

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Diaz et al.

U.S. Patent No.: 11,591,393

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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: 10/4/24

By: _____

Nils Lonberg, Ph.D.

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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 my *curriculum vitae* (EX2002) and my previously filed declaration in this proceeding (EX 2001). 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. 11,591,393 (“the ’393 Patent”) (EX1001) and alleged prior art references relating to its subject matter. I have reviewed the ’393 Patent and its accompanying prosecution history (EX1002). Additionally, I have reviewed the Petition, the materials cited in the Petition, the materials cited in my previously submitted declaration (EX2001), 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);
- Pernot et al., *Colorectal Cancer and Immunity: What We Know and Perspectives*, 20(14) World J. Gastroenterology 3738 (April 2014) (EX1006);

- 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);
- 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);
- Salipante et al., *Microsatellite Instability Detection by Next Generation Sequencing*, 60(9) Clinical Chemistry 1192 (June 2014) (EX1010);
- 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 '393 Patent at the time of the earliest possible priority date of the '393 Patent. Counsel has informed me and I understand that the '393 Patent was filed on September 2, 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 ’393 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 ’393 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 further explains conclusions presented in my prior declaration submitted in this proceeding (EX2001) and supplements those conclusions with additional conclusions 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 ’393 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 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the ’393 Patent;
- The prior art relied on in Grounds 2-8 fails to show that claims 1-42 of the ’393 Patent are obvious; and
- The non-obviousness of claims 1-42 of the ’393 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 ’393 Patent would be “a medical doctor or a professional in a related field with at least five years of experience with treating cancer.” (Pet., 12.) 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. For reasons discussed in detail in my previously submitted declaration, I disagree with Merck’s proposed definition of a POSA and do not believe Merck’s expert, Dr. Neugut, qualifies as a POSA. (*See* EX2001, § VII.) Instead, I maintain my opinion that 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. 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 ’393 Patent and its revolutionary impact on cancer treatment, I previously provided some background about cancer, the immune system, and the state of cancer immunotherapy research at the time of the invention in my prior declaration. (*See* EX2001, § IV). For ease of reference, I once again include this information below.

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 '393 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 ’393 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 (IFN γ), tumor necrosis factor alpha (TNF α). (*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—contrary to what Merck’s expert seems to suggest (*see, e.g.*, EX1003, ¶¶ 105-108)—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.

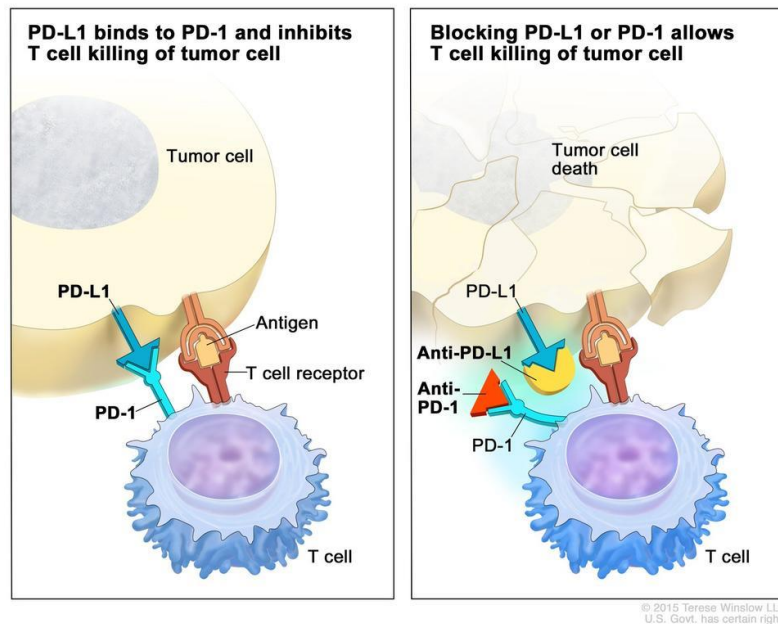
- A **seventh** strategy, known as immune checkpoint blockade therapy, is the class of immunotherapies that pembrolizumab (and the invention of the '393 Patent) falls within. Since the time of the invention of the '393 Patent, this has become the most successful class of cancer immunotherapies, with 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. At the time of invention of the '393 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 in particular, CRC patients seemed like an unlikely choice.

E. Microsatellite Instability / DNA Mismatch Repair

49. Separate from the field of immunotherapy, at the time of the invention of the '393 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. At the time of the invention of the '393 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 '393 Patent) led an international consortium that helped elucidate the clinical implications of MSI on colorectal cancer. (*Id.*, 2.) As such, at the time of the invention, 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.”)).

F. State of the Prior Art at the Time of the Invention of the '393 Patent

53. For the reasons described above, prior to the invention of the '393 Patent there was little reason to suspect 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.

54. Had someone hypothesized that MSI-H CRC patients might be especially responsive to PD-1 checkpoint blockade therapy (as the inventors of the '393 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.)

55. 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 at the time of the invention in 2015 was using human cancer patients in a clinical trial setting.

56. 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., 45; 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.)

57. Indeed, prior to the invention of the ’393 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 '393 PATENT

58. Based on limited initial data, the inventors of the '393 Patent revolutionized the field of cancer immunotherapy by (1) conceiving the groundbreaking hypothesis that MSI-H patients (and in particular, 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 '393 Patent describes this clinical trial, its profound results, and a novel method of treating CRC patients in response to determining their MSI status.

59. The '393 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.*, 8:29-36.) Patients in all three cohorts were treated with pembrolizumab, “administered at 10 mg/kg intravenously every 14 days” (*id.*, 9:52-53.), and the outcomes of these patients were assessed using various endpoints including response rates, progression-free survival rate, and other immune-related criteria. (*Id.*, 9:23-40.) 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.*, 3:15-17.)

60. The results of the trial were extraordinary. The ’393 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.*, 16:4-11.) 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.*)

61. 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 '393 Patent) presentation at the 51st annual meeting of the American Society of Clinical Oncology ("ASCO") in 2015 (EX2003).

62. The clinical trial results described in the '393 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 '393 Patent revolutionized cancer immunotherapy, spearheading the path to approval for an entirely new kind of cancer treatment indication.

63. Supported by the remarkable results of the inventors' clinical trial, the '393 Patent claims (1) a novel method of treating microsatellite instability high or

DNA mismatch repair deficient colorectal cancer in a human patient (EX1001, claim 1), and (2) a novel method of reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer (*id.*, claim 14). Independent claim 1 is representative:

1. A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising:
 - testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and
 - in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.

(*Id.*, claim 1.)

64. In short, independent claim 1 requires testing or having tested a sample from a CRC patient (e.g., a tumor sample) 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 CRC patient with a “therapeutically effective amount of pembrolizumab” in response to determining that the CRC is determined to be 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).

65. 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, as well as several other features recited in the dependent claims.

VI. OVERVIEW OF THE CITED REFERENCES

A. MSI-H Study Record

66. 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 '393 Patent was anticipated. I have also been informed by Counsel and understand that Merck relies on the MSI-H Study Record in Grounds 2-8 of the Petition to argue that the invention of the '393 Patent would have been obvious to a POSA.

67. 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 '393 Patent.

68. 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.

69. 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.)

70. 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, one thing the MSI-H Study Record does not disclose or require is determining the MSI status of potential subjects—especially CRC patients—before recruitment or enrollment in the study. Instead, the MSI-H Study Record allows for patients to be recruited and enrolled first and biopsied later, such that a CRC patient could be enrolled in the study and ***later*** classified into either the MSI-H CRC study arm or the MSI negative CRC study arm based on their biopsy results. (*See id.*) 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.*, 5-6.)

B. Pernot

71. I have been informed by Counsel and understand that Merck relies on Pernot (EX1006) in Grounds 2-8 of the Petition to argue that the invention of the '393 Patent would have been obvious to a POSA. Pernot is a journal article that provides an overview of the relationship between CRC and the immune system including a review of existing research on various immunotherapy approaches for

treating CRC. (EX1006, 2.) Significantly, Pernot does not disclose or suggest any relationship between MSI-H CRC patients and their likelihood of responding to PD-1 checkpoint blockade therapy. Pernot does disclose that “CRC associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy.” (*Id.*, 5.) However, when describing “Immunotherapy in CRC,” Pernot lists 27 different ongoing clinical trials of immunotherapy involving six different types of immunotherapy strategies—none of which included anti-PD-1 therapies. (*Id.*, 10 (Table 1, reproduced below).) And where Pernot **does** briefly mention anti-PD-1 therapies (*id.*, 6), it only does so in the context of melanoma—not MSI-H CRC or other MSI-H tumors. (*Id.*, 6 (“Recently some monoclonal antibodies targeting these molecules (PD1, CTLA-4) have shown more than promising efficacy results in solid neoplasia such as melanoma and others.”).) In my opinion, a POSA would not understand Pernot as disclosing or even suggesting that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy (or for pembrolizumab in particular).

Table 1 Ongoing clinical trials, according to National Cancer Institute registration, using immunotherapy, according to strategy

Principle	Phase	Specificity	Registration number
(A) Peptide vaccine	I	Targeted peptide(s): Ras mutated	NCT01322815
		MUC-1	NCT01556789
		HER2/neu	NCT01730118
	I / II	Survivin	NCT00108875
		Frame shift peptides (MSI)	NCT01461148
	II	Nor-MDP	NCT01376505
(B) Whole cell cancer vaccine	I / II	MUC-1	NCT01462513
		Characteristic of cancer cells:	
		Allogenic cancer cell	NCT00722228
(C) DC-based therapy	I / II		NCT00656123
		Characteristic of DCs:	
		Autologous DCs intratumoral injection	NCT01882946
		Loaded with Frame shift antigens (MSI)	NCT01885702
	II	CEA-pulsed DCs ⁺ IL-2	NCT00154713
(D) Inhibition of immunoregulation	I / II	Autologous DCs	NCT01348256
			NCT01413295
		Immunomodulation strategy:	
(E) Non specific immunostimulation	I / II	Treg depletion	NCT00986518
		Anti-CTLA4 + local radiation therapy	NCT01769222
		Immunostimulatory agent	
		Recombinant vaccinia virus	NCT01394939
	II	IFN, Celecoxib + combination of chemokines	NCT01545141
(F) Cell therapy	III	IL-7	NCT01339000
		Heat killed whole cell mycobacterium	NCT01539824
		PGG beta-glucan: binding to neutrophils	NCT01309126
	II	Characteristic of cells	
		Allogenic activated lymphocytes	NCT00149006
			NCT00855452
	N5	Autologous TILs + lymphocyte depletion	NCT01174121
		Engineered autologous anti-ESO-1 lymphocytes	NCT00670748
		Engineered autologous anti-CEA lymphocytes	NCT01723306
		Autologous natural killer T cells	NCT01801852

Several strategies are used in clinical trials of immunotherapy: (A) Vaccination with direct injection of one or more peptides; (B) Immunization using whole irradiated tumor cells; (C) Vaccination using autologous dendritic cells (DCs) and/or charged DCs with one or more antigens; (D) Inhibition of immunoregulatory mechanisms; (E) Nonspecific stimulation of the immune system; (F) Adoptive cell therapy using tumor infiltrating lymphocytes (TIL) or lymphocytes from peripheral blood, possibly reworked to target specific antigens. Source: <http://clinicaltrials.gov/>. IL: Interleukin; IFN: Interferon.

72. (EX1006, 10 (Table 1).)

73. Furthermore, having reviewed the file history of the '393 Patent, I note that the Examiner already considered other references such as Champiat (EX1032), which teaches the same things that Merck claims Pernot teaches. For example, Champiat discloses that “[o]ther tumors that present foci of localized hypermutations . . . could also be good candidates for immune checkpoint inhibitors, a possibility that should be evaluated in future clinical trials” (*id.*, 5) and “[w]e herein formulate

the hypothesis that high levels of mutational heterogeneity in the tumor could be the key for the success of immune checkpoint-targeting therapies” (*id.*, 1). It is my opinion that Champiat is arguably **more relevant** than Pernot because Champiat not only mentions immunotherapy generally, but specifically discloses 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 (MSI)+ colorectal carcinoma.” (EX1032, 5.) Nevertheless, Champiat still fails to disclose or render the claimed invention obvious because, as Dr. Pardoll explained in his February 4, 2020 declaration, (EX1002, 199-210), a POSA would not have reasonably expected improved outcomes from the claimed method of treatment due to (1) the limited data supporting Champiat’s speculative hypothesis, (2) the distinction between mutational heterogeneity and mismatch repair deficiency, and (3) the lack of any previous approval for treating patients with a biologic therapy based on a particular genetic biomarker. (*Id.*, 200-203.) I agree with Dr. Pardoll’s statements, and apparently so did the Examiner. Indeed, the Examiner considered these arguments and ultimately allowed the ’393 Patent over Champiat. (*Id.*, 543.) In my opinion, Pernot adds nothing new to Champiat that would affect the patentability of the ’393 Patent.

C. Chapelle

74. I have been informed by Counsel and understand that Merck relies on Chapelle (EX1007) in Ground 3 of the Petition to argue that the invention of the '393 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 is MSI-H” (Pet., 47), including by immunohistochemistry (*id.*, 39). However—like Pernot—Chapelle does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy.

75. Furthermore, at Counsel’s request, I have looked through the “References Cited” section of the '393 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 using immunohistochemistry to assess MMR proteins in colon tumor tissue (*id.*, 3). Therefore, Chapelle provides no new reason to alter the Examiner’s patentability analysis of the '393 Patent.

D. Steinert

76. I have been informed by Counsel and understand that Merck relies on Steinert (EX1008) in Grounds 4 and 8 of the Petition to argue that the invention of

the '393 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., 50.) 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.

77. Furthermore, at Counsel’s request, I have looked through the “References Cited” section of the '393 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 '393 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 '393 Patent.

E. Benson

78. I have been informed by Counsel and understand that Merck relies on Benson (EX1008) in Ground 5 of the Petition to argue that the invention of the '393 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, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies.” (Pet., 40; *see also id.* at 51, 53-54.) However—like the other cited prior art—Benson does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy.

79. Furthermore, at Counsel’s request, I have looked through the “References Cited” section of the ’393 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 ’393 Patent and discloses a clinical trial of an anti-PD-1 antibody that included patients with 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 ’393 Patent.

F. Salipante

80. I have been informed by Counsel and understand that Merck relies on Salipante (EX1010) in Ground 6 of the Petition to argue that the invention of the ’393 Patent would have been obvious to a POSA. Salipante is a journal article describing “an approach to detect the MSI phenotype using NGS [next generation DNA sequencing]” (EX1010, 4.) Merck primarily relies on Salipante for its

alleged disclosure of “two types of tests to determine whether tumors are MSI-H”—polymerase chain reaction (PCR) and next generation sequencing. (Pet., 41; *see also id.* at 58-60.) However—like the other cited prior art—Salipante does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy.

81. Furthermore, at Counsel’s request, I have looked through the “References Cited” section of the ’393 Patent (EX1001, 1-7) and, in my opinion, the teachings of Salipante that Merck relies upon add nothing new to the art already considered by the Examiner. For example, Bacher (EX2022) is listed on the ’393 Patent and discloses using PCR to assess MSI-H status. Moreover, The Cancer Genome Atlas Network (EX2025) is listed on the ’393 Patent and describes using next generation sequencing to assess MSI-H status in colon cancer. Therefore, in my opinion, Salipante provides no new reason to alter the Examiner’s patentability analysis of the ’393 Patent.

G. Hamid

82. I have been informed by Counsel and understand that Merck relies on Hamid (EX1011) in Grounds 7 and 8 of the Petition to argue that the invention of the ’393 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., 42; *see also id.* at 61-62.) However—like the other cited prior art—Hamid does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy. In fact, Hamid, which focuses on melanoma patients, does not mention CRC patients at all. Counsel has informed me and I understand that Hamid was considered by the Examiner during prosecution of the '393 Patent.

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

83. As explained above and in my previously submitted declaration, I maintain my opinion that 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; EX2001, § VII.) I also maintain my previously expressed opinions that (i) Merck’s expert, Dr. Neugut, does not qualify as a POSA under this definition and that (ii) Merck’s alternative definition of a POSA is incorrect. (*Id.*)

VIII. CLAIM CONSTRUCTION

84. Counsel has instructed me to opine on my understanding and interpretation of the term “in response to,” as used in the claims of the ’393 Patent. In my opinion, the plain and ordinary meaning of the term requires a causal relationship between (i) determining that a patient’s colorectal cancer 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.”

85. 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 CRC patients who are likely to respond to treatment with pembrolizumab and treat them and (2) identify CRC 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 ’393 Patent in both the present declaration and my previously submitted declaration (EX2001).

IX. CLAIMS 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, AND 27-42 OF THE '393 PATENT ARE PATENTABLE OVER GROUND 1

86. Turning to Merck's substantive arguments for invalidity of the '393 Patent, it is my opinion that Merck, in Ground 1 of the Petition, has not shown that the MSI-H Study Record anticipated or rendered obvious each and every limitation of the claims.

A. The MSI-H Study Record Does Not Disclose Treating a CRC Patient "In Response To" a Determination that the Patient is MSI-H, So It Does Not Anticipate the Challenged Claims

87. Independent claims 1 and 14 each recite treating a patient "in response to" determining that the colorectal cancer is MSI-H or DNA mismatch repair deficient. (EX1001, claims 1 and 14.) However, the MSI-H Study Record fails to say anything at all about testing patients to determine that their colorectal cancer is MSI-H or DNA mismatch repair deficient, and Merck provides no analysis to demonstrate how the MSI-H Study Record discloses the "in response to" limitation. Counsel has informed me and I understand that such a failure renders the Petition deficient.

88. Merck says little about the "in response to" limitation. In the entirety of the Petition, the "in response to" limitation is mentioned just twice—both in Ground 1. With reference to limitation [1.2], Merck says the following:

“The Arms and Interventions section of the MSI-H Study Record discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. (EX1005, 4 (Arms and Interventions); *see also id.*, 2 (Study Identification), 3 (Study Description), 4-5 (Outcome Measures), 5-6 (Eligibility); *supra*, §VI.B.2.a.) That disclosure reads on this limitation. (EX1003, ¶¶ 59-63.)” (Pet., 21.)

89. And with reference to claim limitation [14.2], Merck states:

“This limitation is identical to limitation 1.2, and is disclosed for the same reasons. (Supra, §VI.B.2.c; EX1003, ¶ 77.)” (Pet., 29.)

90. Beyond these statements, the Petition includes no analysis as to how the MSI-H Study Record discloses treating CRC patients “in response to” determining their MSI status. The Petition does not show, for example, that any CRC patient in a clinical trial conducted according to the protocol disclosed in the MSI-H Study Record is treated “in response to” determining their MSI status. On the contrary, it is my opinion that a POSA would have immediately understood that the MSI-H Study Record allows for a CRC patient to be enrolled in the trial **before** their MSI status is even known such that they would be treated regardless of whether they are assigned to the MSI-H CRC or MSI negative CRC study arm.

91. The Petition cites Dr. Neugut’s declaration for support, but his cited testimony is similarly deficient. It simply echoes the claim language by asserting

that “[t]he MSI-H Study Record discusses treating a patient with 10 mg/kg of pembrolizumab every 14 days in response to a patient meeting the eligibility criterion of having MSI-H colorectal cancer.” (EX1003, ¶59.) This statement is incorrect, for reasons described in greater detail below.

1. The MSI-H Study Record is Silent With Respect to Testing a Patient for MSI-H Before Administering Pembrolizumab

92. As an initial matter, the MSI-H Study Record says nothing at all about testing a patient for MSI-H before administering pembrolizumab. That is, the MSI-H Study Record leaves open the possibility that a colorectal cancer patient be tested for MSI-H *after* they are already treated. Under such circumstances, the patient’s treatment cannot be said to be “in response to” determining the patient’s colorectal cancer is MSI-H. Therefore, the MSI-H Study Record’s silence regarding the relative timing of MSI-H testing and treatment means that it cannot anticipate the claims of the ’393 Patent.

93. Since the MSI-H Study Record includes both MSI-H colorectal cancer patients and non-MSI-H colorectal cancer patients, there is no requirement that a colorectal cancer patient be tested for MSI-H to qualify for the study. The MSI-H Study Record simply requires that a patient agree to have a biopsy of their cancer (EX1005, 5). This requirement says nothing about whether the patient is tested for MSI-H before or after treatment with pembrolizumab. Therefore, the MSI-H Study

Record, on its face, allows for a patient to be treated ***before*** they are ever determined to be MSI-H. There is nothing in the MSI-H Study Record that discloses treatment occurring afterward or in reaction to determining that a patient's colorectal cancer is MSI-H.

2. The MSI-H Study Record Does Not Disclose a Casual Relationship Between Testing a Patient for MSI-H and Treating With Pembrolizumab

94. Even if the MSI-H Study Record did disclose testing a patient for MSI-H before treating them with pembrolizumab (which it does not), it still fails to disclose any causal relationship between the two. For a causal relationship to exist, the results of the testing must drive the treatment decision. But the MSI-H Study Record fails to disclose any causal relationship between MSI-H testing and treatment because it (i) does not disclose recruiting patients for the study based on a determination that they are MSI-H CRC patients, and (ii) does not disclose treating patients based on a determination that they are MSI-H CRC patients even after they are enrolled.

95. ***First***, the MSI-H Study Record does not disclose recruiting patients for the study based on a determination that they are MSI-H CRC patients. The MSI-H Study Record discloses recruiting subjects for three different patient populations (MSI-H CRC, MSI negative CRC and MSI-H non-CRC), and then treating the enrolled subjects with pembrolizumab. However, even for patients in the MSI-H

CRC study arm, the MSI-H Study Record does not disclose recruiting the study subjects into the trial based on a determination that they are MSI-H CRC patients. Instead, a POSA would have immediately understood that the MSI-H Study Record allows for an “all-comers” study design, for example, in which CRC patients are recruited without any prior knowledge of whether their cancer was MSI-H and are only biopsied later to determine the patient’s MSI status and to assign the patient to an appropriate arm of the study. This understanding is supported by the inclusion criteria, which requires patients to agree to have a biopsy of their cancer in order to be enrolled in the study. (See EX1005, 5 (“Inclusion Criteria: . . . Agree to have a biopsy of their cancer”).)

96. While the Board appears to criticize JHU’s (and my own) analysis for “focus[ing] on the design of the MSI-H study, rather than on what the MSI-H Study Record discloses about the treatment steps for colorectal cancer” (DI, 15), I believe that the study design is **critical** to understanding if the disclosed treatment steps are “in response to” determining that a patient’s colorectal cancer is MSI-H. Focusing solely on the treatment steps without considering the study design would ignore the **reasons** why the treatment steps were performed—and thus ignore the causal relationship of the “in response to” language of the independent claims.

97. In an “all-comers” study (or “biomarker-stratified design”)—a design strategy known to be appropriate for biomarker validation in Phase II oncology

trials—“all patients meeting the eligibility criteria (***regardless of a particular biomarker status***) are entered.” (EX2026, 1 (emphasis added); *see also* EX2027, 2 (“All patients are randomly assigned regardless of biomarker status . . .”); EX2028, 2 (“If one is less confident about the biomarker’s predictive ability, then a biomarker-stratified design (also known as an all-comers design) . . . can be used. With this design, the treatment effect can be assessed in both the biomarker-positive and biomarker-negative patient populations.”).) This is not to say, however, that the patients’ biomarker status (e.g., MSI status) is meaningless. On the contrary, the fact that “[t]he ability to provide adequate tissue may be an eligibility criterion for these [all-comers] designs” (EX2026, 3) allows for biomarker status to be determined after study recruitment. Indeed, this would explain why the MSI-H Study Record requires subjects to agree to have a biopsy of their cancer. (EX1005, 5.) Furthermore, “[i]n most instances . . . an all-comers design should clearly incorporate a prospectively specified subgroup analyses for retrospective assessment of the treatment effect within biomarker defined subgroups.” (EX2026, 3; EX2027, 2 (“[T]he analysis plan is centered on testing treatment effect dependence on biomarker status.”).) And this is exactly what the MSI-H Study Record achieves with its inclusion of both MSI-H CRC and MSI negative CRC experimental study arms. (EX1005, 5.)

98. Because a POSA would have immediately seen that the MSI-H Study Record allows for an “all-comers” study design, the MSI-H Study Record does not anticipate treating MSI-H CRC patients with pembrolizumab “in response to” a determination of their MSI status. Instead, the MSI-H Study Record allows for a CRC patient who meets all other eligibility criteria to be entered into the study for treatment without *any* knowledge of their MSI-H status. At this point, the subject’s treatment with pembrolizumab is already guaranteed, and the later determination of the subject’s MSI status serves only to assign the CRC patient into either the MSI-H CRC or the MSI negative CRC study arm for analytical purposes. In other words, the patient is not treated with pembrolizumab because of her MSI status, but rather by virtue of being enrolled in the study in the first place (independent of the patient’s MSI-H status). The determination of the CRC patient’s MSI status has no bearing on treatment, and therefore, the treatment is in no way “in response to” the determination of the patient’s MSI-H status.

99. **Second**, the MSI-H Study Record does not disclose treating patients based on a determination that they are MSI-H CRC patients even after they are enrolled. The Petition asserts that the MSI-H CRC arm of the MSI-H Study Record “discusses treating patients having MSI-H colorectal cancer with 10 mg/kg of pembrolizumab every 14 days.” (Pet., 21.) But there is no causal relationship between administration of the treatment and patients having MSI-H CRC. Instead,

the MSI-H Study Record includes three experimental study arms (MSI-H CRC, MSI negative CRC, and MSI-H non-CRC) in which patients in all three study arms of the trial would be **universally** treated with pembrolizumab. In other words, the patients are treated regardless of whether they are MSI-H CRC patients or not.

100. The Petition does not mention that in one of the three experimental arms described in the MSI-H Study Record, MSI negative patients were treated in the same manner as MSI-H CRC and MSI-H non-CRC patients. This second MSI negative arm was more than just a control group; it was an “experimental” study arm, and the MSI-H Study Record explains that “[t]his study will be looking at whether MK-3475 (an antibody that blocks signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations,” including “patients with MSI negative colon cancer.” (EX1005 at 3.) Thus, a POSA would understand that according to the MSI-H Study Record, CRC patients whose cancer is determined to be MSI-H or MSI negative, or patients whose MSI status is undetermined, may **all** be deemed eligible for participation in the study if they meet other inclusion criteria, and might eventually be enrolled in the study to receive treatment with pembrolizumab. As such, the CRC patients’ treatment with pembrolizumab was not dependent upon their MSI status.

101. In my opinion, the treatment described by the MSI-H Study Record might be considered given in response to a study subject’s **enrollment** in the clinical

trial. But this is clearly not the same as treating a patient with pembrolizumab in response to a determination that the patient's colorectal cancer is microsatellite instability high or DNA mismatch repair deficient—especially when the enrollment is also not dependent on determining the patient's MSI status.

B. The MSI-H Study Record Does Not Disclose The Dependent Claims

1. Claims 7, 20, 32, 34, 36, 38, 40, 42: The MSI-H Study Record Does Not Disclose “Received a [Different/Prior] Cancer Therapy” or “Progressed [Following/After] ... [Different/Prior] Cancer Therapy”

102. The MSI-H Study Record also fails to disclose that the patient had “received a [different/prior] cancer therapy” or that the patient's cancer had “progressed [following/after] . . . the [different/prior] cancer therapy”—features included in claims 7, 20, 32, 34, 36, 38, 40, and 42 of the '393 Patent. The MSI-H Study Record says **nothing** about 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.) Indeed, 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.) Thus, Dr. Neugut's interpretation of the MSI-H Study Record's use of “measurable disease” as meaning that “patients would have received prior drug therapies and had their cancer progress after those

therapies” (EX1003, ¶68) is incorrect. If this were true, it would have been superfluous to amend the ClinicalTrials.gov record to add a requirement that was allegedly already disclosed in the MSI-H Study Record. In my opinion, the concept of measurable cancer 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.

2. Claims 29, 30: The MSI-H Study Record Does Not Disclose Treating “Metastatic Colorectal Cancer”

103. The MSI-H Study Record further fails to disclose treating “metastatic colorectal cancer”—a feature included in claims 29 and 30 of the ’393 Patent. 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 “[p]atients with ‘measurable’ disease in the context of the MSI-H Study Record referred to patients having metastatic and advanced cancer and not include patients whose cancer was resectable for the purposes of a cure.” (EX1003, ¶69). 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.

104. 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, ¶69). 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.

105. (EX1048, 3.)

106. 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 drug therapies and had their cancers progress after those therapies” (EX1003, ¶68), and that “[p]atients with ‘measurable’ disease in the context of the MSI-H Study Record referred to patients having metastatic . . . cancer” (EX1003, ¶69).

107. For these reasons, the MSI-H Study Record does not disclose treating “metastatic” colorectal cancer simply because it mentions “measurable” disease.

3. Claims 4, 17, 31, 33, 35, 37, 39, and 41: The MSI-H Study Record Does Not Disclose the Claimed Results

108. In addition to the deficiencies already addressed above, Merck has further failed to show that at least two groups of claims are anticipated by the MSI-H Study Record:

- Claims 4 and 17, which require that a patient “is treated with an amount of pembrolizumab ***shown in a clinical trial*** to” either be “effective in promoting progression-free survival” or “reduce the risk that [MSI-H or MMR-deficient] colon cancer will progress.”

- Claims 31, 33, 35, 37, 39, and 41 require that the method “**results in**” either an objective response rate of 40% or higher (cls. 31, 37), a probability of progression-free survival at 20 weeks of at least 78% (cls. 33, 39), or a probability of progression-free survival at 9 months of at least 60% (cls. 35, 41).

109. Each of these claims requires **actually obtaining the results** of the study disclosed in the MSI-H Study Record. But since the MSI-H Study Record is simply the initial announcement of the study, the MSI-H Study Record pre-dates the actual performance of the study and thus does not include any of the study’s results.

110. With respect to claims 4 and 17, the amount of pembrolizumab used for the claimed treatment method specifically requires being “shown in a clinical trial” to achieve particular results. And with respect to claims 31, 33, 35, 37, 39, and 41, the results recited in the claims correspond directly with the outcome measures obtained by the trial described in the MSI-H Study Record.

111. It would not have been possible to disclose either (i) the effective treatment amount or (ii) the outcomes from such treatment without actually conducting the study announced in the MSI-H Study Record. Thus, the MSI-H Study Record on its own cannot possibly have anticipated claims directed to such narrow and specific features when it pre-dates the production of the very results that support the claims.

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

112. 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.

113. 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, (*see, 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.

114. In addition, at the time of the invention, there was little reason to suspect MSI-H CRC patients would be particularly good candidates for PD-1

checkpoint blockade therapy, (*see, e.g., supra* § IV.E). At the time of the invention of the '393 Patent, there were many factors that taught away from MSI-H CRC patients being good candidates for immunotherapy and especially for checkpoint blockade therapy. 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). 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.”)).

115. Furthermore, the available options for testing the hypothesis that led to the '393 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.)

116. 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 at the time of the invention in 2015 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.

117. Put simply, the inventors of the '393 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.

118. 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 '393 Patent to experimentally determine if their hypothesis was correct. For all of these reasons, the publication MSI-H Study Record was clearly experimental by its very nature.

X. CLAIMS 1-42 ARE PATENTABLE OVER GROUNDS 2-8

119. All of Grounds 2-8 of the Petition are similarly deficient to Ground 1 since Merck never addressed the “in response to” limitations of independent claims 1 and 14. With respect to Ground 2, Merck includes no additional arguments to address the already-mentioned shortcomings of the MSI-H Study Record with respect to the “in response to” limitation. In fact, Merck does not even mention the fact that independent claims 1 and 14 require treating patients “in response to” determining their MSI status. (See Pet., 42-46.) Seeing no further arguments to rebut my positions, Ground 2 of the Petition is deficient for substantially the same reasons as Ground 1. Moreover, with respect to Grounds 3-8, Merck does not rely on any of the additional prior art references cited in Grounds 3-8 to address the already-mentioned shortcomings of the MSI-H Study Record with respect to the “in response to” limitation. Therefore, Grounds 3-8 of the Petition share the same deficiencies as Grounds 1 and 2.

120. I further believe that the prior art in Grounds 2-8 do not render the claims of the '393 Patent obvious for at least the following additional reasons.

A. There Was No Reasonable Expectation of Success For the Treatment Method Claimed in the '393 Patent

121. As of July 10, 2015 (the Critical Date of the '393 Patent), a POSA would have had no reasonable expectation that JHU's proposed use of MSI-H as a biomarker for treating CRC 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 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 '393 Patent.

122. 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., 45) is both different and nonsensical.

123. 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.

124. 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.

125. 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 '393 Patent in my analysis below.

1. Cancer Immunotherapy is Complex and Unpredictable

126. 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 CRC Patients Would Not be Good Candidates for Anti-PD-1 Therapies

127. There would also have been no reasonable expectation of success for the treatment method claimed in the '393 Patent because there was substantial evidence that taught away from treating MSI-H CRC patients with anti-PD-1 therapies such as pembrolizumab. Merck conveniently ignores this evidence and instead focuses on a single responsive MSI-H CRC patient (out of thirty-three total CRC patients) and 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 CRC patients with immunotherapies. (Pet., 1-2, 44). However, even if this hypothesis was floating around at the time of the Critical Date of the

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

128. There were many factors that taught away from MSI-H CRC patients being good candidates for immunotherapy and especially for checkpoint blockade therapy. 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).

129. 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 invention, 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

130. 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.)

131. 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).

132. In other words, nearly a ***decade after*** the Critical Date of the '393 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 CRC 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 MSI 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 '393 Patent

133. 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 '393 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.)

134. The gaps in scientific knowledge around the Critical Date of the '393 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.)

135. It wasn't until after the Critical Date of the '393 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)).

136. Therefore, Merck’s argument that the prior art taught that “PD-1 inhibitors naturally had more efficacy when treating tumors that . . . have many mutations” (Pet. 1-2) is heavily tainted by hindsight bias and misrepresents the true limitations of scientific knowledge at the time of JHU’s invention.

B. None of Merck’s References Provide a Reasonable Expectation of Success

1. The MSI-H Study Record

137. 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”).)

138. 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. Pernot

139. As I stated previously, Pernot has a host of deficiencies with respect to key features of the '393 Patent claims, (*see supra* § VI.B). Given these deficiencies, I do not believe Pernot would provide a POSA with a reasonable expectation of success for the method of treatment claimed in the '393 Patent.

140. First, Pernot does not disclose or suggest any relationship between MSI-H CRC patients and their likelihood of responding to PD-1 checkpoint blockade therapy. Nor does Pernot mention pembrolizumab whatsoever. While anti-PD-1 therapies are briefly mentioned, they are only referenced in the context of melanoma—not MSI-H CRC or other MSI-H tumors. (EX1006, 6) (“Recently some monoclonal antibodies targeting these molecules (PD1, CTLA-4) have shown more than promising efficacy results in solid neoplasia such as melanoma and others.”). A POSA would not have found a reasonable expectation of success for treating MSI-H CRC patients with pembrolizumab based on this singular statement.

141. Furthermore, while Pernot states that “CRC associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy,” (*id.*, 5), Pernot then goes on to list 27 different ongoing clinical trials of immunotherapy involving six

different types of immunotherapy strategies—none of which included anti-PD-1 therapies. (*Id.*, 10 (Table 1, reproduced below).) Once again, a POSA would not have found a reasonable expectation of success for the '393 Patent claims based on this limited disclosure.

Table 1 Ongoing clinical trials, according to National Cancer Institute registration, using immunotherapy, according to strategy			
Principle	Phase	Specificity	Registration number
(A) Peptide vaccine	I	Targeted peptide(s): Ras mutated	NCT01322815
		MUC-1	NCT01556789
		HER2/neu	NCT01730118
	I / II	Survivin	NCT00108875
		Frame shift peptides (MSI)	NCT01461148
	II	Nor-MDP	NCT01376505
(B) Whole cell cancer vaccine	I / II	MUC-1	NCT01462513
		Characteristic of cancer cells:	
		Allogenic cancer cell	NCT00722228
(C) DC-based therapy	I / II		NCT00656123
		Characteristic of DCs:	
		Autologous DCs intratumoral injection	NCT01882946
	II	Loaded with Frame shift antigens (MSI)	NCT01885702
		CEA-pulsed DCs + IL-2	NCT00154713
		Autologous DCs	NCT01348256
(D) Inhibition of immunoregulation	I / II		NCT01413295
		Immunomodulation strategy:	
		Treg depletion	NCT00986518
(E) Non specific immunostimulation	I / II	Anti-CTLA4 + local radiation therapy	NCT01769222
		Immunostimulatory agent	
		Recombinant vaccinia virus	NCT01394939
	II	IFN, Celecoxib + combination of chemokines	NCT01545141
		IL-7	NCT01339000
	III	Heat killed whole cell mycobacterium	NCT01539824
(F) Cell therapy	II	PGG beta-glucan: binding to neutrophils	NCT01309126
		Characteristic of cells	
		Allogenic activated lymphocytes	NCT00149006
	NS		NCT00855452
		Autologous TILs + lymphocyte depletion	NCT01174121
		Engineered autologous anti-ESO-1 lymphocytes	NCT00670748
		Engineered autologous anti-CEA lymphocytes	NCT01723306
		Autologous natural killer T cells	NCT01801852

Several strategies are used in clinical trials of immunotherapy: (A) Vaccination with direct injection of one or more peptides; (B) Immunization using whole irradiated tumor cells; (C) Vaccination using autologous dendritic cells (DCs) and/or charged DCs with one or more antigens; (D) Inhibition of immunoregulatory mechanisms; (E) Nonspecific stimulation of the immune system; (F) Adoptive cell therapy using tumor infiltrating lymphocytes (TIL) or lymphocytes from peripheral blood, possibly reworked to target specific antigens. Source: <http://clinicaltrials.gov/>. IL: Interleukin; IFN: Interferon.

3. Merck's Tertiary References

142. Merck and its expert further rely on fourteen tertiary references in Ground 2 of the Petition to demonstrate what was known in the art at the time of

invention. But these too fail to provide a POSA with a reasonable expectation of success for the methods of treatment claimed in the '393 Patent.

143. First, 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 (primarily from 2014-2015) 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); EX1038, 9 (disclosing 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” (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).

144. Furthermore, in many cases, the teachings of Merck’s references were much broader than the method claimed by the ’393 Patent and thus do not render it obvious. For example, EX1033 suggests the potential benefit of *targeted immunotherapy* in *aggressive* subtypes of colon cancer rather than using checkpoint blockade or anti-PD-1 therapies to treat MSI-H colon cancer. (EX1033, 2969). EX1040 is silent with respect to colorectal cancer, while other references, such as 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.

145. None of the tertiary references Merck string-cites in Ground 2 would have led a POSA to have a reasonable expectation that the claimed method of the ’393 Patent would be successful. Below, I address each of Merck’s numerous tertiary references in turn.

146. **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, ¶110) and further taught 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” (Pet., 44). 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 colorectal cancer such as 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.

147. **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, ¶110) and further taught that

MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors (Pet., 44). 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.*, 2968-2969.) However, these observations would not have provided a POSA with a reasonable expectation of success of the specific claimed invention of the ’393 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 at the time of the invention was not sufficient to provide a POSA a reasonable expectation of success in treating MSI-H CRC patients.

148. **EX1034**: Merck and its expert also state that EX1034 taught that “PD-1 inhibitors inherently had more efficacy when treating tumors that are (1) comprised of cancer cells that are easy for immune cells to recognize . . . and (2) already infiltrated by many immune cells.” (Pet., 44; EX1003, ¶110) and further taught that MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors (Pet., 44; *see also* EX1003, ¶¶43-44, 111). EX1034 is a journal article describing a tumor genome meta-analysis in which the authors state 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.) EX1034 further discloses 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, EX1034 would not have provided a reasonable expectation of success for the method of treatment of the ’393 Patent since, at the time of the invention, there were also many factors of MSI-H tumors that taught away from MSI-H CRC patients being good candidates for immunotherapy and especially for checkpoint blockade therapy (*See supra* § IV.E).

149. 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).

150. 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, EX1034 would not have provide a reasonable expectation of success given the complex and controversial state of the prior art regarding microsatellite instability and its implications for cancer immunotherapy.

151. **EX1035:** Merck and its expert also state that EX1035 taught that MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors. (Pet., 44; *see also* EX1003, ¶45). 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).)

152. **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, ¶110) and further taught that

MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors (Pet., 44; *see also* EX1003, ¶45). EX1036 describes certain features of colorectal cancers with microsatellite instability (*see, e.g.*, EX1036, 1168, 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 CRC patients with PD-1 checkpoint blockade therapy or pembrolizumab.

153. **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, ¶110) and further taught that MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors (Pet., 44; *see also* EX1003, ¶45). 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 CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy. In fact, EX2037 does not mention

checkpoint blockade therapies (including anti-PD-1 therapies and pembrolizumab) whatsoever.

154. **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, ¶110) and further taught 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” (Pet., 44; *see also* EX1003, ¶45). 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 CRC. 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 at the time of the invention and is what was ultimately supplied by the inventors of the ’393 Patent.

155. **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, ¶110) and further taught that MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors (Pet., 44; *see also* EX1003, ¶45). 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” (EX1003, ¶110 (citing EX1039, 243s)) and concluding that “[a] strong IFN γ -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.” (*Id.*) 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.

156. **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 are easy for immune cells to recognize.” (Pet., 44; *see also* EX1003, ¶45.) 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, ¶45 (citing EX1040, 2).) However, EX1040 is silent with respect to colorectal cancer and certainly does not disclose using MSI status as a biomarker for treating CRC 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 ’393 Patent.

157. **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 are easy for immune cells to recognize” (Pet., 44; *see also* EX1003, ¶45), and that “MSI-H tumors naturally displayed those characteristics” (Pet., 44). In particular, Dr. Neugut cites EX1041’s disclosure that “increased counts of CD8+ T-cells were observed in colorectal cancer tumors with high mutational loads and microsatellite instability.” (EX1003, ¶45 (citing EX1041, 9208).)

However, Dr. Neugut conveniently leaves out that the very next sentence of EX1041 states that “[d]ata on the use of immune checkpoint target drugs in colorectal cancer are still limited.” (EX1041, 9208.) Moreover, there is no disclosure or suggestion in EX1041 of using MSI status as a biomarker for treating CRC patients with checkpoint blockade therapy—much less with anti-PD-1 therapies such as pembrolizumab.

158. **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 are easy for immune cells to recognize.” (Pet., 44; *see also* EX1003, ¶45.) 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, ¶45 (citing EX1042, 732).) However, yet again, EX1042 does not disclose or suggest using MSI status as a biomarker for treating CRC (or 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 ’393 Patent.

159. **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, ¶110). 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 CRC patients with anti-PD-1 therapies or pembrolizumab in 2015 (i.e., the Critical Date of the ’393 Patent) is simply incorrect.

160. **EX1058:** Merck and its expert also state that EX1058 taught that MSI-H tumors naturally displayed characteristics that would have inherently made PD-1 inhibitors more effective for treating tumors. (Pet., 44; *see also* EX1003, ¶45). In particular, Dr. Neugut cites EX1058’s disclosure 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)” (EX1003, ¶45 (citing EX1058, 231)) and that “MSI-H tumors have antigenic frameshift peptides” (*id.* (citing EX1058, 236-37)). However, EX1058 is

silent with respect to treating MSI-H CRC 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 '393 Patent.

161. **EX1084:** Merck and its expert also state that EX1084 “urged the POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, like pembrolizumab” (Pet., 44; EX1003, ¶110). In particular, Dr. Neugut cites EX1084’s disclosure that “Dr. Gatalica noted that his findings are similar to those from a Phase 2 study of PD-1 antibody in patients with MSI tumors, conducted at Johns Hopkins University School of Medicine, and that more than five PD-1/PD-L1 trials are ongoing . . .” (EX1003, ¶110 n.8 (citing EX1084, 1).) However, Dr. Neugut conveniently leaves out the fact that the **very same sentence** concludes “. . . the data thus far are **exploratory** and **early**.” (EX1084, 1 (emphases added).) Moreover, as I stated above, we now know in retrospect that multiple PD-1/PD-L1 trials ultimately failed. (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.”). Thus, Merck and Dr. Neugut’s characterization of EX1084’s

reference to “exploratory” and “early” data as “urging” a POSA to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy with a reasonable expectation of success is both misleading and wrong.

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

162. 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.

163. First, Merck argues that “[p]hysicians were treating patients with cancers that were known to have MSI-H subpopulations in the prior art, including colorectal cancer, with PD-1 inhibitors.” (Pet., 43-44.) To support this statement, Merck cites the MSI-H Study Record itself (addressed above), a 2017 copy of the Keytruda® label that is not prior art, and two additional study records for trials involving pembrolizumab. (EX1016, EX1017.)

164. 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 patients with pembrolizumab “in response to” determining their cancer is MSI-H.

165. 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 treating patients based on a determination that their cancer is MSI-H. 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 ’393 Patent.

166. Next, Merck mentions that “[t]he prior art also successfully reported treatment of a colorectal cancer patient having an MSI-H tumor with a PD-1 inhibitor.” (Pet., 44.) But this is a reference to a study in which 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.) Merck’s 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 '393 Patent is clearly not credible.

167. Finally, Merck argues that “because the POSA would have known that pembrolizumab was already approved for another oncology indication in November 2014, the POSA would have had a higher expectation of success” for the MSI-H CRC 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.” (Pet. 45 (citing EX1055, 1-2 and EX1063, 334-335).) The first glaring issue with this analysis though is that it **completely ignores** that the '393 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.

168. 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.

169. 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.

D. Merck Has Not Shown the Dependent Claims Would Have Been Obvious Over the Prior Art in Ground 2

170. In addition to the deficiencies already addressed above, Merck has further failed to show the obviousness of at least two groups of claims in Ground 2:

- Claims 4 and 17, which require that a patient “is treated with an amount of pembrolizumab ***shown in a clinical trial*** to” either be “effective in promoting progression-free survival” or “reduce the risk that [MSI-H or MMR-deficient] colon cancer will progress.”
- Claims 31, 33, 35, 37, 39, and 41 require that the method “results in” either an objective response rate of 40% or higher (cls. 31, 37), a probability of progression-free survival at 20 weeks of at least 78% (cls. 33, 39), or a probability of progression-free survival at 9 months of at least 60% (cls. 35, 41).

171. None of these claims could have been taught by the prior art or made obvious by the prior art without ***actually obtaining the results*** of the trial described in the MSI-H Study Record. With respect to claims 4 and 17, the amount of pembrolizumab used for the claimed treatment method specifically requires being “shown in a clinical trial” to achieve particular results. And with respect to claims 31, 33, 35, 37, 39, and 41, the results recited in the claims correspond directly with the outcome measures obtained by the trial described in the MSI-H Study Record.

172. It would not have been possible to predict or make obvious either (i) the effective treatment amount or (ii) the outcomes from such treatment without actually conducting the study announced in the MSI-H Study Record. Thus, references like Pernot (relied on by Merck in Ground 2) cannot possibly have rendered obvious claims directed to such narrow and specific features when those references pre-date the production of the very results that support the claims.

E. Merck Has Not Shown the Dependent Claims Would Have Been Obvious Over the Prior Art in Grounds 3-8

173. With respect to Grounds 3-8, Merck relies on Chapelle, Steinert, Benson, Salipante, and Hamid for various discrete claim limitations. However, none of these references make obvious the claims of the '393 Patent.

174. In Ground 3, Merck primarily relies on Chapelle for its alleged disclosure of “standard methods of testing whether a tumor is MSI-H” (Pet., 47), including by immunohistochemistry (*id.*, 39). However, Chapelle does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy. (*See supra* § VI.C.) Rather, Chapelle broadly recommends that “all patients with newly diagnosed CRC should be screened for MSI” because of “the implications of MSI for the prognosis, treatment, and diagnosis of Lynch syndrome.” (EX1006, 6.) Nowhere does Chapelle suggest that MSI screening be used in any way to inform whether or not patients should be treated

using pembrolizumab or PD-1 inhibitors. Therefore, Chapelle provides no support for either reasonable expectation of success or the “in response to” claim limitation.

175. In Ground 4, Merck primarily relies on Steinert for its alleged disclosure of “methods of testing whether a tumor was MSI-H using body fluid.” (Pet., 50.) 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.) However, there is no discussion or suggestion in Steinert that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy or pembrolizumab. (*See supra* § VI.D.) Thus, Steinert provides no support for either reasonable expectation of success or the “in response to” claim limitation..

176. In Ground 5, Merck primarily relies on Benson for its alleged disclosure that “under the standard of care, clinical studies would include patients having metastatic cancer whose cancers had progressed after prior drug therapies.” (Pet., 40; *see also id.* at 51, 53-54.) Benson is a journal article from July 2014 describing clinical practice guidelines for colon cancer (EX1009, 1), and it indeed discloses that CRC patients meeting certain criteria should be screened for MSI-H tumors (*id.*, 6). However, this recommendation is made solely in the context of testing patients to identify if they have Lynch syndrome. Nowhere does Benson disclose or suggest

that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy or pembrolizumab. (*See supra* § VI.E.) Nor does Benson disclose or suggest the very specific response and progression-free survival rates recited in claims 37, 39, and 41. Thus, Benson provides no support for either reasonable expectation of success or the “in response to” claim limitation.

177. Notably, Merck provides no support whatsoever in Benson for claims 37, 39, and 41, which claim either a specific objective response rate or progression-free survival rates. (*See Pet.*, 56-57.) Merck points back to claim 29, from which these three claims depend, but claim 29 requires only that the CRC be metastatic; nothing in the identified support for claim 29 discloses or renders obvious the specific response and progression-free survival rates in claims 37, 39, and 41.

178. In Ground 6, Merck primarily relies on Salipante for its alleged disclosure of “two types of tests to determine whether tumors are MSI-H”—polymerase chain reaction (PCR) and next generation sequencing. (*Pet.*, 41; *see also id.* at 58-60.) Specifically, Merck alleges that “Salipante teaches standard methods of testing whether a tumor was MSI-H using a PCR test on the sample” and “teaches methods of testing whether a tumor was MSI-H using next generation sequencing on the sample.” (*Pet.*, 58, 60.) Salipante is a journal article describing “an approach to detect the MSI phenotype using NGS [next generation DNA sequencing]” (EX1010, 4.) Salipante is directed to validating “an approach for determination of

MSI by [next generation sequencing] (mSIGNS) based on microsatellite markers which are incidentally included in targeted gene capture sequencing data.” (EX1010, 5.) However, Salipante does not disclose or suggest that MSI-H CRC patients would be particularly promising candidates for PD-1 checkpoint blockade therapy or pembrolizumab. (*See supra* § VI.F.) Thus, Salipante provides no support for either reasonable expectation of success or the “in response to” claim limitation..

179. In Ground 7, Merck relies on Hamid for the dependent claim limitations requiring that pembrolizumab is administered to the patient intravenously. (Pet., 61-62.) Specifically, Merck alleges that “Hamid provides for intravenous administration of pembrolizumab.” (Pet., 61.) Hamid is a journal article reporting on the first clinical trial of pembrolizumab, in melanoma. Hamid is notably silent as to both CRC and MSI testing. Thus, Hamid also provides no support for the “in response to” claim limitation.

180. Finally, in Ground 8, Merck relies on Steinert and Hamid to teach the combination of administering pembrolizumab intravenously (claims 13 and 26) when the biological sample tested is a body fluid from the patient, as required by claim 3 from which both claims depend. (Pet., 63.) However, disclosure of these limitations necessarily fails to satisfy Merck’s burden to show the “in response to” limitation would have been obvious over the prior art, or to show that there a POSA would have reasonably expected to achieve success in the claimed treatment.

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

181. 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 '393 Patent. My opinion, with my analysis provided in detail below, is that all of these sources of evidence support the non-obviousness of the '393 Patent claims.

A. Industry Praise

182. The abundant praise received for the '393 Patent's invention by patients, doctors, researchers, and Merck itself supports the non-obviousness of the '393 Patent claims. From the moment of their release, the results of the treatment method described and claimed in the '393 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.)

183. 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 ’393 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.

184. 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 ’393 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).

185. All of the above examples of praise are directly related to the specific method of treating MSI-H CRC patients with pembrolizumab that is claimed in the '393 Patent. Therefore, I believe they strongly support the non-obviousness of the '393 Patent claims.

B. Skepticism

186. 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 '393 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 '393 Patent, about the merits of JHU's proposed study. At the time, I acknowledged that the trial would

be very risky, but 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 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 '393 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 colorectal cancer was MSI-H.

C. Unexpected Results

187. The non-obviousness of the '393 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.A-X.C.)

188. Cancer immunotherapy is complex and unpredictable (*supra* § X.A.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 at the time of the invention, (*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 CRC patients would **not** be good candidates for anti-PD-1 therapies (*supra* § X.A.2), the failure of other contemporary trials of anti-PD-1 therapies (*supra* § X.A.3), and the significant gaps and controversies about response to checkpoint blockade therapy that were clarified only after the Critical Date of the '393 Patent (*supra* § X.A.4), and there was simply no way a POSA would have reasonably expected the claimed treatment method of the '393 Patent to succeed.

189. 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 MSI-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 '393 Patent) to be as extraordinary as they were.

D. Nexus

190. 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 '393 Patent. It is my opinion that all of the objective evidence I analyzed satisfies this requirement. For example, in forming this opinion, I met with Dr. Richard Goldberg and reviewed his declaration. I agree with Dr. Goldberg's assessment that the two MSI-H indications listed on the Keytruda label after the FDA's respective approvals in May 2017 and June 2020 both correspond directly to the claims of the '393 Patent. (EX2090, ¶¶66-77.) I also agree with Dr. Goldberg's conclusion that "an oncologist prescribing Keytruda to a CRC patient under the CRC-related indications described above would necessarily practice the method of treatment claimed in at least Claim 1 of the '393 Patent." (*Id.*, ¶77.) Therefore, there is necessarily a nexus between the claims of the '393 Patent and any evidence relating to the administration of Keytruda (pembrolizumab) to MSI-H CRC patients in accordance with the Keytruda label.

XII. CONCLUSION

191. 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.

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

APPENDIX A

Biographical Sketch

Dr. Lonberg is currently an Executive in Residence at Canaan Partners. Prior to Canaan, he was Senior Vice President, Oncology Discovery Biology, at Bristol-Myers Squibb, where he led drug discovery efforts for both targeted and immuno-oncology agents. Dr. Lonberg began his 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, and then by Bristol-Myers Squibb in 2009. In 1998, Dr. Lonberg's drug discovery group at Medarex 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). 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. Dr. Lonberg received his PhD in Biochemistry and Molecular Biology from Harvard University (Cambridge, MA) in 1985, where he studied under Dr. Walter Gilbert. He was a postdoctoral fellow at Memorial Sloan Kettering Cancer Center (New York, NY) and was elected to the National Academy of Engineering in 2015.

Curriculum Vitae

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Education:

<i>Undergraduate:</i>	1974-1977	Reed College
	1977-1978	University of Oregon
	1978-1979	Reed College (no degree)
<i>Graduate:</i>	1979-1985	Harvard University, Ph.D., March 1985
<i>Postdoctoral:</i>	1985-1989	Sloan-Kettering Institute for Cancer Research

Employment:	1990-1994	Senior Scientist GenPharm International, Mountain View, CA
	1994-1997	Director, Molecular Biology GenPharm International, Palo Alto, CA
	1998-2000	Vice President, Scientific Director GenPharm International, San Jose, CA
	2000-2009	Senior Vice President, Scientific Director Medarex, Milpitas, CA
	2009-2019	Senior Vice President, Oncology Discovery Biology Bristol-Myers Squibb, Redwood City, CA
		& Interim Head Oncology Exploratory Clinical Development March, 2012-January, 2013
	2019-present	Executive in Residence, Canaan Partners Menlo Park, CA

Boards:

2019-present	Synthekine, Inc., Board of Directors & Scientific Advisory Board
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2019-present	Bicara Therapeutics, Chairman, Board of Directors
2020-2023	Evolveimmune Therapeutics, Inc., Scientific Advisory Board
2020-present	Bolt Biotherapeutics, Inc., Scientific Advisory Board
2020-present	Biograph55, Board of Directors
2020-present	Compugen, Ltd., Scientific Advisory Board
2021-present	ThirtyFiveBio, Board of Directors
2022-present	Normunity, Scientific Advisory Board

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Awards, Grants, & Memberships:

National Science Foundation Predoctoral Fellowship,	1979-1982
American Cancer Society Postdoctoral Fellowship,	1985-1988
National Institutes of Health Postdoctoral Fellowship,	1988-1989
National Institutes of Health SBIR Grant (phases I & II),	1991-1994
Member, National Academy of Engineering	2015-present

Issued Patents (*USPTO only*):

1. **H.Meade and N. LONBERG** (1989) Isolation of exogenous recombinant proteins from the milk of transgenic mammals. *U.S. Patent #4,873,316*.
2. **N. LONBERG and R. Kay** (1996) Transgenic non-human animals capable of producing heterologous antibodies. *U.S. Patent #5,545,806*.
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18. **J. Buechler, G. Valkirs, J. Gray, and N. LONBERG** (2004) Human antibodies. *U.S. Patent #6,794,132*. **A. Korman, E. Halk, N. LONBERG, Y. Deo, and T. Keler** (2006) Human CTLA-4 antibodies. *U.S. Patent #6,984,720*.
19. **K. Tomizuka, I. Ishida, N. LONBERG, E. Halk** (2006) Transgenic transchromosomal rodents for making human antibodies. *U.S. Patent #7,041,870*.
20. **N. LONBERG and R. Kay** (2006) Transgenic non-human animals capable of producing heterologous antibodies. *U.S. Patent #7,041,871*.
21. **N. LONBERG, R. Kay, and D. Fishwild** (2006) High affinity human antibodies and human antibodies against human antigens. *U.S. Patent #7,084,260*.
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52. **A. Norman, W. Ball, N. LONBERG, and D. Williams** (2019) Compositions and methods for treating cocaine-related disorders. *U.S. Patent* #10,501,556.
53. **N. LONBERG, A. Korman, M. Selby, B. Barnhart, A. Yamniuk, M. Srinivasan, K. Henning, M. Han, M. Lei, L. Schweitzer, S. Hatcher, A. Rajpal** (2020) Antibodies comprising modified heavy constant regions. *U.S. Patent* #10,653,791.
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63. **X. Schebye, D. Chen, A. Rankin, X. Deng, J. Toth, L. Liang, M. HAN, C. Bee, H-A. Truong, Mark J. Selby, N. LONBERG, G. Chen, Richard Y. Huange, K. Deyanova, A. Korman** (2022) Antibodies binding to ILT4. *U.S. Patent* # 11,401,328.

64. **X-T Wang, O. Adedokun, A. Lewin, A. Korman, M. Selby, C. Wang, H. Huang, K. Henning, N. LONBERG, M. Srinivasan, M. Han, G. Chen, R. Huang, I. Chakraborty, S. Wong, H. Li** (2022) Anti-GITR antibodies for cancer diagnostics. *U.S. Patent # 11,408,889*.