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

Patent No. 11,649,287

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,649,287

TABLE OF CONTENTS

LIST OF EXHIBITS

EX1001	U.S. Patent No. 11,649,287 (the "'287 patent")
EX1002	File History of the '287 patent (U.S. Patent Application No. 17/465,096)
EX1003	Declaration of Dr. Alfred I. Neugut, M.D., Ph.D., M.P.H.
EX1004	Curriculum Vitae of Dr. Alfred I. Neugut, M.D., Ph.D., M.P.H.
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)
EX1006	Pernot et al, *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) World J. Gastroenterology 3738 (April 2014)
EX1007	Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)
EX1008	Steinert et al, *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014)
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)
EX1010	Salipante et al, *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) Clinical Chemistry 1192 (June 2014)
EX1011	Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*,369(2) New Eng. J. Medicine 134 (July 2013)
EX1012	Laheru et al, *Immunotherapy for Pancreatic Cancer Science Driving Clinical Progress*, 5 Nature Revs. 459 (June 2005)

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)
EX1014	Pardoll, *The Blockade of Immune Checkpoints in Cancer Immunotherapy*, 12 Nature Revs. 252 (April 2012)
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)
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
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
EX1018	Robinson et al, *Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) Diagnostics*, 99(4) J. Nat'l Cancer Inst. 291 (2007)
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)
EX1020	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014)
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
EX1022	File History of U.S. Patent No. 10,9394,356 (U.S. Patent Application No. 16/144,549)

EX1023	July 27, 2017 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf
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
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
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
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
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)
EX1030	U.S. Provisional Patent App. No. 61/931,512
EX1031	Le et al, *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, 372(26) New Eng. J. Medicine 2509 (June 25, 2015)

EX1032	Champiat et al, *Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy*, 3(1) OncoImmunology e27817-1(January 2014)
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)
EX1034	Brown et al, *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) Genome Research 743 (May 2014)
EX1035	Ogino et al, *Cancer Immunology - Analysis of Host and Tumor Factors for Personalized Medicine*, 8(12) Nature Revs. Clinical Oncology 711 (2011)
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)
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)
EX1038	Kim et al, *Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types*, 28(supp.3) Oncology 15 (November 10, 2014)
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)
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)
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)

EX1042	Kansara et al, *Translational Biology of Osteosarcoma*, 14(11) Nature Revs. Cancer 722 (October 16, 2014)
EX1043	U.S. Provisional Patent App. No. 62/190,977
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)
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)
EX1046	Taggart et al, *High-level Microsatellite Instability in Appendiceal Carcinomas*, 37(8) Am. J. Surgical Pathology 1192 (August 2013)
EX1047	Stintzing et al, *Management of Colorectal Cancer*, 6 F1000 Prime Reports 1 (November 4, 2014)
EX1048	Eisenhauer et al, *New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)*, 45(2) Eur. J. Cancer 228 (2009)
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)
EX1050	Lee et al, *Novel Therapies in Development for Metastatic Colorectal Cance*r, 7(4 Supp. 1) Gastrointestinal Cancer Research 1 (September 2015)
EX1051	Lal et al, An Immunogenomic Stratification of Colorectal Cancer: Implications for Development of Targeted Immunotherapy, 4(3) OncoImmunology 1 (April 2, 2015)
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
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)
EX1055	September 4, 2014 Keytruda Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf
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)
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)
EX1059	Reserved
EX1060	Duval et al, *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas*, 101(14) Procs. Nat'l Acad. of Sciences 5002 (2004)
EX1061	Reserved
EX1062	Reserved
EX1063	Dimasi et al, *Clinical Approval Success Rates for Investigational Cancer Drugs*, 94(3) Clinical Pharmacology & Therapeutics 329 (September 2013)

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
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
EX1066	Merck Sharp & Dohme LLC v. The Johns Hopkins University, 1:22-cv-03059-BPG, ECF 57, Scheduling Order (Filed 10/16/23)
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
EX1068	Henry et al, *Cancer Biomarkers*, 6(2) Molecular Oncology 140 (2012)
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
EX1070	World Health Organization, *International Nonproprietary Names for Pharmaceutical Substances (INN)*, 27(2) WHO Drug Information (2013)
EX1071	Roth, *Frameshift Mutations*, 8 Annual Review of Genetics 319 (1974)
EX1072	Excerpt from Julien Taieb Citations, Google Scholar, available at https://scholar.google.ca/citations?user=niwd5qgAAAAJ&hl=en (accessed 8/25/23)

EX1073	Excerpt from Alexander Eggermount Citations, Google Scholar, available at https://scholar.google.com/citations?user=NWWkhzoAAAAJ&hl=en (accessed 8/25/23)
EX1074	Excerpt from Jean-Charles Soria Citations, Google Scholar, available at https://scholar.google.com/citations?user=wyFxnccAAAAJ (accessed 8/25/23)
EX1075	Henry Lynch, Research.com, available at https://research.com/u/henry-t-lynch (accessed 8/25/23)
EX1076	Excerpt from Daniel Van Hoff Citations, Google Scholar, available at https://scholar.google.com/citations?user=-NTa4oUAAAAJ&hl=en (accessed 8/25/23)
EX1077	Excerpt from Robert A. Holt, Google Scholar, available at https://scholar.google.com/citations?user=CXPlI08AAAAJ&hl=en (accessed 11/27/23)
EX1078	Young et al, *Treatment of Advanced Disease*, 321 British Medical J. 1278 (2000)
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)
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)
EX1081	Excerpt from Shuji Ogino, Google Scholar, available at https://scholar.google.com/citations?user=87TPyfoAAAAJ&hl=en (accessed 8/25/23)
EX1082	Charles Fuchs, Research.com, available at https://research.com/u/charles-s-fuchs (accessed 8/25/23)

EX1083	Excerpt from Jerome Galon Citations, Google Scholar, available at https://scholar.google.com/citations?user=coRgZqUAAAAJ&hl=fr (accessed 8/25/23)
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
EX1085	Imai et al, *Carcinogenesis and Microsatellite Instability: the Interrelationship Between Genetics and Epigenetics*, 29(4) Carcinogenesis 673 (2008)
EX1086	Cheung et al, *Current Advance in Small Bowel Tumors*, 44(1) Clinical Endoscopy 13 (2011)
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)
EX1088	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers Version 1.2014 (May 30, 2014)
EX1089	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2014 (November 27, 2013)
EX1090	Garg et al, *Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer) and Endometrial* Carcinoma, 16(1) Cancer Control 679 (2009)
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)

EX1092	ASCO, Developmental Therapuetics – Immunotherapy, https://meetings.asco.org/2014-asco-annual-meeting/6670?presentation=98450#98450
EX1093	Abdul-Rahman Jazieh, 2015 Annual Meeting Tips, ASCO Connection, https://connection.asco.org/blogs/2015-annual-meeting-tips
EX1094	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1.2014 (May 30, 2014)

I. INTRODUCTION

Petitioner Merck Sharp & Dohme LLC ("Petitioner" or "Merck") requests *inter partes* review of Claims 1-36 of U.S. Patent No. 11,649,287 ("the '287 patent"), which is assigned to Patent Owner The Johns Hopkins University ("JHU").

The '287 patent broadly claims the use of a prior art drug (pembrolizumab) in a treatment of a sub-population of cancer patients (patients whose cancers have a genetic instability called microsatellite instability-high ("MSI-H")) also disclosed in the prior art. It was well known that MSI-H tumors were more immunogenic, and would benefit from the use of an immunotherapy drug like pembrolizumab. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2968-69; EX1036, 1186; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; EX1003, ¶¶41-49.) In fact, the specification of the JHU patent is a clinical study ***published in the prior art more than a year*** before the filing of JHU's patent applications, which was a collaboration by Merck and JHU (the "MSI-H Study Record").

This study was consistent with the teachings of the literature that PD-1 inhibitors naturally had more efficacy when treating tumors that (1) have many mutations, and thus are comprised of cancer cells that are easy for immune cells to recognize and (2) are already infiltrated by many immune cells, which kill the tumor cells. (*Infra*, §III.C.) The literature also taught that MSI-H tumors naturally

displayed those characteristics. (*Infra*, §III.C.) By the relevant time period, the literature had therefore taught that MSI-H tumors exhibited the characteristics that were most relevant for PD-1 efficacy, including many mutations and infiltration by lymphocytes. (*E.g.*, EX1006, 3740-41; EX1003, ¶¶41-49.)

As explained in detail below and in the Declaration of Dr. Alfred I. Neugut, all claims of the '287 patent are unpatentable, as they fail to meet several statutory requirements. (*See, e.g.,* EX1003, ¶¶1-22, 50-58, 187-188.)

First, the independent claims and most dependent claims of the '287 patent are anticipated. (35 U.S.C. § 102; *infra* §VI.B; EX1003, ¶17, §VII.A.) More than a year prior to JHU's first provisional application, the MSI-H Study Record taught the claimed methods, and those methods inherently achieve the claimed efficacy from the treatment. JHU overcame the MSI-H Study Record on the ground that it did not expressly include the results flowing from the treatment, but under controlling precedent of the Court of Appeals for the Federal Circuit, which was not considered during prosecution or brought to the attention of the Examiner, that outcome was legal error.

Second, all of the '287 patent claims would have been obvious to the person of ordinary skill in the art ("POSA") as of the priority date, including all dependent claims. (35 U.S.C. § 103; *infra* §VI.C; EX1003, ¶17, §§VII.B-F.) For example, even if JHU's rationale for overcoming the MSI-H Study Record were accepted,

the prior art provided a motivation to carry out the MSI-H Study Record's protocol and a reasonable expectation of success in doing so. Further, the prior art also taught the routine methods for testing a cancer for the genetic marker of MSI-H (and the patents do not purport to have discovered any new methodology for doing so). All but one of the additional prior art references relied on in the obviousness grounds were not considered by the Examiner, and the Examiner considered none of the obviousness arguments and combinations presented in this petition.

The Board should institute trial and cancel the challenged claims.

II. STANDING AND GROUNDS

Merck certifies under 37 C.F.R. § 42.104(a) that the '287 patent is available for review and Merck is not barred or estopped from requesting review on the grounds identified herein. Merck respectfully requests review of Claims 1-36 of the '287 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable on the following grounds:

Ground 1: Claims 1-2, 4-8, 11-12, 14-18, 21-36 are unpatentable under 35 U.S.C. § 102 as being anticipated by the published MSI-H Study Record (EX1005).

Ground 2: Claims 1-2, 4-8, 11-12, 14-18, 21-36 are unpatentable under 35 U.S.C. § 103 as being obvious over the published MSI-H Study Record (EX1005) in view of Pernot (EX1006).

Ground 3: Claims 2, 9, 10, 12, 19, and 20 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Chapelle (EX1007).

Ground 4: Claims 3 and 13 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Steinert (EX1008).

Ground 5: Claims 6-7, 16-17, 26, 28, 30-36 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Benson (EX1009).

Ground 6: Claims 8 and 18 are unpatentable under 35 U.S.C. § 103 as being obvious over the MSI-H Study Record (EX1005), or the MSI-H Study Record (EX1005) in view of Pernot (EX1006), in view of Hamid (EX1011).

III. BACKGROUND OF THE ’287 PATENT

Unless otherwise noted, the following information was known to the skilled artisan more than a year before the earliest priority date.

A. The Mechanism of the Prior Art Drug at Issue

Claims 1 and 11 of the ’287 patent, the patent’s only independent claims, are directed to identifying colorectal cancer patients who have MSI-H and mismatch

repair deficient tumors and administering Merck's immunotherapeutic drug pembrolizumab (known today by the tradename Keytruda®) to those patients. (EX1001, 24:41-26:63.)

An immunotherapy is a drug that helps the body fight disease by boosting the immune system. (EX1012, 459; EX1003, ¶¶29-32.) One particular type of immunotherapy is called a PD-1 inhibitor. (EX1033, 2965; EX1014, 253; EX1003, ¶29.) By the relevant time period, Merck's drug pembrolizumab was a known PD-1 inhibitor undergoing clinical development, and Merck was not the only company developing anti-PD-1 therapeutics for treating cancer. (EX1011, 135; EX1057, 462; EX1053; EX1003, ¶29.)

The prior art disclosed how PD-1 inhibitors worked to treat cancer. (EX1003, ¶¶29-32.) Normally, immune cells find and kill cancer cells. In response, cancer cells put brakes on the immune system. As Dr. Neugut explains, pembrolizumab blocks receptors that otherwise inhibit the body's immune response, thereby releasing the brakes that the cancer cells put on the immune cells. (EX1003, ¶32.)

Merck began clinically developing pembrolizumab in 2010. (EX1015, 1388.) While developing pembrolizumab, Merck treated cancer patients in clinical studies, including patients having MSI-H cancers. (EX1005, 4 (Arms and Interventions); EX1016; EX1017; EX1023, 42; EX1003, ¶33.)

A person's cancer is considered MSI-H if the cancer cells' DNA contains small tracts of repeating DNA, called microsatellites, that are different in size than regularly occurring microsatellites. (EX1001, 1:32-34; EX1010, 1192-1193; EX1003, ¶¶23-28.) MSI-H is also known throughout the literature as MSI positive, MSI-high, MSIH, or MSI+. (EX1010, 1193, 1196; EX1018, 293 (authors include named '287 patent inventors); EX1019, 1065 (authors include a named '287 patent inventor); EX1003, ¶26.) MSI-H is caused by deficient mismatch repair ("dMMR"), also known as "Mismatch repair deficiency" or "DNA mismatch repair deficient." (EX1001, 1:32-34; EX1010, 1192; EX1003, ¶27.) MSI-H and dMMR are "biologically the same" and testing for one condition was considered "equivalent" to testing for the other. (EX1020, MS-12 (PDF p. 51); EX1007, 3380; EX1001, 10:42-67 (assessing dMMR status using MSI-H testing); EX1003, ¶28.) By 2014, upon diagnosis of colorectal cancer, it was common to test tumors for MSI-H. (EX1003, ¶25.) Whether a colorectal cancer tumor exhibited MSI-H could inform therapeutic choices, prognosis, and familiar cancer risk appraisal. (EX1003, ¶¶41-49.)

B. The Prior Art MSI-H Study Record

In late 2012, JHU approached Merck about collaborating on a clinical study using pembrolizumab to treat cancer patients whose cancers were identified as being MSI-H. (EX1029, ¶¶90-93.) The Parties agreed to collaborate on the

clinical study, which uses the study identifier NCT01876511 (the "MSI-H Study"). (EX1005, 3 (Collaborators); EX1003, ¶34.)

On June 10, 2013, the MSI-H Study Record detailing the parameters and protocols for that clinical study was submitted to and published on www.clinicaltrials.gov. (EX1005, 3 (Study Status); EX1003, ¶35.)[1] The website, www.clinicaltrials.gov, publicizes clinical trials in a searchable and easy to understand manner in order to keep doctors and patients apprised of ongoing clinical trials. (EX1021, 1-4; EX1003, ¶36.) It was indexed by subject matter, and would have been used by the POSA to understand the state of the art. (EX1003, ¶36.)

During prosecution of the '287 patent and its family members, named inventor Andrew Pardoll admitted that the MSI-H Study Record published as early

[1] The MSI-H Study Record was periodically resubmitted (e.g., on June 12, 2013, September 20, 2013, May 21, 2014, and June 25, 2014). (EX1024; EX1025; EX1026; 1027.) Those versions are substantively identical. In any event, however, all submissions remain available in view of the practice of www.clinicaltrials.gov of maintaining archived versions of each submission. (*See, e.g.*, EX1005, 1-2.)

as June 12, 2013. (EX1002, March 22, 2022 Affidavit, 7-8, ¶ 22; EX1022, February 4, 2020 Affidavit, ¶ 22.) And more recently, in district court litigation, JHU similarly admitted that the MSI-H Study Record was published on June 10, 2013 (and on June 12, 2013). (EX1029, ¶¶ 22, 103.)

The MSI-H Study Record is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). *See Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01288, Paper 30 at 14-24 (PTAB Feb. 23, 2022); Grünenthal GM*BH v. Antecip Bioventures II LLC*, PGR2019-00003, Paper 22 at 17-18 (PTAB May 5, 2020).

It was not until more than one year after the MSI-H Study Record published that JHU filed the First Provisional (without Merck's knowledge). (EX1030, PDF p. 1.) Yet the '287 patent's claimed subject matter derives directly from the MSI-H Study. (See EX1002, March 22, 2022 Affidavit, 7-8, ¶¶22-23 (connecting the '287 patent, the MSI-H Study Record, and a New England Journal of Medicine article (EX1031) that discusses the results of the MSI-H Study); EX1005, 2 (using study identifier number NCT0187511); EX1031, 2509 (discussing the results of the MSI-H Study using study identifier number NCT0187511); EX1003, ¶¶37-40.) Indeed, all of the '287 patent's examples, tables, and figures are devoted to the design and results of the MSI-H Study, a "small phase 2 trial of pembrolizumab." (EX1001, 6:52-21:25, 3:19-21; Figs. 1-13; EX1005; EX1003, ¶39.) For instance,

Examples 1-4 (EX1001, 8:7-16:8) are the design of the MSI-H Study, and Examples 5-11 (EX1001, 16:10-18:67) report its results. Further, Tables 1-3 (EX1001, 19:1-21:25) and Figures 1-13 also report the MSI-H Study's results.

The Examiner did not consider the MSI-H Study Record during prosecution of the application that matured into the '287 patent. (*See generally* EX1002.) The Examiner did consider the MSI-H Study Record during prosecution of an earlier patent family member, U.S. Patent No. 10,934,356 ("the '356 patent"), and recognized that the MSI-H Study Record disclosed a mechanism for how pembrolizumab works in a patient whose cancer was MSI-H or dMMR relative to a patient without MSI-H or dMMR cancer. (EX1022, December 14, 2020 Notice of Allowance, 3.) The Examiner nonetheless allowed the '356 patent over the MSI-H Study Record on the rationale that it did not affirmatively disclose the results flowing from the disclosed treatment. (*Id*.) The Examiner's requirement for an express disclosure of an inherent result of the disclosed treatment was incorrect as a matter of law, as shown in detail below. (*See infra* §VI.B.1; *see also infra* §VII.B (explaining why the Board should not exercise its discretion to deny institution under 35 U.S.C. § 325(d).)

C. Other Prior Art Had Recognized the Utility of PD-1 Inhibitors for Treating MSI-H Cancers, Consistent With the Fact that Merck and JHU Used Merck's PD-1 Inhibitor to Treat Such Cancer Patients in the MSI-H Study

In addition to the MSI-H Study Record, before JHU filed the First Provisional, others in the field had published on the use of PD-1 inhibitors to treat patients whose cancers were MSI-H. For example, another clinical study record (EX1053; EX1003, ¶49) and a number of publicly available articles had already recommended evaluating the treatment of patients whose cancers were MSI-H with immunotherapeutic agents like pembrolizumab. (EX1006, 3740-41; EX1032, e27817-5; EX1033, 2969; EX1034, 747; EX1035, 1, 8; EX1036, 1186; EX1037, 2; EX1038, 7; EX1039, 243s; EX1003, ¶¶47-49.)

Indeed, in April 2014, Pernot taught that MSI-H colorectal cancers are "good candidates for immunotherapy." (EX1006, 3740-41.) Further, Champiat taught in January 2014 that "it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma." (EX1032, e27817-5; EX1003, ¶48.) Those suggestions built upon the previously established knowledge that the MSI-H condition made it easier for a patient's immune system to detect and attack the cancer. (EX1040, 2; EX1038, 5; EX1041, 9208; EX1042, 731; EX1006, 3740-41; EX1037, 2; EX1035, 4; EX1036, 1186-87, 1193; EX1003, ¶¶41-46.)

IV. CLAIM CONSTRUCTION

For IPR proceedings, the Board applies the claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 37 C.F.R. § 42.100(b). Under *Phillips*, claim terms are typically given their ordinary and customary meanings, as would have been understood by the POSA, at the time of the invention, having taken into consideration the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; *see also id.* at 1312-16.

The Board only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-00633, Paper 11 at 16 (PTAB Aug. 14, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Here, given the correlation between the MSI-H Study Record, the written description of the '287 patent, and the challenged claims, the Board need not construe any terms of the challenged claims to resolve the underlying controversy, as any reasonable construction reads on the prior art. Merck reserves all rights to raise claim construction and other arguments in other venues.

V. LEVEL OF ORDINARY SKILL IN THE ART

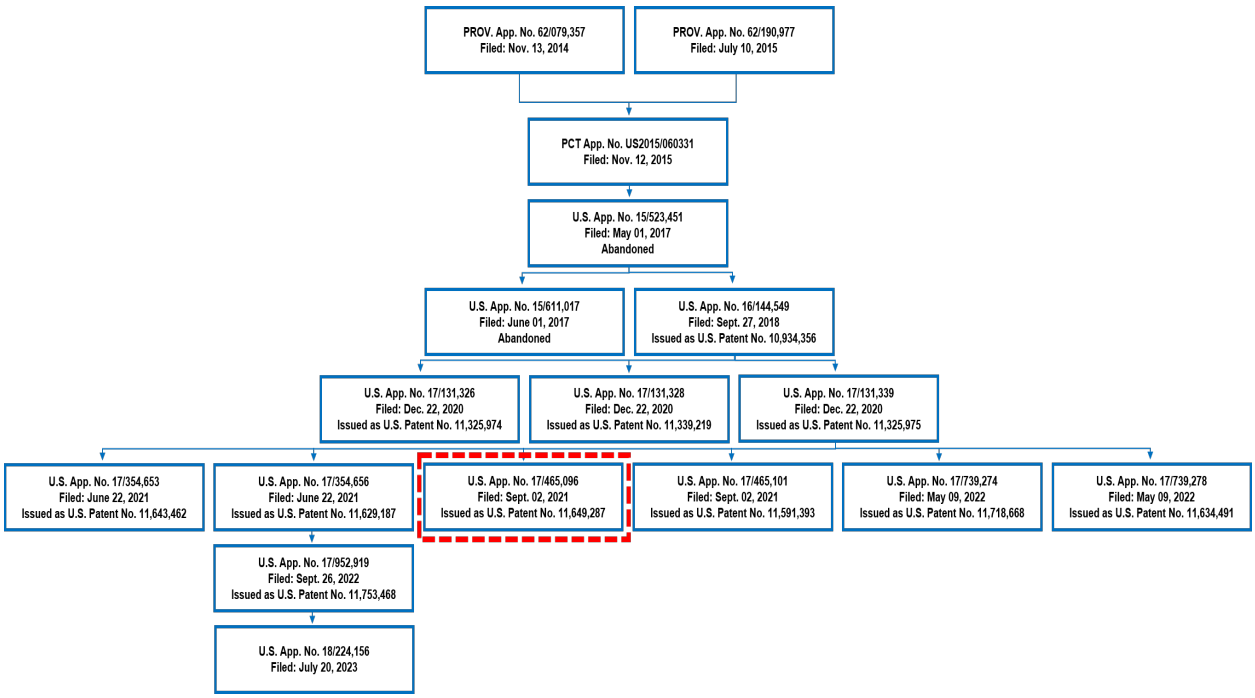
The POSA for purposes of the '287 patent would be a medical doctor or a professional in a related field with at least five years of experience with treating

cancer. (EX1003, ¶19.) The POSA would also have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and a pathologist with comparable experience. (EX1003, ¶19.) The inherent anticipation and obviousness grounds discussed herein, would change due to a modestly lesser or greater level of experience.

VI. THE '287 PATENT CLAIMS ARE UNPATENTABLE

A. If JHU Is Bound to the Representations It Made During Prosecution, It Is Not Entitled to Claim Priority to the First Provisional Patent Application

On its face, the '287 patent cites two provisional patent applications: the First Provisional and U.S. Patent Application No. 62/190,977 (filed July 10, 2015) (the "Second Provisional"). The relationship of the '287 patent to those applications, as well as patents issued therefrom, is shown in the purported priority chain below:



For a non-provisional utility application to be afforded the priority date of a provisional application, "the written description of the provisional must adequately support the claims of the non-provisional application." *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1380 (Fed. Cir. 2017) (citations and quotations omitted) (emphasis removed). The test for adequate written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Nalpropion Pharms., Inc. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344, 1350 (Fed. Cir. 2019) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)) (emphasis removed). Further, the standard for what constitutes proper enablement of a prior art reference for purposes of the enablement standard

under section 112 differs from the enablement standard under section 102. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

Here, JHU submitted declarations during prosecution of a family member of the '287 patent, seeking to distance the patent from the MSI-H Study by arguing that data from the clinical study was the basis for patentability (which thus led the Examiner to a legally erroneous rationale for allowing the patent to issue). (*See* EX1022, February 4, 2020 Affidavit, 7-8, ¶22, June 8, 2020 Affidavit, 8-9, ¶¶27-28.) The First Provisional, however, did not include the data referred to in the declarations. Thus, even though JHU was wrong to assert that the reporting of the data from the MSI-H Study could create patentability for the treatment disclosed in the prior art), JHU must be bound to its positions – JHU cannot claim priority to the First Provisional without contradicting its sworn positions during prosecution. In other words, the First Provisional lacks the disclosure of the data (inherent in the performance of the study), which JHU nonetheless argued was necessary for patentability. As such, applying JHU's own sworn positions, the July 10, 2015 filing date of the Second Provisional is the applicable critical date for purposes of analyzing the prior art.[2]

[2] To be clear, each ground of invalidity discussed in this Petition applies even if the

B. Ground 1: Claims 1-2, 4-8, 11-12, 14-18, 21-36 of the '287 Patent are Anticipated by the MSI-H Study Record

1. Law on Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citations omitted). "[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." *Id.* at 1379.

First Provisional were a basis for priority. And Merck disagrees that the declarations are sufficient to avoid the prior art, both because the inherent efficacy of the treatment taught in the prior art cannot render the treatment itself patentable (see *infra*, §VI.B.1), and because a prior art disclosure may anticipate even if it that same disclosure could not support a claim of priority (*see Rasmusson*, 413 F.3d at 1325-26).

In *Schering*, the Federal Circuit clarified that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering*, 339 F.3d at 1380. For example, *Schering* explained that the prior art disclosure of a method of treatment by administering loratadine, an antihistamine, inherently anticipated a later patent seeking to claim the metabolite naturally produced *in vivo*, even though, at the time of the filing of the metabolite patent, the loratadine method had not been practiced, and the metabolite was neither disclosed in the prior art or even in actual existence. *Schering*, 339 F.3d at 1378, 1380.[3] It was sufficient for anticipation that, if one of skill practiced the use described in the prior art, the metabolite would be produced by the body in vivo. *Schering*, 339 F.3d at 1380. The Federal Circuit reaffirmed that principle as recently as April 2023. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). In

[3] *Schering* also brought clarity to prior precedent. *Schering*-339 F.3d at 1377-80 ("This court recognizes that this may be a case of first impression, because the prior art supplies no express description of any part of the claimed subject matter."). The Examiner may very well have been unfamiliar with this area of the law of anticipation.

Arbutus, the claimed morphology of a composition was inherently anticipated by following a prior art reference's formulations using that same reference's methods. *Arbutus*, 65 F.4th at 664.

The law established by *Schering* has specifically been applied in the context of clinical studies prior to publication of the data from the study. In *In re Montgomery*, the Federal Circuit held that a document disclosing a planned clinical study inherently anticipated method of treatment claims even where the method of treatment had not yet been practiced. *In re Montgomery*, 677 F.3d 1375, 1381, 1385 (Fed. Cir. 2012). In rejecting the argument that the claimed method must have actually been performed, the Federal Circuit explained that, "even if [the documents disclosing the planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." *Id.* at 1382. The Federal Circuit went on to further hold that, "even if the claim includes an efficacy requirement, efficacy is inherent in carrying out the claim steps." *Id.* at 1381; *see also In re Couvaras*, 70 F.4th 1374, 1380 (Fed. Cir. 2023) ("Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.") (citing *In re Montgomery*, 677 F.3d at 1381). The Federal Circuit has also made clear that "[e]xtrinsic evidence can be used to demonstrate what is necessarily present in a prior art embodiment even if the

extrinsic evidence is not itself prior art." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (quotations omitted).

The MSI-H Study Record inherently anticipates Claims 1-2, 4-8, 11-12, 14-18, 21-36 of the '287 patent because the claims are directed to the methods disclosed in the MSI-H Study Record. Indeed, anticipation could not be possibly be clearer because the treatment disclosed in the prior art MSI-H Study Record is written description support for the treatment method of the claims. For example, the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '287 patent, and given to the claimed patient population. (EX1005, 4 (Arms and Interventions); *see also id*., 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶¶37-40.)

2. Claim 1

a. [1.pre]: "A method for treating colorectal cancer in a human patient, the method comprising:"

The Arms and Interventions section of the MSI-H Study Record discloses a method for treating colorectal cancer in a human patient. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility).) This is the method set forth in the preamble. (EX1003, ¶¶59-60.)

b. [1.1]: "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,"

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility).) That disclosure reads on this limitation. (EX1003, ¶¶61-66.)

The MSI-H Study Record does not expressly use the phrase "therapeutically effective" in providing the dosage for the treatment therapy. Nonetheless, the dosage described in the MSI-H Study Record, 10 mg/kg MK-3475 (pembrolizumab), is identical to the dosage described as being "therapeutically effective" in the '287 patent, and any required efficacy is thus inherent to that dosage. (EX1003, ¶62.)

Indeed, the '287 patent itself, which only describes one dosage (EX1001, 8:50-56, 13:31-37)—the same one in the MSI-H Study Record (EX1005, 4 (Arms and Interventions)—asserts that this dosage is effective. (EX1001, 4:23-36 (showing the "[c]linical benefit to pembrolizumab according to MMR status"), 16:12-17, 16:40-43, 20:1-29, Figs. 2, 11; EX1003, ¶63; *see also infra*

§§VI.B.16-20, VI.B.22, VI.B.24 (addressing the efficacy requirements of certain dependent claims).) "To anticipate, the prior art need only meet the inherently disclosed limitation to the extent the patented method does." *See King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010). Other sources reporting the results of the MSI-H Study similarly confirm the efficacy of the dosage used in the MSI-H Study Record. (EX1031, 2509, 2514; Table 1, Table 2, Table 3, Figure 1, Figure 2; EX1064; EX1029, ¶¶ 89, 105, 110, 117; EX1003, ¶63.)

The MSI-H Study Record is also enabled for the purposes of anticipation. In the context of treating cancer, "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation," and disclosure of the method enables the reference. *Rasmusson*, 413 F.3d at 1326. Here, as discussed above, the MSI-H Study Record discloses administering pembrolizumab 10 mg/kg every 14 days to colorectal cancer patients having MSI-H cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶63.)

Further, as discussed above in Section III, the MSI-H Study Record's disclosure of treating "MSI positive" colorectal cancer patients to refers to treating human patients having colorectal cancer that is "MSI-H." (*See, e.g.*, EX1010, 1193, 1196; EX1018, 293; EX1019, 1065; EX1003, ¶64.) Indeed, named inventor

Dr. Pardoll represented in a sworn declaration that the MSI-H Study Record concerns treating human patients having colorectal cancer that is "MSI-H." (EX1022, February 4, 2020 Affidavit, 7-8, ¶¶ 21-23 ("Dr. Dung Le prepared a study proposal for testing anti-PD-1 antibodies . . . in . . . MSI-positive colon cancer patients . . . . The preliminary results of this study demonstrated clinical responses . . . in the MSI-H (MMR deficient) arm.").)

The MSI-H Study Record's disclosure of a method of treating human patients having "MSI positive" cancer also reads on the claimed method of treating human patients having colorectal cancer that is "DNA mismatch repair deficient" cancer. (EX1003, ¶65.) For example, the art taught that "[p]atients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status." (EX1020, MS-12; EX1001, 8:9-36 (using MSI status to characterize patients as dMMR).) And, in his declaration, Dr. Pardoll equated MSI-H and dMMR patients. (EX1022, February 4, 2020 Affidavit, 8, ¶23 ("[T]he MSI-high (MMR deficient) arm.").) Moreover, because MSI-H is caused by dMMR, all cancers that are MSI-H are dMMR. (EX1010, 1192; EX1003, ¶65; *see also* EX1001, 1:32-34.)[4]

[4] Because "[p]atients determined to have defective MMR (dMMR) status are

c. [1.2]: "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."[5]

The Arms and Interventions section of the MSI-H Study Record discloses three study arms, one of which consists of patients having MSI positive colorectal cancer. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶¶67-69.)[6]

---

biologically the same population as those with MSI-H status" (EX1020, PDF p. 51), this Petition's use of MSI-H should be read to mean MSI-H and dMMR, unless otherwise noted.

[5] It is unclear whether this claim limitation requires a separate determination from that in limitation [1.1]. For purposes of this Petition, Petitioner interprets this limitation as permitting reliance on the same determination in limitation [1.1], which is interpretation applied by JHU in district court. In doing so, Petitioner reserves the right to challenge that interpretation in district court.

[6] As discussed above, "MSI positive colorectal cancer" would be understood by the POSA to mean "microsatellite instability high" and "mismatch repair deficient" colorectal cancer. (*Supra*, §III.A.)

According to the MSI-H Study Record's disclosure, in order to place the patients into the proper arm, the MSI-H Study Record required a biological sample from the patient that had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶68.)

3. Claim 2: "The method of claim 1, wherein the biological sample is tumor tissue from the patient."

As discussed in Section VI.B.2.c above, the Arms and Interventions section of the MSI-H Study Record discloses determining whether the patient's colorectal cancer is MSI-H. Further, the Eligibility section of the MSI-H Study Record requires each patient to "[a]gree to have a biopsy of their cancer." (EX1005, 5-6 (Eligibility).) A biopsy of a patient's tumor obtains tumor tissue for testing. As such, in the context of the MSI-H Study Record, where patients are separated into three separate cohorts based, in part, on whether a patient's cancer is MSI-H, the biopsy would obtain tumor tissue to test whether the patient's cancer's is MSI-H (EX1007, 3380, 3383; EX1044, 3309; EX1045, 3485; EX1046,1193; EX1003, ¶¶70-71; *see also* EX1001, 8:12-15 (testing "[a]rchived tumor samples" or "newly obtained biopsies."; EX1003, ¶70.) Therefore, the MSI-H Study Record's disclosure of treating MSI-H patients and the MSI-H Study Record's requirement

that patients agree to have a biopsy demonstrates that the MSI-H Study Record discloses the claim. (EX1003, ¶¶70-71.)

4. Claim 4: "The method of claim 1, wherein the colorectal cancer is microsatellite instability high."

As explained in Section VI.B.2.c, the Arms and Interventions section of the MSI-H Study Record discloses treating colorectal cancer patients whose tumors are MSI-H. (EX1003, ¶¶72-73.)

5. Claim 5: "The method of claim 1, wherein the colorectal cancer is DNA mismatch repair deficient."

As explained in Section VI.B.2.c, the Arms and Interventions section of the MSI-H Study Record discloses treating colorectal cancer patients whose tumors are dMMR. (EX1003, ¶¶74-75.)

6. Claim 6: "The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer."

The MSI-H Study Record discloses that patients participating in the Phase II study must have "measurable disease" and tumors. (EX1005, 2 (Study Identification), 4 (Study Design), 5-6 (Eligibility); EX1003, ¶76.)[7] In the context

[7] It also discusses that a primary endpoint was objective response rate, which refers to tumors shrinking. (*Supra*, §III.B.)

of the MSI-H Study Record, that discloses that patients would have metastatic and advanced cancer. (EX1003, ¶¶76-80.)

Colorectal cancer patients having "[m]easurable" disease in the context of a study record, like the MSI-H Study Record, refers to patients having metastatic and advanced cancer,[8] and does not include patients whose cancer was resectable for the purposes of a cure. (EX1020, PDF p. 25; *infra*, §VI.B.6; EX1003, ¶77.) The POSA would therefore understand that the MSI-H Study Record discloses treating patients having metastatic cancer and locally advanced cancer that is unresectable for purpose of a cure. (EX1003, ¶77.)

Further, if metastatic patients were not included, that would have been highly unusual, especially because the treatment in the study record was not directed to a local treatment, such as radiation or surgery. (EX1003, ¶78.)

Indeed, prior art concerning the MSI-H Study indicates that the physicians understood postings on clinicaltrials.gov indicated that patients had "metastatic tumors." (EX1049, 444; *see also* EX1050, S4; EX1003, ¶79.) *See Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018).

---

[8] Advanced cancer refers to metastatic cancer or cancer that is so locally advanced that it is unresectable for purposes of a cure. (EX1003, ¶77.)

7. Claim 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."

The MSI-H Study Record's title and Eligibility section disclose that patients in the Phase II study must have "tumors" and "measurable disease." (EX1005, 2 (Study Identification), 4 (Study Design), 5-6 (Eligibility).) In the context of the MSI-H Study Record, that discloses that patients would have received prior drug therapies and had their cancers progress after those therapies. (EX1003, ¶¶81-86.)

Colorectal cancer patients having "measurable" disease in the context of the MSI-H Study Record refers to patients having metastatic and advanced cancer and does not include patients whose cancer was resectable for the purposes of a cure. (EX1020, PDF p. 25; EX1003, ¶82.) If a patient had cancer that is resectable for the purposes of a cure, then a practitioner would excise the tumor because surgery "is the only way to achieve a cure." Thus, "measurable" disease in the context of a clinical study does not include cancer that is resectable for the purposes of a cure. (EX1047, 4-7; EX1020, PDF p. 7 (under the standard of care, resection is recommended if it is possible); EX1048, 230; EX1003, ¶82.)

Patients having metastatic and advanced colorectal cancer that would participate in a clinical study, like the MSI-H Study, would have generally received at least two other prior drug therapies, such as standard of care chemotherapy, and had their cancers progress after those drug therapies. (EX1020,

PDF p. 25; *see also* EX1009, 1034; EX1047, 4-7; EX1003, ¶83) Additionally, because the patients were disclosed to still have a "tumor" and "measurable disease," it would mean that the cancer had progressed following that prior treatment. (EX1003, ¶83.) Indeed, the POSA would have found it highly unusual for that patient population, patients who had received two prior drug treatments and had their cancer progress after those treatments, to not be included in the MSI-H Study Record, especially without any explicit carve-out. (EX1003, ¶83.)

Consistent with the above, the Eligibility section of the MSI-H Study Record excludes "[p]atients who have had prior treatment with anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti CTLA-4 antibodies" from the clinical study. (EX1005, 5-6 (Eligibility); EX1003, ¶84.)

Therefore, the POSA would have understood that the MSI-H Study Record disclosed treating patients who had received prior/different cancer therapies, and the patients' cancer had progressed after the patients received the different cancer therapies. (EX1003, ¶85.) *See Acoustic Tech., Inc. v. Itron Networked Sols., Inc*., 949 F.3d 1366, 1373 (Fed. Cir. 2020) ("In an anticipation analysis, the dispositive question is whether a skilled artisan would 'reasonably understand or infer' from a prior art reference that every claim limitation is disclosed in that single reference"); *Genentech, Inc. v. Hospira, Inc*., 946 F.3d 1333, 1340 (Fed. Cir. 2020) (same); *In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991) (same).

Indeed, Petitioner's understanding of the MSI-H Study Record is confirmed by additional evidence. In particular, a poster presentation describing the same clinical study at issue in the MSI-H Study Record indicated that the study required that patients have "progressive disease," that colorectal cancer patients have "at least 2 prior therapies," and that non-colorectal cancer patients have "at least 1 prior therapy." (*See* EX1080,[9] Eligibility Criteria; EX1003, ¶86.)

[9] EX1080 is a poster that Merck and JHU presented at the American Society of Clinical Oncology that confirms how the POSA would have understood the MSI-H Study Record. *See Yeda* at 906 F.3d at 1041. EX1080 is prior art. It was displayed for 3.75 hours at ASCO, which is an annual public conference that would have been attended by tens of thousands of oncologists, including world class experts. (EX1092; EX1093; EX1003, ¶86.) EX1080 indicates that one of the reasons that the poster was on display was increasing attending doctors' awareness of the ongoing MSI-H Study including to potentially expand the patient pool. (EX1080, Abstract, Methods; EX1003, ¶86.) Thus, there was no expectation of confidentiality. (EX1003, ¶86.) *See also In re Klopfenstein* 380 F.3d 1345, 1350 (Fed. Cir. 2004).

8. Claim 8: "The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously."

As discussed in Section VI.B.2.b above, the Arms and Interventions section of the MSI-H Study Record discloses administering 10 mg/kg of pembrolizumab every 14 days. At the time of the alleged invention, pembrolizumab for the treatment of cancer was administered intravenously. (*E.g.* EX1011, 134 ("We administered [pembrolizumab] intravenously."); EX1054, 3; *see also* EX1055, 1 ("Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks."); EX1003, ¶¶87-88.) Thus, the MSI-H Study Record discloses this limitation.

9. Claim 11

a. [11.pre]: "A method for reducing the risk of progression of colorectal cancer in a human patient, the method comprising:"

As discussed above, the Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with 10 mg/kg pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) Thus, for all of the reasons that the MSI-H Study Record discloses limitations of [1.pre], [1.1], and [1.2] (discussed above at §VI.B.2), the MSI-H Study Record discloses this limitation. (EX1003, ¶89.) In

addition, the MSI-H Study Record discloses that primary outcome measures include "Immune-related progression free survival" and as discussed in Section VI.B.1, the data inherently resulting from the MSI-H Study Record demonstrates improvements in this outcome. (EX1005, 4-5 (Outcome Measures); EX1003, ¶90.) For this additional reason, the MSI-H Study Record discloses "[a] method for reducing the risk of progression of colorectal cancer in a human patient."

b. [11.1]: "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,"

This limitation is identical to limitation [1.1], and is disclosed for the same reasons. (*Supra*, §VI.B.2.b; EX1003, ¶91.)

c. [11.2]: "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."

This limitation is identical to limitation [1.2], and is disclosed for the same reasons. (*Supra,* §VI.B.2.c; EX1003, ¶92.)

10. Claim 12: "The method of claim 11, wherein the biological sample is tumor tissue from the patient."

The additional limitation recited in Claim 12 is the same as recited in Claim 2 and disclosed for the same reasons. (*Supra*, §VI.B.3; EX1003, ¶93.)

11. Claim 14: "The method of claim 11, wherein the colorectal cancer is microsatellite instability high."

The additional limitation recited in Claim 14 is the same as recited in Claim 4 and disclosed for the same reasons. (*Supra,* §VI.B.4; EX1003, ¶94.)

12. Claim 15: "The method of claim 11, wherein the colorectal cancer is DNA mismatch repair deficient."

The additional limitation recited in Claim 15 is the same as recited in Claim 5 and disclosed for the same reasons. (*Supra,* §VI.B.5; EX1003, ¶95.)

13. Claim 16: "The method of claim 11, wherein the colorectal cancer is metastatic colorectal cancer."

The additional limitation recited in Claim 16 is the same as recited in Claim 6 and disclosed for the same reasons. (*Supra,* §VI.B.6; EX1003, ¶96.)

14. Claim 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."

The additional limitation recited in Claim 17 is the same as recited in Claim 7 and disclosed for the same reasons. (*Supra,* §VI.B.7; EX1003, ¶97.)

15. Claim 18: "The method of claim 11, wherein the pembrolizumab is administered to the patient intravenously."

The additional limitation recited in Claim 18 is the same as recited in Claim 8 and disclosed for the same reasons. (*Supra,* §VI.B.8; EX1003, ¶98.)

16. Claim 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."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra,* §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶99-101; *see supra,* §§VI.B.1, VI.B.2.b.)

The '287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, 4:23-36 (discussing median progression free survival), 17:8-17 (same), Figure 2 (same); EX1003, ¶100; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

17. Claim 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."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra,* §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶102-104; *see supra,* §§VI.B.1, VI.B.2.b.)

The '287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, 4:23-36 (discussing median overall survival), 17:8-17 (same), Fig. 2 (same); EX1003, ¶103; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

18. Claim 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 microsatellite instability high or DNA mismatch repair deficient."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab

every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶105-107; *see supra,* §§VI.B.1, VI.B.2.b.)

The '287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, 4:23-36 (discussing median progression free survival), 17:8-17 (same), Figure 2 (same); EX1003, ¶106; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

19. Claim 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."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶108-110; *see supra,* §§VI.B.1, VI.B.2.b.)

The ’287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, 4:23-36 (discussing median overall survival), 17:8-17 (same), Fig. 2 (same); EX1003, ¶109; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

20. Claim 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.”

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record’s method of treatment. (EX1003, ¶¶111-113; *see supra,* §§VI.B.1, VI.B.2.b.)

The ’287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001, Fig. 11 (40% of MMR-deficient CRC patients obtained an objective response rate of 40%), 16:40-43 (same), 20:1-29 (same); EX1003, ¶112; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

21. Claim 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."

The additional limitation that Claim 26 recites is essentially the same as Claim 7, but further requires a cancer therapy drug. As discussed in the analysis for Claim 7, under the standard of care in the art, the MSI-H Study Record requires patients having colorectal cancer to have received at least two prior cancer therapy drugs and had their cancers progress after receiving those drugs. (*Supra,* §VI.B.7.) Thus, the additional method of Claim 26 is disclosed for the same reasons as Claim 7. (EX1003, ¶114.)

22. Claim 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%."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶115-117; *see supra,* §§VI.B.1, VI.B.2.b.)

The '287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is the product of the MSI-H Study. (EX1001,

Fig. 11 (immune-related progression free survival at 20 weeks was 78% for MMR-deficient CRC), 16:13-17 (same)); EX1003, ¶116; *see also* EX1031, 2509 (results also disclosed in NEJM article).)

23. Claim 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."

The additional limitation recited in Claim 28 is the same as recited in Claim 26 and disclosed for the same reasons. (*Supra,* §VI.B.21; EX1003, ¶118.)

24. Claim 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%."

The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colon cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.b.) The claimed efficacy is inherent to the MSI-H Study Record's method of treatment. (EX1003, ¶¶119-120; *see supra,* §§VI.B.1, VI.B.2.b.)

The '287 patent itself, which provides the results of the MSI-H Study Record, admits the claimed efficacy is inherent in the MSI-H Study. (EX1001, Fig. 2 (probability of progression-free survival at 9 months for MSI-H colorectal

cancer patients is at least 60%); EX1003, ¶120; *see also* EX1031, 2515 (results also disclosed in NEJM article).)

25. Claim 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."

The additional limitation recited in Claim 30 is the same as recited in Claim 26 and disclosed for the same reasons. (*Supra*, §VI.B.21; EX1003, ¶121.)

26. Claim 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."

The additional limitation recited in Claim 31 is the same as recited in Claim 25 and disclosed for the same reasons. (*Supra*, §VI.B.20; EX1003, ¶122.)

27. Claim 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."

The additional limitation recited in Claim 32 is the same as recited in Claim 26 and disclosed for the same reasons. (*Supra*, §VI.B.21; EX1003, ¶123.)

28. Claim 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%."

The additional limitation recited in Claim 33 is the same as recited in Claim 27 and disclosed for the same reasons. (*Supra*, §VI.B.22; EX1003, ¶124.)

29. Claim 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."

The additional limitation recited in Claim 34 is the same as recited in Claim 26 and disclosed for the same reasons. (*Supra*, §VI.B.21; EX1003, ¶125.)

30. Claim 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%."

The additional limitation recited in Claim 35 is the same as recited in Claim 29 and disclosed for the same reasons. (*Supra*, §VI.B.24; EX1003, ¶126.)

31. Claim 36: "The method of claim 35, 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."

The additional limitation recited in Claim 36 is the same as recited in Claim 26 and disclosed for the same reasons. (*Supra*, §VI.B.21; EX1003, ¶127.)

C. Grounds 2-6: Claims 1-36 of the '287 Patent are Obvious Over the MSI-H Study Record in View of Various References

1. Law of Obviousness

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of evaluating underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and, if produced by Patent Owner, (4) so-called secondary considerations. *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966). Obviousness may be found, for example, where there was "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. Further, claiming the inherent results of an otherwise obvious method does not make the method itself nonobvious. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020); *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

2. Overview of the Additional Prior Art

a. Pernot

Pernot is a journal article titled *Colorectal Cancer and Immunity: What We Know and Perspectives* and was published in the World Journal of Gastroenterology on April 13, 2014. (EX1006, 3738, PDF p. 1; EX1003, ¶¶128-130.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Pernot discloses and discusses how "[a]ltogether, [colorectal cancers] associated with [microsatellite instability]" are "good candidates for immunotherapy." (EX1006, 3740-41; EX1003, ¶129.)

The Examiner did not consider Pernot.

b. Chapelle

Chapelle is a journal article titled *Clinical Relevance of Microsatellite Instability in Colorectal Cancer* and was published in the Journal of Clinical Oncology in 2010. (EX1007, 3380; EX1003, ¶137.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Chapelle discusses testing to determine whether a tumor is MSI-H using the tumor tissue of a patient. (EX1007, 3380, 3383.) Chapelle provides a test to measure MSI by immunohistochemistry, and discusses how, "for practical purposes, [MSI-H] is equivalent to the loss of staining by immunohistochemistry (IHC) of one of the

mismatch repair genes since both signify an abnormality in mismatch repair." (EX1007, 3380; EX1003, ¶138.)

Chapelle also discusses that a test for MSI-H that "was proposed as a standard test for MSI" and has "stood the test of time" comprises testing for "two mononucleotide repeats (BAT26, BAT25)." (EX1007, 3382; EX1003, ¶139.)

The Examiner did not consider Chapelle.

c. Steinert

Steinert is a journal article titled *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer* and was published on March 15, 2014. (EX1008, OF2; EX1003, ¶151.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Steinert is directed towards the testing of circulating colorectal cancer tumor cells to determine how they survive and escape the immune system, which includes determining whether a tumor is MSI-H. (EX1008, OF1.) Steinert further discusses determining whether a tumor is MSI-H using blood samples. (EX1008, OF6; EX1003, ¶152.)

The Examiner did not consider Steinert.

d. Benson

Benson is a journal article titled *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology* and was published in Journal of the National Comprehensive Cancer Network in July 2014. (EX1009; EX1003, ¶157.)

Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Benson discloses that, under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (EX1009, 1034; EX1003, ¶158.)

The Examiner did not consider Benson.

e. Hamid

Hamid is a journal article titled *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma* and was published in the New England Journal of Medicine on July 11, 2013. (EX1011; EX1003, ¶179.) Therefore, it is prior art under § 102(a) and not covered by any of the exceptions under § 102(b). Hamid reflects another name for pembrolizumab (*i.e.*, "lambrolizumab") and discusses that pembrolizumab was administered to cancer patients intravenously. (EX1011, 134; EX1003, ¶180; *see* EX1054, 3 ("MK-3475 (pembrolizumab formerly lambrolizumab).").

3. Ground 2: Claims 1-2, 4-8, 11-12, 14-18, 21-36 of the '287 Patent Are Obvious Over the MSI-H Study Record in View of Pernot

As discussed above, Claims 1-2, 4-8, 11-12, 14-18, 21-36 are anticipated by the MSI-H Study Record. Petitioner presents this alternative ground, however, to demonstrate that (1) even if Patent Owner (erroneously) argues that the MSI-H Study Record cannot anticipate because it did not affirmatively disclose an

improved outcome or that the POSA would not have expected such efficacy (EX1022, December 14, 2020 Notice of Allowance at 3; *see also supra,* §I), and/or (2) even if Patent Owner argues (erroneously) that the MSI-H Study Record does not teach "testing, or having tested, a biological sample obtained from a patient" as recited in Limitations [1.1], [1.2], [14.1], and [14.2], Claims 1-2, 4-8, 11-12, 14-18, 21-36, would at a minimum still be unpatentable for obviousness in view of Pernot and the knowledge of the POSA.

Improved Outcome/Efficacy

The POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study, thus observing the inherent properties of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the MSI-H Study Record. (EX1003, ¶¶131-135.)

Pernot is an article directed to treating colorectal cancer. (*See generally* EX1006.) The POSA would thus have had reason to consider the teachings of Pernot. (EX1003, ¶131.) The MSI-H Study Record is directed to a clinical study treating colorectal cancer patients whose cancers are MSI-H with pembrolizumab, an anti-PD-1 antibody (*supra*, §VI.B.2), and Pernot taught that those patients are "good candidates for immunotherapy," such as PD-1 inhibitors like pembrolizumab (EX1006, 3741; *see also* EX1029, ¶ 82; EX1054, 3; EX1011,

141.) As such, Pernot further motivated the POSA to obtain the results of the MSI-H Study Record. (EX1003, ¶131.)

Indeed, the state of the art would have further compelled the POSA to carry out the clinical study with a reasonable expectation of success. (EX1003, ¶132.) Physicians were treating patients having cancers that were known to have MSI-H subpopulations in the prior art, including colorectal cancer, with PD-1 inhibitors. (EX1005, 3 (Study Description), 3-4 (Conditions), 4 (Arms and Interventions), 5-6 (Eligibility); EX1016; EX1017; EX1003, ¶132.) The prior art also successfully reported treatment of a colorectal cancer patient having an MSI-H tumor with a PD-1 inhibitor. (EX1057, 463-64; EX1003, ¶132.)

Further, in addition to Pernot, several other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab. (EX1032, e27817-5; EX1033, 2968-69; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; *see* also EX1035, 1, 8; EX1036, 1186, EX1003, ¶133.)

Additionally, the 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 (EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, 3-5; EX1003, ¶¶42-43, 134) and (2) already infiltrated by many immune cells. (EX1034, 747; EX1037, 2;

EX1003, ¶¶42, 44, 134.) And the prior art taught that MSI-H tumors naturally displayed those characteristics. (EX1085, 673-74, 677; EX1087, 5002; EX1006, 3740-41; EX1033, 2967; EX1058, 231, 236-37; EX1036, 1186-87, 1193; EX1037, 2, 6; EX1035, 4; EX1041, 9208-09; EX1039, 243s; EX1003, ¶¶45, 134.)

Given the above, the 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. (EX1003, ¶135; *see also* MPEP 2107.03 ("[A]s a general rule . . . Office personnel should presume that [an] applicant has established that the subject matter of [a human clinical] trial is reasonably predictive of having the asserted therapeutic utility."); *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc*., No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023).) Further, because the POSA would have known that pembrolizumab was already approved for another oncology indication by November 2014, the POSA would have had a higher expectation of success. (EX1055, 1-2 (pembrolizumab approved for melanoma); EX1063, 334-335 (for oncology drugs, 55% of second indications were successful if the first indication was successful, but only 9% of first indications were successful.) Thus, the POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. *See Persion Pharms. LLC v. Alvogen Malta*

Operations Ltd., 945 F.3d 1184, 1190 (Fed. Cir. 2019) ("Inherency may supply a missing claim limitation in an obviousness analysis.").

Testing

Limitations [1.1], [1.2], [14.1], and [14.2] each require "determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient" or that "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." To the extent these limitations are interpreted to require testing the patient for such status, and to the extent Patent Owner argues (erroneously) that the MSI-H Study Record does not disclose such testing, it would have been obvious to test patients' tumors for MSI-H.

As discussed above, the POSA would have been motivated and expected success in carrying out the MSI-H Study Record's methods. (*Supra*, §VI.C.3; EX1003, ¶¶131-135.) The MSI-H Study Record discloses treating colorectal cancer patients having MSI-H colorectal cancer in one arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶136.) To the extent not explicitly required, this would have at least motivated the POSA to test patients for MSI-H because the POSA would need to place the patients into the proper study arm. (EX1003, ¶136.) Testing was the way in which it was possible to determine

if the patient had the MSI-H colorectal cancer required for placement in that arm. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); EX1003, ¶136.) The POSA would have expected success in carrying out such testing, because testing for MSI-H was routine in the art. (EX1003, ¶136; *see also infra* §VI.C.4.)

4. Ground 3: Claims 2, 9-10, 12, and 19-20 Are Obvious Over The MSI-H Study Record, or The MSI-H Study Record in View of Pernot, in View of Chapelle

a. Claim 2: "The method of claim 1, wherein the biological sample is tumor tissue from the patient."

As discussed in Section VI.B.2.c above, the MSI-H Study Record discloses determining that the patient's colorectal cancer is MSI-H. Testing tumor tissue from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶140-142.)

Chapelle is directed towards determining whether tumors are MSI-H. (EX1007, 3380, 3383; EX1003, ¶141.) As such, the POSA would have had reason to consider Chapelle, which is in the same field as the MSI-H Study Record and the '287 patent. (EX1003, ¶¶138, 141.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Chapelle to test tumor tissue from the patient, in order to test whether a tumor is MSI-H. (EX1003, ¶142.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's

colorectal cancer is MSI-H. (*Supra* §§VI.B, VI.C.3.) Chapelle teaches standard methods of testing whether a tumor was MSI-H using tumor tissue. (EX1007, 3380, 3383; EX1003, ¶¶138, 142.) The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not affect the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed such testing of tumor tissue well known, as the '287 patent admits. (EX1001, 6:25-26 ("Testing of MSI can be accomplished by any means known in the art"); 6:35-38 ("Samples that can be tested for MSI include tumor tissue as well as body fluids that contain nucleic acids shed from tumors. Testing for tumor DNA in such tissues and body fluids is well known."); EX1003, ¶142.)

b. Claim 9: "The method of claim 4, wherein the biological sample was tested by a method comprising immunohistochemistry testing, next generation sequencing or PCR testing."

A method comprising immunohistochemistry or polymerase chain reaction ("PCR") testing on the biological sample would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶143-144.)

As discussed above in Section VI.C.4.a, the POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶143.) Those methods include

testing with immunohistochemistry and PCR. (EX1007, 3380-84; EX1003, ¶143.) Moreover, as discussed above, the '287 Patent does not suggest the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. (*Supra*, §VI.C.4.a.)

c. Claim 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."

A method 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 would have been obvious to the POSA in view of the general knowledge in the art, such as Chapelle. (EX1003, ¶¶145-147.)

As discussed above in Section VI.C.4.a, the POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) with Chappelle's standard methods for testing for MSI-H and an expectation of success in doing so. (EX1003, ¶145.) Chapelle discusses that a test for MSI-H that "was proposed as a standard test for MSI" and has "stood the test of time" comprises testing for "two mononucleotide repeats (BAT26, BAT25)." (EX1007, 3382.) Moreover, as discussed above, the '287 Patent does not suggest the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors. (*Supra,* §VI.C.4.a).

d. Claim 12: "The method of claim 11, wherein the biological sample is tumor tissue from the patient."

Claim 12 is obvious over the combination for the same reasons Claim 2 is obvious, which are discussed in Section VI.C.4.a. (EX1003, ¶¶140-142, 148.)

e. Claim 19: "The method of claim 14, wherein the biological sample was tested by a method comprising immunohistochemistry testing, next generation sequencing or PCR testing."

Claim 19 is obvious over the combination for the same reasons Claim 9 is obvious, which are discussed in Section VI.C.4.b. (EX1003, ¶¶143-144, 149.)

f. Claim 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."

Claim 20 is obvious over the combination for the same reasons Claim 10 is obvious, which are discussed in Section VI.C.4.c. (EX1003, ¶¶145-147, 150.)

5. Ground 4: Claims 3 and 13 Are Obvious over The MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in View of Steinert

a. Claim 3: "The method of claim 1, wherein the biological sample is a body fluid from the patient."

As discussed in Section VI.B.2.c above, the MSI-H Study Record discloses determining that the patient's colorectal cancer is MSI-H. Testing body fluid from the patient would have been obvious to the POSA in view of the general knowledge in the art, such as Steinert. (EX1003, ¶153.)

Steinert is directed towards determining whether a tumor is MSI-H to understand how colorectal cancer evades the immune system. (EX1008; EX1003, ¶¶152, 154.) As such, the POSA would have had reason to consider Steinert, which is in the same field as the MSI-H Study Record and the '287 patent. (EX1003, ¶154.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Steinert. (EX1003, ¶155.) The MSI-H Study Record discloses, or at least suggests, determining that the patient's colorectal cancer is MSI-H. (*Supra*, §§VI.B, VI.C.3.) Steinert teaches methods of testing whether a tumor was MSI-H using body fluid. (EX1008, OF6; EX1003, ¶155.) The POSA also would have had a reasonable expectation of success given that the method of testing for MSI-H does not change the efficacy of the use of pembrolizumab for treating colorectal cancer patients having MSI-H tumors, and indeed such testing of tumor tissue was well known, as the '287 patent admits. (EX1001, 6:25-26 ("Testing of MSI can be accomplished by any means known in the art"), 6:35-38 ("Samples that can be tested for MSI include tumor tissue as well as body fluids that contain nucleic acids shed from tumors. Testing for tumor DNA in such tissues and body fluids is well known."); EX1003, ¶155.)

b. Claim 13: "The method of claim 11, wherein the biological sample is a body fluid from the patient."

Claim 13 is obvious over the combination for the same reasons Claim 3 is obvious, which are discussed in Section VI.C.5.a. (EX1003, ¶¶153-155, 156.)

6. Ground 5: Claims 6-7, 16-17, 26, 28, 30-36 Are Obvious Over The MSI-H Study Record, or The MSI-H Study Record in View of Pernot, in View of Benson

a. Claim 6: "The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer."

As discussed in Section VI.B.6 above, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal cancer patients having "tumors" and "measurable disease." (EX1005, 2 (Study Identification), 4 (Arms and Interventions, Study Design), 5-6 (Eligibility), EX1003, ¶159.) Treating colorectal cancer patients in the clinical study that the MSI-H Study Record discloses, wherein the colorectal cancer is metastatic colorectal cancer, would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶159-162.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Benson. (EX1003, ¶160.) For instance, both the MSI-H Study Record and Benson discuss treating patients with colorectal cancer. (EX1003, ¶160.) Further, Benson discusses that, under the standard of care, the patient population having tumors and measurable disease that

would take part in a clinical study are patients having metastatic and advanced disease. (EX1009, 1034; EX1003, ¶160.) As such, the POSA would have been motivated to carry out that the MSI-H Study Record's method for a clinical study, wherein the colorectal cancer was metastatic. (EX1003, ¶160.) Further, the MSI-H Study Record's disclosure referred to treating patients having metastatic and advanced disease. (*Supra,* §VI.B.6.)

The POSA would have had a reasonable expectation of success in carrying out the MSI-H Study Record's method, wherein the colorectal cancer was metastatic because that is the patient population that the POSA would use for such a method. (EX1009, 1034; EX1003, ¶161.)

As discussed above, the POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to complete the study, including determining the outcome of patients. (*Supra*, §VI.C.3.) As a result, that POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:29-31 (all patients had metastatic disease); EX1003, ¶106.)

b. Claim 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."

As discussed in Section VI.B.6 above, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating colorectal cancer patients having "tumors" and "measurable disease." (EX1005, 2 (Study Identification), 4 (Arms and Interventions, Study Design), 5-6 (Eligibility), EX1003, ¶163.) Even if the MSI-H Study Record does not explicitly teach that, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the patients' cancers had progressed after the patients received the different cancer therapy, this would have been obvious to the POSA in view of the general knowledge in the art, such as Benson. (EX1003, ¶¶163-167.)

Benson is directed to the ways in which clinical studies involving cancer are conducted. (EX1009, 1034; EX1003, ¶164.) As such, the POSA would have had reason to consider Benson, which is in the same field as the MSI-H Study Record and the '287 patent. (EX1003, ¶164.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Benson. (EX1003, ¶165.) For instance, both the MSI-H Study Record and Benson discuss treating patients having colorectal cancer. (EX1003, ¶165.) Further, Benson discusses that, under the standard of care, the patient population that had tumors and measurable disease

that would take part in a clinical study are patients who have had their cancer progress after two previous drug therapies. (EX1009, 1034; EX1003, ¶165.) As such, the POSA would have been motivated to carry out the MSI-H Study Record's method for a clinical study, wherein, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the patients' cancer had progressed after the patients received the different cancer therapy. (EX1003, ¶165.)

The POSA would have had a reasonable expectation of success in carrying out the MSI-H Study Record's method, wherein, prior to treatment with pembrolizumab, the patient had received a different cancer therapy, and the patient's cancer had progressed after the patient received the different cancer therapy because that is the patient population that the POSA would have expected to use for such a method. (EX1009, 1034; EX1003, ¶166.)

As discussed above, the POSA would have expected patients to respond to a sufficient degree that the POSA would have wanted to complete the study, including determining the outcome of patients. (*Supra*, §VI.C.3,) As a result, that POSA would have seen the inherent properties, discussed above in Sections VI.B.1-2, of treating MSI-H colorectal patients with pembrolizumab at the dosage that was applied in the clinical study. (*See also* EX1001, 8:29-31 (all patients had

treatment-refractory, progressive disease); 15:67-16:4 (all patients having MSI-H colorectal cancer had received two prior chemotherapy regiments); EX1003, ¶167.)

c. Claim 16: "The method of claim 11, wherein the colorectal cancer is metastatic colorectal cancer."

Claim 16 is obvious over the combination for the same reasons Claim 6 is obvious, which are discussed in Section VI.C.6.a. (EX1003, ¶¶159-162, 168.)

d. Claim 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 17 is obvious over the combination for the same reasons Claim 7 is obvious, which are discussed in Section VI.C.6.b. (EX1003, ¶¶163-167, 169.)

e. Claim 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."

The additional limitation that Claim 26 recites is essentially the same as Claim 6, but further requires a cancer therapy drug. As discussed in the analysis for Claim 6, under the standard of care in the art, the MSI-H Study Record requires patients having colorectal cancer to have received at least two prior cancer therapy drugs and had their cancers progress after receiving those drugs. (*Supra* §VI.C.6.a; EX1003, ¶¶159-162.) Thus, the additional method of Claim 26 is disclosed for the same reasons as Claim 6. (EX1003, ¶170.)

f. Claim 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."

Claim 28 is obvious over the combination for the same reasons Claim 26 is obvious, which is discussed in Section VI.C.6.e. (EX1003, ¶¶170-171.)

g. Claim 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."

Claim 30 is obvious over the combination for the same reasons Claim 26 is obvious, which are discussed in Section VI.C.6.e. (EX1003, ¶¶170, 172.)

h. Claim 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."

Claim 31 is obvious over the combination for the same reasons Claim 6 is obvious, which are discussed in Section VI.C.6.a. (EX1003, ¶¶159-162, 173.)

i. Claim 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."

Claim 32 is obvious over the combination for the same reasons Claim 6 and 26 are obvious, which are discussed in Sections VI.C.6.a and VI.C.6.e. (EX1003, ¶¶159-162, 170, 174.)

j. Claim 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%."

Claim 33 is obvious over the combination for the same reasons Claim 6 is obvious, which are discussed in Section VI.C.6.a. (EX1003, ¶¶159-162, 175.)

k. Claim 34: "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%."

Claim 34 is obvious over the combination for the same reasons Claims 6 and 26 are obvious, which are discussed in Sections VI.C.6.a and VI.C.6.e. (EX1003, ¶¶159-162, 170, 176.)

l. Claim 35: "The method of Claim 29, 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 35 is obvious over the combination for the same reasons Claim 6 is obvious, which are discussed in Section VI.C.6.a. (EX1003, ¶¶159-162, 177.)

m. Claim 36: "The method of claim 35, 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."

Claim 36 is obvious over the combination for the same reasons Claims 6 and 26 are obvious, which are discussed in Sections VI.C.6.a and VI.C.6.e. (EX1003, ¶¶159-162, 170, 178.)

7. Ground 6: Claims 8 and 18 Are Obvious over The MSI-H Study Record, or The MSI-H Study Record in view Pernot, in View of Hamid

a. Claim 8: "The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously."

As discussed in Section VI.B.2.b above, the MSI-H Study Record discloses a Phase II clinical study, the MSI-H Study, treating three cohorts of human patients with "[pembrolizumab] 10 mg/kg every 14 days." The method of Claim 1, wherein the pembrolizumab is administered to the patient intravenously would have been obvious to the POSA in view of the general knowledge in the art, such as Hamid. (EX1003, ¶¶181-185.)

Hamid is directed towards administering pembrolizumab. (EX1011.) As such, the POSA would have had reason to consider Hamid, which is in the same field as the MSI-H Study Record and the '287 patent. (EX1003, ¶182.) Hamid provides for intravenous administration of pembrolizumab. (EX1011, 134.).

Hamid refers to pembrolizumab by the name "lambrolizumab", and the POSA would have known that "lambrolizumab" was another name for pembrolizumab. (EX1011, 134; EX1054, 3; EX1003, ¶¶180, 182.)

The POSA would have had motivation to combine the MSI-H Study Record (whether alone or combined with Pernot) and Hamid. (EX1003, ¶183.) For instance, the MSI-H Study Record disclosed administering pembrolizumab. (*Supra* §§VI.B.1, VI.B.2.) Hamid demonstrated success in treating patients having advanced cancer with pembrolizumab. (EX1011, 134; EX1003, ¶¶180, 183.) Thus, the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) with Hamid. (EX1003, ¶183.)

At a minimum, administering pembrolizumab intravenously would have been obvious to try. Indeed, the prior art only discloses intravenous administration of pembrolizumab to treat cancer patients. (EX1011, 134; *see also* EX1055, 1; EX1003, ¶184.) *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1302 (Fed. Cir. 2010); *Procter & Gamble Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 996 (Fed. Cir. 2009).

The POSA would have had a reasonable expectation of success administering the pembrolizumab intravenously, given that administering pembrolizumab intravenously had been successful in the past. (EX1011, 134; EX1003, ¶185; *see also* EX1055, 1-3, 9, 15.)

b. Claim 18: "The method of claim 11, wherein the pembrolizumab is administered to the patient intravenously."

Claim 18 is obvious over the combination for the same reasons Claim 8 is obvious, which are discussed in Section VI.C.7.a. (EX1003, ¶¶180-186.)

VII. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. Discretionary Denial Under *Fintiv* Is Not Appropriate

The factors under *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) ("Fintiv") favor institution. As explained above, the merits of Merck's arguments are compelling and the evidence in support is substantial. (*Supra*, §§VI.B-C.) That "alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*." (EX1065, 4-5.) But in any event, the six *Fintiv* factors do not justify denying institution.

The first *Fintiv* factor favors institution. Merck represents that it will seek a stay of the patent infringement claims in district court upon institution, if not sooner. Given the district court case between Merck and JHU is in an early stage (*see* EX1066), there is a reasonable likelihood such a stay will be granted. Even without a stay, the remaining factors support institution.

The second *Fintiv* factor favors institution. Using the average time to trial in the relevant jurisdiction, the trial would not begin until mid-2026—over 2 years

from the filing of this petition. (EX1067.) As such, a final written decision would precede trial.

The third *Fintiv* factor also favors institution. There is still significant investment required in the district court litigation. Claim construction, discovery, pre-trial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice, all lie in the future. (*See* EX1066.).

The fourth *Fintiv* factor favors institution. There will be no overlap that warrants non-institution because Merck will seek a stay in district court.

The sixth *Fintiv* factor also favors institution. There is a significant public interest against "leaving bad patents enforceable." *Thryv, Inc. v. Click-To-Call Techs., LP*, 140 S. Ct. 1367, 1374 (2020). And as noted above, Merck's arguments are compelling. And with respect to the fifth *Fintiv* factor, although the Parties are the same as in district court, that is true in nearly every case, and under the "holistic view" of whether integrity of the system and efficiency is best served, institution is favored. *Samsung Elecs. Co. Ltd. v. Dynamics Inc.*, IPR2020-00505, Paper 11 at 15 (Aug. 12, 2020).

B. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

The MSI-H Study Record was considered during prosecution of a family member of the '287 patent that issued as U.S. Patent No. 10,934,356. (EX1022,

August 26, 2020 Rejection, 26-32.) Nonetheless, discretionary denial under 35 U.S.C. § 325(d) is inappropriate for at least three reasons.

First, the Examiner did not consider the MSI-H Study Record during prosecution of the '287 patent. As discussed above, the full version of the MSI-H Study Record was not even in front of the Examiner. (*Supra*, §III.B.)

Second, during prosecution of the application that issued as U.S. Patent No. 10,934,356, the Examiner failed to consider whether the MSI-H Study Record inherently anticipates under Federal Circuit precedent. Specifically, the Examiner recognized the MSI-H Study Record contemplated evaluating whether pembrolizumab results in an improved outcome for a patient whose cancer is MSI-H relative to a patient whose cancer is not MSI-H. (EX1022, December 14, 2020 Notice of Allowance, 3.) The Examiner, however, allowed the '356 patent over the MSI-H Study Record on the rationale that it did not affirmatively disclose that improved outcome and that the POSA would purportedly not have expected such efficacy. (*Id.*) That was incorrect as a matter of law, particularly given the evidence that the methods in the MSI-H Study Record were, in fact, shown to be effective, as explained above. (*See supra*, §§VI.B.1, VI.B.2.) Indeed, these patents mean that the POSA – who practiced the prior art MSI-H Study Record just as disclosed or using obvious techniques for carrying out that MSI-H Study Record disclosure – could be accused of infringement, which is antithetical to patent law.

Schering Corp., 339 F.3d at 1379 (discussing the patent law principle "that which would literally infringe if later in time anticipates if earlier.").

Third, the Examiner did not consider many of the other arguments and issues raised in this Petition, including the combinations of references raised in the obviousness grounds. (*Supra*, §§III.B, VI.B-C.)

VIII. MANDATORY NOTICES UNDER 37 CFR § 42.8

Real Parties-in-Interest: Pursuant to 37 C.F.R. § 42.8(b)(1), Merck identifies Merck Sharp & Dohme LLC and Merck & Co., Inc. as the real parties-in-interest.

Related Matters: Pursuant to 37 C.F.R. § 42.8(b)(2), Merck identifies the following related matter. The '393 patent is at issue in the following pending litigation: *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.). Additionally, petitions for U.S. Patent Nos. 11,591,393 (IPR2024-00240), 10,934,356 (IPR2024-00622), 11,325,974 (IPR2024-00623), 11,325,975 (IPR2024-00624), and 11,339,219 (IPR2024-00625), which are family members of the '287 patent, are pending.

Counsel and Service Information: Lead counsel is Naveen Modi (Reg. No. 46,224). Backup counsel are Bruce M. Wexler (Reg. No. 35,409), Preston K. Ratliff II (Reg. No. 43,034), Daniel Zeilberger (Reg. No. 65,349), David J. Feigenbaum (Reg. No. 78,139), and Mark Stewart (Reg. No. 43,936). Service information is Paul Hastings LLP, 2050 M Street NW, Washington, D.C. 20036,

Tel.: 202.551.1700, Fax: 202.551.1705, email:

(1) PH-MSD-JHU-IPR@paulhastings.com; and (2) mark.stewart@merck.com.

Petitioner consents to electronic service.

IX. CONCLUSION

Merck requests institution of IPR for Claims 1-36 of the '287 patent based on the grounds specified in this petition.

Respectfully submitted,

Dated: March 13, 2024

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,648,287 contains, as measured by the word-processing system used to prepare this paper, 13,786words. 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,

Dated: March 13, 2024

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on March 13, 2024, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,649,287 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on the USPTO's Patent Center:

FISH & RICHARDSON P.C. (JOHNS HOPKINS)
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022
UNITED STATES

A courtesy copy was also sent via electronic mail to the Patent Owner's litigation counsel at the following addresses:

Christina Brown- Marshall - brown-marshall@fr.com
Ahmed Davis - Davis@fr.com
Corrin Drakulich - Drakulich@fr.com
Dexter Whitley - whitley@fr.com
Karrie Wheatley - wheatley@fr.com
Madelyn McCormick - MMcCormick@fr.com
Frank Scherkenbach - Scherkenbach@fr.com

SERVICETOFRJHU/Merck22-3059@fr.com

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner