IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Diaz et al.	
U.S. Patent No.:	11,643,462	Attorney Docket No.: 52261-0012IP1
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Title:	CHECKPOINT BLOCKADE AND MICROSATELLITE INSTABILITY	

DECLARATION OF DR. NILS LONBERG

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

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

Dated: 1/23/25 By: _____
Nils Lonberg, Ph.D.

JHU 2072
Merck Sharp v. Johns Hopkins
IPR2024-00648

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I, NILS LONBERG, PH.D., hereby declare the following:

I. QUALIFICATIONS AND BACKGROUND INFORMATION

1. My education and experience are described more fully in the attached *curriculum vitae* (EX2002). For ease of reference, I have highlighted and restated certain information below.

2. I received a doctorate (Ph.D.) in Biochemistry and Molecular Biology from Harvard University in Cambridge, MA in 1985. I attended Reed College and the University of Oregon between 1974 and 1979 for my undergraduate studies, and was a postdoctoral fellow at Memorial Sloan Kettering Cancer Center in New York, NY from 1985-1989.

3. In 1990, I began my career in the biotechnology / pharmaceutical industry, leading the GenPharm International research group that developed genetically engineered strains of mice with germline configuration human immunoglobulin genes. These transgenic animals have been used to discover more than three dozen clinical-stage human sequence antibodies, including 15 FDA-approved products (golimumab, ustekinumab, ofatumumab, canakinumab, ipilimumab, nivolumab, secukinumab, daratumumab, bezlotoxumab, olaratumab, burosumab, teprotumumab, amivantamab, anifrolumab, and relatlimab). GenPharm International was acquired by Medarex in 1997 (maintaining the GenPharm name as

a subsidiary of Medarex), and then by Bristol-Myers Squibb in 2009, where I continued to lead my research group at each respective company.

4. In 1998, my drug discovery group at Medarex (and later Bristol-Myers Squibb) began to focus on antibody therapies that target and modulate immune-attenuating pathways to activate patient immune responses to cancer cells (so-called "checkpoint blockade" therapies). Among these checkpoint blockade cancer therapies, my research group discovered ipilimumab, nivolumab, and relatlimab. Ipilimumab, which began clinical testing in 2000, was the first-ever checkpoint blockade cancer therapy to enter clinical development and to gain regulatory approval. Ipilimumab, approved in 2011, was also the first drug to demonstrate, in a randomized clinical trial, a survival benefit for patients with metastatic melanoma. A second checkpoint blockade cancer therapeutic, nivolumab, entered clinical development in 2006 and gained regulatory approval in 2014. A third checkpoint blockade cancer therapeutic, relatlimab, entered clinical development in 2013 and gained regulatory approval as a combination product with nivolumab in 2022.

5. In 2019, I left my role as Senior Vice President, Oncology Discovery Biology, at Bristol-Myers Squibb and joined Canaan Partners, where I am currently an Executive in Residence. I also serve as a director on the board of four companies and as an advisor on the scientific advisory boards of four companies, all of which are in the biotechnology / pharmaceutical industry.

6. I have received awards for my research, including being elected to the National Academy of Engineering in 2015. I am also an inventor of over 60 patents relating to the fields of immunology and oncology and an author of over 40 manuscripts in peer reviewed journals.

7. I have been retained on behalf of The JOHNS HOPKINS UNIVERSITY ("JHU") to offer technical opinions related to U.S. Patent No. 11,643,462 ("the '462 Patent") (EX1001) and alleged prior art references relating to its subject matter. I have reviewed the '462 Patent and its accompanying prosecution history (EX1002). Additionally, I have reviewed the Petition, the materials cited in the Petition, and the materials cited in the present declaration. For example, I have reviewed at least the following references:

- 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) (EX1005);
- Brown et al., *Neo-Antigens Predicted by Tumor Genome MetaAnalysis Correlate with Increased Patient Survival*, 24(5) Genome Research 743 (May 2014) (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) (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) (EX1009);
- Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. Nat'l Comprehensive Cancer Network 248 (February 2014) (EX1095);
- Ajani et al., *Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines*, 11(5) J. Nat'l Comprehensive Cancer Network 531 (May 2013) (EX1096);
- Chapelle et al., Clinical Relevance of Microsatellite Instability in Colorectal Cancer, 28(20) J. Clinical Oncology 3380 (2010) (EX1007);
- Steinert et al., Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer, 74(6) Cancer Research OF1 (March 2014) (EX1008);
- Hamid et al., Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma, 369(2) New Eng. J. Medicine 134 (July 2013) (EX1011).

8. Counsel has informed me that I should consider these materials through the lens of one of ordinary skill in the art related to the ’462 Patent at the time of the earliest possible priority date of the ’462 Patent. Counsel has informed me and I understand that the ’462 Patent was filed on June 22, 2021 and claims priority to multiple patent applications including two provisional applications. The first provisional application was filed on November 13, 2014, and the second provisional application was filed on July 10, 2015. (EX1001, 1.)

9. Counsel has instructed me to use July 10, 2015 as the Critical Date, and I have done so in my analysis below. Counsel has informed me, and I understand, that the “Critical Date” represents the earliest possible priority date to which the challenged claims of the ’462 Patent are entitled.

10. I have no financial interest in the parties or in the outcome of this proceeding. I am being compensated for my work as an expert on an hourly basis. My compensation is not dependent on the outcome of these proceedings or the content of my opinions.

11. In writing this declaration, I have considered the following: my own knowledge and experience, including my work experience in the fields of immunology, oncology, and related drug discovery/development; and my experience in working with others involved in those fields. In addition, I have

analyzed various publications and materials, in addition to other materials I cite in my declaration.

12. My opinions, as explained below, are based on my education, experience, and expertise in the fields relating to the ’462 Patent. Unless otherwise stated, my testimony below refers to the knowledge of one of ordinary skill in the art as of the Critical Date, or before.

II. OVERVIEW OF CONCLUSIONS FORMED

13. This declaration explains the conclusions that I have formed based on my analysis. To summarize, based on my knowledge and experience and my review of the prior art publications listed above, I believe that:

- A person of ordinary skill in the art (“POSA”) would, as of the priority date of the ’462 Patent, have a M.D. or graduate-level degree (or equivalent work experience) 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—experience that Merck’s expert, Dr. Neugut, does not have;
- The MSI-H Study Record relied on in Ground 1 does not teach or suggest several of the features of claims 1-30 of the ’462 Patent;

- The prior art relied on in Grounds 2-7 fails to show that claims 1-30 of the ’462 Patent are obvious; and
- The non-obviousness of claims 1-30 of the ’462 Patent is clearly demonstrated by various sources of objective evidence.

III. LEGAL STANDARDS

A. Legal Standards for Anticipation

14. I have been informed by Counsel and understand that documents and materials that qualify as prior art can render a patent claim unpatentable as anticipated. I have been informed by Counsel and understand that all prior art references are to be looked at from the viewpoint of a person of ordinary skill in the art.

15. I have been informed by Counsel and understand that a challenged claim is unpatentable as “anticipated” under 35 U.S.C. § 102 if it is determined that all the limitations of the claim are described in a single prior art reference. I have been informed by Counsel and understand that, to anticipate a claim, a prior art reference must disclose, either expressly or inherently, each and every limitation of that claim and enable one of ordinary skill in the art to make and use the invention.

16. I have been informed by Counsel and understand that in an *inter partes* review, “the petitioner shall have the burden of proving a proposition of

unpatentability," including a proposition of anticipation, "by a preponderance of the evidence." 35 U.S.C. § 316(e).

B. Legal Standards for Obviousness

17. I have been informed by Counsel and understand that documents and materials that qualify as prior art can render a patent claim unpatentable as obvious. I have been informed by Counsel and understand that all prior art references are to be looked at from the viewpoint of a person of ordinary skill in the art at the time of the invention, and that this viewpoint prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

18. I have been informed by Counsel and understand that a claim is unpatentable for obviousness under 35 U.S.C. § 103 "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." I have been informed by Counsel and understand that obviousness may be based upon a combination of references. I have been informed by Counsel and understand that the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. However, I have been informed by Counsel and understand that a patent claim composed of several

elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.

19. I have been informed by Counsel and understand that when a patented invention is a combination of known elements, a court must determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue by considering the teachings of prior art references, the effects of demands known to people working in the field or present in the marketplace, and the background knowledge possessed by a person having ordinary skill in the art.

20. I have been informed by Counsel and understand that a patent claim composed of several limitations is not proved obvious merely by demonstrating that each of its limitations was independently known in the prior art. I have been informed by Counsel and understand that identifying a reason those elements would be combined can be important because inventions in many instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. I have been informed by Counsel and understand that it is improper to use hindsight in an obviousness analysis, and that a patent's claims should not be used as a "roadmap."

21. I have been informed by Counsel and understand that an obviousness inquiry requires consideration of the following factors: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of

ordinary skill in the pertinent art; and (4) any objective indicia of non-obviousness, such as commercial success, long-felt but unresolved need, failure of others, industry recognition, copying, and unexpected results. I understand that the foregoing factors are sometimes referred to as the "Graham factors."

22. I have been informed by Counsel and understand that an obviousness evaluation can be based on a combination of multiple prior art references. I understand that the prior art references themselves may provide a suggestion, motivation, or reason to combine, but that the nexus linking two or more prior art references is sometimes simple common sense. I have been informed by Counsel and understand that obviousness analysis recognizes that market demand, rather than scientific literature, often drives innovation, and that a motivation to combine references may be supplied by the direction of the marketplace.

23. I have been informed by Counsel and understand that if a technique has been used to improve one device, and a person of ordinary skill at the time of invention would have recognized that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

24. I have been informed by Counsel and understand that practical and common sense considerations should guide a proper obviousness analysis, because familiar items may have obvious uses beyond their primary purposes. I have been

informed by Counsel and understand that a person of ordinary skill looking to overcome a problem will often be able to fit together the teachings of multiple prior art references. I have been informed by Counsel and understand that obviousness analysis therefore takes into account the inferences and creative steps that a person of ordinary skill would have employed at the time of invention.

25. I have been informed by Counsel and understand that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill at the time of invention, not just the patentee. Accordingly, I understand that any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

26. I have been informed by Counsel and understand that a claim can be obvious in light of a single reference, without the need to combine references, if the elements of the claim that are not found explicitly or inherently in the reference can be supplied by the common sense of one of skill in the art.

27. I have been informed by Counsel and understand that secondary indicia of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent

by others; (6) deliberate copying of the invention; (7) failure of others to find a solution to the long felt need; and (8) skepticism by experts. I understand that evidence of secondary indicia of non-obviousness, if available, should be considered as part of the obviousness analysis.

28. I have been informed by Counsel and understand that there must be a relationship between any such secondary considerations and the invention, and that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

29. In sum, my understanding is that prior art teachings are properly combined where one of ordinary skill having the understanding and knowledge reflected in the prior art and motivated by the general problem facing the inventor, would have been led to make the combination of elements recited in the claims. Under this analysis, the prior art references themselves, or any need or problem known in the field of endeavor at the time of the invention, can provide a reason for combining the elements of multiple prior art references in the claimed manner.

30. I have been informed by Counsel and understand that in an *inter partes* review, "the petitioner shall have the burden of proving a proposition of unpatentability," including a proposition of obviousness, "by a preponderance of the evidence." 35 U.S.C. § 316(e).

C. Level Of Ordinary Skill in The Art

31. I understand that Merck contends that a person of ordinary skill in the art ("POSA") as of the Critical Date of the '462 Patent would be "a medical doctor or a professional in a related field with at least five years of experience with treating cancer." (Pet., 11.) I also understand that Merck contends a POSA would "have experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and a pathologist with comparable experience." (*Id.*)

32. I disagree with Merck's proposed definition of a POSA and do not believe Merck's expert, Dr. Neugut, qualifies as a POSA due, for example, to his lack of relevant experience in immunology or genetics research. (*See infra* § VII.) In my opinion, a POSA would have a M.D. or graduate-level degree (or equivalent work experience) 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. A higher level of education may compensate for less work experience, and vice versa. Based on my knowledge, skill, and experience, I have applied this definition of a POSA for the purpose of the analysis provided in this declaration.

IV. TECHNICAL BACKGROUND ON CANCER IMMUNOTHERAPIES

33. To contextualize the origins of the ’462 Patent and its revolutionary impact on cancer treatment, some background about cancer, the immune system, and the state of cancer immunotherapy research at the Critical Date of the ’462 Patent is called for.

A. Cancer

34. The National Cancer Institute defines cancer as “a disease in which some of the body’s cells grow uncontrollably and spread to other parts of the body.” (EX2032, 1.) Cancer can arise from viral infections or exposure to DNA-damaging carcinogens. After cancer is initiated, the disease will progress if the cancer cells are able to grow rapidly without adequate suppression by the immune system. However, cancer cells are typically very different from the healthy normal cells they were derived from, (*id.*, 2), and this presents opportunities for the immune system to target and kill cancer cells to prevent the progression of cancer.

B. The Immune System

35. The immune system polices the body to identify and eliminate foreign pathogens by distinguishing between “self” and “non-self.” (EX2033, 1.) Non-self can also include near-self (e.g., transplanted organs) and altered-self (e.g., cancer cells). (*Id.*, 1-2.) In this way, the immune system plays an important role in fighting off cancer. The mechanisms employed by the body to perform these immune

functions are exceedingly complex and the subject of ongoing intense scientific inquiry. Accordingly, those of ordinary skill in this art are immersed in this ongoing research and possess a high level of expertise (e.g., a Ph.D. and/or M.D. with multiple years of relevant research experience) needed to remain current on developments in the field. I provide a high-level description of some important immune system mechanisms below.

36. The immune system is able to distinguish between self and non-self using immune receptors on immune system cells that bind to molecular structures called antigens. Cancer cells, in particular, include two type of antigens that can potentially be recognized as non-self by the immune system—tumor associated antigens (TAAs) and neoantigens. TAAs can be proteins or carbohydrate structures that are normally expressed only during early development, so they often go undetected by the immune system. Neoantigens are products of genes that are mutated in the cancer cells and are completely novel to the immune system. The mutations can be functional (i.e., "driver mutations") or non-functional (i.e., "passenger mutations").

37. The immune system identifies and eliminates non-self (including cancer cells) using a complex interaction of differentiated cell types, which can be broadly classified as "adaptive" immune cells or "innate" immune cells.

1. Adaptive Immune Cells

38. Adaptive immune cells include T cell and B cells, which are extremely diverse and have different cell surface receptors that recognize different antigens. These cells can expand in diversity in response to infections and vaccinations.

- **T Cells:** There are many types of T cells including CD8 T cells, CD4 T cells, gamma-delta T cells, and NK T cells, each of which can be further divided into different subtypes. T cells recognize non-self antigens through protein complexes called T cell receptors (TCRs).
- **B Cells:** There are three broad categories of B cells: primary repertoire B cells, secondary repertoire B cells, and plasma cells. B cell receptors (BCRs) can be expressed as cell surface molecules that either trigger activation of the cells or internalize bound antigens for processing and presentation on class II MHC molecules in the cell membrane. Fully mature plasma cells do not express cell surface BCRs, but instead produce large quantities of antibody molecules into the blood.

2. Innate Immune Cells

39. The innate arm of the immune system recognizes "pathogen associated molecular patterns" (PAMPS), which are danger signals that cause the innate arm of the immune system to activate the adaptive arm of the immune system. This PAMP-mediated activation serves as a protective gate against autoimmune inflammation.

The innate immune cells include macrophages, dendritic cells (DCs), natural killer cells (NK cells), neutrophils (also called granulocytes), innate lymphoid cells (ILCs), eosinophils, mast cells, etc., which can be further divided into different subtypes. Each cell type has its own mechanism of action.

- **Macrophages:** Macrophages eat other cells, pathogens, and debris, and they can be either immune activating or dampening.
- **Dendritic Cells (DCs):** DCs consume matter in their environment, break down the matter into smaller components, and then present these components on their cell surface to other immune cells. They also recognized PAMPs and can produce signals that can activate or suppress the adaptive arm of the immune system in response to PAMP recognition.
- **Natural Killer (NK) Cells:** NK cells recognize and kill abnormal cells based on recognition of (i) specific molecules expressed by stressed/infected cells and (ii) absence of major histocompatibility complexes (MHC), which are typically expressed on the surface of healthy cells. MHC molecules themselves come in two classes—MHC Class I and MHC Class II. (EX2034, 1.)

3. Homeostatic Mechanisms

40. Immune system processes that restrict autoimmunity (e.g., PAMP-mediated activation of the adaptive immune cells) are not perfect, and inflammation

from infection can be destructive to normal cells. Thus, the immune system comprises a complex and overlapping set of homeostatic mechanisms that can dampen inflammation. It is these homeostatic mechanisms that certain immunotherapies, including that of the '462 Patent, attempt to modulate.

41. One homeostatic mechanism is acquired tolerance, in which reactive immune cells are eliminated ("deletional tolerance") or inactivated ("non-deletional tolerance"). An example of non-deletional tolerance is a 3-step process described by Jenkins and Schwartz, in which three separate signals must be present for T cell activation. (*See* EX2035, 15.) Another example of non-deletional tolerance is described by Wherry and Ahmed, in which T cells can become "exhausted" (i.e., inactivated) by persistent exposure to antigens. (*See* EX2036, 1.) These exhausted T cells can be found in human solid tumors (*see generally* EX2037) and are thought to be the substrate for immune checkpoint blockade therapies such as pembrolizumab—which is implicated in the '462 Patent.

42. Another homeostatic mechanism is the secretion of immune system suppressive and activating factors such as interleukin-10 and interleukin-27 (IL-10, IL-27), interleukin-2, interleukin-12, interleukin-15 (IL-2, IL-12, IL-15), gamma interferon (IFNγ), tumor necrosis factor alpha (TNFα). (*See generally* EX2038.)

43. A third mechanism for maintaining immune homeostasis involves regulatory cells (e.g., regulatory T cells and regulatory B cells) that play a role in

establishing tolerance and rejecting cancer cells. (*See generally* EX2039, EX2040, EX2041.)

C. Cancer Immunotherapy

44. Given the wide array of immune system cells and the various homeostatic mechanisms that govern their interactions, there is an equally diverse set of cancer immunotherapy strategies that have been explored to treat cancer. In general, cancer immunotherapy encompasses therapeutics comprising immune system components or having mechanisms of action that include immune system pathways. However, beyond this broad theme, immunotherapy strategies are numerous and extremely varied. Thus, one could not reasonably expect one strategy (e.g., checkpoint blockade therapy) to work for a particular indication merely because other immunotherapy strategies showed promise for the same indication. And there would be even less reason to believe a specific therapeutic (e.g., pembrolizumab) would be effective given the highly unpredictable nature of this technical field. (*See, e.g.*, EX2042, 2 (describing a "multitude of unsuccessful trials" for novel immunotherapies); *id.*, 6-7 (discussing the "complex interactions" involved in the human immune response and "numerous factors [that] significantly impede our full understanding of the immune system and its interaction with tumors").) To demonstrate the wide diversity of immunotherapy strategies for treating cancer, a sampling is provided below.

- A **first** strategy involves the development of tumor targeting monoclonal antibodies that bind to antigens on the cancer cell surface, leading to growth arrest, cell death, or recruitment of NK cells or macrophages. Examples of therapeutics falling under this category include rituximab, trastuzumab, daratumumab, and cetuximab.
- A **second** strategy involves treating with secreted immune-activating factors such as high-dose IL-2 and interferon alpha.
- A **third** strategy involves innate agonists, which activate receptors on innate immune cells to produce a heightened immune response. Examples of therapeutics in this category include Bacillus Calmette-Guerin (BCG) used for bladder cancer and imiquimod for basal cell carcinoma.
- A **fourth** strategy involves the development of agonist antibodies that target co-stimulatory receptors on T cells in order to activate them.
- A **fifth** strategy involves blocking or depleting regulatory T cells that cause the immune system to tolerate cancer cells.
- A **sixth** strategy, called adaptive cell therapy, involves the isolation of quiescent T cells from a patient's tumor and reactivating them *ex-vivo* (e.g., using cytokines such as IL-2) or modifying them to produce an engineered receptor (e.g., CAR-T therapy). The T cells are then injected back into the patient to strengthen their immune response to cancer cells.

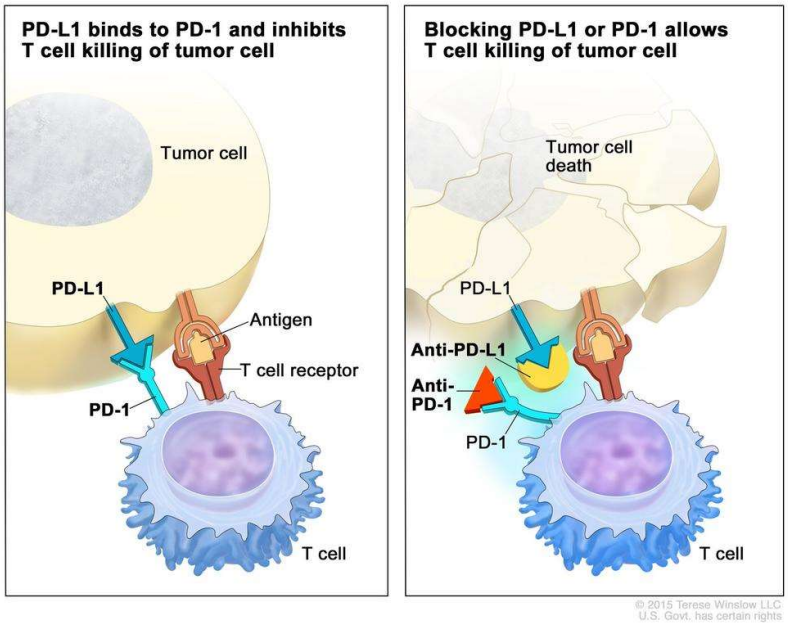
- A **seventh** strategy, known as immune checkpoint blockade therapy, is the class of immunotherapies that pembrolizumab (and the invention of the '462 Patent) falls within. Since the time of the invention of the '462 Patent, this has become the most successful class of cancer immunotherapies, with almost a dozen monoclonal antibodies that target checkpoint receptors CTLA-4, PD-1 (or its ligand PD-L1), or LAG3 now approved for use by the FDA in over two dozen cancer histologies. (*See generally* EX2043.) The general mechanism of action of checkpoint blockade therapy is described in further detail below.

D. Checkpoint Inhibitors and Checkpoint Blockade Therapy

45. Immune checkpoint proteins (e.g., CTLA-4, PD-1, LAG 3) naturally occur on T cells and can prevent a T cell from killing healthy cells in the body. (*See* EX2044, 1.) In particular, when an immune checkpoint protein binds to a complementary "partner protein" on another cell, the T cell can receive a signal that prevents it from killing the other cell, or the T cell can be prevented from receiving a signal that is necessary for acquiring the capacity to kill the other cell. (*Id.*) However, cancer cells can take advantage of the immune checkpoint mechanism to evade being killed by the immune system's T cells. (*Id.*)

46. Immune checkpoint inhibitors ("ICIs") are a specific set of immunotherapies that block the immune checkpoint proteins on T cells from binding

to partner proteins on cancer cells. (*Id.*) In so doing, checkpoint inhibitors allow the T cells to kill the cancer cells. (*Id.*) These checkpoint inhibitors work by binding to the immune checkpoint protein on the T cell (e.g., PD-1) and/or by binding to the partner protein on the cancer cell (e.g., PD-L1). (*Id.*) For example, with respect to the PD-1 immune checkpoint, the former mechanism of action is referred to as "anti-PD1" therapy while the latter mechanism is referred to as "anti-PD-L1" therapy, with anti-PD1 therapy and anti-PD-L1 therapy constituting distinct groups of drugs. The PD-1 checkpoint is shown in its normal and blocked state in the illustration below.



47. (EX2044, 1.)

48. As of the Critical Date of the '462 Patent, an anti-PD-1 therapy called pembrolizumab was a very recently FDA-approved checkpoint inhibitor for certain

types of cancer. (EX2007, 1.) It was known to work by binding to the PD-1 checkpoint protein. (*Id.*) However, previous trials had shown that pembrolizumab and similar anti-PD-1 therapies were not a cure-all for all types of cancers. For example, in prior art clinical trials, an anti-PD-1 drug known as nivolumab failed to produce a response in 32/33 patients with colorectal cancer (CRC). (*See* EX1001, 2:63-67 ("[O]nly one of 33 colorectal cancer (CRC) patients responded to this treatment, in contrast to substantial fractions of patients with melanomas, renal cell cancers, and lung tumors."); *see also* EX2024, 3 (reporting that 1 of 14 CRC patients responded); EX1013, 3-4 (reporting that 0 of 19 CRC patients responded).) As such, there remained substantial uncertainty as to which patients would be most responsive to anti-PD-1 treatment, and patients with certain kinds of cancer, such as CRC, seemed like an unlikely choice.

E. Microsatellite Instability / DNA Mismatch Repair

49. Separate from the field of immunotherapy, by the Critical Date of the '462 Patent, geneticists were aware of a condition called "microsatellite instability" (MSI) that results from impairments in a patient's natural DNA error correction process. Such patients are referred to as "mismatch repair (MMR) deficient" and/or "microsatellite instability high" ("MSI-High" or "MSI-H").

50. By the Critical Date of the '462 Patent, it was known that a small percentage of cancer patients (including CRC patients) were MSI-H, and that the

tumors of such patients tended to have higher mutational loads and were infiltrated by immune cells. (*See generally* EX2045.) Indeed Dr. Vogelstein (a co-inventor of the ’462 Patent) led an international consortium that helped elucidate the clinical implications of MSI on colorectal cancer. (*Id.*, 2.) As such, as of the Critical Date of the ’462 Patent, there was some interest in investigating the use of immunotherapies for treating MSI-H CRC patients. Nevertheless, there were also many factors that taught away from MSI-H CRC patients being good candidates for immunotherapy and especially for checkpoint blockade therapy.

51. For example, MSI-H patients were known to lose Human Leukocyte Antigen (HLA) expression, which can allow cancer cells to avoid being killed by escaping T cell cytotoxicity. (*See, e.g.*, EX2046, 2 (“From a practical standpoint, the correlation between mutator phenotype (MSI-H) and HLA loss suggests that immunotherapy against colorectal carcinoma may be of limited value”); EX1006, 5 (“CRC associated with MSI may develop specific mechanisms to escape the immune system . . . . Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation though the association between HLA class I downregulation and MSI is still controversial.”); EX2047, 2-7).

52. Moreover, researchers had identified other discouraging mechanisms of immune evasion in MSI-H CRC identified including elevated levels of regulatory

T cells that "can interfere with efficient antitumoral immune responses in CRC." (EX2047, 5; *see also* EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients.")).

53. Outside of CRC, MSI-H is known to occur in at least 29 other types of cancers and likely occurs in many more. Indeed, since the Critical Date of the '462 Patent new MSI-H cancers continue to be detected, making this an ever-growing group of indefinite size. For example, as Bonneville et al. describe, in 2017—well after the Critical Date—"the prevalence of MSI in many other cancer types [was] less well described" compared to colorectal and endometrial cancer, and "[t]he ability to detect MSI in novel cancer types would permit the investigation of immune-enhancing therapies in these cancers, with the potential to benefit ***previously unknown subsets of patients with cancer with MSI***." (EX2303, 2.) In that study, Bonneville et al. analyzed data from 11,139 tumor samples and identified microsatellite instability in 27 out of 39 cancer types with varying levels of prevalence, including adrenocortical carcinoma, cervical cancer, and mesothelioma—***cancer types in which microsatellite had not previously been well described***. (*Id.*, 1, 3-4.) Similarly, in 2021, Akagi et al. reported analyzing 26,237 samples and detected MSI-H in 30 out of 43 cancer types, noting that with additional cases, "***it might be possible to identify MSI-H cases for [the remaining 13] cancer***

types as well." (EX2304, 4.) As these investigations demonstrate, the group of MSI-H cancer types is large and has continued to grow since the Critical Date of the '462 Patent.

F. State of the Prior Art at the Critical Date of the '462 Patent

54. For the reasons described above, prior to the Critical Date of the '462 Patent there was little reason to suspect MSI-H cancer patients generally (including MSI-H CRC patients) would be particularly good candidates for PD-1 checkpoint blockade therapy. And, in my opinion, Merck has failed to identify any prior art that either disclosed this intellectual advance or would have made it obvious to a person of ordinary skill in the art.

55. Had someone hypothesized that MSI-H cancer patients generally might be especially responsive to PD-1 checkpoint blockade therapy (as the inventors of the '462 Patent did), the available options for testing such a hypothesis were limited. Mouse syngeneic tumor models, often used for animal testing of cancer therapeutics, are not suitable for immunotherapies such as checkpoint blockade therapy. In particular, they do not reflect the differences in treatment responses to specific cancer histologies that are seen in human patients. (EX2048, 1 ("The relative immunogenicity of these ten syngeneic tumors does not resemble typical human tumors derived from the same tissue of origin.").) For example, the B16 model is derived from a melanoma; however, it is resistant to immune checkpoint inhibition

("ICI"), while human melanoma is perhaps the ***most*** ICI sensitive tumor type in human cancer patients. (*Id.*, 6-8.) In contrast, the CT26 model is derived from an MSI negative CRC tumor that lacks mismatch repair (MMR) mutations. (EX2049, 3.) The CT26 model is very sensitive to ICI, while comparable human CRC tumors are resistant. *(Id.,* 3-4.)

56. The lack of translatability of syngeneic models is probably responsible for many failed clinical trials of cancer immunotherapies conducted at considerable expense, and even today, these models do not faithfully recapitulate the interactions between cancer cells and the immune systems of human solid tumor patients. *See, e.g.*, EX2073, 271-272 (a 2022 review article stating that "a new challenge for researchers is to elucidate the factors distinguishing tumors that respond to checkpoint therapy from those that do not" and that "new mouse models of cancer immunology" are still needed to fill this "critical gap"). These shortcomings can be attributed, at least in part, to the fact that many of the mouse models of immunology used today were not originally developed to study questions in the relatively new field of cancer immunology (*id.*, 269), and that they represent a very early stage in the immune response to newly transplanted cancer cells compared to the relatively mature stage found in human patients at the time of treatment. For all these reasons, the most reliable way for testing hypotheses relating to ICI therapies as of the 2015 Critical Date was using human cancer patients in a clinical trial setting.

57. Merck cites the Patent Office's general presumption that "[an] applicant has established that the subject matter of [a human clinical] trial is reasonably predictive of having the asserted therapeutic utility." (Pet., 44; MPEP 2107.03.) But this is at odds with the realities of how research is conducted in this field. It is very common for clinical trials of cancer immunotherapeutics to be designed to test a speculative hypothesis, or even as an exploratory, hypothesis-generating trial without ***any*** pre-formed speculative hypothesis. In fact, phase 1 and phase 2 oncology trials are frequently designed as so-called "basket trials" where multiple histologies are enrolled simply to explore if there is a signal in any one particular cancer type. (*See* EX2050, 3-5.)

58. Indeed, prior to the Critical Date of the '462 Patent, other exploratory and speculative clinical trials using PD-1 checkpoint blockade therapies had already been conducted with CRC and other cancer patients. (*See, e.g.*, EX2024; EX1013, 3-4.) However, these trials yielded limited success, especially for CRC patients. For example, in previous reports of the effects of PD-1 blockade in human tumors, "only one of 33 colorectal cancer (CRC) patients responded to this treatment, in contrast to substantial fractions of patients with melanomas, renal cell cancers, and lung tumors." (EX1001, 2:63-67; EX2024, 3 (reporting that 1 of 14 CRC patients responded); EX1013, 3-4 (reporting that 0 of 19 CRC patients responded).) Although it was later determined that the one responsive CRC patient was MSI-H,

this single patient represented no more than a statistically meaningless result. In my opinion, it was certainly a far cry from suggesting a reasonable expectation of success that MSI-H patients would be particularly responsive to PD-1 checkpoint blockade therapy.

V. OVERVIEW OF THE '462 PATENT

59. Based on limited initial data, the inventors of the '462 Patent revolutionized the field of cancer immunotherapy by (1) conceiving the groundbreaking hypothesis that MSI-H cancer patients (including MSI-H CRC patients) might be unusually responsive to anti-PD1 therapy, (2) performing a clinical trial—in the face of low odds of success—to test their hypothesis, and (3) sharing the benefits of their findings and invention with the public, which has since led to the saving of numerous lives. The '462 Patent describes this clinical trial, its profound results, and a novel method of treating cancer patients based on their MSI status.

60. The '462 Patent describes a phase 2 trial designed "to evaluate immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency." (EX1001, 3:19-21.) The trial consisted of three parallel patient cohorts: "Cohort A was composed of MMR-deficient colorectal adenocarcinomas [i.e., MSI-H CRC]; Cohort B was composed of patients with MMR-proficient colorectal adenocarcinomas [i.e., MSI negative CRC]; and Cohort C was composed of patients

with MMR-deficient cancers of types other than colorectal [i.e., MSI-H non-CRC]." (*Id.*, 8:34-38.) Patients in all three cohorts were treated with pembrolizumab, "administered at 10 mg/kg intravenously every 14 days" (*id.*, 8:54-55), and the outcomes of these patients were assessed using various endpoints including response rates, progression-free survival rate, and other immune-related criteria. (*Id.*, 9:24-40.) The goal of this study was to test the inventors' hypothesis that "MMR-deficient tumors [i.e., MSI-H tumors] are more responsive to PD-1 blockade than are MMR-proficient tumors [i.e., MSI negative tumors]." (*Id.*, 3:16-18.)

61. The results of the trial were extraordinary. The '462 Patent reports that mismatch repair-deficient colorectal cancers (i.e., MSI-H CRC) had an immune-related objective response rate and immune-related progression-free survival rate of 40% and 78%, respectively—a huge difference compared to the 0% and 11% rates found in mismatch repair-proficient colorectal cancers (i.e., MSI negative CRC). (*Id.*, 16:14-21.) Moreover, patients with mismatch repair-deficient non-colorectal cancers (i.e., MSI-H non-CRC) had responses similar to those of patients with mismatch repair-deficient colorectal cancer (i.e., MSI-H CRC), with an immune-related objective response rate of 71% and immune-related progression-free survival rate of 67%. (*Id.*)

62. In my opinion, the results definitively show that the inventors' hypothesis turned out to be true. Indeed, the oncology community appears to agree,

with the results of the inventors' study being published in the New England Journal of Medicine, the world's top medical journal (EX1031), and with many of the world's leading cancer researchers tuning in to Dr. Le's (an inventor of the '462 Patent) presentation at the 51st annual meeting of the American Society of Clinical Oncology ("ASCO") in 2015 (EX2003).

63. The clinical trial results described in the '462 Patent further became the basis for an accelerated approval by FDA of the first-ever tissue/site-agnostic indication for cancer treatment. (EX2004,1.) As Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence acknowledged, "[t]his [was] an important first for the cancer community." (*Id.*) While previously the FDA had approved cancer treatments "based on where in the body the cancer started—for example, lung or breast cancers," this was the first time a drug had been approved "based on a tumor's biomarker without regard to the tumor's original location." (*Id.*) As an expert in the field, it is my opinion that the invention of the '462 Patent revolutionized cancer immunotherapy, spearheading the path to approval for an entirely new kind of cancer treatment indication.

64. Supported by the remarkable results of the inventors' clinical trial, the '462 Patent claims (1) a novel method for treating a patient having a solid tumor

selected from a group of sixteen cancer types (EX1001, claim 1), and (2) a novel method for prescribing a treatment for a solid tumor selected from the same group of sixteen cancer types (*id.*, claim 11). Independent claim 1 is representative:

> 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, choloangiocarcinoma, 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, the method 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.

(*Id.*, claim 1.)

65. In short, independent claim 1 requires testing or having tested a biological sample (e.g., a tumor sample) from a patient whose cancer progressed after at least one previous treatment having one of sixteen specific cancer types to determine their MSI status and then treating the patient based on the results of that testing. In particular, independent claim 1 recites treating the patient with a

"therapeutically effective amount of pembrolizumab" in response to determining that the patient's solid tumor is MSI-H or DNA mismatch repair deficient. The point of determining the patient's MSI-H status is to use it as a biomarker for treatment—discriminating between patients who are likely to respond to treatment (and should be treated) and patients who are not likely to respond (and should not be treated).

66. For the reasons I discuss in this declaration, Merck has not shown that any of the prior art cited in its Petition anticipates or renders obvious these features or the features disclosed in independent claim 11, as well as several other features recited in the dependent claims.

VI. OVERVIEW OF THE CITED REFERENCES

A. MSI-H Study Record

67. I have been informed by Counsel and understand that Merck relies on the MSI-H Study Record (EX1005) in Ground 1 of the Petition to argue that the invention of the '462 Patent was anticipated. I have also been informed by Counsel and understand that Merck relies on the MSI-H Study Record in Grounds 2-7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA.

68. The MSI-H Study Record is the initial announcement of a clinical trial designed to test the inventors' hypothesis that identifying MSI-H cancers might be used to identify patients more likely to respond to anti-PD-1 antibody therapy.

Indeed, the MSI-H Study Record is the initial announcement of the same clinical trial later described, with additional details and results, in the '462 Patent. Nothing in the initial announcement teaches or suggests that the results of the trial would ultimately validate the inventors' hypothesis that MSI-H status could be used as a biomarker to inform pembrolizumab treatment in multiple cancer types.

69. The trial disclosed in the MSI-H Study Record was designed to explore whether MK-3475 (also known as pembrolizumab) had anti-tumor activity and would be safe in three patient populations—(1) patients with MSI positive colon cancer ("MSI-H CRC" patients), (2) patients with MSI negative colon cancer ("MSI negative CRC" or "MSS CRC" patients), and (3) patients with other MSI positive cancers ("MSI-H non-CRC" patients). As anyone with experience in this field would understand, it is a federal requirement to publish documents such as the MSI-H Study Record on www.clinicaltrials.gov in order to perform human clinical trials—even if it is merely an exploratory or speculative trial. *See* Food and Drug Administration Amendments Act of 2007, § 801 (42 U.S.C. § 282(j)); 42 C.F.R. Part 11.

70. In compliance with federal law, the MSI-H Study Record discloses "descriptive information" about the study, "recruitment information," "location and contact information," and "administrative data." (*See* 42 U.S.C. § 282(j); EX1005, 2-6.) In particular, the MSI-H Study Record discloses an interventional study with

three "experimental" study arms directed, respectively, to MSI-H CRC patients, MSI negative CRC patients, and MSI-H non-CRC patients. (EX1005, 4.) Across all three study arms, patients were universally treated with 10 mg/kg of MK-3475 (pembrolizumab) every 14 days, and assessed using outcome measures such as immune-related progression free survival, objective response rate, overall survival, disease control rate, number of patients experiencing immune-related toxicities, and predictive value of MSI as a biomarker for treatment response. (*Id.*, 4-5.)

71. The MSI-H Study Record discloses a variety of eligibility criteria for study recruitment. (*Id.*, 5-6.) These inclusion criteria non-exhaustively include adults falling within any of the study arms with measurable disease, adequate organ function, willingness and ability to comply with study procedures, and agreement to submit to a biopsy of their cancer. (*Id.*, 5.) However, the MSI-H Study Record does not disclose any of the sixteen cancers specifically recited in claims 1 and 11 of the '462 Patent, and the MSI-H Study Record certainly does not disclose treating patients with these cancers "in response to" determining that the patient's solid tumor is MSI-H. Nor does the MSI-H Study Record disclose or require (1) the patient's cancer "progressed following at least one prior treatment" (claims 1 and 11) or (2) the cancer is metastatic (claims 6, 16, 24, 28, 30). (*See* EX1005, 5-6.) The exclusion criteria disclosed in the MSI-H Study Record include patients with certain medical conditions, patients having prior treatment with other antibodies, and

patients who received another investigational product within 28 days prior to receiving pembrolizumab. (*Id.*)

B. Brown

72. I have been informed by Counsel and understand that Merck relies on Brown (EX1034) in Grounds 2-7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Brown is a journal article describing a tumor genome meta-analysis in which the authors speculate that "patients with tumors showing naturally immunogenic mutations and associated TIL are ***potential*** candidates for treatment with immune modulator such as . . . PDCD1-targeted antibodies" and that "[t]here is evidence that such therapies are most effective against tumors infiltrated by T cells." (EX1034, 747.) Brown further discloses that "colorectal tumors, many of which had very high mutational loads, showed the strongest association between predicted immunogenic mutation counts and CD8A expression" (*id.*), and that "the abundance of predicted immunogenic mutations may be useful for identifying patients likely to benefit from checkpoint blockade and related immunotherapies" (*id.*, 743). However, none of these statements discloses that MSI-H cancer patients are likely to respond to PD-1 inhibitors with any reasonable expectation of success.

73. Merck relies on Brown as allegedly teaching that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells

that are easy for immune cells to recognize" and allegedly motivating a POSA "to treat patients having common types of MSI-H cancers, including endometrial, small bowel, and gastric cancer in the MSI-H Study." (Pet., 42-43.) However, Brown itself acknowledges that, "the number of subjects [in Brown's study] varied widely among cancer types" and noted that "comprehensive evaluation of immunogenic mutations specific to ***individual cancer types*** remains an important topic for ***future study***." (EX1034, 747 (emphases added).) Therefore, Brown would not have provided a POSA with a reasonable expectation of success in treating any of the specifically claimed MSI-H Cancers in the '462 Patent with pembrolizumab. Brown also would not have provided a reasonable expectation of success for the method of treatment of the '462 Patent since, 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 (*See supra* § IV.E).

74. For example, MSI-H patients were known to lose Human Leukocyte Antigen (HLA) expression, which can allow cancer cells to avoid being killed by escaping T cell cytotoxicity. (*See, e.g.*, EX2046, 2 ("From a practical standpoint, the correlation between mutator phenotype (MSI-H) and HLA loss suggests that immunotherapy against colorectal carcinoma may be of limited value"); EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune

system . . . . Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation though the association between HLA class I downregulation and MSI is still controversial."); EX2047, 2-7).

75. Moreover, researchers had identified other discouraging mechanisms of immune evasion in MSI-H CRC identified including elevated levels of regulatory T cells that "can interfere with efficient antitumoral immune responses in CRC." (EX2047, 5; *see also* EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients.")). Therefore, Brown would not have provided a reasonable expectation of success given the complex and controversial state of the prior art regarding microsatellite instability and its implications for cancer immunotherapy.

76. Brown also fails to demonstrate the obviousness of the method of treatment of the '462 Patent since Brown's discussion of microsatellite instability is limited to the context of Lynch syndrome and CRC. (EX1034, 747.) In its discussion of CRC, Brown concludes that "a mutator tumor phenotype may, in general, enhance immunoreactivity," but Brown fails to connect the broad concept of immunoreactivity to response to PD-1 inhibitors. (*Id.*) Therefore, Brown fails to disclose any connection between MSI-H and response to PD-1 inhibitors in CRC,

and Brown certainly fails to disclose any similar connection for other types of cancers such as the sixteen cancer types recited in claims 1 and 11 of the ’462 Patent.

C. Duval

77. I have been informed by Counsel and understand that Merck relies on Duval (EX1087) in Grounds 2-7 of the Petition to argue that the invention of the ’462 Patent would have been obvious to a POSA. Duval is a journal article reporting the results of a study on the occurrence of MSI-H tumors in Non-Hodgkin lymphomas (NHL), (EX1087, 1), and is not directed to MSI-H cancers generally as Merck alleges. (Pet., 42). In fact, non-tumorous cancers such as lymphomas are not even included among the sixteen solid tumor cancer types recited in independent claims 1 and 11 of the ’462 Patent and are thus irrelevant to the current proceeding.

78. Merck also incorrectly relies on Duval as allegedly teaching that “MSI-H cancers have cancer cells that are easy for immune cells to recognize.” (Pet., 42). Duval does not make any general connection between MSI-H status and immune cell recognition and—having nothing to do with cancer treatment—Duval fails to create a reasonable expectation of success for treating patients having the claimed MSI-H cancers, especially not with specific treatments such as checkpoint inhibitors or pembrolizumab.

79. To the contrary, in Duval, the authors observed that (i) although MSI-H lymphomas are extremely rare, they comprise 2-8% of lymphomas in

immunodeficient patients (and occur significantly only in these patients), and (ii) unlike MSI-H solid tumors, MSI-H lymphomas are not associated with β2M mutations (and thus, corresponding loss of type I HLA expression). (EX1087, 1, 4.) Based on these findings, Duval recognized that "the target gene mutation profile associated with MSI-H [immunodeficiency-related lymphomas] ***is specific for this tumor subtype***, when compared to other MSI-H cancers such as gastrointestinal and endometrial tumors." (*Id.*, 4). Therefore, Duval's finding that the data 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—both of which Duval leaves unaddressed. In fact, Duval actually supports the 1995 hypothesis of Branch et al. (EX2046) that MSI-H tumors are generally ***non-immunogenic*** because of low HLA expression, and that patients with MSI-H tumors are consequently ***poor*** candidates for immunotherapy.

D. Benson

80. I have been informed by Counsel and understand that Merck relies on Benson (EX1009) in Grounds 2-7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Benson is a journal article describing clinical practice guidelines for colon cancer. (EX1009, 1.) Merck

primarily relies on Benson for its alleged disclosure that "under the standard of care, the patient population that had tumors and measurable disease that would take part in a clinical study are generally patients who have had their cancer progress after previous drug therapies," (Pet., 49; *see also id.*, 20, 50-51), and that "under the standard of care, the patient population with tumors and measurable disease that would take part in a clinical study are patients having metastatic, advanced, and recurrent disease," (*id.*, 50). However, Benson does not disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic cancer to be enrolled in clinical trials. On the contrary, Benson explicitly provides for clinical trials as first-line therapy, stating that "when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." (EX1009, 2.) Benson further explains that "NCCN [provider of the guidelines] believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." (*Id.*, 1 (emphasis added).) Moreover—like the other cited prior art—Benson does not disclose or suggest that MSI-H patients would be particularly promising candidates for PD-1 checkpoint blockade therapy, much less pembrolizumab.

81. Furthermore, at Counsel's request, I have looked through the "References Cited" section of the '462 Patent (EX1001, 1-7) and, in my opinion, the teachings of Benson that Merck relies upon add nothing new to the art already

considered by the Examiner. For example, Brahmer (EX2024) is listed on the '462 Patent and discloses a clinical trial of an anti-PD-1 antibody that included patients with advanced metastatic cancers that had progressed after prior drug treatment (*id.*, 3). Therefore, in my opinion, Benson provides no new reason to alter the Examiner's patentability analysis of the '462 Patent.

E. Koh

82. I have been informed by Counsel and understand that Merck relies on Koh (EX1095) in Grounds 3 and 5-7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Koh is a journal article describing clinical practice guidelines for endometrial cancer. (EX1095, 1.) Merck primarily relies on Koh for its alleged disclosure that "the patients having endometrial cancer 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." (Pet., 52.) However, Koh does not disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic cancer to be enrolled in clinical trials. On the contrary, Koh includes the same disclosure as Benson that "NCCN believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." (EX1095, 1 (emphasis added).) Moreover—like the other cited prior art—Koh does not disclose or suggest that MSI-H patients would be particularly

promising candidates for PD-1 checkpoint blockade therapy, much less pembrolizumab.

83. Furthermore, at Counsel's request, I have looked through the "References Cited" section of the '462 Patent (EX1001, 1-7) and, in my opinion, the teachings of Koh that Merck relies upon add nothing new to the art already considered by the Examiner. For example, Brahmer (EX2024) is listed on the '462 Patent and discloses a clinical trial of an anti-PD-1 antibody that included patients with advanced metastatic cancers that had progressed after prior drug treatment (*id.*, 3). Therefore, in my opinion, Koh provides no new reason to alter the Examiner's patentability analysis of the '462 Patent.

F. Ajani

84. I have been informed by Counsel and understand that Merck relies on Ajani (EX1096) in Grounds 4-7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Ajani is a journal article describing clinical practice guidelines for gastric cancer. (EX1096, 1.) Merck primarily relies on Ajani for its alleged disclosure that "the patients having gastric cancer 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." (Pet., 54.) However, Ajani does not disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic cancer to be

enrolled in clinical trials. On the contrary, Ajani includes the same disclosure as Benson and Koh that "NCCN believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." (EX1096, 3 (emphasis added).) Moreover—like the other cited prior art—Ajani does not disclose or suggest that MSI-H patients would be particularly promising candidates for PD-1 checkpoint blockade therapy, much less pembrolizumab.

85. Furthermore, at Counsel's request, I have looked through the "References Cited" section of the '462 Patent (EX1001, 1-7) and, in my opinion, the teachings of Ajani that Merck relies upon add nothing new to the art already considered by the Examiner. For example, Brahmer (EX2024) is listed on the '462 Patent and discloses a clinical trial of an anti-PD-1 antibody that included patients with advanced metastatic cancers that had progressed after prior drug treatment (*id.*, 3). Therefore, in my opinion, Ajani provides no new reason to alter the Examiner's patentability analysis of the '462 Patent.

G. Chapelle

86. I have been informed by Counsel and understand that Merck relies on Chapelle (EX1007) in Ground 5 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Chapelle is a journal article describing the "clinical relevance of microsatellite instability in colorectal cancer,"

(EX1007, 1), and Merck primarily relies on Chapelle for its alleged disclosure of "standard methods of testing whether a tumor was MSI-H" (Pet., 56-57), including by using a panel consisting of BAT26, BAT25 (*id.*, 57). However—like the other cited prior art—Chapelle does not disclose or suggest that MSI-H cancer patients would be particularly promising candidates for PD-1 checkpoint blockade therapy, much less pembrolizumab.

87. Furthermore, at Counsel's request, I have looked through the "References Cited" section of the '462 Patent (EX1001, 1-7) and, in my opinion, the teachings of Chapelle that Merck relies upon add nothing new to the art already considered by the Examiner. For example, like Chapelle, Bacher (EX2022) describes the relationship between microsatellite instability and DNA mismatch repair deficiency and further describes using BAT-25, BAT-26, NR-21, NR-24 and MONO-27 as markers for detection of MSI-H tumors. (*Id.*, 1.) Therefore, Chapelle provides no new reason to alter the Examiner's patentability analysis of the '462 Patent.

H. Steinert

88. I have been informed by Counsel and understand that Merck relies on Steinert (EX1008) in Ground 6 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Steinert is a journal article describing "a detailed genomic analysis of single colorectal cancer-derived CTC [circulating

tumor cells] by array comparative genomic hybridization (aCGH), mutational profiling, and microsatellite instability (MSI) analysis." (EX1008, 1.) Merck primarily relies on Steinert for its alleged disclosure of "methods of testing whether a tumor was MSI-H using body fluid." (Pet., 58.) However—like the other cited prior art—Steinert does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy.

89. Furthermore, at Counsel's request, I have looked through the "References Cited" section of the '462 Patent (EX1001, 1-7) and, in my opinion, the teachings of Steinert that Merck relies upon add nothing new to the art already considered by the Examiner. For example, Diaz (EX2023) is listed on the '462 Patent and discloses that tumor DNA in blood samples can be assessed for point mutations, amplifications, and rearrangements (*id.*, 3). Therefore, in my opinion, Steinert provides no new reason to alter the Examiner's patentability analysis of the '462 Patent.

I. Hamid

90. I have been informed by Counsel and understand that Merck relies on Hamid (EX1011) in Ground 7 of the Petition to argue that the invention of the '462 Patent would have been obvious to a POSA. Hamid is a journal article describing an investigation of the "safety and tumor responses" of treating advanced melanoma patients with lambrolizumab (another name for pembrolizumab). (EX1011, 1.)

Merck primarily relies on Hamid for its alleged disclosure of administering pembrolizumab to cancer patients intravenously. (Pet., 59-61.) However—like the other cited prior art—Hamid does not disclose or suggest that MSI-H patients would be particularly promising candidates for PD-1 checkpoint blockade therapy. In fact, Hamid, does not mention microsatellite instability at all. Counsel has informed me and I understand that Hamid was considered by the Examiner during prosecution of the ’462 Patent.

VII. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

91. As explained above, in my opinion, a POSA would have a M.D. or graduate-level degree (or equivalent work experience) 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. (*See supra* § III.C.) A higher level of education may compensate for less work experience, and vice versa. (*Id.*)

A. A POSA Would Have Relevant 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

92. First, I believe evidence supports my definition of a POSA. Counsel has informed me and I understand that to determine the level of ordinary skill in the art, I should consider (1) the educational level of the inventor, (2) type of problems encountered in the art, (3) prior art solutions to those problems, (4) rapidity with which innovations are made, (5) sophistication of the technology, and (6) educational level of active workers in the field. I have used these criteria to arrive at my definition of a POSA and to support my definition over Merck's definition.

93. Educational level of the inventors(s): The backgrounds of the inventors of the '462 Patent support my definition of a POSA, while Merck's proposed definition would actually exclude some of the inventors. For example, Counsel has informed me and I understand that inventors Drs. Kinzler and Papadopoulus are well-respected cancer geneticists having PhDs and that inventor Dr. Vogelstein is a well-respected cancer geneticist having an MD. But none of Drs. Kinzler, Papadopoulus, and Vogelstein treat cancer patients. I therefore believe that Merck's proposed POSA definition is improper as it does not even encompass several of the named inventors of the '462 Patent.

94. Types of problems encountered in the prior art: The prior art had problems that included (1) recognizing new immunotherapies based on genetic biomarkers for cancer treatments and (2) recognizing and evaluating new hypotheses regarding cancer subjects who would benefit from the new immunotherapies. A POSA cannot lack experience in immunology or genetics research directed to the treatment of cancer, or conducting clinical trials on new cancer treatments in the field of immunology or genetics research because such experience is necessary for addressing these problems encountered in the prior art. For example, a medical doctor who focuses on treating cancer subjects with already approved therapeutics would be unlikely to solve problems relating to the discovery and development of novel cancer immunotherapy approaches based on genetic biomarkers.

95. Prior art solutions to the problems encountered in the prior art: As I have noted above, the research that laid the foundation for the invention of the ’462 Patent resulted in the first ever approval for a cancer therapy that is based on the presence of a biomarker and independent of the tumor location within a patient’s body. (EX2004, 1.) There were no known solutions like this before. Previous research involving checkpoint inhibitors merely evaluated and tested the efficacy of therapies with subjects with specific cancers (e.g., lung cancer, skin cancer, etc.), (*see, e.g.*, EX2024; EX1013). In my opinion, in order to reach the inventive concept of the ’462 Patent, further progress in this work would have at least necessitated

individuals having experience carrying out research directed to investigational cancer therapies and/or novel methods of cancer treatment in the fields of immunology and/or genetics.

96. Sophistication of the technology and educational level of active workers in the field: As I have described above, cancer immunotherapies include a broad range of treatment strategies that necessitate an extensive comprehension of immunology, oncology, and cancer genetics. (*See supra*, § IV.) For this reason, the field of cancer immunotherapy development is made up of individuals who are credentialed with MDs and/or PhDs along with multiple years of experience conducting research in relevant fields. Likewise, costly clinical trials and intensively regulated experiments are usually arranged by individuals with PhDs and/or MDs and multiple years of experience designing such trials. Furthermore, I believe that high levels of technological knowledge, experience, and educational level were necessary to invent the claimed invention than is typically required in this field. This is because the ’462 Patent describes a paradigm-changing invention that led to FDA granting a first-of-its-kind site-agnostic approval. (EX2004, 1.)

B. Merck's Definition of a POSA is Overly Broad Because it Includes Individuals Without 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

97. Merck's definition of a POSA is overly broad because it is inclusive of professionals such as medical doctors who do not have any experience formulating and testing hypotheses directed to investigational cancer therapies and/or methods of cancer treatment in the fields of immunology and/or genetics. Moreover, unlike my POSA definition, Merck provides no evidence to support its definition beyond the uncorroborated opinion of Dr. Neugut. (Pet., 11; EX1003, ¶19.) As far as I can tell, Merck and Dr. Neugut do not present ***any*** explanation for their purported POSA skill level.

98. It is my opinion that medical doctors or professionals without relevant 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 would not be capable of understanding and addressing problems related to the development and testing of new hypotheses relating to investigational cancer therapeutic products and/or methods of cancer treatment in the fields of immunology and genetics.

99. I acknowledge that professionals such as medical doctors with the experience of at least five years in treating cancer might understand the need for novel immunotherapy methods, which have already been approved for particular patients, and how to implement those methods. However, they would lack the sophistication and experience necessary to develop novel immunotherapeutic methods for treating cancer prior to approval. I believe a POSA in this case would have specialized experience researching and/or developing new treatment methods for cancer instead of simply treating cancer patients with already known methods.

VIII. CLAIM CONSTRUCTION

100. Counsel has instructed me to opine on my understanding and interpretation of the term "in response to," as used in the claims of the '462 Patent. In my opinion, the plain and ordinary meaning of the term requires a causal relationship between (i) determining that a patient's tumor is microsatellite instability high or DNA mismatch repair deficient and (ii) treating the patient with pembrolizumab. Ignoring this causal relationship—for example, by interpreting the claim term as simply meaning "after"—would contradict the plain meaning of the word "response."

101. Counsel has informed me and I understand that they propose that the Board interpret the term "in response to" as meaning "in reaction to." I agree with this interpretation since it preserves the causal relationship embedded in the term "in

response to," and aligns with the purpose of the claimed method, which is to (1) identify cancer patients who are likely to respond to treatment with pembrolizumab and treat them and (2) identify cancer patients who are unlikely to respond to treatment with pembrolizumab and not treat them. I confirm that Counsel's proposed construction is consistent with my analysis of the '462 Patent throughout the present declaration.

IX. CLAIMS 1-30 OF THE '462 PATENT ARE PATENTABLE OVER GROUND 1

102. Turning to Merck's substantive arguments for invalidity of the '462 Patent, it is my opinion that Merck, in Ground 1 of the Petition, has not shown that the MSI-H Study Record anticipated each and every limitation of the claims.

A. The MSI-H Study Record Cannot Anticipate Because It Does Not Expressly or Inherently Disclose Any of the Sixteen Cancer Types Recited in Independent Claims 1 and 11 ("the Claimed MSI-H Cancers")

103. As I described above, the trial disclosed in the MSI-H Study Record was designed to explore whether pembrolizumab had anti-tumor activity and would be safe in three patient populations—(1) patients with MSI positive colon cancer ("MSI-H CRC" patients), (2) patients with MSI negative colon cancer ("MSI negative CRC" or "MSS CRC" patients), and (3) patients with other MSI positive cancers ("MSI-H non-CRC" patients). (*Supra* § VI.A.) However, 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 independent claims 1 and 11 of the '462 Patent. Consequently, a POSA reading the MSI-H Study Record would have understood the third patient population of MSI-H non-CRC patients to be open to individuals with ***any*** kind of MSI-H cancer aside from colorectal cancer and ***not*** just individuals with a specifically enumerated subset of cancers. Indeed, as I explained previously, MSI-H is known to occur in at least 29 types of non-CRC cancers and this group continues to grow as new MSI-H cancers are detected. (*Supra* § IV.E.) As a result, no one knows how many MSI-H non-CRC cancers there are, and given the large size of this group, a POSA would not (and could not) have understood the MSI-H Study Record as specifically disclosing any of the Claimed MSI-H Cancers simply by virtue of its reference to the very broad class of MSI-H non-CRC patients.

B. The MSI-H Study Record Cannot Anticipate Because It Does Not Disclose Treating the Claimed MSI-H Cancers "In Response To" Those Cancers Being Determined to Be MSI-H

104. Independent of its failure to disclose the Claimed MSI-H Cancers, the MSI-H Study Record additionally fails to disclose treating any of those cancers "in response to" determining the patient's solid tumor is MSI-H or DNA mismatch repair deficient. The MSI-H Study Record discloses treating ***all*** MSI-H non-CRC patients with pembrolizumab. It does not disclose specifically treating a patient "in

response to" determining that their solid tumor of a ***specific type*** (e.g., "breast cancer" or "testicular cancer") is MSI-H. In other words, since the MSI-H Study Record discloses treating all MSI-H non-CRC patients the same, it 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. For this reason, the MSI-H Study Record cannot anticipate the claims of the '462 Patent.

C. The MSI-H Study Record Cannot Anticipate Because It Does Not Expressly or Inherently Disclose "a Solid Tumor…That Has Progressed Following at Least One Prior Treatment"

105. The MSI-H Study Record further fails to disclose that the treated patient's solid tumor (belonging to one of the sixteen claimed cancer types) "has progressed following at least one prior treatment," as recited in independent claims 1 and 11 of the '462 Patent. In fact, the MSI-H Study Record says ***nothing*** about tumor or cancer progression, and in the one place where the MSI-H Study Record mentions prior treatments, it ***excludes*** (rather than includes) individuals who had received certain prior treatments. (EX1005, 6.)

106. Dr. Neugut's interprets the MSI-H Study Record, including its use of "measurable disease," as meaning that patients would have "received prior cancer therapies and had their cancer progress following those prior therapies." (EX1003, ¶51; *see also id.*, ¶¶65, 68.) According to Dr. Neugut, this is because "[a] physician following the standard of care would generally include a patient in such a clinical

study" if that patient satisfied these criteria. (*Id.*, ¶51.) However, Dr. Neugut's reliance on what is "generally" the case in practice is very different from the MSI-H Study Record actually disclosing this limitation. Indeed, the MSI-H Study Record says nothing about enrolling patients whose cancer progressed after prior treatment, nor would this have been implicitly required. In fact, Merck's own reference, Ajani, advises that certain Stage IV gastric cancer patients proceed directly to clinical trials ***without prior treatment***. (EX1096, 3, 7.) And another of Merck's references, Benson, states that although cancer treatment generally follows guidelines, "when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy." (EX1009, 2.) Furthermore, Benson, Koh, and Ajani—all relied upon by Merck—state that "NCCN believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." (*Id.*, 3 (emphasis added).)" (EX1009, 1; EX1095, 1; EX1096, 3).

107. It was only later in January 2016—three years after the MSI-H Study Record and well after the Critical Date—that the ClinicalTrials.gov record for this study was updated to require prior cancer treatment. (EX2165, 8.) If Dr. Neugut's interpretation of the MSI-H Study Record were correct, 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. Moreover, contrary to what Dr. Neugut alleges (*see* EX1003, ¶¶51, 65, 68), the concept of measurable

disease, as used in the MSI-H Study Record, is markedly different than cancer that has progressed after receiving prior therapies. While ***measurable cancer*** refers to a cancer that has a minimum size (e.g., as determined by imaging), this has little to do with whether or not a patient's cancer has ***progressed*** after the patient received prior therapies.

D. The MSI-H Study Record Cannot Anticipate Dependent Claims 6, 16, 24, 28, and 30 Because It Does Not Disclose Treating "Metastatic" Cancer

108. In addition to the deficiencies already addressed above, the MSI-H Study Record further fails to disclose treating "metastatic" cancers or tumors, as recited in claims 6, 16, 24, 28, and 30. Merck and its expert conflate the MSI-H Study Record's disclosure of "measurable" disease with "metastatic" cancer in an attempt to reach this claim language. For example, Dr. Neugut states that patients with measurable cancer "in the context of a clinical study treating patients having tumors, like the MSI-H Study Record, referr[ed] to patients having metastatic, advanced, and recurrent cancer." (EX1003, ¶66; s*ee also id.*, ¶56 (arguing that since "the MSI-H Study Record requires patients with 'measurable disease' to receive an experimental treatment … the standard of care dictated that these patients had metastatic or advanced disease"); Pet., 19-20.) While it may be true that "measurable" disease may be related to how "advanced" a cancer is, the words "measurable" and "metastatic" are not equivalent. As already discussed,

measurable cancer refers to a cancer that has a minimum size. ***Metastatic cancer***, on the other hand, refers to cancer that spreads from its site of origin to another part of the body. When used in the context of cancer, the words "measurable" and "metastatic" unambiguously refer to distinct concepts. 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.

109. Aside from the fact that Dr. Neugut's testimony regarding the term "measurable disease" is simply wrong, his opinion is not even consistent with the references that he cites to for support. In fact, they are contradictory. Take, for example, EX1048. Dr. Neugut cites this reference in his declaration to support his interpretation of the term "measurable disease." (EX1003, ¶¶61, 96). But EX1048 actually says the following:

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*
Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

110. (EX1048, 3.)

111. As shown above, EX1048's definition of "measurable" is based strictly on tumor size. It is not dependent on whether the cancer is "metastatic" or whether the cancer progressed after a patient received prior therapies. Therefore, EX1048 does not support, but actually ***contradicts***, Dr. Neugut's opinions that "measurable disease" means patients would have "received prior cancer therapies and had their cancer progress following those prior therapies" (EX1003, ¶51; *see also id.*, ¶¶65, 68), and that patients with measurable disease "in the context of a clinical study … like the MSI-H Study Record, referr[ed] to patients having metastatic, advanced, and recurrent cancer." (EX1003, ¶66; s*ee also id.*, ¶56.)

112. For these reasons, the MSI-H Study Record does not disclose treating "metastatic" cancers or tumors simply because it mentions "measurable" disease.

E. The MSI-H Study Record Was Experimental in Nature and Required To Be Published Under Federal Laws and Regulations

113. Counsel has informed me and I understand that certain activities (e.g., public uses, sales, and offers to sell) do not count as prior art if they were conducted for experimental purposes. Accordingly, Counsel has instructed me to provide my opinion on whether the MSI-H Study Record was experimental in nature. In my opinion, it was highly experimental in nature.

114. As I described above, cancer immunotherapy is an extremely complex and unpredictable technical field. (*See, e.g.*, *supra* § IV.C). Trials for novel immunotherapies fail all the time, (s*ee, e.g.*, EX2042, 2 (describing a "multitude of unsuccessful trials" for novel immunotherapies)), and even today, Merck continues to struggle with getting its pembrolizumab trials to succeed, suffering dozens of failures of clinical trials of pembrolizumab, including at least five failures within the last year alone (EX2076, 1; EX2077, 1; EX2078, 1; EX2079, 1-2). Moreover, when the JHU inventors were developing the MSI-H clinical study protocol, pembrolizumab had not yet been approved for treatment of ***any*** cancer. Nor had the FDA ***ever*** approved a cancer-type-agnostic treatment like the one that resulted from JHU's MSI-H study.

115. In addition, as of the Critical Date of the '462 Patent, there was little reason to suspect MSI-H cancer patients (including MSI-H CRC patients and patients with the Claimed MSI-H Cancers) would be particularly good candidates for PD-1 checkpoint blockade therapy, (*see, e.g.*, *supra* § IV.E). At the Critical Date of the '462 Patent, there were many factors that taught away from MSI-H cancer patients being good candidates for immunotherapy and especially for checkpoint blockade therapy. For example, MSI-H cancer patients were known to lose Human Leukocyte Antigen (HLA) expression, which can allow cancer cells to avoid being killed by escaping T cell cytotoxicity. (*See, e.g.*, EX2046, 2 ("From a practical

standpoint, the correlation between mutator phenotype (MSI-H) and HLA loss suggests that immunotherapy against colorectal carcinoma may be of limited value"); EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune system . . . . Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation though the association between HLA class I downregulation and MSI is still controversial."); EX2047, 2-7). Moreover, researchers had identified other discouraging mechanisms of immune evasion in MSI-H CRC identified including elevated levels of regulatory T cells that "can interfere with efficient antitumoral immune responses in CRC." (EX2047, 5; *see also* EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients.")).

116. Furthermore, the available options for testing the hypothesis that led to the '462 Patent were limited due to the lack of reliable animal models for checkpoint blockade therapy. (*See, e.g.*, *supra* § IV.F). Mouse syngeneic tumor models, often used for animal testing of cancer therapeutics, are not suitable for immunotherapies such as checkpoint blockade therapy. In particular, they do not reflect the differences in treatment responses to specific cancer histologies that are seen in human patients. (EX2048, 1 ("The relative immunogenicity of these ten syngeneic tumors does not resemble typical human tumors derived from the same tissue of

origin.”).) For example, the B16 model is derived from a melanoma; however, it is resistant to immune checkpoint inhibition (“ICI”), while human melanoma is perhaps the ***most*** ICI sensitive tumor type in human cancer patients. (*Id.*, 6-8.) In contrast, the CT26 model is derived from an MSI negative CRC tumor that lacks mismatch repair (MMR) mutations. (EX2049, 3.) The CT26 model is very sensitive to ICI, while comparable human CRC tumors are resistant. *(Id.,* 3-4.)

117. The lack of translatability of syngeneic models is probably responsible for many failed clinical trials of cancer immunotherapies conducted at considerable expense, and even today, these models do not faithfully recapitulate the interactions between cancer cells and the immune systems of human solid tumor patients. *See, e.g.*, EX2073, 271-72 (a 2022 review article stating that “a new challenge for researchers is to elucidate the factors distinguishing tumors that respond to checkpoint therapy from those that do not” and that “new mouse models of cancer immunology” are still needed to fill this “critical gap”). These shortcomings can be attributed, at least in part, to the fact that many of the mouse models of immunology used today were not originally developed to study questions in the relatively new field of cancer immunology (*id.*, 269), and that they represent a very early stage in the immune response to newly transplanted cancer cells compared to the relatively mature stage found in human patients at the time of treatment. For all these reasons, the most reliable way for testing hypotheses relating to ICI therapies at the 2015

Critical Date was using human cancer patients in a clinical trial setting. The MSI-H Study Record was the initial announcement of one such hypothesis-testing study and the mere fact that it was performed with human subjects does not detract from its experimental nature given the dearth of suitable alternatives.

118. Put simply, the inventors of the ’462 Patent would not have known or expected their hypothesis to be true prior to conducting the speculative and experimental trial described by the MSI-H Study Record. They performed the study not with the goal of achieving FDA approval for an indication they expected to succeed, but to investigate whether their abstract theory had any validity to it whatsoever.

119. Finally, as I pointed out previously, it is a federal requirement to publish documents such as the MSI-H Study Record on www.clinicaltrials.gov in order to perform human clinical trials—even if it is merely an exploratory or speculative trial. (*See supra* § VI.A). Therefore, publication of the MSI-H Study Record was a ***pre-requisite*** for the inventors of the ’462 Patent to experimentally determine if their hypothesis was correct. For all of these reasons, the publication of the MSI-H Study Record was clearly experimental by its very nature.

X. CLAIMS 1-30 ARE PATENTABLE OVER THE OBVIOUSNESS GROUNDS 2-7

A. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating Any of the Claimed MSI-H Cancers

120. As I described above, the MSI-H Study Record fails to anticipate the claims of the '462 Patent because the MSI-H Study Record does not disclose any of the Claimed MSI-H Cancers or treatment thereof. *See supra* §§ IX.A, IX.B. In Grounds 2-7, Merck attempts to address these shortcomings by arguing that (1) ***all*** MSI-H cancers were obvious to treat with pembrolizumab and (2) it would then have been obvious to treat at least some of the Claimed MSI-H Cancers. However, as I explain in further detail below (*see infra* §§ X.D-X.F), a POSA would ***not*** have had a reasonable expectation of success for treating all MSI-H cancers with pembrolizumab as of the Critical Date, and consequently, it would not have been obvious to treat the ***specific*** Claimed MSI-H Cancers recited in claims 1 and 11 of the '462 Patent since none are disclosed by the MSI-H Study Record.

B. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating the Claimed MSI-H Cancers "In Response To" Determining that a Patient is MSI-H

121. Grounds 2-7 of the Petition not only fail to disclose or render obvious treating the Claimed MSI-H Cancers, but also fail to render obvious treating a patient having one of the Claimed MSI-H Cancers "in response to" determining that their tumor is MSI-H. Like the MSI-H Study Record discussed in Section IX.B, *supra*,

none of the eight additional references that Merck relies upon in its obviousness grounds discloses a causal relationship between treatment with pembrolizumab and a determination that the patient's tumor is MSI-H. Nor does Merck attempt to argue otherwise. Grounds 2-4 are the ***only*** obviousness grounds that Merck sets forth to address independent claims 1 and 11, and Merck never relies on Brown, Duval, Benson, Koh, or Ajani in ***any*** of these grounds to provide the requirement of treating a patient having one of the specifically Claimed MSI-H Cancers with pembrolizumab in response to determining their MSI status. Instead, Merck relies on these references merely to address other features such as "Improved Outcome/Efficacy" (Pet., 42-45), and progressive or metastatic disease (*id.*, 48-54). Moreover, for reasons discussed below (*see infra* § X.E) none of the references relied on in Merck's obviousness grounds would have provided a POSA with a reasonable expectation of success for achieving the claimed invention.

C. Merck's Obviousness Combinations Do Not Disclose or Render Obvious Treating a Patient Whose Cancer Has Progressed Following Prior Treatment/Has Metastatic Cancer

122. In an attempt to cure the deficiencies of the MSI-H Study Record (*see supra* §§ IX.C, IX.D), Merck relies on Benson, Koh, and Ajani in Grounds 2-4 as allegedly disclosing "Treating Patients Having Characteristics Related to Progressive and Metastatic Disease." (Pet., 48-51, 52-54.) Here, Merck seems to argue that Benson, Koh, and Ajani disclose the limitations "a solid tumor…that has

progressed following at least one prior treatment" (claims 1 and 11) and "metastatic" tumors/cancer (claims 6, 16, 24, 28, 30). But nowhere do any of these references disclose that a patient must receive prior treatment, have their cancer progress after such prior treatment, or have metastatic tumors/cancer to be enrolled in clinical trials. On the contrary, Benson, Koh, and Ajani explicitly provide for clinical trials as first-line therapy. For example, Benson states that "when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy" (EX1009, 2). As another example, Ajani advises that certain Stage IV gastric cancer patients proceed directly to clinical trials ***without prior treatment***. (EX1096, 3, 7.) And Benson, Koh, and Ajani each explain that "NCCN [provider of the guidelines] believes that the best management for ***any cancer patient*** is in a clinical trial" and "[p]articipation in clinical trials is especially encouraged." (EX1009, 1; EX1095, 1; EX1096, 3.) Even if Benson, Koh, and Ajani disclose that in ***some*** scenarios it may make sense to recruit patients whose tumors had progressed after prior therapy and who have metastatic tumors/cancer, Merck has not provided any rationale for why a POSA would have selectively handpicked these characteristics—while ignoring other disclosures from Benson, Koh, and Ajani that encourage using clinical trials as first-line therapy—to add as inclusion criteria for carrying out the study described in the MSI-H Study Record.

D. There Was No Reasonable Expectation of Success For the Treatment Method Claimed in the '462 Patent

123. As of July 10, 2015 (the Critical Date of the '462 Patent), a POSA would have had no reasonable expectation that JHU's proposed use of MSI-H as a biomarker for treating cancer patients with pembrolizumab would ultimately be successful. This is because (1) cancer immunotherapy is a complex and unpredictable technical field; (2) there was substantial evidence that MSI-H cancer patients (including MSI-H CRC patients) would ***not*** be good candidates for anti-PD-1 therapies; (3) in retrospect, many other contemporary trials of anti-PD-1 therapies failed; and (4) evolving scientific knowledge has since clarified important gaps that existed at the Critical Date of the '462 Patent.

124. As a preliminary matter, Counsel has informed me and I understand that the proper standard is whether a POSA would have reasonably expected to achieve success in the claimed treatment. In contrast, Merck's applied standard of whether a POSA "would have reasonably expected patients to respond to a sufficient degree that the POSA would have wanted to obtain the data from the MSI-H Study," (Pet., 44) is both different and nonsensical.

125. The whole point of spending time and money on a clinical study is to obtain useful scientific data. Thus, a POSA would always be interested in obtaining the data from a proposed trial. On the other hand, it is not always true that clinical

trials come with a reasonable expectation of success. Researchers sometimes take risks on studies that are unlikely to succeed—for example, if the implications of a massive success make the low odds worthwhile. This, of course, does not mean that the researchers are any less interested in obtaining data from such studies. Therefore, it is illogical to conflate the expectation of a study's success with the motivation to obtain data from such a study.

126. Tellingly, while Merck claims that a POSA would have wanted to obtain the data from the MSI-H Study, the fact of the matter is that both Merck and Bristol-Myers Squibb declined to fund the very study that would allow them to obtain that data. So, even if Merck was interested in obtaining the data from JHU's MSI-H Study, Merck evidently did not think the study was likely to be the success that it was.

127. For these reasons, at Counsel's request, I have applied the standard of whether a POSA would have reasonably expected to achieve success in the claimed treatment method of the '462 Patent in my analysis below.

1. Cancer Immunotherapy is Complex and Unpredictable

128. As I discussed above, "the immune system comprises a complex and overlapping set of homeostatic mechanisms" (*supra*, § IV.B) that has led to an equally diverse set of immunotherapy strategies being explored to treat cancer (*supra*, § IV.C). These treatment strategies—although falling within a single broad

class of "cancer immunotherapies"—are distinct from one another, and just because one immunotherapy strategy is effective for certain indications does not mean that other immunotherapy strategies (e.g., checkpoint blockade therapy) will be effective as well. Moreover, it is even more unpredictable that any specific ***drug***, such as pembrolizumab, will be effective in a given scenario. Indeed, investigations of novel immunotherapies have resulted in a "multitude of unsuccessful trials" (EX2042, 2) due to the "complex interactions" involved in the human immune response and "numerous factors [that] significantly impede our full understanding of the immune system and its interaction with tumors" (*id.*, 6-7).

2. Substantial Evidence Existed That MSI-H Cancer Patients Would *Not* be Good Candidates for Anti-PD-1 Therapies

129. There would also have been no reasonable expectation of success for the treatment method claimed in the '462 Patent because there was substantial evidence that taught away from treating MSI-H cancer patients with anti-PD-1 therapies such as pembrolizumab. Merck conveniently ignores this evidence and instead focuses on a couple of characteristics of MSI-H tumors (e.g., mutational load and infiltration by immune cells) that led some scientists to suggest investigating the treatment of MSI-H patients with immunotherapies. (Pet., 1-2, 10, 43-44). However, even if this hypothesis was floating around at the time of the Critical Date

of the ’462 Patent, the evidence certainly did not amount to providing a POSA with a reasonable expectation of success.

130. There were many factors that taught away from MSI-H cancer patients being good candidates for immunotherapy and especially for checkpoint blockade therapy. For example, MSI-H cancer patients were known to lose Human Leukocyte Antigen (HLA) expression, which can allow cancer cells to avoid being killed by escaping T cell cytotoxicity. (*See, e.g.*, EX2046, 2 (“From a practical standpoint, the correlation between mutator phenotype (MSI-H) and HLA loss suggests that immunotherapy against colorectal carcinoma may be of limited value”); EX1006, 5 (“CRC associated with MSI may develop specific mechanisms to escape the immune system . . . . Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation though the association between HLA class I downregulation and MSI is still controversial.”); EX2047, 2-7).

131. Moreover, researchers had identified other discouraging mechanisms of immune evasion in MSI-H CRC including elevated levels of regulatory T cells that “can interfere with efficient antitumoral immune responses in CRC.” (EX2047, 5; *see also* EX1006, 5 (“CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients.”)). Given the full state of the scientific

evidence at the time of the Critical Date, a POSA would not have had a reasonable expectation that JHU's claimed method of treatment would succeed.

3. Many Other Contemporary Trials of Anti-PD-1/Anti-PD-L1 Therapies Have Failed

132. The lack of any reasonable expectation of success is further evidenced by the fact that many other contemporary trials of anti-PD-1 and anti-PD-L1 therapies have failed and continue to do so even to this day. A 2023 article summarizes some of the challenges of checkpoint inhibitors for treating solid tumors, describing that "[s]o far, multiple PD-1/PD-L1 inhibitors have failed in phase 3 clinical trials. Pembrolizumab has failed in second-line liver cancer, second-line TNBC and first-line gastric cancer, meanwhile nivolumab has also failed in glioblastoma and liver cancer." (EX2074, 18.) And a 2022 review article similarly states that "[d]espite several spectacular and successful immunotherapy trials of recent years, many cancer patients do not respond to immunotherapy, or their response remains short-lived, and the recurrence of the disease seems to be inevitable mainly due to the rapidly evolving resistance. In fact, it is the resistance itself, either primary or acquired, that remains poorly understood; thus, it is impossible to overcome without further detailed research." (EX2075, 1.)

133. Merck itself has ample firsthand knowledge with such failures. For example, in February 2014—six months ***after*** JHU began its MSI-H trial—Merck

launched its own study of pembrolizumab on CRC patients (using PD-L1 as the selection criteria), and all but one patient failed to respond, resulting in a dismal response rate of 4%. (EX2080, 8.)[1] Furthermore, even today, Merck continues to struggle with getting its pembrolizumab trials to succeed, suffering dozens of failures of clinical trials of pembrolizumab, including at least five failures within the last year alone (EX2076, 1; EX2077, 1; EX2078, 1; EX2079, 1-2).

134. In other words, nearly a ***decade after*** the Critical Date of the '462 Patent, trials of anti-PD-1 inhibitors including pembrolizumab still routinely fail. Yet, Merck would have the Board believe that back in ***2015***, a mere ***trial announcement*** of a first-of-its kind study would have provided a POSA a reasonable expectation of success for JHU's groundbreaking method of administering pembrolizumab to cancer patients on the basis of their MSI-H status. Merck's view is blatantly wrong.

[1] It turns out the one responder happened to be MSI-H, and Merck would later go on to cite JHU's clinical study to explain this surprising result. (EX2132, 10-11.)

4. Evolving Scientific Knowledge Has Since Clarified Important Gaps that Existed at the Critical Date of the ’462 Patent

135. The lack of any reasonable expectation of success is further evidenced by the fact that, in retrospect, scientific knowledge has since clarified important gaps and controversies about sensitivity to immune checkpoint inhibitors that existed at the Critical Date of the ’462 Patent. For example, while it was known that there was some relationship between somatic mutations and immunogenicity of tumors, it was not clear if checkpoint blockade efficacy was driven by responses to neoantigens or shared tumor antigens, such as NYESO-1 or MAGE-1, which are normal gene products that are upregulated in cancer cells. (*See, e.g.*, EX2081, 4.) In addition, the role of tumor mutation burden (TMB) on sensitivity to immune checkpoint inhibitors across different histologies was not at all apparent since we knew that clear cell renal cancer was sensitive to ICB therapy despite having a relatively low TMB compared to melanoma. (*See, e.g.*, EX2082, 2.) To further complicate things, in 2012, work by Alex Lesokhin and colleagues showed that the level of a particular myeloid cell type (MDSCs) correlated with response to immune checkpoint inhibitors, raising the question that sensitivity to immune checkpoint inhibitors might depend more on the immune cell context rather than the antigen quality or quantity. (*See* EX2083, 1-2.)

136. The gaps in scientific knowledge around the Critical Date of the ’462 Patent were so substantial that, when Snyder and colleagues from Sloan Kettering Cancer Center published a paper in 2014 that found a correlation between TMB and the efficacy of ipilimumab therapy (i.e., another checkpoint blockade therapy) in melanoma patients (EX2084), the paper was highly controversial. Indeed, it was so controversial that I organized a symposium at Bristol-Myers Squibb where I invited one of the authors (Timothy Chan) and other scientists to speak. The discussion revealed a lack of consensus on the interpretation of the data. I also became aware, through discussions with another author on that paper, Jedd Wolchok, that a Stanford immunologist and bioinformatician, Ash Alizadeh, had objected to the methodology used in the paper and had written a formal letter of complaint Sloan Kettering. The authors later issued a correction to the paper. (EX2085.)

137. It wasn’t until after the Critical Date of the ’462 Patent, in 2016, that Swanton and colleagues helped refine our understanding of the importance of TMB to immune checkpoint inhibitor sensitivity by showing that clonal expression of neoantigens by tumor cells, rather than overall mutational burden, determines the response to ICB therapy. (EX2086, 5.) And only more recent trials have convincingly demonstrated that TMB could be a reliable biomarker for predicting the success of ICB therapy. (*See, e.g*, EX2087 (showing, in 2018, that TMB correlates with response to ipilimumab plus nivolumab in small-cell lung cancer).)

Yet even today, "[current evidence] is not yet sufficient to confidently determine the predictive value of TMB in colorectal cancer." (EX2178, 9.) As a 2024 review by Marques et al. points out, TMB has substantial limitations as a predictive biomarker (*id.*), and MSI status remains the "***only*** predictive marker of ICI response in colorectal cancer" (*id.*, 2 (emphasis added)).

138. Therefore, Merck's argument that the prior art taught that "PD-1 inhibitors naturally had more efficacy when treating tumors that . . . have many mutations . . . and . . . are already infiltrated by many immune cells" (Pet., 1) is heavily tainted by hindsight bias and misrepresents the true limitations of scientific knowledge at the Critical Date of the '462 Patent.

E. None of Merck's References Provide a Reasonable Expectation of Success

1. The MSI-H Study Record

139. As stated above, "[t]he MSI-H Study Record is the initial announcement of a clinical trial designed to test the inventors' ***hypothesis*** that identifying MSI-H cancers might be used to identify patients more likely to respond to anti-PD-1 antibody therapy." (*Supra* § VI.A (emphasis added)). However, a mere hypothesis for a study is ***not*** the same as having a reasonable expectation of success, especially in a field as unpredictable and complex as cancer immunotherapy research, where trials routinely fail. (*See, e.g.*, EX2042, 2 (describing a "multitude

of unsuccessful trials" for novel immunotherapies); *id.*, 6-7 (discussing the "complex interactions" involved in the human immune response and "numerous factors [that] significantly impede our full understanding of the immune system and its interaction with tumors").)

140. As a matter of fact, the hypothesis that the JHU researchers presented for testing in the MSI-H Study Record was even ***less*** likely to have a reasonable expectation of success given its speculative nature. There was no data or any other evidence—e.g., from *in vitro* experiments, *in vivo* animal studies, or human studies—disclosed in the MSI-H Study Record that support pembrolizumab's efficacy in MSI-H individuals or the likelihood of the trial's success. Indeed, as I have already explained elsewhere, there did not even ***exist*** adequate preclinical models to facilitate reliable testing of the inventors' hypothesis prior to the announced trial. (*See supra* § IV.F.) Furthermore, no patients had been enrolled in the announced trial or treated with pembrolizumab in accordance with the stated protocol by the time of the MSI-H Study Record's publication, and pembrolizumab had not yet been approved to treat any kind of cancer. For all these reasons, the possible success of JHU's proposed trial was a long shot to say the least—so much so that when JHU came to Bristol-Myers Squibb and Merck to request funding for the study, both companies declined. I myself was leading a highly successful cancer immunotherapy drug discovery group at Bristol-Myers Squibb at the time, and based

on my experience, I do not believe any POSA would have interpreted the MSI-H Study Record as providing a reasonable expectation of the announced trial's ultimate success.

2. Brown

141. I believe Brown also would have failed to provide a POSA with a reasonable expectation of success for the method of treatment claimed in the '462 Patent. (*See supra* § VI.B.)

142. Brown is a journal article describing a tumor genome meta-analysis in which the authors speculate that "patients with tumors showing naturally immunogenic mutations and associated TIL are ***potential*** candidates for treatment with immune modulator such as . . . PDCD1-targeted antibodies" and that "[t]here is evidence that such therapies are most effective against tumors infiltrated by T cells." (EX1034, 747.) Brown further discloses that "colorectal tumors, many of which had very high mutational loads, showed the strongest association between predicted immunogenic mutation counts and CD8A expression" (*id.*), and that "the abundance of predicted immunogenic mutations may be useful for identifying patients likely to benefit from checkpoint blockade and related immunotherapies" (*id.*, 743). However, none of these statements discloses that MSI-H cancer patients are likely to respond to PD-1 inhibitors with any reasonable expectation of success.

143. Merck relies on Brown as allegedly teaching that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize" and allegedly motivating a POSA "to treat patients having common types of MSI-H cancers, including endometrial, small bowel, and gastric cancer in the MSI-H Study." (Pet., 42.) However, Brown itself acknowledges that, "the number of subjects [in Brown's study] varied widely among cancer types" and noted that "comprehensive evaluation of immunogenic mutations specific to ***individual cancer types*** remains an important topic for ***future study***." (EX1034, 747 (emphases added).) Therefore, Brown would not have provided a POSA with a reasonable expectation of success in treating any of the specifically Claimed MSI-H Cancers in the '462 Patent with pembrolizumab. Brown also would not have provided a reasonable expectation of success for the method of treatment of the '462 Patent since, 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 (*See supra* § IV.E).

144. For example, MSI-H patients were known to lose Human Leukocyte Antigen (HLA) expression, which can allow cancer cells to avoid being killed by escaping T cell cytotoxicity. (*See, e.g.*, EX2046, 2 ("From a practical standpoint, the correlation between mutator phenotype (MSI-H) and HLA loss suggests that immunotherapy against colorectal carcinoma may be of limited value"); EX1006, 5

("CRC associated with MSI may develop specific mechanisms to escape the immune system . . . . Frameshift mutations can also induce inactivation of beta2-microglobulin leading to HLA class I downregulation though the association between HLA class I downregulation and MSI is still controversial."); EX2047, 2-7).

145. Moreover, researchers had identified other discouraging mechanisms of immune evasion in MSI-H CRC identified including elevated levels of regulatory T cells that "can interfere with efficient antitumoral immune responses in CRC." (EX2047, 5; *see also* EX1006, 5 ("CRC associated with MSI may develop specific mechanisms to escape the immune system as for example particularly high levels of intratumoral Treg described in these patients.")). Therefore, Brown would not have provided a reasonable expectation of success given the complex and controversial state of the prior art regarding microsatellite instability and its implications for cancer immunotherapy.

146. Brown also fails to demonstrate the obviousness of the method of treatment of the '462 Patent since Brown's discussion of microsatellite instability is limited to the context of Lynch syndrome and CRC. (EX1034, 747.) In its discussion of CRC, Brown concludes that "a mutator tumor phenotype may, in general, enhance immunoreactivity," but Brown fails to connect the broad concept of immunoreactivity to response to PD-1 inhibitors. (*Id.*) Therefore, Brown fails to

disclose any connection between MSI-H and response to PD-1 inhibitors in CRC, and Brown certainly fails to disclose any similar connection for other types of cancers such as the sixteen cancer types recited in claims 1 and 11 of the ’462 Patent.

3. Duval

147. I believe Duval also would have failed to provide a POSA with a reasonable expectation of success for the method of treatment claimed in the ’462 Patent. (*See supra* § VI.C.)

148. Duval is a journal article reporting the results of a study on the occurrence of MSI-H tumors in Non-Hodgkin lymphomas (NHL), (EX1087, 1), and is not directed to MSI-H cancers generally as Merck alleges, (Pet., 42). In fact, non-tumor cancers such as lymphomas are not even included among the sixteen cancer types recited in independent claims 1 and 11 of the ’462 Patent and are thus irrelevant to the current proceeding.

149. Merck also incorrectly relies on Duval as allegedly teaching that “MSI-H cancers have cancer cells that are easy for immune cells to recognize.” (Pet., 42). Duval does not make any general connection between MSI-H status and immune cell recognition and—having nothing to do with cancer treatment—Duval fails to create a reasonable expectation of success for treating patients having the Claimed

MSI-H Cancers, especially not with specific treatments such as checkpoint inhibitors or pembrolizumab.

150. To the contrary, in Duval, the authors observed that (i) although MSI-H lymphomas are extremely rare, they comprise 2-8% of lymphomas in immunodeficient patients (and occur significantly only in these patients), and (ii) unlike MSI-H solid tumors, MSI-H lymphomas are not associated with β2M mutations (and thus, corresponding loss of type I HLA expression that make MSI-H solid tumors ***harder*** for the immune system to recognize). (EX1087, 1, 4; EX1006, 5.) Based on these findings, Duval recognized that "the target gene mutation profile associated with MSI-H [immunodeficiency-related lymphomas] ***is specific for this tumor subtype***, when compared to other MSI-H cancers such as gastrointestinal and endometrial tumors." (*Id.*, 4). Therefore, Duval's finding that the data 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—both of which Duval leaves unaddressed. In fact, Duval actually supports the 1995 hypothesis of Branch et al. (EX2046) that MSI-H tumors are generally ***non-immunogenic*** because of low HLA expression, and that patients with MSI-H tumors are consequently ***poor*** candidates for immunotherapy.

4. Benson, Koh, and Ajani

151. I believe Benson (EX1009), Koh (EX1095), and Ajani (EX1096) also would have failed to provide a POSA with a reasonable expectation of success for the method of treatment claimed in the '462 Patent. (*See supra* §§ VI.D-VI.F.) These references are journal articles describing clinical practice guidelines for colon cancer (EX1009,1), endometrial cancer (EX1095, 1), and gastric cancer (EX1096, 1), respectively. Merck primarily relies on these references for their alleged disclosure of (1) tumor progression following at least one prior treatment and (2) metastatic cancer. (Pet., 20, 49-54.) However—like the MSI-H Study Record, Brown, and Duval—none of these references would 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. Ajani (EX1096) does not discuss microsatellite instability whatsoever, while Benson and Koh only discuss it in the context of identifying individuals at risk for Lynch syndrome—not for using as a biomarker for treatment. (EX1009, 6; EX1095, 3, 9-11, 16.)

5. Chapelle, Steinert, and Hamid

152. In Grounds 5-7, Merck additionally relies on Chapelle, Steinert, and Hamid as allegedly teaching discrete limitations in the dependent claims. For example, Merck primarily relies on Chapelle for "standard methods of testing

whether a tumor was MSI-H" (Pet., 56-57), including by using a panel consisting of BAT26, BAT25 (*id.*, 57). Meanwhile Merck primarily relies on Steinert for its alleged disclosure of "methods of testing whether a tumor was MSI-H using body fluid" (*id.*, 58), and on Hamid for its alleged disclosure of administering pembrolizumab to cancer patients intravenously (*id.*, 59-61).

153. None of these alleged teachings have to do with treating the Claimed MSI-H Cancers or treating the Claimed MSI-H Cancers "in response to" determining that the patient's tumor is MSI-H, as addressed above. Therefore, they fail 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. As such, Merck's reliance on Chapelle, Steinert, and Hamid do nothing to resolve the deficiencies in Merck's obviousness analysis of claims 1-30, as laid out in Sections X.A-X.E.4, *supra*. (*See supra* §§ X.A-X.E.4.)

6. Merck's Additional References

154. Merck and its expert further rely on a host of additional references with little to no explanation to demonstrate what was allegedly known in the art at the Critical Date of the '462 Patent. (Pet., 43-44.) But these too fail to provide a POSA

with a reasonable expectation of success for the methods of treatment claimed in the '462 Patent.

155. First, the sources Merck cites do not support Merck's assertions that:

- "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that are easy for immune cells to recognize and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize." (Pet., 43; EX1003, ¶138); and
- "[S]everal sources independently urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab." (Pet., 44, EX1003, ¶139).

156. These references disparately discuss MSI-H in general (EX1085), hypotheses for anti-PD-1/PD-L1 therapies (EX1038; EX1032), and cancer-specific considerations (EX1040 (breast cancer); EX1041 (CRC); EX1042 (osteosarcoma)). But if anything, these references show the highly unpredictable nature of this technical field and the prevailing notion at the Critical Date that cancers should be treated individually by histology. For example, EX1038 states that "meticulous artistry in clinical trial design is essential to carve out the clinical benefits [of anti-PD-1/PD-L1 antibodies] for carefully selected patients" (EX1038, 9 (emphases added)), and EX1040 emphasizes the stark differences between the mutational load of triple negative breast cancer from carcinogen-induced solid cancer types

(EX1040, 2). Under this paradigm, even if a POSA would have expected the claimed method to succeed in CRC (they would not), there would have been no reason to extend that expectation to a particular non-CRC cancer, let alone the Claimed MSI-H Cancers, based on references discussing the treatment of CRC. (*See* Pet. 44 (citing EX1006, EX1032, EX1033, EX1036, EX1037, EX1038, EX1051, EX1039).) Moreover, the sources Merck cites were not independently "urging" the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab, because they reasonably expected such treatments to succeed. At best, these sources were inviting researchers to take an outside chance on investigating additional speculative hypotheses. *See, e.g.*, EX1032, e27817-5 ("***if*** high levels of mutational heterogeneity increase the tumor immunogenicity, ***it will be interesting*** to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MS) colorectal carcinoma) (emphases added); EX1041, 9208 (acknowledging that "[d]ata on the use of immune checkpoint target drugs in colorectal cancer are still limited"); EX1042, 732 (stating that "[n]ewer agents, including the T cell checkpoint inhibitors, antibodies against PD1, PDL1 or CTLA 4, are yet to be fully explored in osteosarcoma but are likely to present further opportunities to improve survival in certain patient groups . . . ***if biomarkers of response are discovered***") (emphasis added); EX1051, e976052-6 ("[MSI-CRC] patients ***may*** . . . have greater responses

to checkpoint blockade therapies"); EX1084, 1 ("the data [concerning PD-1/PD-L1 trials] thus far are ***exploratory*** and ***early***") (emphases added).

157. Second, in many cases, the teachings of Merck's references were much broader than the method claimed by the '462 Patent and thus do not render it obvious. For example, EX1033 suggests the potential benefit of ***targeted immunotherapy*** rather than using checkpoint blockade or anti-PD-1 therapies to treat MSI-H cancer. (EX1033, 2969). Likewise, EX1036, EX1037, and EX1058 are silent regarding checkpoint blockade therapy therapies, anti-PD-1 therapies and pembrolizumab. And still other references, such as EX1039, suggest targeting PD-L1 instead of PD-1.

158. Third, and contrary to what is implied in the Petition (*see* Pet., 47), a POSA also would not have had a reasonable expectation of success in treating the Claimed MSI-H Cancers based on the possibility that the patients might have Lynch Syndrome. Although it was known that there was a connection between Lynch Syndrome and MSI-H, as of the Critical Date, there was no known connection between MSI-H and ***responsiveness to checkpoint inhibition***. Further, given the treatment paradigm at the time was explicitly tied to cancer type, there certainly would have been no reason to expect this (then unknown) relationship to extend across multiple cancer types, much less to the specific Claimed Cancers. Thus,

success in treating one cancer type would not have created a reasonable expectation of success in treating another.

159. For all of these reasons, none of the additional references Merck string-cites in the Petition would have led a POSA to have a reasonable expectation that the claimed method of the '462 Patent would be successful. Below, I address each of Merck's numerous additional references in further detail.

160. **EX1032:** Merck and its expert misleadingly state that EX1032 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139) and further taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1032 is a journal article about the promise of anti-PD-1/PD-L1 antibodies as anticancer therapeutics, in which the authors, "based on a limited amount of data" hypothesize "that mutagen-induced tumors appear to exhibit an improved response to these immunotherapeutic agents." (EX1032, e27817-5.) Extending this admittedly speculative hypothesis even further, the authors state that "***if*** high levels of mutational heterogeneity increase the tumor immunogenicity, ***it will be interesting*** to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MS) colorectal

carcinoma." (*Id.* (emphases added).) These cautious suggestions for exploration certainly did not "urge" the treatment of MSI-H cancer with PD-1 inhibitors, as Merck alleges. Nor does EX1032 provide a reasonable expectation of success merely because the authors proposed an "interesting" investigation ***if*** the authors' hypothesis (formed on the basis of "limited data") ultimately proved to be correct. On the other hand, substantial evidence in EX1032 pointed ***away*** from the use of checkpoint blockade therapy for certain cancers such as colorectal cancer including the fact that Table 1 of the same reference shows a ***0% response rate*** for anti-PD1 agents and anti-PD-L1 agents among colorectal cancer patients.

161. **EX1033:** Merck and its expert also state that EX1033 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab." (Pet., 44; EX1003, ¶139.) EX1033 is a journal article reporting on PD-1 and PD-L1 in common cancers and their correlation with molecular cancer type, finding that "[i]n the colon cancer cohort, MSI-H tumors exhibited a significantly higher rate of positivity for PD-1$^+$ TILS than MSS colon cancers" and "the proportion of PD-L1$^+$ cancers was significantly higher in MSI-H than in the MSS colon cancers." (EX1033, 2967). The authors also observed that "PD-1/PD-L1 were differently expressed in molecular subtypes of . . . colon cancer (MSI-H v. MSS cases) providing an indication for potential benefit of targeted immunotherapy in aggressive subtypes of . . . colon cancers for which no targeted therapy is currently

available." (*Id.*, 2968-69.) However, these observations would not have provided a POSA with a reasonable expectation of success of the specific claimed invention of the '462 Patent. First, the authors themselves acknowledged that their data differed from another contemporary study that "reported more frequent expression of PD-L1 in the MSS than in MSI-H colon cancers." (*Id.*, 2969.) Second, EX1033 never directly suggested—much less "urged"—using MSI-H as a biomarker for treating CRC patients with PD-1 checkpoint blockade therapy (or pembrolizumab specifically). Instead, EX1033 merely stated that the data pointed to a much broader suggestion of a "potential benefit of targeted immunotherapy in ***aggressive*** subtypes of . . . colon cancer." (*Id.*) And finally, in February 2014—six months ***after*** JHU began its MSI-H trial—Merck announced its own study of pembrolizumab on CRC patients (using PD-L1 as the selection criteria), and all but one patient failed to respond, resulting in a dismal response rate of 4%. (EX2080, 8.) Evidently, without the benefit of hindsight that Merck now relies on, the existing research on PD-1 and PD-L1 as of the Critical Date was not sufficient to provide a POSA a reasonable expectation of success in treating MSI-H cancer patients.

162. **EX1035:** Merck and its expert also state that EX1035 taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43;

EX1003, ¶138). EX1035 discloses that "a lymphoid reaction is frequently associated with MSI-high in colorectal cancer" and that "MSI-high tumor cells have frameshift mutations in coding sequences throughout the genome, which might include gene products that regulate in immunity." (EX1035, 4.) However, EX1035 does not teach or suggest using MSI-H as a biomarker for treating CRC patients with PD-1 checkpoint blockade therapy or pembrolizumab. In fact, EX1035 teaches away from such a hypothesis, stating that "[a]s tumors are heterogeneous and show distinctive genetic and epigenetic profiles, there may ***not*** be a single biomarker that will prove sufficient information for predicting treatment response and patient outcome." (*Id.*, 2 (emphasis added).)

163. **EX1036:** Merck and its expert also state that EX1036 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139) and further taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1036 describes certain features of colorectal cancers with microsatellite instability (*see, e.g.*, EX1036, 1186, 1193), and ultimately concludes that the data "argues for the clinical relevance of T-cell immunotherapy strategies in this type of tumors" and "provides evidence that *ASTE1/HT001* and *PTEN* could be especially

promising targets." (*Id.*, 1193.) However, EX1036 is silent with respect to checkpoint blockade therapies—much less anti-PD-1 therapies and pembrolizumab—and therefore does not teach or suggest using MSI-H as a biomarker for treating MSI-H cancer patients with PD-1 checkpoint blockade therapy or pembrolizumab.

164. **EX1037:** Merck and its expert also state that EX1037 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139) and further taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). However, while EX1037 discusses some evidence of a relationship between microsatellite instability and host immune response (*see, e.g.*, EX1037, 2, 6), it does not disclose or suggest that MSI-H cancer patients would be particularly promising candidates for PD-1 checkpoint blockade therapy. In fact, EX1037 does not mention checkpoint blockade therapies (including anti-PD-1 therapies and pembrolizumab) whatsoever.

165. **EX1038:** Merck and its expert also state that EX1038 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139) and further taught that "PD-1 inhibitors

inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1038 is a review article about targeting PD-1 and PD-L1 for cancer therapy and discusses how, based on an "early report" of a single responder with MSI-H CRC, it had been "***hypothesized*** that MSI-high tumors with a high propensity for mutation would generate more neoantigens and make them more susceptible to immune recognition and attack." (EX1038, 7 (emphasis added).) But EX1038 fails to provide any indication that this mere hypothesis amounted to a reasonable expectation of success for treating patients with pembrolizumab in response to determining they had MSI-H cancer. For example, EX1038 mentions another contemporary trial involving nivolumab (i.e., another anti-PD-1 therapy) in MSI-H CRC patients. But EX1038 fails to provide any evidence that this trial was (or was even expected to be) successful. Instead, EX1038 discloses that, while anti-PD-1/PD-L1 antibodies showed "early" promise, "***meticulous artistry*** in clinical trial design is ***essential*** to carve out the clinical benefits for carefully selected patients." (*Id.*, 9.) Such "meticulous artistry" was well beyond the skill level of a POSA as of the Critical Date and is what was ultimately supplied by the inventors of the '462 Patent.

166. **EX1039:** Merck and its expert also state that EX1039 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139) and further taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1039 is a poster abstract stating that "MSI CRC has been characterized by an intense immune infiltration which was assumed to be related to a high density of mutations creating numerous neoantigens" and concluding that "[a] strong IFNg-driven inflammatory response in MSI CRC patients triggered the expression of PD-L1 and IDO-1 which could be targeted to enhance clinical benefit and be predictive of response to immune checkpoint inhibitors." (EX1039, 243s.) However, EX1039 does ***not*** specifically disclose or suggest the targeting of ***PD-1*** (distinct from ***PD-L1***) with anti-PD-1 inhibitors such as pembrolizumab. Nor would EX1039 provide a POSA with a reasonable expectation of success for such treatments since the abstract merely presents an invitation to investigate the relationship between PD-L1/IDO-1 expression with a patient's response to immune checkpoint inhibitors.

167. **EX1040:** Merck and its expert also state that EX1040 taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H

cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). In particular, Dr. Neugut cites EX1040's disclosure that "[h]igh mutational load is thought to be related to the responses observed with anti-PD-1 antibodies in lung cancer and melanoma. Neoantigens are created through mutant peptides, some of which are immunogenic, and are recognized by T cells that can trigger an immune response." (EX1003, ¶44 (citing EX1040, 2).) However, EX1040 is silent with respect to using MSI status as a biomarker for treating MSI-H cancer patients with anti-PD-1 therapies such as pembrolizumab. Therefore, EX1040 would not have provided a POSA with a reasonable expectation of success for the claimed treatment method of the '462 Patent.

168. **EX1041:** Merck and its expert also state that EX1041 taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1041 states that "increased counts of CD8+ T-cells were observed in colorectal cancer tumors with high mutational loads and microsatellite instability." (EX1041, 9208.) However, the very next sentence of EX1041 states that "[d]ata on the use of immune checkpoint target drugs in colorectal cancer are still limited." (*Id.*) Moreover, there is no disclosure or suggestion in EX1041 of

using MSI status as a biomarker for treating cancer patients with checkpoint blockade therapy—much less with anti-PD-1 therapies such as pembrolizumab.

169. **EX1042:** Merck and its expert also state that EX1042 taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1042 is a review article about osteosarcoma, and Dr. Neugut cites its disclosure that "[h]igh levels of genomic instability may make immunotherapies particularly suitable, because of the constant generation of neo-epitopes that are the substrate for immune-mediated killing of cancer cells. Certainly, the cancers that have shown the greatest promise for newer immunotherapies have been characterized by high rates of genomic instability." (EX1003, ¶44 (citing EX1042, 732).) However, yet again, EX1042 does not disclose or suggest using MSI status as a biomarker for treating cancer patients (even osteosarcoma patients) with checkpoint blockade therapy such as anti-PD-1 therapies or pembrolizumab. Indeed, EX1042 does not speculate as to any particular biomarker at all, simply stating that "[n]ewer agents, including the T cell checkpoint inhibitors, antibodies against PD1, PDL1 or CTLA 4, are yet to be fully explored in osteosarcoma but are likely to present further opportunities to improve survival in certain patient groups, particularly ***if biomarkers of response are discovered***."

(EX1042, 732.) Therefore, EX1042 would not have provided a POSA with a reasonable expectation of success for the claimed treatment method of the '462 Patent.

170. **EX1051:** Merck and its expert also state that EX1051 "urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab" (Pet., 44; EX1003, ¶139). EX1051 discusses that "the immune landscape of MSI-H CRC, which is characterized by a high mutational burden including frameshift mutations, is dominated by T helper cell infiltration and activation, class II expression and coordinated upregulation of a range of immune checkpoint genes. These patients ***may*** therefore have greater responses to checkpoint blockade therapies." (EX1051, e976052-6 (emphasis added)). However, this is nothing more than a hypothesis and an invitation to investigate. The mere identification of certain tumor characteristics that are correlated with checkpoint blockade therapy responses would not provide a POSA with a reasonable expectation of success for treatment in such an unpredictable technical field—especially when, in retrospect, we know that many trials of checkpoint blockade therapies and anti-PD-1/PD-L1 inhibitors ultimately failed. (*See, e.g.*, EX2074, 18 ("In solid tumours, ICB agents have encountered some dilemmas. So far, multiple PD-1/PD-L1 inhibitors have failed in phase 3 clinical trials. Pembrolizumab has failed in second-line liver cancer, second-line TNBC and first-line gastric cancer,

meanwhile nivolumab has also failed in glioblastoma and liver cancer."); EX2075, 1 ("Despite several spectacular and successful immunotherapy trials of recent years, many cancer patients do not respond to immunotherapy, or their response remains short-lived, and the recurrence of the disease seems to be inevitable mainly due to the rapidly evolving resistance. In fact, it is the resistance itself, either primary or acquired, that remains poorly understood; thus, it is impossible to overcome without further detailed research.").) The notion that there was a reasonable expectation of success for treating MSI-H cancer patients with anti-PD-1 therapies or pembrolizumab in 2015 (i.e., the Critical Date of the '462 Patent) is simply incorrect.

171. **EX1058:** Merck and its expert also state that EX1058 taught that "PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize" (Pet., 43; EX1003, ¶138). EX1058 discloses that "[p]atients with MSI-H colon cancers had increased percentages of CD8+ TILs (cytotoxic T cells) as compared to individuals with MSS colon cancer (47.3% vs. 24.04% of the infiltrate CD8+, respectively)" (EX1058, 231) and that "MSI-H tumors have antigenic frameshift peptides" (*id.*, 236-37). However, EX1058 is silent with respect to treating MSI-H cancer patients with checkpoint blockade therapies, anti-PD-1 inhibitors, or pembrolizumab, and it certainly does not disclose using MSI status as a biomarker to inform such treatment.

Therefore, EX1058 would not have provided a POSA with a reasonable expectation of success for the claimed treatment method of the ’462 Patent.

172. **EX1085:** Merck and its expert also state that EX1085 taught that “PD-1 inhibitors inherently had more efficacy when treating tumors that are comprised of cancer cells that were easy for immune cells to recognize, and that all MSI-H cancer…have cancer cells that are easy for immune cells to recognize” (Pet., 43; EX1003, ¶138). In particular, Dr. Neugut cites EX1085’s disclosure that “[c]ancers in the MSI pathway accumulate hundreds of thousands of somatic mutations in simple repeated sequences or microsatellites,” (EX1003, ¶46 (citing EX1085, 673)), and that “[t]umors with MSI-H demonstrate a high frequency of frameshift mutations that result in the generation of premature translation termination codons,” (EX1003, ¶46 (citing EX1085, 677)). However, EX1085 is silent with respect to treating MSI-H cancer patients with checkpoint blockade therapies, anti-PD-1 inhibitors, or pembrolizumab, and it certainly does not disclose using MSI status as a biomarker to inform such treatment. Therefore, EX1085 would not have provided a POSA with a reasonable expectation of success for the claimed treatment method of the ’462 Patent.

173. Collectively, Merck’s references fail to show that MSI-H cancer would be more responsive to treatment with pembrolizumab than MSI-stable cancers. And while some of the references speculate that MSI-H cancer patients might be

candidates for immunotherapy generally, Merck's reliance on just a few hand-selected quotations from these references ignores the countering evidence at the Critical Date that MSI-H cancers would not respond to immunotherapy—sometimes found in the very same references that Merck relies upon. Furthermore, while much of the speculation in these references was based on the correlation between indicators of antitumor response and mutational burden in the tumor, further research has shown that this relationship only holds in a minority of cancer types. For example, in a 2024 letter by Hsiehchen, et al. in Cancer Cell, the authors reported analyzing patients distributed across 26 different cancer histologies and found that (1) "IGES [immune gene expression signatures] and infiltrating immune cells implicated in anti-tumor responses are only associated with TMB [tumor mutation burden] in a minority of cancer types" and that (2) "many immune features associated with outcomes across histologies appear idiosyncratic, without consistent patterns of immune cell enrichment or depletion between cancer types." (EX2281, 1-2.) The letter goes on to say that the results "highlight the ***limited utility*** of immune classes to describe the clinical behaviors of cancers" and that "the utility of immune and genetic biomarkers for predicting anti-PD-1/L1 therapy efficacy is ***histology dependent***." (*Id.*, 2 (emphases added).) Therefore, a POSA considering Merck's references as a whole would not have found a reasonable expectation of success in

achieving the invention of the ’462 Patent based upon the dubious indicators of antitumor response and mutational burden that Merck emphasizes so heavily.

F. The State of the Art Does Not Create a Reasonable Expectation of Success

174. Merck also argues that “the state of the art would have further compelled a POSA to carry out the clinical study with a reasonable expectation of success.” (Pet., 43.) But again, Merck is wrong.

175. First, Merck argues that “[p]hysicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art with PD-1 inhibitors.” (*Id.*) To support this statement, Merck cites the MSI-H Study Record itself (addressed above) and two additional study records for trials involving pembrolizumab. (EX1016, EX1017.)

176. EX1016 describes a trial “to investigate the safety, tolerability and anti-tumor activity of MK-3475 [i.e., pembrolizumab] in participants with advanced triple negative breast cancer (TNBC), advanced head and neck cancer, advanced urothelial cancer, or advanced gastric cancer.” (EX1016, 4.) However, the trial does not describe ***any*** screening of patients to determine their MSI status, and even if some of them ***happened*** to be MSI-H, the disclosure of EX1016 is a far cry from suggesting the treatment of MSI-H cancer patients with pembrolizumab would produce a better outcome than MSI-stable cancer patients.

177. EX1017 describes another trial designed to "assess the efficacy and safety of pembrolizumab administered to participants with incurable advanced biomarker-positive solid tumors that have not responded to current therapy or for which current therapy is not appropriate." (EX1017, 4.) But the study record makes no indication of a specific biomarker, does not mention screening patients to determine their MSI status, and certainly does not suggest that MSI-H cancer patients will demonstrate an improved outcome as compared to MSI-stable patients. As such, this "state of the art" would not provide a POSA with any reasonable expectation of success for the specific treatment method claimed in the '462 Patent.

178. On the contrary, while anti PD-1 inhibitors had begun to show success in melanoma and non-small cell lung cancer, attempts in other types of cancer had largely failed to elicit responses. (*See, e.g.,* EX2024.) For example, although one prior art publication reported successful treatment of a colorectal cancer patient having an MSI-H tumor with a PD-1 inhibitor, this was a study in which only a ***single*** CRC patient responded to treatment with a different drug and in which there was ***no*** intention to investigate MSI-H as a potential biomarker for treatment. (EX1057, 2-3.) In fact, this singular responsive patient was the only responder out of ***thirty-three*** (33) CRC patients when combining the results of multiple contemporary studies reporting on the effects of PD-1 blockade in human tumors. (*See supra* § IV.F.) Any suggestion that this statistically meaningless result in the

face of a ***97% failure rate*** for treating CRC patients with pembrolizumab would somehow provide a POSA with a reasonable expectation of success for the claimed treatment method of the '462 Patent is clearly not credible.

179. Merck additionally argues that "because the POSA would have known that pembrolizumab was already approved for another oncology indication by November 2014, the POSA would have had a higher expectation of success" for the MSI-H-related indication. (Pet., 45.) Here, Merck points to pembrolizumab's approval for treating melanoma and supplies the statistic that "for oncology drugs, 55% of second indications were successful if the first indication was successful, but only 9% of first indications were successful." (*Id.* (citing EX1055, 1-2 and EX1063, 334-35).) The first glaring issue with this analysis though is that it ***completely ignores*** that the '462 Patent is not directed to any ordinary second indication for an oncology drug. Rather, it resulted in a historical first approval of its kind. (*See supra* § V ("While previously the FDA had approved cancer treatments 'based on where in the body the cancer started—for example, lung or breast cancers,' this was the first time a drug had been approved 'based on a tumor's biomarker without regard to the tumor's original location.') (quoting EX2004, 1).) Therefore, a POSA would recognize that overly broad success statistics do not apply. Indeed, even if there were previous approvals for pembrolizumab, they would have been irrelevant to the expectation of success for treating all MSI-H cancers.

180. Another issue with Merck's reliance on its second indication statistic is that it excluded drugs that were sponsored "exclusively by academic, government, or non-profit organizations." *See* EX1063, 1. Studies run by these types of institutions are far more likely than pharmaceutical companies to be high risk, experimental studies. Consequently, the exclusion of these drugs misleadingly inflates the success rate that Merck relies upon.

181. Furthermore, as I described above, in the field of cancer immunotherapy, one cannot reasonably expect one strategy (e.g., checkpoint blockade therapy) to work for a particular indication merely because other immunotherapy strategies showed promise for the same indication. (*See supra* § IV.C.) And there would be even less reason to believe a specific therapeutic (e.g., pembrolizumab) would be effective given the highly unpredictable nature of this technical field. (*See, e.g.*, EX2042, 2 (describing a "multitude of unsuccessful trials" for novel immunotherapies); *id.*, 6-7 (discussing the "complex interactions" involved in the human immune response and "numerous factors [that] significantly impede our full understanding of the immune system and its interaction with tumors").) Indeed, as I pointed out above, Merck itself has repeatedly struggled with getting its pembrolizumab trials to succeed, suffering dozens of failures of clinical trials of pembrolizumab, including at least five failures within the last year alone (EX2076, 1; EX2077, 1; EX2078, 1; EX2079, 1-2). For these reasons, a POSA

would not have found a reasonable expectation of success based on the state of the art, even after pembrolizumab's first approval for treating melanoma.

XI. JHU'S OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS SUPPORTS UPHOLDING THE PATENTABILITY OF THE CHALLENGED CLAIMS

182. As noted above, I have been informed by Counsel and understand that evidence of secondary indicia of non-obviousness should be considered as part of an obviousness analysis. (*See supra* § III.B.) Counsel has instructed me to provide my analysis of the evidence regarding (1) industry praise, (2) skepticism by experts, (3) unexpected results achieved by the invention, and (4) the relationship between such evidence and the claims of the '462 Patent. My opinion, with my analysis provided in detail below, is that all of these sources of evidence support the non-obviousness of the '462 Patent claims.

A. Industry Praise

183. The abundant praise received for the '462 Patent's invention by patients, doctors, researchers, and Merck itself supports the non-obviousness of the '462 Patent claims. From the moment of their release, the results of the treatment method described and claimed in the '462 Patent were considered extraordinary. Indeed, the results were so notable that they were published in the world's top medical journal, the New England Journal of Medicine (EX1031), in an article that has since been cited over 9,700 times. In addition, Merck itself put out a press

release publicizing the findings with Dr. Roger Dansey, therapeutic area head and senior vice president, oncology late-stage development, Merck Research Laboratories, acknowledging that "[t]hese exciting results, while early, suggest that evidence of DNA mismatch repair deficiency may be an important way of identifying tumors that are responsive to checkpoint blockade." (EX2061, 2.)

184. When the results of JHU's study were announced, I was leading a highly successful drug discovery group at Bristol-Myers Squibb at the forefront of discovering checkpoint blockade therapies and anti-PD-1 drugs such as ipilimumab, nivolumab, and relatlimab. While we were disappointed that we had not made the discovery ourselves, there was great excitement at Bristol-Myers Squibb about JHU's trial results and the significance they held for our own anti-PD-1 drugs. I distinctly remember Luis Diaz, a co-inventor of the '462 Patent, presenting the results at the 2015 Society for Immunotherapy in Cancer Conference (SITC) to an enraptured audience, and I was so struck by the findings that I made it a point to track down and speak to Diaz personally after his talk.

185. Importantly, the remarkable reception of JHU's findings were not limited to researchers alone. Since being approved by FDA, the treatment method described in the '462 Patent claims has been described by doctors as "absolutely brilliant" with "insane" results (EX2005, 1, 3) and further credited by patients as giving them "a great life." (*Id.*) Scientific commentators have called the approved

indication "a tipping point for disease reclassification based on tumor-specific factors" that "propels oncology further toward the goal of precision medicine," (EX2089, 5), and Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence has acknowledged, "[t]his [was] an important first for the cancer community," (EX2004, 1).

186. All of the above examples of praise are directly related to the specific method of treating MSI-H cancer patients with pembrolizumab that is claimed in the '462 Patent. Therefore, I believe they strongly support the non-obviousness of the '462 Patent claims.

B. Skepticism

187. Prior to the actual release of JHU's trial results, there was substantial skepticism from experts that such a study was worth performing, and this further supports the non-obviousness of the '462 Patent claims. In fact, when JHU approached Bristol-Myers Squibb about contributing its anti-PD-1 drug, nivolumab, to investigate the potential use of MSI-H status as a biomarker for treating CRC patients, Bristol-Myers Squibb declined. It was this skepticism that led JHU to then approach Merck and prevented Bristol-Myers Squibb from playing the role that Merck eventually filled in JHU's MSI-H trial. Having worked at Bristol-Myers Squibb at the time, I heard about Bristol-Myers Squibb's initial declination and

personally spoke to Dr. Drew Pardoll, a co-inventor of the ’462 Patent, about the merits of JHU’s proposed study. At the time, I acknowledged that the trial would be very risky—even for CRC patients—since the odds of success seemed so low in light of the repeated failures of PD-1 inhibitors in this population. However, feeling the potential upside of a positive result could justify this risk, I reached out to several people within Bristol-Myers Squibb to advocate for our involvement in JHU’s study. Nevertheless, my efforts were unsuccessful and the skepticism among decisionmakers within Bristol-Myers Squibb prevailed. In other words, Bristol-Myers Squibb regrettably passed up on the opportunity to be involved in JHU’s MSI-H trial not once, but ***multiple times*** after careful consideration. This skepticism is directly related to the claims of the ’462 Patent since it related to the very MSI-H trial that JHU eventually performed, and it is further evidence that it was not obvious to those working in the field to administer anti-PD-1 therapies to patients in response to determining their cancer was MSI-H.

C. Unexpected Results

188. The non-obviousness of the ’462 Patent claims is further evidenced by the unexpected results yielded by the invention. As I have described in detail above, there was no reasonable expectation of success for the treatment method tested in JHU’s MSI-H trial. (*See supra* §§ X.D-X.F.)

189. Cancer immunotherapy is complex and unpredictable (*supra* § X.D.1), such that it cannot be expected that immunotherapy strategies (e.g., checkpoint blockade therapy) will be generally effective just because one immunotherapy strategy is effective for certain cancers. Nor can it be expected that a specific target drug candidate will be safe and effective in humans simply because it shows promise *in vitro* or *in vivo*. Indeed, as I explained previously, there were ***no*** reliable animal models for checkpoint blockade therapy in human cancers as of the Critical Date of the '462 Patent, (*see supra* § IV.F), so the inventors had no access to (and could not generate) reliable preclinical data that would have raised their expectation of success. Add to this the substantial evidence that MSI-H patients (including MSI-H CRC patients) would ***not*** be good candidates for anti-PD-1 therapies (*supra* § X.D.2), the failure of other contemporary trials of anti-PD-1 therapies (*supra* § X.D.3), and the significant gaps and controversies about response to checkpoint blockade therapy that were clarified only after the Critical Date of the '462 Patent (*supra* § X.D.4), and there was simply no way a POSA would have reasonably expected the claimed treatment method of the '462 Patent to succeed.

190. Even beyond being surprised by the success of JHU's MSI-H trial, those of us working in the field were struck by just ***how*** unexpectedly successful the trial results proved to be. The response rates and strength of responses observed in both MSI-H non-CRC and MSI-H CRC patients were startling, especially when

compared to the fact that previous trials with Bristol-Myers Squibb's anti-PD-1 drug, nivolumab, failed to produce a response in 32/33 patients with colorectal cancer (CRC). (*See* EX1001, 2:63-67 ("[O]nly one of 33 colorectal cancer (CRC) patients responded to this treatment, in contrast to substantial fractions of patients with melanomas, renal cell cancers, and lung tumors."); *see also* EX2024, 3 (reporting that 1 of 14 CRC patients responded); EX1013, 3-4 (reporting that 0 of 19 CRC patients responded).) Consequently, when JHU's trial results were publicized, there was a strong sense within Bristol-Myers Squibb that we had missed out on a tremendous opportunity. Simply put, no one expected the results of JHU's MSI trial (and the directly corresponding treatment method claimed in the '462 Patent) to be as extraordinary as they were.

D. Nexus

191. Counsel has informed me and I understand that the objective evidence of non-obviousness presented in this declaration must have a connection to the claims of the '462 Patent. It is my opinion that all of the objective evidence I analyzed satisfies this requirement. For example, in forming this opinion, I reviewed Dr. Richard Goldberg's declaration (EX2090). I agree with Dr. Goldberg's assessment that the tissue-agnostic MSI-H indication listed on the Keytruda label after the FDA's approval in May 2017 along with the endometrial cancer indication approved in 2022 correspond directly to the claims of the '462 Patent. (EX2090,

¶¶82-93.) I also agree with Dr. Goldberg's conclusion that "an oncologist prescribing Keytruda to a cancer patient under the MSI-H-related indications described above would necessarily practice the method of treatment claimed in at least Claim 1 of the '462 Patent." (*Id.*, ¶93.) Therefore, there is necessarily a nexus between the claims of the '462 Patent and any evidence relating to the administration of Keytruda (pembrolizumab) to MSI-H patients in accordance with the Keytruda label.

XII. CONCLUSION

192. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information introduced throughout this proceeding.

193. I declare under penalty of perjury that the foregoing is true and accurate to the best of my ability.