002, 225-226.

After FDA approval, Merck admitted that the prevailing belief had been that pembrolizumab would **not** work in CRC patients, that it was "very interesting," that "there have been prior small numbers of colon cancer patients who'd been treated with anti-PD-1 agents, and the responses were pretty much zero, and so the idea was, early on, that *it really wasn't going to work* in colon cancer, as a monotherapy." EX2121, 17. In fact, while Merck agreed to provide pembrolizumab for JHU to run the study, it declined to provide any initial funding for the study. See EX2183, 1; EX2131. Merck's unwillingness to fund JHU's limited clinical trial contrasts sharply with Merck's approach to funding other, later, pembrolizumab clinical trials. For tissue-specific cancers, Merck effectively gave its scientists a blank check. EX2051, 15-16. For JHU's hypothesis about MSI-H cancers, however, Merck only jumped on the bandwagon to fund follow-on studies after seeing the positive results starting to flow from JHU's initial study. See EX2080.

Nor was Merck the only company skeptical of JHU's proposed clinical study and hypothesis. As Dr. Lonberg explains, when he was Senior Vice President, Oncology Discovery Biology at BMS, JHU approached BMS, in addition to

Merck, about using BMS's checkpoint inhibitor nivolumab and funding its study. EX2072, ¶191. Dr. Lonberg believed then that JHU's study was high-risk because there was no reason to expect it would work in CRC patients when PD-1 inhibitors had failed repeatedly in that population. *Id.* BMS therefore declined to provide either its drug or funding. When the preliminary results of JHU's clinical trial were announced, however, BMS regretted missing such an opportunity. EX2072, ¶¶188, 194.

With no funding from either Merck or BMS, JHU ultimately funded its study through Swim Across America, a charity that stages swim meets to fund cancer research.¹¹ Swim Across America's CEO, Rob Butcher, explained that the organization "like[s] doing high-risk, high-reward projects, the ones where there is a potential for a breakthrough, but where there is just no funding for it. We seek those out." EX2121, 6. As inventor Dr. Diaz explained later, "I had applied for funding to an endless number of organizations," but "I was denied by all of them." EX2184, 3. "Merck finally agreed to give us a sample of Keytruda...but I had to come up with funding for the clinical trials. Enter Swim Across America[.]" *Id.*

¹¹ Notably, just after the FDA approved Keytruda® for the MSI-H indication, Merck gave Swim Across America a \$3 million dollar donation. EX2134.

While the pharmaceutical companies had closed their doors on JHU, a charity took a chance. And the results were “unbelievable!” EX2121, 6.

Even *after* JHU had presented its results at ASCO and in NEJM, some members of the oncology community continued to question whether these remarkable results could really be true. For example, Dr. Le testified that when she presented the results again, one colleague questioned her data as premature during the public question-and-answer session, arguing she needed more data before associating MSI-H status with responsiveness to pembrolizumab. EX2130, ¶50.

This skepticism from Merck and the industry at large further supports the non-obviousness of the claimed method of treatment. *Envtl. Designs*, 713 F.2d at 697-98.

D. Long-Felt Need

“Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious.” *Apple*, 839 F.3d at 1056. Before the invention of the claimed treatment method, a long-felt unmet need existed for therapies that could treat CRC, and in particular, treat advanced or metastatic CRC as well as CRC developed by patients who have MSI-H tumors. EX2090, ¶¶28-45 (citing EX2091-2114).

Before the priority date of the '287 Patent in 2015, the five-year survival rate of patients diagnosed with unresectable metastatic CRC was roughly 9.8%, meaning that after 5 years, **only 9.8% of patients were still alive**. These patients had a median overall survival (OS) of 20.2 months—**less than 2 years**. EX2090, ¶38. In patients who had failed their first and second line of therapies, the outlook was even worse, with a median survival of only 6-7 months. EX2090, ¶¶43-45. Comparatively, the median survival in patients treated with best supportive care—i.e., “comfort care”—was 4.5 months. EX2090, ¶45; *see also* EX2130, ¶28. Thus, in patients who had failed two prior therapies, the **best** therapies available before the invention only increased life expectancy by **1-2 months**, often with the harsh side effects of chemotherapy. EX2090, ¶45. Yet even these meager gains were significant to the oncology community, and these chemotherapeutics were “quickly adopted into practice.” *Id.*

As these numbers suggest, with the **best** five-year overall survival rate less than 10%, being diagnosed with advanced CRC was like a death sentence in 2015. EX2090, ¶¶38, 41. As Merck’s expert, Dr. Neugut, testified, “[c]uring a patient with a metastatic solid tumor, it’s a very rare phenomenon. I would say in my career, which stretches back 40 years and encompasses thousands of patients, I’ve cured seven.” EX2163, 181:15-25.

But statistics show only one facet of long-felt unmet need; the CRC patients suffering and in desperate need of new therapies show the true human face of this unmet need. The journeys of some of these patients before being treated with the claimed method have been documented. For example, Dr. Goldberg has told of meeting his 26-year-old patient, Beth Carner, who was dying of advanced CRC when they met. EX2121, 7; EX2090, ¶63. After treating Beth with pembrolizumab, Dr. Goldberg described “[l]iterally, I saw for the first time in my career, the Lazarus effect,” continuing, “I treated her, and within a couple of months she was completely normal...and she went back to dancing—from dead to dancing.” EX2121, 7; EX2090, ¶63.

The journey of another CRC patient, Stefanie Joho, was documented in the Washington Post. EX2006; EX2090, ¶64. Prior to being treated with pembrolizumab, her cancer was “raging out of control,” and she was “in agony from a malignant mass in her midsection.” EX2006, 1-2; *id.*, 3; EX2090, ¶64. After treatment, “her tumor shrank and ultimately disappeared.” EX2006, 2. She has since stopped treatment, “free from all signs of disease.” *Id.*; EX2090, ¶64. And the personal stories go on and on. EX2176.

Without JHU’s claimed method of determining MSI-H status and treating MSI-H CRC patients with pembrolizumab, Beth, Stefanie, and many, many others suffering with MSI-H CRC would have succumbed to their illness. EX2090, ¶65.

During the approval process, Merck repeatedly told FDA that [REDACTED]

[REDACTED]

EX2168, 10-13, 31; EX2169, 2 (Merck [REDACTED])

[REDACTED]; *see also*

EX2170, 5; EX2171, 11, 18-20, 30, 32, 36-37; EX2172, 29; EX2167, 8;

EX2173, 17; EX2174, 4.

And FDA recognized the long-felt unmet need in the CRC population. FDA has a number of programs “intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition,” including breakthrough therapy designation, priority review, and accelerated approval. EX2186, 5. These programs “are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies’ benefits justify their risks.” *Id.*; EX2090, ¶¶58-59. FDA specifically defines “unmet medical need” as “a condition whose treatment or diagnosis is not addressed adequately by available therapy.” EX2186, 8. To expedite MSI-H CRC patients’ access to pembrolizumab, FDA granted Keytruda® breakthrough therapy designation, priority review, and accelerated approval, finding that [REDACTED]

████████████████████ EX2181, 2; *see also* EX2182; EX2062; EX2133; EX2205. Merck’s expert, Dr. Neugut, explained that, under a normal FDA approval timeline, “the number of patients who are not going to be treated and suffer during that time is certainly in the hundreds,” and for a drug like pembrolizumab, “which has such a dramatic benefit, would really be unethical to – or it would be detrimental not to fast track it and do something more rapidly.” EX2163, 183:19-184:8. In fact, “[i]t’s not done except in such dramatic circumstances.” *Id.*, 184:8-9.

The significant evidence of long-felt, unmet need here weighs in favor of non-obviousness of the claimed method of treatment. *Apple*, 839 F.3d at 1056; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082-83 (Fed. Cir. 2012).

E. Unexpected Results

“Unexpected results are useful to show the improved properties provided by the claimed [inventions] are much greater than would have been predicted.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (cleaned up). No one expected JHU’s method of treatment embodied in the claimed invention to succeed. Rather, “[t]he indication—and the trial—resulted from a hunch.” EX2121, 4; *see also id.*, 5.

As discussed above, cancer treatment is inherently unpredictable. The unexpectedness of the results of JHU's clinical study highlight this unpredictability. Indeed, as discussed above, the only studies that had tested pembrolizumab or other PD-1 inhibitors in CRC patients had failed resoundingly, with **97% and 95% failure rates**. See *supra* §VI.B.3.a.

Even JHU's investigators were skeptical at first. Drew Pardoll told his co-inventor "that checkpoint inhibitors didn't seem to be working in [CRC]." EX2121, 6. The results therefore surpassed any expectation the inventors had. EX2130, ¶¶29-32. As co-inventor Diaz explained, "we start[ed] enrolling patients, and these patients are doing miraculously well"; their "tumors are melting away." EX2121, 6. Put simply, in oncology, "[t]hings don't work a lot," and "[w]hen something works, it's unbelievable!" *Id.*

The powerful results from JHU's research supporting its claimed invention were not just anecdotal; they were borne out by robust and surprising data. The preliminary results reported in the NEJM and in the specification of the '287 Patent showed significant promise in MSI-H (i.e., MMR-deficient) patients:

	MMR-deficient¹⁸ CRC (n = 10)	MMR-proficient CRC (n = 18)	MMR-deficient non-CRC (n = 7)
Complete Response (%)	0 (0)	0 (0)	1 (14)
Partial Response (%)	4 (40)	0 (0)	4 (57)
Stable Disease (Week 12) (%)	5 (50)	2 (11)	0 (0)
Progressive Disease (%)	1 (10)	11 (61)	2 (29)
Not Evaluable (%)	0 (0)	5 (28)	0 (0)
Immune-related objective response rate (<u>irORR</u>) (95% CI)	40 (12-74)	0 (0-19)	71 (29-96)
Immune-related disease control rate (95% CI)	90 (55-100)	11 (1-35)	71 (29-96)
Immune-related <u>PFS</u> at 20 weeks (95% CI)	78 (40-97)	11 (1-35)	67 (22-96)

EX1001, Fig. 11 (cleaned up); *see also* EX1031, 1, 5. Specifically and notably, 90% of MMR-deficient CRC patients showed either a partial response or stable disease at week 12, while only 11% of MMR-proficient CRC patients had stable disease at week 12; the rest of the patients' tumors had progressed. *Id.* Likewise, 78% of MMR-deficient CRC patients had progression free survival (PFS) at 20 weeks, compared to only 11% of MMR-proficient CRC patients. In fact, the MMR-deficient CRC patients had not even reached the median progression-free survival or overall survival at the time of this analysis. EX1001, Fig. 2A. In

contrast, the MMR-proficient CRC patients, had a progression free survival of only 2.2 months, and a median overall survival of 5.0 months. EX1001, 17:8-15.

For perspective, as described above, in 2015 an increased life expectancy of only **1-2 months** had been significant enough in patients who had failed two prior therapies to be “quickly adopted into practice.” EX2090, ¶45; *see* §VII.D, *supra*. Here, the median follow-up time for the MMR-deficient CRC patients was 36 weeks—9 months—and still median progression free survival had not been met, in a patient population confirmed to have failed at least two prior therapies. Put differently, not enough patients had their tumors progress yet—**after 9 months**—to calculate a median. EX1031, 1; *see also* EX2130, ¶¶29-31; EX2090, ¶56. Even after JHU published the full results of its study in Science, median progression-free survival had **still** not been reached, after a median follow-up time of **12.5 months**. EX2118, 2. As even Merck’s expert, Dr. Neugut, admits—“the survival benefit is impressive[.]” EX2163, 182:25-183:9; *see also id.*, 181:17-25 (comparing curing 7 patients over a 40-year career treating thousands of patients to curing “another seven in the last five years” with Keytruda® in MSI-H CRC patients); *id.*, 178:4-7. Indeed, the 5-year OS rate for MSI-H CRC patients in the JHU study turned out to be an astounding **57.5%**. EX2090, ¶41; EX2130, ¶30.

The results of JHU’s clinical trial were so unbelievable and unexpected that they caught Merck off guard. Surely, if Merck had anticipated the success of

JHU's clinical trial, or truly believed the results were going to be obvious, then Merck would have either sponsored JHU's clinical trial, or initiated its own clinical trial sooner, so that Merck could take the quickest path to FDA approval. It is basic common sense that the faster FDA approves an indication, the sooner a company can profit from sales under that indication. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005) ("the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art."). Indeed, Merck rushed to get as many indications approved as quickly as possible. *See* EX2051, 15-16 ("Former Merck executive Reicin recalls presenting [Merck research chief] Perlmutter with a prioritized list of potential Keytruda clinical studies and asking him, based on resources, where to draw the line. 'There is no line,' Perlmutter reportedly responded. 'Do them all.'").

But Merck did not initially do an MSI-H CRC study. Instead, JHU conducted its study in an Investigator-Initiated Clinical Trial ("IICT"), meaning that it was investigators at JHU, an academic institution, and *not* Merck, running the trial. EX2130, ¶¶20, 37. It is not common for IICTs to be used to support FDA submissions. EX2130, ¶37. Typically, if an IICT yields promising results, the pharmaceutical company will run a follow-up trial that it sponsors itself, so that the data is collected in a format suitable for submission to FDA. *Id.* Here, Merck

was in such a rush to get approval after seeing JHU's data that, instead of completing its own follow-on trial first, Merck collaborated with JHU to collect JHU's data and format for FDA submission—a non-trivial task. EX2130, ¶¶35-38; EX2169, 3.

Finally, to the extent Merck argues that the fact that FDA had approved pembrolizumab for other therapies means a POSA would have expected pembrolizumab to work in a completely different patient population—MSI-H CRC patients—Merck is wrong, for the same reasons discussed in §VI.B.3.b, *supra*.

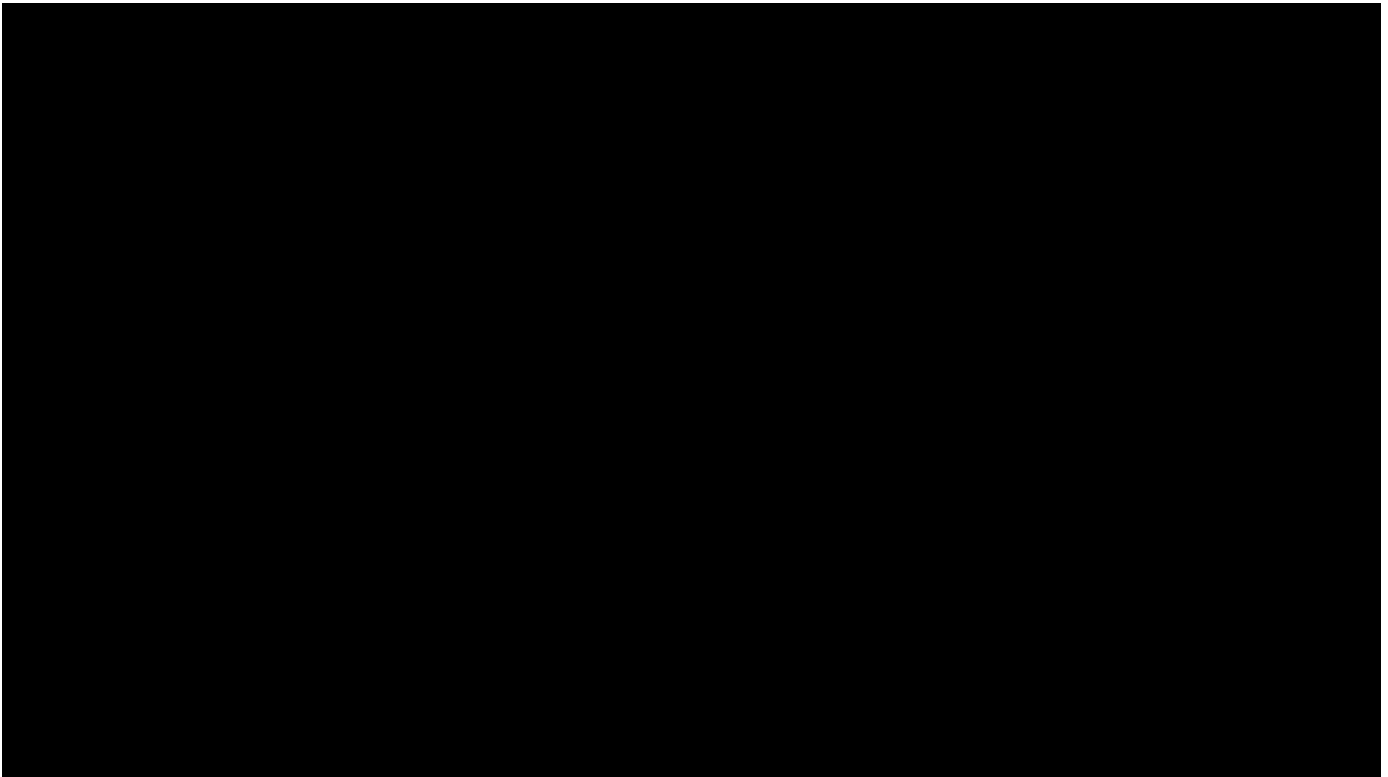
The extensive evidence of unexpected results further supports the non-obviousness of the claimed method of treatment. *Leo Pharm.*, 726 F.3d at 1358. *See also* EX2072, ¶¶192-194.

F. Commercial Success

The Federal Circuit has repeatedly recognized commercial success as highly relevant objective evidence of non-obviousness. *See Merck*, 395 F.3d at 1376. “[A] patentee can demonstrate commercial success” with “significant sales in a relevant market,” *Chemours Co. v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021) (cleaned up), and by growth in the number of users of the patented product, including increase in sales and annual growth rate in the relevant industry, *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000). “[S]ales figures alone are also evidence of commercial success.” *Tec Air, Inc. v. Denso Mfg. Mich.*

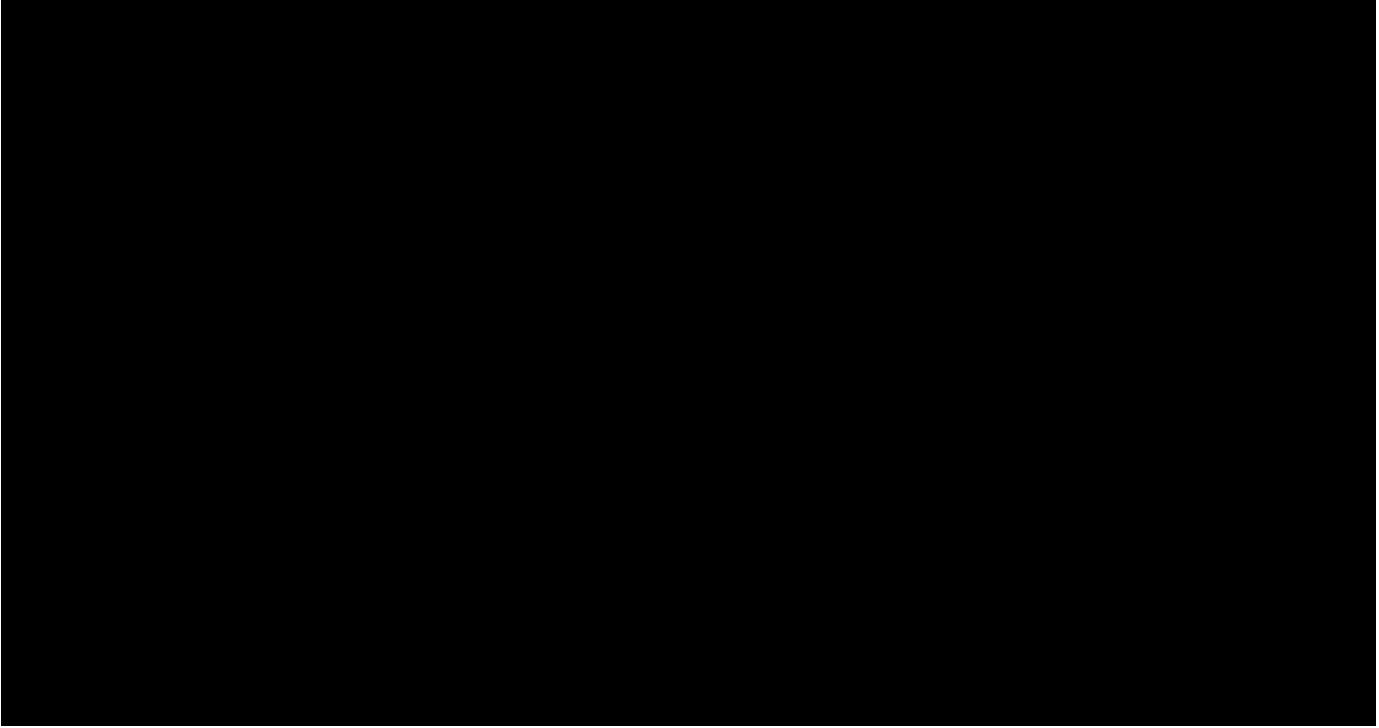
Inc., 192 F.3d 1353, 1361 (Fed. Cir. 1999). Under these and other metrics, Keytruda®'s use in MSI-H CRC cancers is a commercial success. EX2191, ¶¶8-44.

Since its approval for treatment in MSI-H or dMMR patients, Keytruda® sales have been large and consistently growing. EX2191, ¶¶23-30. To start, Keytruda® overall sales grew significantly from [REDACTED] in 2015 to [REDACTED] in 2023, totaling over [REDACTED]:



EX2191, Appendix 2. Additionally, the timing of Merck's approval for Keytruda®'s use in MSI-H patients coincided with an apparent inflection point in Keytruda® sales trajectory. EX2191, ¶¶24-26.

Sales of Keytruda® for the treatment of MSI-H CRC specifically also experienced consistent and rapid growth since FDA approval for JHU's patented method of use, [REDACTED]

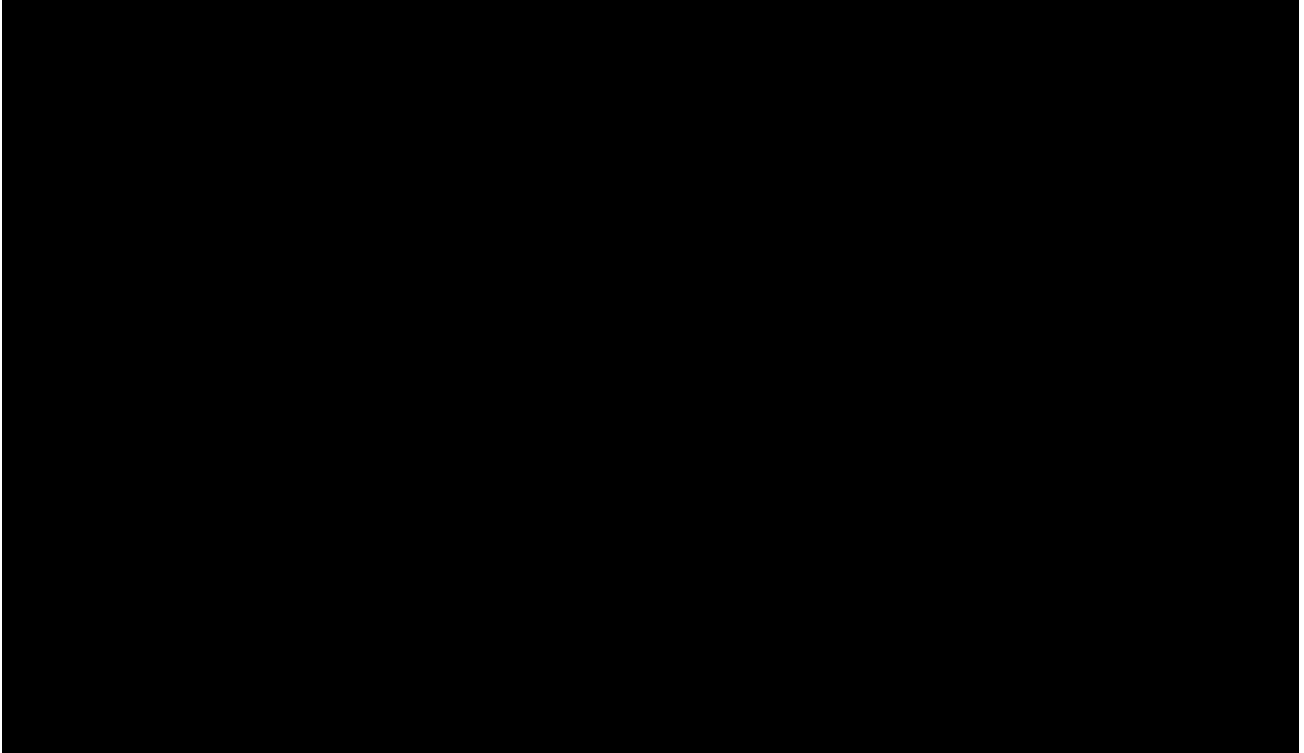


Id., Appendix 5; *see also id.*, ¶¶27-30. This growth is strong compared to competitor products in the market. *Id.*, ¶¶33-35. These sales and growth show the commercial success of JHU's claimed invention. *See Ruiz*, 234 F.3d at 668; *Tec Air*, 192 F.3d at 1361.

Not only have Keytruda® sales grown, but so has the number of MSI-H patients taking Keytruda®. EX2191, ¶¶31-32. In 2017, [REDACTED] [REDACTED] treated with Keytruda. *Id.*, ¶31. By 2023, the [REDACTED]. *Id.* In 2017, [REDACTED]

[REDACTED]. *Id.*, ¶32.

Further, Keytruda®'s [REDACTED] despite entry of competing products Opdivo®, Yervoy®, and Jemperli:



Id., Appendix 9; *id.*, ¶34.

There is more. Keytruda®'s use in MSI-H CRC cancers [REDACTED]
[REDACTED] that Merck management said accounted for significant shares of Keytruda® overall sales. EX2191, ¶35.

Indeed, use of Keytruda® for MSI-H CRC patients is [REDACTED]
[REDACTED].

Id.

And to be clear, these specific Keytruda® sales for treatment of the MSI-H CRC indications could not have been made **but for** JHU's invention of the claimed method. EX2090, ¶¶66-77; *see also* EX2191, ¶¶36-44. In other words, **0%** of Merck's Keytruda® sales for treatment of MSI-H CRC patients would have been made without JHU's patented invention. That is because FDA monitors the marketing Merck is permitted to do in the United States by governing what Merck puts on the Keytruda® label, and Merck was only able to get FDA approval to put this indication on its label by relying on JHU's clinical study data. Indeed, earlier versions of Keytruda®'s label do not contain an indication for MSI-H CRC and Merck was not permitted to market it for this treatment. EX2090, ¶¶66-67; EX1055; EX2125; EX2128.

Moreover, even if other factors contributed in some way to the sales for treating MSI-H CRC patients, “[i]t is not necessary...that the patented invention be **solely** responsible for the commercial success,” in order for nexus to exist; it can “be given weight appropriate to the evidence.” *Cont'l Can Co.*, 948 F.2d at 1273; *see also Fox Factory, Inc. v. SRAM, LLC*, 813 F. App'x 539, 543 (Fed. Cir. 2020). Thus, the Federal Circuit authorizes the Board to credit Keytruda®'s commercial success in MSI-H CRC patients, even if it finds the patented method not “solely responsible” for it.

Keytruda®'s commercial success in MSI-H CRC patients is thus directly attributable to the method of treating MSI-H CRC patients claimed in the '287 Patent, which strongly supports the non-obviousness and patentability of the claimed invention. EX2191, ¶¶8-10, 22; *Merck*, 395 F.3d at 1376.

VIII. CONCLUSION

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

Respectfully submitted,

Dated: 01/23/2025

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

The undersigned hereby certifies that the word count for the foregoing
Patent Owner Response totals 17,238, which is less than the 17,500 authorized by
the Board in Paper 12 dated December 9, 2024.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4), the undersigned certifies that on January 23, 2025, a complete and entire copy of this Patent Owner's Response was provided by email to the Petitioner by serving the correspondence address of record as follows:

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