

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner

IPR2025-00602
Patent No. 10,174,113

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. 10,174,113 (the '113 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 April 28, 2016.

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*. EX2023. 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-PD1, anti-PDL1, anti-CTLA4, 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-PD1, anti-PDL1, anti-CTLA4 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 '113 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. 10,174,113
EX1002	Prosecution History of U.S. Patent No. 10,174,113
EX1003	Declaration of Dr. Brent Hanks M.D., Ph.D.
EX1005	Postow et al., <i>Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma</i> , N Engl J Med., 2015 May 21; 372(21):2006-17.
EX1007	NCT01968109 Version 1, Brief Title: “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors” (Last Update Posted to clinicaltrials.gov: October 23, 2013)
EX1008	Wang et al., Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. <i>J Clin Pharmacol.</i> 2009 Sep; 49(9):1012-24.

EX1014	NCT01844505 Version 1, Brief Title: “Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma” (Last Update Posted to clinicaltrials.gov: May 1, 2013)
EX2001	U.S. Patent No. 9,856,320
EX2002	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 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
EX2003	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 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
EX2004	YERVOY, FDA Approved label and prescribing information, Rev. 5/2025
EX2005	OPDIVO, FDA Approved label and prescribing information, Rev. 5/2025
EX2008	Press Release, Amgen, <i>Amgen Reports First Quarter 2025 Financial Results</i> (May 1, 2025), available at https://www.amgen.com/newsroom/press-releases/2025/05/amgenreports-first-quarter-2025-financial-results
EX2023	Curriculum Vitae of Peter P. Lee, M.D.
EX2024	U.S. Food and Drug Administration, <i>The Drug Development Process, Step 3: Clinical Research</i> (Content current as of Jan. 4, 2018), available at https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

EX2025	Umscheid, C.A. et al. <i>Key Concepts of Clinical Trials: A Narrative Review</i> , Postgraduate Medicine, 2011 Sep; 123:5, 194-204
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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 no later than April 28, 2016 for the ’113 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 Amgen's expert Dr. Hanks 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, and at least two years of experience in the field of cancer immunotherapy, including experience with melanoma treatments. The levels of education, experience and knowledge described above can trade off against one another. A POSA would also have either been skilled in pharmacokinetics or able to communicate as part of a team with pharmacokinetics experts if necessary. A POSA would also have been capable of understanding and applying the teachings of the '113 patent and the prior-art references discussed in this declaration—including understanding literature regarding clinical trials for melanoma." EX1003, ¶41.

22. I have not been asked to take a position on whether I agree with Dr. Hanks'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. Hanks.

23. By April 28, 2016, I met and exceeded Dr. Hanks's level of skill of a POSA. 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. Hanks'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 April 28, 2016.

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 '113 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 '113 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. “The 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.” EX2001, 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. EX2001, 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.” EX2001, 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. EX2001, 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. EX2025, 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”); EX2024, 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. EX2025, 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. EX2024, 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. EX2024, 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.” EX1008, 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. EX2024, 3-4. A Phase 2 trial may last several months to two years. EX2024, 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. EX2025, 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. EX2024, 4; EX2025, 197. According to the FDA, only about 33% of drugs that enter Phase 2 trials proceed to Phase 3 trials. EX2024, 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. EX2025, 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. EX2024, 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.” EX1008, 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. EX2024, 5.

V. THE '113 PATENT

41. I have reviewed the '113 Patent, including the claims and the specification, and summarize some of the key points below.

42. The '113 Patent, titled “Treatment of PD-L1-Negative Melanoma Using an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody,” issued on January 8, 2019 and names Dr. Arvin Yang as inventor. EX1001.

43. The '113 Patent has two independent claims, claims 1 and 2.

44. Claim 1 is a method of treatment for melanoma that has multiple parts:

1. A method for treating a melanoma tumor in a human patient in need thereof comprising:

(i) identifying a patient having a PD-L1-negative melanoma tumor; and

(ii) administering to the patient:

(a) about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 (“an anti-PD-1 antibody”) and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 (“an anti-CTLA-4 antibody”) every three weeks for about 4 doses; followed by

(b) a dose of the anti-PD-1 antibody, wherein the dose in (b) is a flat dose of about 240 mg or about 480 mg.

45. Claim 2 is also a method of treatment for melanoma that has multiple parts, and does not include the step of “identifying a patient having a PD-L1-negative melanoma tumor”:

2. A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient:

- (a) about 1 mg/kg of an antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 (“an anti-PD-1 antibody”) and a dose of an antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 (“an anti-CTLA-4 antibody”) every three weeks for about 4 doses; followed by
 - (b) a dose of the anti-PD-1 antibody,
- wherein the dose in (b) is a flat dose of about 240 mg or about 480 mg.

46. Both claims 1 and 2 provide a multi-part treatment regimen. In the first part, patients receive a combination of an anti-PD-1 antibody (like OPDIVO® (nivolumab)) and an anti-CTLA-4 antibody (like YERVOY® (ipilimumab)). In that combination, the anti-PD-1 antibody doses are based on the patient’s weight. This is followed by the second part of the regimen, where patients receive the anti-PD-1 antibody at “a flat dose of about 240 mg or about 480 mg.”

47. As described in the ’113 Patent, the flat dose is “administered to a patient without regard for the weight or body surface area (BSA) of the patient”—i.e., every patient gets the same amount. EX1001, 7:52-55.

48. The '113 Patent also has several dependent claims. I understand that dependent claims include all of the limitations in the claims to which they refer and add the additional elements of the dependent claim.

VI. SUMMARY OF THE ASSERTED PRIOR ART

A. NCT-505

49. NCT-505 is a printout of the study details for clinical trial NCT01844505, version 1, entitled “Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma.” EX1014, 3. The record states that it was last updated May 1, 2013. EX1014, 3. The stated purpose of the study was “to show that Nivolumab and/or Nivolumab in combination with Ipilimumab will extend survival compared to Ipilimumab alone.” EX1014, 4. The primary outcome measured was overall survival. EX1014, 5. Amgen points to the dosing in Arm B, where nivolumab was administered at a weight-based dose of 1 mg/kg is combined with ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab monotherapy at 3 mg/kg every 2 weeks. EX1014, 4. NCT-505 does not suggest flat dosing and does not describe the impact of body weight on the treatment.

B. Postow

50. Postow is a publication in the New England Journal of Medicine entitled, “Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma.”

EX1005, 2006. The article lists publication dates of April 20, 2015 and May 21, 2015. EX1005, 2006. Postow reports “the results of a randomized, double-blind trial comparing nivolumab in combination with ipilimumab with standard-of-care ipilimumab monotherapy as a first-line treatment in patients with advanced melanoma.” EX1005, 2007. The primary end point was objective response. EX1005, 2008.

51. Certain patients in the Postow study received nivolumab at a weight-based dose of 1 mg/kg combined with ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab monotherapy at 3 mg/kg every 2 weeks. EX1005, 2006. Postow does not suggest flat dosing and does not describe the impact of body weight on the treatment.

C. NCT-109

52. NCT-109 is a printout of the study details for clinical trial NCT01968109, version 1, that states that it was last updated October 23, 2013. EX1007, 4. The study in NCT-109 is entitled “A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors.” EX1007, 4. The Brief Summary in NCT-109 states that the objective of the study is “[t]o assess the safety and tolerability, characterize the dose-limiting

toxicities, and identify the maximum tolerated dose of BMS-986016 alone and in combination with Nivolumab in subjects with select advanced (metastatic and/or unresectable) solid tumors and to provide preliminary information on the clinical benefits of the combination.” EX1007, 4. In the first arm of the study, the anti-LAG-3 antibody (BMS-986106) is administered on its own:

Experimental: Part A-Dose Escalation: BMS-986016

BMS-986016 20, 80, 240, and 800 mg solution intravenously, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

EX1007, 5. In the second and third arms, the anti-LAG-3 antibody is administered in combination with the anti-PD-1 antibody (BMS-936558, nivolumab):

Experimental: Part B-Dose Escalation: BMS-986016 + BMS-936558

BMS-986016 3, 20, 80, and 240 mg solution + BMS-936558 80 and 240 mg solution intravenously, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

Experimental: Part C-Cohort Expansion: BMS-986016 + BMS-936558

BMS-986016 + BMS-936558 at doses selected in Part B, during each 8 week cycle: every 2 weeks (i.e. during weeks 1, 3, 5, 7), up to 96 weeks

EX1007, 5. NCT-109 does not report any testing of an anti-PD-1 antibody as a monotherapy.

53. The dose escalation of anti-LAG-3 antibody with and without anti-PD-1 antibody was also described in the Korman patent application (EX1002, 161-250), entitled “Combination of Anti-LAG-3 Antibodies and Anti-PD-1 Antibodies to Treat Tumors.” Korman describes the same treatment arms as the NCT-109 document:

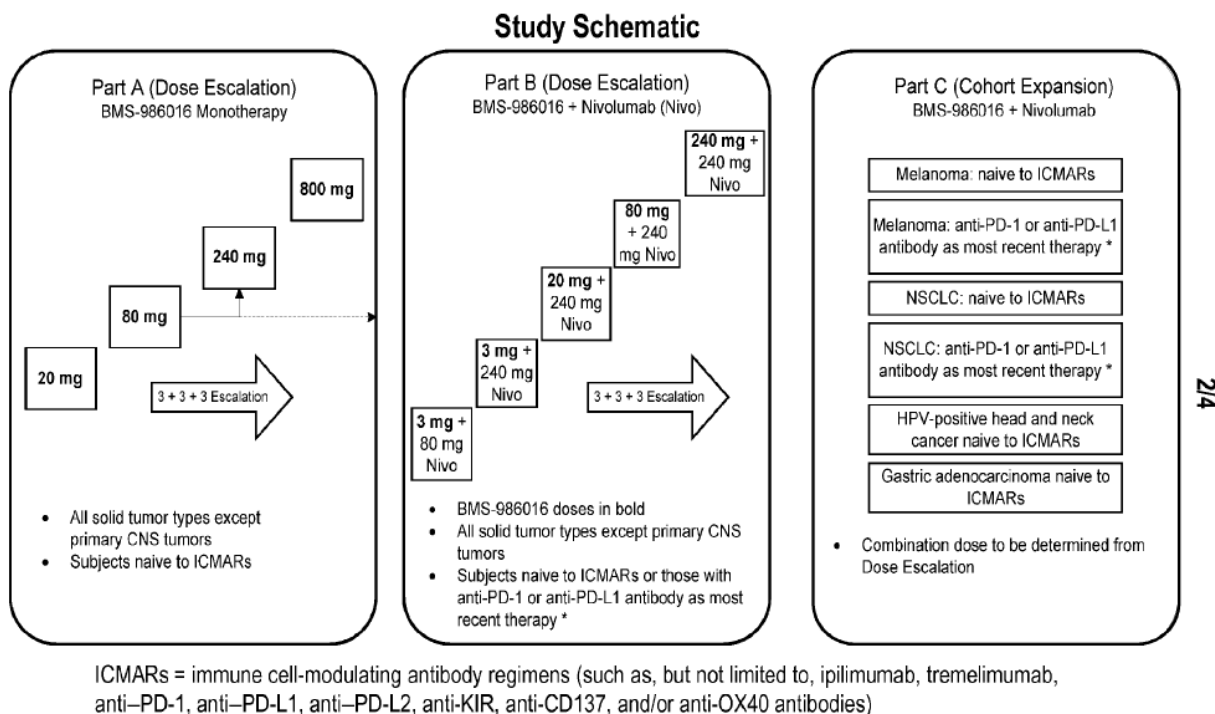


Fig. 2A

EX1002, 248, Fig. 2A. Korman goes on to describe the reasons for testing the combination of anti-LAG-3 and anti-PD-1 antibodies. First, “BMS-986016 [anti-LAG-3 antibody] has the potential to augment the frequency and severity of previously described adverse events associated with BMS-936558 [nivolumab], or to produce new toxicities.” EX1002, 202. Thus, “[t]he primary objective of the study is to assess the safety and tolerability of BMS-986016 [anti-LAG-3 antibody]

given in combination with BMS-936558 [nivolumab] and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination, in subjects with advanced solid tumors.” EX1002, 195.

VII. OPINIONS REGARDING PATENTABILITY OF THE CLAIMS

54. I have been asked to respond to certain arguments raised in the Petition with respect to the use of NCT-109 in combination with NCT-505 or Postow, combinations which Amgen relies on for every ground in its Petition.

55. I have considered the arguments presented by Amgen and its expert Dr. Hanks to suggest that the POSA would have been motivated to modify the regimens described in NCT-505 or Postow based on combining them with the anti-LAG-3/anti-PD-1 combination being tested in NCT-109.

56. For the reasons described below, I disagree that the POSA would have been motivated to modify NCT-505 or Postow based on NCT-109. I also disagree that NCT-505 provides any basis for a reasonable expectation of success for the proposed combinations of NCT-505 or Postow with NCT-109.

57. As described above, the only use of anti-PD-1 antibodies described in NCT-109 is in combination with anti-LAG-3 antibodies. NCT-109 does not disclose anti-PD-1 monotherapy. Thus, there is no basis in NCT-109 for what the dose would be for an anti-PD-1 antibody monotherapy.

58. Amgen suggests that the 240 mg dose of anti-PD-1 antibody used in combination with anti-LAG-3 antibody in NCT-109 would have been used by a POSA to modify NCT-505 and Postow. I have reviewed Amgen's Petition, and I find no explanation at all for why the dose of anti-PD-1 antibody in combination with anti-LAG-3 antibody would be understood to be appropriate for anti-PD-1 monotherapy.

59. I have considered the statement from Amgen's expert Dr. Hanks that: POSAs would have understood that a 240 mg nivolumab dose would have been appropriate for a monotherapy as well because nivolumab and BMS-986016 have different mechanisms of action, binding to different targets, and thus a suitable dose of nivolumab in the combination therapy disclosed by NCT-109 would also have been considered a suitable dose for administering nivolumab alone.

EX1003, ¶89.

60. I disagree with Dr. Hanks for the reasons set forth below.

61. First, the antibodies described in NCT-109 have related immunomodulatory effects, even though they bind to different molecular targets, LAG-3 and PD-1. Nivolumab (anti-PD-1) and BMS-986016 (anti-LAG-3) both target immune checkpoint molecules to modulate the immune response. They share this immunomodulatory function, even though they bind to different target

molecules. A POSA would not have understood that a suitable dose for nivolumab administered in combination with the anti-LAG-3 antibody would necessarily be a suitable dose for nivolumab administered alone, particularly when following treatment with a different combination of antibodies (anti-PD-1/anti-CTLA-4) because each combination of antibodies is going to have a different cumulative effect on the immune system and the patient's immune state may be altered by the combination of antibodies.

62. LAG-3 had been reported to play an important role in negatively regulating T cell activation and proliferation. EX1002, 162. The action of LAG-3 was linked to the exhaustion of T cells, which interferes with their ability to respond to an immune challenge. EX1002, 163. "Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity." EX1002, 163. Antibodies that block CTLA-4, PD-1, or LAG-3 can remove the inhibition, releasing the brake on T cell activity.

63. Both anti-PD-1 and anti-LAG-3 antibodies interfere with the inhibitory mechanisms that, without treatment, can lead to tumors evading the immune system. But how these antibodies may interact *in vivo* and what would be the optimal dosages and frequencies for the combined usage were unclear. Each different combination

of checkpoint inhibitors may have a different cumulative effect on the immune system than any individual checkpoint inhibitor administered alone. Dr. Hanks points to their “different mechanisms of action” as support for why a dosage would be the same for combination therapy and monotherapy, but he never accounts for what those differences are or how they impact the immune response in the context of combination or monotherapy. Dr. Hanks is incorrect when he suggests that the dosing of anti-PD-1 would be interchangeable between monotherapy and combination treatments simply because anti-LAG-3 and anti-PD-1 antibodies bind to different target molecules.

64. The POSA would not have considered the doses being explored in the dose escalation study in NCT-109 to necessarily be suitable for use of nivolumab alone. The protocol in NCT-109 is a Phase 1 dose escalation study, meaning that the suitable dose was not known for the combination of anti-LAG-3 and anti-PD-1 antibodies that were the subject of the study. The 240 mg flat dose was not known to be suitable, even for the combination. Other cited studies (including NCT-505 and Postow) used weight-based dosing for anti-PD-1 antibodies. In addition, a POSA would have understood that one cannot simply import the dose from a combination therapy into a different treatment protocol where the antibody is given as a monotherapy following a different combination therapy.

65. The dose escalation study described in NCT-109 specifically tested not only the new anti-LAG-3 antibody, but also the combination of the anti-LAG-3 antibody with various doses of anti-PD-1 antibody. The impact of the combination was not known ahead of time, and the doses that had been previously used for anti-PD-1 antibodies were not just assumed to be suitable for the combination. As Korman states, “BMS-986016 [anti-LAG-3 antibody] has the potential to augment the frequency and severity of previously described adverse events associated with BMS-936558 [nivolumab], or to produce new toxicities.” EX1002, 202. “The primary objective of the study is to assess the safety and tolerability of BMS-986016 [anti-LAG-3 antibody] given in combination with BMS-936558 [nivolumab] and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination, in subjects with advanced solid tumors.” EX1002, 195.

66. Dr. Hanks is incorrect to suggest that a dose that is suitable for “administering nivolumab alone” would necessarily be suitable for use in the claimed invention. The first part of the claimed treatment regimen uses a combination of anti-CTLA-4 and anti-PD-1 antibodies for multiple rounds of treatment. The anti-CTLA-4/anti-PD-1 antibody combination treatment impacts the immune system in ways that the POSA would have understood could be durable even after the anti-CTLA-4 antibody is no longer administered. The earlier rounds

of combination treatment could then affect the safety and efficacy of doses of anti-PD-1 antibody monotherapy in the subsequent treatment rounds.

67. The POSA would not have been motivated to modify the anti-PD-1/anti-CTLA-4 combination treatments in NCT-505 or Postow based on combining them with NCT-109. As described above, NCT-109 presents a dose escalation study for anti-LAG-3 antibody with and without anti-PD-1 antibody. The appropriate dose for the combination of anti-LAG-3 and anti-PD-1 antibody was not known, and NCT-109 provides no teaching about what the suitable dose would have been. The purpose of the dose escalation study was to try to determine a possible dose. The potential toxicities of the combination were unknown, and would have influenced the selection of the doses for study. The right dose was not known to the POSA from NCT-109.

68. The dose of anti-PD-1 antibody in combination with anti-LAG-3 antibody would not have been known to be suitable for use in a multi-part treatment regimen where anti-CTLA-4 and anti-PD-1 antibodies are used in combination for multiple rounds, followed by anti-PD-1 antibody alone. The POSA would have understood that the potentially durable effect of the anti-CTLA-4 antibody on the immune system would have impacted the safety and efficacy of the following anti-PD-1 antibody treatment, even after the anti-CTLA-4 antibody was no longer being

administered. The POSA would not have been motivated to substitute the dosing of NCT-109 into the second part of the regimens of NCT-505 or Postow.

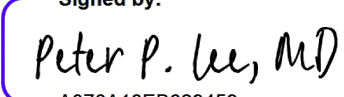
69. The POSA would also not have had a reasonable expectation of success. Again, the dose escalation study in NCT-109 is designed to test increasing doses to find out what the suitable dose was. The POSA would not have understood that there was any reasonable expectation that one of the doses would be successful. Also, the POSA would not have a reasonable expectation that a substitution of dosing from an anti-LAG-3/anti-PD-1 antibody treatment would be successful to use in a PD-1 antibody monotherapy regimen that followed a combination anti-CTLA-4/anti-PD-1 antibody regimen. For the reasons described above, the effects of those combinations would not have been predictable. Thus, the POSA would have had no reasonable expectation of success in making the modifications that Amgen proposes.

70. Amgen is proposing to start with weight-based treatment regimens, in NCT-505 and Postow, that were Phase 3 clinical protocols using anti-CTLA-4 and anti-PD-1 antibodies, and to modify those protocols based on a Phase 1 dose escalation study for anti-LAG-3 antibodies in combination with anti-PD-1 antibodies. Based on the actual content of NCT-109, as described above, the POSA would not be motivated to make that modification and would not have a reasonable expectation of success in the modified protocol.

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.