

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AMGEN INC.,  
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,  
Patent Owner

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IPR2025-00601  
Patent No. 9,856,320

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**DECLARATION OF PETER P. LEE, M.D.**

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I, Peter P. Lee, M.D., declare as follows:

1. I have been retained by Akin, Gump, Strauss, Hauer, & Feld LLP to provide expert opinions regarding immunotherapy, clinical trials involving immunotherapies, and the validity of U.S. Patent No. 9,856,320 (the '320 Patent") assigned to Bristol-Myers Squibb Co. I have also been retained to provide analysis regarding certain documents identified and relied on by Amgen in its Petition for *inter partes* review ("the Petition") and what a person of ordinary skill in the art would have understood before May 15, 2012.

2. This declaration summarizes the opinions I have formed to date based on my review of the materials cited here, as well as my education, experience, and knowledge that I have acquired through my career.

3. I reserve the right to modify or amend my opinions, if necessary, based on further review and analysis of information I receive after this declaration is filed, including in response to any arguments or information presented by Amgen or its experts.

## **I. PERSONAL AND PROFESSIONAL BACKGROUND**

4. My qualifications, credentials, and testimony history are stated more fully in my *curriculum vitae*. EX2024. Here, I provide a summary of my qualifications.

5. I was awarded a B.S. in Microbiology in 1985 from the University of California, Los, Angeles and was awarded an M.D. in 1989 from the University of California, San Diego. I did my residency in Internal Medicine at Scripps Clinic in La Jolla, California.

6. I completed fellowships at the University of California, San Francisco (clinical immunology and allergy, 1992-1995) and Stanford (hematology, 1995-1999).

7. I am Board certified by the American Board of Internal Medicine and the American Board of Allergy and Immunology, and I have been licensed to practice medicine since 1990.

8. From 1999-2011, I was part of the faculty at Stanford University, where I first served as an Assistant Professor of Medicine (Hematology) from 1999-2006 and then as an Associate Professor of Medicine from 2006-2011. In 2011, I became Professor and Associate Chair of Cancer Immunotherapies and Tumor Immunology at the City of Hope Comprehensive Cancer Center. In 2013, I became the Billy Wilder Endowed Professor and Chair of the Department of Immuno-Oncology at the City of Hope Comprehensive Cancer Center.

9. Since 1995, I have been involved in the care of hundreds of patients with hematological malignancies (leukemia, lymphoma, myeloma, myelodysplastic syndrome, etc.) using chemotherapy, radiotherapy, targeted therapy, and various

forms of immunotherapies (immune checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibodies, stem cell transplantation, and cytokines).

10. Since 1999, I have been involved in the design, conduct, and analysis of dozens of clinical trials involving various forms of cancers (melanoma, breast cancer, colorectal cancer, leukemia, lymphoma, myeloma) and different immunotherapies (immune checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibodies, stem cell transplantation, cancer vaccines, and cytokines).

11. Over my career, I have participated as an Ad Hoc member on multiple NIH Study Sections and NIH/NCI Program Project review boards. In this role, I have evaluated numerous cutting-edge approaches in cancer immunotherapy and biomarkers to understand their impact on patient outcomes.

12. I am an Editorial Board Member for the journals Hematologist and Cancer Immunology Research. I also review articles for numerous high impact journals, including Nature Medicine and the New England Journal of Medicine.

13. Over the past 25 years, my research has focused on understanding how cancer affects the host immune system, and on developing effective cancer immunotherapy based on mechanistic insights. In 1999, I was first to demonstrate conclusively that some cancer (melanoma) patients mount an endogenous immune response against their own cancers, but their immune responses were ineffective – this is now known to be mediated via inhibitory checkpoint molecules. Prevailing

view before then was that the immune system played no role in cancer. This sparked a gradual paradigm shift in the field: cancer progression is now viewed as the balance between cancer cell proliferation and host immune control. Over the ensuing years, my efforts entailed development of novel approaches to identify, isolate, and study tumor-reactive T cells, which have been applied by my group and others to understand de novo anti-tumor immune responses and those elicited via immunotherapies including anti-PD-1 and anti-CTLA-4. Some of my other accomplishments include showing that T cell responses to cancer are strongly dependent upon their recognition efficiency of tumor-associated antigens for efficacy; and demonstrating the importance of immune function and cytokine signaling within tumor-draining lymph nodes and blood. Many of these findings were from melanoma patients. My work has led to a number of awards, including Stand Up to Cancer (SU2C) Convergence Award, Dept. of Defense (DoD) Era of Hope Scholar Award, DoD Multi-Team Award, American Cancer Society Research Scholar Award, Damon Runyon Scholar Award.

14. I have an extensive publication record. I am an author on more than 140 journal articles. Throughout my career, I have published findings relating to immunotherapies, immunology, and cancer. I am also an author on several book chapters related to immunology, T cell responses, and cancer.

15. I am an Elected member of the American Society for Clinical Investigation (ASCI), American Society of Hematology (ASH), and American Association of Cancer Research (AACR).

## II. COMPENSATION AND MATERIALS CONSIDERED

16. I am being compensated for my services as an expert at my standard rate. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

17. In forming my opinions, I have reviewed the Petition, the '320 Patent and its prosecution history. I have also reviewed and considered the following materials in preparing this Declaration:

| Exhibit | Description                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EX1001  | U.S. Patent No. 9,856,320                                                                                                                                                                                                                                                                                                                                                                                             |
| EX1002  | Prosecution History of U.S. Patent No. 9,856,320                                                                                                                                                                                                                                                                                                                                                                      |
| EX1003  | Declaration of Paul A. Antony, M.D.                                                                                                                                                                                                                                                                                                                                                                                   |
| EX1005  | NCT01024231 Version 3, "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma" (Last Update Posted Jan. 5, 2010), available at <a href="https://clinicaltrials.gov/study/NCT01024231?tab=history&amp;a=3#version-content-panel">https://clinicaltrials.gov/study/NCT01024231?tab=history&amp;a=3#version-content-panel</a> |
| EX1006  | International Patent Publication No. WO 2006/121168                                                                                                                                                                                                                                                                                                                                                                   |
| EX1007  | Wolchok, J.D. et al. <i>Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind,</i>                                                                                                                                                                                                                                                                                         |

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|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|        | <i>multicentre, phase 2, dose-ranging study</i> , Lancet Oncol., 2010 Feb; 11(2):155–64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| EX1009 | Sznol, M. et al. <i>Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1 BMS-936558/ONO4538) in patients with advanced refractory malignancies</i> , J Clin Oncology, 2010 May 20; 28(15)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| EX1010 | Fife, B.T. et al. <i>Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways</i> , Immunol Rev., 2008 Aug; 224:166–182                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| EX1030 | Curran, M.A. et al. <i>PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors</i> , Proc Natl Acad Sci USA, 2010 Mar 2; 107(9):4275–4280                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| EX1031 | NCT01024231 Version 58, “Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted May 1, 2012), available at <a href="https://clinicaltrials.gov/study/NCT01024231?tab=history&amp;a=58#version-content-panel">https://clinicaltrials.gov/study/NCT01024231?tab=history&amp;a=58#version-content-panel</a>                                                                                                                                                                                                                                                                                                                       |
| EX1032 | Humphrey, R.W. et al. <i>Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer</i> , J Natl Cancer Inst. 2011 Aug 17; 103(16):1222–1226                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| EX1040 | Tourneau, C.L. et al. <i>Dose escalation methods in Phase 1 cancer clinical trials</i> , J Natl Cancer Inst., 2009 May 20; 101(10):708–720                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| EX1042 | Simeone, E. et al. <i>Immunomodulating antibodies in the treatment of metastatic melanoma: The experience with anti-CTLA-4, anti-CD137, and anti-PD1</i> , J Immunotoxicol., 2012 Jul-Sep; 9(3):241-7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| EX1045 | Korman, A. et al. <i>Activity of Anti-PD-1 in murine tumor models: Role of ‘host’ PD-L1 and synergistic effect of anti-PD-1 and anti-CTLA-4</i> , J Immunology, 2007 Apr; 178(1_Supplement):S82 (abstract)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| EX2001 | Press Release, Bristol-Myers Squibb, <i>FDA Approves Yervoy™ (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer</i> (Mar. 25, 2011), available at <a href="https://news.bms.com/news/details/2011/FDA-Approves-YERVOY-ipilimumab-for-the-Treatment-of-Patients-with-Newly-Diagnosed-or-Previously-Treated-Unresectable-or-Metastatic-Melanoma-the-Deadliest-Form-of-Skin-Cancer/default.aspx">https://news.bms.com/news/details/2011/FDA-Approves-YERVOY-ipilimumab-for-the-Treatment-of-Patients-with-Newly-Diagnosed-or-Previously-Treated-Unresectable-or-Metastatic-Melanoma-the-Deadliest-Form-of-Skin-Cancer/default.aspx</a> |

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|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EX2002 | Press Release, Bristol-Myers Squibb, <i>Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration</i> (Dec. 22, 2014), available at <a href="https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx">https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx</a> |
| EX2003 | YERVOY, FDA Approved label and prescribing information, Rev. 5/2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| EX2004 | OPDIVO, FDA Approved label and prescribing information, Rev. 5/2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| EX2007 | Press Release, Amgen, <i>Amgen Reports First Quarter 2025 Financial Results</i> (May 1, 2025), available at <a href="https://www.amgen.com/newsroom/press-releases/2025/05/amgenreports-first-quarter-2025-financial-results">https://www.amgen.com/newsroom/press-releases/2025/05/amgenreports-first-quarter-2025-financial-results</a>                                                                                                                                                                                                           |
| EX2024 | Curriculum Vitae of Peter P. Lee, M.D.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| EX2025 | U.S. Food and Drug Administration, The Drug Development Process, Step 3: Clinical Research (Content current as of Jan. 4, 2018), available at <a href="https://www.fda.gov/patients/drug-development-process/step-3-clinical-research">https://www.fda.gov/patients/drug-development-process/step-3-clinical-research</a>                                                                                                                                                                                                                           |
| EX2026 | Wang, D.D. et al. <i>Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials</i> , J Clin Pharmacol., 2009 Sep; 49(9):1012-24                                                                                                                                                                                                                                                                                                                                                                                  |
| EX2027 | NCT01024231, “Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted Mar. 22, 2021), available at <a href="https://clinicaltrials.gov/study/NCT01024231">https://clinicaltrials.gov/study/NCT01024231</a>                                                                                                                                                                                                                            |
| EX2028 | Press Release, Bristol-Myers Squibb, <i>Bristol-Myers Squibb Completes Acquisition of Medarex, Inc.</i> (Sept. 1, 2009), available at <a href="https://news.bms.com/news/details/2009/Bristol-Myers-Squibb-to-Acquire-Medarex/default.aspx">https://news.bms.com/news/details/2009/Bristol-Myers-Squibb-to-Acquire-Medarex/default.aspx</a>                                                                                                                                                                                                         |
| EX2029 | National Institutes of Health, National Cancer Institute, NCI Dictionary of Cancer Terms, Definition of “complete response” available at <a href="https://www.cancer.gov/publications/dictionaries/cancer-terms/def/complete-response">https://www.cancer.gov/publications/dictionaries/cancer-terms/def/complete-response</a> (last visited July 9, 2025)                                                                                                                                                                                          |
| EX2030 | National Institutes of Health, National Cancer Institute, NCI Dictionary of Cancer Terms, Definition of “partial response”                                                                                                                                                                                                                                                                                                                                                                                                                          |

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|        | available at<br><a href="https://www.cancer.gov/publications/dictionaries/cancer-terms/def/partial-response">https://www.cancer.gov/publications/dictionaries/cancer-terms/def/partial-response</a> (last visited July 9, 2025)                                                   |
| EX2031 | NCT00730639, “A Phase 1 Study of Nivolumab (BMS-936558) in Subjects With Advanced or Recurrent Malignancies (MDX1106-03)” (Last Update Posted Dec. 3, 2021), available at <a href="https://clinicaltrials.gov/study/NCT00730639">https://clinicaltrials.gov/study/NCT00730639</a> |
| EX2032 | Umscheid, C.A. et al. <i>Key Concepts of Clinical Trials: A Narrative Review</i> , Postgraduate Medicine, 2011 Sep; 123:5, 194-204                                                                                                                                                |

### III. RELEVANT LEGAL STANDARDS

18. I am not a lawyer. In forming my opinions here, I am relying on certain legal principles that counsel have explained to me, as listed below. I have applied this understanding in my analysis.

#### A. Burden of Proof

19. For patent invalidity in an *inter partes* review, I understand the burden is on the party asserting unpatentability to prove it by a preponderance of the evidence. I understand that “a preponderance of the evidence” is evidence sufficient to show that a fact is more likely than not.

#### B. Person of Ordinary Skill in the Art

20. I have been informed that the claims of a patent are judged from the perspective of a hypothetical “person of ordinary skill in the art” (“POSA”) at the time of the invention, which I have been advised is May 15, 2012 for the ’320 Patent. I understand that the POSA is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

21. I understand that Dr. Antony has defined a POSA as someone who “would have a Ph.D. degree in immunology or a related field (for example, biochemistry), or alternatively a M.D. with a particular focus on cancer immunotherapy, plus at least two years of experience in the field of cancer immunotherapy, including experience with cancer treatments. The levels of education, experience and knowledge described above can trade off against one another. POSAs would also have either been (1) skilled in pharmacokinetics or (2) able to communicate as part of a team with pharmacokinetics experts if necessary. This person would have been capable of understanding and applying the teachings of the ’320 patent and the prior-art references discussed in this declaration—including understanding literature regarding clinical trials for cancer.” EX1003, ¶30.

22. I have not been asked to take a position on whether I agree with Dr. Antony’s definition of a POSA. For the purposes of the opinions expressed here, I have been asked to assume the perspective of a POSA as defined by Dr. Antony.

23. By May 2012, I met and exceeded Dr. Antony’s level of skill of a POSA. By May 2012, I had been practicing medicine and actively treating patients for more than 20 years. My practice has included treating patients by administering immunotherapy for more than 15 years. I have been engaged in research related to cancer, immunology and immunotherapy for more than 15 years. And I have worked

with other practitioners with specific experience in pharmacokinetics for more than 15 years. This experience includes being involved in the design, conduct, and/or analysis of clinical trials involving various forms of cancer immunotherapies.

24. Although I have exceeded Dr. Antony's level of skill of a POSA as I just described, the opinions I have provided in this declaration are from the perspective of a POSA as of May 2012.

### **C. Claim Construction**

25. I have been informed that patent claims are construed from the viewpoint of a person of ordinary skill in the art and that patent claims generally should be understood consistent with their ordinary and customary meaning given to them by a POSA at the time of the invention.

26. I understand that neither party has proposed a specific construction for any term in the claims of the '320 Patent. Therefore, I have applied the ordinary and customary meaning in my analysis here. To the extent any specific construction is proposed, I reserve the right to supplement my opinions.

### **D. Obviousness**

27. Amgen contends that the claims of the '320 Patent are invalid as obvious. I understand the factual inquiries in determining obviousness include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) objective

indicia of nonobviousness, including commercial success, long-felt need, and the failure of others. I understand that an invention is obvious when 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.

28. I understand that to prove that prior art, or a combination of prior art, renders a patent obvious, it is necessary to: (1) identify the particular references that singly, or in combination, make the patent obvious and (2) specifically identify which elements of the patent claim appear in each of the asserted references. Also, a finding of obviousness requires a showing that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.

29. I 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, and that obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.

## IV. BACKGROUND

### A. Immunotherapy and the PD-1 Pathway

30. The human immune system is a complex system formed of organs, (spleen, lymph nodes, etc.), specialized cells (T, B, myeloid cells, etc.), and different substances (antibodies, cytokines, etc.) that work together to protect individuals from infections and disease. The immune system is made up of the innate and adaptive immune system. As the '320 Patent explains, “[t]he adaptive immune system, comprised of T and B lymphocytes, has powerful anti-cancer potential, with a broad capacity and exquisite specificity to respond to diverse tumor antigens. Further, the immune system demonstrates considerable plasticity and a memory component.” EX1001, 1:35-40. T cells are a type of white blood cell that have the ability to recognize and kill cancer cells. In order to perform this function, T cells must distinguish between healthy cells and cells that are infected or cancerous. EX1001, 1:33-38.

31. One way in which T cells are able to modulate their activity and avoid killing healthy cells is through unique receptors that are found on the surface of T cells. EX1001, 1:57-2:25. These receptors function to stimulate or downregulate the T cell response. Receptors that downregulate the immune response are often called inhibitory receptors or checkpoints. One of the inhibitory receptors that T cells express on their surface is a protein called programmed death-1 receptor (“PD-

1”). PD-1 “is a key immune checkpoint receptor expressed by activated T and B cells and mediates immunosuppression. PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA.” EX1001, 2:4-8. PD-1 acts as a brake on the immune system by downregulating T cell activity to prevent T cells from killing healthy cells. Cytotoxic T lymphocyte-associated protein 4 (“CTLA-4”) is another inhibitory receptor found on T cells that also acts as a brake on the immune system by downregulating T cell activity.

32. Immunotherapy is a type of treatment that functions by enhancing the immune system’s ability to recognize and kill cancer cells. One form of immunotherapy involves using antibodies to block the inhibitory receptors that are found on the surface of T cells. For example, antibodies that bind to PD-1 (“anti-PD-1 antibodies”) and CTLA-4 (“anti-CTLA-4 antibodies”) can block the “braking” effect of PD-1 and CTLA-4 when they bind to those inhibitory receptors. By blocking the PD-1 and CTLA-4 inhibitory receptors, anti-PD-1 and anti-CTLA-4 antibodies are able to increase or activate an immune response. More specifically, by binding to PD-1 and CTLA-4, respectively, these antibodies shut off the brakes on the immune system, freeing the immune cells to recognize, attack and destroy cancer cells. EX1001, 1:57-2:25. These antibodies are sometimes referred to as “immune checkpoint inhibitors” because they block the receptor proteins that act as checkpoints on the immune system.

## **B. Purposes of Clinical Trials at Different Phases**

33. The clinical testing of pharmaceutical products proceeds through phases. Importantly, the goals of the testing change as the phases proceed.

34. The primary goal of Phase 1 clinical trials is to test the safety of a new active ingredient and to gather information about a maximum tolerated dose (MTD), i.e., the maximum dose that has an acceptable level of toxicity. EX2032, 197 (Phase 1 trials are “designed to test the safety and maximum tolerated dose [] of a drug, human pharmacokinetics and pharmacodynamics, and drug-drug interactions”); EX2025, 3. A Phase 1 trial is often the first time a new drug is tested in the clinic, making it a so-called first-in-human (FIH) study. The trial can include a dose-escalation study, where initial doses are tested across a small number of different patients to gather preliminary information about how the body responds to different doses. If an initial dose is found safe, then that dose is incrementally increased as clinicians study the safety of higher doses. EX2032, 197 (“Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a sufficient period”). Efficacy is not typically a primary objective of Phase 1 trials. It may be a secondary objective, but efficacy is typically determined in larger trials (Phase 2 and 3) that extend over a longer period of time. EX2025, 3-4.

35. One drug property often analyzed in a Phase 1 trial is pharmacokinetics (“PK”), which deals with how the patient’s body interacts with the drug over time, including how the drug is absorbed and eliminated, and how long the drug remains in the body after a dose. Another property often evaluated in a Phase 1 trial is pharmacodynamics (“PD”), which tries to assess how the drug interacts with biological targets in the body. EX2025, 3.

36. Different patients can react differently to the drug for several reasons, including stage of disease, concurrent medical conditions, genetics, age, sex, and body weight. Different body weights lead not only to different volumes for the drug to disperse within the body but can also lead to different rates and mechanisms for drug absorption and elimination from the body. “When [a monoclonal antibody] (mAb) is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown.” EX2026, 1023. But again, the protocol of the Phase 1 or FIH trial is not intended as a guide for treatment methods. These preliminary studies are intended to test for safety and potentially gather information on PK and PD.

37. The primary goals of Phase 2 and Phase 3 clinical trials, on the other hand, are to test the safety and efficacy of the drug in larger groups of patients. Phase 2 trials may include dozens to several hundred patients, who are generally divided into different groups that receive either the new drug or a placebo. EX2025, 3-4. A Phase 2 trial may last several months to two years. EX2025, 3-4. The primary

objective of a Phase 2 trial is typically to assess the initial efficacy of a drug on a particular disease or condition. EX2032, 197. Dose level and frequency are common secondary objectives in Phase 2 trials. Phase 2 trials are not typically large enough to conclusively establish that a drug is beneficial. They do provide some safety data about a new drug and that data is often used by researchers to design the Phase 3 protocol. EX2025, 4; EX2032, 197. According to the FDA, only about 33% of drugs that enter Phase 2 trials proceed to Phase 3 trials. EX2025, 4.

38. Phase 3 trials include hundreds to thousands of patients for the purpose of determining efficacy and comparing the new treatment to the standard of care. EX2032, 198. They are typically conducted at multiple treatment centers and can last several years. Because of their high enrollment and long duration, Phase 3 trials provide most of the safety data necessary for drug approval. EX2025, 4.

39. The Phase 3 treatment protocol is designed based on a detailed understanding of how the drug interacts in the human body, including how body weight impacts PK and PD. As the Wang reference makes clear, “[t]he final dosing approach for phase 3 trials in adults should be selected based on the established body size effect on PK and PD, the therapeutic window of the mAbs, along with other factors that may impact the outcome of the study, benefit to patients, and overall drug development.” EX2026, 1023-24. The Phase 3 treatment protocol is intended to confirm the safety and efficacy of a method to be used in clinical practice.

40. Phase 3 trials typically provide most of the information that is needed for labeling after a drug is approved by the FDA. According to the FDA, only about 25-30% of drugs that enter Phase 3 trials move to the next phase of clinical development. EX2025, 5.

## **V. THE '320 PATENT**

41. I have reviewed the claims, specification, and file history of the '320 Patent and summarize some of the key points below.

42. The '320 Patent is entitled "Cancer Immunotherapy by Disrupting PD-1/PD-L1 Signaling."

43. The '320 Patent "relates to methods for immunotherapy of a cancer patient comprising administering to the patient antibodies that disrupt the PD-1/PD-L1 signaling pathway." EX1001, 1:24-26. "Certain embodiments comprise the use of an anti-PD-1 Ab in combination with another anti-cancer agent, preferably an anti-CTLA-4 Ab, to treat cancer." EX1001, 7:59-62.

44. There are two independent claims in the '320 Patent, claims 1 and 5.

45. Claim 1 of the '320 Patent provides a dosing schedule for combination anti-PD-1 and anti-CTLA-4 therapy for the treatment:

1. A method of treating a human subject afflicted with a cancer comprising administering to the subject:

(a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) (“anti-PD-1 antibody”); and

(b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (“anti-CTLA-4 antibody”);

(i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses; followed by

(ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses; and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages:

(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

- (b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
- (c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;
- (d) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (e) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;
- (j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody;
- (k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody;
- (l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody; or
- (m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.

46. Claim 5 sets forth a different dosing schedule for the treatment of cancer:

5. A method of treating a human subject afflicted with a cancer comprising administering to the subject 1 mg/kg of an anti-PD-1 antibody and 3 mg/kg of an anti-CTLA-4 antibody every 3 weeks for 4 doses, followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.

47. The '320 Patent also includes several dependent claims. I understand that dependent claims include all of the limitations in the claims to which they refer and add the additional features of the dependent claim.

## **VI. SUMMARY OF THE ASSERTED PRIOR ART**

48. The Petition provides two grounds for unpatentability:

| <b>Ground</b>                                                          | <b>Claims</b>    |
|------------------------------------------------------------------------|------------------|
| <b><u>Ground 1:</u></b><br>Obvious in view of NCT-231, Korman, Wolchok | 1-4, 6-12, 14-17 |
| <b><u>Ground 2:</u></b><br>Obvious in view of Korman, Wolchok, Sznol   | 5, 13, 18-22     |

### **A. NCT-231**

49. NCT-231 is a printout of the study details for clinical trial NCT01024231 that was last updated as of January 5, 2010. NCT01024231, a Phase 1 clinical trial, was a first-of-its-kind clinical trial evaluating the combination of an anti-PD-1 and an anti-CTLA-4 antibody in humans. In particular, NCT01024231

was a Phase 1 clinical trial sponsored by BMS “to assess the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma.” EX1005, 4.

50. The NCT01024231 clinical trial started on December 14, 2009 and completed on April 1, 2019. EX2027, 1. Complete results from the NCT01024231 trial were not posted until March 22, 2021. EX2027, 1. Preliminary results from the NCT01024231 trial were published July 11, 2013. EX2027, 1. The NCT01024231 trial was designed as a dose-escalation study, meaning that its primary objective was to identify the maximum tolerated dose. EX1005.

51. The reference identified in the Petition as NCT-231 provides information about the trial protocol as was posted to the clinicaltrials.gov website on January 5, 2010. EX1005, 4. That information includes the Study Description: “The purpose of this study is to assess the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma.” EX1005, 4.

52. NCT-231 includes 5 cohorts and provides the following dosing schedule for each of the cohorts:

**Drug:** Nivolumab every 3 weeks for 21 weeks in induction and every 12 weeks for 84 weeks in maintenance

**Drug:** Ipilimumab every 3 weeks for 9 weeks in induction and every 12 weeks for 84 weeks in maintenance

EX1005, 4.

53. The dosages administered for each cohort are as follows:

| Arms                                                             |
|------------------------------------------------------------------|
| <b>Cohort 1:</b><br>Nivolumab: 0.3 mg/kg<br>Ipilimumab: 3 mg/kg  |
| <b>Cohort 2:</b><br>Nivolumab: 0.3 mg/kg<br>Ipilimumab: 10 mg/kg |
| <b>Cohort 3:</b><br>Nivolumab: 1 mg/kg<br>Ipilimumab: 10 mg/kg   |
| <b>Cohort 4:</b><br>Nivolumab: 3 mg/kg<br>Ipilimumab: 10 mg/kg   |
| <b>Cohort 5:</b><br>Nivolumab: 10 mg/kg<br>Ipilimumab: 10 mg/kg  |

EX1005, 4.

54. The Primary Outcome Measure for NCT-231 was the “Maximum tolerated dose.” EX1005, 5. As Secondary Outcome Measures, NCT-231 lists “1. Safety assessment based on Adverse Event reports, results of clinical laboratory tests, immune safety tests, physical exam, vital signs, ECG evaluation and ECOG [Time Frame: Safety is assessed at all study timepoints]; 2. Tumor response evaluations [Time Frame: Tumor response is assessed at weeks 12, 18, 24, 30, 36, 48, 60, 72, 84, 96 and 108]; and 3. Pharmacokinetic peak and trough concentration of each study drug when given in combination compared to historical monotherapy data [Time Frame: PK is collected pre and post dose].” EX1005, 5.

55. As of the January 5, 2010 posting date for NCT-231, the clinical trial was “Not yet recruiting.” EX1005, 3. In other words, the trial protocol had been designed, but no patients had been recruited to participate in the trial.

#### **B. Korman**

56. Korman is an International Patent Application with the publication number WO2006/121168, and a publication date of November 16, 2006. It names Ono Pharmaceutical Co., Ltd. and Medarex, Inc. as applicants. EX1006. BMS acquired Medarex in September 2009, and as a result gained ownership rights in Korman. EX2028. Korman discloses isolated monoclonal antibodies that bind to PD-1, i.e., anti-PD-1 antibodies. More specifically, Korman describes the development and evaluation of the anti-PD-1 antibody, 5C4, which is the antibody that eventually became nivolumab, the active ingredient in BMS’s OPDIVO®. According to Korman’s Abstract, “[t]he present invention further provides methods for using a combination immunotherapy, such as the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat hyperproliferative disease, such as cancer.” EX1006, abstract.

57. Examples 13-17 in Korman evaluated the administration of anti-PD-1, anti-CTLA-4, and combination anti-PD-1/anti-CTLA-4 in mouse tumor models. EX1006, 66, 87-95. According to Korman, “the results of Examples 14, 16, and 18 show that the combination treatment of anti-CTLA-4 antibody and anti-PD-1

antibody had a significant (synergistic) effect on tumor growth even at sub-optimal therapeutic doses as compared to treatment with either antibody alone (*i.e.*, the combination therapy was surprisingly more effective at subtherapeutic doses than either monotherapy).” EX1006, 66. Example 17, for instance, found an “unexpected synergistic effect of an anti-PD-1 antibody combined with an anti-CTLA-4 antibody, along with the surprising effectiveness of subtherapeutic levels of an anti-CTLA-4 antibody in the combination.” EX1006, 94. Korman does not include any information about the toxicity or adverse effects observed with respect to combination therapy. The mouse tumor model examples in Korman focus almost entirely on tumor response. EX1006, 87-95.

58. Korman contains dosage information for antibodies, including anti-PD-1 and anti-CTLA-4 antibodies. EX1006, 55. Korman further explains that “[t]he selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular composition of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.” EX1006, 55-56. Korman does not

include any human data or any examples that administer antibodies according to an induction/maintenance schedule in which antibodies are provided in combination and then followed with the administration of a single antibody alone.

### **C. Wolchok**

59. Wolchok is an article from The Lancet Oncology journal published February 2010 that reports the results of a Phase 2 melanoma trial in which patients were administered a weight-based dose of ipilimumab monotherapy every three weeks for four cycles (i.e., the induction phase) followed by maintenance therapy every three months. EX1007, 155. In this study, a total of 214 patients were randomly assigned to receive 0.3 mg/kg (71 patients), 3.0 mg/kg (71 patients), or 10 mg/kg (72 patients). EX1007, Figure 1. “As the dose of ipilimumab increased, best overall response rate rose.” EX1007, 161. Complete responses were seen in 2 patients administered the 10 mg/kg dose. EX1007, Table 2. Partial responses were observed in 3 patients in the 3.0 mg/kg group and 6 patients in the 10 mg/kg group. EX1007, Table 2. “Ipilimumab had a manageable safety profile at all three doses (table 3).” EX1007, 161.

60. A pharmacokinetic analysis was performed to evaluate whether each dose was able to achieve the target serum concentration of 20 µg/mL before the fourth dose in the induction phase. EX1007, 162. The analysis indicated that the “target concentration was expected to be exceeded by about 95% of patients in the

10 mg/kg group, but by only 30% and 0% in the 3 mg/kg and 0.3 mg/kg groups, respectively (figure 3B).” EX1007, 162. Additionally, the 10 mg/kg group “induced a greater mean rate of increase in absolute lymphocyte count than did the lower doses (figure 4).” EX1007, 162.

61. According to Wolchok, the study “results indicate that treatment with ipilimumab monotherapy at 10 mg/kg showed activity in heavily pretreated patients with advanced melanoma, with high-grade immune-related adverse events well managed with specific treatment guidelines.” EX1007, 163. Based on these results, the authors concluded, “[f]urther investigations of ipilimumab efficacy and safety at 10 mg/kg in patients with advanced melanoma are warranted.” EX1007, 163.

#### **D. Sznol**

62. Sznol is an abstract in the Journal of Clinical Oncology from 2010 that reports preliminary results from a Phase 1 trial in which patients were administered MDX-1106 (nivolumab) at 1 mg/kg (4 patients), 3 mg/kg (4 patients), or 10 mg/kg (8 patients) on a biweekly basis. EX1009. Objective tumor responses were observed in 3 patients who received a 1 mg/kg dose, 2 patients who received a 3 mg/kg dose, and 1 patient who received a 10 mg/kg dose. EX1009. As of the report, the 1 mg/kg and 3 mg/kg cohorts had been expanded to 16 patients and the 10 mg/kg cohort was in the process of being expanded. EX1009. The study did not reach a maximum tolerated dose. The study concluded that “MDX-1106 administered biweekly is well

tolerated and has antitumor activity at 1-10 mg/kg.... Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.” EX1009.

## **VII. OPINIONS REGARDING PATENTABILITY OF THE CLAIMS**

### **A. Opinions Regarding the Patentability of the Ground 1 Claims**

63. I have been asked to respond to certain arguments raised in the Petition with respect to Ground 1.

#### **1. Motivation to Combine**

64. The Petition states that “A POSA would have had reason to combine the known and studied dosing concentrations disclosed in Korman and Wolchok to arrive at *any one* of the dosing concentrations listed in limitations ((a) through (m)) for use in the induction-maintenance dosing structure of NCT-231.” Pet., 29.

65. In my opinion A POSA would have had insufficient information to modify an existing dosing regimen, such as the one disclosed in NCT-231, in the absence of more information about how the initial combinations of dosages performed or how the two antibodies interact in vivo.

66. A POSA would have understood that dose escalation studies, like the one described in NCT-231, function in a stepwise manner. EX2032, 197; EX1040, 709. Although there are multiple ways to design dose escalation studies, the unifying feature among these models is that they start with treating subjects with a small

number of defined doses that increase in a stepwise fashion. EX1040, 709-710. Then based on data obtained from those treatments, POSAs determine appropriate future doses to try. They do not randomly test any number of possible doses without reason.

67. NCT-231 is a Phase 1 dose-escalation study for the combination of anti-PD-1 and anti-CTLA-4 antibodies. EX1005. Its stated purpose was to “assess the safety and tolerability of treatment with [anti-PD-1 antibody] in combination with [anti-CTLA-4 antibody].” EX1005, 4. Its primary outcome measure was to identify the maximum tolerated dose for the antibody combination (because it was unknown at that time). EX1005, 5.

68. NCT-231 does not report any results for the clinical trial. It is just a preliminary protocol and the trial was not yet recruiting. EX1005, 3. As of May 15, 2012, NCT-231 (and anti-PD-1/anti-CTLA-4 combination therapy generally) was still in its early stages and included no data on which a POSA might have relied to make the iterative changes suggested in the Petition. EX1031. For example, since anti-PD-1 and anti-CTLA-4 antibodies both bind to inhibitory checkpoint molecules, how these may interact in vivo to either enhance efficacy or toxicity was not known at the time. Absent such data, a POSA would not have had any reason other than hindsight to modify NCT-231 at all, much less to implement

concentrations taken from Korman's animal data or Wolchok's anti-CTLA-4 monotherapy trial.

## **2. Reasonable Expectation of Success**

69. In arguing that a POSA "would have reasonably expected success" in selecting doses from Korman and Wolchok and combining them with NCT-231, the Petition states that "Studies such as Sznol and Wolchok provided baseline information about anti-PD-1 and anti-CTLA-4 dosing concentrations, respectively when each was given alone." Pet., 40.

70. I disagree that a POSA would consider dosing concentrations from monotherapy studies in Sznol and Wolchok to be sufficient "baseline information" for dose concentrations in combination therapies being tested NCT-231. There are important biological differences between the monotherapies in Sznol and Wolchok and the combination therapy in NCT-231. Both CTLA-4 and PD-1 are inhibitory checkpoint molecules that may be expressed on multiple immune cell types (CD4 helper T cells, CD4 regulatory T cells, CD8 cytotoxic T cells, B cells, NK cells, monocytes/macrophages, and others) at different phases of the immune response. How antibodies against these two inhibitory molecules in combination therapy may interact in vivo was unknown and could require significantly different dose levels or frequencies than in monotherapy. As such, dosing in the specific multi-step combination therapy and monotherapy of the Ground 1 claims could not be

considered obvious simply based on monotherapies in Sznol and Wolchok. This is further supported by the observation that, as stated earlier, anti-CTLA-4 and anti-PD-1 antibodies given together have synergistic effects that could not have been predicted based on results of monotherapy.

71. The preliminary nature of Sznol would have also limited its importance to a POSA since in 2012, this study was still ongoing and results were not yet matured. Sznol reported preliminary results for the first 16 patients treated in a Phase 1 OPDIVO monotherapy trial, only 6 of which showed any response to the anti-PD-1 monotherapy. EX1009. By that time, other patients in Sznol were still undergoing treatment and being evaluated. EX1009 (“All responses are ongoing (3-13+ mo)”). And the ultimate conclusion in Sznol was “Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.” EX1009. In my opinion, Sznol did not contain sufficient information from a sufficient number of patients over a long enough period of time for a POSA to have considered it adequate “baseline information” about dosing concentrations that should be used in a multi-step combination therapy regimen. Sznol had not determined appropriate dosing for PD-1 monotherapy.

72. The Petition next states that the dosing information in Sznol and Wolchok “would be bolstered by disclosure of concurrent administration of the two antibodies (EX1006, 56; EX1005, 4) and evidence of relative safety and efficacy for

the combination therapy in animal models. EX1006, 97; EX1030, 4276; EX1045, 1.” Pet., 40.

73. It is not clear to me what the Petition means by “bolstered.” Neither the petition nor Dr. Antony provide any more explanation for what “bolstered” is intended to mean. Regardless of the specific meaning, evidence of relative safety and efficacy for the combination therapy in animal models would lend support for use in humans, but would not impact how a POSA would have viewed the dosing information in monotherapy studies by Sznol and Wolchok in the context of the claims that are challenged in Ground 1.

74. In my opinion, the “disclosure of concurrent administration” in Korman (EX1006) or NCT-231 (EX1005) would not change how a POSA would have viewed the monotherapy dose concentrations in Wolchok or Sznol. There are important differences between those references that would have prevented a POSA from reaching any conclusions about the dosing information in Wolchok and Sznol based on Korman and NCT-231. These differences include that (1) Korman only uses mouse models, (2) NCT-231 describes a multi-step combination therapy regimen, but provided no efficacy or toxicity data, (3) Wolchok and Sznol describe monotherapy, and (4) NCT-231 discloses different combinations of doses than the Ground 1 claims. The Petition does not address these differences.

75. It is also my opinion that the “evidence of relative safety and efficacy for the combination therapy in animal models” would not have changed how a POSA would have viewed the monotherapy dose concentrations in Wolchok or Sznol. None of EX1006, EX1030, or EX1045 discuss the safety of combination therapy for humans in connection with the mouse tumor models.

**B. Opinions Regarding the Patentability of the Ground 2 Claims**

**1. Subsequently Administering**

76. Claim 5 requires administering to a patient a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody “followed by subsequently administering” an anti-PD-1 antibody alone. EX1001, cl. 5.

77. The Petition states that “[i]n view of the less severe toxicity profile for anti-PD-1 antibodies and the sequentially later mechanistic action of anti-PD-1 relative to anti-CTLA-4 in blocking the T-cell ‘off signal’ to kill cancer cells,” a POSA would have continued anti-PD-1 monotherapy after the combination therapy. Pet., 57-58. This is a naïve view that a POSA would not have accepted. The immune response is dynamic and involves iterative cycles rather than isolated bursts. Effector T cells die over time and are continually replaced by newly activated T cells. Even if CTLA-4 acts early and PD-1 acts later within a single T cell cycle, both molecules continue to operate within the continued immune response. As such,

POSA would not have been motivated to switch from combination therapy to administer an anti-PD-1 antibody alone based on this reasoning.

78. First, even if toxicity were a concern for a POSA attempting the combination, none of Korman, Wolchok, or Sznol describe administering an anti-PD-1 antibody alone subsequent to combination therapy with anti-PD-1 and anti-CTLA-4 antibodies. The concept of subsequent administration is not disclosed in any of the references relied on in Ground 2 of the Petition.

79. Additionally, because anti-PD-1/anti-CTLA-4 combination therapy was so new as of May 15, 2012, a POSA would not have known what to expect in terms of the toxicity of the combination. The Petition does not provide any specific measures of toxicity or specific toxicity concerns associated with the combination therapy.

80. Furthermore, in the event that the combination therapy caused sufficient toxicity issues to warrant modifying the combination therapy, a POSA would have had several different options to consider **depending on what the toxicity issues were**, including (1) adjusting the individual dose of each antibody of the combination, (2) adjusting the frequency of each antibody of the combination, (3) if need be, discontinuing the combination therapy and switching to other forms of cancer therapy. Indeed, Korman teaches to use subtherapeutic doses to limit the potential toxicity of the combination. EX1006, 66 (“In another embodiment, the

present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, comprising administering an anti-PD-1 antibody and a subtherapeutic dose of anti-CTLA-4 antibody to a subject”), 72.

81. Second, in my opinion, a POSA would not have been motivated by “the sequentially later mechanistic action of anti-PD-1 relative to anti-CTLA-4 in blocking the T-cell ‘off signal’ to kill cancer cells,” to formulate a method of treatment administering anti-PD-1 and anti-CTLA-4 antibodies as in Ground 2. This statement, taken from EX1010 (“Fife”), was not discussing cancer or methods of treating cancer. It is a general statement about the role that PD-1 and CTLA-4 play in the immune system. Fife “examines the role of CTLA-4 and PD-1 in limiting autoreactivity and establishing peripheral self-tolerance with the hypothesis that CTLA-4 signals are required early in the lymph node during initiation of an immune response and PD-1 pathways act late at the tissue sites to limit T-cell activity.” EX1010, 166. The Petition does not explain how Fife’s discussion of peripheral tolerance and autoimmunity would have been relevant to a POSA developing specific dosing regimens to be used in methods of treating cancer with anti-PD-1 and anti-CTLA-4 antibodies.

82. Additionally, the statement in Fife does not account for the continuous nature of immune responses. The immune system is dynamic and constantly

cycling. There are continually new T cells being generated within lymph nodes and effector cells dying within tumors, so even if one receptor acts early and another acts later within one immunity cycle, different cells in the immune system will be at different points in the response. The Petition does not account for the fluidity of the immune response. Furthermore, this theory also does not account for the effect that the initial combination therapy would have had on the overall state of the immune system that could impact its response to subsequent monotherapy. As such, dosing information from standalone monotherapy such as Wolchok or Sznol may not predict effects of the monotherapy phase after combination immunotherapy which would be expected by POSA to have altered the overall state of the immune system.

83. The Petition also refers to NCT-231 as disclosing a “ ‘combination followed by anti-PD-1 alone’ format.” Pet., 58. In my opinion, a POSA would not have arrived at Ground 2 methods by looking at NCT-231. The protocol in NCT-231 involves staged dosing of combination therapy with an induction phase and a maintenance phase where the combination of an anti-PD-1 antibody and anti-CTLA-4 antibody are administered in both phases. EX1005, 4. Although the induction phase includes administering the anti-CTLA-4 antibody once every three weeks for four doses and the anti-PD-1 antibody once every three weeks for eight doses, it is followed by the maintenance phase where the patient is again administered combination therapy. EX1005, 4. This is a different design than the “format” in the

Ground 2 claims which do not include subsequent administrations of the combination of an anti-PD-1 and anti-CTLA-4 antibody, but rather monotherapy of anti-PD-1 antibody alone.

## 2. Biweekly Dosing

84. The Petition states that “A POSA would have had reason to continue administering anti-PD-1 antibody as a monotherapy even after completion of the combination and would have looked to existing reports of success with anti-PD-1 as a monotherapy, **such as the bi-weekly dosing reported by Sznol.**” Pet., 58. I disagree that a POSA would view existing reports of success with anti-PD-1 as a monotherapy, such as the bi-weekly dosing reported in Sznol to be sufficient prior information when developing combination therapy methods for treatment with anti-PD-1 and anti-CTLA-4 antibodies.

85. Sznol reports preliminary results for the first 16 patients treated in a Phase 1 OPDIVO monotherapy trial. EX1009. Although Sznol observes some anti-tumor activity in 6 of the 16 patients it reports, Sznol does not reach any definitive conclusions regarding anti-PD-1 monotherapy dosing or frequency. The ultimate conclusion reached in Sznol is that further study of anti-PD-1 monotherapy was warranted. EX1009. A POSA would not have administered the anti-PD-1 antibody alone biweekly following anti-PD-1/anti-CTLA-4 combination therapy based on a preliminary report from a Phase 1 trial with limited patient data like Sznol.

86. The Petition also points to Korman's disclosure of biweekly dosing. Pet., 58 (citing EX1006, 55). Korman states that exemplary treatment regimens include administering antibodies anywhere from once per week to once every three to six months, and identifies "preferred dosage regimens" for monotherapy as "(i) every four weeks for six dosages, then every three months; (ii) every three weeks; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks." EX1006, 55.

87. In my opinion, a POSA would not have understood Korman to suggest that anti-PD-1 antibodies should be given on a biweekly basis when administered alone subsequent to combination therapy. The quoted passage from Korman discusses anti-PD-1 monotherapy and provides a wide range of possible dosages. The list of preferred dosages does not include biweekly dosing. And Korman does not disclose a method of treatment in which anti-PD-1 antibodies are administered alone subsequent to combination treatment with anti-PD-1 and anti-CTLA-4 antibodies.

### **3. Motivation to Combine**

88. The Petition states that a POSA would have had reason to combine Korman, Wolchok, and Sznol to arrive at the Ground 2 claims with a reasonable expectation of success. It is my opinion that the Petition fails to address several factors that a POSA would need to consider and account for before reaching any

conclusion regarding how or if a motivation existed to combine Korman, Wolchok, and Sznol to arrive at the Ground 2 claims.

89. The anti-PD-1 and anti-CTLA-4 antibodies administered in Claim 5 are checkpoint inhibitors. Checkpoint inhibitors function by blocking immune signaling pathways to alter a patient's immune response. As a result, there is a possibility that when checkpoint inhibitors are administered together, the toxicity and/or efficacy of the inhibitors may be different than what has been observed when the inhibitors are administered alone. EX1030, 4275-76. This will influence the dose and frequency a POSA would have selected for both combination therapy and monotherapy following combination therapy.

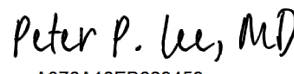
90. Additionally, a POSA would have been aware that the initial combination therapy step of administering anti-PD-1 and anti-CTLA-4 antibodies would have generated an immune response in the patient that could enhance the toxicity or reduce the efficacy of any subsequently administered composition, including anti-PD-1 antibodies. EX1030, 4275-76; EX1040, 715. And that knowledge would have influenced a POSA's decision-making.

I declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like

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

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Dated: 07/10/2025

Signed by:  
  
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\_\_\_\_\_  
Peter P. Lee, M.D.