

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner

v.

The Johns Hopkins University,
Patent Owner

IPR2024-00648
Patent No. 11,643,462

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

CONTENTS

I.	INTRODUCTION	4
II.	SUMMARY OF MY OPINIONS.....	5
III.	MY QUALIFICATIONS	11
IV.	MATERIALS CONSIDERED	16
V.	CLAIM CONSTRUCTION.....	19
VI.	PERSON OF ORDINARY LEVEL OF SKILL.....	19
VII.	THE CLAIMS OF THE '462 PATENT ARE TAUGHT OR SUGGESTED BY THE PRIOR ART	21
A.	Point 1: Dr. Lonberg's Deposition Testimony Undermines JHU's Arguments	21
B.	Point 2: Dr. Goldberg's Deposition Testimony Undermines JHU's Arguments	24
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	26
1.	[REDACTED]	27
2.	[REDACTED]	31
3.	[REDACTED]	32
4.	Dr. Le's Deposition Testimony.....	33
5.	Dr. Pardoll's Deposition Testimony	34
D.	Point 4: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-30 of the '462 Patent Is Found in the MSI-H Study Record	36

1.	Claim 1	36
2.	Claim 6: “The method of claim 1, wherein the solid tumor is metastatic.”	48
3.	Claim 11	50
4.	Claim 16: “The method of claim 1, wherein the solid tumor is metastatic.”	53
5.	Claim 24: “The method of claim 21, wherein the solid tumor is metastatic endometrial cancer.”.....	53
6.	Claim 28: “The method of claim 25, wherein the solid tumor is metastatic gastric cancer.”	54
7.	Claim 30: “The method of claim 29, wherein the solid tumor is metastatic small bowel cancer.”	54
E.	Point 5: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-30 of the '462 Patent Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson	55
F.	Point 6: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-24 of the '462 Patent Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson, When Considered in Combination with Koh.....	62
G.	Point 7: Each and Every Limitation of Claims 1, 2, 4-7, 9, 11, 12, 14-17, 19, 25, and 26 of the '462 Patent Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson, When Considered in Combination with Ajani.....	64
H.	Point 8: Each and Every Limitation of Claims 2, 8, 12, and 18 of the '462 Patent Is Found in the References Discussed in Above Points 5, 6, or 7, When Considered in Combination with Chapelle.....	66

1.	Claims 2 and 12: “The method of claim [1/11], wherein the biological sample is tumor tissue from the patient.”	67
2.	Claims 8 and 18: “The method of claim [1/18], wherein the step of testing or having tested comprises assessing one or more of: BAT-25, BAT-26, MONO-27, NR-21 and NR-24.”	68
I.	Point 9: Each and Every Limitation of Claims 3 and 13 of the '462 Patent Is Found in the References Discussed in Above Points 5, 6, or 7, When Considered in Combination with Steinert	69
J.	Point 10: Each and Every Limitation of Claims 7 and 17 of the '462 Patent Is Found in the MSI-H Study Record in the References Discussed in Above Points 5, 6, or 7, When Considered in Combination with Hamid	71
K.	Point 11: JHU’s Alleged Secondary Considerations Are Fundamentally Flawed	73
VIII. CONCLUSION		81

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. 11,643,462 (the “’462 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, 160-359) made on behalf of JHU regarding certain patent claims of the ’462 patent, and to provide this Rebuttal Declaration to respond to specific issues raised by them. I was also asked to review deposition transcripts from the depositions of Dr. Lonberg (EX1138; EX1245), Dr. Le (EX1139; EX1246), Dr. Goldberg (EX1136; EX1243), and Dr. Pardoll (EX1140).

3. As I explain below, based on the information that I reviewed and my knowledge applying the perspective of a person of ordinary skill in the art (“POSA”), all claims of the ’462 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 “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma,² pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer” limitation found in Claims 1 and 11.

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.

² I use this spelling of cholangiocarcinoma throughout my declaration, even where the patent specification and/or claims may use a different spelling.

2. I disagree with Dr. Lonberg that the MSI-H Study Record does not provide the “in response to” limitation found in Claims 1 and 11.
3. I disagree with Dr. Lonberg that the MSI-H Study Record does not provide the “cancer that has progressed following at least one prior treatment” limitation found in Claims 1 and 11.
4. I disagree with Dr. Lonberg’s opinion that the MSI-H Study Record does not disclose the “metastatic” cancer limitation found in Claims 6 and 16, the “metastatic endometrial cancer” limitation found in Claim 24, the “metastatic gastric cancer” limitation found in Claim 28, or the “metastatic small bowel cancer” limitation found in Claim 30.
5. I agree with Dr. Neugut that every limitation of Claims 1 and 11, as well as the additional limitations of Claims 2, 4-7, 9, 10, 12, 14-17, and 19-30, are found in the MSI-H Study Record.
6. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, and Benson do not provide the “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder

cancer, testicular cancer and oral cancer” limitation or a reasonable expectation of success.

7. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, and Benson do not provide the “in response to” limitation or a reasonable expectation of success.
8. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, and Benson do not provide the “cancer that has progressed following at least one prior treatment” limitation or a reasonable expectation of success.
9. I disagree with Dr. Lonberg’s opinion that the MSI-H Study Record in combination with Brown, Duval, and Benson do not provide the “metastatic” cancer limitations found in Claims 6 and 16, the “metastatic endometrial cancer” limitation found in Claim 24, the “metastatic gastric cancer” limitation found in Claim 28, or the “metastatic small bowel cancer” limitation found in Claim 30.
10. I agree with Dr. Neugut that every limitation of Claims 1 and 11, as well as the additional limitations of Claims 2, 4-7, 9, 10, 12, 14-17, and 19-30, are found in the MSI-H Study Record in combination with Brown, Duval, and Benson.

11. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Koh do not provide the “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer” limitation or a reasonable expectation of success.
12. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Koh do not provide the “in response to” limitation or a reasonable expectation of success.
13. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Koh do not provide the “cancer that has progressed following at least one prior treatment” limitation or a reasonable expectation of success.
14. I disagree with Dr. Lonberg’s opinion that the MSI-H Study Record in combination with Brown, Duval, Benson, and Koh do not provide the “metastatic” cancer limitations found in Claims 6 and 16, or the “metastatic endometrial cancer” limitation found in Claim 24.

15. I agree with Dr. Neugut that every limitation of Claims 1 and 11, as well as the additional limitations of Claims 2, 4-7, 9, 10, 12, 14-17, and 19-24, are found in the MSI-H Study Record in combination with Brown, Duval, Benson, and Koh.
16. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Ajani do not provide the “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer” limitation or a reasonable expectation of success.
17. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Ajani do not provide the “in response to” limitation or a reasonable expectation of success.
18. I disagree with Dr. Lonberg that the MSI-H Study Record in combination with Brown, Duval, Benson, and Ajani do not provide the “cancer that has progressed following at least one prior treatment” limitation or a reasonable expectation of success.

19. I disagree with Dr. Lonberg's opinion that the MSI-H Study Record in combination with Brown, Duval, Benson, and Ajani do not provide the "metastatic" cancer limitations found in Claims 6 and 16.
20. I agree with Dr. Neugut that every limitation of Claims 1 and 11, as well as the additional limitations of Claims 2, 4-7, 9, 12, 14-17, 19, 25, and 26 are found in the MSI-H Study Record in combination with Brown, Duval, Benson, and Ajani.
21. I agree with Dr. Neugut that every limitation of Claims 1, 3-7, 9-11, 13-17, and 19-30, as well as the additional limitations of Claims 2, 8, 12, and 18, are found in the reference combinations discussed in points 6-20 above, when considered in combination with Chapelle.
22. I agree with Dr. Neugut that every limitation of Claims 1, 2, 4-12, and 14-30, as well as the additional limitations of Claims 3 and 13, are found in the reference combinations discussed in points 6-20 above, when considered in combination with Steinert.
23. I agree with Dr. Neugut that every limitation of Claims 1-6, 8-16, and 18-30, as well as the additional limitations of Claims 7 and 17, are found in the reference combinations discussed in points 6-20 above, when considered in combination with Hamid.

III. MY QUALIFICATIONS

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

6. I am also the co-Director of the Pancreas Disease Center at NYU Langone Health and an Associate Professor in the Department of Medicine at NYU Langone Health. I was formerly Director of GI Oncology at the Perlmutter Cancer Center at NYU Langone Health and Assistant/Interim Director of the Pancreatic Cancer Center at the Perlmutter Cancer Center at NYU Langone Health.

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

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

9. I became board certified in Internal Medicine in 2009 and in Medical Oncology in 2014. Then, in 2015, I obtained my Masters in Biostatistics from Columbia University, where I focused on issues related to clinical and translational investigation and the design and statistical analysis of clinical studies.

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

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

12. I am also a member of the Protocol Review and Monitoring Committee (“PRMC”) in the Perlmutter Cancer Center at NYU Langone Health. The PRMC is tasked with reviewing the detailed plans and protocols for proposed clinical studies to evaluate their scientific quality and validity, among other things. If the PRMC approves the proposed clinical study, the clinical study protocol is sent to the Institutional Review Board (“IRB”) for review. The IRB assesses the

safety, efficacy, benefits, adverse reactions, and outcomes of proposed clinical studies with the primary goal of ensuring patient safety. There is a scientific review committee at every healthcare facility that conducts clinical research, and typically, the scientific review committee reviews all proposed clinical studies before they go to the facility's IRB for approval.

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

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

portion of my time to mentoring and advising predoctoral and postdoctoral students and oncology faculty.

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

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

17. My experience and qualifications are further detailed in my curriculum vitae, which I understand has been labeled as Exhibit 1141. I am being compensated at \$800/hour, which is my normal consulting rate, for the time I

spend on this matter. My compensation is not dependent on any of my findings, the presentation of my findings, or the outcome of this proceeding.

IV. MATERIALS CONSIDERED

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

- The declaration of Dr. Alfred I. Neugut, dated March 13, 2024 (EX1003),
- The declaration of Dr. Nils Lonberg, dated January 23, 2025 (EX2072),
- The declaration of Dr. Richard Goldberg, dated January 22, 2025 (EX2090),
- The declaration of Dr. Dung Le, dated January 22, 2025 (EX2130),
- The deposition transcripts of Dr. Lonberg (EX1138), Dr. Goldberg (EX1136), and Dr. Le (EX1139) from the IPR2024-00240 proceeding involving U.S. Patent No. 11,591,393 (the '393 proceeding),
- The deposition transcripts of Dr. Lonberg (EX1245), Dr. Goldberg (EX1243), and Dr. Le (EX1246) from this proceeding,

- [REDACTED]
[REDACTED]
[REDACTED]
- The '462 patent (EX1001),
- The MSI-H Study Record (EX1005),
- Brown et al, *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) *Genome Research* 743 (May 2014) ("Brown") (EX1034),
- Duval et al, *The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas*, 101(14) *Proceedings of the National Academy of Sciences* 5002 (2004) ("Duval") (EX1087),
- 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),
- Koh et al, *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) *J. Nat'l Comprehensive Cancer Network* 248 ("Koh") (February 2014),
- Ajani et al, *Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines*, 11(5) *J. Nat'l Comprehensive Cancer Network* 531 ("Ajani") (May 2013),

- 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),
- Hamid et al, *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) New England J. Medicine 134 (July 2013) (“Hamid”) (EX1011),
- Le et al, *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency*, 372(26) New Eng. J. Medicine 2509 (June 25, 2015) (“NEJM 2015”) (EX1031),
- The materials in Appendix A (Table of Exhibits).

19. My opinions are also based on my appreciation of how a POSA would have understood the claims at issue and the specification of the '462 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 '462 patent, the MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Chapelle, Steinert, and Hamid, and the state of the art as of July 10, 2015.

V. CLAIM CONSTRUCTION

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

VI. PERSON OF ORDINARY LEVEL OF SKILL

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

22. I understand a POSA for purposes of my analysis of the '462 patent is an oncologist or a medical professional in a related field with at least five years of experience with treating cancer patients. A POSA would also have experience in, or access to a person with knowledge of, clinical studies for therapeutics and how they work, as well as experience with, or access to, a pathologist with comparable

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

23. Further, I understand JHU argues a POSA would have a M.D. or graduate-level degree “in the fields of immunology, genetics, or a related field and at least five years of experience (i) conducting immunology research relating to oncology, (ii) conducting genetics research relating to oncology, or (iii) developing and conducting clinical trials on novel cancer therapies in those fields,” and that Dr. Neugut does not meet JHU’s definition for a POSA. (POR at 5-6; EX2072, ¶¶31-32.) I disagree with JHU’s definition for a POSA given that the ’462 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 ’462 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.)

24. All of my opinions expressed in this Declaration are from this perspective of a POSA as of the Alleged Invention Date for the ’462 patent, *i.e.*, July 10, 2015. During this period, I possessed at least the qualifications of a person of ordinary level of skill, as I defined above. Even if JHU’s definition for a

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

VII. THE CLAIMS OF THE '462 PATENT ARE TAUGHT OR SUGGESTED BY THE PRIOR ART

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

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

- The claimed method of treatment requires only two steps, including “testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient” and “in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, prescribing treatment with a therapeutically effective amount of pembrolizumab for the patient determined to have a tumor that is microsatellite instability high or DNA mismatch repair deficient.” (EX1138, 36:18-37:20; 56:7-57:6.)
- As of July 10, 2015, a POSA would know that to determine MSI-H status you could test tumor tissue or bodily fluid. (EX1138, 47:19-48:5.)

- The treatment method in the MSI-H Study Record is not limited to only patients who have had their cancer progress following at least one prior cancer treatment. (EX1245 57:10-14, 57:20-58:2.)
- The treatment method in the MSI-H Study Record does not require treatment of only patients who have had their cancer progress following at least one prior cancer treatment. (*Id.*)
- The MSI-H Study Record does not tell the reader to exclude from the study a patient that has received at least one prior cancer treatment or has had their tumor progress following a prior cancer treatment if the patient has met the inclusion criteria and does not meet any of the exclusion criteria. (EX1245, 48:1-11, 49:2-12.)
- Dr. Neugut's understanding of the type of patients that would be treated in the study described by the MSI-H Study Record (i.e., metastatic cancer patients and patients that received prior treatment or had their cancer progress following prior treatment) is consistent with what actually occurred in the underlying clinical study. (EX1245, 54:20-56:10, 64:6-14, 65:18-21, 66:16-71:14.)
- The rationale for conducting the study described by the MSI-H Study Record would have included (1) that pembrolizumab had shown activity in multiple tumor types, including melanoma and non-small cell lung

cancer, (2) nivolumab had shown activity in melanoma and non-small cell lung cancer, and (3) the complete response of the MSI-H colorectal cancer patient treated with nivolumab. (EX1245, 79:5-80:16.)

- Oncologists would not need specialized experience researching or developing new treatments for cancer to understand the steps of the methods claimed in the '462 patent (EX1245, 13:20-14:1, 14:8-10, 18:22-19:17.)
- A POSA would read the art logically, rationally, and with ordinary creativity. (EX1138, 83:4-85:10.)

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

27. Ultimately, while Dr. Lonberg and I have points of agreement, I disagree with Dr. Lonberg's analysis in several ways. As an initial matter, Dr. Lonberg incorrectly claims that a POSA would read the prior art literature with a "skeptical lens" or disbelief towards what is disclosed, (EX1138, 84:14-16, 85:20-21), even where none of the literature itself has expressed any such skepticism or

teaching away. I do not agree that a POSA would independently inject skepticism or disbelief into analysis of the prior art literature, as I understand a POSA is presumed to have knowledge of all pertinent prior art and to read it logically and rationally, rather than manufacturing motivations or holding any specific emotional biases and beliefs that are not explicitly expressed by the art as a whole.

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

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

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

- As of July 10, 2015, a POSA would know that PD-1 inhibitors could be used to treat MSI-H cancer. (EX1136, 62:2-16; 108:21-110:22.)
- As of July 10, 2015, a POSA would know that MSI-H was a relevant factor in considering potential treatment to explore with clinical trials. (EX1136, 103:18-105:15.)
- Part of the rationale for why a scientist or physician would conduct the study described by the MSI-H Study Record was the known complete

response of the MSI-H cancer patient treated with nivolumab and that nivolumab and pembrolizumab had shown activity as PD-1 inhibitors in other tumor types. (EX1243, 54:17-55:1, 56:7, 62:16-63:8.)

- Before July 10, 2015, a POSA would know that BMS was conducting its own study to treat MSI-H cancer patients with its PD-1 inhibitor. (EX1243, 61:5-13.) A 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.)
- As of July 10, 2015, a POSA, upon hearing a reference to non-colorectal cancer, would have had several non-colorectal cancer types come to mind, including endometrial, small bowel, and gastric cancer, as just a few examples. (EX1136, 115:5-116:22.)

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

31. Further, like Dr. Goldberg, I also frequently ordered MSI testing on my patients prior to July 10, 2015. (EX1243, 48:11-2, 48:22-49:1.)

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

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

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

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

35. As an initial matter, the FDA requires all sponsors of clinical studies involving investigational new drugs that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act to submit an IND to the FDA that includes, among

other things, the protocol for the clinical study. JHU, as the study sponsor for the MSI-H Study with Merck, made IND submissions to the FDA beginning [REDACTED]

[REDACTED].

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. Dr. Le's Deposition Testimony

51. I note the following observations:

- Dr. Le did not seem to recall many aspects of the MSI-H Study as she testified that she could not recall when Merck provided funding (EX1139, 280:9-281:19), could not recall when they began recruiting patients (EX1139, 105:3-112:9), could not recall when patients started being treated (*e.g.*, EX1139 at 114:21-118:18), could not recall when they started observing responses in the patients treated (EX1139, 290:2-292:16), and could not recall any Merck personnel involved in the study (EX1139, 265:17-276:2.)
- Dr. Le did not seem familiar with patents on which she is a named inventor. (*See, e.g.*, EX1139, 11:3-17:10, 234:2-238:5; EX1246, 17:10-21:2, 38:9-20.)

- Dr. Le did not seem familiar with her declaration. (*See, e.g.*, EX1139, 33:14-38:14, 39:5-42:4, 52:15-53:7, 114:1-125:14, 129:14-136:3, 204:15-205:8.)
- Dr. Le did not seem familiar with [REDACTED]
[REDACTED] (*See, e.g.*, EX1139, 239:22-246:3.)

52. Dr. Le did, however, testify that she did not have any recollection that the FDA or JHU's IRB ever challenged the rationale of the MSI-H Study. (*See, e.g.*, EX1139, 258:16-259:15, 264:14-265:3.) Further, Dr. Le confirmed that she and her team ***did not tell the FDA***, based on publications by Topalian (EX1013) and Brahmer (EX2024), that the studies reported were “resoundingly unsuccessful” or should lead to the belief that “colorectal cancer patients should not be understood to be candidates” for PD-1 therapy as JHU suggests in its POR. (EX1139, 249:7-258:2; *see also* POR, 21; EX2130, ¶9.)

5. Dr. Pardoll's Deposition Testimony

53. I note the following observations:

- Dr. Pardoll testified that he was not involved in the MSI-H Study and his “knowledge is really minimal.” (*See, e.g.*, EX1140, 25:16-17, 28:1, 48:3-16, 102:19-103:5.)

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

54. Ultimately, Dr. Pardoll testified that he disagreed with the rationale and anticipated outcome that JHU [REDACTED]

[REDACTED] (*See* EX1140, 57:7-14, 61:17-65:3.) I disagree with Dr. Pardoll.

D. Point 4: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-30 of the '462 Patent Is Found in the MSI-H Study Record

55. Dr. Lonberg responds to Dr. Neugut's opinion that the MSI-H Study Record discloses each and every limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-30 (*see* EX2072, ¶¶102-119), by asserting that the MSI-H Study Record does not disclose certain claim limitations of Claims 1 and 11, and also certain additional limitations found in Claims 2, 4-7, 9, 10, 14-17, and 19-30. (EX2072, ¶¶102-119.) I, however, disagree because I agree with Dr. Neugut's opinions that every limitation of Claims 1 and 11, and the additional limitations of Claims 2, 4-7, 9, 10, 14-17, and 19-30, are found in the MSI-H Study Record. (EX1003, ¶¶50-128.)

56. I note that Dr. Lonberg does not include any testimony in Section IX of his declaration regarding the additional limitations of Independent Claims 1 and 11, and the additional limitations of Claims 2, 4-7, 9, 10, 14-17, and 19-30. Therefore, my analysis in the section below reflects only the claim limitations addressed by Dr. Lonberg.

1. Claim 1

57. Claim 1 recites a method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate

cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, comprising testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab. (EX1001, Claim 1.) Dr. Neugut explained that a POSA would have found every limitation of Claim 1, including the preamble limitations (Limitations [1.pre.a], [1.pre.b], [1.pre.c], and [1.pre.d]), Limitation [1.1], and Limitation [1.2], in the MSI-H Study Record. (EX1003, ¶¶59-79.) Dr. Lonberg alleges that the MSI-H Study Record does not disclose treating “any of the claimed MSI-H cancers” (*i.e.*, Limitation [1.pre.c]), “progressed following at least one prior treatment” (*i.e.*, Limitation [1.pre.d]), and does not disclose “treating the claimed cancers ‘in response to’” determining a patient is MSI-H (*i.e.*, Limitation [1.2]). (EX2072, ¶¶103-106.) I disagree for the reasons I explain below.

- a. **[1.pre.c]: a patient having a solid tumor “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer”**

58. Dr. Lonberg responds to Dr. Neugut’s opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶63-64; EX2072, ¶103.) In that section of Dr. Neugut’s declaration, he explains that the MSI-H Study Record explicitly discusses treating patients having “non-colorectal MSI-H cancer”, and that in the context of the MSI-H Study Record, a POSA would have immediately pictured treating a patient with MSI-H non-CRC cancer as including treating a patient having one of several different types of cancers, including endometrial cancer, small bowel cancer, and gastric cancer. (EX1003, ¶¶63-64.) Dr. Neugut also explains that those tumor types are common in Lynch syndrome, which was known at the time to be closely related to MSI-H. (*Id.*) Therefore, this claim limitation is met.

59. Dr. Lonberg alleges that the MSI-H Study Record “makes no mention” of any specific non-CRC cancers for inclusion in the third patient population, much less one of the sixteen cancer types recited in the independent claims. (EX2072, ¶103.) Dr. Lonberg alleges that a POSA would not (and could not) have understood the specific disclosures of the listed group of cancers “given

the large size” and because “this group continues to grow” (*Id.*) Yet Dr. Lonberg has not provided any reason for why this group of cancers is special in any way, as compared to other types of non-MSI-H non-CRC cancers. Indeed, and as explained, a POSA would have immediately envisaged endometrial cancer, small bowel cancer, or gastric cancer (which are listed in the claims) as types of “non-colorectal cancer.” (*Supra*, ¶58.) Dr. Goldberg also agreed, confirming during deposition that for a POSA at the relevant time seeing a reference to MSI-H non-CRC, a number of cancers would come to mind, including endometrial, gastric, and small bowel cancer, as well as other well-known solid tumors. (EX1243, 115:5-116:22.).

60. As Dr. Neugut explains, and I agree, patients having one of these three types of non-colorectal cancer (endometrial, gastric, or small bowel) would include patients with Lynch syndrome, which was known to be closely related to MSI-H, and therefore would have been routinely tested for MSI-H pursuant to standard practice at the time. (EX1003, ¶¶25, 63, 142.) Notably, the context in which this group of potential cancer types appears in the patent specification in a list of cancers generally known to display the MSI phenotype or a high mutational burden, and which could have been tested and treated at the time. (EX1001, 1:34-41, 6:17-25.)

61. As such, neither the patent nor Dr. Lonberg or Dr. Goldberg suggest or provide support that any particular non-CRC MSI-H cancer in this broad list was different or special in some way.³ I understand that JHU also characterized its purported inventions as concerning “identification of MSI-H as a predictive biomarker”, and the basis for a “tumor-agnostic” indication, rather than on the treatment of any particular non-CRC MSI-H cancers. The treatment limitations in the claims therefore directly match a POSA’s understanding of the disclosures of the MSI-H Study Record in view of the state of the art.

62. Indeed, in the MSI-H Study that is discussed and disclosed in the MSI-H Study Record, the patients actually included and treated in Arm 3 all were

³ Dr. Lonberg points to two references—Bonneville (EX2303) and Akagi (EX2304)—to emphasize the (irrelevant) notion that MSI-H cancers continued to be detected after the Alleged Invention Date, “making this an ever-growing group of indefinite size.” (EX2072, ¶53.) Besides the fact that these references were not available to a POSA by the Alleged Invention Date (and therefore don’t inform a POSA’s understanding during the relevant time frame), if anything they only serve to confirm that by 2017 MSI-H was known to occur in certain cancer types, including for example endometrial cancer, one of the listed non-colorectal cancer types.

reported as having cancer of the following type: gastric, small bowel, endometrial, ampullary, or cholangiocarcinoma. (See EX1031, 3.) Thus, I disagree that the MSI-H Study Record does not disclose a patient that would have had one of the listed cancers.⁴

b. [1.pre.d]: “that has progressed following at least one prior treatment, the method comprising:”

63. Dr. Lonberg responds to Dr. Neugut’s opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (See EX1003, ¶¶65-70; EX2072, ¶¶105-107.) In that section of Dr. Neugut’s declaration, he explains that in the context of the MSI-H Study Record, a POSA would have understood that a patient would have received prior drug therapy and

⁴ Dr. Lonberg’s assertions that the group of MSI-H cancers at the time might have been “large,” or that the group “continues to grow as new MSI-H cancers are detected” are irrelevant in my opinion, as they have no bearing on the undisputed opinion that a POSA would have immediately envisaged a number of the cancers from which a patient may be selected as required by Claim 1. (See EX2072, ¶103.) I also note that Dr. Lonberg (in mentioning that the group “continues to grow”) does not appear to be viewing the prior art from the perspective of a POSA *as of the Alleged Invention Date*.

had the cancer progress after that therapy. (EX1003, ¶¶65-70.) Therefore, this claim limitation is met. (EX1003, ¶¶65-70.)

64. 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, ¶¶105-107.) In that section of Dr. Neugut's declaration, however, he explains that the MSI-H Study Record's Eligibility Criteria requires that patients have "measurable disease," and Study Identification section mentions "tumors," and these disclosures in the *context of the MSI-H Study Record* tell a POSA that the cancer patients being treated would have received prior drug therapies and had their cancers progress after those therapies. (See EX1003, ¶¶65-70; see also EX1005, 2 (Study Identification), 5-6 (Eligibility Criteria).)

65. At the time of the study, there were two standard chemotherapy regimens (FOLFOX and FOLFIRI) for colorectal cancer. It is reasonable to assume that patients would typically receive such standard of care before trying a novel therapeutic agent. This would meet and exceed the '462 patent requirement of at least one prior therapy. I agree with Dr. Neugut that in the context of the MSI-H Study Record, where the underlying phase 2 clinical study involves a new immunotherapy drug, that was not yet FDA-approved, and which was known to

elicit a strong immune response in patients, a POSA would understand that patients with metastatic and advanced cancer that would participate in such a study would have received prior drug therapies and had their cancers progress after such therapies. (EX1003, ¶¶65-70; *see also* EX1020, PDF p. 25; EX1009, 1034; EX1047, 4-7.) Accordingly, if the intent was to only treat “first line” patients, who had not been previously treated, a POSA would therefore expect an explicit carve out excluding all patients who had been previously treated. There is no such carve out in the MSI-H Study Record. In fact, during his deposition, even Dr. Lonberg himself, explained that his opinion is that the treatment method in the MSI-H Study Record is not limited or does not require *only* patients who have received at least one prior cancer therapy and had their cancer progress, and confirmed that he is not asserting that the MSI-H Study Record excludes or otherwise suggests that such patients are ineligible. (EX1245, 57:5-58:2; *id.*, 49:2-1.)

66. I also agree with Dr. Neugut that because the MSI-H Study Record’s Eligibility Criteria specifically excludes only “[p]atients who have had prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies” from the clinical study, a POSA would have understood and expected a patient to have instead undergone other prior and/or different cancer therapies before enrollment. (EX1003, ¶68; EX1005, 5-6 (Eligibility Criteria).)

67. I understand that an update to the MSI-H Study Record was posted in January of 2016. This update included a few changes, to both inclusion and exclusion criteria for any new patients recruited after that time, and among them, specified “[p]atients with colon cancer must have received at least two prior cancer therapy regimens,” and “[p]atients with other cancer types must have received at least one prior cancer therapy.” (EX2166, 8.) I understand that Dr. Lonberg opines that “it would have been superfluous to later amend the ClinicalTrials.gov record to add a requirement that was allegedly already disclosed in the MSI-H Study Record.” (EX2072, ¶107.) I disagree.

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

treatment with a prior cancer therapy drug. This is consistent with the reality that the patients enrolled and treated prior to January 2016 did, in fact, meet those requirements.⁵ (*See* EX1031, 4-5 (confirming that the MSI-H Study Record enrolled patients with CRC that had at least two prior cancer therapies and non-CRC patients having at least one); EX1001, 15:67-16:9.)

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

⁵ I also understand that JHU similarly cites to a 2014 ASCO poster. This reference, likewise, has no bearing on how a POSA would have understood the MSI-H Study Record at the Alleged Invention Date, and also serves to confirm that the actually treated patients were consistent with a POSA's understanding of the disclosures of the MSI-H Study Record. These documents also serve a very different purpose, with the MSI-H Study Record being used, in part, as a way to recruit patients, while the 2014 ASCO poster publicizes and explain the details of the study that had already been completed to a wider audience.

- c. **[1.2]: “in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.”**

70. Dr. Lonberg responds to Dr. Neugut’s opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record 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 ’462 patent (with any required efficacy being a natural result of that dosage), in response to a patient meeting the eligibility criterion of having MSI-H non-colorectal cancer. (See EX2072, ¶104; EX1003, ¶¶76-79; *see also* EX1005, 5-6 (Eligibility Criteria), 4 (Arms and Interventions); EX1001, 8:52-56, 13:28-30.)

71. Dr. Lonberg argues that the MSI-H Study Record does not provide this limitation because the MSI-H Study Record discloses treating “all” MSI-H non-CRC patients with pembrolizumab “the same,” and thus the MSI-H Study Record does not provide any instruction to treat individuals in response to specifically identifying one of the claimed cancer types as having the MSI-H biomarker. (EX2072, ¶104.) I disagree.

72. 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 non-colorectal cancer. (EX1003, ¶¶63-64, 76; 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, ¶¶71-79.) Indeed, the Inclusion Criteria discusses that MSI-H non-colorectal cancer patients can be placed **only** in the arm of the study that is composed of patients having MSI-H non-colorectal cancer. (See EX1005 at 5 (Inclusion Criteria) ("1. Arm 3 only: Patients with MSI positive non-colorectal cancer"); see also EX1003, ¶¶76-79.) Additionally, the Arms and Interventions section provides that patients in the MSI-H non-colorectal cancer arm are treated with 10 mg/kg pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions), see also EX1003, ¶¶76-79.)

73. As stated in his declaration, Dr. Lonberg agrees that the MSI-Study Record discloses treating an MSI-H non-colorectal cancer patient with pembrolizumab, including a non-CRC MSI-H patient with one of the claimed cancer types. (EX2072, ¶104.) And as Dr. Lonberg testified, he also agrees that a POSA would have understood a non-CRC MSI-H patient to have been tested for their MSI status tested prior to participating in the MSI-H Study. (EX1138, 101:8-102:5, 114:15-115:21.) Yet despite these points of agreement, Dr. Lonberg concludes that although the MSI-H Study Record makes these disclosures, it therefore does not disclose ***the specific list of sixteen cancers as a whole***, which he appears to believe would be necessary to identify a patient with a tumor type

selected from any of the sixteen identified cancers, as required by Claim 1. (*Id.*) I disagree. As discussed by Dr. Neugut and Dr. Goldberg, I also agree a POSA would have had several types of non-colorectal cancer come to mind, including endometrial, small bowel, and gastric cancer, which are included in the list of cancers that appears in the independent claim. Therefore, there can be no credible dispute that a MSI-H non-CRC patient enrolled and treated in the study was treated in response to determining the patient had a non-CRC MSI-H solid tumor, as set out in Claim 1.

**2. Claim 6: “The method of claim 1,
wherein the solid tumor is metastatic.”**

74. Dr. Lonberg responds to Dr. Neugut’s opinion that a POSA would have concluded that this limitation was found in the MSI-H Study Record. (*See* EX1003, ¶¶65-70, 86; EX2072, ¶¶108-112.) In that section of Dr. Neugut’s declaration, he explains that in the context of the MSI-H Study Record a POSA would have understood that patients would have metastatic and advanced cancer, and therefore, this claim limitation is met. (EX1003, ¶86-87.)

75. 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, ¶¶108-112.) Specifically, Dr. Lonberg states that “the words ‘measurable’ and ‘metastatic’ are not equivalent,” and therefore, “to the extent Dr.

Neugut relies on the MSI-H Study's use of 'measurable disease' as disclosing 'metastatic cancer,' such conflation is incorrect." (EX2072, ¶¶108-112.) Dr. Neugut, however, does not state in his declaration that those words *are* equivalent. (EX1003, ¶¶65-70, 86-87.) Instead, in that section of Dr. Neugut's declaration, he explains that the MSI-H Study Record's Eligibility Criteria requires that patients have "measurable disease," and Study Identification section mentions "tumors," and these disclosures in the *context of the MSI-H Study Record* tell a POSA that the colorectal cancer patients being treated have metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. (See EX1003, ¶¶65-70, 86-87; see also EX1005, 5-6 (Eligibility), 2 (Study Identification).)

76. I agree with Dr. Neugut that in the context of the MSI-H Study Record, where the underlying phase 2 clinical study involves a new immunotherapy drug, a POSA would understand that the MSI-H Study Record requires that the cancer patients being treated have metastatic cancer or cancer that is so locally advanced it is unresectable for purposes of a cure. (EX1003, ¶¶65-70; see also EX1020, PDF p. 25; EX1078, 1278.) Otherwise, if a cancer patient had cancer that is resectable for the purposes of a cure, then a POSA would expect that a physician would excise the tumor(s) for cure. (EX1003, ¶¶65-70; 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.)

77. I also agree with Dr. Neugut that a POSA would have found it extremely unusual for a study like the MSI-H Study described by the MSI-H Study Record to not include a patient with metastatic colorectal cancer, especially without any kind of explicit carve-out. (EX1003, ¶68.) In fact, even Dr. Lonberg agreed in his deposition that the MSI-H Study Record does not exclude patients with metastatic disease, only asserting that is not so limited. (EX1245, 50:7-10, 51:4-7, 58:3-10.)

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

3. Claim 11

79. While Dr. Lonberg alleges that Claim 11 is not met by the disclosures of the MSI-H Study Record, he does not provide any analysis specific to Claim 11, or to distinguish it in any way from Claim 1. Instead, Dr. Lonberg alleges that Claim 11 is not met for the same reason he alleges Claim 1 is not met; that the

MSI-H Study Record does not disclose treating “any of the claimed MSI-H cancers” (*i.e.*, Limitation [11.pre.c]), “progressed following at least one prior treatment” (*i.e.*, Limitation [11.pre.d]), and does not disclose “treating the claimed cancers ‘in response to’” determining a patient is MSI-H (*i.e.*, Limitation [11.2]). (EX2072, ¶¶103-106.) I disagree.

- a. **[11.pre.c]: a patient having a solid tumor “selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer”**

80. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 11 limitation [11.pre.c] for the same reason as he argues for Claim 1 limitation [1.pre.c]. (EX2072, ¶103.) Dr. Neugut explains that the analysis for Claim 1 limitation [1.pre.c] is the same for Claim 11 limitation [11.5] because the limitation recited in Claim 1 limitation [1.pre.c] is the same as recited in Claim 11 limitation [11.pre.c]. (EX1003, ¶¶98-99; *see also* ¶¶25-26, 63-64.) I agree with Dr. Neugut, and thus, a POSA would have concluded that limitation [11.pre.c] of Claim 11 was found in the MSI-H Study Record for the same reason as Claim 1 limitation [1.pre.c]. (EX1003, ¶¶98-99; *see also id.* ¶¶25-26, 63-64.)

b. [11.pre.d]: “that has progressed following at least one prior treatment, the method comprising:”

81. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 11 limitation [11.pre.d] for the same reason as he argues for Claim 1 limitation [1.pre.d]. (EX2072, ¶¶105-107.) Dr. Neugut explains that the analysis for Claim 1 limitation [1.pre.d] is the same for Claim 11 limitation [11.pre.d] because the limitation recited in Claim 1 limitation [1.pre.d] is the same as recited in Claim 11 limitation [11.pre.d]. (EX1003, ¶100; *see also* ¶¶65-70.) I agree with Dr. Neugut, and thus, a POSA would have concluded that limitation [11.pre.d] of Claim 11 was found in the MSI-H Study Record for the same reason as Claim 1 limitation [1.pre.d]. (EX1003, ¶100; *see also id.* ¶¶65-70.)

c. [11.2]: “in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, prescribing treatment with a therapeutically effective amount of pembrolizumab for the patient determined to have a tumor that is microsatellite instability high or DNA mismatch repair deficient.”

82. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 11 limitation [11.2] for the same reason as he argues for Claim 1 limitation [1.2]. (EX2072, ¶104.) Dr. Neugut explains that the analysis for Claim 1 limitation [1.2] is the same for Claim 11 limitation [11.2] because the limitation recited in Claim 1 limitation [1.2] is the same as recited in Claim 11 limitation [11.2]. (EX1003, ¶102; *see also* ¶¶76-79.) I agree with Dr.

Neugut, and thus, a POSA would have concluded that limitation [11.2] of Claim 11 was found in the MSI-H Study Record for the same reason as Claim 1 limitation [1.2]. (EX1003, ¶102; *see also id.* ¶¶76-79.)

**4. Claim 16: “The method of claim 1,
wherein the solid tumor is metastatic.”**

83. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 16 for the same reason as he argues for Claim 6. (EX2072, ¶¶108-112.) Dr. Neugut explains that the analysis for Claim 16 is the same as for Claim 6 because the additional limitation recited in Claim 16 is the same as recited in Claim 6. (EX1003, ¶106.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 16 was found in the MSI-H Study Record for the same reason as Claim 6. (EX1003, ¶106; *see also id.* ¶¶65-70, 86-87.)

**5. Claim 24: “The method of claim 21,
wherein the solid tumor is metastatic endometrial cancer.”**

84. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 24 for the same reason as he argues for Claim 6. (EX2072, ¶¶108-112.) Dr. Neugut explains that the analysis for Claim 24 is the same as for Claim 6 because the additional limitation recited in Claim 24 is the same as recited in Claim 6. (EX1003, ¶¶116-117.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 24 was found in the MSI-H Study

Record for the same reason as Claim 6. (EX1003, ¶¶116-117; *see also id.* ¶¶65-70, 86-87.)

**6. Claim 28: “The method of claim 25,
wherein the solid tumor is metastatic gastric cancer.”**

85. Dr. Lonberg asserts that the MSI-H Study Record does not disclose the method of treatment of Claim 28 for the same reason as he argues for Claim 6. (EX2072, ¶¶108-112.) Dr. Neugut explains that the analysis for Claim 28 is the same as for Claim 6 because the additional limitation recited in Claim 28 is the same as recited in Claim 6. (EX1003, ¶¶124-25.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 28 was found in the MSI-H Study Record for the same reason as Claim 6. (EX1003, ¶¶124-25; *see also id.* ¶¶65-70, 86-87.)

**7. Claim 30: “The method of claim 29,
wherein the solid tumor is metastatic small bowel cancer.”**

86. 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 6. (EX2072, ¶¶108-112.) Dr. Neugut explains that the analysis for Claim 30 is the same as for Claim 6 because the additional limitation recited in Claim 30 is the same as recited in Claim 6. (EX1003, ¶¶127-28.) I agree with Dr. Neugut, and thus, a POSA would have concluded that Claim 26 was found in the MSI-H Study

Record for the same reason as Claim 9. (EX1003, ¶¶127-28; *see also id.* ¶¶65-70, 86-87.)

E. Point 5: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-30 of the '462 Patent Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson

87. Dr. Lonberg responds to Dr. Neugut's opinion that Brown, Duval, and Benson provide a POSA with additional motivation to carry out the methods of treatment found in the MSI-H Study Record and to reasonably expect success in doing so. (*See* EX2072, ¶¶141-151; *see also id.* ¶¶120-138.) In that section of his declaration, Dr. Neugut explains that Brown discusses that PD-1 inhibitors naturally have more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize. (EX1003, ¶¶129-149; *see also* EX1034, 747.) Dr. Neugut also explains that Duval discusses that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1003, ¶¶129-149; *see also* EX1087, 5002.) Dr. Neugut further explains that Benson sets forth that, under the standard of care, a patient who would take part in a clinical study such as the one disclosed in the MSI-H Study Record is a patient who has had their cancer progress after previous drug therapy. (EX1003, ¶147, *see also* EX1009, 1034.) Additionally, Dr. Neugut explains that the state of the art known to a POSA as of July 10, 2015 would counsel a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success.

(EX1003, ¶¶129-149; *see also* EX1016; EX1005; EX1017; EX1023, 42; EX1057, 463-64.)

88. Dr. Lonberg, however, asserts that Brown does not provide a POSA with an expectation of success for the claimed methods of treatment because, “at the Critical Date, there were also many factors of MSI-H tumors that taught away from MSI-H cancer patients being good candidates for immunotherapy and especially for checkpoint blockade therapy,” and because “Brown’s discussion of microsatellite instability is limited to the context of Lynch syndrome and CRC.” (EX2072, ¶¶141-146.) Dr. Lonberg further asserts that the data and findings in Duval that “suggested a ‘clinical relationship between the emergence of the tumoral mutator phenotype and host immunodeficiency in a *particular subset of tumors* represented by human lymphomas’ has little to no relevance for *other* kinds of cancers (e.g., those with MSI-H solid tumors) or for *non-immunodeficient* patients with MSI-H tumors.” (EX2072, ¶¶147-150.)

89. I disagree with Dr. Lonberg. First, Dr. Lonberg does not properly consider Brown and Duval (and Benson) together and in the context of the clear disclosures already provided by the primary prior art, the MSI-H Study Record, but instead attempts to address them separately and without appropriate context. Second, as Dr. Neugut explains, and I agree, the MSI-H Study Record discusses treating MSI-H non-colorectal cancer patients with pembrolizumab, an

immunotherapy that targets the PD-1 pathway. (EX1005; *see also* EX1003, ¶¶30-33.) Further, Brown would have told a POSA reading the MSI-H Study Record, and the other references, that PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize, and (2) already infiltrated by many immune cells. (EX1003, ¶130, *see also* EX1034, 743.) Brown also specifically advises a POSA that the “abundance of predicted immunogenic mutations” may be useful to identify patients “likely to benefit from checkpoint blockade.” (EX1034, 743.) As Dr. Neugut further explains, and I agree, Duval further adds to that teaching in disclosing that MSI-H cancers have cancer cells that are easy for immune cells to recognize. (EX1003, ¶132, *see also* EX1087, 5002.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated by Brown and Duval to carry out the methods of treatment found in the MSI-H Study Record.

90. Dr. Lonberg also considers Benson without the context of the MSI-H Study Record when he argues that Benson does not provide a POSA with an expectation of success for the claimed methods of treatment (EX2072, ¶151.) Lonberg also asserts that “nowhere do[es] [Benson] disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic cancer/colorectal cancer progress after such prior treatment, or

have metastatic cancer/colorectal cancer to be enrolled in clinical trials.”

(EX2072, ¶122.)

91. I disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, Benson discusses that, under the standard of care at the Alleged Invention Date, a patient that had a tumor or measurable disease that would take part in a clinical study is a patient who have had their cancer progress after previous drug therapy. (EX1009, 1034; *see also* EX1003, ¶¶146-147.) Further, Benson provides that, under the standard of care, a patient that had a tumor or measurable disease that would take part in a clinical study is a patient having metastatic and advanced disease. (EX1009, 1034; *see also* EX1003, ¶¶146-147.) The MSI-H Study Record discusses treating MSI-H non-colorectal cancer patients with pembrolizumab, an immunotherapy that targets the PD-1 pathway. (EX1005; *see also* EX1003, ¶¶30-33.) Therefore, I agree with Dr. Neugut that a POSA also would have been motivated by Benson to carry out the methods of treatment found in the MSI-H Study Record.

92. Additionally, I agree with Dr. Neugut that the state of the art at the relevant time would motivate a POSA to carry out the methods of treatment found in the MSI-H Study Record with a reasonable expectation of success because a POSA would have known that physicians had successfully treated a non-colorectal cancer patient whose cancer was MSI-H with a PD-1 inhibitor and that

pembrolizumab was approved for another oncology indication. (See EX1003, ¶¶137-140; *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]. (EX2072, ¶178; EX1116, 19; *see also supra*, Section VII.C.1; EX2072, ¶165.) [REDACTED] [REDACTED] [REDACTED]

93. Dr. Lonberg asserts more generally that a POSA would have had no reasonable expectation of success for the claimed methods of treatment because “cancer immunotherapy is a complex and unpredictable technical field;” “there was substantial evidence that MSI-H patients (including 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 ’462 Patent.” (EX2072, ¶¶123-138.)

94. I disagree with Dr. Lonberg, and instead, agree with Dr. Neugut because, in addition to Brown, Duval, and Benson, several other sources independently urged a POSA to treat MSI-H cancer with PD-1 inhibitors or other

immunotherapy. (EX1003, ¶¶137-139; *see also* EX1033, 2968-69; EX1032, e27817-5; EX1037, 2; EX1038, 7; EX1051, e976052-6; EX1039, 243s; *see also* EX1035, 1, 8; EX1036, 1186.) While Dr. Lonberg alleges these “additional references” do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-173), [REDACTED]

[REDACTED]

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

95. Moreover, I agree with Dr. Neugut that the prior art discussed that PD-1 inhibitors naturally had more efficacy when treating tumors that display certain characteristics, which MSI-H tumors were known to display. (*See* EX1003, ¶¶42-47, 137-139; *see also* EX1034, 743, 747; EX1040, 2; EX1038, 5-7, 9; EX1041, 9208-09; EX1042, 731-32; EX1032, e27817-1, -3-5; EX1037, 2.) Again, while Dr. Lonberg alleges these “additional references” do not provide a POSA with a reasonable expectation of success for the methods of treatment claimed (*see* EX2072, ¶¶154-173), [REDACTED]

 (See *supra*, Section VII.C.1; *see also* EX1116, 18-19.)

96. Further, while Dr. Lonberg asserts that “many other contemporary trials of anti-PD-1” failed, this section of his declaration omits any discussion of the contemporary clinical study involving BMS’s anti-PD-1 drug to treat MSI-H colorectal cancer patients. (EX2072, ¶¶132-134; *see also* EX1053.) The study record describing BMS’s treatment of MSI-H colorectal cancer patients with its anti-PD-1 drug posted to clinicaltrials.gov in February 2014, more than 17 months before July 10, 2015. (EX1053.) Indeed, BMS ultimately received accelerated approval from the FDA for the treatment of metastatic MSI-H colorectal cancer based on the results of its contemporary clinical study, which Dr. Lonberg deemed a success. (See EX1120; *see also* EX1138, 238:2-240:15.)

97. Therefore, I agree with Dr. Neugut that Brown, Duval, and Benson would provide a POSA with additional motivation to carry out the claimed methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (See EX1003, ¶¶129-149.)



F. Point 6: Each and Every Limitation of Claims 1, 2, 4-7, 9-12, 14-17, and 19-24 of the '462 Patent Is Found in the MSI-H Study Record in View of Brown, Duval, and Benson, When Considered in Combination with Koh

98. Dr. Lonberg responds to Dr. Neugut's opinion that Brown, Duval, and Benson, when considered in combination with Koh, provide a POSA with additional motivation to carry out the methods of treatment found in the MSI-H Study Record and to reasonably expect success in doing so. (*See* EX2072, ¶151; *see also id.* ¶¶82-83, 106, 121-122.) In that section of his declaration, Dr. Neugut explains that Koh discusses, under the standard of care, clinical studies would include patients having metastatic cancer whose cancer had progressed following prior drug therapies, and that Koh would have motivated a POSA to treat endometrial cancer patients that received prior treatment and who had progressive metastatic disease, and expected success in doing so. (*See* EX1003, ¶¶150-155; EX1095, 256; EX1089, PDF p. 17.) Dr. Neugut also explains that Koh discusses endometrial cancer patients that would participate in a clinical study generally would have had a tumor that has progressed following at least one prior cancer treatment and metastatic cancer. (EX1003, ¶154, EX1095, 256; EX1089, PDF p. 17; *see also* EX1080 at Eligibility Criteria.)

99. In response, Dr. Lonberg asserts more generally that, for the same reasons as Benson, Koh also “would have failed to provide a POSA with a

reasonable expectation of success for the method of treatment claimed in the '462 Patent.” (EX2072, ¶151; *see also* ¶¶82-83.) Specifically, Dr. Lonberg alleges that “like the MSI-H Study Record, Brown, and Duval,” Koh would not have “provided a POSA with a reasonable expectation of success for testing patients who have one of the Claimed MSI-H Cancers for MSI-H status and, in response to determining the patient is MSI-H, treating the patient with pembrolizumab. (*Id.*)

100. I disagree with Dr. Lonberg’s general assertions regarding Koh for the same reasons as discussed regarding Benson in Point 5 above. (*Supra*, Section VII.E.) In particular, in Koh (as in Benson), clinical trials are specified as the standard of care after at least one prior cancer therapy and cancer progression. (EX1009, 1034; EX1095, 256; EX1096, 533-37). I also agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by the MSI-H Study Record (in view of Brown, Duval, and Benson), in combination with Koh, and the general knowledge in the art, to carry out the claimed methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (*See* EX1003, ¶¶150-155.)

**G. Point 7: Each and Every
Limitation of Claims 1, 2, 4-7, 9, 11, 12,
14-17, 19, 25, and 26 of the '462 Patent Is Found
in the MSI-H Study Record in View of Brown, Duval,
and Benson, When Considered in Combination with Ajani**

101. Dr. Lonberg responds to Dr. Neugut's opinion that Brown, Duval, and Benson, when considered in combination with Ajani, provide a POSA with additional motivation to carry out the methods of treatment found in the MSI-H Study Record and to reasonably expect success in doing so. (*See* EX2072, ¶151; *see also id.* ¶¶84-85, 106, 121-122.) In that section of his declaration, Dr. Neugut explains that Ajani discusses, under the standard of care, clinical studies would include patients having metastatic cancer whose cancer had progressed following prior drug therapies, and that Ajani would have motivated a POSA to treat gastric cancer patients that received prior treatment and who had progressive metastatic disease, and expected success in doing so. (*See* EX1003, ¶¶156-161; EX1096 at 533-37; EX1095 at 256; EX1089 at PDF p. 17.)) Dr. Neugut also explains that Ajani discusses gastric cancer patients that would participate in a clinical study generally would have had a tumor that has progressed following at least one prior cancer treatment and metastatic cancer. (EX1003, ¶160, (EX1096 at 533-37 (gastric cancer patients would generally receive a standard first line therapy, unless diagnosis was late stage); EX1094 at PDF p. 12, 15 (same.).))

102. In response, Dr. Lonberg asserts more generally that, for the same reasons as Benson, Ajani also “would have failed to provide a POSA with a reasonable expectation of success for the method of treatment claimed in the ’462 Patent.” (EX2072, ¶151; *see also* ¶¶84-85.) Specifically, Dr. Lonberg alleges that “like the MSI-H Study Record, Brown, and Duval,” Ajani would not have “provided a POSA with a reasonable expectation of success for testing patients who have one of the Claimed MSI-H Cancers for MSI-H status and, in response to determining the patient is MSI-H, treating the patient with pembrolizumab. (*Id.*)

103. I disagree with Dr. Lonberg’s general assertions regarding Ajani for the same reasons as discussed regarding Benson in Point 5 above. (*Supra*, Section VII.E.) In particular, in Ajani (as in Benson and Koh), clinical trials are specified as the standard of care after at least one prior cancer therapy and cancer progression. (EX1009, 1034; EX1095, 256; EX1096, 533-37). I also agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by the MSI-H Study Record (in view of Brown, Duval, and Benson), in combination with Ajani, and the general knowledge in the art, to carry out the claimed methods of treatment found in the MSI-H Study Record with a reasonable expectation of success. (*See* EX1003, ¶¶156-161.)

**H. Point 8: Each and Every
Limitation of Claims 2, 8, 12, and 18
of the '462 Patent Is Found in the References Discussed in Above
Points 5, 6, or 7, When Considered in Combination with Chapelle**

104. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) 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, ¶¶152-53; *see also* ¶¶86-87.) In that section of his declaration, Dr. Neugut explains that Chapelle discusses standard methods of testing to determine whether a tumor is MSI-H, including a test to measure MSI by immunohistochemistry. (EX1003, ¶¶162-171.) I agree with Dr. Neugut that a POSA would have found the additional limitations of Claims 2, 8, 12, and 18 in the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) in combination with Chapelle.

105. Dr. Lonberg does not appear to disagree with what Chapelle teaches regarding methods of testing MSI status. Dr. Lonberg asserts only that Chapelle does not additionally address certain other limitations, including arguing that a POSA would not have a reasonable expectation of achieving success in the claimed treatment of the '462 Patent. (EX2072, ¶¶86-87, 152-53.) But as discussed in Sections VII.E-G above, Chapelle combined with the MSI-H Study

Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) discloses every limitation of Claims 1,2, 4-12, and 14-30.

106. I also disagree with Dr. Lonberg because, as Dr. Neugut explains, and I agree, Chapelle would have motivated a POSA to detect microsatellite markers in a DNA sequence in a tumor sample obtained from the patient with a reasonable expectation of success in doing so. (EX1007, 3380, 3383; *see also* EX1003, ¶¶162-171.) Further, a POSA would have had reason to consider Chapelle, in addition to the MSI-H Study Record and the references discussed in Points 5, 6, or 7, (*supra*, Sections VII.E-G), as these references are in the same field, and Chapelle further discusses standard methods of testing whether a tumor was MSI-H, such as detecting in a tumor sample obtained from the patient a microsatellite marker in a DNA sequence. (EX1007, 3380, 3383; *see also* EX1003, ¶¶162-171.) Therefore, I agree with Dr. Neugut that a POSA would have been motivated by Chapelle to carry out the methods of treatment found in the MSI-H Study Record.

1. Claims 2 and 12: “The method of claim [1/11], wherein the biological sample is tumor tissue from the patient.”

107. As explained, I agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Chapelle, and the general knowledge in the art, to test tumor tissue from the patient and expected success in doing so. (EX1003, ¶¶162-166; EX1007, 3380, 3384; *see also* EX1001, 6:26-27 (“Testing of MSI can

be accomplished by any means known in the art”); 6:36-39 (“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, a 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.”).)

108. Therefore, a POSA would have found the additional limitations of Claims 2 and 12 in the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) in combination with Chapelle.

2. Claims 8 and 18: “The method of claim [1/18], wherein the step of testing or having tested comprises assessing one or more of: BAT-25, BAT-26, MONO-27, NR-21 and NR-24.”

109. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claims 8 and 18. (EX2072, ¶152-153; *see also* EX1003, ¶¶167-169.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that a POSA, in view of the general knowledge in the art, such as Chapelle, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to test tumor tissue from the patient where the microsatellite marker is BAT-25, BAT-26, MONO-27,

NR-21 or NR-24, and expected success in doing so. (*See* EX2072, ¶¶152-153; *see also* EX1003, ¶¶167-169; EX1007 at 3380-84.)

110. I also agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by Chapelle, and the general knowledge in the art, to carry out the method of Claims 8 and 18, wherein the microsatellite marker is BAT-25, BAT-26, MONO-27, NR-21, or NR-24 and expected success in doing so. (EX1003, ¶¶167-169; EX1007 at 3380-84.) Moreover, I agree with Dr. Neugut that the '462 patent does not discuss that the method of testing for MSI-H changes the efficacy of the use of pembrolizumab for treating cancer patients having MSI-H tumors. (EX1003, ¶¶167-169.)

**I. Point 9: Each and Every
Limitation of Claims 3 and 13 of the '462 Patent
Is Found in the References Discussed in Above Points 5, 6, or 7,
When Considered in Combination with Steinert**

111. Dr. Lonberg responds to Dr. Neugut's opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) and Steinert to test body fluid from a patient to determine whether a tumor is MSI-H. (EX2072, ¶¶152-53; *see also* ¶¶88-89.) 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, ¶¶172-177; EX1008, OF6; *see also id.*

OF1.) I agree with Dr. Neugut that a POSA would have found the additional limitations of Claims 3 and 16 in the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) in combination with Steinert.

112. Dr. Lonberg does not disagree in his declaration with Dr. Neugut's opinion regarding the additional limitations of Claim 3 and 13. (EX2072, ¶152-153; *see also* EX1003, ¶¶172-177.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut's opinion that a POSA, in view of the general knowledge in the art, such as 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, ¶152-153; *see also* EX1003, ¶¶172-177.) Instead, Dr. Lonberg asserts more generally that Steinert "fail[s] to address the Petition's shortcomings with respect to showing that a POSA would have a reasonable expectation of achieving success in testing patients who have one of the Claimed MSI-H Cancers for MSI-H status and, in response to determining the patient is MSI-H, treating the patient with pembrolizumab." (EX2072, ¶153.)

113. I disagree because I agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of treatment found in the MSI-H Study Record would have been motivated by 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, ¶¶172-177; EX1008, OF6; EX1001, 6:26-27 (“Testing of MSI can be accomplished by any means known in the art”); 6:36-39 (“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, a POSA would know to test body fluid from a patient to determine MSI-H status. (EX1138, 47:19-48:5.)

114. Therefore, a POSA would have found the additional limitation of Claims 3 and 13 in the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) in combination with Steinert.

J. Point 10: Each and Every Limitation of Claims 7 and 17 of the '462 Patent Is Found in the MSI-H Study Record in the References Discussed in Above Points 5, 6, or 7, When Considered in Combination with Hamid

115. Dr. Lonberg responds to Dr. Neugut’s opinion that a POSA would have been motivated to combine the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) and Hamid to administer pembrolizumab intravenously. (EX2072, ¶¶152-153; *see also* ¶90.) 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, ¶¶178-185; *see also* EX1011, 134.)

116. Dr. Lonberg does not disagree in his declaration with Dr. Neugut’s opinion regarding the additional limitation of Claims 7 and 17. (EX2072, ¶¶152-153; *see also* EX1003, ¶¶178-185.) Specifically, Dr. Lonberg does not state disagreement with Dr. Neugut’s opinion that a POSA, in view of the general knowledge in the art, such as Hamid, carrying out the methods of treatment found in the MSI-H Study Record would have been motivated to administer pembrolizumab to the patient intravenously and expected success in doing so. (*See* EX2072, ¶¶152-153; EX1003, ¶¶178-185; *see also* EX1011, 134-35.) Instead, Dr. Lonberg asserts more generally that Hamid “fail[s] to address the Petition’s shortcomings with respect to showing that a POSA would have a reasonable expectation of achieving success in testing patients who have one of the Claimed MSI-H Cancers for MSI-H status and, in response to determining the patient is MSI-H, treating the patient with pembrolizumab.” (EX2072, ¶153.)

117. I disagree with Dr. Lonberg’s general assertions for the same reasons as discussed in Points 5, 6, or 7 above. (*Supra*, Sections VII.E-G.) I also agree with Dr. Neugut that, as of July 10, 2015, a POSA carrying out the methods of

treatment found in the MSI-H Study Record would have been motivated by Hamid, and the general knowledge in the art, to administer pembrolizumab to the patient intravenously and expected success in doing so. (EX1003, ¶¶178-185; EX1011, 134-35; *see also* EX1055, 1.) Indeed, Dr. Lonberg also agrees that, as of July 10, 2015, a POSA would know to administer pembrolizumab to a patient intravenously. (EX1138, 179:19-183:16.)

118. Therefore, a POSA would have found the additional limitations of Claims 7 and 17 in the MSI-H Study Record (combined with the references discussed in Points 5, 6, or 7 (*supra*, Sections VII.E-G)) in combination with Hamid.

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

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

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

the prior art. (*See, e.g.*, EX2072, ¶¶182-91; EX2130 ¶¶10, 25-31, 41, 50; EX2090 ¶¶27-74.)

121. Dr. Lonberg, Dr. Goldberg, and Dr. Le also do not put forth evidence from the correct time period. (*See, e.g.*, EX2072, ¶¶182-91; EX2130 ¶¶10, 25-31, 41, 50; EX2090 ¶¶27-74.) For example, Dr. Lonberg alleges generally that skepticism for the claimed methods of treatment existed based on a personal narrative about the reason why “decisionmakers within Bristol-Myers Squibb” declined conducting a study with JHU involving BMS’s anti-PD-1 drug in MSI-H colorectal cancer patients. (EX2072, ¶187.) Setting aside that BMS’s study would involve nivolumab, which is not tied to the patent claims, BMS’s decision came in 2012, more than two-and-a-half years before July 10, 2015. (EX2072, ¶187; EX2090, ¶61.) I also note that BMS did, in fact, decide to pursue its own study of its anti-PD-1 drug in MSI-H colorectal cancer patients as early as February 10, 2014, and Dr. Lonberg agreed that as of February 10, 2014, BMS considered that study worth performing. (EX1138, 211:7-10; *see also id.* 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8.) Dr. Goldberg’s opinions regarding BMS are similarly from the incorrect point in time. (EX2090 ¶61.) Further, this alleged evidence is not tied to any of the patent claims.

122. A 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.)

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

[REDACTED]

[REDACTED]

[REDACTED].⁶ (See

⁶ During his deposition, Dr. Goldberg also acknowledged that part of the rationale

supra ¶39; EX1116, 19-20.) [REDACTED]

[REDACTED]

[REDACTED] (See *supra* ¶38;

EX1116, 24.)

124. Dr. Le also points to alleged evidence used to support skepticism and unexpected results from the wrong point in time and not tied to any of the patent claims. For example, Dr. Le alleges that “Merck personnel involved” with the MSI-H Study “did not initially act as though they expected it to be successful” and that “Merck did not provide any financial support for the initiation of the trial and only later provided financial support for conduct of the trial.”⁷ (EX2130, ¶¶20, 35.) While Dr. Le did not provide any additional details regarding her alleged

for why a scientist or a physician in the field would conduct a phase 2 study of pembrolizumab in patients with MSI-H tumors was the known complete response in the MSI-high colorectal cancer patient treated with nivolumab. (*Supra*, ¶29.)

⁷ And in the ’393 proceeding, Dr. Le alleged that “Merck did not provide any financial support for the initial phase” of the study (later changed to “initiation or conduct of the trial until later”). (IPR2024-00240, EX2130, ¶¶19, 34; IPR2024-00240, EX1145 ¶19.)

observations or when Merck's funding began, this purported evidence is from the time period at the start of the MSI-H Study, more than two years before July 10, 2015. (*See* EX1139, 67:20-74:7; 269:1-276:16.) Dr. Goldberg's opinions regarding funding are similarly from the incorrect point in time. (EX2090, ¶¶61.)

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

126. 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, ¶¶28-74.) In particular, Dr. Goldberg discusses chemotherapy and targeted therapies available in 2010-2015, as well as the state of MSI testing before and after 2017 (when pembrolizumab received FDA approval for the MSI-H cancer and MSI-H colorectal cancer indications) because Dr. Goldberg's view is that the long-felt unmet need was for an FDA-approved method of treatment. (EX2090, ¶¶37-81; EX1243, 98:8-11.) The '462 patent claims, however, do not require FDA approval.

127. Further, Dr. Goldberg omits any discussion of the prior art known to a POSA as of July 10, 2015, including the MSI-H Study Record that describes the claimed method of treatment. (EX2090, ¶¶31-81; *see also* EX1003, ¶¶34-49.) For example, Dr. Goldberg does not account for the fact that, as of July 10, 2015, (1) the MSI-H Study Record was in the prior art, (2) a number of other prior art references independently urged a POSA to consider treating MSI-H cancer with PD-1 inhibitors and PD-1 inhibitors, like pembrolizumab, were showing promise in treating tumors displaying certain characteristics that MSI-H tumors were known to display, and (3) a contemporary study of another anti-PD-1 inhibitor to treat patients with MSI-H colorectal cancer was ongoing. (EX2090 ¶¶31-81; *see also supra*, Section VII.C.1; EX1003 ¶¶34-49.) By ignoring the MSI-H Study

Record and the other prior art known to a POSA as of July 10, 2015, Dr. Goldberg's analysis of an alleged long-felt unmet need focuses on cancer, including colorectal cancer, more generally and the incorrect point in time, arguing the need was unmet until pembrolizumab received FDA approval for the treatment of MSI-H cancer patients.

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

129. Further, Merck itself has at least four patents that were filed or issued before the Alleged Invention Date, and which cover pembrolizumab, the active antibody in Keytruda, as well as its use in the treatment of cancer. (EX1214,

EX1215, EX1217, EX1238.) In contrast, as discussed above, the '462 patent only claims a particular method of treating patients with MSI-H non-colorectal cancer.

130. As of July 10, 2015, the method of treating a cancer patient by determining that the patient has a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, and then administering an effective amount of pembrolizumab to the patient,⁸ was already being met and was reasonably expected to be successful. (EX1005; *see also supra*, Sections VII.D-J.)

⁸ And then, of course, determining the result.

VIII. CONCLUSION

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

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

PUBLIC VERSION

Dated: May 6, 2025

By: *Paul Oberstein*

Paul E. Oberstein, M.D.

Appendix A

EX1001	U.S. Patent No. 11,643,462 (the “’462 patent”)
EX1002	File History of the ’462 patent (U.S. Patent Application No. 17/354,653)
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> , <i>J. Clin. Oncol.</i> 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/NEJMoal500596/suppl_file/nejmoal500596_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)

EX1073	Excerpt from Alexander Eggermount Citations, Google Scholar, available at https://scholar.google.com/citations?user=NWWkhzoAAAAJ&hl=en (accessed 8/25/23)
EX1074	Excerpt from Jean-Charles Soria Citations, Google Scholar, available at https://scholar.google.com/citations?user=wyFxnccAAAAJ (accessed 8/25/23)
EX1075	Henry Lynch, Research.com, available at https://research.com/u/henry-t-lynch (accessed 8/25/23)
EX1076	Excerpt from Daniel Van Hoff Citations, Google Scholar, available at https://scholar.google.com/citations?user=-NTa4oUAAAAJ&hl=en (accessed 8/25/23)
EX1077	Excerpt from Robert A. Holt, Google Scholar, available at https://scholar.google.com/citations?user=CXPli08AAAAJ&hl=en (accessed 11/27/23)
EX1078	Young et al, <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)
EX1082	Charles Fuchs, Research.com, available at https://research.com/u/charles-s-fuchs (accessed 8/25/23)

EX1083	Excerpt from Jerome Galon Citations, Google Scholar, available at https://scholar.google.com/citations?user=coRgZqUAAAAJ&hl=fr (accessed 8/25/23)
EX1084	Press Release, <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
EX1087	Duval et al, <i>The Mutator Pathway is a Feature of Immunodeficiency-Related Lymphomas</i> , 101(14) Proceedings of the National Academy of Sciences 5002 (2004)
EX1088	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers Version 1.2014 (May 30, 2014)
EX1089	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2014 (November 27, 2013)
EX1094	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1.2014 (May 30, 2014)
EX1095	Koh et al, <i>Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology</i> , 12(2) J. Nat'l Comprehensive Cancer Network 248 (February 2014)
EX1096	Ajani et al, <i>Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines</i> , 11(5) J. Nat'l Comprehensive Cancer Network 531 (May 2013)
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
EX1119	[HIGHLY CONFIDENTIAL ATTORNEY EYES ONLY – PROTECTIVE ORDER MATERIAL] July 15, 2013 IND Submission to the FDA, SN03
EX1120	FDA grants nivolumab accelerated approval for MSI-H or dMMR colorectal cancer (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-nivolumab-accelerated-approval-msi-h-or-dmmr-colorectal-cancer)
EX1130	CDER Breakthrough Therapy Designation Approvals, https://www.fda.gov/media/95302/download (last accessed January 8, 2025)
EX1134	Keytruda Labeling (12.11.2024)
EX1136	Deposition Transcript of Richard M. Goldberg, M.D., taken on December 13, 2024
EX1138	Deposition Transcript of Nils Lonberg, Ph.D., taken on December 20, 2024
EX1139	Deposition Transcript of Dung Thi Le, M.D., taken on January 9, 2025
EX1140	Deposition Transcript of Andrew M. Pardoll, M.D., taken on January 24, 2025
EX1145	Declaration of Dr. Dung Le, marked up during January 9, 2025 deposition
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)
EX1214	U.S. Patent No. 8,900,587 (the “587 patent”)

EX1215	U.S. Patent No. 9,834,605 (the “’605 patent”)
EX1217	U.S. Patent No. 9,220,776 (the ’776 patent”)
EX1238	U.S. Patent No. 8,354,509 (the “’509 patent”)
EX1243	Deposition Transcript of Richard M. Goldberg, M.D., taken on April 15, 2025
EX1245	[CONF.] Deposition Transcript of Nils Lonberg, Ph.D. taken on April 17, 2025
EX1246	Deposition Transcript of Dung Thi Le, M.D., taken on April 18, 2025
EX1279	June 29, 2020 first-line CRC approval (FDA approves pembrolizumab for first-line treatment of MSI-H/dMMR colorectal cancer FDA)
EX2024	Brahmer et al., <i>Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates</i> , 28(19) J. Clinical Oncology 3167-75 (July 1, 2010)
EX2166	ClinicalTrials.gov, NCT01876511, “Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C),” (January 5, 2016) available at https://www.clinicaltrials.gov/study/NCT01876511?tab=history&a=12