

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. 11,591,393

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. 11,591,393 (the “’393 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, 199-399) made on behalf of JHU regarding certain patent claims of the ’393 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), Dr. Le (EX1139), Dr. Goldberg (EX1136), 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 ’393 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 “in response to” limitation found in Claims 1 and 14, or the additional limitations of Claims 4, 7, 17, 20, and 29-42. I agree with Dr. Neugut that every limitation of Claims 1 and 14, as well as the additional limitations of Claims 4, 7, 17, 20, and 29-42, are found in the MSI-H Study Record.
2. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Pernot does not provide the “in response to” limitation or a reasonable expectation of success. I agree with Dr. Neugut that every limitation of Claims 1-2, 4-7, 11-12, 14-15, 17-20,

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.

24-25, and 27-42 are found in the MSI-H Study Record in combination with Pernot.

3. I disagree with Dr. Lonberg that the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle does not provide the “in response to” limitation or a reasonable expectation of success. I agree with Dr. Neugut that every limitation of Claims 2, 8, 15, and 21 are found in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle.

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 November 28, 2023 (EX1003),
- The declaration of Dr. Nils Lonberg, dated October 4, 2024 (EX2072),
- The declaration of Dr. Richard Goldberg, dated October 4, 2024 (EX2090),

- The declaration of Dr. Dung Le, dated October 4, 2024 (EX2130),
- The annotated declaration of Dr. Dung Le, dated January 9, 2025 (EX1145),
- The deposition transcripts of Dr. Lonberg (EX1138), Dr. Goldberg (EX1136), and Dr. Le (EX1139),
- [REDACTED]
[REDACTED]
[REDACTED]
- The '393 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),
- Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010) ("Chapelle") (EX1007),
- Steinert et al, *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) Cancer Research OF1 (March 2014) ("Steinert") (EX1008),

- 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),
- Salipante et al, *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) Clinical Chemistry 1192 (June 2014) ("Salipante") (EX1010),
- 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),
- The materials in Appendix A (Table of Exhibits).

19. My opinions are also based on my appreciation of how the POSA would have understood the claims at issue and the specification of the '393 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 '393 patent, the MSI-H Study Record, Pernot, Salipante, Chapelle, Steinert, 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.

21. I understand that JHU argues that the term "in response to" should be construed to mean "in reaction to." Further, I understand that the Parties do not dispute that the term "in response to" requires causality. My opinions discussed herein would not be changed if JHU's construction of "in response to" were adopted by the Board.

VI. PERSON OF ORDINARY LEVEL OF SKILL

22. I have been informed by Counsel that the POSA is a hypothetical person that is presumed to have knowledge of all pertinent prior art as of the critical date for the patent at issue.

23. I understand the POSA for purposes of my analysis of the '393 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.

24. Further, I understand JHU argues the 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 the POSA. (POR at 5; EX2072, ¶¶31-32.) I disagree with JHU’s definition for the POSA given that the ’393 patent relates to cancer therapy and provides a method of treating a cancer patient. (EX1001, 1:27-28, 3:39-40.) As I discuss in further detail below, Dr. Lonberg agrees that the ’393 patent provides cancer treatment methods, not methods for conducting genetic or immunology research. (EX1138, 32:2-36:17.) 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. (EX1138, 32:9-15, 34:2-35:9.)

25. All of my opinions expressed in this Declaration are from this perspective of the POSA as of the critical date for the ’393 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 the POSA is adopted, my opinions expressed in this Declaration would still apply and would not change.

VII. THE CLAIMS OF THE '393 PATENT ARE TAUGHT OR SUGGESTED BY THE PRIOR ART

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

26. I have reviewed the deposition transcript of Dr. Lonberg's December 20, 2024 deposition (EX1138) and note the following points from his testimony that I agree with:

- The methods of treatment of Claims 1 and 14 require only two steps, including "testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or DNA mismatch repair deficient" and "in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab." (EX1138, 36:18-37:20; 56:7-57:6.)
- As of July 10, 2015, the POSA would know that to determine MSI-H status you could test tumor tissue or bodily fluid. (EX1138, 47:19-48:5.)

- As of July 10, 2015, the POSA would know that to determine MSI-H status you could carry out testing by polymerase chain reaction (“PCR”), immuno-histochemistry (“IHC”), or next-generation sequencing (“NGS”). (EX1138, 48:6-22; 154:13-155:10; 163:13-18.)
- Oncologists would not need specialized experience researching or development new treatments for cancer to understand the steps of the methods claimed in the ’393 patent (EX1138, 32:6-36:17.)
- The POSA would read the art logically, rationally, and with ordinary creativity. (EX1138, 83:4-85:10.)

27. 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, Salipante, 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.)

28. 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 the 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 the POSA would independently inject skepticism or disbelief into analysis of the prior art literature, as I understand the 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.

29. I also disagree with Dr. Lonberg because, while he testified that the POSA would read the art logically and rationally, he also claims the POSA would illogically seek to treat colorectal cancer patients in the MSI-H Study according to the MSI-H Study Record without first determining their MSI status. (EX1138, 83:11-17, 103:18-4; *see also id.* 97:2-109:22.)

30. 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**

31. I have reviewed the deposition transcript of Dr. Goldberg's December 13, 2024 deposition (EX1136) and note the following points from his testimony that I agree with:

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

- As of July 10, 2015, the POSA would know that PD-1 inhibitors could be used to treat MSI-H colon cancer. (EX1136, 62:2-16; 108:21-110:22.)
- As of July 10, 2015, the POSA would know that MSI-H was a relevant factor in considering potential treatment to explore with clinical trials. (EX1136, 103:18-105:15.)
- 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.)

32. 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.)

33. 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.

34. 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

35. I have reviewed the Investigational New Drug Application ("IND") submissions [REDACTED] (EX1116), [REDACTED] (EX1118), [REDACTED] (EX1119). I have also reviewed the transcripts of the January 9, 2025 deposition of Dr. Le (EX1139) and January 24, 2025 deposition of Dr. Pardoll (EX1140).

36. 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].

37. 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]

38.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

39.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

40.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

41. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

42. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

43. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

44. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (See, e.g., EX2072, ¶¶48-

57, 133-34, 188-89; EX2090, ¶¶46-52; EX2130, ¶¶9, 10, 20, 23; EX1002, 205 ¶20;
see also EX1140, 57:7-21, 58:7-16, 61:17-65:3.)

45.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.

[REDACTED]

46.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

47. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

48. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.

[REDACTED]

49.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

50.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

51. [REDACTED]

[REDACTED]

4. Dr. Le's Deposition Testimony

52. 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 the '393 patent, on which she is a named inventor. (*See, e.g.*, EX1139, 11:3-17:10, 234:2-238:5.)
- 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 the stated rationale recited in the IND submission for the MSI-H Study. (*See, e.g.*, EX1139, 239:22-246:3.)

53. 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, 26; EX2130, ¶9.)

5. Dr. Pardoll's Deposition Testimony

54. 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.)

55. Ultimately, Dr. Pardoll testified that he disagreed with the rationale and anticipated outcome that JHU previously communicated to the FDA in its IND submissions. (*See* EX1140, 57:7-14, 61:17-65:3.) I disagree with Dr. Pardoll.

D. Point 4: Each and Every Limitation of Claims 1, 4, 7, 14, 17, 20, and 29-42 of the '393 Patent is Found in the MSI-H Study Record

56. Dr. Lonberg responds to Dr. Neugut's opinion that the MSI-H Study Record discloses each and every limitation of Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 (*see* EX2072, ¶¶86-118), by asserting that the MSI-H Study Record does not disclose all of the claim limitations of Claims 1 and 14, and also certain additional limitations found in Claims 4, 7, 17, 20, and 29-42. (EX2072, ¶¶86-118.) I, however, disagree because I agree with Dr. Neugut's opinions that

every limitation of Claims 1 and 14, and the additional limitations of Claims 4, 7, 17, 20, and 29-42, are found in the MSI-H Study Record. (EX1003, ¶¶50-63, 65, 68-72, 75, 79, 82, 87-104.)

57. I note that Dr. Lonberg does not include any testimony in Section IX of his declaration regarding the additional limitations of Dependent Claims 2, 5, 6, 11, 12, 15, 18, 19, 24, 25, 27, and 28. Therefore, my analysis in the section below reflects only the claim limitations addressed by Dr. Lonberg.

1. Claim 1

58. Claim 1 recites a method of treatment involving testing a colorectal cancer patient's cancer for MSI-H and then, in response to determining the patient's cancer is MSI-H, administering a therapeutically effective amount of pembrolizumab. (EX1001, Claim 1.) Dr. Neugut determined that the POSA would have found every limitation of Claim 1, including the preamble, Limitation [1.1], and Limitation [1.2], in the MSI-H Study Record. (EX1003, ¶¶53-63.) Dr. Lonberg responds arguing that the MSI-H Study Record does not “disclose[] the ‘in response to’ limitation” (*i.e.*, Limitation [1.2]). (EX2072, ¶¶87-101.) I disagree for the reasons I explain below.

- a. [1.2]: “and in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.”

59. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record because the MSI-H Study Record discusses treating a patient with 10 mg/kg of pembrolizumab every 14 days, the same dosage described as being therapeutically effective in the ’393 patent, in response to a patient meeting the eligibility criterion of having MSI-H colorectal cancer. (*See* EX2072, ¶¶87-101; EX1003, ¶¶59-63; *see also* EX1005, 5-6 (Eligibility Criteria), 4 (Arms and Interventions); EX1001, 8:52-56, 13:28-30.)

60. Dr. Lonberg argues that the MSI-H Study Record does not provide this limitation because (1) the MSI-H Study Record allegedly does not tell the POSA to test the colorectal cancer patient’s MSI status before administering pembrolizumab and (2) he asserts the MSI-H Study Record does not “disclose any causal relationship between MSI-H testing and treatment.” (EX2072, ¶¶87-101.) I disagree with both of Dr. Lonberg’s conclusions.

61. **First**, as Dr. Neugut explains, and I agree, the MSI-H Study Record discusses that one arm of the study is entirely composed of patients having MSI-H colorectal cancer. (EX1003, ¶¶53-63; EX1005, 4 (Arms and Interventions), 3

(Study description), 3-4 (Conditions), 5-6 (Inclusion Criteria).) Placing patients into that proper arm of the study would not be possible without first determining that the patient's tumor was MSI-H. (EX1003, ¶¶58-63.) Dr. Lonberg asserts that because the MSI-H Study Record "includes both MSI-H colorectal cancer patients and non-MSI-H colorectal cancer patients, there is no requirement that a colorectal cancer patient be tested for MSI-H to qualify for the study." (EX2072, ¶93.)

62. The Inclusion Criteria, however, that Dr. Neugut points to in this section of his declaration discusses that MSI-H colorectal cancer patients can be placed *only* in the arm of the study that is composed of patients having MSI-H colorectal cancer. (See EX1005 at 5 (Inclusion Criteria) ("1. Arm 1 only: Patients with MSI positive colorectal cancer"); see also EX1003, ¶¶58-63.) Additionally, the Arms and Interventions section provides that patients in the MSI-H colorectal cancer arm are treated with 10 mg/kg pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions), see also EX1003, ¶¶58-63.)

63. Contrary to Dr. Lonberg's assertion, the MSI-H Study Record also discussing one arm of the study being entirely composed of patients with colorectal cancer that is not MSI-H actually further supports the need to first determine the colorectal cancer patient's MSI status to place the patient into the proper arm of the study. (See EX1003, ¶¶58-63; EX2072, ¶¶92-93; see also EX1005, 4 (Arms and Interventions); 5 (Inclusion Criteria) ("2. Arm 2 only: Patients with MSI negative

colorectal cancer”).) Thus, I agree with Dr. Neugut that the POSA would understand the MSI-H Study Record requires first determining that the patient’s colorectal cancer is MSI-H and then, in response to determining the patient’s colorectal cancer is MSI-H, administering a therapeutically effective amount of pembrolizumab.

64. ***Second***, Dr. Lonberg asserts that the MSI-H Study Record does not “disclose any causal relationship between MSI-H testing and treatment.” (EX2072, ¶¶94-101.) Dr. Lonberg alleges that the MSI-H Study Record does not disclose “recruiting patients for the study based on a determination that they are MSI-H CRC” and “treating patients based on a determination that they are MSI-H CRC patients even after they are enrolled.” (EX2072, ¶¶94-101.) But, as Dr. Neugut discussed, and I discuss above (*supra* ¶¶59-63), one arm of the study described by the MSI-H Study Record is entirely composed of patients having MSI-H colorectal cancer and that arm of the study is assigned the intervention of treatment with 10 mg/kg pembrolizumab every 14 days. (EX1003, ¶¶58-63; EX1005 at 4 (Arms and Interventions), 3 (Study description), 3-4 (Conditions), 5-6 (Inclusion Criteria).) I agree with Dr. Neugut that it would not be possible to place an MSI-H colorectal cancer in the proper arm for treatment with the assigned intervention without first determining that the colorectal cancer patient’s cancer is

MSI-H, and then treating the MSI-H colorectal cancer patient with the assigned intervention of 10 mg/kg pembrolizumab every 14 days. (EX1003, ¶¶58-63.)

65. Dr. Lonberg also asserts that the MSI-H Study Record does not describe “recruiting patients for the study based on a determination that they are MSI-H CRC” because the POSA would purportedly understand the MSI-H Study Record describes an “all-comers” study. (EX2072, ¶¶94-101.) In particular, Dr. Lonberg argues the MSI-H Study Record describes an all-comers study where “all patients meeting the eligibility criteria (*regardless of a particular biomarker status*) are entered” and a “retrospective analysis” of the patients MSI status is conducted to identify “the impact of MSI[] positivity or negativity” to the therapeutic outcome. (EX2072, ¶¶95-98; EX1138, 104:5-18.)²

² I note that while Dr. Lonberg believes the MSI-H Study described by the MSI-H Study Record was a retrospective clinical study, he could not recall whether the Keytruda[®] labeling describes the study as such. (EX1138, 110:15-111:17.) Contrary to Dr. Lonberg’s beliefs, and consistent with the disclosures of the MSI-H Study Record to the POSA, the Keytruda labeling describes the MSI-H Study design as a prospective study. (EX1023, 42.) Other Merck MSI-H studies (Keynote-012 and Keynote-028) are described as retrospective analyses. *Id.*

66. I disagree as these assertions are not consistent with or supported by the disclosures of the MSI-H Study Record. The MSI-H Study Record's Eligibility Criteria requires that MSI-H colorectal cancer patients be placed in "Arm 1 only" of the study. (*See* EX1005, 5 (Inclusion Criteria) ("1. Arm 1 only: Patients with MSI positive colorectal cancer"); *see also* EX1003, ¶¶58-63.) Therefore, a colorectal cancer patient could not "meet the eligibility criteria" and begin treatment without first determining whether the colorectal cancer patient's cancer was MSI-H. (EX1003, ¶¶58-63; EX1005, 5-6.)

67. Further, the MSI-H Study Record describes in the Study Design section that the allocation of patients in the arms of the study is non-randomized. (EX1005, 4 (Study Design).) Therefore, the POSA would understand that patients could not be "randomly assigned [to receive treatment] regardless of biomarker status" as Dr. Lonberg asserts. (EX2072, ¶97.)

68. Additionally, the MSI-H Study Record describes in the Study Design section that the anticipated enrollment of the study is 71 patients. (EX1005, 4 (Study Design).) Given the low incidence of MSI-H in the colorectal cancer population (about 15%), and even lower in the metastatic colorectal cancer population that would be treated in the MSI-H Study, the POSA would understand that the MSI-H Study Record requires that a patient is tested to determine whether the patient is MSI-H before being enrolled and treated in the study. (*See* EX2072,

¶50 (“[A] small percentage of cancer patients (including CRC patients) were MSI-H”); EX1138, 91:4-17; *see also* EX1003, ¶¶58-63; EX1007, 3380, 3382.)

Otherwise, with an anticipated enrollment of 71 total patients, the POSA would understand that there would not be enough MSI-H colorectal cancer patients treated in the study to measure the outcomes described by the MSI-H Study Record. (*See* EX1005, 4-5 (Outcome Measures).)

69. I also disagree with Dr. Lonberg’s assertion that an all-comers study “explain[s] why the MSI-H Study Record requires subjects to agree to have a biopsy of their cancer.” (EX2072, ¶97.) Instead, I agree with Dr. Neugut that, in the context of the MSI-H Study Record, where colorectal cancer patients are separated into different arms for treatment based whether the patient’s cancer is MSI-H, the POSA would have understood that the MSI-H Study Record’s Eligibility Criteria requires each patient to “[a]gree to have a biopsy of their cancer” to test whether the patient’s cancer’s is MSI-H. (*See* EX1003, ¶¶51, 58; *see also* EX1005, 5-6 (Eligibility Criteria), 4 (Arms and Interventions); EX1007, 3380, 3383; EX1044, 3309; EX1045, 3485; EX1046, 1193; *see also* EX1001, 8:13-15 (testing “[a]rchived tumor samples” or “newly obtained biopsies.”).)

70. Thus, consistent with Dr. Neugut’s opinion, the POSA would have concluded that Limitation [1.2] was found in the MSI-H Study Record.

2. **Claim 4: “The method of claim 1, wherein the patient is treated with an amount of pembrolizumab shown in a clinical trial to be effective in promoting progression-free survival in multiple human subjects whose colorectal cancer is microsatellite instability high or mismatch repair deficient.”**

71. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶65; EX2072, ¶¶108-11.) 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 colorectal 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 colorectal cancer is MSI-H, this claim limitation is met. (EX1003, ¶65; *see also id.* ¶¶40, 53-57, 60-62; EX1005, 4, (Arms and Interventions).)

72. 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, ¶¶108-111.)

73. 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 colorectal cancer patients will be treated with 10 mg/kg pembrolizumab

every 14 days. (EX1003, ¶65; *see also id.* ¶¶53-57; 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 colorectal cancer patients treated in the study described by the MSI-H Study Record. (EX1003, ¶65; *see also id.* ¶¶40, 60-62; EX1001, 4:31-36, 16:4-8, 16:29-32, 19:40-21:1, Fig. 2, Fig. 11.)

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

3. **Claim 7: “The method of claim 1, 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.”**

75. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶68-72; EX2072, ¶102.) In that section of Dr. Neugut’s declaration, he explains that in the context of the MSI-H Study Record, the POSA would have understood that patients would have received prior drug therapies and had their cancers progress after those therapies. (EX1003, ¶¶68-72.) Therefore, this claim limitation is met. (EX1003, ¶¶68-72.)

76. Dr. Lonberg alleges that the MSI-H Study Record does not disclose that patients would have received prior drug therapies and had their cancers

progress after those therapies based solely on his mischaracterization of Dr. Neugut's opinions regarding "measurable" disease. (EX2072, ¶102.) 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 the POSA that the cancer patients being treated would have received prior drug therapies and had their cancers progress after those therapies. (See EX1003, ¶¶68-72; see also EX1005, 2 (Study Identification), 5-6 (Eligibility Criteria).) Further, Dr. Neugut explains that the MSI-H Study Record discusses that one of the Primary Outcome Measures was objective response rate, which refers to tumors shrinking. (See EX1003, ¶68, n.4; see also EX1005, 4 (Outcome Measures); EX1048, 236.)

77. 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 both regimens before trying a novel therapeutic agent. However, the '393 patent states the requirement of only one prior therapy, not two. I nevertheless 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, the POSA would understand that patients with metastatic and advanced cancer that would participate in such a study would have

received at least two other prior drug therapies and had their cancers progress after both drug therapies. (EX1003, ¶¶68-72; *see also* EX1020, PDF p. 25; EX1009, 1034; EX1047, 4-7.) Further, I agree with Dr. Neugut that because the MSI-H Study Record’s Eligibility Criteria 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, the POSA would have expected a patient to have undergone at least two prior and/or different cancer therapies prior to enrollment. (EX1003, ¶71; EX1005, 5-6 (Eligibility Criteria).)

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

4. Claim 14

79. While Dr. Lonberg alleges that Claim 14 is not met by the disclosures of the MSI-H Study Record, he does not provide any analysis specific to Claim 14, or to distinguish it in any way from Claim 1. Instead, Dr. Lonberg alleges that Claim 14 is not met for the same reason he alleges Claim 1 is not met; that the MSI-H Study Record does not “disclose[] the ‘in response to’ limitation” (*i.e.*, Limitation [14.2]). (EX2072, ¶¶87-101.) I disagree.

- a. **[14.2]: “in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.”**

80. Dr. Neugut discusses that the analysis for Limitation [14.2] is the same as for Limitation [1.2] because those claim limitations are the same.

(EX1003, ¶¶75-77.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Limitation [14.2] was found in the MSI-H Study Record.

5. **Claim 17: “The method of claim 14, wherein the patient is treated with an amount of pembrolizumab shown in a clinical trial to reduce the risk that microsatellite instability high or mismatch repair deficient colon cancer will progress.”**

81. Dr. Lonberg asserts that the MSI-H Record does not disclose the method of treatment of Claim 17 for the same reason he argues for Claim 4.

(EX2072, ¶¶108-111.) Dr. Neugut explains that the analysis for Claim 17 is the same as for Claim 4 because the additional limitation recited in Claim 17 is the same as recited in Claim 4. (EX1003, ¶79.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 17 was found in the MSI-H Study Record for the same reason as Claim 4. (EX1003, ¶79; *see also id.* ¶65.)

6. **Claim 20: “The method of claim 14, wherein, prior to treatment with the step of selecting pembrolizumab for treating the patient’s colorectal cancer, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”**

82. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 20 for the same reason as he argues for Claim 7. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 20 is the same for Claim 7 because the additional limitation recited in Claim 20 is the same as recited in Claim 7. (EX1003, ¶82.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 20 was found in the MSI-H Study Record for the same reason as Claim 7. (EX1003, ¶82.)

7. **Claim 29: “The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer.”**

83. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (See EX1003, ¶¶87-90; EX2072, ¶¶103-107.) In that section of Dr. Neugut’s declaration, he explains that in the context of the MSI-H Study Record the POSA would have understood that patients would have metastatic and advanced cancer, and therefore, this claim limitation is met. (EX1003, ¶¶87-90.)

84. 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, ¶¶103-107.) Specifically, Dr. Lonberg states that "the words 'measurable' and 'metastatic' are not equivalent," and therefore, "the MSI-H Study Record does not disclose treating 'metastatic' colorectal cancer simply because it mentions 'measurable' disease." (EX2072, ¶¶103-107.) Dr. Neugut, however, does not state in his declaration that those words *are* equivalent. (See EX1003, ¶¶87-90.) 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 the 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, ¶¶87-90; see also EX1005, 5-6 (Eligibility), 2 (Study Identification).)

85. 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, the POSA would understand that the MSI-H Study Record requires 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. (EX1003, ¶¶87-90; see also EX1020, PDF p. 25; EX1078,1278.) Otherwise, if a colorectal cancer patient had cancer that is resectable for the purposes of a cure,

then the POSA would expect that a physician would excise the tumor(s) for cure. (EX1003, ¶¶87-90; *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.)

86. I also agree with Dr. Neugut that the 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 metastatic colorectal cancer patients. (EX1003, ¶89.)

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

8. Claim 30: “The method of claim 14, wherein the colorectal cancer is metastatic colorectal cancer.”

88. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 30 for the same reason as he argues for Claim 29. (EX2072, ¶¶103-107.) Dr. Neugut explains that the analysis for Claim 30 is the same as for Claim 29 because the additional limitation recited in Claim 30 is the same as recited in Claim 29. (EX1003, ¶91.) I agree with Dr. Neugut, and thus,

the POSA would have concluded that Claim 30 was found in the MSI-H Study Record for the same reason as Claim 29. (EX1003, ¶¶91; *see also id.* ¶¶87-90.)

9. Claim 31: “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.”

89. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶92; EX2072, ¶¶108-11.) In that section of Dr. Neugut’s declaration, he explains that because the claimed objective response rate outcomes naturally result from the methods of treatment in the MSI-H Study Record, this claim limitation is met. (EX1003, ¶¶92.)

90. 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, ¶¶108-111.)

91. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, the methods of treatment found in the MSI-H Study Record, and claimed in the ’393 patent, naturally led to the objective response rate outcome also claimed in the patent. (*See* EX1003, ¶¶92; *see also id.* ¶¶40, 60-62; EX1001, Fig. 11 (discussing that 40% of MMR-deficient CRC patients obtained an objective response rate), 16:29-32 (same), 19:40-21:15 (same); EX1031, 2509 (“the

immune-related objective response rate [was] . . . 40% (4 of 10 patients) . . . for mismatch repair–deficient colorectal cancers.”.) Indeed, Dr. Lonberg acknowledged that this claim limitation “correspond[s] directly with the outcome measures obtained by the trial described in the MSI-H Study Record.” (EX2072, ¶110.)

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

10. 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.”

93. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 32 for the same reason as he argues for Claim 7. (EX2072, ¶102.) Dr. Neugut, however, explains that because the claimed outcomes naturally result from the methods of treatment in the MSI-H Study Record and the MSI-H Study Record treats patients with colorectal cancer who have received at least two prior cancer therapy drugs and had their cancers progress after receiving those drugs, this claim limitation is met. (EX1003, ¶¶93-94; *see also id.* 40, 60-62, 68-72.) I agree with Dr. Neugut for the same reasons discussed above (*supra* ¶¶71-78.), and thus, the POSA would have concluded that that this limitation was found in the MSI-H Study Record.

11. **Claim 33: “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%.”**

94. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶95; EX2072, ¶¶108-11.) In that section of Dr. Neugut’s declaration, he explains that because the claimed outcomes naturally result from the methods of treatment in the MSI-H Study Record, this claim limitation is met. (EX1003, ¶95.)

95. 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, ¶¶108-111.)

96. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, the methods of treatment found in the MSI-H Study Record, and claimed in the ’393 patent, naturally led to the outcomes also claimed in the patent. (*See* EX1003, ¶95; *see also id.* ¶¶40, 60-62; EX1001, Fig. 11 (discussing that the immune-related progression free survival at 20 weeks was 78% for MMR-deficient CRC), 16:4-8 (same)); *see also* 1031, 2509 (“immune-related progression-free survival rate [was] . . . 78% (7 of 9 patients) . . . for mismatch repair-deficient colorectal cancers.”).) Indeed, Dr. Lonberg acknowledged that this claim

limitation “correspond[s] directly with the outcome measures obtained by the trial described in the MSI-H Study Record.” (EX2072, ¶110.)

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

12. 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.”

98. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 34 for the same reason as he argues for Claim 32. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 34 is the same for Claim 32 because the additional limitation recited in Claim 34 is the same as recited in Claim 32. (EX1003, ¶96.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 34 was found in the MSI-H Study Record for the same reason as Claim 32. (EX1003, ¶96; *see also id.* ¶¶93-94.)

13. Claim 35: “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%.”

99. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶97; EX2072, ¶¶108-11.) In that section of Dr. Neugut’s declaration, he

explains that because the claimed outcomes naturally result from the methods of treatment in the MSI-H Study Record, this claim limitation is met. (EX1003, ¶¶97.)

100. 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, ¶¶108-111.)

101. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, the methods of treatment found in the MSI-H Study Record, and claimed in the '393 patent, naturally led to the outcomes also claimed in the patent. (*See* EX1003, ¶¶97; *see also id.* ¶¶40, 60-62; EX1001, Fig. 2 (discussing that the probability of progression-free survival at 9 months for MSI-H colorectal cancer patients is at least 60%); EX1031, 2515 (the probability of progression-free survival at 9 months for MSI-H colorectal cancer patients is at least 60%).) Indeed, Dr. Lonberg acknowledged that this claim limitation “correspond[s] directly with the outcome measures obtained by the trial described in the MSI-H Study Record.” (EX2072, ¶110.)

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

14. **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.”**

103. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 36 for the same reason as he argues for Claim 32. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 36 is the same for Claim 32 because the additional limitation recited in Claim 36 is the same as recited in Claim 32. (EX1003, ¶98.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 36 was found in the MSI-H Study Record for the same reason as Claim 32. (EX1003, ¶98; *see also id.* ¶¶93-94.)

15. **Claim 37: “The method of claim 29, 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.**

104. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 37 for the same reason as he argues for Claim 31. (EX2072, ¶¶108-111.) Dr. Neugut explains that the analysis for Claim 37 is the same for Claim 31 because the additional limitation recited in Claim 37 is the same as recited in Claim 31. (EX1003, ¶99.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 37 was found in the MSI-H Study Record for the same reason as Claim 31. (EX1003, ¶99; *see also id.* ¶92.)

16. **Claim 38: “The method of claim 37, 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.”**

105. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 38 for the same reason as he argues for Claim 32. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 38 is the same for Claim 32 because the additional limitation recited in Claim 38 is the same as recited in Claim 32. (EX1003, ¶100.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 38 was found in the MSI-H Study Record for the same reason as Claim 32. (EX1003, ¶100; *see also id.* ¶¶93-94.)

17. **Claim 39: “The method of claim 29, 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%.”**

106. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 39 for the same reason as he argues for Claim 33. (EX2072, ¶¶108-111.) Dr. Neugut explains that the analysis for Claim 39 is the same for Claim 33 because the additional limitation recited in Claim 39 is the same as recited in Claim 33. (EX1003, ¶101.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 39 was found in the MSI-H Study Record for the same reason as Claim 33. (EX1003, ¶101; *see also id.* ¶95.)

- 18. Claim 40: “The method of claim 39, 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.”**

107. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 40 for the same reason as he argues for Claim 32. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 40 is the same for Claim 32 because the additional limitation recited in Claim 40 is the same as recited in Claim 32. (EX1003, ¶102.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 40 was found in the MSI-H Study Record for the same reason as Claim 32. (EX1003, ¶102; *see also id.* ¶¶93-94.)

- 19. Claim 41: “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%.”**

108. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 41 for the same reason as he argues for Claim 35. (EX2072, ¶¶108-111.) Dr. Neugut explains that the analysis for Claim 41 is the same for Claim 35 because the additional limitation recited in Claim 41 is the same as recited in Claim 35. (EX1003, ¶103.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 41 was found in the MSI-H Study Record for the same reason as Claim 35. (EX1003, ¶103; *see also id.* ¶97.)

- 20. Claim 42: “The method of Claim 41, 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.”**

109. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 42 for the same reason as he argues for Claim 32. (EX2072, ¶102.) Dr. Neugut explains that the analysis for Claim 42 is the same for Claim 32 because the additional limitation recited in Claim 42 is the same as recited in Claim 32. (EX1003, ¶104.) I agree with Dr. Neugut, and thus, the POSA would have concluded that Claim 42 was found in the MSI-H Study Record for the same reason as Claim 32. (EX1003, ¶104; *see also id.* ¶¶93-94.)

E. Point 5: Each and Every Limitation of Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the '393 Patent is Found in the MSI-H Study Record, when Considered in Combination with Pernot

110. Dr. Lonberg responds to Dr. Neugut’s opinion that Pernot provides the 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, ¶¶139-141; *see also id.* ¶¶121-136.) 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, ¶¶105-113; *see also* EX1006, 3740-41.)

Additionally, Dr. Neugut explains that the state of the art known to the POSA as of

July 10, 2015 would counsel the POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (EX1003, ¶¶105-113; *see also* EX1016; EX1005; EX1017; EX1023, 42; EX1057, 463-64.)

111. Dr. Lonberg, however, asserts that Pernot does not provide the 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 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, ¶¶139-141.)

112. I disagree with Dr. Lonberg because, 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, ¶¶105-112; EX1006 at 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; *see also* EX1003, ¶¶105-112.) 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, ¶¶29-32.) Therefore, I agree with Dr. Neugut that the POSA would have been motivated by Pernot to carry out the methods of treatment found in the MSI-H Study Record.

113. Additionally, I agree with Dr. Neugut that the state of the art at the relevant time would motivate the POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success because the 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, ¶¶109-112; *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,” but

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

114. Dr. Lonberg asserts more generally that the 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 ’393 Patent.” (EX2072, ¶¶131-36.)

115. I disagree with Dr. Lonberg, and instead, agree with Dr. Neugut because, in addition to Pernot, several other sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy. (EX1003, ¶¶110-11; *see also* EX1033, 2968-69; EX1032, e27817-5; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; *see also* EX1034, 747; EX1035, 1, 8; EX1036, 1186.) While Dr. Lonberg alleges these “tertiary references” do not provide the POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶142-61), [REDACTED]
[REDACTED]
[REDACTED] (EX1116, 19; *see also supra* §VII.C.1.)

116. 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, ¶¶41-46, 110-111; *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 “tertiary references” do not provide the POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶142-61), [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. (*See supra* §VII.C.1; *see also* EX1116, 18-19.)

117. 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, ¶¶130-132; *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.)

118. Therefore, I agree with Dr. Neugut that Pernot would provide the 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, ¶¶105-13; *see also id.* ¶¶40, 60-62.)

F. Point 6: Each and Every Limitation of Claims 2, 8, 15, and 21 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, When Considered in Combination with Chapelle

119. Dr. Lonberg responds to Dr. Neugut's opinion that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Chapelle to test tumor tissue from a patient to determine whether a tumor is MSI-H and to test MSI status by carrying out an immunohistochemistry test. (EX2072, ¶174.) 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 and a test to measure MSI by immunohistochemistry. (EX1003, ¶¶114-122.) I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 2, 8, 15, and 21 in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle.

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

120. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 2. (EX2072, ¶174; *see also* EX1003, ¶¶114-118.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the 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 and expected success in doing so. (*See* EX2072, ¶174; *see also* EX1003, ¶¶116-118; EX1007, 3380, 3384.) Instead, Dr. Lonberg asserts more generally that Chapelle “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶174.)

121. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Chapelle, and the general knowledge in the art, to test tumor tissue from the patient and expected success in doing so. (EX1003, ¶¶116-18; EX1007, 3380, 3384; *see also* 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.”).) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the

POSA would know to test tumor tissue from a patient to determine whether a tumor is MSI-H. (EX1138, 47:19-48:4 (Dr. Lonberg: “The standard procedure is tumor tissue.”).)

122. Therefore, the POSA would have found the additional limitation of Claim 2 in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle.

2. Claim 8: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample.”

123. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 8. (EX2072, ¶174; *see also* EX1003, ¶¶119-20.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the 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 carry out an immunohistochemistry test on the patient’s sample and expected success in doing so. (*See* EX2072, ¶174; *see also* EX1003, ¶¶119-20.) Instead, Dr. Lonberg asserts more generally that Chapelle “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶174.)

124. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record

would have been motivated by Chapelle, and the general knowledge in the art, to use standard methods for testing for MSI-H, including immunohistochemistry, and would have had an expectation of success in doing so. (EX1003, ¶¶119-20; *see also* EX1007, 3380, 3384; 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.”).) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know to test for MSI-H by carrying out an immunohistochemistry test. (EX1138, 154:13-155:10.)

125. Therefore, the POSA would have found the additional limitation of Claim 8 in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle.

3. Claim 15: “The method of claim 14, wherein the biological sample is a tumor tissue sample from the patient.”

126. For the reasons stated above in Section VI.D.1, I disagree with Dr. Lonberg and agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 15 in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle. (*See also* EX1003, ¶121.)

4. **Claim 21: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out an immunohistochemistry test on the sample.”**

127. For the reasons stated above in Section VI.D.2, I disagree with Dr. Lonberg and agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 21 in the MSI-H Study Record (alone or combined with Pernot) in combination with Chapelle. (*See also* EX1003, ¶122.)

- G. **Point 7: Each and Every Limitation of Claims 3 and 16 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in Combination with Steinert**

128. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Steinert to test body fluid from a patient to determine whether a tumor is MSI-H. (EX2072, ¶175.) In that section of his declaration, Dr. Neugut explains that Steinert discusses determining whether a tumor is MSI-H using body fluid, specifically blood samples. (EX1003, ¶¶123-24; EX1008, OF6; *see also id.* OF1.) I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 3 and 16 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert.

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

129. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 3. (EX2072, ¶175; *see also*

EX1003, ¶¶125-27.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the POSA, in view of the general knowledge in the art, such as Steinert, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to test body fluid from the patient and expected success in doing so. (See EX2072, ¶175; *see also* EX1003, ¶¶125-27.) Instead, Dr. Lonberg asserts more generally that Steinert “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶175.)

130. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Steinert, and the general knowledge in the art, to test whether a tumor was MSI-H using body fluid and would have had an expectation of success in doing so. (EX1003, ¶¶125-27; EX1008, OF6; 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.”).) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know to test body fluid from a patient to determine MSI-H status. (EX1138, 47:19-48:5.)

131. Therefore, the POSA would have found the additional limitation of Claim 3 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert.

2. Claim 16: “The method of claim 14, wherein the biological sample is a body fluid from the patient.”

132. For the reasons stated above in Section VI.E.1, I disagree with Dr. Lonberg and agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 16 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert. (*See also* EX1003, ¶128.)

H. Point 8: Each and Every Limitation of Claims 7, 20, 29-30, 32, 34, and 36-42 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in Combination with Benson

133. Dr. Lonberg responds to Dr. Neugut’s opinions that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Benson to (1) treat patients wherein, prior to treatment with pembrolizumab, the patients had received a different/prior cancer therapy, and the patients’ cancer had progressed after the patient received the different/prior cancer therapy, (2) treat patients wherein the colorectal cancer is metastatic colorectal cancer, and (3) treat patients wherein the treatment results in certain outcomes and expected success in doing so. (EX2072, ¶¶176-77.) In that section of his declaration, Dr. Neugut explains that Benson discusses that, under the

standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies. (EX1003, ¶¶129-50; EX1009, 1034.) I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 7, 20, 29-30, 32, 34, and 36-42 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert.

1. **Claim 7: “The method of claim 1, 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.”**

134. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 7. (EX2072, ¶¶176-77; *see also* EX1003, ¶¶129-35.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the POSA, in view of the general knowledge in the art, such as Benson, carrying out the methods of treatment found in the MSI-H Study Record, would have been motivated to treat patients wherein, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the patients’ cancer had progressed after the patient received the different cancer therapy and expected success in doing so. (*See* EX2072, ¶¶176-77; *see also* EX1003, ¶¶129-35.) Instead, Dr. Lonberg asserts more generally that Benson “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶176.)

135. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Benson, and the general knowledge in the art, to treat patients wherein, prior to treatment with pembrolizumab, the patients had received a different cancer therapy, and the patients' cancer had progressed after the patient received the different cancer therapy and expected success in doing so. (EX1003, ¶¶131-35; EX1009, 1034.)

136. Further, I agree with Dr. Neugut that Benson provides the POSA with additional motivation to carry out the methods of treatment described by the MSI-H Study Record, and the POSA would have expected patients to respond to a sufficient degree to the methods that the POSA would have wanted to obtain the data from the study, including determining the outcomes for patients. (EX1003, ¶¶131-35; EX1009, 1034.) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know that the NCCN guidelines recommended clinical studies as a therapy for metastatic cancer patients who had progression after two or more lines of therapy for their cancer. (EX1136, 175:20-179:16.)

137. As such, the POSA would have seen the natural results of treating patients having MSI-H colorectal cancer whose cancer had progressed following a prior drug therapy with pembrolizumab at the dosage that was applied in the clinical study, 10 mg/kg pembrolizumab every two weeks. (See EX1003, ¶¶131-

35; EX1005, 4 (Arms and Interventions); *see also* EX1001 at 8:29-31 (all patients had treatment-refractory, progressive disease); 15:59-63 (all patients with MSI-H colorectal cancer had received two prior chemotherapy regimens).)

138. Therefore, the POSA would have found the additional limitation of Claim 7 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson.

2. **Claim 20: “The method of claim 14, wherein, prior to treatment with the step of selecting pembrolizumab for treating the patient’s colorectal cancer, the patient had received a different cancer therapy, and the patient’s cancer had progressed after the patient received the different cancer therapy.”**

139. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 20 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claims 7. (*See supra* §VII.H.1; EX1003, ¶136; *see also id.* ¶¶131-35.)

3. **Claim 29: “The method of claim 1, wherein the colorectal cancer is metastatic colorectal cancer.”**

140. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 29. (EX2072, ¶¶176-77; *see also* EX1003, ¶¶137-40.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the POSA, in view of the general knowledge in the art, such as Benson, carrying out the methods of treatment found in the MSI-H

Study Record would have been motivated to treat patients wherein the colorectal cancer is metastatic colorectal cancer and expected success in doing so. (*See* EX2072, ¶¶176-77; *see also* EX1003, ¶¶137-40.) Instead, Dr. Lonberg asserts more generally that Benson “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶176.)

141. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record, would have been motivated by Benson, and the general knowledge in the art, to treat patients wherein the colorectal cancer is metastatic colorectal cancer and expected success in doing so because that is the patient population that the POSA would use for such methods of treatment. (EX1003, ¶¶137-40; EX1009, 1034; *see also* EX1005.)

142. Further, I agree with Dr. Neugut that Benson provides the POSA with additional motivation to carry out the methods of treatment described by the MSI-H Study Record, and the POSA would have expected patients to respond to a sufficient degree to the methods that the POSA would have wanted to obtain the data from the study, including determining the outcomes for patients. (EX1003, ¶¶137-40; EX1009, 1034.) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know that the NCCN guidelines recommended clinical

studies as a therapy for metastatic cancer patients who had progression after two or more lines of therapy for their cancer. (EX1138, 175:20-179:16.)

143. As such, the POSA would have seen the natural results of treating patients having MSI-H colorectal cancer whose cancer was metastatic colorectal cancer with pembrolizumab at the dosage that was applied in the clinical study, 10 mg/kg pembrolizumab every two weeks. (*See* EX1003, ¶¶137-40; EX1005, 4 (Arms and Interventions); *see also* EX1001, 8:29-31 (all patients had metastatic disease).)

144. Therefore, the POSA would have found the additional limitation of Claim 29 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson.

4. Claim 30: “The method of claim 14, wherein the colorectal cancer is metastatic colorectal cancer.”

145. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 30 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 29. (*See supra* §VII.H.3; EX1003, ¶141; *see also id.* ¶¶137-40.)

5. **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.”**

146. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 32 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 7. (See *supra* §VII.H.1; EX1003, ¶142; see also *id.* ¶¶131-35.)

6. **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.”**

147. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 34 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 32. (See *supra* §VII.H.5; EX1003, ¶143; see also *id.* ¶142.)

7. **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.”**

148. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 36 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 32. (See *supra* §VII.H.5; EX1003, ¶144; see also *id.* ¶142.)

8. **Claim 37: “The method of claim 29, 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.”**

149. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 37 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 29. (*See supra* §VII.H.3; EX1003, ¶145; *see also id.* ¶137-40.)

9. **Claim 38: “The method of claim 37, 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.”**

150. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 38 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claims 29 and 32. (*See supra* §§VII.H.3, H.5; EX1003, ¶146; *see also id.* ¶¶134-40, 142.)

10. **Claim 39: “The method of claim 29, 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%.”**

151. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 39 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 29. (*See supra* §VII.H.3; EX1003, ¶147; *see also id.* ¶¶134-40.)

11. **Claim 40: “The method of claim 39, 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.”**

152. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 40 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claims 29 and 32. (*See supra* §§VII.H.3, H.5; EX1003, ¶148; *see also id.* ¶¶134-40, 142.)

12. **Claim 41: “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%.”**

153. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 41 in the MSI-H Study Record (alone or combined with Pernot) in combination with Benson for the same reasons stated for Claim 29. (*See supra* §VII.H.3; EX1003, ¶149; *see also id.* ¶¶137-40.)

13. **Claim 42: “The method of claim 41, 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.”**

154. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 42 in the MSI-H Study Record (alone or combined

with Pernot) in combination with Benson for the same reasons stated for Claims 29 and 32. (*See supra* §§VII.H.3, H.5; EX1003, ¶150; *see also id.* ¶¶137-40, 142.)

I. Point 9: Each and Every Limitation of Claims 9, 10, 22, and 23 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, When Considered in Combination with Salipante

155. Dr. Lonberg responds to Dr. Neugut’s opinion that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Salipante to test MSI status by carrying out a PCR or NGS test. (EX2072, ¶178.) In that section of his declaration, Dr. Neugut explains that Salipante discusses different tests to determine whether tumors are MSI-H, including PCR and NGS. (EX1003, ¶¶151-52; EX1010, 1192.) Further, Dr. Neugut explains that Salipante explains that NGS “allows MSI status to be reliably deduced at the same time that other genes of interest are sequenced, without the need for dedicated inclusion of specific markers.” (EX1003, ¶¶151-52; EX1010, 1193.)

156. I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 9, 10, 22, and 23 in the MSI-H Study Record (alone or combined with Pernot) in combination with Salipante.

1. **Claim 9: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample.”**

157. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 9. (EX2072, ¶178; *see also* EX1003, ¶¶153-56.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the POSA, in view of the general knowledge in the art, such as Salipante, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to carry out a PCR test on the sample and expected success in doing so. (*See* EX2072, ¶178; EX1003, ¶¶153-56.) Instead, Dr. Lonberg asserts more generally that Salipante “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶178.)

158. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Salipante, and the general knowledge in the art, to carry out a PCR test on the sample and expected success in doing so. (EX1003, ¶¶153-56; *see also* EX1010, 1192 (“PCR detection of instability at informative microsatellite markers (MSI-PCR) is the chief DNA-based method in current clinical use.”), 1192-93 (Referring to PCR testing as the “gold standard”).) Indeed,

Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know to test MSI status by carrying out a PCR test. (EX1138, 48:6-22.)

159. Therefore, the POSA would have found the additional limitation of Claim 9 in the MSI-H Study Record (alone or combined with Pernot) in combination with Salipante.

2. Claim 10: “The method of claim 1, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample.”

160. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claim 10. (EX2072, ¶178; *see also* EX1003, ¶¶157-60.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that the POSA, in view of the general knowledge in the art, such as Salipante, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to carry out a NGS test on the sample and expected success in doing so. (*See* EX2072, ¶178; EX1003, ¶¶157-60.) Instead, Dr. Lonberg asserts more generally that Salipante “provides no support for either reasonable expectation of success or the ‘in response to’ claim limitation.” (EX2072, ¶178.)

161. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Salipante, and the general knowledge in the art, to

carry out a NGS test on the sample and expected success in doing so. (EX1003, ¶¶157-60; *see also* EX1010, 1192-93; EX1001, 6:25-26 (“Testing of MSI can be accomplished by any means known in the art”); 23:25-27 (citing a paper about next generation sequencing methods).) Indeed, Dr. Lonberg agrees that Salipante describes “an approach to detect the MSI phenotype using NGS.” (EX2072, ¶178 (citing EX1010, 4); *see also* EX1138, 49:2-21, 163:13-18.)

162. Therefore, the POSA would have found the additional limitation of Claim 10 in the MSI-H Study Record (alone or combined with Pernot) in combination with Salipante.

3. Claim 22: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out a polymerase chain reaction test on the sample.”

163. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 22 in the MSI-H Study Record (alone or combined with Pernot) in combination with Salipante. (*See* EX1003, ¶161; *see also* ¶¶153-56.)

4. Claim 23: “The method of claim 14, wherein the testing or having tested comprises carrying out or having carried out next generation sequencing on the sample.”

164. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 23 in the MSI-H Study Record (alone or combined

with Pernot) in combination with Salipante. (*See* EX1003, ¶162; *see also* ¶¶157-60.)

J. Point 10: Each and Every Limitation of Claims 11-12 and 24-25 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in Combination with Hamid

165. Dr. Lonberg responds to Dr. Neugut's opinion that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Hamid to administer pembrolizumab intravenously. (EX2072, ¶179.) 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, ¶¶163-72; *see also* EX1011, 134.)

166. I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 11, 12, 24, and 25 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid.

1. Claim 11: "The method of claim 1, wherein the pembrolizumab is administered to the patient intravenously."

167. Dr. Lonberg does not disagree in his declaration with Dr. Neugut's opinion regarding the additional limitation of Claim 11. (EX2072, ¶179; *see also* EX1003, ¶¶163-69.) Specifically, Dr. Lonberg does not state disagreement with

Dr. Neugut’s opinion that the 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, ¶179; EX1003, ¶¶163-69; *see also* EX1011, 134-35.) Instead, Dr. Lonberg asserts more generally that Hamid “provides no support for the ‘in response to’ claim limitation.” (EX2072, ¶179.)

168. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, the 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, ¶¶163-69; EX1011, 134-35; *see also* EX1055, 1.) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, the POSA would know to administer pembrolizumab to a patient intravenously. (EX1138, 179:19-183:16.)

169. Therefore, the POSA would have found the additional limitation of Claim 11 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid.

**2. Claim 12: “The method of claim 2,
wherein the pembrolizumab is
administered to the patient intravenously.”**

170. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 12 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid for the same reasons stated for Claim 11. (*See supra* §VII.J.1; EX1003, ¶170; *see also id.* ¶¶165-69.)

**3. Claim 24: “The method of claim 14,
wherein the pembrolizumab is
administered to the patient intravenously.”**

171. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 24 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid for the same reasons stated for Claim 11. (*See supra* §VII.J.1; EX1003, ¶171; *see also id.* ¶¶165-69.)

**4. Claim 25: “The method of claim 15,
wherein the pembrolizumab is
administered to the patient intravenously.”**

172. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 25 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid for the same reasons stated for Claim 11. (*See supra* §VII.J.1; EX1003, ¶172; *see also id.* ¶¶165-69.)

K. Point 11: Each and Every Limitation of Claims 13 and 26 is Found in the MSI-H Study Record, or the MSI-H Study Record in View of Pernot, in Combination with Hamid

173. Dr. Lonberg responds to Dr. Neugut's opinion that the POSA would have been motivated to combine the MSI-H Study Record (whether alone or combined with Pernot) and Hamid and Steinert to administer pembrolizumab intravenously and to test body fluid from the patient. (EX2072, ¶180.)

174. I agree with Dr. Neugut that the POSA would have found the additional limitations of Claims 11, 12, 24, and 25 in the MSI-H Study Record (alone or combined with Pernot) in combination with Hamid and Steinert.

1. Claim 13: "The method of claim 3, wherein the pembrolizumab is administered to the patient intravenously."

175. Dr. Lonberg does not disagree in his declaration with Dr. Neugut's opinion regarding the additional limitation of Claim 13. (EX2072, ¶180; *see also* EX1003, ¶173.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut's opinion that the POSA, in view of the general knowledge in the art, such as Steinert and Hamid, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to test body fluid from the patient and administer pembrolizumab to the patient intravenously and expected success in doing so. (*See* EX2072, ¶180; EX1003, ¶173.) Instead, Dr. Lonberg asserts more

generally that Steinert and Hamid do not provide a reasonable expectation of success. (EX2072, ¶180.)

176. I disagree because I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 13 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert and Hamid for the same reasons stated for Claims 3 and 11. (*See supra* §§VII.G.1, J.1; EX1003, ¶173; *see also id.* ¶¶123-27, 165-69.)

2. Claim 26: “The method of claim 16, wherein the pembrolizumab is administered to the patient intravenously.”

177. I agree with Dr. Neugut that the POSA would have found the additional limitation of Claim 26 in the MSI-H Study Record (alone or combined with Pernot) in combination with Steinert and Hamid for the same reasons stated for Claims 11 and 16. (*See supra* §§VII.G.2, J.1; EX1003, ¶174; *see also id.* ¶¶123-28, 165-69.)

L. Point 12: JHU’s Alleged Secondary Considerations Are Fundamentally Flawed

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

179. 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, ¶¶181-90; EX2130 ¶¶10, 24-30, 40, 49; EX2090 ¶¶27-65.) Further, Dr. Lonberg, Dr. Goldberg, and Dr. Le do not put forth evidence from the correct time period. (*Id.*)

180. 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, ¶186.) 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, ¶186; EX2090, ¶55.) 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.) Dr. Goldberg’s opinions regarding BMS are similarly from the incorrect point in time. (EX2090 ¶55.) Further, this alleged evidence is not tied to any of the patent claims.

181. 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.)

182. Similarly, Dr. Lonberg points to “the unexpected results yielded by the invention.” (EX2072, ¶187.) 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, ¶189; *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 the POSA knew as of January 2013. (See EX2072, ¶189; *see also* EX1057, 2.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (*See supra*

¶¶40, 113; EX1116, 19-20.) Further, [REDACTED]

[REDACTED]

183. 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 initial phase” of the study (later changed to “initiation or conduct of the trial until later”). (EX2130, ¶¶19, 34, EX1145 ¶19.) 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, ¶55.)

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

185. 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, ¶¶28-65.) In particular, Dr. Goldberg discusses chemotherapy and targeted therapies available in 2010-2015 but does not tie any of this evidence to any of the patent claims. (EX2090, ¶¶28-65.) Further, Dr. Goldberg omits any discussion of the prior art known to the POSA as of July 10, 2015, including the MSI-H Study Record that describes the claimed method of treatment. (EX2090, ¶¶28-65; *see also* EX1003, ¶¶33-49.)

186. 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 the 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 ¶¶28-64; *see also supra* §VII.C.1; EX1003 ¶¶33-49.) By ignoring the MSI-H Study Record and the other prior art known to the POSA as of July 10, 2015, Dr. Goldberg's analysis of an alleged long-felt unmet need focuses on the incorrect point in time and colorectal cancer more generally.

187. The approvals of Keytruda to treat patients with metastatic MSI-H cancer and metastatic 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.) Indeed, as of July 10, 2015, the method of treating a colorectal cancer patient by testing to determine that the patient's colorectal cancer is MSI-H, and in response to that determination, treating the patient with a therapeutically effective amount of pembrolizumab was already being met and was reasonably expected to be successful. (EX1005; *see also supra* §§VII.D-K.)

VIII. CONCLUSION

188. In summary, it is my opinion that, consistent with Dr. Neugut's declaration and deposition testimony, 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.

189. 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 so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: January 31, 2025

By: Paul Oberstein

Paul E. Oberstein, M.D.

Appendix A

EX1001	U.S. Patent No. 11,591,393 (the “’393 patent”)
EX1002	File History of the ’393 patent (U.S. Patent Application No. 17/465,101)
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, <i>Colorectal Cancer and Immunity: What We Know and Perspectives</i> , 20(14) World J. Gastroenterology 3738 (April 2014)
EX1007	Chapelle et al, <i>Clinical Relevance of Microsatellite Instability in Colorectal Cancer</i> , 28(20) J. Clinical Oncology 3380 (2010)
EX1008	Steinert et al, <i>Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer</i> , 74(6) Cancer Research OF1 (March 2014)
EX1009	Benson et al, <i>Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology</i> , 12(7) J. Nat’l Comprehensive Cancer Network 1028 (July 2014)
EX1010	Salipante et al, <i>Microsatellite Instability Detection by Next Generation Sequencing</i> , 60(9) Clinical Chemistry 1192 (June 2014)
EX1011	Hamid et al, <i>Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma</i> , 369(2) New Eng. J. Medicine 134 (July 2013)
EX1012	Laheru et al, <i>Immunotherapy for Pancreatic Cancer Science Driving Clinical Progress</i> , 5 Nature Revs. 459 (June 2005)

EX1013	Topalian et al, <i>Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer</i> , 366(26) New Eng. J. Med. 2443 (June 28, 2012)
EX1014	Pardoll, <i>The Blockade of Immune Checkpoints in Cancer Immunotherapy</i> , 12 Nature Revs. 252 (April 2012)
EX1015	Kang et al, <i>Pembrolizumab KEYNOTE-001: An Adaptive Study Leading to Accelerated Approval for Two Indications and a Companion Diagnostic</i> , 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, <i>Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) Diagnostics</i> , 99(4) J. Nat’l Cancer Inst. 291 (2007)
EX1019	Fujiwara et al, <i>Accumulated Clonal Genetic Alterations in Familial and Sporadic Colorectal Carcinomas with Widespread Instability in Microsatellite Sequences</i> , 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	<i>Merck Sharp & Dohme LLC v. The Johns Hopkins University</i> , 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, <i>PD-1 Blockade in Tumors with Mismatch-Repair Deficiency</i> , 372(26) New Eng. J. Medicine 2509 (June 25, 2015)
EX1032	Champiat et al, <i>Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy</i> , 3(1) OncoImmunology e27817-1(January 2014)

EX1033	Gatalica et al, <i>Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type</i> , <i>Cancer, Epidemiology</i> , 23(12) Biomarkers & Prevention 2965 (November 12, 2014)
EX1034	Brown et al, <i>Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival</i> , 24(5) <i>Genome Research</i> 743 (May 2014)
EX1035	Ogino et al, <i>Cancer Immunology - Analysis of Host and Tumor Factors for Personalized Medicine</i> , 8(12) <i>Nature Revs. Clinical Oncology</i> 711 (2011)
EX1036	Tougeron et al, <i>Tumor-Infiltrating Lymphocytes in Colorectal Cancers with Microsatellite Instability Are Correlated with the Number and Spectrum of Frameshift Mutations</i> , 22(9) <i>Modern Pathology</i> 1186 (2009)
EX1037	Nosho et al, <i>Tumour-infiltrating T-cell Subsets, Molecular Changes in Colorectal Cancer and Prognosis: Cohort Study and Literature Review</i> , 222(4) <i>J. Pathology</i> 350 (2010)
EX1038	Kim et al, <i>Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types</i> , 28(supp.3) <i>Oncology</i> 15 (November 10, 2014)
EX1039	Llosa et al, <i>Immune Checkpoints Expression in MSI Versus MSS Colorectal Cancers and Their Potential Therapeutic Implications</i> , J. 32(15) <i>Clinical Oncology</i> 243s (May 2014)
EX1040	Loi et al, <i>Host Antitumor Immunity Plays a Role in the Survival of Patients With Newly Diagnosed Triple-Negative Breast Cancer</i> , 32(27) <i>J. Clinical Oncology</i> 2935 (July 28, 2014)
EX1041	Donnard et al, <i>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</i> , 5(19) <i>OncoTarget</i> 199 (October 15, 2014)
EX1042	Kansara et al, <i>Translational Biology of Osteosarcoma</i> , 14(11) <i>Nature Revs. Cancer</i> 722 (October 16, 2014)

EX1043	U.S. Provisional Patent App. No. 62/190,977
EX1044	Tay et al, <i>A Combined Comparative Genomic Hybridization and Expression Microarray Analysis of Gastric Cancer Reveals Novel Molecular Subtypes</i> 1,2, 63(12) Cancer Research 3309 (2003)
EX1045	Wahlberg et al, <i>Evaluation of Microsatellite Instability and Immunohistochemistry for the Prediction of Germ-Line MSH2 and MLH1 Mutations in Hereditary Nonpolyposis Colon Cancer Families</i> , 62(12) Cancer Research 3485 (2002)
EX1046	Taggart et al, <i>High-level Microsatellite Instability in Appendiceal Carcinomas</i> , 37(8) Am. J. Surgical Pathology 1192 (August 2013)
EX1047	Stintzing et al, <i>Management of Colorectal Cancer</i> , 6 F1000 Prime Reports 1 (November 4, 2014)
EX1048	Eisenhauer et al, <i>New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)</i> , 45(2) Eur. J. Cancer 228 (2009)
EX1049	Matikas et al, <i>The Place of Targeted Agents in the Treatment of Elderly Patients with Metastatic Colorectal Cancer</i> , 7(1) Cancers 439 (March 13, 2015)
EX1050	Lee et al, <i>Novel Therapies in Development for Metastatic Colorectal Cancer</i> , 7(4 Supp. 1) Gastrointestinal Cancer Research 1 (September 2015)
EX1051	Lal et al, <i>An Immunogenomic Stratification of Colorectal Cancer: Implications for Development of Targeted Immunotherapy</i> , 4(3) OncoImmunology 1 (April 2, 2015)
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, <i>Future Perspectives in Melanoma Research: Meeting Report from the “Melanoma Bridge”, Napoli, December 5th-8th 2013</i> , 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
EX1057	Lipson et al, <i>Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody</i> , 19(2) Clinical Cancer Research 462 (January 2015)
EX1058	Drescher et al, <i>Lymphocyte Recruitment into the Tumor Site is Altered in Patients with MSI-H Colon Cancer</i> , 8(3) Familial Cancer 231 (2009)
EX1063	Dimasi et al, <i>Clinical Approval Success Rates for Investigational Cancer Drugs</i> , 94(3) Clinical Pharmacology & Therapeutics 329 (September 2013)
EX1064	Le et al, Supplementary Appendix to <i>PD-1 Blockade in Tumors with Mismatch-Repair Deficiency</i> , 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
EX1068	Henry et al, <i>Cancer Biomarkers</i> , 6(2) Molecular Oncology 140 (2012)
EX1069	Garon et al, <i>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)</i> , 25(4) Annals of Oncology September 2014
Ex1070	World Health Organization, <i>International Nonproprietary Names for Pharmaceutical Substances (INN)</i> , 27(2) WHO Drug Information (2013)
EX1071	Roth, <i>Frameshift Mutations</i> , 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)

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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, <i>Treatment of Advanced Disease</i> , 321 British Medical J. 1278 (2000)
EX1079	Le et al, <i>Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors</i> , 32 (15) J. Clinical Oncology (May 2014)
EX1080	Poster presented at ASCO, Le et al, <i>Phase 2 Study of Programmed Death-1 Antibody (Anti-PD-1, MK-3475) in Patients with Microsatellite Unstable (MSI) Tumors</i> (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)
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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, <i>Caris Life Sciences Research Provides Key Clinical Insights on Immunotherapeutic Targets in a Broad Range of Cancers</i> (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
EX1116	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] May 9, 2013 IND Submission to the FDA, SN00
EX1118	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] June 11, 2013 IND Submission to the FDA, SN01
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EX1135	Deposition Transcript of Jennifer Newberger, taken on December 11, 2024
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EX1148	ClinicalTrials.gov, NCT02460198, “Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Previously-Treated Locally Advanced Unresectable or Metastatic Colorectal Cancer (MK-3475-164/KEYNOTE-164),” (May 29, 2015)