UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner

v.

The Johns Hopkins University,
Patent Owner

IPR2024-00623
Patent No. 11,325,974

REBUTTAL DECLARATION OF PAUL E. OBERSTEIN, M.D.

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I, Paul E. Oberstein, M.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Merck Sharp & Dohme LLC ("Merck") as an expert consultant in this proceeding before the United States Patent and Trademark Office regarding U.S. Patent No. 11,325,974 (the "'974 patent"), assigned to The Johns Hopkins University ("JHU").

2. I have been asked by Counsel to review declarations from Nils Lonberg, Ph.D. (EX2072), Richard Goldberg, M.D. (EX2090), Dung Le, M.D. (EX2130), and Andrew Pardoll, M.D., Ph.D. (EX1002, 264-463) made on behalf of JHU regarding certain patent claims of the '974 patent, and to provide this Rebuttal Declaration to respond to specific issues raised by them. I was also asked to review deposition transcripts from the depositions of Dr. Lonberg (EX1138; EX1245), Dr. Le (EX1139; EX1246), Dr. Goldberg (EX1136; EX1243), and Dr. Pardoll (EX1140).

3. As I explain below, based on the information that I reviewed and my knowledge applying the perspective of a person of ordinary skill in the art ("POSA"), all claims of the '974 patent are taught or suggested by the MSI-H

Study Record (EX1005) alone and in combination with various prior art references.[1]

II. SUMMARY OF MY OPINIONS

4. Based on my experience and expertise, and my review of the documents and materials set forth in this Declaration, I conclude the following points:

1. I disagree with Dr. Lonberg that the MSI-H Study Record does not provide the "received a prior cancer therapy drug" limitation of Claim 1, or the "progressed after the patient received the prior cancer therapy drug" limitation found in Claim 2.
2. I disagree with Dr. Lonberg that the MSI-H Study Record does not provide the "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab" limitation found in Claim 1, or the "wherein the outcome that is improved is an improved objective response rate

[1] Although I respond to certain opinions and statements of Drs. Lonberg, Goldberg, Le, and Pardoll, doing so does not mean that I agree with any of their declaration or deposition testimony that I do not specifically respond to in this Declaration.

(ORR), an improved progression-free survival (PFS), and improved overall survival (OS)" of Claim 3.

3. I disagree with Dr. Lonberg's opinion that the MSI-H Study Record does not disclose the "metastatic cancer" limitation found in Claim 5, or the "metastatic colorectal cancer" limitation found in Claims 6.

4. I agree with Dr. Neugut that every limitation of Claim 1, as well as the additional limitations of Claims 2-3 and 5-7, are found in the MSI-H Study Record.

5. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Pernot and Benson do not provide the "received a prior cancer therapy drug" limitation of Claim 1, or the "progressed after the patient received the prior cancer therapy drug" limitation found in Claim 2.

6. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Pernot and Benson do not provide the "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab" limitation found in Claim 1, or the "wherein the outcome that is improved is an

improved objective response rate (ORR), an improved progression-free survival (PFS), and improved overall survival (OS)" of Claim 3.

7. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Pernot and Benson do not provide the "metastatic cancer" limitation found in Claim 5, or the "metastatic colorectal cancer" limitation found in Claim 6.

8. I agree with Dr. Neugut that every limitation of Claim 1, as well as the additional limitations of Claims 2-3 and 5-7, are found in the MSI-H Study Record in combination with Pernot and Benson.

9. I disagree with Dr. Lonberg that the MSI-H Study Record in view of Brown, Duval, and Benson do not provide the "received a prior cancer therapy drug" limitation of Claim 1, or the "progressed after the patient received the prior cancer therapy drug" limitation found in Claim 2.

10. I disagree with Dr. Lonberg that the MSI-H Study Record in view of Brown, Duval, and Benson do not provide the "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab" limitation found in Claim 1, or the "wherein the outcome that is improved is an improved objective

response rate (ORR), an improved progression-free survival (PFS), and improved overall survival (OS)" of Claim 3.

11. I disagree with Dr. Lonberg that the MSI-H Study Record in view of Brown, Duval, and Benson do not provide the "metastatic cancer" limitation found in Claim 5, or the "metastatic colorectal cancer" limitation found in Claim 6.

12. I agree with Dr. Neugut that every limitation of Claim 1, as well as the additional limitations of Claims 2-3 and 5-7, are found in the MSI-H Study Record in view of Brown, Duval, and Benson.

13. I agree with Dr. Neugut that every limitation of Claims 1-3 and 5-7, as well as the additional limitations of Claim 4, are found in the MSI-H Study Record in view of Pernot and Benson, in view of Chapelle.

14. I agree with Dr. Neugut that every limitation of Claims 1-3 and 5-7, as well as the additional limitations of Claim 4, are found in the MSI-H Study Record in view of Brown, Duval, and Benson, further in view of Chapelle.

15. I agree with Dr. Neugut that every limitation of Claims 1-6, as well as the additional limitations of Claim 7, are found in the MSI-H Study Record in view of Pernot, Benson, Chapelle, and Hamid.

16. I agree with Dr. Neugut that every limitation of Claims 1-6, as well as the additional limitations of Claim 7, are found in the MSI-H Study Record in view of Brown, Duval, Benson, Chapelle, and Hamid.

III. MY QUALIFICATIONS

5. I am a board-certified medical oncologist focused in gastrointestinal ("GI") tract cancers, especially colorectal, pancreatic, and gastric cancers. I currently serve as the Service Chief in the GI Oncology practice within the Perlmutter Cancer Center at NYU Langone Health. In this role, I have primary oversight of 10 physicians and patient care teams in Manhattan, Brooklyn, and Long Island. Our GI Oncology group sees over 1500 new, unique patients per year and has over 350 patient encounters a week. On a weekly basis, I see 70-80 patients, and about one-third of my patients have colorectal cancer. In addition to seeing patients, I oversee weekly meetings with multidisciplinary teams, including medical oncology, radiation oncology, palliative care, social work, nutrition, and research to provide group oversight. Since starting at NYU Langone Health in 2018, my focus on multidisciplinary collaboration has led to rapid access referrals of patients in our clinics and increased clinical trial participation by over 100%.

6. I am also the co-Director of the Pancreas Disease Center at NYU Langone Health and an Associate Professor in the Department of Medicine at

NYU Langone Health. I was formerly Director of GI Oncology at the Perlmutter Cancer Center at NYU Langone Health and Assistant/Interim Director of the Pancreatic Cancer Center at the Perlmutter Cancer Center at NYU Langone Health.

7. Since my recruitment to NYU, I have served as the co-leader for the GI Disease Management Group at the Perlmutter Cancer Center at NYU Langone Health. In this role, I have primary responsibility for all clinical trials involving GI cancers at NYU Langone Health. In this role, I oversee a team consisting of regulatory and data specialists, clinical research coordinators and research nurses. I oversee a weekly meeting in which we review all prospective and active studies in this group, as well as review individual patients enrolled in clinical studies. We currently have a portfolio of over 40 clinical studies and in 2024 enrolled over 80 unique patients on interventional clinical studies.

8. I received my M.D. from The Ohio State University in 2006. After receiving my medical degree in 2006, I completed a residency in Internal Medicine at Temple University Hospital in Philadelphia, PA. I then pursued a fellowship in Hematology and Oncology for three years at Columbia University in New York, followed by a two-year fellowship in Patient Oriented Research at Columbia University.

9. I became board certified in Internal Medicine in 2009 and in Medical Oncology in 2014. Then, in 2015, I obtained my Masters in Biostatistics from

Columbia University, where I focused on issues related to clinical and translational investigation and the design and statistical analysis of clinical studies.

10. My research activities have focused on designing and conducting clinical trials using novel agents including immunotherapies for the treatment of colorectal, pancreatic, and other GI cancer patients. I am particularly interested in building collaborative teams to design and implement novel translational clinical trials in colorectal, pancreatic, and other GI cancers, and improving care delivery and multi-disciplinary collaborative care for GI cancer patients.

11. I have served as a principal investigator or site principal investigator on more than 20 multi-center clinical studies, including investigator-initiated studies and studies involving pembrolizumab and other PD-1-inhibitors. Currently, I am the site principal investigator on three active clinical studies involving metastatic colorectal cancer patients and two active clinical studies involving PD-1 inhibitors, including pembrolizumab. I have received more than $4.5 million in funding from various pharmaceutical companies related to my research activities.

12. I am also a member of the Protocol Review and Monitoring Committee ("PRMC") in the Perlmutter Cancer Center at NYU Langone Health. The PRMC is tasked with reviewing the detailed plans and protocols for proposed clinical studies to evaluate their scientific quality and validity, among other things.

If the PRMC approves the proposed clinical study, the clinical study protocol is sent to the Institutional Review Board ("IRB") for review. The IRB assesses the safety, efficacy, benefits, adverse reactions, and outcomes of proposed clinical studies with the primary goal of ensuring patient safety. There is a scientific review committee at every healthcare facility that conducts clinical research, and typically, the scientific review committee reviews all proposed clinical studies before they go to the facility's IRB for approval.

13. In addition, I have also been involved in developing the curriculum for the Graduate Medical Education Program at NYU Langone Health. For example, in 2019, I received the Cancer Clinical Investigator Team Leadership Award from the National Cancer Institute, which provided funding to design and implement a lecture series. The lecture series I designed and implemented focused on clinical and translational research covering the topics of trial design, basic biostatistics, regulatory considerations, and practical applications of clinical research.

14. Additionally, in 2019, I developed a new didactic course for the fellowship program to provide a comprehensive course in all aspects of GI cancers. In developing this course, I recruited faculty members for participation, designed the curriculum, and led lectures covering topics related to GI cancers, including pathology, genetics, and translational research. I have also led various peer-

lectures and talks, including on colorectal cancer immunology and topics relating to pancreatic cancer. Additionally, throughout my career I have dedicated a portion of my time to mentoring and advising predoctoral and postdoctoral students and oncology faculty.

15. Before joining NYU Langone Health in 2018, I held appointments as an Assistant Attending Physician at New York Presbyterian Hospital and Assistant Professor in the Department of Medicine at Columbia University. From 2014 to 2018 I also served as a member on the Protocol Review and Monitoring Committee for the Herbert Irving Comprehensive Cancer Center at Columbia University. Similar to the PRMC that I serve on currently, the Protocol Review and Monitoring Committee at Columbia University is tasked with reviewing proposed clinical studies for their scientific validity and merit before the clinical study protocol is reviewed by the IRB.

16. I have published more than 30 peer-reviewed papers and have presented more than 25 oral and poster presentations regarding GI cancers, including the use of checkpoint inhibitors to treat GI cancers. I have also sat on several advisory boards and served on the editorial board of several journals in the past, including the Journal of Clinical Oncology, JAMA, and Clinical Cancer Research.

17. My experience and qualifications are further detailed in my curriculum vitae, which I understand has been labeled as Exhibit 1141. I am being compensated at $800/hour, which is my normal consulting rate, for the time I spend on this matter. My compensation is not dependent on any of my findings, the presentation of my findings, or the outcome of this proceeding.

IV. MATERIALS CONSIDERED

18. My opinions contained in this Declaration are based on my professional experience and knowledge, as well as the documents that I reviewed in connection with my analysis. Specifically, in forming my opinions expressed in this Declaration, I reviewed the following documents and materials:

- The declaration of Dr. Alfred I. Neugut, dated March 4, 2024 (EX1003),
- The declaration of Dr. Nils Lonberg, dated January 11, 2025 (EX2072),
- The declaration of Dr. Richard Goldberg, dated January 11, 2025 (EX2090),
- The declaration of Dr. Dung Le, dated January 12, 2025 (EX2130),
- The deposition transcripts of Dr. Lonberg (EX1138), Dr. Goldberg (EX1136), Dr. Le (EX1139), and Dr. Pardoll (EX1140) from the

IPR2024-00622 proceeding involving U.S. Patent No. 11,591,393 (the '393 proceeding),

- The deposition transcripts of Dr. Lonberg (EX1245), Dr. Goldberg (EX1243), and Dr. Le (EX1246) from this proceeding,
- [redacted]
- The '974 patent (EX1001),
- The MSI-H Study Record (EX1005),
- Pernot et al, *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) World J. Gastroenterology 3738 (April 2014) ("Pernot") (EX1006),
- Brown et al, *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) Genome Research 743 (May 2014) ("Brown") (EX1034)
- Duval et al, *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas*, 101(14) Proceedings of the National Academy of Sciences 5002 (2004) ("Duval") (EX1087)

- Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010) ("Chapelle") (EX1007),
- Benson et al, *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. Nat'l Comprehensive Cancer Network 1028 (July 2014) ("Benson") (EX1009),
- Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New England J. Medicine 134 (July 2013) ("Hamid") (EX1011),
- Le et al, *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, 372(26) New Eng. J. Medicine 2509 (June 25, 2015) ("NEJM 2015") (EX1031),
- The materials in Appendix A (Table of Exhibits).

19. My opinions are also based on my appreciation of how a POSA would have understood the claims at issue and the specification of the '974 patent as of July 10, 2015, which I was asked by Counsel to assume was the relevant time period for my analysis. My opinions reflect agreement with Dr. Neugut as to how one of ordinary skill in the art would have understood the '974 patent, the MSI-H Study Record, Pernot, Brown, Duval, Chapelle, Benson, Hamid, and the state of the art as of July 10, 2015.

V. CLAIM CONSTRUCTION

20. I have been informed by Counsel that terms used in patent claims are typically given their ordinary and customary meaning in their technological field. When claim terms have no standard meaning in the art, I understand that the terms must be interpreted in light of the patent claims, the patent's disclosure (referred to as the "specification"), and the "prosecution history" (the record of the back-and-forth between the patent applicant and the United States Patent and Trademark Office during the process of obtaining allowance of the patent's claims). I have applied this understanding in my analysis below. No reasonable interpretation of the claim terms, however, would alter my conclusions.

VI. PERSON OF ORDINARY LEVEL OF SKILL

21. I have been informed by Counsel that a POSA is a hypothetical person that is presumed to have knowledge of all pertinent prior art as of July 10, 2015 (the "Alleged Invention Date" for the patent at issue).

22. I understand a POSA for purposes of my analysis of the '974 patent is an oncologist or a medical professional in a related field with at least five years of experience with treating cancer patients. The POSA would also have experience in, or access to a person with knowledge of, clinical studies for therapeutics and how they work, as well as experience with, or access to, a pathologist with

comparable experience. My opinions discussed in this Declaration would not be changed due to a modestly lesser or greater level of experience.

23. Further, I understand JHU argues a POSA would have a M.D. or graduate-level degree "in the fields of immunology, genetics, or a related field and at least five years of experience (i) conducting immunology research relating to oncology, (ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields," and that Dr. Neugut does not meet JHU's definition for a POSA. (POR, 5-6; EX2072, ¶¶31-32.) I disagree with JHU's definition for a POSA given that the '974 patent relates to cancer therapy and provides a method of treating a cancer patient. (EX1001, 1:25-26, 3:35-36.) As I discuss in further detail below, Dr. Lonberg agrees that the '974 patent provides cancer treatment methods, not methods for conducting genetic or immunology research. (EX1245, 13:20-14:1, 14:8-10, 15:16-16:11.) Dr. Lonberg also agrees that a clinical oncologist would not need specialized experience researching or developing novel cancer treatments to understand the steps of the claimed methods of treatment. (EX1245, 15:21-16:3.)

24. All of my opinions expressed in this Declaration are from this perspective of a POSA as of the Alleged Invention Date for the '974 patent, *i.e.*, July 10, 2015. During this period, I possessed at least the qualifications of a person of ordinary level of skill, as I defined above. Even if JHU's definition for a

POSA is adopted, my opinions expressed in this Declaration would still apply and would not change.

VII. THE CLAIMS OF THE '974 PATENT ARE TAUGHT OR SUGGESTED BY THE PRIOR ART

A. Point 1: Dr. Lonberg's Deposition Testimony Undermines JHU's Arguments

25. I have reviewed the deposition transcript of Dr. Lonberg's December 20, 2024 deposition (EX1138), as well as the deposition transcript of Dr. Lonberg's April 17, 2025 deposition (EX1245), and note the following points from his testimony that I agree with:

- As of July 10, 2015, a POSA would know that to determine MSI-H status you could test tumor tissue or bodily fluid. (EX1138, 47:19-48:5.)
- The treatment method in the MSI-H Study Record is not limited to only patients who have metastatic cancer. (EX1245, 58:3-10, 50:7-10, 51:4-7.)
- The MSI-H Study Record does not tell the reader to exclude from the study a patient that has metastatic cancer. (EX1245, 58:3-10, 50:7-10, 51:4-7.)
- Dr. Neugut's understanding of the type of patients that would be treated in the study described by the MSI-H Study Record (i.e., metastatic cancer

patients) is consistent with what actually occurred in the underlying clinical study. (EX1245, 54:20-56:10, 64:6-14, 65:18-21, 66:16-71:14.)

- The rationale for conducting the study described by the MSI-H Study Record would have included (1) that pembrolizumab had shown activity in multiple tumor types, including melanoma and non-small cell lung cancer, (2) nivolumab had shown activity in melanoma and non-small cell lung cancer, and (3) the complete response of the MSI-H colorectal cancer patient treated with nivolumab. (EX1245, 79:5-80:16.)
- Oncologists would not need specialized experience researching or developing new treatments for cancer to understand the steps of the methods claimed in the '974 patent (EX1245, 13:20-14:1, 14:8-10, 15:16-16:11.)
- The POSA would read the art logically, rationally, and with ordinary creativity. (EX1138, 83:4-85:10.)

26. I also agree with Dr. Lonberg's deposition testimony regarding the many teachings in the relevant field concerning immunotherapy and treating cancers, including MSI-H cancers. These publications include Champiat, Gatalica, Llosa, Benson, and Hamid. (*See* EX1138, 153:4-156:22, 165:16-166:12, 171:13-172:19, 177:21-183:16, 184:2-12, 185:9-22, 190:10-191:9, 195:21-200:14, 201:20-202:10, 203:13-211:10; *see also id.* 93:15-19, 95:8-13, 144:5-11.)

27. Ultimately, while Dr. Lonberg and I have points of agreement, I disagree with Dr. Lonberg's analysis in several ways. As an initial matter, Dr. Lonberg incorrectly claims that a POSA would read the prior art literature with a "skeptical lens" or disbelief towards what is disclosed, (EX1138, 84:14-16, 85:20-21), even where none of the literature itself has expressed any such skepticism or teaching away. I do not agree that a POSA would independently inject skepticism or disbelief into analysis of the prior art literature, as I understand a POSA is presumed to have knowledge of all pertinent prior art and to read it logically and rationally, rather than manufacturing motivations or holding any specific emotional biases and beliefs that are not explicitly expressed by the art as a whole.

28. Further, I disagree with those aspects of Dr. Lonberg's deposition testimony where he expressed opinions consistent with those in his declaration for the same reasons as discussed herein.

B. Point 2: Dr. Goldberg's Deposition Testimony Undermines JHU's Arguments

29. I have reviewed the deposition transcript of Dr. Goldberg's December 13, 2024 deposition (EX1136), as well as the deposition transcript of Dr. Goldberg's April 15, 2025 deposition (EX1243), and note the following points from his testimony that I agree with:

- As of July 10, 2015, a POSA would know that immunotherapy could work in colon cancer. (EX1136, 86:15-87:3.)

- As of July 10, 2015, a POSA would know that PD-1 inhibitors could be used to treat MSI-H cancer. (EX1136, 62:2-16; 108:21-110:22.)
- As of July 10, 2015, a POSA would know that MSI-H was a relevant factor in considering potential treatment to explore with clinical trials. (EX1136, 103:18-105:15.)
- Part of the rationale for why a scientist or physician would conduct the study described by the MSI-H Study Record was the known complete response of the MSI-H colorectal cancer patient treated with nivolumab and that nivolumab and pembrolizumab had shown activity as PD-1 inhibitors in other tumor types. (EX1243, 54:17-55:1, 56:7, 62:16-63:8.)
- Before July 10, 2015, a POSA would know that BMS was conducting its own study to treat MSI-H cancer patients with its PD-1 inhibitor. (EX1243, 61:5-13.) The POSA, while knowing that the literature suggested that MSI-H patients had a higher likelihood of response to PD-1 inhibitors, would still have included an MSS cohort in the construction of a protocol testing the efficacy of a PD-1 inhibitor in MSI-H and MSS CRC. (EX1136, 169:5-176:8.)

30. I also agree with Dr. Goldberg's deposition testimony regarding the teachings of Topalian (EX1013). (*See* EX1136, 81:1-20, 82:9-13, 97:15-98:7, 106:6-111:8, 162:9-11, 176:6-8, 189:10-16, 190:10-13.)

31. Further, like Dr. Goldberg, I also frequently ordered MSI testing on my patients prior to July 10, 2015. (EX1243, 48:11-12, 48:22-49:1.)

32. While Dr. Goldberg and I have points of agreement, I disagree with Dr. Goldberg's analysis in several ways. Most notably, Dr. Goldberg's opinion that, although the MSI-H Study protocol expressly required MSI testing pre-study, it did not "specify that the results needed to be known," (EX1136, 121:4-127:3), and therefore, an oncologist would not necessarily look at those results prior to enrolling patients onto the clinical trial. (EX1136, 127:1-129:20.) This is plainly illogical.

33. Further, I disagree with those aspects of Dr. Goldberg's deposition testimony where he expressed opinions consistent with those in his declaration for the same reasons as discussed herein.

C. Point 3: Testimony From the Named Inventors Reveals A Lack of Familiarity With JHU's Earlier Representations to the FDA and Undermines JHU's Arguments

34. I have reviewed the IND submissions [redacted] (EX1116), [redacted] (EX1118), and [redacted] (EX1119). I have also reviewed the transcripts of the January 9, 2025 and April 18, 2025 depositions of Dr. Le (EX1139; EX1246), and January 24, 2025 deposition of Dr. Pardoll (EX1140).

35. As an initial matter, the FDA requires all sponsors of clinical studies involving investigational new drugs that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act to submit an IND to the FDA that includes, among other things, the protocol for the clinical study. JHU, as the study sponsor for the MSI-H Study with Merck, made IND submissions to the FDA beginning on [redacted].

36. Because Dr. Lonberg takes positions regarding the prior art that are not consistent with the prior art's teachings or statements that JHU previously made to the FDA regarding the state of the art, and in view of testimony from Dr. Le and Dr. Pardoll, I believe it is helpful to provide an overview of JHU's IND submissions, as well as my observations regarding testimony from Dr. Le and Dr. Pardoll, as context for points I discuss later in my declaration.

1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2. [redacted]

[redacted]

[redacted]

3. [redacted]

[redacted]

[redacted]

4. Dr. Le's Deposition Testimony

51. I note the following observations:

- Dr. Le did not seem to recall many aspects of the MSI-H Study as she testified that she could not recall when Merck provided funding (EX1139, 280:9-281:19), could not recall when they began recruiting patients (EX1139, 105:3-112:9), could not recall when patients started being treated (*e.g.*, EX1139 at 114:21-118:18), could not recall when they started observing responses in the patients treated (EX1139, 290:2-292:16), and could not recall any Merck personnel involved in the study (EX1139, 265:17-276:2.)

- Dr. Le did not seem familiar with patents on which she is a named inventor. (*See, e.g.*, EX1139, 11:3-17:10, 234:2-238:5; EX1246, 17:10-21:2, 38:9-20.)
- Dr. Le did not seem familiar with her declaration. (*See, e.g.*, EX1139, 33:14-38:14, 39:5-42:4, 52:15-53:7, 114:1-125:14, 129:14-136:3, 204:15-205:8.)
- Dr. Le did not seem familiar with [redacted] submission for the MSI-H Study. (*See, e.g.*, EX1139, 239:22-246:3.)

52. Dr. Le did, however, testify that she did not have any recollection that the FDA or JHU's IRB ever challenged the rationale of the MSI-H Study. (*See, e.g.*, EX1139, 258:16-259:15, 264:14-265:3.) Further, Dr. Le confirmed that she and her team ***did not tell the FDA***, based on publications by Topalian (EX1013) and Brahmer (EX2024), that the studies reported were "resoundingly unsuccessful" or should lead to the belief that "colorectal cancer patients should not be understood to be candidates" for PD-1 therapy as JHU suggests in its POR. (EX1139, 249:7-258:2; *see also* POR, 12; EX2130, ¶9.)

5. Dr. Pardoll's Deposition Testimony

53. I note the following observations:

- Dr. Pardoll testified that he was not involved in the MSI-H Study and his "knowledge is really minimal." (*See, e.g.*, EX1140, 25:16-17, 28:1, 48:3-16, 102:19-103:5.)
- Dr. Pardoll testified that he did not know one way or the other whether Merck personnel were involved in the conduct of the MSI-H Study. (*See, e.g.*, EX1140, 100:9-101:6, 102:19-103:5, 106:2-107:8, 124:9-125:3.)
- Dr. Pardoll testified that he did not believe Merck provided any financial funding for the MSI-H Study, but he also did not see any documents regarding financial funding. (*See, e.g.*, EX1140, 75:12-19, 81:9-15.)
- Dr. Pardoll testified that he did not know whether Merck personnel were involved with drafting the clinical study protocol. (*See, e.g.*, EX1140, 102:19-103:5.)
- Dr. Pardoll testified that the version of the ClinicalTrials.gov study record that he cited and submitted with his declaration was different from the MSI-H Study Record (EX1005) here. (*See, e.g.*, EX1140, 28:4-30:19, 35:18-37:3.)
- Dr. Pardoll testified that he did not remember what date he was referring to in his declaration when he wrote "at the time of the invention." (EX1140, 54:15-57:6.)

54. Ultimately, Dr. Pardoll testified that he disagreed with the rationale and anticipated outcome that JHU [redacted] (*See* EX1140, 57:7-14, 61:17-65:3.) I disagree with Dr. Pardoll.

D. Point 4: Each and Every Limitation of Claims 1-3 and 5-7 of the '974 Patent Is Found in the MSI-H Study Record

55. Dr. Lonberg responds to Dr. Neugut's opinion that the MSI-H Study Record discloses each and every limitation of Claims 1-3 and 5-7, by asserting that the MSI-H Study Record does not disclose certain claim limitations of Claims 1-3 and 5-7. (EX2072, ¶¶95-110.) I, however, disagree because I agree with Dr. Neugut's opinions that every limitation of Claims 1-3 and 5-7 are found in the MSI-H Study Record. (EX1003, ¶¶51-90.)

56. I note that Dr. Lonberg does not include any testimony in Section VIII of his declaration regarding the additional limitations of Independent Claim 1, or the additional limitations of Dependent Claims 2-3 and 5-7. Therefore, my analysis in the section below reflects only the claim limitations addressed by Dr. Lonberg.

1. Claim 1

57. Claim 1 recites a method of treatment involving selecting a patient who has MSI-H cancer and the patient having received a prior cancer therapy drug, administering an effective amount of pembrolizumab to the patient, wherein the patient exhibits an outcome that is improved "as compared to a corresponding

outcome that would be observed in a reference patient." (EX1001, Claim 1.) Dr. Neugut determined that a POSA would have found every limitation of Claim 1, including the preamble, Limitation [1.1], Limitation [1.2], Limitation [1.3], and Limitation [1.4], in the MSI-H Study Record. (EX1003, ¶¶59-80.) Dr. Lonberg responds arguing that the MSI-H Study Record does not disclose "the patient having received a prior cancer therapy drug" (*i.e.*, Limitation [1.2]), and does not disclose the claimed clinical results (*i.e.*, Limitation [1.4]). (EX2072, ¶¶96-98.) I disagree for the reasons I explain below.

a. [1.2]: "the patient having received a prior cancer therapy drug"

58. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶67-72; EX2072, ¶96.) In that section of Dr. Neugut's declaration, he explains that in the context of the MSI-H Study Record, a POSA would have understood that a patient would have received prior cancer therapy and had the cancer progress after that therapy. (EX1003, ¶¶67-72.) Therefore, this claim limitation is met. (EX1003, ¶¶67-72.)

59. Dr. Lonberg alleges that the MSI-H Study Record does not disclose that the patient would have received a prior drug therapy and had their cancer progress after that therapy based solely on his mischaracterization of Dr. Neugut's opinions regarding "measurable" disease. (EX2072, ¶96.) In that section of Dr.

Neugut's declaration, however, he explains that the MSI-H Study Record's Eligibility Criteria requires that patients have "measurable disease," and Study Identification section mentions "tumors," and these disclosures in the ***context of the MSI-H Study Record*** tell a POSA that the cancer patient being treated would have received prior drug therapies and had their cancer progress after those therapies. (*See* EX1003, ¶¶67-72; *see also* EX1005, 2 (Study Identification), 5-6 (Eligibility Criteria).)

60. At the time of the study, there were two standard chemotherapy regimens (FOLFOX and FOLFIRI) for colorectal cancer. It is reasonable to assume that patients would typically receive such standard of care before trying a novel therapeutic agent. This would meet and exceed the '974 patent requirement of at least one prior therapy. I agree with Dr. Neugut that in the context of the MSI-H Study Record, where the underlying phase 2 clinical study involves a new immunotherapy drug, that was not yet FDA-approved, and which was known to elicit a strong immune response in patients, a POSA would understand that a patient with metastatic and advanced cancer that would participate in such a study would have received prior drug therapies and had their cancer progress after such therapies. (EX1003, ¶¶67-72; *see also* EX1020, PDF p. 25; EX1009, 1034; EX1047, 4-7.) Accordingly, if the intent was to only treat "first line" patients, who had not been previously treated, a POSA would therefore expect an explicit carve

out excluding all patients who had been previously treated. There is no such carve out in the MSI-H Study Record. In fact, during his deposition, even Dr. Lonberg himself, explained that his opinion is that the treatment method in the MSR is not limited or does not require ***only*** patients who have received at least one prior cancer therapy and had their cancer progress, and confirmed that he is not asserting that the MSI-H Study Record excludes or otherwise suggests that such patients are ineligible. (EX1245, 57:5-58:2; *id.*, 49:2-1.)

61. I also agree with Dr. Neugut that because the MSI-H Study Record's Eligibility Criteria specifically excludes only "[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, a POSA would have understood and expected a patient to have instead undergone other prior and/or different cancer therapies before enrollment. (EX1003, ¶70; EX1005, 5-6 (Eligibility Criteria).)

62. I understand that an update to the MSI-H Study Record was posted in January of 2016. This update included a few changes, to both inclusion and exclusion criteria for any new patients recruited after that time, and among them, specified "[p]atients with colon cancer must have received at least two prior cancer therapy regiments," and "[p]atients with other cancer types must have received at least one prior cancer therapy." (EX2166, 7-8.) I understand that Dr. Lonberg

opines that "it would have been superfluous to later amend the ClinicalTrials.gov record to add a requirement that was allegedly already disclosed in the MSI-H Study Record." (EX2072, ¶96.) I disagree.

63. Dr. Lonberg's conclusions rely on unsupported speculation about the reasons behind any of the revisions specified in 2016 for new patients being recruited at that time, in particular as the 2016 revision occurred after the initial 41 participants included in the New England Journal of Medicine article and in the patent specification, were already treated and results discussed. (EX1031, 4-5.) Further, any changes to the inclusion or exclusion criteria, or to any part of the MSI-H Study Record more generally, in 2016, would not be relevant to a POSA's understanding of the scope and purpose of the MSI-H Study Record as initially filed. As discussed, a POSA would understand that the MSI-H Study Record discloses—consistent with the standard of care—treating at least a patient who received a prior cancer therapy drug or had their tumor progress following treatment with a prior cancer therapy drug. This is consistent with the reality that the patients enrolled and treated prior to January 2016 did, in fact, meet those requirements.[2] (*See* EX1031, 4-5 (confirming that the MSI-H Study Record

[2] I also understand that JHU similarly cites to a 2014 ASCO poster. This

enrolled patients with CRC that had at least two prior cancer therapies and non-CRC patients having at least one); EX1001, 15:60-67.)

64. Therefore, I agree with Dr. Neugut that a POSA would have concluded that this limitation was found in the MSI-H Study Record.

b. [1.4]: "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab"

65. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶78-80; EX2072, ¶¶97-98.) In that section of Dr. Neugut's declaration, he explains that because the Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H cancer, including colorectal

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reference, likewise, has no bearing on how a POSA would have understood the MSI-H Study Record at the Alleged Invention Date, and also serves to confirm that the actually treated patients were consistent with a POSA's understanding of the disclosures of the MSI-H Study Record. These documents also serve a very different purpose, with the MSI-H Study Record being used, in part, as a way to recruit patients, while the 2014 ASCO poster publicizes and explain the details of the study that had already been completed to a wider audience. (EX1080.)

cancer, with 10 mg/kg of pembrolizumab every 14 days, and that method of treatment was shown in the underlying clinical trial to be naturally effective in promoting progression-free survival in multiple human subjects whose cancer, including colorectal cancer, is MSI-H, this claim limitation is met. (EX1003, ¶¶78-80; *see also id.* ¶41; EX1005, 4 (Arms and Interventions).)

66. Dr. Lonberg alleges that this limitation requires "actually obtaining the results of the study disclosed in the MSI-H Study Record" and that it would not have been possible to disclose this limitation without conducting the study described in the MSI-H Study Record. (EX2072, ¶¶97-98.)

67. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, the MSI-H Study Record provides in the Arms and Interventions section that MSI-H cancer patients, including one Arm with MSI-H colorectal cancer patients and one Arm with MSI-H non-CRC patients, will be treated with 10 mg/kg pembrolizumab every 14 days. (EX1003, ¶35; *see also id.* ¶¶51; EX1005 at 4, (Arms and Interventions).) Indeed, 10 mg/kg pembrolizumab every 14 days was naturally effective in promoting progression-free survival in MSI-H cancer patients, including colorectal cancer patients, treated in the study described by the MSI-H Study Record. (EX1003, ¶¶73-80; *see also id.* ¶41; EX1001, 4:19-32, 16:3-8, 16:60-17:3, 20:20-21:15,, Fig. 2, Fig. 11.)

68. The MSI-H Study Record also has a Secondary Outcomes section

discussing that one outcome is "[d]oes MSI as a marker predict treatment response," and a Primary Outcomes section that discloses outcomes include "[i]mmune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)" and "[o]bjective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)." (EX1005, 4-5 (Outcome Measures; *see also id.*, 3 (Study Description), 4 (Arms and Interventions), 5 (Inclusion Criteria).) A POSA would understand these passages from the MSI-H Study Record further disclose determining outcomes in patients with MSI-H cancer in comparison to patients with non-MSI-H cancer.

69. Therefore, I agree with Dr. Neugut that a POSA would have concluded that this limitation was found in the MSI-H Study Record.

2. Claim 2: "progressed after the patient received the prior cancer therapy drug"

70. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 2 for the same reason as he argues for Claim 1 limitation [1.2]. (EX2072, ¶96.) Dr. Neugut explains that the analysis for Claim 2 is the same as for Claim 1 limitation [1.2], because the additional limitation recited in Claim 2 is the same as recited in Claim 1 limitation [1.2]. (EX1003, ¶¶ 81-82.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 2 was

found in the MSI-H Study Record for the same reason as Claim 1 limitation [1.2]. (EX1003, ¶¶81-82; *see also id.* ¶¶67-72.)

3. Claim 3: "wherein the outcome that is improved is an improved objective response rate (ORR), and improved progression-free survival (PFS), or an improved overall survival (OS)."

71. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 3 for the same reason as he argues for Claim 1 limitation [1.4]. (EX2072, ¶¶97-98.) Dr. Neugut explains that the analysis for Claim 3 is the same as for Claim 1 limitation [1.4], because the additional limitation recited in Claim 3 is the same as recited in Claim 1 limitation [1.4]. (EX1003, ¶¶83-84.) In particular, as Dr. Neugut explains, improved objective response rate, progression-free survival, and overall survival, are the natural results of the methods of the MSI-H Study Record. (EX1003, ¶¶40-41; EX1001, 4:19-32 (showing the "[c]linical benefit to pembrolizumab according to MMR status" and discussing figure 2), Figures 2 (showing overall survival for the three cohorts), 11 (showing objective response rates and progression free survival for the three cohorts), 16:3-8 (discussing objective response rate and progression free survival), 16:61-17:3 (discussing overall survival and progression-free survival), 19:55-21:15).)

72. I agree with Dr. Neugut, and thus, a POSA would have concluded that this limitation of Claim 3 was found in the MSI-H Study Record for the same

reason as Claim 1 limitation [1.4]. (EX1003, ¶¶83-84].)

4. Claim 5: "The method of claim 1, wherein the cancer is a metastatic cancer."

73. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶85-86, 86; EX2072, ¶¶99-103.) In that section of Dr. Neugut's declaration, he explains that in the context of the MSI-H Study Record, a POSA would have understood that patients would have metastatic and advanced cancer, and therefore, this claim limitation is met. (EX1003, ¶¶85-86.)

74. Dr. Lonberg alleges that the MSI-H Study Record does not disclose treating metastatic colorectal cancer patients based solely on his mischaracterization of Dr. Neugut's opinions regarding "measurable" disease. (EX2072, ¶¶99-103.) Specifically, Dr. Lonberg states that "the words 'measurable' and 'metastatic' are not equivalent," and therefore, "to the extent Dr. Neugut relies on the MSI-H Study's use of 'measurable disease' as disclosing 'metastatic cancer,' such conflation is incorrect." (EX2072, ¶99.) Dr. Neugut, however, does not state in his declaration that those words ***are*** equivalent. (EX1003, ¶¶68, 85-86.) Instead, in that section of Dr. Neugut's declaration, he explains that the MSI-H Study Record's Eligibility Criteria requires that patients have "measurable disease," and Study Identification section mentions "tumors," and these disclosures in the ***context of the MSI-H Study Record*** tell a POSA that

the colorectal cancer patients being treated have metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. (*See* EX1003, ¶¶68, 85-86; *see also* EX1005, 5-6 (Eligibility), 2 (Study Identification).)

75. I agree with Dr. Neugut that in the context of the MSI-H Study Record, where the underlying phase 2 clinical study involves a new immunotherapy drug, a POSA would understand that the MSI-H Study Record requires that the cancer patients being treated have metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. (EX1003, ¶¶68, 85-86; *see also* EX1020, PDF p. 25; EX1078,1278.) Otherwise, if a cancer patient had cancer that is resectable for the purposes of a cure, then a POSA would expect that a physician would excise the tumor(s) for cure. (EX1003, ¶¶68, 85-86; *see also* EX1047, 4-7; EX1020, PDF p. 7 (under the standard of care, resection is recommended if it is possible).) For example, the 2014 NCCN Colon Cancer guidelines that Dr. Neugut cites in this section of his declaration recommended that patients with "colon cancer appropriate for resection (non-metastatic)" undergo surgery to remove their cancer. (EX1020, PDF p. 7.) In contrast, patients with advanced or metastatic colorectal cancer are recommended to be treated in a clinical trial after undergoing at least two prior treatments and having their cancer progress. (EX1020, PDF p. 25.)

76. I also agree with Dr. Neugut that a POSA would have found it

extremely unusual for a study like the MSI-H Study described by the MSI-H Study Record to not include a patient with metastatic colorectal cancer, especially without any kind of explicit carve-out. (EX1003, ¶68.) In fact, even Dr. Lonberg agreed in his deposition that the MSI-H Study Record does not exclude patients with metastatic disease, only asserting that is not so limited. (EX1245, 50:7-10, 51:4-7, 58:3-10.) Consistent with this understanding of the MSI-H Study Record and the standard of care by a POSA, all 41 patients treated in the study described by the MSI-H Study Record, and discussed in the '974 patent specification, did have metastatic cancer. (EX1001, 8:27-29; EX1031, 1; EX1245, 68:18-70:14.)

77. Therefore, I agree with Dr. Neugut that a POSA would have concluded that this limitation was found in the MSI-H Study Record.

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

78. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 6 for the same reason as he argues for Claim 5. (EX2072, ¶¶99-103.) Dr. Neugut explains that the analysis for Claim 6 is the same as for Claim 5, because the additional limitation recited in Claim 6 is the same as recited in Claim 5. (EX1003, ¶¶87-88.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 6 was found in the MSI-H Study Record for the same reason as Claim 5. (EX1003, ¶¶87-88; *see also id.* ¶68.)

E. Point 5: Each and Every Limitation of Claims 1-3 and 5-7 of the '974 Patent is Found in the MSI-H Study Record, When Considered in Combination with Pernot and Benson

79. Dr. Lonberg responds to Dr. Neugut's opinion that Pernot and Benson provide a POSA with additional motivation to carry out the methods of treatment found in the MSI-H Study Record and to reasonably expect success in doing so. (*See* EX2072, ¶¶112-122; *see also id.* ¶¶123-179.) In that section of his declaration, Dr. Neugut explains that Pernot discusses treating MSI-H colorectal cancer and concluded that MSI-H colorectal cancer patients are "good candidates for immunotherapy." (EX1003, ¶¶96-107; *see also* EX1006, 3740-41.) Dr. Neugut also explains that Benson sets forth that, under the standard of care, a patient who would take part in a clinical study such as the one disclosed in the MSI-H Study Record is a patient with metastatic cancer who has had their cancer progress after previous drug therapy. (EX1003, ¶¶104-107, *see also* EX1009, 1034.) Additionally, Dr. Neugut explains that the state of the art known to a POSA as of July 10, 2015 would counsel a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (EX1003, ¶¶98, 104-107; *see also* EX1016; EX1005; EX1009; EX1017; EX1023, 42; EX1057, 463-64.)

80. Dr. Lonberg, however, asserts that Pernot does not provide a POSA with an expectation of success for the claimed methods of treatment because (1)

"Pernot does not disclose or suggest any relationship between MSI-H CRC patients, let alone MSI-H cancer patients in general, and their likelihood of responding to PD-1 checkpoint blockade . . . [nor] mention pembrolizumab;" and (2) Pernot does not list any anti-PD-1 antibody clinical studies. (EX2072, ¶¶141-143.)

81. I disagree with Dr. Lonberg. First, Dr. Lonberg does not properly consider Pernot (and Benson) in the context of the clear disclosures already provided by the primary prior art, the MSI-H Study Record. Second, as Dr. Neugut explains, and I agree, Pernot states that MSI-H colorectal cancer "could lead to a more intense immune response . . . making them good candidates for immunotherapy." (*See* EX1003, ¶¶91-93, 96-97; EX1006,3741.) Further, Pernot provides that "[t]he most promising [immunotherapy] strategies are boosting the immune system with . . . inhibition of immunoregulatory checkpoints," and "[r]ecently, some monoclonal antibodies targeting [immune checkpoint] molecules (PD1, CTLA-4) have shown more than promising efficacy results in solid neoplasia such as melanoma and others." (EX1006, 3738, 3742.) The MSI-H Study Record discusses treating MSI-H colorectal cancer patients with pembrolizumab, an immunotherapy that targets the PD-1 pathway. (EX1005; *see also* EX1003, ¶¶35-37.) Therefore, I agree with Dr. Neugut that a POSA would

have been motivated by Pernot to carry out the methods of treatment found in the MSI-H Study Record.

82. Dr. Lonberg also considers Benson without the context of the MSI-H Study Record when he argues that Benson does not provide a POSA with an expectation of success for the claimed methods of treatment (EX2072, ¶¶115, 120, 144.) Dr. Lonberg also asserts that "nowhere does Benson disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic cancer/colorectal to be enrolled in clinical trials." (EX2072, ¶115.)

83. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, Benson discusses that, under the standard of care at the Alleged Invention Date, a patient that had a tumor or measurable disease that would take part in a clinical study is a patient who have had their cancer progress after previous drug therapy. (EX1003, ¶¶94-95, 104-107; EX1009, 1034.) Further, Benson provides that, under the standard of care, a patient that had a tumor or measurable disease that would take part in a clinical study is a patient having metastatic and advanced disease. (EX1003, ¶105; EX1009, 1034.) The MSI-H Study Record discusses treating MSI-H cancer patients, including CRC patients, with pembrolizumab, an immunotherapy that targets the PD-1 pathway. (EX1005; *see also* EX1003, ¶¶35-37.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated

by Benson to carry out the methods of treatment found in the MSI-H Study Record.

84. Additionally, I agree with Dr. Neugut that the state of the art at the relevant time would motivate a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success because a POSA would have known that physicians had successfully treated a colorectal cancer patient whose cancer was MSI-H with a PD-1 inhibitor and that pembrolizumab was approved for another oncology indication. (*See* EX1003, ¶¶98-101; *see also* EX1055, 1 (pembrolizumab approved for melanoma); EX1057, 463-64.) Dr. Lonberg refers to the prior successful treatment of an MSI-H colorectal cancer patient with a PD-1 inhibitor as "statistically meaningless," but [redacted].[3] (EX2072, ¶¶57, 176; EX1116, 19; *see also supra* §VII.C.1; EX2072, ¶163.) [redacted]

[3] JHU states: "But EX1038 fails to provide any indication that this mere hypothesis amounted to a reasonable expectation of success for treating patients with pembrolizumab ***in response to*** determining they had MSI-H cancer." (EX2072, ¶163.) However, there is no such "in response to" requirement in the '974 patent.

[redacted]

85. Dr. Lonberg asserts more generally that a POSA would have had no reasonable expectation of success for the claimed methods of treatment because "cancer immunotherapy is a complex and unpredictable technical field;" "there was substantial evidence that MSI-H CRC patients would not be good candidates for anti-PD-1 therapies;" "in retrospect, many other contemporary trials of anti-PD-1 therapies failed;" and "evolving scientific knowledge has since clarified important gaps that existed at the Critical Date of the '974 Patent." (EX2072, ¶¶123-138.)

86. I disagree with Dr. Lonberg, and instead, agree with Dr. Neugut because, in addition to Pernot and Benson, several other sources independently urged a POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy. (EX1003, ¶¶99-100; *see also* EX1033, 2968-69; EX1032, e27817-5; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; *see also* EX1035, 1, 8; EX1036, 1186.) While Dr. Lonberg alleges these "additional references" do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-171), [redacted]

[redacted]

(EX1116, 19; *see also supra* §VII.C.1.)

87. Moreover, I agree with Dr. Neugut that the prior art discussed that PD-1 inhibitors naturally had more efficacy when treating tumors that display certain characteristics, which MSI-H tumors were known to display. (*See* EX1003, ¶¶42-47, 100; *see also* EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, -3-5; EX1037, 2.) Again, while Dr. Lonberg alleges these "additional references" do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-171), [redacted] (*See* *supra* §VII.C.1; EX1116, 18-19.)

88. Further, while Dr. Lonberg asserts that "many other contemporary trials of anti-PD-1" failed, this section of his declaration omits any discussion of the contemporary clinical study involving BMS's anti-PD-1 drug to treat MSI-H colorectal cancer patients. (EX2072, ¶¶132-134; *see also* EX1053.) The study

record describing BMS's treatment of MSI-H colorectal cancer patients with its anti-PD-1 drug posted to clinicaltrials.gov in February 2014, more than 17 months before July 10, 2015. (EX1053.) Indeed, BMS ultimately received accelerated approval from the FDA for the treatment of metastatic MSI-H colorectal cancer based on the results of its contemporary clinical study, which Dr. Lonberg deemed a success. (*See* EX1120; *see also* EX1138, 238:2-240:15.)

89. Therefore, I agree with Dr. Neugut that Pernot and Benson would provide a POSA with additional motivation to carry out the claimed methods of treatment found in the MSI-H Study Record with a reasonable expectation of success and would have seen the results that naturally flow from those methods. (*See* EX1003, ¶¶96-101, 104-107; *see also id.* ¶¶40, 74-76.)

F. Point 6: Each and Every Additional Limitation of Claim 4 Is Found in the MSI-H Study Record in View of Pernot and Benson, When Considered in Combination with Chapelle

90. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with Pernot and Benson) and Chapelle to identify the MSI-H tumor as exhibiting instability in one or more microsatellite markers or deficiency of one or more mismatch repair markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, or where the mismatch repair marker is POLE, POLD1, or MYH. (EX2072, ¶¶180-181.) In that section of his declaration, Dr. Neugut explains that

Chapelle discusses standard methods of testing a patient's colorectal cancer to determine MSI status. (EX1003, ¶¶108-113.) I agree with Dr. Neugut that a POSA would have found the additional limitations of Claim 4 in the MSI-H Study Record (combined with Pernot and Benson) in combination with Chapelle.

91. Dr. Lonberg does not state disagreement with Dr. Neugut's opinion that a POSA, in view of the general knowledge in the art, such as Chapelle, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to test tumor tissue from the patient where the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, and expected success in doing so. (*See* EX2072, ¶180-181; *see also* EX1003, ¶¶108-113; EX1007, 3380-84.) Dr. Lonberg asserts only that Chapelle does not additionally address certain other limitations, including arguing that a POSA would not have a reasonable expectation of achieving success in the claimed treatment of the '974 patent. (EX2072, ¶¶112, 114, 181.) But as discussed in Section VII.E above, Chapelle combined with the MSI-H Study Record (and Pernot and Benson) discloses every limitation of Claims 1-3 and 5-7, as well as the additional limitations of Claim 4.

92. I also disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, Chapelle would have motivated a POSA to detect microsatellite markers in a DNA sequence in a tumor sample obtained from the patient with a reasonable expectation of success in doing so. (EX1007, 3380, 3383; *see also* EX1003,

¶¶102, 112.) Further, a POSA would have had reason to consider Chapelle, in addition to the MSI-H Study Record, Pernot, and Benson, as these references are in the same field, and Chapelle further discusses standard methods of testing whether a tumor was MSI-H, such as detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence. (EX1007, 3380, 3383; *see also* EX1003, ¶¶108-113.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated by Chapelle to carry out the methods of treatment found in the MSI-H Study Record.

93. Moreover, I agree with Dr. Neugut that the '974 patent does not discuss that the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (EX1003, ¶113.)

G. Point 7: Each and Every Limitation of Claims 1-3 and 5-7 Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson

94. Dr. Lonberg responds to Dr. Neugut's opinion that Brown, Duval, and Benson provide a POSA with additional motivation to carry out the methods of treatment found in the MSI-H Study Record and to reasonably expect success in doing so. (*See* EX2072, ¶¶115, 118, 120-122 ; *see also id.* ¶¶145-153 .) In that section of his declaration, Dr. Neugut explains that Brown discusses that PD-1 inhibitors naturally have more efficacy when treating tumors that are comprised of

cancer cells that are easy for immune cells to recognize. (EX1003, ¶¶114-115; *see also* EX1034, 747.) Dr. Neugut also explains that Duval discusses that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1003, ¶¶116-117; *see* also EX1087, 5002.) As noted above, Benson sets forth that, under the standard of care, a patient who would take part in a clinical study such as the one disclosed in the MSI-H Study Record is a patient with metastatic cancer who has had their cancer progress after previous drug therapy. (*Supra*, ¶83;*see also* EX1009, 1034.) Additionally, Dr. Neugut explains that the state of the art known to a POSA as of July 10, 2015 would counsel a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (EX1003, ¶¶125, 131; *see also* EX1016; EX1005; EX1017; EX1023, 42; EX1057, 463-64.)

95. Dr. Lonberg, however, asserts that Brown does not provide a POSA with an expectation of success for the claimed methods of treatment because, "at the Critical Date, there were also many factors of MSI-H tumors that taught away from MSI-H cancer patients being good candidates for immunotherapy and especially for checkpoint blockade therapy," and because "Brown's discussion of microsatellite instability is limited to the context of Lynch syndrome and CRC." (EX2072, ¶¶145-150.) Dr. Lonberg further asserts that the data and findings in Duval that "suggested a 'clinical relationship between the emergence of the

tumoral mutator phenotype and host immunodeficiency in a ***particular subset of tumors*** represented by human lymphomas' has little to no relevance for ***other*** kinds of cancers (e.g., those with MSI-H solid tumors) or for ***non-immunodeficient*** patients with MSI-H tumors." (EX2072, ¶¶151-153.)

96. I disagree with Dr. Lonberg. First, Dr. Lonberg once again does not properly consider these references taken together and in the context of the clear disclosures already provided by the primary prior art, the MSI-H Study Record, but instead attempts to address them separately and without appropriate context. Second, as Dr. Neugut explains, and I agree, the MSI-H Study Record discusses treating MSI-H cancer patients, including MSI-H colorectal cancer patients, with pembrolizumab, an immunotherapy that targets the PD-1 pathway. (EX1005; *see also* EX1003, ¶¶35-37, 119.) Further, Brown would have told a POSA reading the MSI-H Study Record, and the other references, that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize, and (2) already infiltrated by many immune cells. (EX1003, ¶¶119, 121-122, *see also* EX1034, 347.) As Dr. Neugut further explains, and I agree, that Duval further adds to that teaching in disclosing that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1003, ¶¶119, 121, *see also* EX1087, 5002.) As discussed, Benson would add to these disclosures in specifying the patient who would participate in this type of

study under the standard of care. (EX1003, ¶¶127-131, *see also* EX1009, 1034.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated by Brown, Duval, and Benson to carry out the methods of treatment found in the MSI-H Study Record.

97. Additionally, I agree with Dr. Neugut that the state of the art at the relevant time would motivate a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success because a POSA would have known that physicians had successfully treated a colorectal cancer patient whose cancer was MSI-H with a PD-1 inhibitor and that pembrolizumab was approved for another oncology indication. (*See* EX1003, ¶¶98-101, 120; *see also* EX1055, 1 (pembrolizumab approved for melanoma); EX1057 at 463-64.) Dr. Lonberg refers to the prior successful treatment of an MSI-H colorectal cancer patient with a PD-1 inhibitor as "statistically meaningless," [redacted].[4] (EX2072,

[4] JHU states: "But EX1038 fails to provide any indication that this mere hypothesis amounted to a reasonable expectation of success for treating patients with pembrolizumab ***in response to*** determining they had MSI-H cancer." (EX2072, ¶163.) However, there is no such "in response to" requirement in the '974 patent.

¶¶57,176; EX1116, 19; *see also supra* §VII.C.1; EX2072, ¶163.) [redacted]

98. Dr. Lonberg asserts more generally that a POSA would have had no reasonable expectation of success for the claimed methods of treatment because "cancer immunotherapy is a complex and unpredictable technical field;" "there was substantial evidence that MSI-H CRC patients would not be good candidates for anti-PD-1 therapies;" "in retrospect, many other contemporary trials of anti-PD-1 therapies failed;" and "evolving scientific knowledge has since clarified important gaps that existed at the Critical Date of the '974 Patent." (EX2072, ¶¶123-138.)

99. I disagree with Dr. Lonberg, and instead, agree with Dr. Neugut because, in addition to Brown, Duval, and Benson, several other sources independently urged a POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy. (EX1003, ¶124; *see also* EX1033, 2968-69; EX1032, e27817-5; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; *see also* EX1035, 1, 8; EX1036, 1186.) While Dr. Lonberg alleges these "additional references" do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-171), [redacted]

[redacted] (EX1116, 19; *see also supra* §VII.C.1.)

100. Moreover, I agree with Dr. Neugut that the prior art discussed that PD-1 inhibitors naturally had more efficacy when treating tumors that display certain characteristics, which MSI-H tumors were known to display. (*See* EX1003, ¶¶42-47, 100; *see also* EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, -3-5; EX1037, 2.) Again, while Dr. Lonberg alleges these "additional references" do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-171), [redacted] (*See supra* §VII.C.1; EX1116, 18-19.)

101. Further, while Dr. Lonberg asserts that "many other contemporary trials of anti-PD-1" failed, this section of his declaration omits any discussion of the contemporary clinical study involving BMS's anti-PD-1 drug to treat MSI-H

colorectal cancer patients. (EX2072, ¶¶132-134; *see also* EX1053.) The study record describing BMS's treatment of MSI-H colorectal cancer patients with its anti-PD-1 drug posted to clinicaltrials.gov in February 2014, more than 17 months before July 10, 2015. (EX1053.) Indeed, BMS ultimately received accelerated approval from the FDA for the treatment of metastatic MSI-H colorectal cancer based on the results of its contemporary clinical study, which Dr. Lonberg deemed a success. (*See* EX1120; *see also* EX1138, 238:2-240:15.)

102. Therefore, I agree with Dr. Neugut that Brown, Duval, and Benson would provide a POSA with additional motivation to carry out the claimed methods of treatment found in the MSI-H Study Record with a reasonable expectation of success and would have seen the results that naturally flow from those methods. (*See* EX1003, ¶¶114-131; *see also id.* ¶¶40, 74-76.)

H. Point 8: Each and Every Additional Limitation of Claim 4 Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson, When Considered in Combination with Chapelle

103. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with Brown, Duval, and Benson) and Chapelle to identify the MSI-H tumor as exhibiting instability in one or more microsatellite markers or deficiency of one or more mismatch repair markers, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, or where the mismatch repair marker is POLE,

POLD1, or MYH. (EX2072, ¶¶180-181.) In that section of his declaration, Dr. Neugut explains that Chapelle discusses standard methods of testing a patient's colorectal cancer to determine MSI status. (EX1003, ¶132; *id.* ¶¶108-113.) I agree with Dr. Neugut that a POSA would have found the additional limitations of Claim 4 in the MSI-H Study Record (combined with Brown, Duval, and Benson) in combination with Chapelle.

104. Dr. Lonberg does not state disagreement with Dr. Neugut's opinion that a POSA, in view of the general knowledge in the art, such as Chapelle, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to test tumor tissue from the patient where the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21 or NR-24, and expected success in doing so. (*See* EX2072, ¶180-181; *see also* EX1003, ¶132; *id.* ¶¶108-113; EX1007 at 3380-84.) Dr. Lonberg asserts only that Chapelle does not additionally address certain other limitations, including arguing that a POSA would not have a reasonable expectation of achieving success in the claimed treatment of the '974 patent. (EX2072, ¶¶112, 114, 181.) But as discussed in Sections VII.E, Gabove, Chapelle combined with the MSI-H Study Record (with Brown, Duval, and Benson) discloses every limitation of Claims 1-3 and 5-7, as well as the additional limitations of Claim 4.

105. I also disagree with Dr. Lonberg because, as Dr. Neugut explains, and

I agree, Chapelle would have motivated a POSA to detect microsatellite markers in a DNA sequence in a tumor sample obtained from the patient with a reasonable expectation of success in doing so. (EX1007, 3380, 3383; *see also* EX1003, ¶132; *id.* ¶¶102, 112.) Further, a POSA would have had reason to consider Chapelle, in addition to the MSI-H Study Record, Brown, Duval, and Benson, as these references are in the same field, and Chapelle further discusses standard methods of testing whether a tumor was MSI-H, such as detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence. (EX1007, 3380, 3383; *see also* EX1003, ¶132; *id.* ¶¶108-113.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated by Chapelle to carry out the methods of treatment found in the MSI-H Study Record.

106. Moreover, I agree with Dr. Neugut that the '974 patent does not discuss that the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (EX1003, ¶113].)

I. Point 9: Each and Every Additional Limitation of Claim 7 Is Found in the MSI-H Study Record in View of Pernot, Benson, and Chapelle, in Combination with Hamid

107. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with Pernot, Benson, and Chapelle) and Hamid to administer pembrolizumab intravenously.

(EX2072, ¶¶180-181.) In that section of his declaration, Dr. Neugut explains that Hamid discusses that pembrolizumab was administered to cancer patients intravenously and demonstrated "a high rate of sustained tumor regression," when treating patients with advanced melanoma with 10 mg/kg pembrolizumab every two weeks. (EX1003, ¶¶133-139; *see also* EX1011, 134.)

108. Dr. Lonberg does not disagree in his declaration with Dr. Neugut's opinion regarding the additional limitation of Claim 7. (EX2072, ¶¶180-81; *see also* EX1003, ¶¶133-139.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut's opinion that a POSA, in view of the general knowledge in the art, such as Hamid, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to administer pembrolizumab to the patient intravenously and expected success in doing so. (*See* EX2072, ¶180-81; EX1003, ¶¶137-139; *see also* EX1011, 134-35.) Instead, Dr. Lonberg asserts more generally that Hamid provides no support for other limitations. (EX2072, ¶181.)

109. I disagree with Dr. Lonberg's general assertions for the same reasons as discussed above. (*See e.g.*, §§VII.D-G.) I also agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Hamid, and the general knowledge in the art, to administer pembrolizumab to the patient intravenously and expected success in doing so. (EX1003, ¶¶135-139; EX1011, 134-35; *see also* EX1055, 1.)

Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, a POSA would know to administer pembrolizumab to a patient intravenously. (EX1138, 179:19-183:16.)

110. Therefore, a POSA would have found the additional limitation of Claim 7 in the MSI-H Study Record (combined with Pernot, Benson, and Chapelle) in combination with Hamid.

J. Point 10: Each and Every Additional Limitation of Claim 7 Is Found in the MSI-H Study Record in View of Brown, Duval, Benson, and Chapelle, in Combination with Hamid

111. I agree with Dr. Neugut that a POSA would have found the additional limitations of Claim 7 in the MSI-H Study Record (combined with Brown, Duval, Benson, and Chapelle) in combination with Hamid for the same reasons stated for Point 9. (*See supra* §VII.I; EX1003, ¶140.)

K. Point 11: JHU's Alleged Secondary Considerations Are Fundamentally Flawed

112. I understand from Counsel that any alleged evidence of secondary considerations must be evaluated as of the Alleged Invention Date, which is July 10, 2015, and must be tied to what is claimed by the patent and not known in the prior art.

113. Dr. Lonberg, Dr. Goldberg, and Dr. Le each put forth arguments regarding alleged evidence of certain secondary considerations. Neither Dr. Lonberg, Dr. Goldberg, or Dr. Le, however, tie any of the alleged evidence discussed to any patent claims or any limitations of claims not already known in

the prior art. (*See, e.g.*, EX2072, ¶¶182-191; EX2130 ¶¶10, 25-31, 41, 48-50; EX2090 ¶¶27-81.)

114. While Dr. Goldberg discusses Claim 1 of the '974 patent (EX2090, ¶90), I note that this claim would not be practiced by an oncologist following the Keytruda labeling. In particular, the Keytruda labeling provides an oncologist with the approved treatments for the drug, and does not tell an oncologist to treat a MSI-H cancer patient with comparison to a reference patient that is not MSI-H, nor is that how an oncologist would think about treating a MSI-H patient in regular practice.

115. Dr. Lonberg, Dr. Goldberg, and Dr. Le also do not put forth evidence from the correct time period. (*See, e.g.*, EX2072, ¶¶187, 189; EX2130 ¶¶10, 25, 27, 35; EX2090 ¶¶27-74.) For example, Dr. Lonberg alleges generally that skepticism for the claimed methods of treatment existed based on a personal narrative about the reason why "decisionmakers within Bristol-Myers Squibb" declined conducting a study with JHU involving BMS's anti-PD-1 drug in MSI-H colorectal cancer patients. (EX2072, ¶187.) Setting aside that BMS's study would involve nivolumab, which is not tied to the patent claims, BMS's decision came in 2012, more than two-and-a-half years before July 10, 2015. (EX2072, ¶187; EX2090, ¶61.) I also note that BMS did, in fact, decide to pursue its own study of its anti-PD-1 drug in MSI-H colorectal cancer patients as early as February 10,

2014, and Dr. Lonberg agreed that as of February 10, 2014, BMS considered that study worth performing. (EX1138, 211:7-10; *see also id.* 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8.) Dr. Goldberg's opinions regarding BMS are similarly from the incorrect point in time. (EX2090 ¶61.) Further, this alleged evidence is not tied to any of the patent claims.

116. The POSA would also be aware as of May 29, 2015 that Merck had initiated an additional study evaluating pembrolizumab in MSI-H colon cancer. (*See* EX1148.)

117. Similarly, Dr. Lonberg points to "the unexpected results yielded by the invention." (EX2072, ¶188.) Dr. Lonberg points to the earlier study of BMS's anti-PD-1 drug that led to a complete response in an MSI-H colorectal cancer patient, and reported in Lipson in January 2013, as a comparison to assert that the results of the MSI-H Study were unexpected because the BMS study "failed to produce a response in 32/33 patients with colorectal cancer." (EX2072, ¶190; *see also* EX1057.) The results of the BMS study, however, were reported in January 2013, more than two years before July 10, 2015. (EX1057, 1.) And, as I discuss above in Section VII.E., Dr. Lonberg omits that the one complete response in the BMS study was the MSI-H colorectal cancer patient, which a POSA knew as of January 2013. (*See* EX2072, ¶190; *see also* EX1057, 2.) [redacted]

[redacted][5] (*See supra* ¶¶84, 97; EX1116, 19-20.) Further, [redacted] (*See supra* ¶38; EX1116, 24.)

118. Dr. Le also points to alleged evidence used to support skepticism and unexpected results from the wrong point in time and not tied to any of the patent claims. For example, Dr. Le alleges that "Merck personnel involved" with the MSI-H Study "did not initially act as though they expected it to be successful" and that "Merck did not provide any financial support for the initiation of the trial and only later provided financial support for conduct of the trial."[6] (EX2130, ¶¶20,

[5] During his deposition, Dr. Goldberg also acknowledged that part of the rationale for why a scientist or a physician in the field would conduct a phase 2 study of pembrolizumab in patients with MSI-H tumors was the known complete response in the MSI-high colorectal cancer patient treated with nivolumab. (*Supra*, ¶29.)

[6] And in the '393 proceeding, Dr. Le alleged that "Merck did not provide any financial support for the initial phase" of the study (later changed to "initiation or

35.) While Dr. Le did not provide any additional details regarding her alleged observations or when Merck's funding began, this purported evidence is from the time period at the start of the MSI-H Study, more than two years before July 10, 2015. (*See* EX1139, 67:20-74:7; 269:1-276:16.) Dr. Goldberg's opinions regarding funding are similarly from the incorrect point in time. (EX2090, ¶61.)

119. Moreover, with respect to alleged unexpected results, Dr. Lonberg and Dr. Le do not even address unexpected results tied to the claimed methods of treatment, as compared to what was known to a POSA as of the Alleged Invention Date. (*See, e.g.*, EX2072, ¶¶188-190; EX2130, ¶¶27, 29-31, 35-36.) Instead, Dr. Lonberg and Dr. Le focus only on the ***degree*** of the results achieved in the MSI-H Study. (EX2072, ¶¶188-190; EX2130, ¶¶29-32, 36.) In particular, as of July 10, 2015, a POSA would know that (1) the MSI-H Study was actually being conducted, and was therefore considered to have merit by Merck and JHU, as well as approval from the FDA and JHU's IRB (*see* EX1005; EX1116; EX1118-1119), (2) that BMS was conducting its own study of its anti-PD-1 drug in MSI-H colorectal cancer patients (EX1053), (3) that Merck had initiated an additional study evaluating pembrolizumab in MSI-H colon cancer (*see* EX1148), and (4) all

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conduct of the trial until later"). (IPR2024-00240, EX2130, ¶¶19, 34; IPR2024-00240, EX1145 ¶19.)

of the teachings of the prior art literature discussed above in Sections VII.D-VII.J. Therefore, as of July 10, 2015, a POSA would not have found a positive outcome for the claimed methods of treatment unexpected.

120. Dr. Goldberg also points to alleged evidence used to support a long-felt unmet need from the wrong point in time and not tied to any of the patent claims. (EX2090, ¶¶27-74.) In particular, Dr. Goldberg discusses chemotherapy and targeted therapies available in 2010-2015, as well as the state of MSI testing before and after 2017 (when pembrolizumab received FDA approval for the MSI-H cancer and MSI-H colorectal cancer indications) because Dr. Goldberg's view is that the long-felt unmet need was for an FDA-approved method of treatment. (EX2090, ¶¶37-81; EX1243, 98:8-11.) The '974 patent claims, however, do not require FDA approval.

121. Further, Dr. Goldberg omits any discussion of the prior art known to a POSA as of July 10, 2015, including the MSI-H Study Record that describes the claimed method of treatment. (EX2090, ¶¶27-81; *see also* EX1003, ¶¶24-50.) For example, Dr. Goldberg does not account for the fact that, as of July 10, 2015, (1) the MSI-H Study Record was in the prior art, (2) a number of other prior art references independently urged a POSA to consider treating MSI-H cancer with PD-1 inhibitors and PD-1 inhibitors, like pembrolizumab, were showing promise in treating tumors displaying certain characteristics that MSI-H tumors were

known to display, and (3) a contemporary study of another anti-PD-1 inhibitor to treat patients with MSI-H colorectal cancer was ongoing. (EX2090 ¶¶27-81; *see also supra* §VII.C.1; EX1003 ¶¶34-50.) By ignoring the MSI-H Study Record and the other prior art known to a POSA as of July 10, 2015, Dr. Goldberg's analysis of an alleged long-felt unmet need focuses on colorectal cancer more generally and the incorrect point in time, arguing the need was unmet until pembrolizumab received FDA approval for the treatment of MSI-H cancer patients.

122. The approvals of Keytruda to treat patients with MSI-H cancer and MSI-H colorectal cancer are attributable to Merck's wonderful drug and are among the more than 40 approvals that Keytruda now has on its labeling, including at least 12 breakthrough therapy designation approvals (more than any other drug included in the Center for Drug Evaluation and Research (CDER) statistics). (EX1130; EX1134.) These approvals are almost all directed to the treatment of many various cancers without regard, or mention, as to whether patients with those cancers have MSI-H/dMMR status, and where the supporting clinical results do not mention or consider MSI-H/dMMR status. (EX1130; EX1134.) Moreover, with Merck's continued development of Keytruda, and its approval as a first-line therapy for MSI-H colorectal cancer patients in June 2020 (EX1279), Keytruda is currently used as a first-line therapy in most MSI-H colorectal cancer patients.

123. Further, Merck itself has at least four patents that were filed or issued before the Alleged Invention Date, and which cover pembrolizumab, the active antibody in Keytruda, as well as its use in the treatment of cancer. (EX1214, EX1215, EX1217, EX1238.) In contrast, as discussed above, the '974 patent only claims a particular method of treating patients with MSI-H cancer.

124. As of July 10, 2015, the method of treating a cancer patient by determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, and then administering an effective amount of pembrolizumab to the patient,[7] was already being met and was reasonably expected to be successful. (EX1005; *see also supra* §§VII.D-J.)

[7] And then, of course, determining the result.

VIII. CONCLUSION

125. In summary, it is my opinion that, consistent with Dr. Neugut's declaration, every limitation of every claim is found in the MSI-H Study Record or in the MSI-H Study Record in combination with various prior art references. Further, it is my opinion that no secondary considerations detract from these disclosures.

126. I declare that all statements made herein to my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like when so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: May 1, 2025

By: Paul Oberstein

Paul E. Oberstein, M.D.

Appendix A

EX1001	U.S. Patent No. 11,325,974 (the "'974 patent")
EX1002	File History of the '974 patent (U.S. Patent Application No. 17/131,326)
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
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)
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EX1118	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] June 11, 2013 IND Submission to the FDA, SN01
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EX1120	FDA grants nivolumab accelerated approval for MSI-H or dMMR colorectal cancer (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-nivolumab-accelerated-approval-msi-h-or-dmmr-colorectal-cancer)
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EX1145	Declaration of Dr. Dung Le, marked up during January 9, 2025 deposition
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