PUBLIC VERSION

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

IPR2024-00649
Patent No. 11,629,187

PETITIONER'S REPLY

TABLE OF CONTENTS

I. INTRODUCTION 1

II. TESTIMONY ELICITED FROM JHU'S POR DECLARANTS SUPPORTS THAT ALL JHU CLAIMS ARE UNPATENTABLE 5

III. GROUND 1: CLAIMS 1-2, 4-7, 9-12, 14-17, AND 19-28 OF THE '187 PATENT ARE ANTICIPATED BY THE MSR 8

A. ClinicalTrials.gov Study Records Are Prior Art Printed Publications and Therefore Not Subject to Experimental Use 8

B. The MSR Discloses Treating a Patient with a Non-CRC MSI-H Cancer 9

C. The MSR Explicitly Discloses Treating a Non-CRC Patient "In Response To" Determining the Non-CRC is MSI-H and "Based on Previous Testing" 12

D. Any Clinical Results Inherently Flow from the Treatment Method Taught to a POSA by the MSR 13

E. The MSR Teaches Treating a MSI-H Cancer Patient with a Tumor that Would Have "Progressed Following at Least One Prior [Cancer] Treatment" 15

F. The MSR Teaches Treating a Patient with "Metastatic" Cancer 19

IV. GROUNDS 2-6: ALL CLAIMS OF THE '187 PATENT ARE OBVIOUS OVER THE MSR IN VIEW OF THE PRIOR ART 21

A. The Prior Art Renders Obvious Treating a Non-CRC Patient with Pembrolizumab "In Response To" Determining the Patient is MSI-H and "Based on Previous Testing" 21

B. The Prior Art Combinations in Grounds 2 and 3 Teach Treating a Cancer Patient Whose Tumor Progressed Following Prior Treatment or That Has Metastatic Cancer 23

C. A POSA Would Have Had a Reasonable Expectation of Success in Carrying Out the Claimed Two-Step Treatment Method 25

V. JHU'S ALLEGED SECONDARY CONSIDERATIONS EVIDENCE SHOULD BE AFFORDED LITTLE TO NO WEIGHT 28

A. JHU Fails to Meet Its Burden to Establish Nexus 28

B. JHU Has Not Shown the Claimed Method of Treatment Was Unexpected as of the Alleged Invention Date....29

C. JHU Has Not Shown Any Industry Skepticism as of the Alleged Invention Date....31

D. JHU Ignores the Rapid Development of Pembrolizumab and PD-1 Inhibitors by the Alleged Invention Date....32

E. JHU Does Not Present Any Evidence of Industry Praise Tied to Novel Features of the Claimed Invention....35

VI. CONCLUSION....36

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Cases

In re '318 Patent Infringement Litig.,
583 F.3d 1317 (Fed. Cir. 2009) 9

Acorda Theras., Inc. v. Roxane Labs., Inc.,
903 F.3d 1310 (Fed. Cir. 2018) 32-33

Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.,
25 F.4th 1354 (Fed. Cir. 2022) 34

Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.,
IPR2016-00286, Paper 86 (P.T.A.B. July 26, 2019).....33

Ex parte Balzarini,
21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991).....9

Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.,
713 F.3d 1369 (Fed. Cir. 2013) 35

Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha,
No. IPR2022-00578, Paper 78 (P.T.A.B. Aug. 29, 2023).....8

Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.,
IPR2015-01780, Paper 70 (P.T.A.B. Feb. 23, 2017).....33

Genentech, Inc. v. Hospira, Inc.,
946 F.3d 1333 (Fed. Cir. 2020) 35

Hoffmann–La Roche Inc. v. Apotex Inc.,
748 F.3d 1326 (Fed. Cir. 2014) 30

In re Huai-Hung Kao,
639 F.3d 1057 (Fed. Cir. 2011) 29

In re Ikeda Food Rsch. Co., Ltd.,
758 Fed. Appx. 952 (Fed. Cir. 2019).....34

Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.,
97 F.4th 915 (Fed. Cir. 2024) 5

In re Montgomery,
677 F.3d 1375 (Fed. Cir. 2012) 13

Novartis AG v. Torrent Pharms. Ltd.,
853 F.3d 1316 (Fed. Cir. 2017) 29

Salix Pharms., Ltd. v. Norwich Pharms. Inc.,
98 F.4th 1056, 1061 (Fed. Cir. 2024) 8

Sanofi-Synthelabo v. Apotex, Inc.,
550 F.3d 1075, 1084 (Fed. Cir. 2008) 10

Schering Corp. v. Geneva Pharms.,
339 F.3d 1373 (Fed. Cir. 2003) 13

Teva Pharma. Int'l GmbH v. Eli Lilly & Co.,
8 F.4th 1349 (Fed. Cir. 2021) 29

Volvo Penta of the Americas, LLC v. Brunswick Corp.,
81 F.4th 1202 (Fed. Cir. 2023) 28

WBIP, LLC v. Kohler Co.,
829 F.3d 1317 (Fed. Cir. 2016) 28

LIST OF EXHIBITS

Ex. No.	Description	Previously Submitted
EX1001	U.S. Patent No. 11,629,187 (the "'187 patent")	X
EX1002	File History of the '187 patent (U.S. Patent Application No. 17/354,656)	X
EX1003	Declaration of Dr. Alfred I. Neugut, M.D., Ph.D., M.P.H.	X
EX1004	Curriculum Vitae of Dr. Alfred I. Neugut, M.D., Ph.D., M.P.H.	X
EX1005	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1 ("MSI-H Study Record"); also available at Merck Sharp & Dohme LLC v. The Johns Hopkins University, 1:22-cv-03059-BPG, ECF 1, Complaint, Exhibit B (11/29/22)	X
EX1006	Pernot et al, *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) World J. Gastroenterology 3738 (April 2014)	X
EX1007	Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)	X
EX1008	Reserved	
EX1009	Benson et al, *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014)	X

EX1010	Salipante et al, *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) Clinical Chemistry 1192 (June 2014)	X
EX1011	Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New Eng. J. Medicine 134 (July 2013)	X
EX1012	Laheru et al, *Immunotherapy for Pancreatic Cancer Science Driving Clinical Progress*, 5 Nature Revs. 459 (June 2005)	X
EX1013	Topalian et al, Safety, *Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer*, 366(26) New Eng. J. Med. 2443 (June 28, 2012)	X
EX1014	Pardoll, *The Blockade of Immune Checkpoints in Cancer Immunotherapy*, 12 Nature Revs. 252 (April 2012)	X
EX1015	Kang et al, *Pembrolizumab KEYNOTE-001: An Adaptive Study Leading to Accelerated Approval for Two Indications and a Companion Diagnostic*, 28(6) Annals of Oncology 1388 (2017)	X
EX1016	ClinicalTrials.gov, NCT01848834, "Study of MK-3475 in Participants With Advanced Solid Tumors (MK-3475-012)," (October 18, 2013) available at https://classic.clinicaltrials.gov/ct2/history/NCT01848834?A=12&B=12&C=merged#StudyPageTop	X
EX1017	ClinicalTrials.gov, NCT02054806, "Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-028/KEYNOTE-28)," (July 7, 2014) available at https://clinicaltrials.gov/study/NCT02054806?tab=history&a=14	X

EX1018	Robinson et al, *Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) Diagnostics*, 99(4) J. Nat'l Cancer Inst. 291 (2007)	X
EX1019	Fujiwara et al, *Accumulated Clonal Genetic Alterations in Familial and Sporadic Colorectal Carcinomas with Widespread Instability in Microsatellite Sequences*, 153(4) Am. J. Pathology 1063 (1998)	X
EX1020	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014)	X
EX1021	Press Release, National Institutes of Health Launches "ClinicalTrials.gov" (February 20, 2000), Available at https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html	X
EX1022	File History of the '356 patent (U.S. Patent Application No. 16/144,549)	X
EX1023	July 27, 2017 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf	X
EX1024	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 12, 2013) available at https://www.clinicaltrials.gov/study/NCT01876511?tab=history&a=2	X
EX1025	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (September 20, 2013) available at https://www.clinicaltrials.gov/study/NCT01876511?tab=history&a=3	X

EX1026	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (May 21, 2014) available at https://www.clinicaltrials.gov/study/NCT01876511?tab=history&a=4	X
EX1027	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 25, 2014) available at https://www.clinicaltrials.gov/study/NCT01876511?tab=history&a=5	X
EX1028	Reserved	
EX1029	*Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-BPG, ECF 40, The Johns Hopkins University's First Amended Answer and Counterclaims to Merck's Complaint for Declaratory Relief (Filed 5/22/23)	X
EX1030	U.S. Provisional Patent App. No. 61/931,512	X
EX1031	Le et al, *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, 372(26) New Eng. J. Medicine 2509 (June 25, 2015)	X
EX1032	Champiat et al, *Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy*, 3(1) OncoImmunology e27817-1(January 2014)	X
EX1033	Gatalica et al, *Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type, Cancer*, Epidemiology, 23(12) Biomarkers & Prevention 2965 (November 12, 2014)	X
EX1034	Brown et al, *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) Genome Research 743 (May 2014)	X

EX1035	Ogino et al, *Cancer Immunology - Analysis of Host and Tumor Factors for Personalized Medicine*, 8(12) Nature Revs. Clinical Oncology 711 (2011)	X
EX1036	Tougeron et al, *Tumor-Infiltrating Lymphocytes in Colorectal Cancers with Microsatellite Instability Are Correlated with the Number and Spectrum of Frameshift Mutations*, 22(9) Modern Pathology 1186 (2009)	X
EX1037	Nosho et al, *Tumour-infiltrating T-cell Subsets, Molecular Changes in Colorectal Cancer and Prognosis: Cohort Study and Literature Review*, 222(4) J. Pathology 350 (2010)	X
EX1038	Kim et al, *Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types*, 28(supp.3) Oncology 15 (November 10, 2014)	X
EX1039	Llosa et al, *Immune Checkpoints Expression in MSI Versus MSS Colorectal Cancers and Their Potential Therapeutic Implications*, J. 32(15) Clinical Oncology 243s (May 2014)	X
EX1040	Loi et al, *Host Antitumor Immunity Plays a Role in the Survival of Patients With Newly Diagnosed Triple-Negative Breast Cancer*, 32(27) J. Clinical Oncology 2935 (July 28, 2014)	X
EX1041	Donnard et al, *Mutational Analysis of Genes Coding for Cell Surface Proteins in Colorectal Cancer Cell Lines Reveal Novel Altered Pathways, Druggable Mutations and Mutated Epitopes for Targeted Therapy*, 5(19) OncoTarget 199 (October 15, 2014)	X
EX1042	Kansara et al, *Translational Biology of Osteosarcoma*, 14(11) Nature Revs. Cancer 722 (October 16, 2014)	X
EX1043	U.S. Provisional Patent App. No. 62/190,977	X

EX1044	Tay et al, *A Combined Comparative Genomic Hybridization and Expression Microarray Analysis of Gastric Cancer Reveals Novel Molecular Subtypes1,2*, 63(12) Cancer Research 3309 (2003)	X
EX1045	Wahlberg et al, *Evaluation of Microsatellite Instability and Immunohistochemistry for the Prediction of Germ-Line MSH2 and MLH1 Mutations in Hereditary Nonpolyposis Colon Cancer Families*, 62(12) Cancer Research 3485 (2002)	X
EX1046	Taggart et al, *High-level Microsatellite Instability in Appendiceal Carcinomas*, 37(8) Am. J. Surgical Pathology 1192 (August 2013)	X
EX1047	Stintzing et al, *Management of Colorectal Cancer*, 6 F1000 Prime Reports 1 (November 4, 2014)	X
EX1048	Eisenhauer et al, *New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)*, 45(2) Eur. J. Cancer 228 (2009)	X
EX1049	Matikas et al, *The Place of Targeted Agents in the Treatment of Elderly Patients with Metastatic Colorectal Cancer*, 7(1) Cancers 439 (March 13, 2015)	X
EX1050	Lee et al, *Novel Therapies in Development for Metastatic Colorectal Cance*r, 7(4 Supp. 1) Gastrointestinal Cancer Research 1 (September 2015)	X
EX1051	Lal et al, *An Immunogenomic Stratification of Colorectal Cancer: Implications for Development of Targeted Immunotherapy*, 4(3) OncoImmunology 1 (April 2, 2015)	X
EX1052	Reserved	

EX1053	ClinicalTrials.gov, NCT02060188, "Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)," (February 10, 2014) available at https://clinicaltrials.gov/study/NCT02060188?tab=history&a=1	X
EX1054	Ascierto et al, *Future Perspectives in Melanoma Research: Meeting Report from the "Melanoma Bridge", Napoli, December 5th-8th 2013*, 12 J. Translational Medicine 277 (October 2024)	X
EX1055	September 4, 2014 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf	X
EX1056	Reserved	
EX1057	Lipson et al, *Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody*, 19(2) Clinical Cancer Research 462 (January 2015)	X
EX1058	Drescher et al, *Lymphocyte Recruitment into the Tumor Site is Altered in Patients with MSI-H Colon Cancer*, 8(3) Familial Cancer 231 (2009)	X
EX1059	Reserved	
EX1060	Reserved	
EX1061	Reserved	
EX1062	Reserved	
EX1063	DiMasi et al, *Clinical Approval Success Rates for Investigational Cancer Drugs*, 94(3) Clinical Pharmacology & Therapeutics 329 (September 2013)	X

EX1064	Le et al, Supplementary Appendix to *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, 372(26) New Eng. J. Medicine 2509 (June 25, 2015), available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1500596/suppl_file/nejmoa1500596_appendix_1.pdf	X
EX1065	June 21, 2022 Memo From Katherine Vidal on Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022), available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf	X
EX1066	*Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-BPG, ECF 57, Scheduling Order (Filed 10/16/23)	X
EX1067	Maryland, U.S. District Court – Judicial Caseload Profile, available at https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distprofile0630.2023.pdf	X
EX1068	Henry et al, *Cancer Biomarkers*, 6(2) Molecular Oncology 140 (2012)	X
EX1069	Garon et al, *Antitumor Activity of Pembrolizumab (Pembro; Mk-3475) and Correlation with Programmed Death Ligand 1 (Pd-L1) Expression in a Pooled Analysis of Patients (Pts) with Advanced Non–Small Cell Lung Carcinoma (Nsclc)*, 25(4) Annals of Oncology September 2014	X
EX1070	World Health Organization, *International Nonproprietary Names for Pharmaceutical Substances (INN)*, 27(2) WHO Drug Information (2013)	X
EX1071	Roth, *Frameshift Mutations*, 8 Annual Review of Genetics 319 (1974)	X

EX1072	Excerpt from Julien Taieb Citations, Google Scholar, available at https://scholar.google.ca/citations?user=niwd5qgAAAAJ&hl=en (accessed 8/25/23)	X
EX1073	Excerpt from Alexander Eggermount Citations, Google Scholar, available at https://scholar.google.com/citations?user=NWWkhzoAAAAJ&hl=en (accessed 8/25/23)	X
EX1074	Excerpt from Jean-Charles Soria Citations, Google Scholar, available at https://scholar.google.com/citations?user=wyFxnccAAAAJ (accessed 8/25/23)	X
EX1075	Henry Lynch, Research.com, available at https://research.com/u/henry-t-lynch (accessed 8/25/23)	X
EX1076	Excerpt from Daniel Van Hoff Citations, Google Scholar, available at https://scholar.google.com/citations?user=-NTa4oUAAAAJ&hl=en (accessed 8/25/23)	X
EX1077	Excerpt from Robert A. Holt, Google Scholar, available at https://scholar.google.com/citations?user=CXPlI08AAAAJ&hl=en (accessed 11/27/23)	X
EX1078	Young et al, *Treatment of Advanced Disease*, 321 British Medical J. 1278 (2000)	X
EX1079	Le et al, *Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors*, 32 (15) J. Clinical Oncology (May 2014)	X
EX1080	Poster presented at ASCO, Le et al, *Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors* (Jun. 1, 2014)	X

EX1081	Excerpt from Shuji Ogino, Google Scholar, available at https://scholar.google.com/citations?user=87TPyfoAAAAJ&hl=en (accessed 8/25/23)	X
EX1082	Charles Fuchs, Research.com, available at https://research.com/u/charles-s-fuchs (accessed 8/25/23)	X
EX1083	Excerpt from Jerome Galon Citations, Google Scholar, available at https://scholar.google.com/citations?user=coRgZqUAAAAJ&hl=fr (accessed 8/25/23)	X
EX1084	Press Release, *Caris Life Sciences Research Provides Key Clinical Insights on Immunotherapeutic Targets in a Broad Range of Cancers* (June 10, 2014), available at https://www.carislifesciences.com/about/news-and-media/caris-life-sciences-research-provides-key-clinical-insights-on-immunotherapeutic-targets-in-a-broad-range-of-cancers/?gad_source=1&gclid=EAIaIQobChMIzba8u6LlggMVGlBHAR1ZPAHNEAAYASAAEgIaFvD_BwE	X
EX1085	Imai et al, *Carcinogenesis and Microsatellite Instability: the Interrelationship Between Genetics and Epigenetics*, 29(4) Carcinogenesis 673 (2008)	X
EX1086	Cheung et al, *Current Advance in Small Bowel Tumors*, 44(1) Clinical Endoscopy 13 (2011)	X
EX1087	Duval et al, *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas*, 101(14) Proceedings of the National Academy of Sciences 5002 (2004)	X
EX1088	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers Version 1.2014 (May 30, 2014)	X

EX1089	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2014 (November 27, 2013)	X
EX1090	Garg et al, *Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer) and Endometrial* Carcinoma, 16(1) Cancer Control 679 (2009)	X
EX1091	Kim et al, *Microsatellite Instability Status in Gastric Cancer: A Reappraisal of Its Clinical Significance and Relationship with Mucin Phenotypes*, 47(1) Korean J. Pathology 28 (February 2013)	X
EX1092	ASCO, *Developmental Therapuetics – Immunotherapy,* https://meetings.asco.org/2014-asco-annual-meeting/6670?presentation=98450#98450	X
EX1093	Abdul-Rahman Jazieh, 2015 Annual Meeting Tips, ASCO Connection, https://connection.asco.org/blogs/2015-annual-meeting-tips	X
EX1094	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1.2014 (May 30, 2014)	X
EX1095	Koh et al, *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. Nat'l Comprehensive Cancer Network 248 (February 2014)	X
EX1096	Ajani et al, *Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines*, 11(5) J. Nat'l Comprehensive Cancer Network 531 (May 2013)	X
EX1097-1101	Reserved	

EX1102	Benson et al, *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014)	Not Filed
EX1103	Brown et al, *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) Genome Research 743 (May 2014)	Not Filed
EX1104	Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)	Not Filed
EX1105	Duval et al, *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas*, 101(14) Proceedings of the National Academy of Sciences 5002 (2004)	Not Filed
EX1106	Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New Eng. J. Medicine 134 (July 2013)	Not Filed
EX1107	Reserved	
EX1108	Steinert et al, *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014)	Not Filed
EX1109	Reserved	
EX1110	Koh et al, *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. Natl Comprehensive Cancer Network 248 (February 2014)	Not Filed
EX1111	Reserved	
EX1112	Declaration of Jessica Stauring in Support of Motion for Pro Hac Vice	X

EX1113	Biography Page of Jennifer D. Newberger, Hyman, Phels & MacNamara , P.C. https://hpm.com/professionals/newberger-jennifer/ (last accessed December 10, 2024)	
EX1114	Hyman Phelps, FDA Law Blog, FDA Crack Down on ClinicalTrials.gov Reporting Failures https://www.thefdalawblog.com/2021/05/fda-cracks-down-on-clinicaltrials-gov-reporting-failures/ (last accessed December 10, 2024)	
EX1115	Ciombor, Wu, Goldberg, Recent Therapeutic Advances in the Treatment of Colorectal Cancer (Annu. Rev. Med. 2015)	
EX1116	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] May 9, 2013 IND Submission to the FDA, SN00	
EX1117	Public Version of MSI-H Study Protocol in NEJM Article Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20. DOI: 10.1056/NEJMoa1500596	
EX1118	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] June 11, 2013 IND Submission to the FDA, SN01	
EX1119	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] July 15, 2013 IND Submission to the FDA, SN03	
EX1120	FDA grants nivolumab accelerated approval for MSI-H or dMMR colorectal cancer (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-nivolumab-accelerated-approval-msi-h-or-dmmr-colorectal-cancer)	

EX1121	RESERVED	
EX1122	Overman, M, Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study, Lancet Oncol. 2017 September; 18(9): 1182–1191	
EX1123-1127	RESERVED	
EX1128	CDER 2012-2023 https://www.fda.gov/drugs/ind-activity/breakthrough-therapy-designation-requests (last accessed January 8, 2025)	
EX1129	CDER 2023-2024 https://www.fda.gov/drugs/ind-activity/breakthrough-therapy-designation-requests (last accessed January 8, 2025)	
EX1130	CDER Breakthrough Therapy Designation Approvals, https://www.fda.gov/media/95302/download (last accessed January 8, 2025)	
EX1131-1133	RESERVED	
EX1134	Keytruda Labeling (12.11.2024)	
EX1135	Deposition Transcript of Jennifer Newberger, taken on December 11, 2024	
EX1136	Deposition Transcript of Richard Goldberg, taken on December 13, 2024	
EX1137	RESERVED	
EX1138	Deposition Transcript of Nils Lonberg, taken on December 20, 2024	

EX1139	Deposition Transcript of Dung Thi Le, M.D., taken on January 9, 2025	
EX1140	Deposition Transcript of Andrew Pardoll, M.D., taken on January 24, 2025	
EX1141	Paul E. Oberstein, M.D., CV	
EX1142-1144	Reserved	
EX1145	Declaration of Dr. Dung Le, marked up during January 9, 2025 deposition	
EX1146	Dr. Dung Le's notes regarding Keytruda's approvals relating to the PD-L1 biomarker made during January 9, 2025 deposition	
EX1147	Excerpt of 16/144549 - Application	
EX1148	ClinicalTrials.gov, NCT02460198, "Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Previously-Treated Locally Advanced Unresectable or Metastatic Colorectal Cancer (MK-3475-164/KEYNOTE-164)," (May 29, 2015)	
EX1149	Excerpt '356 FH (Feb. 4, 2020 Reply to Office Action)	
EX1150	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] Declaration of Paul E. Oberstein, M.D., dated May 6, 2025	
EX1151-1241	Reserved	
EX1242	Deposition Transcript of Jennifer Newberger, taken on April 10, 2025	

EX1243	Deposition Transcript of Richard M. Goldberg, taken on April 15, 2025	
EX1244	Reserved	
EX1245	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] Deposition Transcript of Nils Lonberg, taken on April 17, 2025	
EX1246	Deposition Transcript of Dung Thi Le, M.D., taken on April 18, 2025	
EX1247-1278	Reserved	
EX1278	NCCN Clinical Practice Guidelines in Oncology - Rectal Cancer (Version 2.2025-March 31, 2025), available at www.nccn.org/patients	
EX1279	June 29, 2020 first-line CRC approval (FDA approves pembrolizumab for first-line treatment of MSI-H/dMMR colorectal cancer | FDA) https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer	
EX1280	Declaration of Ms. Jennifer Newberger, in IPR2024-00240, Ex. 2137 (11,591,393)	
EX1281	Declaration of Ms. Jennifer Newberger, in IPR2024-00622, Ex. 2137 (10,934,356)	
EX1282	Declaration of Ms. Jennifer Newberger, in IPR2024-00623, Ex. 2137 (11,325,974)	
EX1283	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] Deposition Transcript of Paul E. Oberstein, M.D., taken on February 19, 2025	

I. INTRODUCTION

JHU's POR repeats the same irrelevant and misleading arguments it made in IPR2024-00240. This is not a case that turns on how well the claimed cancer treatment method works or whether the Parties were excited by the results of the clinical trial on which they collaborated. Instead, this case centers on the MSR's prior disclosure of JHU's claimed treatment method using the following two steps: (1) determining a patient has a solid tumor that is MSI-H and (2) in response to that determination, treating the patient with an effective amount of pembrolizumab.[1]

It is irrefutable that the treatment method disclosed in the MSR is the only written description support for JHU's claims and that the claimed method was disclosed ***more than two years before*** JHU's alleged July 2015 invention date.[2] JHU apparently recognizes the insurmountable hurdle the MSR poses because, just as it argued in IPR2024-00240, JHU argues here for an unprecedented change in the law in hopes of disqualifying the MSR as prior art. As explained below, no change in law is warranted.

[1] Pet., 1-9; EX1003 ¶¶34-41.

[2] Pet., 16-17; EX1003 ¶¶36, 38-41.

JHU also disingenuously belittles the MSR calling it a "bare-bones clinical trial announcement posting."[3] But nothing about the MSR is bare bones. Even according to JHU's declarant Ms. Jennifer Newberger, the MSR is full of detail and fulfilled its intended purpose of informing the public about an available treatment method for critically-ill cancer patients.[4]

And as it incorrectly argued in IPR2024-00240, JHU argues again that the Board "disregard[ed]" the causal relationship between the "determining" and "treating" steps.[5] The Board's construction at institution in IPR2024-00240, however, was correct. Specifically, the Board recognized a causal relationship between the two steps (treatment would be performed only after MSI-H status was determined) and noted Merck's showing of that "causal relationship" in the MSR.[6]

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[3] POR, 2.

[4] EX1135, 118:18-121:16, 124:4-18, 134:19-136:11, 148:13-20, 153:19-156:12, 200:14-201:1; *id.* 124:19-125:12.

[5] POR, 6.

[6] *Merck Sharp & Dohme LLC v. Johns Hopkins University*, IPR2024-00240, Paper 10, at 16, 18-19 (P.T.A.B. June 13, 2024); *see also* EX1138, 125:5-14 (Dr. Lonberg, confirming the Board did not ignore the causal relationship).

Contrary to JHU's arguments, the MSR discloses all claim limitations of the '187 patent that JHU argues are missing. In particular, the MSR teaches treating a MSI-H non-colorectal cancer patient. And as Merck declarant Dr. Alfred Neugut and JHU declarant Dr. Richard Goldberg agree, a POSA would immediately envisage a MSI-H endometrial, small bowel, or gastric cancer patient.[7] Further, JHU declarant Dr. Nils Lonberg agreed that according to the MSR, a non-colorectal MSI-H cancer patient would be tested before receiving pembrolizumab, which matches the requirements of the "in response to" limitation.[8] The MSR likewise discloses the other limitations that JHU continues to assert are not met as it did in IPR2024-00240.

As to obviousness, JHU offers more of the same: it focuses on how well the claimed two-step treatment method works and alleged missing limitations in the MSR.[9] Dr. Lonberg persists with his incorrect view that a POSA is a skeptic

[7] EX1003, ¶¶25-26, 50-52, 63-64, 93-96, 101-102, 114-121, 124-126; EX1136, 115:5-116:22.

[8] EX1138, 101:8-102:5, 114:15-115:21. Dr. Le confirmed that all patients treated in the MSI-H Study were tested prior to treatment. EX1246, 34:4-9, 36:7-11; *id.*, 32:10-34:3.

[9] POR, 32-55.

refusing to accept the prior art for what it teaches. Yet, Dr. Lonberg readily agreed the same prior art Merck identified in its Petition would serve as part of the rationale for conducting the trial described in the MSR.[10] And he could not identify any evidence that questioned whether the trial described in the MSR would work.[11]

Finally, as in IPR2024-00240, JHU devotes an unwarranted amount of space, given the weakness of JHU's purported evidence, and multiple declarations to secondary considerations. As Dr. Paul Oberstein explains, JHU fails to meet its burden to show actual nexus between any alleged secondary considerations evidence and any novel features of the '187 patent claims.[12] And even if JHU were credited with a presumption of nexus, the substantial weight of the evidence presented by Merck and its declarants compels a finding that, to the extent they are not anticipated, all challenged claims are obvious.

[10] EX1245, 79:5-80:16; EX1138, 141:13-19, 142:12-143:17.

[11] EX1245, 36:5-9, 38:10-19.

[12] EX1150, ¶¶114-116, 119-122.

II. TESTIMONY ELICITED FROM JHU'S POR DECLARANTS SUPPORTS THAT ALL JHU CLAIMS ARE UNPATENTABLE

The deposition testimony of JHU's POR declarants undermines and conflicts with their declarations. For example, Dr. Lonberg, friend of two named inventors (EX1138, 165:10-11), revealed his conclusions were grounded in his belief that a POSA "reads the literature skeptically, always." (EX1138, 84:14-16.) But that is contrary to the perspective that the Federal Circuit instructs. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 928 (Fed. Cir. 2024) (finding analysis of prior art must utilize the perspective of a POSA "capable of deducing what references ***fairly suggest or employing ordinary creativity***") (emphasis added).

Despite that lens, Dr. Lonberg agrees with Dr. Neugut on many key facts, including that as of July 10, 2015 (the "Alleged Invention Date") the literature was replete with information about (1) MSI testing, (2) the clinical relevance of MSI-H in cancers, (3) the correlation between mutational load and susceptibility to treatment with PD-1 inhibitors, and (4) the prior successful treatment of cancer patients with PD-1 inhibitors. (*See, e.g.*, EX1138, 48:16-52:3, 93:15-19, 95:8-13, 153:4-155:10, 162:16-163:18, 165:16-166:12, 171:13-172:19, 175:12-176:1, 180:2-183:16, 190:10-191:9, 195:21-200:4, 203:13-211:10; *see also* EX1150, ¶¶25-26; EX1243, 48:11-12, 48:22-49:1.) Dr. Lonberg also agrees that specialized experience researching or developing new treatments for cancer is not needed to

practice the '187 patent claims, as those claims are not directed to methods for conducting immunology or genetics research. (EX1245, 13:20-14:1, 14:8-10, 19:18-20:13.) Accordingly, his view that a POSA must have specialized experience in these areas is unsupported. (EX2072, ¶¶90-97.)

JHU declarant Dr. Goldberg, another friend of a named inventor (EX1136, 24:20-21), admitted that, before JHU's Alleged Invention Date, PD-1 inhibitors showed promise and "companies all over the world began more aggressively researching immune-oncology opportunities once the first break-through [with nivolumab] had occurred." (EX1136, 80:13-82:13, 188:15-190:13; *see also* EX1150, ¶¶29-33) That this admission conflicts with Dr. Goldberg's declaration regarding an alleged long-felt unmet need is not surprising as he had not actually reviewed highly relevant pieces of prior art (*e.g.*, Pernot (EX1006), Champiat (EX1032)) before rendering his opinions, and was, therefore, unaware of critical information known by a POSA as of the Alleged Invention Date. (*See, e.g.*, EX1136, 85:20-87:22, 89:13-91:17; EX1243, 51:15-52:16, 54:17-55:1, 56:7.)

Named inventor Dr. Dung Le's deposition revealed a lack of familiarity with the content of her declaration, undermining the credibility of her allegations regarding Merck, as well as JHU's purported invention. (EX1139, 11:3-17:10, 105:3-112:10, 114:21-118:18, 234:2-246:3, 290:2-292:16.) Dr. Le could not recall a single Merck individual involved in the trial described in the MSR (the "MSI-H

Study"), despite earlier statements about her alleged "observations" of "Merck personnel involved with [the] study." (EX1139, 66:2-5, 264:3-274:21; *see also* EX2130, ¶35; EX1150, ¶¶51-52.) Additionally, Dr. Le admitted Merck provided funding for the study—contrary to several JHU declarants' assertions.[13] (EX1139, 278:17-286:14; *see also* EX2072 ¶125; EX2090 ¶14.) Likewise, named inventor Dr. Drew Pardoll revealed he was neither involved with nor knowledgeable about the MSI-H Study despite JHU's attempt to rely on his declaration to support alleged skepticism for the MSI-H Study. (POR, 70; EX1140, 25:16-17, 29:3-4, 48:3-16, 71:3-5, 102:19-103:5, 119:3-121:12, 122:7-125:3; *see also* EX1150, ¶¶53-54.)

Another JHU declarant, Ms. Newberger, an attorney at a private law firm, testified that, despite submitting a declaration in this proceeding regarding publication of the MSR on ClinicalTrials.gov, she had "not seen the patent," "did not ask about the patent," and "did not see" what was actually submitted to ClinicalTrials.gov on June 10, 2013. (EX1135, 11:18-19; 36:4-7, 62:16-17;

[13] Dr. Lonberg also has no bases for his allegation that Merck did not provide any MSI-H Study funding as he revealed his understanding came from Dr. Pardoll who testified he "[did not] recall saying that" to Dr. Lonberg. (EX1140, 82:11-13; EX1138, 228:19-22; *see also* EX1138, 229:7-9.)

EX1242, 12:16-22, 13:12-14:11, 24:14-22.) Her testimony purportedly in support of JHU's experimental use argument is therefore irrelevant and not reliable.

III. GROUND 1: CLAIMS 1-2, 4-7, 9-12, 14-17, AND 19-28 OF THE '187 PATENT ARE ANTICIPATED BY THE MSR

A. ClinicalTrials.gov Study Records Are Prior Art Printed Publications and Therefore Not Subject to Experimental Use

Telling of the anticipating disclosures of the MSR, JHU argues the MSR should not qualify as prior art. (POR, 26-32.) But the Federal Circuit has found that ClinicalTrials.gov study records, like the MSR, are Section 102 prior art. *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024); *see also Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, No. IPR2022-00578, Paper 78 (P.T.A.B. Aug. 29, 2023) (relying on ClinicalTrials.gov study record for purposes of anticipation and obviousness). JHU does not cite any case law to support its request that the Board exclude the MSR as an experimental "use." (POR, 26-27.) That is because there is no such case law.

Instead, JHU relies on Ms. Newberger to argue JHU submitted only required information to ClinicalTrials.gov (POR, 26-32; EX2137, ¶¶10-52), which is irrelevant and provides no justification for disqualifying a printed publication as prior art. Moreover, her assertions are unreliable. In addition to not knowing what ClinicalTrials.gov stated or required in 2013 (EX1135, 240:9-242:15), the authority she cites also makes plain that certain information in the MSR was not

required in 2013.[14] (EX2137, ¶33 (citing EX2149); EX1242, 35:6-14, 37:21-38:7; EX1135, 127:19-128:11, 250:18-253:20.)

Separately, JHU argues that had JHU patented the claimed methods of treatment any earlier, it would not have met the requirements of §101 or §112. (POR, 24-26.) It is well established, however, that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112. *In re '318 Patent Infringement Litig*., 583 F.3d 1317, 1324 (Fed. Cir. 2009); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (cited by MPEP 2107.03).

B. The MSR Discloses Treating a Patient with a Non-CRC MSI-H Cancer

JHU argues the MSR does not anticipate the "sixteen individual species that make up" the listed cancers in the claims because the MSR "lists no particular cancer types" for the MSI-H non-colorectal cancer ("non-CRC") cohort. (POR, 10-11.) JHU's argument ignores the plain language of the claims and the knowledge of a POSA.

[14] Ms. Newberger's declarations in related proceedings provide inconsistent testimony as to allegedly required information. (*Compare* EX1281, Table 1 *with* EX1282, Table 1 *with* EX1280, Table 1; *see also* EX1242, 46:8-49:1, 50:5-54:18.)

The claims require "***a*** patient…***selected from the group consisting of*** [the listed cancers]." (EX1001, Claim 1.) The claims do not require a patient to have ***each and every*** one of the sixteen listed cancers. Therefore, JHU's genus versus species argument and cited cases miss the mark. (POR, 11-14.)

A disclosure of a genus ***can*** anticipate a species in some circumstances. In particular, in *Sanofi*, the Federal Circuit held the prior art did not anticipate the claimed invention because the description of the genus would not lead a POSA to a small ***recognizable*** class of species. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008). Here, however, the MSR's disclosure of a treatment method for a non-CRC MSI-H patient would have led a POSA to a small recognizable class of non-CRC MSI-H cancers, including at least one of three claimed cancer types (endometrial, gastric, and small bowel cancer).[15] (EX1003, ¶¶25-26, 63; EX1150, ¶¶58-62). JHU's own clinician agreed. (EX1243, 115:5-116:22.) Such patients, including patients with Lynch syndrome, would have been routinely tested for MSI-H pursuant to standard practice at the time. (EX1003, ¶¶25-26, 63; EX1150, ¶¶58-62.) Even the patent specification identifies the list of

[15] Tellingly, JHU does not dispute in its POR that a POSA would have envisaged at least treatment of a MSI-H endometrial, gastric, or small bowel patient. (POR, 10-14.)

cancers in the claims as ones generally known to display the MSI phenotype, or a high mutational burden, which could be tested and treated. (EX1001, 1:34-41, 6:16-24.)

Neither the patent nor JHU's declarants suggest anything special about any particular non-CRC MSI-H cancer in this list.[16] Indeed, Dr. Goldberg expressly agreed during deposition that when a POSA sees a reference to MSI-H non-CRC, a number of cancers readily come to mind, including endometrial, gastric, and small bowel cancer, as well as other well-known solid tumors. (EX1243, 115:5-116:22.) As such, the treatment limitations in the claims directly match a POSA's understanding of the disclosures of the MSR in view of the state of the art.

Importantly, JHU's arguments are contradicted by what was actually done in the MSI-H Study, where non-CRC MSI-H patients treated in Arm 3 were reported as having cancer of the following type: gastric, small bowel, endometrial, ampullary, or cholangiocarcinoma. (EX1031, 3.)

[16] To the contrary, JHU elsewhere asserts that its purported inventions are about "identification of MSI-H as a predictive biomarker", and the basis for a "tumor-agnostic" indication. (POR, 1, 68.)

C. The MSR Explicitly Discloses Treating a Non-CRC Patient "In Response To" Determining the Non-CRC is MSI-H and "Based on Previous Testing"

JHU mischaracterizes the Board's analysis of the "in response to" limitation in IPR2024-00240. (POR, 6-10.) Dr. Lonberg, candidly admitted in deposition that the Board did not ignore a causal relationship for the "in response to" limitation as JHU originally contended. (EX1138, 125:5-14.) In response, JHU mischaracterizes what is required by the claims and focuses its "in response to" argument on the MSR's alleged failure to disclose all 16 cancers specifically listed in the claims. (POR, 15.)

But for the reasons discussed in Section III.B., a POSA would immediately envisage treating a patient having one of the claimed cancer types based on the MSR's treatment of MSI-H non-CRC patients. The MSR's Eligibility Criteria makes plain that ***only*** patients with MSI-H non-CRC are placed in Arm 3, and a patient in that arm is then treated with 10 mg/kg pembrolizumab every 14 days—a therapeutically effective amount. (*See* EX1150, ¶¶57-73, 79-82; *see also* Pet., 18-23, 27-29; EX1003, ¶¶63-73, 80-82.) There can be no credible dispute that a MSI-H non-CRC patient enrolled and treated in the study was treated "in response to" determining the patient was MSI-H and "based on previous testing." Indeed, Dr. Lonberg readily admitted that a POSA would understand that non-CRC patients

would have their MSI status tested ***prior*** to enrollment and treatment with pembrolizumab. (EX1138, 101:8-102:5, 114:15-115:21.)

D. Any Clinical Results Inherently Flow from the Treatment Method Taught to a POSA by the MSR

JHU argues the MSR "fails to inherently disclose the clinical results of JHU's study." (POR, 20-24.) This argument is legally incorrect and also ignores that none of the claims of the '187 patent require any specific clinical outcome other than treating a patient with a therapeutically effective amount of pembrolizumab.[17] (EX1001, 25:5-26:51.)

Even if clinical results were recited in the claims, the Federal Circuit has explained that results that ***inevitably flow*** from the prior art, here the MSR, constitute an inherent disclosure. (*See, e.g.*, EX1150 ¶63); *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373, 1378, 1380 (Fed. Cir. 2003); *In re Montgomery*, 677 F.3d 1375, 1381-82, 1385 (Fed. Cir. 2012).

While JHU apparently recognizes the law as to inherency, it argues the study described in the MSR is an "abstract theory" and "invitation to investigate" in hopes of aligning itself with the dissenting opinion in *Montgomery*. (POR, 20-24.)

[17] Dr. Lonberg does not dispute the disclosure of a therapeutically effective amount by the MSR. (*See* EX2072, §IX.)

JHU's argument is both not based on the law and incorrect. The trial described in the MSR is a Phase 2 clinical study to treat critically ill cancer patients with a drug, which a POSA would have understood had been allowed to move forward by the FDA based on scientific rationales.[18] (EX1150, ¶¶37-50.) [redacted].[19] (EX1150, ¶¶37-44.) Moreover, in contrast to its current arguments regarding the "unexpected[ness]" of the results (POR, 48), JHU previously told the FDA [redacted] (EX1150, ¶38; EX1116, 24.)

[18] The MSR also contains extensive detail about the trial and its methods. (EX1150, ¶¶55-84; EX1135, 118:18-121:16, 124:4-18, 134:19-136:11, 148:13-20, 153:19-156:12, 200:14-201:1; *id.* 124:19-125:12.)

[19] This success was known prior to the publication of the MSR as reported in Lipson (Jan. 2013), and later in Kim (Nov. 2014). (EX1150, ¶¶85, 92-93; EX1057, 463-64; EX1038, 7.)

[redacted] (EX1246, 43:15-45:6; EX1245, 94:8-12.) [redacted] (EX1150, ¶¶45-47, EX1118, 4.)

E. The MSR Teaches Treating a MSI-H Cancer Patient with a Tumor that Would Have "Progressed Following at Least One Prior [Cancer] Treatment"

JHU argues the MSR is "silent" on whether eligible patients have had a prior treatment and had that treatment fail. (POR, 16.) As Dr. Neugut explains in his declaration, however, a POSA reading the MSR would understand a patient to be treated in the study would have had a tumor that had progressed following a prior cancer therapy.[20] (Pet., §§VI.B.2.h, VI.B.10.d; EX1003, ¶¶74-79, 103-104; *see*

[20] The cases JHU cites for the proposition that "missing" disclosures cannot be replaced by "attorney argument or expert testimony" fall flat (POR, 16-17)—JHU ignores that this limitation is not "missing" from the MSR and Drs. Neugut and Oberstein provide testimony regarding a POSA's understanding of the context provided by the MSR and relevant prior art.

also EX1150, ¶¶67-73.)[21] This is further confirmed by the fact that all patients treated in the MSI-H Study did have at least one prior treatment. (EX1031, 4; EX1001, 15:67-16:8; EX1245, 53:9-17, 55:22-56:7.)

JHU declarant Dr. Lonberg agrees. He candidly admitted in deposition the treatment method in the MSR applies to a patient who has received a prior cancer therapy and where the cancer progressed following a prior cancer therapy. (EX1245, 57:5-58:2; *id.*, 40:5-14, 48:1-11, 49:2-12.) He explained his opinion regarding the treatment method in the MSR is that it "does not require treatment of ***only*** patients who have received at least one prior cancer therapy." (EX1245, 57:10-14.)

Dr. Oberstein likewise agrees this type of patient is eligible and included in the treatment method in the MSR. (EX1150, ¶¶69-70; EX1283, 266:4-268:9, 275:7-279:4.) The MSR explains that patients with "measurable disease" will receive an experimental treatment in a clinical study. (EX1003 ¶¶51, 74-79;

[21] JHU misleadingly asserts Dr. Neugut conceded the MSR is silent on this point. (POR, 16.) In context, however, Dr. Neugut's response can only be understood as agreeing the specific wording in counsel's question was not present. (EX2163, 96:1-99:21.) Dr. Neugut's testimony in his declaration stands. (*E.g.*, EX1003, ¶¶74-79.)

EX1005, 2 (Study Identification), 5-6 (Eligibility); *see also id.*, 4-5 (Outcome Measures).) A physician following the standard of care would generally include a patient[22] in such a clinical study if that patient had their cancer progress following a prior cancer therapy. (Pet., 23-26; EX1003 ¶¶76-77; EX1020, PDF p.25; EX1009, 1034.)

JHU mischaracterizes Benson, Koh, and the NCCN guidelines (POR, 18, 35-36) because, while those references encourage clinicians to include patients in clinical trials, where appropriate, clinical trials are specified as the ***standard of care*** after at least one prior cancer therapy.[23] (EX1009, 1034; EX1095, 256.) Had the study described by the MSR been limited to only patients who did ***not*** receive

[22] In particular, all claims are directed to "a patient" and a POSA would understand there to be at least "a patient" whose treatment follows the standard of care. (EX1150, ¶67.)

[23] That Ajani (which Merck does not rely on in this proceeding) recommends clinical trials for patients who are diagnosed late stage does not undermine that, generally, a POSA following the standard of care would treat a patient in a clinical trial after the patient received standard first line therapy and had their cancer progress. (POR, 18, 36.)

prior treatment, *i.e.*, "first line" patients, prior treatment would have been expressly excluded in the MSR's exclusion criteria. (EX1150, ¶69.) It was not.

Indeed, the MSR's Exclusion Criteria expressly specify individuals who received certain prior treatments. (EX1005, 5-6 (Eligibility); EX1003, ¶77.) Contrary to JHU's argument, a POSA would understand the MSR is directed at a minimum to a patient who had at least one ***different*** prior cancer therapy than those specifically excluded. (EX1150, ¶70.)

JHU also argues inclusion criteria added in January 2016 evidence this claim limitation is allegedly not "'necessarily present' to a POSA reading the original MSR." (POR, 18.). The fact that after January 2016 ***only*** CRC patients who received two or more prior therapies and non-CRC patients who received one or more prior therapies could be treated in the study does nothing to undermine that, before July 10, 2015, a POSA would understand the MSR discloses—consistent with the standard of care—treating at least a patient who had their cancer progress following treatment with a prior cancer therapy. (EX1150, ¶¶71-73.) Notably, all patients treated prior to January 2016 did, in fact, meet those requirements. (*Id.*; *see also* EX1001, 15:67-16:8; EX1031, 4-5; EX1245, 62:8-14, 64:1-14, 65:18-21, 66:16-68:16.)

Likewise, JHU's argument that a POSA would interpret the ***inclusion*** of certain criteria listed in the 2014 ASCO poster as necessarily implying ***exclusion***

from the MSR is incorrect and illogical. (POR, 19.) The poster,[24] which came later, in no way relates to the sufficiency of the earlier MSR disclosures. (EX1150, ¶72n.4.) Indeed, the poster confirms these inclusion criteria regarding prior cancer therapy were not missing from the MSR and were followed. (Pet., 26-27; EX1003, ¶79; EX1080 (Eligibility Criteria).)

F. The MSR Teaches Treating a Patient with "Metastatic" Cancer

JHU argues Dependent Claims 6, 16, 24, and 28 limited more specifically to a patient with "metastatic" cancer are not met because allegedly "the MSR does not disclose treatment of metastatic cancer." (POR, 19.) As Dr. Neugut explains, however, a POSA would have understood a patient having "measurable" disease in the context of the MSR refers to a patient having metastatic or advanced cancer.[25]

[24] JHU does not dispute the poster is prior art that a POSA would have knowledge of before the Alleged Invention Date. (Pet., 27n.6.)

[25] JHU alleges Dr. Neugut "conced[es]" that "metastatic" and "measurable" are "total different terms," and metastatic tumors "would not necessarily be measurable." (POR, 20.) Dr. Neugut's declaration, however, is entirely consistent with the MSR's context of a phase 2 clinical study of a not yet FDA-approved

(EX1003, ¶¶75, 89-90, 112, 122-123, 127; EX1089, PDF p.17; EX1020, PDF p.25.)

Dr. Lonberg admitted at deposition that metastatic patients are included, clarifying that the "MSR is not limited or does not require treatment of only patients who have metastatic disease." (EX1245, 58:3-10; *see also id.* 50:7-10, 51:4-7.) Dr. Oberstein likewise agrees these types of patients are eligible and included in the treatment method of the MSR. (EX1150, ¶¶67-78 EX1283, 112:12-115:14, 266:4-268:9.) Further, if a patient having metastatic cancer was not included, a POSA would have understood that to be highly unusual, especially because the treatment in the MSR was not directed to a local treatment, such as radiation or surgery, but rather to an immunotherapy drug. (EX1003, ¶75.)

Moreover, according to the standard of care at the time, a MSI-H cancer patient enrolled in a study of this type would be understood to be critically ill, with either metastatic or locally advanced cancer. (*See, e.g.*, EX1150, ¶¶67-78, 83-84; EX1003, ¶¶75-76; EX1009, 1034; EX1095, 256.) Consistent with the disclosures of the MSR and the standard of care, all 41 patients treated in the study described

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cancer therapy drug known to elicit a strong immune response in patients. (*See* EX1003, ¶¶30-33; EX1150, ¶74-78; EX1005, 3; *see also* EX1011.).

by the MSR did have metastatic cancer.[26] (EX1001, 8:31-33; EX1031, 1; EX1245, 68:18-70:16.)

IV. GROUNDS 2-6: ALL CLAIMS OF THE '187 PATENT ARE OBVIOUS OVER THE MSR IN VIEW OF THE PRIOR ART

A. The Prior Art Renders Obvious Treating a Non-CRC Patient with Pembrolizumab "In Response To" Determining the Patient is MSI-H and "Based on Previous Testing"

To the extent the Board needs to reach Merck's obviousness challenges, the MSR (alone or in view of the references discussed in Grounds 2-6) would have rendered obvious treating a non-CRC patient with pembrolizumab "in response to" determining the patient is MSI-H and "based on previous testing." Rather than address Merck's arguments head-on, JHU and its declarants mischaracterize the Petition as containing a "two-stage argument" and continue to disregard the disclosures of the MSR and other prior art references. (POR, 32-35.)

As explained in the Petition, the MSR discloses treating a patient having non-CRC MSI-H cancer. (*E.g.*, Pet., 17-23; EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria).) Further, at the time of the MSR's posting,

[26] JHU fails to address this reality, reflected in the NEJM article authored by Dr. Le. (EX1031, 1.)

MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel, and gastric cancer. (EX1003, ¶25; EX1085, 673, 675; EX1086, 14; *see also* EX1243, 115:5-116:22.) Those tumor types, as well as colorectal, are also common in Lynch syndrome, which was known at the time to be closely associated with MSI-H. (EX1003, ¶26; EX1085, 673-74.) Thus, a POSA would have been motivated to and expect success in carrying out the MSR's methods to treat a non-CRC MSI-H patient, such as an endometrial, small bowel, and gastric cancer patient. JHU fails to rebut these arguments on the merits.

Quite simply, JHU's flawed arguments are based on an erroneous interpretation of the claims—JHU argues "a POSA would not have reasonably expected the claimed methods to work in ***all*** MSI-H cancers" (POR, 32-33), while the patent claims are directed to "a patient" having ***one*** of the claimed MSI-H cancers. (*See supra*, §III.B.) Given this incorrect framing, JHU's argument that the MSR and prior art references do not disclose the "in response to" and "based on previous testing" limitations (POR, 32-35) necessarily fails.[27]

[27] JHU's contention that inherency in the obviousness context is not met fails for the same reason. As explained, the MSR alone (or in combination with the prior art references of Grounds 2-6) disclose all elements of the asserted claims.

JHU also devotes two paragraphs in Section VI.D. of its POR to its incorrect argument that "[b]eyond failing to establish any reasonable expectation of success, the Petition does not establish any motivation to pursue the claimed treatment for the Claimed MSI-H Cancers, as opposed to other MSI-H Cancers." (POR, 52-54.) But JHU provides no basis for its contention that a POSA would have been required to have motivation to treat certain MSI-H cancers ***to the exclusion of others***. Again, JHU tries to require Merck to prove more than the case law requires.[28]

A POSA would have been motivated by the prior art to treat a patient having common types of MSI-H cancer, including endometrial, small bowel, and gastric cancer using the method of treatment disclosed in the MSR, and further would have been motivated to obtain the results of the MSR. (EX1150, ¶¶85-98.)

B. The Prior Art Combinations in Grounds 2 and 3 Teach Treating a Cancer Patient Whose Tumor Progressed Following Prior Treatment or That Has Metastatic Cancer

The combinations of prior art described in Ground 2 (MSR, Brown, Duval, and Benson) and Ground 3 (MSR, Brown, Duval, Benson, and Koh) disclose the

[28] The only case JHU cites is *Xerox*, in which the Board gave little weight to an expert declaration that offered nothing more than mere, conclusory assertions. (POR, 54.) That does not apply here.

prior cancer treatment limitation of Independent Claims 1 and 11 and the metastatic cancer limitation of Dependent Claims 6, 16, 24, and 28 to a POSA, highlighting the knowledge of a POSA and the context in which a POSA would read the MSR. (Pet., 41-54.)

JHU's claim that Benson and Koh "allow for clinical trials as a first-line therapy" misses the mark.[29] (POR, 35.) That these references may ***permit*** clinical trials for all cancer patients does not undermine their teaching that clinical trials are generally specified as the ***standard of care*** after a prior cancer treatment. (EX1009, 1034; EX1095, 256.) As such, a POSA would be motivated by the disclosures of Benson and Koh to follow the standard of care for a patient, including in terms of when to place a patient in an ongoing clinical study. (Pet., 441-54; EX1003, ¶¶144-150, 153-156; EX1150, ¶¶85-98.) Indeed, this is how the MSR's underlying clinical study was performed as reflected in the ASCO poster. (EX1080, (Eligibility Criteria.)

[29] It is telling of the weakness of JHU's argument here that JHU did not dispute these limitations were obvious in IPR2024-00240.

C. A POSA Would Have Had a Reasonable Expectation of Success in Carrying Out the Claimed Two-Step Treatment Method

As it did in IPR2024-00240, JHU misleadingly argues that Merck applies the "wrong standard" for reasonable expectation of success. (POR, 36-38.) Merck applied the correct standard in its analysis, *i.e.*, that in view of the MSR and prior art teachings as of the Alleged Invention Date, a POSA had a reasonable expectation of success in carrying out the claimed two-step treatment method of (1) determining a patient has a tumor that is MSI-H and (2) administering an effective amount of pembrolizumab to the patient. The *Eli Lilly* case JHU cites does not apply a different standard. (POR, 37-38.)

JHU and its declarants present generalized obviousness arguments for all claims based on the unsupported assertion that there was no reasonable expectation of success for the claimed methods of treatment. (POR, 38-52; EX2072 ¶¶122-180.) But JHU misrepresents what a POSA would have known and understood based on the prior art. (EX1150, ¶¶85-113.)

Contrary to JHU's current assertions, the scientific rationales provided by JHU to the FDA to conduct the MSI-H Study are consistent with the prior art cited

by Merck and what was known by a POSA at the time.[30] (*Supra*, 14-15; EX1150, ¶¶34-44, 92-93, 118 *see also* EX1138, 141:13-19, 142:12-143:17; EX1243, 56:13-57:3, 57:14-58:20, 59:17-60:7, 61:5-13, 62:4-9, 62:16-63:8.) [redacted][31] (EX1150, ¶¶37-44; *see also id.* ¶¶45-50.) [redacted] (*Id.*)

Dr. Lonberg also admitted that even prior to the publication of the MSR, he had "expressed enthusiasm" about doing such a study, and BMS had, in fact, pursued a study of its own PD-1 inhibitor in patients with MSI-H before the

[30] As JHU's own exhibit reflects, Merck "felt that [the MSI-H Study] was something worth supporting" because it "had a compelling scientific rationale" and "was based on really good science." (EX2121, 17.)

[31] Dr. Lonberg agreed this information published in the prior art would have provided rationale for conducting the study described by the MSR prior to the Alleged Invention Date. (EX1245, 79:5-80:16.)

Alleged Invention Date. (EX1138, 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8, 225:15-21.) According to Dr. Lonberg, BMS's study was also a success. (*Id.*, 240:4-15.)

Instead of addressing the understanding of a POSA reading the MSR, when taken in combination with prior art discussed by JHU itself [redacted], JHU improperly focuses on various allegations regarding separate pieces of prior art. (POR, 38-52.) These arguments mischaracterize the disclosures of those references, such as Brown, which JHU alleges "does not suggest that [patients with tumors showing naturally immunogenic mutations and associated tumor infiltrating lymphocytes] are likely to respond to PD-1 inhibitors." (POR, 42.) Brown does, however, discuss "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes]" as "potential candidates for treatment with…[PD-1]-targeted antibodies" and found that the "abundance of predicted immunogenic mutations" may be useful to identify patients "likely to benefit from checkpoint blockade." (EX1150, ¶¶85-87 EX1003, ¶¶44-45; EX1034, 743.)[32] [redacted], and which a POSA would understand to provide

[32] As Dr. Oberstein explains, JHU's approach to other references likewise mischaracterizes the art and lacks context. (EX1150, ¶¶88-95.)

both motivation and expectation for success for conducting the study set forth in the MSR. (EX1150, ¶¶37-41; EX1245, 79:5-80:16.)

V. JHU'S ALLEGED SECONDARY CONSIDERATIONS EVIDENCE SHOULD BE AFFORDED LITTLE TO NO WEIGHT

A. JHU Fails to Meet Its Burden to Establish Nexus

JHU alleges it is "entitled" to a presumption of nexus. (POR, 56-63.) But JHU's cited cases make plain, a presumption of nexus exists where the purported evidence is tied to a specific product and that ***product*** "embodies the claimed features, and is coextensive with them." (POR, 56, 62); *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023) (citation omitted); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). The '187 patent is not a product patent and JHU does not argue for a presumption of nexus to the Keytruda product generally.

Instead, JHU attempts to stretch the cases it cites to apply a presumption based on the Keytruda labeling and Dr. Goldberg's unsupported allegation that the patent claims broadly cover the use of Keytruda according to certain specific indications.[33] (POR, 56-63; EX2090, ¶¶82-93.) That argument—even if supported

[33] Dr. Goldberg testified he never used or followed the Keytruda labeling when he treated MSI-H cancer patients, undermining his declaration testimony. (EX1243,

(it is not)—is insufficient to establish co-extensiveness between the treatment method claims here and the use of Keytruda. *See e.g., Teva Pharma. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360-61 (Fed. Cir. 2021).

JHU also does not tie any of its purported evidence to specific claims or allegedly novel features. (POR, 63-65.) There can be no nexus when a claimed feature was "indisputably known in the prior art." *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017); *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

B. JHU Has Not Shown the Claimed Method of Treatment Was Unexpected as of the Alleged Invention Date

JHU's allegations of unexpectedness fail for the same reasons as in IPR2024-00240. (POR, 78-83.) Notably JHU argues before the Board "no one knew" that pembrolizumab would be effective in MSI-H patients and the outcome was "unpredictable" as of the Alleged Invention Date. (POR, 41, 48.) [redacted]

38:10-39:19, 40:19-41:2, 42:15-21; *see also id.* 30:11-31:7, 33:5-13, 36:22-38:9, 39:6-19, 42:22-43:8.)

[redacted] (EX1116, 24; EX1150, ¶¶38-42; Pet., 10-11.)

JHU's arguments regarding unexpectedness (POR, 78, 81-82) also disregard that by July 10, 2015: (1) the MSR had published (EX1005), (2) other prior art references taught that checkpoint inhibitors would likely be successful in treating MSI-H tumors (EX1003, ¶¶42-49), (3) Merck had initiated another clinical study of pembrolizumab in MSI-H patients (EX1148), and (4) BMS had already begun its own study aimed at treating MSI-H patients using its PD-1 inhibitor (EX1053).[34] (EX1150, ¶¶114-123.) The overwhelming evidence in the record provides that a POSA would have clearly expected positive results from using pembrolizumab to treat MSI-H cancer. (Pet., 6-11; EX1003, ¶¶42-49; EX1150, ¶¶85-113; EX1116, 24.) JHU's focus on the specific MSI-H Study results incorrectly conflates ***degree*** of success with unexpectedness. *Hoffmann–La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1333-34 (Fed. Cir. 2014).

[34] JHU confusingly alleges Merck "***declined*** to do a MSI-H cancer study." (POR, 82.) It is indisputable that Merck collaborated with JHU on the MSI-H study and provided its drug free of charge. (EX1005; EX1139, 73:3-6; EX2131, 10-11; EX1243, 76:6-12.) JHU fails to put forth evidence of Merck "declin[ing]" to provide funding. (POR, 67, 80-81; EX1243, 67:12-19.)

C. JHU Has Not Shown Any Industry Skepticism as of the Alleged Invention Date

JHU's allegations of skepticism fail for the same reasons as in IPR2024-00240 as JHU does not evidence skepticism at or near the Alleged Invention Date. (POR, 70-73.)

More than two years before the Alleged Invention Date, Merck collaborated with JHU and provided support, including its not-yet-approved expensive drug.[35] (EX1005, 3; EX1139, 66:20, 73:3-6; EX2130 ¶¶14, 15, 38.) While JHU alleges "Merck admitted that the prevailing belief had been that pembrolizumab would not work even in CRC patients," the context of the statement JHU cites makes plain that Merck was referring to a time period ***prior*** to the Parties' collaboration and the relevant prior art here. (POR, 70; EX2121, 17.) As discussed, Merck stated it believed the study was "worth supporting" as it was "based on really good science." (*Supra*, 26.) JHU's purported support for its allegation that Merck did

[35] JHU's declarants lack foundation for their allegations regarding Merck's views on the MSI-H Study as of the Alleged Invention Date because, as they testified, they had no knowledge of what Merck knew or thought. (*See* EX1138, 228:10-16; EX1136, 137:5-11; *id.*, 112:1-4; EX1243, 66:14-21; EX1140, 48:3-16; EX1139, 268:8-278:16.)

not "believe[] in the inventors' hypothesis" is Dr. Pardoll. (POR, 70.) But he testified he did not provide any statements or comments regarding Merck's or the industry's beliefs in the portions of his declaration JHU cites. (EX1140, 119:10-124:2.)

More than one year before the Alleged Invention Date, BMS also announced its own study of its PD-1 inhibitor to treat MSI-H cancer. (EX1053; EX1138, 217:19-218:5; EX1245, 33:4-8; EX1243, 61:5-13.) Additionally, JHU's purported industry expert "expressed enthusiasm" about doing a clinical study like that described by the MSR before the MSR even published. (EX1138, 225:15-21.) JHU's purported evidence reflects only that BMS chose not to do the study with JHU in 2012—not skepticism of the claimed treatment method. (POR, 71; EX2072, ¶186; *see also* EX1138, 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8.)

D. JHU Ignores the Rapid Development of Pembrolizumab and PD-1 Inhibitors by the Alleged Invention Date

Any purported evidence of long-felt unmet need here is undermined by Merck's patents (EX1214; EX1215; EX1217; EX1238) covering its drug and its use broadly in the treatment of cancer. *See Acorda Theras., Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1338-42 (Fed. Cir. 2018) (discounting the weight of commercial success, failure of others, and long-felt unmet need in view of

blocking patent); EX1243, 64:1-4 (Dr. Goldberg: "The only way to obtain [pembrolizumab] would have been to have an agreement with Merck to provide a drug that they owned and had sole ability to provide.").)

Moreover, Dr. Goldberg, who JHU relies on for its allegations of long-felt need, revealed his view is that a long-felt need existed for an ***FDA-approved*** method of treating MSI-H cancer patients. (EX1243, 98:8-11, 104:11-16.) The '187 patent claims do not require FDA-approval and Keytruda's 2017 MSI-H approvals were not achieved on the bases of the '187 patent claims. As such, JHU's purported evidence has no nexus to the claims.[36] *See Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 86, at 38 (P.T.A.B. Jan. 17, 2018); *Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.*, IPR2015-01780, Paper 70, at 55-56 (P.T.A.B. Feb. 23, 2017).

By the Alleged Invention Date, any alleged need for the claimed method of treatment was neither unmet nor long-felt because the MSR publicly disclosed the method of treating a MSI-H cancer patient with pembrolizumab two years prior. (EX1150, ¶¶121-125.) Additionally, the development of pembrolizumab and other PD-1 inhibitors was rapid following BMS's 2010 study results for its PD-1

[36] JHU's arguments regarding Merck's statements to the FDA are not relevant here for the same reason. (POR, 74-76.)

inhibitor. (*Id.*; EX1243, 102:16-103:1; EX1136, 188:15-190:13; *see also* EX1136, 80:13-82:13, 105:2-15, 106:6-18, 107:7-110:22, 119:4-120:14.) JHU incorrectly ignores these facts. *See Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1376 (Fed. Cir. 2022); *In re Ikeda Food Rsch. Co., Ltd.*, 758 Fed. Appx. 952, 955-56 (Fed. Cir. 2019) (A problem must be "both recognized in the prior art and there existed a failure of others to provide 'a feasible solution to the long-standing problem.'").

Tellingly, JHU does not (because it cannot) provide any evidence others tried to treat MSI-H patients with pembrolizumab (or any other anti-PD-1 drug) and failed. *See Adapt Pharma*, 25 F.4th at 1376 (failure of others is "particularly probative" evidence of a long-felt need) (citations omitted). Indeed, prior to the Alleged Invention Date, it was known that BMS's PD-1 inhibitor had led to a complete response in a MSI-H CRC patient.[37] (EX1150, ¶118; EX1136, 106:19-110:22; EX1138, 141:20-142:11.).

[37] JHU attempts to mislead by calling the prior BMS study "resoundingly unsuccessful" and a "failure" while omitting it was known that the complete response observed was in a MSI-H CRC patient. (POR, 21-22, 48; EX1057, 463; EX1038, 7.)

E. JHU Does Not Present Any Evidence of Industry Praise Tied to Novel Features of the Claimed Invention

JHU fails to establish nexus between purported industry praise evidence and the claimed method of treatment. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020). Specifically, JHU does not show that (1) ASCO's selection of the abstract or Dr. Le's presentation was due to the specific method of treatment claimed (POR, 65-66),[38] (2) FDA's approval of pembrolizumab to treat MSI-H cancers or comments thereafter were due to the specific method of treatment claimed (POR, 67-68), or (3) Merck's comments regarding JHU's scientific work were due to the specific method of treatment claimed (POR, 69-70).

[38] Dr. Le's testimony regarding statements made at ASCO is merely "self-referential commendation [that] fall[s] short of demonstrating true industry praise." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

VI. CONCLUSION

The Board should find the challenged claims unpatentable.

Respectfully submitted,

Dated: May 6, 2025

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply contains, as measured by the word-processing system used to prepare this paper, 6,985 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I caused to be served on the counsel identified below a true and correct copy of the foregoing Petitioner's Reply by electronic means on May 6, 2025:

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