

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY,
Patent Owner.

Case No. IPR2025-00602
Patent No. 10,174,113

DECLARATION OF BRENT HANKS M.D., PH.D.

Amgen Exhibit 1003 Amgen v. BMS

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I, Dr. Brent Hanks, M.D., Ph.D., declare:

I. INTRODUCTION

1. I have been retained by counsel to render certain opinions as an expert witness, for the above-referenced inter partes review (“IPR”) proceeding regarding U.S. Patent No. 10,174,113 (“the ’113 patent”). In connection with my analysis, I have reviewed the ’113 patent (EX1001), its file history (EX1002), and the documents listed in Appendix A to this Declaration. I have been asked to provide a declaration regarding my opinions on the validity of claims 1-20 (the “Challenged Claims”) of the ’113 patent.

2. This declaration sets forth the opinions I have formed in this IPR and provides the bases and reasons for those opinions. I have summarized my educational background, professional experience, and publications herein and have attached my complete curriculum vitae, labeled as EX1004.

3. This report is based on information currently available to me. I declare that I have personal knowledge of the facts set forth in this declaration and, if called to testify as a witness, could and would do so competently.

4. I am being compensated at my usual consulting rate, plus actual expenses, for my work on this matter. My compensation is in no way dependent upon my opinions or testimony or the outcome of this proceeding. My analysis

here is based on my years of education, research, and experience, as well as my investigation and study of relevant materials, including those cited herein.

II. SUMMARY OF OPINIONS

5. I have been asked to provide my opinion concerning whether claims 1-20 of the '113 patent ("Challenged Claims") would have been obvious to a POSA in light of the prior-art references identified in the Petition. For the reasons explained below, it is my opinion that each of claims 1-20 would have been obvious to a POSA, as set forth below:

Ground Number and Reference(s)		Claim(s)	Basis
1A	NCT-505 and NCT-109	1-4, 10, 13-15, and 19-20	§103
1B		11 and 17	
1C		12 and 18	
2	NCT-505, NCT-109, and Cogswell	5-9 and 16	
3A	Postow and NCT-109	1-6, 9-10, 13-15, and 19-20	
3B		11 and 17	
3C		12 and 18	
4	Postow, NCT-109, and Cogswell	5-9 and 16	

III. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

6. A description of my professional background and qualifications is provided below. An additional account of my work experience and qualifications is included in my curriculum vitae, which is labeled as Exhibit 1004.

7. I earned my bachelor's degree in Chemistry and Biology from Southwestern University, graduating Magna Cum Laude. I earned my M.D. and Ph.D. at Baylor College of Medicine. My Ph.D. is in the field of Tumor Immunology. I did my internship and residency in internal medicine and my fellowship training in the field of Medical Oncology/Hematology at Duke University Medical Center.

8. Following my fellowship in 2012, I continued on at Duke University Medical Center as an Assistant Professor (Tenure Track) in the Duke Cancer Institute, Department of Internal Medicine, Division of Medical Oncology. In 2018, I also became an Assistant Professor in the Department of Pharmacology and Cancer Biology at Duke University. In 2019, I was named Associate Director, Basic and Translational Research, at the Duke Center for Cancer Immunotherapy. In 2020, I was promoted to Associate Professor at the Duke Cancer Institute.

9. In February 2025, I became an Associate Professor with Tenure in the Department of Medicine, Division of Medical Oncology and the Department of Microbiology and Immunology at the University of North Carolina Lineberger Cancer Center, a position I still hold today.

10. My research focuses on understanding how tumors develop resistance to the immune system and why select tumors are resistant to checkpoint inhibitor immunotherapies. More specifically, my work investigates tumor-intrinsic

signaling pathways that drive adaptive resistance to checkpoint inhibitor immunotherapies as well as signaling pathways that tumors utilize to suppress dendritic cell-dependent antigen cross-presentation and the activation of tumor antigen-specific T cell responses. Finally, my lab also conducts studies to understand underlying mechanisms of certain immune-related adverse events associated with checkpoint inhibitor immunotherapies in cancer patients. This work involves studying the treatment and response of genetically engineered tumor models to immunotherapy as well as examining clinical specimens harvested from cancer patients undergoing immunotherapy. The primary objectives of my work are to discover and validate novel pharmacologic targets to overcome immunotherapy resistance, identify those tumors more likely to be sensitive to tailored immunotherapy regimens, and to develop more effective management strategies for select immune-related adverse events.

11. My research and findings have been published in over 50 articles published by numerous renowned peer-reviewed journals, including *Nature Cancer*, *Nature Medicine*, *Cancers*, *Cancer Research*, *Clinical Cancer Research*, *Immunity*, *Cancer Medicine*, *Journal of Immunotherapy*, *Journal of Immunotherapy of Cancer*, *Journal of Gastrointestinal Cancer*, *Journal of Clinical Investigation*, *Science Translational Medicine*, *Cell Reports*, *International Journal*

of Immunology, Journal of Clinical Oncology, Cancer Immunology Research, and Discovery Medicine, among others.

12. I authored the book chapter “Immune Checkpoint Combinations with Inflammatory Pathway Modulators” in *Cancer Immunotherapy* (2017).

13. I am a named inventor of U.S. Patent No. 10,617,749 (titled “Composition of matter and methods for alteration of dendritic cell metabolism to augment cancer vaccine efficacy”) and am a named inventor of several other pending patent applications.

14. I have received a number of awards recognizing my teaching and scholarship. For example, I was awarded a R37 MERIT Award by the National Cancer Institute in 2020, an Advanced Clinical Research Award in Tumor Immunotherapy by the American Society of Clinical Oncology/Conquer Cancer Foundation in 2021, and a Mid-Career Accelerator Award from the Department of Defense Melanoma Research Program in 2024. In 2024, I was also elected to the American Society for Clinical Investigation.

15. I am board-certified in internal medicine and am a licensed physician in North Carolina.

IV. MATERIALS REVIEWED AND CONSIDERED

16. My findings, as explained below, are based on my years of education, research, experience, and background in the field of tumor immunology and

immunotherapy, as well as my investigation and study of relevant materials for this declaration. When developing the opinions set forth in this declaration, I assumed the perspective of a person having ordinary skill in the art, as set forth in Section V.B below. In forming my opinions, I have studied and considered the materials identified in Appendix A. This includes the February 26, 2025 Declaration of Dr. Dhaval K. Shah, who I understand to be an expert in clinical pharmacology and pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.

17. In this declaration, citations to issued patents are made by column and line number. Citations to patent application publications are made by paragraph number. Citations to all other exhibits are to the original page number (to the extent one exists) or otherwise to the page number added by the exhibit label.

V. UNDERSTANDING OF THE APPLICABLE LEGAL STANDARDS

18. I understand that there are a number of legal principles that are involved in assessing the proper construction of the claims of a patent and evaluating the validity of claims of a patent. I am not, however, an attorney. I have therefore relied upon the legal principles that Petitioner's attorneys have provided and explained to me. Below is my understanding of those legal principles, which I have applied in my analysis contained in this declaration.

A. Burden of Proof

19. I understand that “*inter partes* review” (IPR) is a proceeding before the United States Patent & Trademark Office for evaluating the patentability of an issued patent’s claims based on prior-art patents and printed publications.

20. I understand that, in this proceeding, Petitioner has the burden of proving that the challenged claims of the ’113 patent are unpatentable by a preponderance of the evidence. I understand that “preponderance of the evidence” means that a fact or conclusion is more likely true than not true.

B. Person of Ordinary Skill in the Art (“POSA”)

21. I understand that both the interpretation of the claims of a patent and the scope of the prior art are evaluated from the vantage point of a POSA at the time of the alleged invention. I understand that a POSA is a hypothetical person who is presumed to be aware of all prior art pertinent to the relevant field. I further understand that a POSA is a person of ordinary creativity—not a mere “automaton.”

22. I understand that factors that may be considered in determining the level of ordinary skill in the art may include: (A) type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and (E) educational

level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.

C. Interpretation of Claims

23. I understand that, in IPR proceedings, claim terms in a patent are given their ordinary and customary meaning as understood by a POSA in the context of the entire patent and the prosecution history pertaining to the patent. If the specification provides a special definition for a claim term that differs from the meaning the term would otherwise possess, the specification's special definition controls. I have applied these standards in preparing the opinions in this declaration.

D. Prior Art

24. I understand that determining whether a particular patent or printed publication constitutes prior art to a challenged patent claim can require determining the effective filing date (also known as the priority date) to which the challenged patent claim is entitled.

25. I understand that the prior art available in an IPR includes printed publications published before the effective filing date of the claimed invention. I understand that a reference qualifies as a "printed publication" if it was publicly accessible as of the effective filing date, meaning that the reference was disseminated or otherwise made available such that a POSA, exercising reasonable

diligence, would have been able to access it. For publication via the Internet, factors that may be relevant to public accessibility include whether the website is searchable or indexed and whether the reference was published on a website well known to POSAs. I understand that it is not necessary to show that a reference was actually retrieved or read.

E. Validity of a Patent

26. I understand that for an invention claimed in a patent to be patentable, it must be, among other things, new (novel—*i.e.*, not anticipated) and not obvious in view of the prior art.

1. Anticipation

27. I understand that, for a patent claim to be “anticipated” by the prior art (and therefore not novel), each and every limitation of the claim must be found, expressly or inherently, in a single prior-art reference that enables practice of the claim. I understand that a claim limitation is disclosed for the purpose of anticipation if a POSA would have understood the reference to disclose the limitation based on inferences that a POSA would reasonably be expected to draw from the explicit teachings in the reference when read in light of the POSA’s knowledge and experience.

28. I understand that a claim limitation is inherent in a prior art reference if that limitation is necessarily present when practicing the teachings of the

reference, regardless of whether a person of ordinary skill recognized the presence of that limitation in the prior art. Further, I understand that the results of prior art processes are inherent to the prior art and newly discovered results of known processes directed to the same purposes are therefore not patentable.

29. In the context of anticipation, I understand that enabling practice of a claim requires the prior art reference to allow a POSA to practice without undue experimentation at least one embodiment falling within the scope of the claim.

2. Obviousness

30. I understand that a patent claim may be unpatentable if it would have been obvious in view of a single prior-art reference or a combination of prior-art references.

31. I understand that a patent claim is obvious if the differences between the subject matter of the claim and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the relevant field at the time the invention was made. Specifically, I understand that the obviousness question involves a consideration of:

- the scope and content of the prior art;
- the differences between the prior art and the claims at issue;
- the knowledge of a person of ordinary skill in the pertinent art; and

- if present, objective factors indicative of non-obviousness, sometimes referred to as “secondary considerations.” These include evidence: that the alleged invention found commercial success for reasons causally related to the alleged invention; that the technical direction followed by those skilled in the art taught away from the approach of the alleged invention; of long-felt but unsatisfied need for the alleged invention; that the alleged invention achieves results that are unexpected to those skilled in the art; that the alleged invention rapidly replaced prior-art devices in the industry; competitors copied the alleged invention; that those skilled in the art unsuccessfully attempted to make the invention; that the industry acquiesced to the patent’s validity by taking licenses or not infringing; of skepticism, disbelief in or incredulity on the part of those skilled in the art that the patentee’s approach worked; and of recognition of alleged invention by technically competent peers. To my knowledge, the Patent Owner has not asserted any such secondary considerations with respect to the ’113 patent.

I understand that in order for a claimed invention to be considered obvious, a POSA must have had a reason for combining teachings from multiple prior-art references (or for altering a single prior-art reference, in the case of obviousness in view of a single reference) in the manner proposed.

32. I further understand that in determining whether a prior-art reference would have been combined with other prior art or with other information within the knowledge of a POSA, the following are examples of approaches and rationales that may be considered:

- combining prior-art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;
- use of a known technique to improve similar devices in the same way;
- applying a known technique to a known device ready for improvement to yield predictable results;
- applying a technique or approach that would have been “obvious to try,” *i.e.*, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;
- some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior-art reference or to

combine prior-art reference teachings to arrive at the claimed invention. I understand that this teaching, suggestion or motivation may come from a prior-art reference or from the knowledge or common sense of one of ordinary skill in the art.

33. I understand that for a single reference or a combination of references to render the claimed invention obvious, a POSA must have been able to arrive at the claimed invention by altering or combining the applied references, and must have had a reasonable expectation of success in doing so. I understand that a reasonable expectation of success refers to the likelihood of success in combining the teachings in references to meet the limitations of the claimed invention, e.g., to achieve the claimed invention. I understand that in evaluating a combination, a predictable result means not only that the prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.

VI. BACKGROUND OF THE '113 PATENT

34. The '113 patent, filed on April 28, 2016, lists U.S. Provisional Application No. 62/153,973 ("973 Provisional", attached as EX1018) as a related application. EX1001 ('113 patent) at p. 1. The '973 Provisional itself was filed on April 28, 2015. *Id.* The '113 patent claims priority to the '973 Provisional (*see id.*

at col. 1, ll. 9-10), but as discussed further in Section VI.D, the claimed methods of claims 1-10, 12-16, and 18-20 are not described by the '973 Provisional.

A. Described Embodiments

35. The '113 patent discloses “a method of treating a melanoma comprising (i) identifying a patient having a PD-L1-negative melanoma and (ii) administering to the patient a combination of an anti-PD-1 antibody or an antigen-binding portion thereof and an anti-CTLA-4 antibody or an antigen-binding portion thereof.” EX1001, Abstract. The '113 patent also discloses another embodiment where the “concurrent regimen comprises ... combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of once about every 2 weeks, at least once about every 3 weeks, or at least once about every 4 weeks, ... for 2, 4, 6 or 8 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once about every 2 weeks, at least once about every 3 weeks, or at least once about every 4 weeks....” EX1001 at 23:26-37.

36. The '113 patent discloses both “weight based” and “flat” dosing of antibodies. EX1001 at 7:66-8:1, 24:15-16. It defines a “*weight based dose*” as “a dose that is administered to a patient [that] is calculated based on the weight of the patient.” EX1001 at 7:66-8:1. For example, “a dose of about 1 mg/kg of an anti-PD-1 antibody” is an example of a weight based dose. EX1001, 23:47-52. To

calculate the amount of anti-PD-1 antibody to administer for a weight based dose of 1 mg/kg, the patient's weight (in kg) would be multiplied by 1 mg/kg. The patent also discloses administering "a *flat dose*," which is "a dose that is administered to a patient without regard for the weight or body surface area (BSA) of the patient." EX1001 at 7:52-55. For example, the '113 patent discloses that "each of the anti-PD-1 antibody with the anti-CTLA-4 antibody may be administered at a flat dose of 20, 50, 75, 80, 160, 200, 240, 300, 360, 400, 480, 500, 750 or 1500 mg, *without regard to the patient's weight*." EX1001 at 24:17-20. Thus, no calculation is required to determine the amount to administer given that the dose is fixed regardless of a patient's characteristics.

37. To the extent that the '113 patent discloses any data, it is limited to the results of weight-based doses. *See* EX1001, 26:44-38:41.

B. The Challenged Claims

38. I understand that all twenty claims are being challenged. I understand that claims 1 and 2 are written in independent form, which I understand means that they stand on their own. I understand that claims 3-20 are all dependent claims and require all of the elements of the claim from which they depend in addition to the added claimed element in the claim itself. I understand that some claims (claim 8, for example) depends on a dependent claim, which means it requires all of the

limitations from all of the claims in the chain of dependencies through to an independent claim.

39. I've listed all twenty claims broken about by individual limitations below with reference numbers in brackets (“[]”) to aid in my analysis later in this declaration:

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

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

[1](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

[1](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.

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

[2](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

[2](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.

- 3.** The method of claim 2, wherein the patient is characterized by (i) extended progression-free survival for over 8 months following the administration, (ii) tumor size reduction at least about 10% compared to the tumor size prior to the administration, or (iii) both (i) and (ii).
- 4.** The method of claim 2, further comprising measuring a PD-L1 expression on the melanoma tumor prior to the administration.
- 5.** The method of claim 4, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.
- 6.** The method of claim 5, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.
- 7.** The method of claim 6, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.
- 8.** The method of claim 7, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2.
- 9.** The method of claim 2, wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.
- 10.** The method of claim 2, wherein the anti-PD-1 antibody is nivolumab.
- 11.** The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.

12. The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
13. The method of claim 2, wherein the anti-CTLA-4 antibody is ipilimumab.
14. The method of claim 2, wherein the dose of the anti-CTLA-4 antibody is from 0.1 mg/kg to 10.0 mg/kg.
15. The method of claim 14, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.
16. The method of claim 2, further comprising administering an anti-cancer agent.
17. The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.
18. The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
19. The method of claim 1, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.
20. The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.

C. Person of Ordinary Skill in the Art (“POSA”)

40. The ’113 patent involves technology in the field of cancer immunology. I have been asked to provide my opinions as to the state of the art in this field as of early 2015. I use this timeframe because the face of the ’113 patent indicates an earliest claimed priority date of April 28, 2015. Whenever I offer an opinion in this declaration about the knowledge of a POSA, the manner in which a

POSA would have understood the claims of the '113 patent or its description, the manner in which a POSA would have understood the prior art, or what a POSA would have been led to do based on the prior art, I am referencing the early 2015 timeframe, even if I do not say so specifically in each case.

41. In my opinion, a person of ordinary skill in the art in early 2015 (“POSA”) 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 the field of 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.

42. By 2015, I had already completed my M.D. and Ph.D. degrees, had completed my residency and fellowship, had been an Assistant Professor at the Duke Cancer Institute for three years, and had over three years of experience in oncology, including immunotherapy for the treatment of melanoma. I, therefore

qualified as a POSA as of 2015, with somewhat more education with my dual M.D. Ph.D. and somewhat more years of experience, having already completed my residency, fellowship, and being three years into my teaching career. I also worked with many people who fit the characteristics of the POSA, and I am familiar with their level of skill. When developing the opinions set forth in this declaration, I assumed the perspective of a person having ordinary skill in the art, as set forth above.

D. The Methods of Challenged Claims 1-10, 12-16, and 18-20 Are Not Disclosed by the '973 Provisional Application

43. Claims 1-10, 12-16, and 18-20 all recite (or depend from a claim reciting) a 480 mg flat dose of an anti-PD-1 antibody as an option or a requirement. But the '973 Provisional does not disclose administering 480 mg of anti-PD-1 antibody and therefore does not support the Challenged Claims reciting 480 mg anti-PD-1 antibody (whether as an option or a requirement).

44. The '973 Provisional nowhere discloses a **480 mg** dose of anti-PD-1 antibody. The '973 Provisional merely discloses doses of the anti-PD-1 antibody of “about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, or about 300 mg.” EX1018 at ¶[0111]. Thus, the highest dose the '973 Provisional discloses is 300 mg for the anti-PD-1 antibody. EX1018 at

¶[0111]. Nowhere does the '973 Provisional disclose an anti-PD-1 antibody dose of 480 mg.

45. While the '973 Provisional uses the word “about” as a word of approximation in, e.g., ¶[0111], the '973 Provisional limits the “acceptable error range” to a maximum of $\pm 20\%$. EX1018 at ¶[0054]. For example, according to the '973 Provisional, “about 3mg can include any number between 2.7 mg and 3.3 mg (for 10%) or between 2.4 mg and 3.6 mg (for 20%).” EX1018 at ¶[0054]. That means the disclosure of “about 300 mg” of anti-PD-1 antibody at most means 360mg (20% more). Thus, even the use of the word “about” provides no disclosure of the **480 mg** dose of anti-PD-1 antibody claimed by the Challenged Claims.

46. The '973 Provisional also discloses administering a flat dose of “20, 50, 75, 80, 160, 200, 240, 300, 400, 500, 750, or 1500 mg” (EX1018 at ¶[0110]), but still nowhere discloses a dose of 480 mg, and does not use the word “about” to encompass variation around the disclosed 400 or 500 mg doses in [0110].

47. Simply put, the '973 Provisional nowhere discloses administering a **480 mg** dose of anti-PD-1 antibody. POSAs would thus not have understood the inventor to have had possession of the claimed methods recited in Challenged Claims 1-10, 12-16, and 18-20 based on the disclosure in the '973 Provisional.

VII. TECHNICAL BACKGROUND

48. Human cancers, including melanoma, often express Programmed Death Ligand-1 (PD-L1), which has been shown to down-regulate T cell activation. That downregulation inhibits the immune system from attacking such cancers. By 2012 (i.e., years prior to early 2015), persons of ordinary skill in the art were aware that anti-PD1 antibodies were effective at fighting PD-L1–positive melanoma by preventing the melanoma from downregulating the immune system. *See* Topalian (EX1011) at p. 2443. But, Topalian (published in 2012) also reported that in that study, “Of 17 patients with ***PD-L1-negative*** tumors, ***none*** had an objective response”, suggesting that anti-PD1 antibodies may not be effective against PD-L1–negative melanoma tumors. *Id.*

49. As early as 2013 (i.e., shortly after Topalian’s publication), clinical trials were underway to see if a combination of nivolumab, an anti-PD1 antibody, and ipilimumab, an anti-CTLA4 antibody, could successfully treat melanoma tumors, including PD-L1–negative melanoma tumors where an anti-PD1 monotherapy may not have been expected to be successful. *See generally* NCT-505, Postow. NCT-505, for example, discloses a clinical trial for treating melanoma using the nivolumab/ipilimumab combination. NCT-505 at p. 4. It was first posted on ClinicalTrials.gov on May 1, 2013 – two years before the provisional application to which the ’113 patent purports to claim priority was

filed. *Id.* at p. 1. By 2015, results showed that administering 1 mg/kg of nivolumab in combination with ipilimumab every three weeks for 4 doses followed by 3 mg/kg nivolumab every two weeks was effective at treating both PD-L1–positive and PD-L1–negative melanoma tumors. For example, Postow, an article published in the New England Journal of Medicine on April 20, 2015, discloses that the above nivolumab/ipilimumab combination and dosing regimen was *successful* in treating both PD-L1–positive and PD-L1–negative melanoma tumors. EX1005 at p. 2009, 2016.

50. Certain publications concerning nivolumab refer to it by code names such as “BMS-936558,” “MDX-1106,” and “ONO-4538.” As of early 2015, persons of ordinary skill in the art would have known that these code names corresponded to nivolumab. *See, e.g.*, EX1014 at 4 (“Nivolumab...Other Names: BMS-936558 [and] MDX-1106”); EX1005, reference 17 (“Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL).”); *see also* EX1009 at 3168 (“MDX-1106 (BMS-936558/ONO-4538) is a genetically engineered, fully human immunoglobulin G4 (IgG4) mAb specific for human PD-1....”). Accordingly, to the extent particular references discussed herein refer to “BMS-936558,” “MDX-1106,” and “ONO-4538,” persons of ordinary skill in the art would have known that these references

were discussing nivolumab even if the reference itself does not expressly refer to “nivolumab” by name. While not necessary for my conclusion, I also note that the ’113 patent confirms the same. See EX1001 at 17:61-67 (“Nivolumab (also known as ... BMS-936558, MDX-1106...) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody....”).

VIII. CLAIM INTERPRETATION

51. With reference to my understanding of the legal framework explained in Section V.C, I am not presently aware of any claim term that a POSA would understand differently than its ordinary and customary meaning.

IX. PRIOR ART REFERENCES

52. I briefly introduce in this Section below various prior-art references discussed in this declaration.

A. NCT-505 (EX1014)

53. NCT-505 is Version 1 of a clinical trial protocol with the Brief Title “Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma.” EX1014 at 3. The “Last Update Posted” date for Version 1 on ClinicalTrials.gov was May 1, 2013. *Id.* I routinely access ClinicalTrials.gov to lookup clinical trials suitable for my own patients and believe POSAs would be familiar with the website for similar reasons, because POSAs understood that the purpose of ClinicalTrials.gov is to provide the

public access to clinical trial information, like NCT-505, as widely and promptly as possible.

54. NCT-505 (Version 1) bears a “Last update posted” date of May 1, 2013. EX1014 at 3. The “Last update posted” date is “[t]he most recent date on which changes to a study record were made available on ClinicalTrials.gov.” EX1019 at 10. By early 2015, POSAs were aware that such clinical trial protocols were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. POSAs routinely used ClinicalTrials.gov as a source of clinical trial information and in particular as a means to readily search for trials of interest. ClinicalTrials.gov had search functionality that facilitated such queries. For example, when searching ClinicalTrials.gov for clinical trials involving “nivolumab/ipilimumab” and “PD-L1” when treating metastatic melanoma, NCT-505 is among the first results returned. A POSA could have readily located NCT-505 on ClinicalTrials.gov by searching for key terms such as melanoma or metastatic melanoma, PD-L1, nivolumab, or ipilimumab. The “Last update posted” date for NCT-505 therefore demonstrates that it was publicly available as of May 1, 2013. I understand and was informed that NCT-505 qualifies as prior art to the ’113 patent.

55. NCT-505 discloses that the “purpose of this study is to show that ... Nivolumab in combination with Ipilimumab will extend progression free survival

and overall survival compared with Ipilimumab alone.” *Id.* at p. 4. NCT-505 discloses that “Nivolumab 1 mg/kg solution” is “combined with Ipilimumab 3 mg/kg” and administered “intravenously every 3 weeks for 4 doses,” then “Nivolumab 3 mg/kg solution intravenously every 2 weeks.” *Id.*

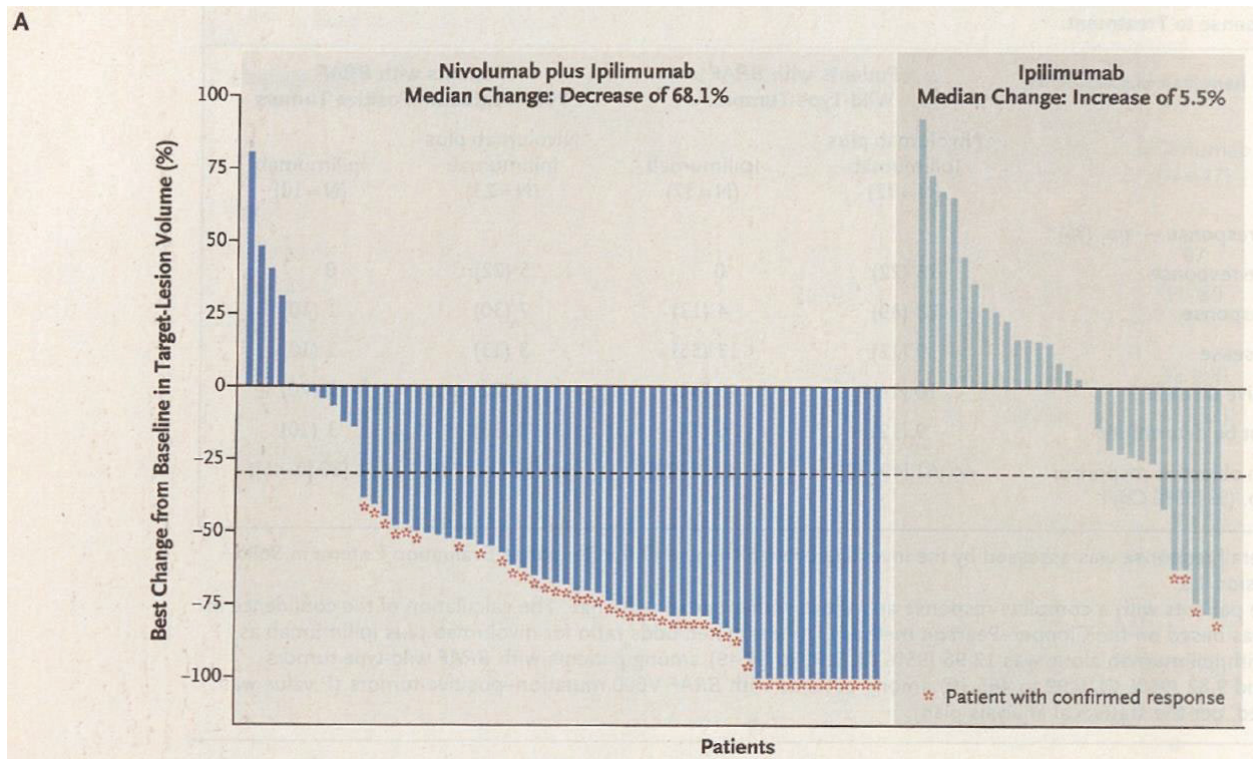
B. Postow (EX1005)

56. Postow is an article entitled “Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma,” published by the New England Journal of Medicine online at NEJM.org on “April 20, 2015.” EX1005 at p. 2006. The New England Journal of Medicine was well-known to POSAs as of early 2015. At the time of Postow’s April 20, 2015, online publication, POSAs were aware that many journals published online and kept abreast of developments of interest by reading articles posted on journal websites. As of early 2015, the New England Journal of Medicine was already recognized as a leading medical journal, and POSAs would have routinely consulted that journal’s website to stay abreast concerning developments in the treatment of melanoma. Additionally, the website of the New England Journal of Medicine was searchable and external search engine website searches would also return NEJM articles. Accordingly, as of the date of its online posting (April 20, 2015), Postow would have been accessible to POSAs seeking information concerning melanoma treatments. I understand and was informed that Postow qualifies as prior art to the ’113 patent.

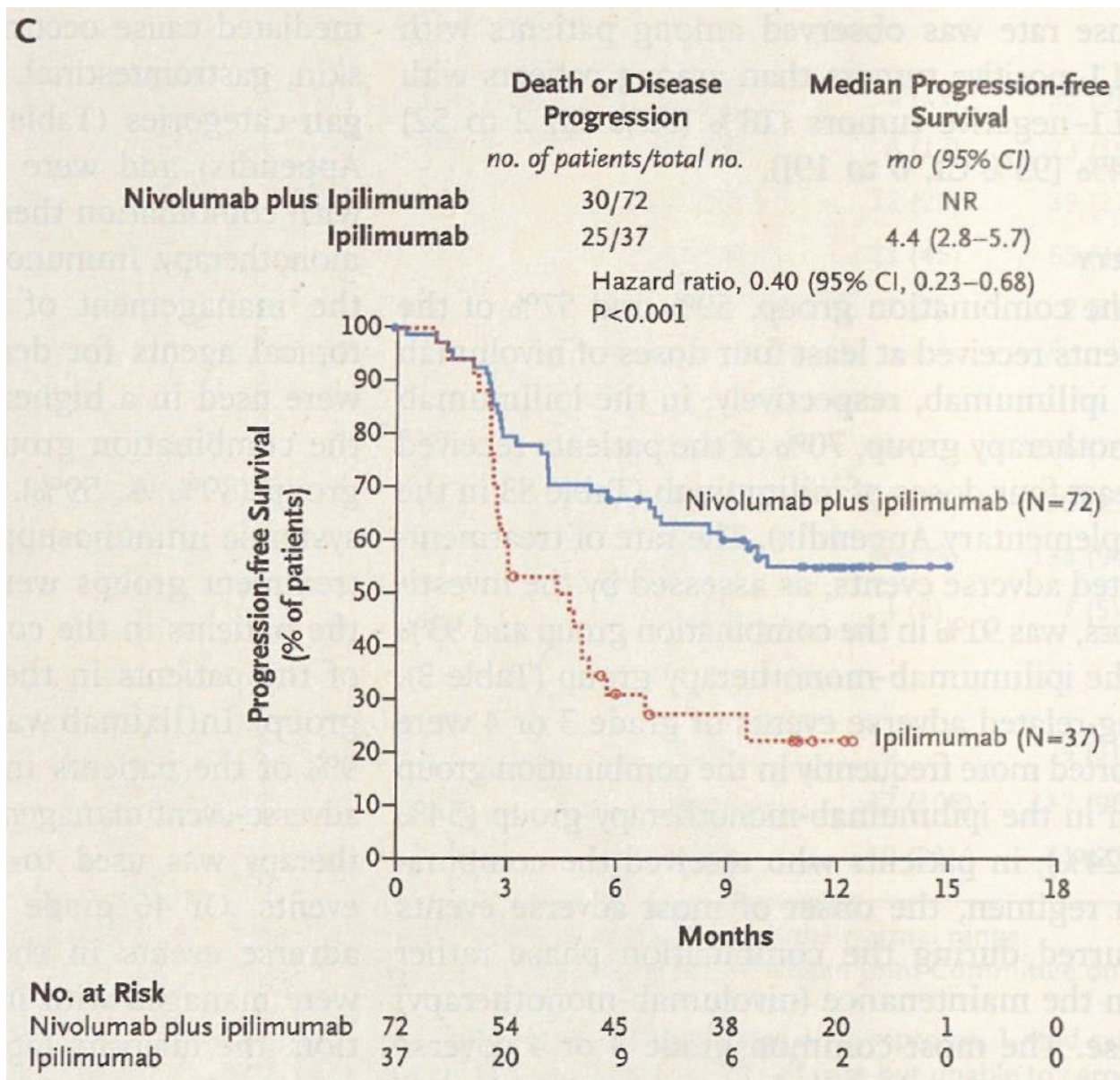
57. Postow discloses the results from a “double-blind study involving 142 patients with metastatic melanoma.” EX1005 at p. 2006. Postow discloses that patients were administered “ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects.” *Id.*

58. Postow discloses that the “median change in investigator-assessed tumor volume was a 68.1% decrease in the combination group,” and a “complete response was observed in 16 patients (22%).” *Id.* at p. 5. “Figure 1A shows the distribution of tumor-burden change from baseline among patients with BRAF

wild-type tumors.” *Id.* (EX1005 at Fig. 1A, reproduced below).



59. Postow discloses that “[i]n the population with BRAF wild-type tumors, the median progression-free survival was not reached with the combination therapy ... (Fig. 1C).” EX1005 at p. 2009 (EX1005, Fig. 1C reproduced below). Postow’s statement that “the median progression-free survival was not reached” means that progression-free survival was achieved for over half the patients over the period of the study.



60. Postow discloses that “[i]n the combination group, the objective response rate was independent of tumor PD-L1 status: 58% (95% CI, 37 to 78) among patients with PD-L1–positive tumors and 55% (95% CI, 41 to 69) among patients with PD-L1–negative tumors (Table S2 in the Supplementary Appendix).” EX1005 at p. 2009 (EX1005, Table 2 reproduced below).

Table 2. Response to Treatment.				
Variable	Patients with <i>BRAF</i> Wild-Type Tumors		Patients with <i>BRAF</i> V600 Mutation-Positive Tumors	
	Nivolumab plus Ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab plus Ipilimumab (N=23)	Ipilimumab (N=10)
Best overall response — no. (%) [*]				
Complete response	16 (22)	0	5 (22)	0
Partial response	28 (39)	4 (11)	7 (30)	1 (10)
Stable disease	9 (12)	13 (35)	3 (13)	1 (10)
Progressive disease	10 (14)	15 (41)	5 (22)	7 (70)
Could not be determined	9 (12)	5 (14)	3 (13)	1 (10)
Patients with objective response — no. (%) [95% CI] [†]	44 (61 [49–72])	4 (11 [3–25])	12 (52 [31–73])	1 (10 [0–45])

* The best overall response was assessed by the investigator with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1.

† Data include patients with a complete response and those with a partial response. The calculation of the confidence interval (CI) was based on the Clopper–Pearson method. The estimated odds ratio for nivolumab plus ipilimumab as compared with ipilimumab alone was 12.96 (95% CI, 3.91 to 54.49) among patients with *BRAF* wild-type tumors ($P<0.001$) and 9.82 (95% CI, 0.99 to 465.39) among patients with *BRAF* V600 mutation-positive tumors (P value was not calculated, per the statistical analysis plan).

61. Postow concludes “the combination of ipilimumab plus nivolumab resulted in durable responses and a substantially higher objective response rate, longer progression-free survival, and higher rates of complete response than ipilimumab monotherapy among patients with *BRAF* wild-type advanced melanoma and those with *BRAF*-mutant advanced melanoma.” EX1005 at p. 2016.

C. NCT-109 (EX1007)

62. NCT-109 is Version 1 of a clinical trial protocol with the Brief Title “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors.” EX1007, 4. The “Last Update Posted” date for Version 1 on ClinicalTrials.gov was October 23, 2013. *Id.* As discussed above in Section IX.A,

ClinicalTrials.gov publicizes clinical trial protocols and NCT-109's "Last Updated Posted" date demonstrates that it was publicly available as of October 23, 2013. POSAs knew that clinical trial protocols like NCT-109 were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. As discussed, ClinicalTrials.gov was well-known, readily-searchable source of clinical trial information as of early 2015. For example, a POSA would have readily located NCT-109 by searching for key terms like nivolumab, anti-PD-1, immunotherapy, or solid tumor. A POSA interested in dosing of nivolumab would have readily located NCT-109 on ClinicalTrials.gov by searching for nivolumab. The "Last update posted" date for NCT-109 therefore demonstrates that that NCT-109 was publicly available as of October 23, 2013. I understand and was informed that NCT-109 qualifies as prior art to the '113 patent.

63. NCT-109 discloses a phase 1 clinical trial for the treatment of "Advanced Solid Tumors." *Id.* at p. 3. As part of that treatment, NCT-109 discloses administering "BMS-936558 80 and 240 mg solution intravenously, ... every 2 weeks." *Id.* at p. 5. NCT-109 discloses "Nivolumab" in the list of "Other Names" for "BMS-936558." *Id.* NCT-109 further discloses "Inclusion Criteria" that include "melanoma subjects progressing while on- or after receiving CTLA-4

and anti-PD-1 or PD L-1 antibody therapy (in sequential or combination regimens).” *Id.* at p. 6.

D. Cogswell (EX1015)

64. Cogswell published as International Publication No. WO 2013/173223 A1 on November 21, 2013. I understand and was informed that Cogswell qualifies as prior art to the ’113 patent.

65. Cogswell discloses a “method for immunotherapy of a cancer patient comprising selecting a patient who is a suitable candidate for immunotherapy based on an assessment that the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface exceeds a predetermined threshold level.” Cogswell at Abstract. Cogswell discloses “rabbit mAbs that bind specifically to a cell surface-expressed PD-L1 antigen in a FFPE tissue sample and an automated IHC method for assessing cell surface expression in FFPE tissues using the provided anti-PD-L1 Abs.” *Id.* Cogswell discloses “[m]ore preferably, the predetermined threshold value is at least about 5%.” *Id.* at p. 15, l. 26. Cogswell discloses Example 8 where the “percentage of tumor cells exhibiting cell surface staining for PD-L1 was scored” and “PD-L1 positivity was defined per specimen by a 5% expression threshold.” *Id.* at p. 111, ll. 16-18.

66. Cogswell discloses “[a]nti-PD-L1 Abs of the invention also include isolated Abs selected for their ability to bind to PD-L1 in formalin-fixed, paraffin-

embedded (FFPE) tissue specimens.” *Id.* at p. 3, ll. 25-26. Cogswell discloses “pre-treatment PD-L1 expression was measured by IHC in FFPE tumor specimens using the rabbit anti-PD-L1 mAb, 28-8, and an automated assay developed by Dako (Carpinteria, CA).” *Id.* at p. 125, ll. 23-25. Cogswell discloses “[t]he clone that produced the most robust detection specifically of membranous PD-L1, rabbit clone 28-8, was selected for the IHC assays” and that “[t]he sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively.” *Id.* at p. 35, ll. 9-12.

X. DETAILED ANALYSIS OF THE CHALLENGED CLAIMS

67. My analysis below is divided into two parts. A first set of grounds include NCT-505. Grounds 1A, 1B, and 1C concern NCT-505 and NCT-109. Ground 2 includes NCT-505, NCT-109, and Cogswell. The second set of grounds include Postow. Grounds 3A, 3B, and 3C concern Postow and NCT-109. Ground 4 concerns Postow, NCT-109, and Cogswell.

68. As further explained below, Grounds 1 and 3 are each divided into three parts. *See* Sections X.A and X.C. Grounds 1A and 3A concern claims permitting doses of either “about 240 mg or about 480 mg” of an anti-PD-1 antibody for the anti-PD-1 monotherapy phase of treatment. Plainly, and as described in Section VI.E, the methods of these claims—and in particular the option of “about 480 mg” of an anti-PD-1 antibody—are not described by the April

28, 2015 provisional application referenced in the '113 Patent. I understand that these claims accordingly have an effective filing date no earlier than the '113 Patent's actual April 28, 2016 date. Grounds 1B and 3B concern claims requiring a dose of "about 240 mg" of an anti-PD-1 antibody for the anti-PD-1 monotherapy phase. I have not separately analyzed the effective filing date of those claims and instead have assumed the April 28, 2015 provisional application filing date for purposes of my analysis. Finally, Grounds 1C and 3C concern claims requiring a dose of about 480 mg" of an anti-PD-1 antibody for the anti-PD-1 monotherapy phase. As with the claims covered in Grounds 1A and 3A, these claims are not described by the April 28, 2015 provisional application—meaning that they have an effective filing date no earlier than the '113 Patent's actual April 28, 2016 date. The difference between Grounds 1A and 3A on the one hand versus Grounds 3A and 3C on the other hand is that Grounds 1A and 3A explain why it would have been obvious for a POSA to practice the relevant teachings (NCT-505 in the case of Ground 1A and Postow in the case of Ground 3A) concerning the anti-PD-1 monotherapy stage by administering a 240 mg flat dose of the anti-PD-1 antibody nivolumab once every two weeks (as expressly disclosed in NCT-109), whereas Grounds 3A and 3C explain why it also would have been obvious for a POSA to practice those same teachings in NCT-505 and Postow by administering a 480 mg

flat dose of the anti-PD-1 antibody nivolumab once every four weeks (consistent with teachings in other prior art references such as Brahmer).

A. Grounds 1A, 1B, and 1C: NCT-505 and NCT-109 Render Obvious Challenged Claims 1-4, 10-12, 13-15, and 17-20

69. Grounds 1A, 1B, and 1C center on NCT-505, which formed the basis for Example 1 in the '113 patent and discloses anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) combination therapy followed by anti-PD-1 (nivolumab) monotherapy to treat melanoma tumors. NCT-505 discloses all elements of Challenged Claims 1-4, 10-15, and 17-20 aside from administering the subsequent anti-PD-1 monotherapy as a flat dose rather than a weight-dependent dose. NCT-109 discloses anti-PD-1 monotherapy as a flat dose—including 240 mg nivolumab once every two weeks to treat melanoma tumors. Given the multiple known benefits of flat dosing, a POSA would have reason to modify NCT-505 to administer a flat dose of the anti-PD-1 antibody nivolumab as disclosed in NCT-109.

70. Ground 1A concerns claims 1-4, 10, 13-15, and 19-20. As discussed above at Section VI.D, I have been informed that at least claims 1-4, 10, 13-15, and 19-20 are not entitled to the benefit of the '973 Provisional because they encompass anti-PD-1 monotherapy flat doses of either 240 mg or 480 mg, which lacks support in the '973 Provisional. *See* my discussion above in Section VI.D. I further understand that, because these claims are not entitled to the priority date of

the '973 Provisional, Postow is indisputable prior art to these claims. Postow discloses that the NCT-505 dosing regime was successful in treating melanoma. Accordingly, Ground 1A shows obviousness over NCT-505 in view of NCT-109. Postow also further confirms a POSA's reasonable expectation of success in treating melanoma patients using the modified NCT-505-NCT-109 protocol.

71. Ground 1B concerns dependent claims 11 and 17, which require an anti-PD-1 monotherapy flat dose of 240 mg once every two weeks, and which are likewise obvious over NCT-505 in view of NCT-109. Ground 1B is set out separately because I was not asked to (and do not) render an opinion regarding whether claims 11 and 17 find support in the April 28, 2015 '973 Provisional. As I will discuss, claims 11 and 17 are obvious even if they are entitled to that priority date.

72. Ground 1C concerns dependent claims 12 and 18, which require an anti-PD-1 monotherapy flat dose of 480 mg once every four weeks. Doubling the dosage (i.e., from 240 mg to 480 mg) while also doubling the intervals between treatments (i.e., from two weeks to four weeks) was an obvious variant of the NCT-505-NCT-109 protocol—delivering the same amount of anti-PD-1 monotherapy while decreasing the number of required injections.

73. I have been informed that a combination need not be the most desirable or preferred combination in the prior art in order to be obvious. As

shown by the Grounds I discuss in this declaration, there are indeed multiple obvious variants of NCT-505-NCT-109, including—but not necessarily limited to—240 mg once every two weeks (which I discuss in Grounds 1A-1B) and 480 mg once every four weeks (which I discuss in Ground 1C).

1. GROUND 1A: NCT-505 and NCT-109 Render Obvious Claims 1-4, 10, 13-15, and 19-20

74. Together, NCT-505 and NCT-109 disclose all of the dosing amounts and frequencies of anti-PD-1 and anti-CTLA-4 that are recited in Challenged Claims 1-4, 10, 13-15, and 19-20, and POSAs would have had reason to combine these teachings to arrive at the claimed method of treatment with a reasonable expectation of success.

75. NCT-505, which formed the basis for Example 1 in the '113 patent, discloses the combination therapy recited in claims 1-4, 10, 13-15, and 19-20 and the weight-based combination frequency and amounts. In addition, the specific anti-PD-1 antibody disclosed by NCT-505, nivolumab, was already being administered as a flat dose in the context of a clinical trial, as disclosed in NCT-109, due to its wide therapeutic window and its known features as a well-tolerated and long-lasting therapeutic. EX1009 at 3169, 3171. Indeed, for antibodies with such wide therapeutic windows as nivolumab, flat dosing was known to have “numerous advantages over body size-based dosing.” EX1008 at 1023. For example, NCT-109 discloses administering a flat dose of 240 mg nivolumab once

every two weeks to melanoma patients. EX1007 at 5. A POSA would have had ample reason to combine the teachings of NCT-505 and NCT-109 to practice NCT-505 while obtaining the advantages of flat dosing over NCT-505's weight-based dosing for the nivolumab monotherapy.

76. It would have been obvious in particular to administer the nivolumab monotherapy at a flat 240 mg dose once every two weeks following nivolumab's coadministration with an anti-CTLA-4 antibody to treat melanoma.¹ A flat dose of 240 mg would have been obvious, starting from NCT-505's weight-based dose of 3 mg/kg nivolumab, because 240 mg is simply the product of multiplying the 3 mg/kg weight-based dose by an 80 kg patient weight. For example, it was reported that the median weight of melanoma patients in an immunotherapy clinical trial using ipilimumab was 80.11 kg. EX1035 at 108. For a patient weighing 80 kg, a 240 mg flat dose of nivolumab once every two weeks indeed is equivalent to the

¹ Ground 1A focuses on the obviousness of the 240 mg dosage alternative in the claims, which I understand is enough to render claims 1-4, 10, 13-15, and 19-20 unpatentable. I have been informed that when the claim recites alternatives—e.g., 240 mg “or” 480 mg—the claim is obvious if any one of the alternatives is obvious. I note that the 480 mg dosage alternative was *also* obvious, as I explain in Ground 1C, below.

weight-based dose of 3 mg/kg nivolumab once every two weeks as expressly disclosed in NCT-505.

a. NCT-505 Discloses Treating Melanoma with a Combination of Nivolumab and Ipilimumab Followed by Nivolumab Alone

77. NCT-505 expressly discloses treating melanoma tumors using “Nivolumab in combination with Ipilimumab.” EX1014 at 4.

78. Nivolumab, which was also known as “BMS-936558”, was a known anti-PD-1 antibody. EX1001 at 17:61-67 (“Nivolumab (also known as ... BMS-936558, MDX-1106...) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody....”); *see also* EX1001 at 17:61-67; EX1014 at 4 (“Nivolumab...Other Names: BMS-936558”).

79. Ipilimumab was a known anti-CTLA-4 antibody. EX1028; EX1001 at 21:29-37 (“Ipilimumab is a fully human, IgG1 monoclonal antibody that blocks the binding of CTLA-4 to its B7 ligands....”).

80. NCT-505 discloses a two-stage treatment regime: (1) co-administration of nivolumab and ipilimumab, followed by (2) administration of nivolumab alone. In the co-administration phase, NCT-505 discloses that “Nivolumab 1 mg/kg solution” is “combined with Ipilimumab 3 mg/kg” and administered “intravenously every 3 weeks for 4 doses.” EX1014 at 4. In the

subsequent anti-PD-1 monotherapy stage, NCT-505 discloses that nivolumab is given at a dose of “3 mg/kg solution intravenously every 2 weeks.” EX1014 at 4.

81. NCT-505 further disclosed that (1) “Progression Free Survival,” (2) “Objective Response Rate,” and (3) “OS [(Overall Survival)] based on PD-L1 expression” were three of the study’s outcome measures. EX1014 at 5.

b. Reason to Modify: POSAs Would Have Had Reason to Use a Flat Dose of Nivolumab for Monotherapy Instead of the Body Weight Dose Given the Known Benefits of Flat Dosing

82. POSAs would have had reason to modify NCT-505’s anti-PD-1 monotherapy stage to administer a flat dose of nivolumab in lieu of the 3 mg/kg weight-based dose expressly disclosed in NCT-505, given the multiple known advantages of flat dosing coupled with nivolumab’s favorable safety profile. Nivolumab itself was known to be “well tolerated,” “dose-independent” over a wide dose range, and long-lasting (“≥ 57 days”). EX1009 at 3167, 3171. POSAs were aware that administering a flat dose offered advantages over a weight based dose. For example, a 2009 article by Wang disclosed that for antibodies with a wide therapeutic window, such as nivolumab, “[f]ixed dosing provides numerous advantages over body size–based dosing.” EX1008 at 1023. Specifically, Wang explained that:

It is more convenient for pharmacists or nurses to prepare and administer a unit dose to patients. This has an important safety

implication as it could avoid or reduce errors in calculating and preparing an individualized dose for each patient. By administering a unit dose, it could also prevent from wasting leftovers in contrast to individualized dosing based on body size. This is especially important for mAbs because mAb manufacturing is often expensive and time consuming.

EX1008 at 1023. “Fixed dosing” is an alternative way to describe “flat dosing.” Compare EX1001 at 7:52-58 (“The use of the term “flat dose” with regard to the composition of the invention means a dose that is administered to a patient without regard for the weight or body surface area (BSA) of the patient. The flat dose is therefore not provided as a mg/kg dose, but rather as an absolute amount of the agent (e.g., the anti-CTLA-4 antibody and/or anti-PD-1 antibody).”) with EX1034 at 119 (discussing “body weight-independent (*fixed*) dosing regimens” and contrasting with “body weight-based” approaches”). Indeed, medical literature also referred to this concept as “flat-fixed dosing.” E.g., EX1033 at 918 (“*Flat-fixed* dosing refers to dosing strategies without correction for body size or other (pharmacological) parameters.”).

83. Wang concludes that “when there is no advantage of one dosing approach over another from a PK and PD perspective, *fixed dosing is the approach of choice*.” EX1008 at 1023 (fixed dosing has “numerous advantages over body size-based dosing”). POSAs would understand that Wang’s teaching

was applicable to NCT-505’s nivolumab monotherapy phase because weight-based dosing of nivolumab alone did not offer any advantage from a PK or PD perspective and likewise did not offer any particular practical benefit when administered on its own.

84. Other prior art confirms Wang’s recommendations. For example, Mathijssen notes that flat-dosing provides advantages including “positive economic implications”; “safety implications, because fewer errors will be made in calculation, preparing, and administering the proper individual dose”; better “patient adherence” and avoidance of “false feeling of being precise” from size-based dosing, and thus may be preferred to size-based dosing unless the therapeutic agent exhibits “a narrow therapeutic window and high interindividual variability in exposure.” EX1033 at 918. Bai likewise teaches that most monoclonal antibodies have “a relatively large therapeutic window” and “fixed dosing is recommended” as “the first option in first-in-human studies” given the “many practical advantages” fixed dosing provides. EX1034 at 133. As discussed above, it was well known that nivolumab had a wide therapeutic window. EX1009 at 3169, 3171. Further, POSAs knew that numerous other monoclonal antibodies—including multiple mAbs indicated for oncology—were administered via flat doses. EX1036 at 25-26.

85. Accordingly, POSAs would have had reason to practice NCT-505's nivolumab monotherapy step using a flat dose of nivolumab rather than the weight-based dose disclosed in NCT-188. At minimum, such flat dosing of nivolumab would have been obvious to try given that flat doses are one of a small, finite number of dosing schemes suitable for the use of monoclonal antibodies.

86. In particular, POSAs would have had reason to administer NCT-505's nivolumab monotherapy step via a flat dose while still using weight-based dosing for the earlier step involving co-administration of both nivolumab and the anti-CTLA-4 antibody ipilimumab. As compared to nivolumab, ipilimumab has a less forgiving safety profile. By early 2015, ipilimumab was known to exhibit toxicity and could cause immune-related adverse events ("IRAEs"). EX1022 at 865. These IRAEs were "associated with tumor regression" in melanoma patients and were "dependent both on peak dosing and area under the curve." EX1022 at 865. POSAs would have recognized that a body weight dose of ipilimumab (consistent with NCT-505's express teachings, and later confirmed by Postow to be reasonable and efficacious) offered advantages to mitigate those toxic side effects. POSAs would have also recognized the practical benefits (such as greater convenience and streamlined protocols) of administering both ipilimumab and nivolumab according to a single dosage scheme, as opposed to administering ipilimumab via a weight-based dose and nivolumab via a flat dose. But such practical benefits are not

applicable when administering nivolumab as a monotherapy (as taught in NCT-505).

c. The Modification: 240 mg Every Two Weeks

87. In particular, POSAs would have had reason to select a flat dosage of 240 mg of nivolumab, which is consistent with one of the dosages expressly disclosed in NCT-109, given the knowledge that when bodyweight-based dosing has been used previously, “[t]he dose of fixed dosing approach [is] set to the dose that would be given to a subject with median [bodyweight] by [bodyweight]-based dosing.” EX1008 at 1014.

88. Indeed, a flat dose of 240 mg every two weeks results from the simple conversion of translating NCT-505’s 3 mg/kg weight-based dosage into the actual dose a typical 80 kg clinical trial subject would receive. A POSA knew that 80 kg was a typical average weight for melanoma patients undergoing immunotherapy trials. EX1035 at 108 (reporting mean body weight of 80.11 kg).

$$\begin{array}{rcl} 3 \text{ mg/kg} & \text{once every two weeks} & \\ \times \text{ } \sim 80 \text{ kg} & & \\ \hline = & \mathbf{240 \text{ mg} \text{ once every two weeks}} & \end{array}$$

89. Confirming this logic, prior art reference NCT-109 discloses a clinical trial that used 240 mg nivolumab once every two weeks for treating melanoma patients. EX1007 at 5-6 (disclosing “BMS-936558” (a.k.a. nivolumab) “240 mg

solution intravenously” “every 2 weeks” for “incurable melanoma”). While the clinical trial disclosed in NCT-109 involved administering nivolumab along with BMS-986016, an anti-LAG-3 antibody, 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.

90. POSAs would thus have modified the method of treatment disclosed by NCT-505 by administering 240 mg nivolumab disclosed by NCT-109 once every two weeks following the combination therapy with nivolumab and ipilimumab (hereinafter “NCT505–NCT109”).

d. Reasonable Expectation of Success: POSAs Knew Nivolumab Had a Wide Therapeutic Window

91. POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 240 mg nivolumab once every two weeks, following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 3 mg/kg nivolumab every two weeks.

92. Indeed, prior art had already disclosed a flat dose of 240 mg nivolumab for melanoma treatment before the effective filing dates of the Challenged Claims. As noted above, NCT-109, which was publicly accessible at

least as early as October 23, 2013 (i.e., over a year before the earliest alleged priority date of all the Challenged Claims), discloses a 2013 clinical trial that used 240 mg nivolumab once every two weeks for treating melanoma patients specifically. EX1007 at 5-6 (disclosing “BMS-936558” (a.k.a. nivolumab) “240 mg solution intravenously” “every 2 weeks” for “incurable melanoma”). Thus, flat doses of 240 mg nivolumab were already in use in the context of a clinical trial to treat cancer generally, including melanoma.

93. Moreover, nivolumab was known to be a drug with a wide therapeutic window. EX1009 at 3169, 3171. Brahmer discloses a “phase I study” where “[t]hirty-nine patients with advanced metastatic melanoma ... received a single intravenous infusion of [nivolumab] in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg....” EX1009 at 3167. (While Brahmer refers to “MDX-1106,” POSAs would understand that this was a codename for nivolumab. See paragraph 50 above.) For a cancer immunotherapy patient of average weight, ~80kg (EX1035 at 108), that translated into doses of 24 mg, 80 mg, 240 mg, and 800 mg because $0.3 \text{ mg/kg} \times 80 \text{ kg} = 24 \text{ mg}$; $1 \text{ mg/kg} \times 80 \text{ kg} = 80 \text{ mg}$; $3 \text{ mg/kg} \times 80 \text{ kg} = 240 \text{ mg}$; and $10 \text{ mg/kg} \times 80 \text{ kg} = 800 \text{ mg}$.

94. Brahmer discloses that across that wide range of doses, “PD-1 occupancy appeared to be *dose-independent*.” EX1009 at 3171. As discussed above, PD-1 occupancy refers to a calculation of the percentage of PD-1 occupied

by the drug out of the total number of PD-1 receptors. Bramer’s statement that occupancy appears to be dose-independent over a wide range of doses means that, within the referenced range of doses, increasing dosage does not yield a significant increase in occupancy. In other words, sites available to be occupied are already occupied, and further increases, within the range of doses, does not increase occupancy and would not be expected to increase effectiveness.

95. Brahmer also discloses administration of 3 mg/kg or 10 mg/kg nivolumab every four weeks. EX1009 at 3168 (“Those [patients] with continued clinical benefit could receive two more doses, spaced by 4 weeks.”). Topalian discloses a phase I study in which melanoma patients received a dose of 0.1-10 mg/kg nivolumab and reports that the “pharmacokinetics of the antibody were linear” and exhibited “with a dose-proportional increase in the peak concentration and area under the curve calculated from day 1 to day 14 in the dose range of 0.1 to 10.0 mg per kilogram (35 patients).” EX1011 at 2443, 2449.

96. Given the dose independency and linear pharmacokinetics of nivolumab across a wide dose range, POSAs would have expected a flat dose of 240 mg every two weeks—within the range of doses tested by Brahmer and Topalian—to be comparable to a body weight dose of 3 mg/kg every two weeks. The dose independency, wide therapeutic window, and linear pharmacokinetics support the flat dose rather than the weight based dose because, in view of these

factors, a POSA would expect that giving somewhat less antibody on a mg/kg basis to a heavier patient, or somewhat more antibody on a mg/kg basis to a lighter patient, would have a minimal impact on the treatment.

97. A POSA also would have also expected flat doses of 240 mg every two weeks to be safe. Both Brahmer and Topalian report that in dose escalation studies, no maximum tolerated dose was reached even when 10 mg/kg was administered. EX1009 at 3172 (“MDX-1106 [*i.e.*, nivolumab] was well tolerated to the maximum planned dose of 10 mg/kg.”); EX1011, 2443 (“No maximum tolerated dose was defined.”), 2447 (patients received up to 10.0 mg/kg).

98. Such reports further confirmed the safety of a 240 mg flat dose even for lightweight patients. For example, 240 mg nivolumab corresponds to less than 7 mg/kg even for an 80 pound (36 kg) patient. A corresponding weight-based dose may be calculated from the flat dose and the patient weight by dividing the dose by the weight, that is: $240 \text{ mg} / 36 \text{ kg} = 6.7 \text{ mg/kg}$. Comparing this calculated value for a dose for a light-weight patient shows that even for a light-weight patient, the dose would be less than the 10 mg/kg dose administered in the dose escalation studies. Conversely, even at twice the 80 kg average weight (*i.e.*, a 160 kg patient), a patient would still receive more on a per kg basis (*i.e.*, 1.5 mg/kg) than a patient receiving 1 mg/kg as reported by Brahmer or Topalian.

99. Numerous other monoclonal antibodies—including multiple antibodies indicated for cancer treatment—had successfully been administered via flat dosing before the effective filing date. For example, a 2010 review article indicated that eleven of the twenty-six listed monoclonal antibodies have been used with flat dosing. EX1036 at 25-26. The fact that numerous other monoclonal antibodies had successfully been administered via flat dosing before the effective filing date further confirms the reasonable expectation of success.

e. Claim-by-Claim Analysis

100. NCT505-NCT109 discloses every limitation of claims 1, 2, 4, 10, 11, 13-15, 17, 19, and 20, rendering them obvious.

i. Claim 1

(1) Preamble: Method for Treating Melanoma

101. The preamble of claim 1 recites: “A method for treating a melanoma tumor in a human patient in need thereof comprising:...” To the extent the preamble of claim 1 is limiting, NCT505-NCT109 satisfies it because NCT-505 discloses a method for treating “advanced melanoma” in a human patient. EX1014 at 3.

(2) Limitation 1(i): Identifying a Patient Having a PD-L1-Negative Melanoma

102. Limitation 1(i) recites “(i) identifying a patient having a PD-L1-negative melanoma tumor.” NCT505-NCT109 satisfies limitation 1(i) because

NCT-505 discloses that one of the secondary outcome measures of the disclosed trial was “OS [(overall survival)] based on *PD-L1 expression*.” EX1014 at 5.

Immediately under the line identifying PD-L1 expression, NCT-505 identifies the “Time frame” as “Baseline (Day 1)”. EX1014 at 5. This means that, according to the disclosures in NCT-505, identification of PD-L1 expression was to be made on “Day 1.” EX1014 at 5.

103. POSAs would understand that to measure overall survival based on PD-L1 expression, the patients’ melanoma tumors would need to be tested for PD-L1 expression, thereby identifying both PD-L1-positive melanoma tumors and PD-L1-negative melanoma tumors. It had already been reported more than one year before the earliest alleged priority date of the Challenged Claims that PD-L1 negative melanoma patients were responsive to the combination of nivolumab and ipilimumab. EX1028 at 1. Accordingly, POSAs would have had reason to identify patients having a PD-L1 negative melanoma tumor. They likewise would have had a reasonable expectation of success that such patients could be successfully treated using a combination of nivolumab and ipilimumab.

(3) Limitation 1(ii)(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

104. Limitation 1(ii)(a) recites: “(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...”

105. NCT505-NCT109 satisfies limitation 1(ii)(a) because NCT-505 discloses that “*Nivolumab [i.e., a known anti-PD-1 antibody] 1 mg/kg solution*” is “combined with *Ipilimumab [i.e., a known anti-CTLA-4 antibody] 3 mg/kg*” and *administered “intravenously every 3 weeks for 4 doses”* to the patient.

EX1014 at 4. Nivolumab is a known anti-PD-1 antibody, and ipilimumab is a known anti-CTLA-4 antibody. EX1001 at 17:61-67, 21:29-37. Moreover, it was well known by 2015 that anti-PD-1 and anti-CTLA-4 antibodies could be administered in combination at the already approved “every 3 weeks for 4 doses” regimen for anti-CTLA-4 antibodies. *See e.g.*, EX1025.

(4) Limitation 1(ii)(b): Administering a Subsequent Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

106. Limitation 1(ii)(b) recites: “(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.”

107. NCT505-NCT109 satisfies limitation 1(ii)(b) because NCT-505 discloses administering to the patient “*Nivolumab 3 mg/kg solution intravenously every 2 weeks*” following the four doses of the combination therapy. EX1014 at 4.

And NCT-109 discloses administering a flat dose of “**240 mg**” nivolumab “every 2 weeks” (EX1007, 5), including to patients with “incurable melanoma” (*id.*, 6).

108. As explained above in my discussion in Section X.A.1.b, POSAs would have had reason to modify the weight-based 3 mg/kg nivolumab monotherapy dose once every two weeks disclosed by NCT-505 to the known alternative of a flat dose of 240 mg every two weeks given the “numerous advantages” of flat dosing that were recognized by a POSA. As explained above, this includes the many advantages disclosed in Wang and confirmed in multiple other prior art references such as Bai and Mathijssen. EX1008 at 1023; EX1033 at 918; EX1034 at 1055.

109. As explained above in Section X.A.1.d, POSAs would have had at least a reasonable expectation of making the substitution and achieving comparable clinical results because of (1) nivolumab’s wide therapeutic window, which would have given POSAs a reasonable expectation that dosing could be modified while continuing to achieve a comparable effect, (2) NCT-109’s disclosure of using a 240 mg flat dose of nivolumab to treat melanoma, as well as (3) the multiple other monoclonal antibodies known to have been successfully administered via flat dosing. EX1009 at 3167, 3169, 3171; EX1036 at 25-26.

110. NCT505–NCT109 thus satisfies limitation 1(ii)(b), rendering claim 1 obvious.

ii. Claim 2

111. Claim 2 is similar to claim 1, but does not recite “identifying a patient having a PD-L1-negative melanoma tumor.”

(1) Preamble: Method for Treating a Melanoma

112. The preamble of claim 2 recites: “A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient...”

113. To the extent the preamble of claim 2 is alleged to be limiting, NCT505-NCT109 discloses it for the same reason it discloses preamble of claim 1. *See* my discussion above in Section X.A.1.e.i(1).

(2) Limitation 2(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

114. Limitation 2(a) recites: “(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 ...”

115. NCT505-NCT109 satisfies limitation 2(a) for the same reasons it discloses limitation 1(ii)(a). *See* §X.A.1.e.i(3).

(3) Limitation 2(b): Administering a Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

116. Limitation 2(b) recites: “(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.”

117. NCT505-NCT109 satisfies limitation 2(b) for the same reasons it satisfies limitation 1(ii)(b), rendering claim 2 obvious. *See* §X.A.1.e.i(4).

iii. Claim 3: Over 8 Months Progression-Free Survival and/or At Least About 10% Tumor Size Reduction

118. Claim 3 depends from claim 2 and further requires that “the patient is characterized by (i) extended progression-free survival for over 8 months ..., (ii) tumor size reduction at least about 10% ..., or (iii) both (i) and (ii).” There are multiple independent reasons why claim 3 is unpatentable in view of NCT505-NCT109, which I discuss below.

119. First, I understand that a statement in a claim does not limit the claim if it is a statement of an “intended result” of administering a drug or if it is a statement that has no “manipulative difference” which I understand means that it does not make any actual change. The additional language in claim 3 merely recites the “intended result” of the method claimed by claim 2 and does not result in a “manipulative difference” in the steps of the claim 2. Thus, in my opinion, in the context of this case, the limitation in claim 3 should be interpreted as non-

limiting. Because NCT505–NCT109 satisfies claim 2, it also satisfies claim 3, which merely recites an intended result and is nonlimiting for that reason.

120. Second, I have been informed that inherency may satisfy a claim limitation in an obviousness analysis and that results are inherent in a process where they are the natural result flowing from performing the process. Therefore, even if claim 3’s recited result were considered limiting, NCT505–NCT109 still renders it obvious because the claimed outcomes are the natural results of administering nivolumab and ipilimumab according to NCT505–NCT109.

121. Here, Postow discloses that administering nivolumab and ipilimumab, as disclosed by NCT-505, achieved progression-free survival for over 8 months and tumor size reduction of at least about 10%. EX1005 at p. 2009. Specifically, Postow discloses that “the median progression-free survival was not reached with the combination therapy” for patients with BRAF wild-type tumors and was 8.5 months for patients with BRAF mutation-positive tumors. EX1005 at p. 2006. Accordingly, the median progression-free survival was at least 8.5 months meaning half of patients in this population were progression free at 8.5 months and better for the BRAF wild-type tumors. EX1005 at p. 2009. POSAs would understand this to mean that progression-free survival was well over 8 months for many patients. Moreover, Postow discloses a “complete response was observed in 16 patients (22%) in the combination group.” EX1005 at p. 2009. POSAs would

understand Postow's disclosed "complete response" exceeds the claimed "at least about 10%" tumor size reduction.

122. This is because Postow explains that its data metrics conform to the Response Evaluation Criteria in Solid Tumors (RECIST) standards. EX1005 at p. 2008-2009; EX1039. Under the RECIST criteria, a "Complete Response" or "CR" is defined as the "[d]isappearance of all target lesions" and a "Partial Response" or "PR" is defined as "[a]t least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters." EX1039 at 232. Target lesions are a set of up to five lesions "selected on the basis of their size (lesions with the longest diameter), [to] be representative of all involved organs" and are lesions that "lend themselves to reproducible repeated measurements." EX1039 at 232.

123. Postow explains that "[i]n the combination group, the objective response rate was independent of tumor PD-L1 status: 58% (95% CI, 37 to 78) among patients with PD-L1-positive tumors and 55% (95% CI, 41 to 69) among patients with PD-L1-negative tumors." EX1005 at p. 2009. "Among patients treated with the combination regimen in [Postow's] study, however, there was no significant difference in response rates between patients whose pretreatment tumors were defined as PD-L1-positive and those whose tumors were PD-L1-negative." EX1005 at p. 2016.

124. Separately, Postow discloses that nivolumab and ipilimumab, as disclosed by NCT-505, achieved a median decrease in tumor burden of 68.1% pursuant to the RECIST standard. EX1005 at p. 2008-2009; EX1039. Postow explains that patients with a 30% or more reduction in tumor burden were considered to have a response to treatment, as provided under the RECIST guidelines. EX1005 at p. 2013.

125. Because nivolumab is “*dose-independent*” over a wide range of doses (EX1009 at 3171), administering 240 mg nivolumab once every two weeks would have resulted in substantially the same results as disclosed by Postow when administering 3 mg/kg nivolumab once every two weeks. The results recited by claim 3 are thus the natural result of administering the NCT505–NCT109 dosing regimen, thus rendering claim 3 obvious.

iv. Claim 4: Measuring PD-L1 Expression Prior to Administration

126. Claim 4 depends from claim 2 and recites: “further comprising measuring a PD-L1 expression on the melanoma tumor prior to the administration.”

127. NCT505–NCT109 satisfies claim 4 (and renders it obvious) because NCT-505 discloses that one of the secondary outcome measures was “OS [(overall survival)] based on PD-L1 expression.” EX1014 at 5. POSAs would have understood that to measure overall survival based on PD-L1 expression, the

patients' melanoma tumor would need to be measured for PD-L1 expression. NCT-505 states that identification of PD-L1 expression was to be made on "Day 1." EX1014 at 5.

128. Moreover, POSAs would have been motivated to measure PD-L1 expression prior to administration of the antibodies as required by claim 4 because that would be a logical time to take such a measurement, at least for the purposes of potentially categorizing patients based on expression of this biomarker and/or tracking patients' progress based on expression of this biomarker, and in case the administration of the antibodies had eliminated the tumor, leaving nothing left to measure. EX1011 at 2445 ("Immunohistochemical analysis for PD-L1 was performed on archival or newly obtained *pretreatment* . . . tumor specimens").

129. For the reasons discussed above regarding claim 1 and these additional reasons relating to PD-L1 expression, claim 4 would have been obvious over NCT505-NCT-109.

v. Claims 10 and 20: the Anti-PD-1 Antibody Is Nivolumab

130. Claims 10 and 20 depend from claims 2 and 1, respectively, and further recites: "wherein the anti-PD-1 antibody is nivolumab."

131. NCT505–NCT109 satisfies claims 10 and 20 because NCT-505 discloses the anti-PD1 antibody "nivolumab" (EX1014 at 4), the same anti-PD1

antibody disclosed in NCT-109 (EX1007 at 5), thus rendering claims 10 and 20 obvious.

vi. Claim 13: the Anti-CTLA-4 Antibody Is Ipilimumab

132. Claim 13 depends from claim 2 and further recites: “wherein the anti-CTLA-4 antibody is ipilimumab.”

133. NCT505–NCT109 satisfies claim 13, thus rendering it obvious because NCT-505 discloses the anti-CTLA-4 antibody “ipilimumab.” NCT-505 at 4.

vii. Claims 14, 15, and 19: the Anti-CTLA-4 Antibody Is from 0.1 mg/kg to 10.0 mg/kg or 3 mg/kg

134. Claim 14 depends from claim 2 and further recites “wherein the dose of the anti-CTLA-4 antibody is from 0.1 mg/kg to 10.0 mg/kg.” Claims 15 and 19 depend from claims 14 and 1, respectively, and further recites: “wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.”

135. NCT505-NCT109 satisfies claims 14, 15, and 19, thus rendering them obvious because NCT-505 discloses administering 3 mg/kg of the anti-CTLA-4 antibody ipilimumab—the dose claimed by claims 15 and 19 and within the 0.1 mg/kg to 10 mg/kg range claimed by claim 14. EX1014 at 4.

* * *

136. Because NCT505-NCT109 discloses each and every limitation of Challenged Claims 1-4, 10, 13-15, and 19-20 (as I discussed above in Section X.A.1.e) and because POSAs would have had reason to combine these teachings to arrive at the claimed methods with a reasonable expectation of success (as I discussed above in Section X.A.1.d), these Challenged Claims are obvious over the prior art and therefore unpatentable.

2. GROUND 1B: NCT-505 and NCT-109 Render Obvious Claims 11 and 17

137. Claims 11 and 17 are addressed separately (i.e., as Ground 1B) because I was not asked to and did not render an opinion, in Section VI.D, regarding whether claims 11 and 17 are entitled to the benefit of the April 28, 2015 '973 Provisional.

138. Claims 11 and 17 depend from claims 2 and 1, respectively, and further recite: “wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.”

139. Claims 11 and 17 are unpatentable as obvious over NCT505–NCT109 for the same reasons set forth in Ground 1A. Claims 11 and 17 depend from claims 2 and 1, respectively, and are thus identical to claims 2 and 1, respectively, aside from reciting additional requirements concerning the flat dose monotherapy. They require the flat dose to be “about 240 mg” (as opposed to either “about 240 mg or

about 480 mg,” as recited in claims 1 and 2) and further require the flat dose to be “administered once every two weeks.”

140. NCT505–NCT109 renders obvious claims 11 and 17. As explained in Section X.A.1, above, POSAs would have administered the known flat dose of 240 mg nivolumab once every two weeks instead of the 3 mg/kg every two weeks as disclosed by NCT-505 to achieve the “numerous advantages” of flat dosing known to one of skill in the art and as disclosed by Wang. NCT-109 itself specifically discloses administering a flat dose of “240 mg” nivolumab “every 2 weeks” (EX1007 at 5), including to patients with “incurable melanoma” (EX1007 at 6).

141. NCT505–NCT109 renders obvious claims 11 and 17. As explained in §X.A.1.c, above, POSAs would have administered the known flat dose of 240 mg nivolumab once every two weeks instead of the 3 mg/kg every two weeks as disclosed by NCT-505 to achieve the “numerous advantages” of flat dosing known to one of skill in the art and as disclosed by Wang. NCT-109 itself specifically discloses administering a flat dose of “**240 mg**” nivolumab “**every 2 weeks**” (EX1007 at 5), including to patients with “incurable melanoma” (*id.* at 6).

Accordingly, claims 11 and 17 were obvious over NCT505–NCT109.

3. GROUND 1C: NCT505 and NCT109 Render Obvious Claims 12 and 18

142. Claims 12 and 18 depend from claims 2 and 1, respectively, which are obvious over NCT505—NCT109 for the reasons set forth in Ground 1A. Claims

12 and 18 merely require that the flat dose anti-PD-1 antibody be “about 480 mg” (as opposed to *either* “about 480 mg” or “about 240 mg”) as in the independent claims) and further that it be “administered once every four weeks.”

143. Such a dosage schedule would have been an obvious variant of NCT505-NCT109’s flat dosage of 240 mg nivolumab every two weeks as expressly taught in NCT109 (EX1007 at 5-6). Indeed, it was known that nivolumab had a favorable safety profile and could be administered once every four weeks (as required by claims 12 and 18) at dosages of between 0.3-10 mg/kg. EX1009 at 3168 (“Those [patients] with continued clinical benefit could receive two more doses, spaced by 4 weeks.”), 3169 (“Thirty-nine patients with advanced metastatic NSCLC, melanoma, castrate-resistant prostate cancer, RCC, or CRC received MDX-1106 in four escalating dose cohorts of 0.3 to 10 mg/kg and an expansion cohort at 10 mg/kg”), 3172 (“this phase 1 trial” showed “promising safety profile and evidence of durable clinical activity”). This corresponds to dosages of 24-800 mg for an average 80 kg melanoma patient undergoing immunotherapy. EX1035 at 108. A POSA would have been motivated to optimize such dosages and select a 480 mg flat dose—thereby achieving flat dosing’s “numerous advantages” (EX1008) and delivering the same amount of nivolumab over time as the 240 mg dose once every two weeks (as expressly disclosed in NCT109, EX1007 at 5-6)—while enhancing patient convenience and compliance

levels by reducing the number of required treatments. NCT505 and NCT109 therefore also render obvious claims 12 and 18.

a. Reason to Use a 480 mg Dose Once Every Four Weeks

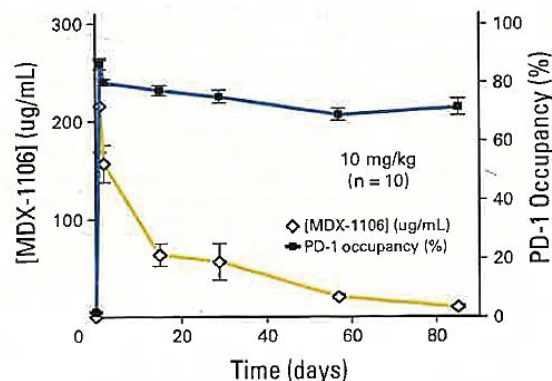
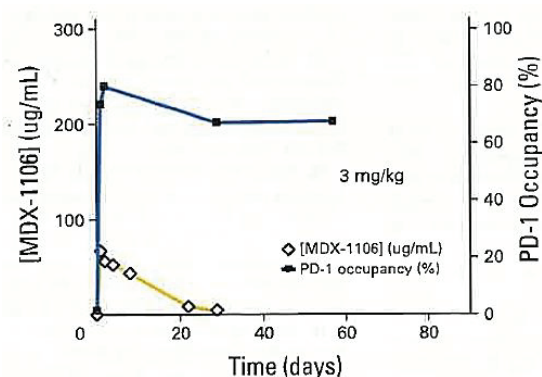
144. POSAs would have had reason to administer a flat dose of nivolumab once every four weeks as an alternative to every two weeks. POSAs knew that “market pressures for higher patient convenience and compliance continue to drive antibody drug programs toward less frequent dosing schedules.” EX1021 at 158. POSAs would have recognized that reducing the frequency would have been more convenient to patients, requiring them to come in for infusions less often, and thus desirable for that reason. EX1021 at 158 (teaching the desire of “less frequent dosing schedules”). Improving compliance means that patients will receive the full benefit available from the treatment.

145. Being thus motivated to adopt less frequent dosing, a POSA would have specifically selected once every four weeks for dosing because that frequency was previously disclosed by Brahmer, which discloses dosing nivolumab “spaced by 4 weeks.” EX1009 at 3168. POSAs would have thus had reason to administer a flat dose of nivolumab once every four weeks as an alternative to every two weeks.

146. Furthermore, POSAs seeking to administer the nivolumab monotherapy less frequently than once every two weeks (as disclosed in both NCT-505 and NCT-109) would have had particular reason to select the four-week

frequency previously disclosed by Brahmer. POSAs would have had reason to administer 480 mg nivolumab every four weeks (as taught in Brahmer) as an alternative to every two weeks (as taught in NCT-505 and NCT-109). Brahmer investigated the pharmacokinetics and pharmacodynamics of nivolumab, and taught that a 3 mg/kg dose – equivalent to a 240 mg flat dose – was nearly eliminated after 21 days (3 weeks) but a 10 mg/kg dose – equivalent to an 800 mg flat dose – resulted in measurable amounts of nivolumab well past 80 days. EX1009 at 3173 (*see* figures reproduced below).

147. In selecting a flat dose of nivolumab to be administered once every four weeks as an alternative to 240 mg once every two weeks, 480 mg would have been a logical choice for POSAs because it is twice the 240 mg dose—consistent with the doubling of time between treatments (from two to four weeks) while administering the same total amount of nivolumab as in NCT-109. Additionally, the administration of a dose every four weeks was taught by Brahmer. EX1009 at 3168.



148. Thus, POSAs would have been motivated to administer a flat dose of 480 mg nivolumab once every four weeks following the combination therapy with ipilimumab as an alternative to administering 240 mg once every two weeks.

b. Reasonable Expectation that 480 mg Nivolumab Once Every Four Weeks Would Be Comparable to 3 mg/kg Once Every Two Weeks

149. POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering a flat dose of 480 mg nivolumab once every four weeks following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 3 mg/kg once every two weeks (as expressly disclosed in NCT-505) and likewise comparable to administering a flat dose of 240 nivolumab every two weeks per NCT-505-NCT-109 (as expressly disclosed in NCT-109).

150. As reflected in Brahmer, nivolumab was known to have a wide therapeutic window and long-lasting effects. EX1009 at 3171 (“PD-1 occupancy appeared to be dose-independent” and “mean plateau occupancy of 72%” was observed “ ≥ 57 days ... after one infusion.”). Thus, POSAs would have expected that one infusion of 480 mg nivolumab would produce a sufficient concentration of nivolumab to achieve efficacy for over 57 days – about eight weeks. Consequently, POSAs would have expected 480 mg nivolumab every four weeks to have substantially the same efficacy as 3 mg/kg nivolumab every two weeks (i.e., 240

mg for an average 80 kg patient—consistent with NCT-109) because Brahmer taught that nivolumab was dose-independent and effective much longer—up to eight weeks. EX1009 at 3171.

151. For purposes of my analysis concerning this issue, I also relied in part on the Declaration of Dr. Dhaval K. Shah (EX1029). As discussed in Section VI.C, a POSA would either have (1) been skilled in pharmacokinetics or (2) able to communicate as part of a team with pharmacokinetics experts if necessary. As reflected in his CV (EX1030), Dr. Shah is a pharmacokinetics expert. He developed a mathematical model to characterize the clinical pharmacokinetics of nivolumab in cancer patients. EX1029, ¶¶19, 40-51. That model was based on data from the Brahmer (EX1009) and Topalian (EX1011) articles discussed herein. EX1029, ¶¶35-43. Based on that model, Dr. Shah concluded that a dose of 480 mg of nivolumab every four weeks would have been expected to have a comparable effect to NCT-109's disclosed dose of 240 mg of nivolumab every two weeks. EX1029, ¶¶23, 52-57, 59. This conclusion—based on data and related modeling available as of early 2015 (and indeed earlier, as Dr. Shah explains)—would have confirmed a POSA's reasonable expectation of success in implementing NCT505-NCT109 while administering 480 mg nivolumab every four weeks (rather than 240 mg nivolumab every two weeks) for the nivolumab monotherapy.

152. The use of 480 mg nivolumab every four weeks is further supported by NCT02713867 (“NCT-867”), a posting from ClinicalTrials.gov that was posted on March 21, 2016 (EX1013) – over a month before April 28, 2016, the earliest possible effective filing date of claims 12 and 18 (*see* above in Section IV). NCT-867 disclosed using 480 mg nivolumab once every four weeks to treat cancer. EX1013 at 4. While NCT-867 does not specifically disclose treating melanoma, POSAs would have expected the 480 mg nivolumab dose once every four weeks to be suitable for treating melanoma, at least because Brahmer discloses that nivolumab was “well tolerated,” “dose-independent” over a wide dose range and long-lasting (“≥ 57 days”), specifically for the treatment of melanoma, and tested a range of doses of nivolumab for the treatment of melanoma that span the flat 480 mg dose disclosed by NCT-867. EX1009 at 3167, 3171. That is, Brahmer discloses that “mean plateau occupancy of 72%” was observed “≥ 57 days ... *after one infusion.*” EX1009 at 3171. Brahmer further discloses that “even when serum levels are *undetectable* (< 1.2 µg/mL), *sufficient concentrations persist* to maintain plateau PD-1 occupancy.” EX1009 at 3171. At least based on these teachings, POSAs would have expected that one infusion of 480 mg nivolumab would produce a sufficient concentration of nivolumab to achieve efficacy for over 57 days – about eight weeks. Consequently, POSAs would have expected 480 mg nivolumab every four weeks to have substantially the same efficacy as 3 mg/kg

nivolumab every two weeks because Brahmer taught that nivolumab was dose-independent over a wide dose range and effective much longer than four weeks – up to eight weeks. EX1009 at 3171.

153. Accordingly, POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 480 mg nivolumab once every four weeks following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 240 mg nivolumab every two weeks per NCT-505-NCT-109.

c. Obviousness of 480 mg Dose Falling Within Prior Art Range

154. Brahmer disclosed a range of doses “.3, 1, 3, or 10 mg/kg” (EX1009 at 3167), which translates to flat doses of 24 mg, 80 mg, 240 mg, and 800 mg for an average 80 kg person with administration “spaced by 4 weeks”. Accordingly, the claimed 480 mg dose falls within Brahmer’s 24 mg – 800 mg dosage range.

155. I was asked to review the prosecution history of the ’113 Patent to determine whether Patent Owner ever presented any data or evidence during prosecution suggesting that the 480 mg dose was critical, or yielded results that were unexpected, or was otherwise thought not to work. *See* EX1002. No such data or evidence was presented by Patent Owner.

d. Conclusion: Claims 12 and 18 Are Obvious

156. NCT505–NCT109, as practiced with a flat dose of 480 mg once every four weeks (as suggested by Brahmer) in lieu of a 240 mg flat dose once every two weeks (as disclosed in NCT-109), renders obvious claims 12 and 18.

B. GROUND 2: NCT-505, NCT-109, and Cogswell Render Obvious Claims 5-9 and 16

157. Claims 5-9 depend from dependent claim 4 and specify particular details concerning how “PD-L1 expression of the melanoma tumor” is measured prior to treatment. Claim 16 depends from claim 2 and requires “administering an anti-cancer agent” in addition to claim 2’s immunotherapy. Such techniques were already well known and recommended for cancer immunotherapy, as disclosed in Cogswell. There was nothing inventive about using them to practice NCT-505 either on its own or when implemented in view of NCT-109 to use a 240 mg flat dose. Claims 5-9 and 16 are therefore unpatentable as obvious over NCT-505 in view of NCT-109 and Cogswell.

1. Reason to Combine Cogswell With NCT505-NCT109

158. NCT-505 discloses a method of testing for PD-L1 expression (*see my discussion above in Section X.A.1.e.i.2*), but does not specify the details of such testing. POSAs would have been motivated to implement NCT-505 using Cogswell’s pre-treatment PD-L1 expression measurement method to measure PD-L1 expression. EX1015 at 125:23-25 (disclosing “*pre-treatment PD-L1 expression*

was measured by IHC in FFPE tumor specimens using the rabbit anti-PD-L1 mAb, 28-8, and an automated assay developed by Dako.”). In particular, POSAs would have been motivated to turn to the detailed disclosure of PD-L1 expression measurement included in Cogswell when making the assessment of PD-L1 expression as disclosed by NCT-505 in combination with NCT-109 (hereinafter, “NCT505-NCT109-Cogswell”). Indeed, Cogswell expressly references NCT-5050. EX1015 at 53:9.

2. Reasonable Expectation of Success

159. POSAs would have had at least a reasonable expectation that the PD-L1 testing disclosed by Cogswell would successfully measure the PD-L1 expression of the melanoma tumors, as taught in NCT-505, because Cogswell discloses that its rabbit clone 28-8 “produced the most robust detection specifically of membranous PD-L1.” EX1015 at 35:9-12. POSAs would thus have had at least a reasonable expectation of successfully detecting PD-L1, as Cogswell disclosed a detection method that was effective at doing exactly that.

3. Claim-by-Claim Analysis

160. As I discussed above in Sections X.B.1-2, POSAs would have had reason to practice NCT505-NCT109 using Cogswell’s detailed PD-L1 testing method and would have had a reasonable expectation of success in doing so. And

as detailed below, NCT505-NCT109-Cogswell discloses all limitations of claims 5-9 and 16.

161. For at least these reasons as well as those discussed in Ground 1A regarding why independent claim 2 and dependent claim 4 would have been obvious based on the state of the art as of April 28, 2015 (*i.e.*, one year before the earliest priority date to which those claims are possibly entitled, as discussed above in Section X.A.1), dependent claims 5-9 and 16 would have also been obvious as of this date.

a. Claim 5: Providing a Sample of Tumor Cells

162. Claim 5 depends from claim 4 and further recites: “wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.”

163. NCT505–NCT109–Cogswell satisfies claim 5, thus rendering it obvious. Specifically, NCT505–NCT109–Cogswell satisfies claim 4, from which claim 5 depends, for the same reasons explained in Ground 1A. *See* my discussion above in Section X.A.1.e.iv. As to claim 5’s additional requirement of providing a “test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells,” Cogswell discloses a “method of immunotherapy of a subject afflicted with cancer” by which one

“provide[s] a test tissue sample...comprising tumor cells and tumor-infiltrating inflammatory cells.” EX1015 at 3:26-30.

b. Claim 6: Assessing the Portion of the Cells that Express PD-L1 on the Cell Surface

164. Claim 6 depends from claim 5 and further recites: “wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.”

165. NCT505–NCT109–Cogswell satisfies claim 6, thus rendering it obvious. Specifically, NCT505–NCT109–Cogswell satisfies claim 5 (from which claim 6 depends) for the reasons explained in the Section immediately above. As to claim 6’s additional requirement of “assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface,” Cogswell’s above-quoted passage further discloses “assessing the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface.” EX1015 at 3:26-30; *see also* EX1015 at Abstract (disclosing measuring “the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface”).

c. Claim 7: IHC Assay on a FFPE Sample

166. Claim 7 depends from claim 6 and further recites: “wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.”

167. NCT505–NCT109–Cogswell satisfies claim 7, thus rendering it obvious. Specifically, NCT505–NCT109–Cogswell satisfies claim 6 (from which claim 7 depends) for the reasons explained in the Section immediately above. As to claim 7’s additional requirements that the “test tissue sample” be a “formalin-fixed paraffin-embedded (FFPE) tissue sample” and further that the “presence of PD-L1 [be] determined using an automated IHC assay,” Cogswell discloses that in certain embodiments “the test tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample” and the determination of “the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is achieved by immunohistochemical (IHC) staining of the FFPE sample.” EX1015 at 5:18-20.

168. Additionally, Cogswell discloses that the “[a]nti-PD-L1 Abs of the invention also include isolated Abs selected for their ability to bind to PD-L1 in *formalin-fixed, paraffin-embedded (FFPE) tissue specimens*” and that “pre-treatment PD-L1 expression was measured by *IHC in FFPE tumor specimens* using the rabbit anti-PD-L1 mAb, 28-8, and an *automated assay* developed by Dako.” EX1015 at 3:25-26, 125:23-25.

169. Accordingly, POSAs would have understood that these teachings were applicable to the earlier portions quoted in connection with claims 5 and 6. *See also* EX1015 at 139-140 (claims 4-7).

d. Claim 8: the Anti-PD-L1 mAb Has a Heavy Variable Region Comprising the Amino Acids in SEQ ID NO:

**1 and a Light Variable Region Comprising the Amino
Acids in SEQ ID NO: 2**

170. Claim 8 depends from claim 7 and further recites: “wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2.”

171. NCT505–NCT109–Cogswell satisfies claim 8, thus rendering it obvious. NCT505–NCT109–Cogswell satisfies claim 7 (from which claim 8 depends) for the reasons explained in the Section immediately above. As to claim 8’s additional requirements related to the anti-PD-L1 monoclonal antibody, Cogswell discloses that “[t]he clone that produced the most robust detection specifically of membranous PD-L1, rabbit clone 28-8, was selected for the IHC assays” and that “[t]he sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively.” EX1015 at 35:9-12; EX1027.

Cogswell’s SEQ ID NOs. 35 and 36 are identical to the ’113 Patent’s SEQ ID NO: 1 and SEQ ID NO: 2. *Compare* EX1015 at 133 (defining SEQ ID NO: 35 as “V_H amino acid sequence of 28-8” and SEQ ID NO: 36 as “V_L amino acid sequence of 28-8”) *with* EX1001 at 38:45-65 (defining SEQ ID NO: 1 as “V_H amino acid

sequence of 28-8 (*Oryctolagus cuniculus*)” and SEQ ID NO: 2 as “V_L amino acid sequence of 28-8 (*Oryctolagus cuniculus*)”).

e. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

172. Claim 9 depends from claim 2 and further recites: “wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.”

173. NCT505–NCT109–Cogswell satisfies claim 9, thus rendering it obvious. NCT505–NCT109–Cogswell satisfies claim 2 (from which claim 9 depends) for the same reasons that NCT505–NCT109 satisfies claim 2 as detailed above in Section X.A.1.e.ii. As to claim 9’s additional requirements, Cogswell discloses “***PD-L1 positivity was defined per specimen by a 5% expression threshold.***” EX1015 at 111:16-18. POSAs would thus have understood Cogswell to disclose a threshold of less than 5% of tumor cells showing binding to an anti-PD-L1 antibody as being PD-L1-negative. Moreover, it was already known that PD-L1 negative melanoma patients were responsive to the combination of nivolumab and ipilimumab—thereby motivating POSAs to include such patients (i.e., including those with expression thresholds under 5%) when practicing NCT505–NCT109. EX1028 at 1.

f. Claim 16: Anti-Cancer Agent

174. Claim 16 depends from claim 2 and further requires “administering an anti-cancer agent.” NCT505–NCT109 discloses each and every element of claim 2, as explained in Ground 1A. *See* my discussion above in Section X.A.1.e.ii.

Cogswell further discloses that a “combined PD-1 and CTLA-4 blockade may also be further combined with standard cancer treatments,” such as “chemotherapeutic regimes.” EX1015 at 63:25-27; *see also* EX1015 at 40:5-8.

175. POSAs would have been motivated to administer chemotherapy in addition to the administration of nivolumab and ipilimumab per NCT505–NCT109 to “increase[e] levels of tumor antigen in the antigen presentation pathway,” resulting in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1. POSAs would have had at least a reasonable expectation that such additional anti-cancer agents would be at least additive because Cogswell discloses that, in fact, such additional anti-cancer agents resulted in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1.

176. Cogswell also discloses that its “Abs may be used alone or in combination.... either or both of these Abs may be used in conjunction with other immunogenic and/or anti-cancer agents.” EX1015 at 40:5-8. POSAs would have been motivated to administer chemotherapy in addition to the administration of nivolumab and ipilimumab according to NCT505–NCT109 to “increase[e] levels

of tumor antigen in the antigen presentation pathway,” resulting in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1. POSAs would have had at least a reasonable expectation that such additional anti-cancer agents would be at least additive because Cogswell discloses that, in fact, such additional anti-cancer agents resulted in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1.

177. Thus, administering an anti-cancer agent (per Cogswell) in addition to nivolumab and ipilimumab (per NCT505-NCT109) would satisfy claim 16, thus rendering it obvious.

C. GROUND 3A, 3B, 3C: Postow and NCT-109 Render Obvious Claims 1-6, 9-10, 13-15, and 19-20

178. Grounds 3A, 3B, and 3C center on Postow, which confirms that the dosing regimen previously published by NCT-505 (including the combination of nivolumab and ipilimumab, followed by nivolumab monotherapy once every two weeks at 3 mg/kg) was successful in treating melanoma. Thus, Postow in view of the known 240 mg flat dosing option for nivolumab recited in NCT-109 discloses all of the dosing amounts and frequencies of the claimed combination therapy recited in Challenged Claims 1-6, 9-10, 13-15, and 19-20. It would have been obvious to implement Postow’s nivolumab monotherapy with flat dosing of 240 mg every two weeks (as disclosed in NCT-109) or alternatively 480 mg every four weeks (within Brahmer’s range)—thereby delivering the same amount of

nivolumab for an average 80 kg melanoma patient—for substantially the same reasons detailed in Grounds 1A, 2A, and 3A.

179. As explained in Ground 1A, the anti-PD-1 antibody nivolumab disclosed by Postow (and NCT-505) was known to have a wide therapeutic window that was well-tolerated, dose-independent over a wide dose range, and long-lasting. EX1009 at 3169, 3171. For such antibodies, flat dosing was known to have “numerous advantages over body size-based dosing.” EX1008 at 1023. POSAs would have been motivated to substitute, and would have had at least a reasonable expectation of successfully substituting, a known flat dose of 240 mg nivolumab once every two weeks or a flat dose of 480 mg once every four weeks for the 3 mg/kg dose once every two weeks as disclosed by Postow.

1. Ground 3A: Postow and NCT-109 Render Obvious Claims 1-6, 9-10, 13-15, and 19-20

180. Postow and NCT-109 together disclose all of the dosing amounts and frequencies of anti-PD-1 and anti-CTLA-4 recited in Challenged Claims 1-6, 9-10, 13-15, and 19-20, and POSAs would have had reason to combine these teachings to arrive at the claimed treatment method with a reasonable expectation of success.

a. Postow Discloses Successfully Treating Melanoma with a Combination of Nivolumab and Ipilimumab Followed by Nivolumab Alone

181. Postow discloses that metastatic melanoma patients were administered “ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab

(1 mg per kilogram) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects.” EX1005 at p. 2006.

182. Postow’s combination therapy was effective at treating melanoma and achieved a “*complete response*... in 16 patients (22%)” for the combination therapy (EX1005 at p. 2006). The reference to complete response means that all target melanoma tumors “[d]isappear[ed].” EX1039 at 232 (defining complete response). Moreover, “the median progression-free survival *was not reached*.” EX1005 at p. 2006, 2009. This means that more than half of the patients did not experience any cancer progression through at least 11 months. Postow concludes “the combination of ipilimumab plus nivolumab resulted in *durable responses* and a *substantially higher objective response rate, longer progression-free survival, and higher rates of complete response* than ipilimumab monotherapy among patients with BRAF wild-type advanced melanoma and those with BRAF-mutant advanced melanoma.” EX1005 at p. 2016.

b. Reason to Modify: POSAs Would Have Preferred Using a Flat Dose of Nivolumab Instead of the Body Weight Dose

183. While Postow disclosed a body weight dose of 3 mg/kg nivolumab every two weeks following coadministration with ipilimumab, POSAs would have had reason to change that body weight dose to a known flat dose for the same

reasons previously discussed in Ground 1A. *See* my discussion above in Section X.A.1.b.

c. The Modification: 240 mg Every Two Weeks or 480mg Every Four Weeks

184. POSAs would have chosen the known 240 mg flat dose of nivolumab once every two weeks for the same reasons previously discussed in Ground 1A. *See* my discussion above in Section X.A.1.c (reasons for a 240 mg flat dose every two weeks). POSAs would thus have modified the method of treatment disclosed by Postow by administering 240 mg once every two weeks, following the combination therapy with nivolumab and ipilimumab (hereinafter the “Postow–NCT109”).

d. Reasonable Expectation of Success: POSAs Knew Nivolumab Was Long-Lasting and Had a Wide Therapeutic Window

185. POSAs would have had at least a reasonable expectation that the efficacy and tolerability of administering 240 mg nivolumab once every two weeks following the combination therapy with nivolumab and ipilimumab would have been comparable to administering 3 mg/kg nivolumab every two weeks as disclosed by Postow for the same reasons previously discussed in Ground 1A. *See* my discussion above in Section X.A.1.d (expectation of success for a 240 mg flat dose every two weeks). Nivolumab’s wide therapeutic window of nivolumab would have provided POSAs at least a reasonable expectation that the efficacy of

240 mg nivolumab once every two weeks, following the combination therapy with nivolumab and ipilimumab, would have been comparable to administering 3 mg/kg nivolumab every two weeks as disclosed by Postow.

2. Claim-by-Claim Analysis

186. Postow–NCT109 satisfies every element of claims 1-6, 9-10, 13-15, and 19-20, rendering them obvious.

a. Claim 1

i. Preamble: Method for Treating a Melanoma

187. The preamble of claim 1 recites: “A method for treating a melanoma tumor in a human patient in need thereof comprising...” To the extent the preamble of claim 1 is limiting, Postow–NCT109 satisfies it because Postow discloses a method for treating “advanced melanoma” in a human patient as recited in the preamble of claim 1. EX1005 at p. 2006.

ii. Limitation 1(i): Identifying a Patient Having a PD-L1-Negative Melanoma

188. Limitation 1(i) recites “(i) identifying a patient having a PD-L1-negative melanoma tumor.” Postow–NCT109 satisfies limitation 1(i) because Postow discloses assessing the “expression of PD-L1 on the surface of tumor cells” “in pretreatment tumor samples” (EX1005 at p. 2008), which was then used to track any differences in efficacy depending on whether the patient had a PD-L1-positive or PD-L1-negative melanoma tumor (EX1005 at p. 2009 (“response rate

was independent of tumor PD-L1 status”), p. 2016 (“no significant difference in response rates between patients whose pretreatment tumors were defined as PD-L1–positive and those whose tumors were PD-L1–negative”)). Postow discloses at least 69 patients “in the combination group” “with PD-L1-negative tumors.” EX1005 at p. 2009.

189. The finding that ipilimumab-nivolumab *combination therapy* was effective in both PD-L1-negative patients as well as PD-L1-positive patients was especially relevant for PD-L1-negative patients. This was because an earlier 2012 study suggested that anti-PD-1 *monotherapy* may not be effective for PD-L1-negative melanoma, providing motivation to find treatments for PD-L1-negative melanoma. EX1011, 1 (“Of 17 patients with PD-L1–negative tumors, none had an objective response.”). Because Postow discloses ipilimumab-nivolumab combination therapy was effective with both PD-L1-positive and PD-L1-negative patients, Postow states “PD-L1 should not be used to *select* patients to receive combination treatment.” EX1005, at p. 2016.

190. This is consistent with limitation 1(i), which does not require that PD-L1-negative patients be “selected” but instead requires that at least one patient being administered the combination be identified as PD-L1-negative. As disclosed in Postow, it was standard in the art as of early 2015 to test tumor samples for PD-L1 expression when administering anti-PD1 antibodies in part to track any

differences in efficacy and in part because PD-L1-positive patients would have been strong candidates for anti-PD-1 monotherapy. POSAs would have thus been motivated to continue to test tumor samples for PD-L1 and administer PD-L1-negative patients the ipilimumab-nivolumab combination therapy taught by Postow since those patients would not have been considered strong candidates for anti-PD1 monotherapy. EX1005, at p. 2016 (“Positive expression of PD-L1, one of the ligands of PD-1, has been associated with increased response rates among patients treated with nivolumab as a single agent.”)

191. Accordingly, a POSA would have treated PD-L1-negative patients in view of Postow.

iii. Limitation 1(ii)(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

192. Limitation 1(ii)(a) recites “(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...”

193. Postow–NCT109 satisfies limitation 1(ii)(a) because Postow discloses administering to the patient “*ipilimumab (3 mg per kilogram of body weight)*”

combined with either *nivolumab (1 mg per kilogram)* or placebo once *every 3 weeks for four doses.*” EX1005 at p. 2006. Specifically, Postow discloses an “objective response rate ... [of] 55% (95% CI, 41 to 69) among patients with PD-L1–negative tumors.” EX1005 at p. 2009.

iv. Limitation 1(ii)(b): Administering a Flat Dose of About 240 mg of the Anti-PD-1 Antibody

194. Limitation 1(ii)(b) recites “(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.” Postow–NCT109 satisfies limitation 1(ii)(b). Postow discloses administering “*nivolumab (3 mg per kilogram)*” “every 2 weeks” following the coadministration of nivolumab and ipilimumab. EX1005 at p. 2006. And NCT-109 discloses administering a flat dose of “**240 mg**” nivolumab “every 2 weeks” (EX1007 at 5), including to “melanoma subjects” “after- receiving CTLA-4 and anti-PD-1 or PD L-1 antibody therapy” (EX1007 at 6).

195. A POSA would have had reason to modify the 3 mg/kg nivolumab once every two weeks disclosed by Postow for the known option of a flat dose of 240 mg every two weeks to take advantage of the “numerous advantages” that Wang discloses flat doses have over body weight doses (Wang at 1023) for the same reasons explained above in Sections X.A.1.b-c.

196. A POSA would have had at least a reasonable expectation of making the substitution and achieving comparable clinical results to the results Postow

discloses because of the wide therapeutic window and long-lasting effects of nivolumab for the same reasons explained above in Section X.A.1.d. *See also* EX1009 at 3167, 3169, 3171; EX1036 at 25-26.

197. Postow–NCT109 thus satisfies limitation 1(ii)(b), rendering claim 1 obvious.

b. Claim 2

i. Preamble: Method for Treating a Melanoma

198. The preamble of claim 2 recites: “A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient...” To the extent the preamble of claim 2 is limiting, Postow–NCT109 satisfies it for the same reasons it satisfies the preamble of claim 1. EX1005 at p. 2006; *See* my discussion above in Section X.C.2.a.i.

ii. Limitation 2(a): Administering 1 mg/kg of an Anti-PD-1 Antibody and an Anti-CTLA-4 Antibody Every Three Weeks for About 4 Doses

199. Limitation 2(a) recites: “(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...”

200. Postow–NCT109 satisfies limitation 2(a) for the same reasons it satisfies limitation 1(ii)(a). *See* my discussion above in Section X.C.2.a.iii.

iii. Limitation 2(b): Administering a Flat Dose of About 240 mg or About 480 mg of the Anti-PD-1 Antibody

201. Limitation 2(b) recites: “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.”

202. Postow–NCT109 satisfies limitation 2(b) for the same reasons it satisfies limitation 1(ii)(b), rendering claim 2 obvious. *See* my discussion above in Section X.C.2.a.iv.

c. Claim 3: Over 8 Months Progression-Free Survival and/or At Least About 10% Tumor Size Reduction

203. Claim 3 depends from claim 2 and further recites: “wherein the patient is characterized by (i) extended progression-free survival for over 8 months following the administration, (ii) tumor size reduction at least about 10% compared to the tumor size prior to the administration, or (iii) both (i) and (ii).”

204. Postow–NCT109 satisfies claim 3, thus rendering it obvious. Specifically, Postow discloses that “the median progression-free survival was not reached with the combination therapy.” EX1005 at p. 2006; *see also* EX1005 at p. 2009 (describing progression-free survival for more than 60% of patients at eight months), 2012 (Fig. 1). A POSA would have understood this to mean that progression-free survival was well over 8 months for many patients.

205. Moreover, Postow discloses a “complete response was observed in 16 patients (22%) in the combination group.” EX1005 at p. 2009. A POSA would have understood this to mean that the tumor was reduced by more than the claimed “at least about 10%.” As discussed above in Section X.A.1.e.iii, a complete response means that all target melanoma tumors “[d]isappear[ed].” EX1039 at 232 (defining complete response). A POSA would expect these results to apply to PD-L1 negative tumors because Postow disclosed that “[i]n the combination group, the objective response rate was independent of tumor PD-L1 status.” EX1005 at p. 2009.

206. Separately, Postow discloses that nivolumab and ipilimumab, as disclosed by NCT-505, achieved a median decrease in tumor burden of 68.1% pursuant to the RECIST standard. EX1005 at p. 2008-2009; EX1039. While claim 3 depends from claim 2 and is agnostic as to tumor PD-L1 status, POSAs would have expected these results to apply to PD-L1 negative tumors because Postow expressly disclosed that “[i]n the combination group, the objective response rate was independent of tumor PD-L1 status.” EX1005 at p. 2009.

207. As I discussed in Section X.C.1.d above, POSAs would have had at least a reasonable expectation that the efficacy of 240 mg nivolumab once every two weeks, following the combination therapy with nivolumab and ipilimumab, would have been comparable to administering 3 mg/kg nivolumab every two

weeks given nivolumab's wide therapeutic window and the multiple other monoclonal antibodies for which flat dosing had proven successful. *See also* EX1009 at 3167, 3169, 3171; EX1036 at 25-26.

d. Claim 4: Measuring PD-L1 Expression

208. Claim 4 depends from claim 2 and further recites: “further comprising measuring a PD-L1 expression on the melanoma tumor prior to the administration.” Postow–NCT109 satisfies claim 4, thus rendering it obvious because Postow discloses that the “expression of PD-L1 on the surface of tumor cells was assessed in pretreatment tumor samples.” EX1005 at p. 2008. A POSA would have understood that, in order to be able to make this statement, Postow would have measured PD-L1 expression on the melanoma tumor prior to the administration.

e. Claim 5: Providing a Sample of Tumor Cells

209. Claim 5 depends from claim 4 and further recites: “wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.”

210. Postow–NCT109 satisfies claim 5 because Postow discloses “the expression of PD-L1 on the surface of tumor cells was assessed in pretreatment tumor samples.” EX1005 at p. 2008. POSAs would have understood that to assess

the expression of PD-L1 on the surface of tumor cells, a test tissue sample would need to be obtained from the patient, thus rendering claim 5 obvious.

f. Claim 6: Assessing the Proportion of the Cells that Express PD-L1 on the Cell Surface

211. Claim 6 depends from claim 5 and further recites: “wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.”

212. Postow–NCT109 satisfies claim 6, thus rendering it obvious because Postow discloses a “tumor was considered to be PD-L1–positive if at least 5% of tumor cells showed cell-surface PD-L1 staining.” EX1005 at p. 2008. POSAs would have understood that the “at least 5%” threshold meant assessing the proportion of cells in the test tissue sample that express PD-L1 as recited in claim 6 because a percentage is a proportion, and the proportion of cells that express PD-L1 would need to be determined to evaluate whether the “at least 5%” threshold was met.

g. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

213. Claim 9 depends from claim 2 and further recites: “wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.”

214. Postow–NCT109 satisfies claim 9, thus rendering it obvious because Postow discloses a “tumor was considered to be PD-L1–positive if at least 5% of tumor cells showed cell-surface PD-L1 staining” and Postow discloses at least 69 patients “in the combination group” “with PD-L1-negative tumors.” EX1005 at p. 2008-2009. Because Postow states that “tumor was considered to be PD-L1–positive if at least 5% of tumor cells showed cell-surface PD-L1 staining,” POSAs would understand that Postow understood a tumor to be PD-L1 negative if the tumor exhibited 5% or less of tumor cells showing cell-surface PD-L1 staining. POSAs would have understood that meant a PD-L1–*negative* tumor would have less than 5% of tumor cells showing binding to the anti-PD-L1 antibody used in the assay as required by claim 9. Accordingly, Postow’s PD-L1-negative patients would have had less than 5% of tumor cells showing binding to the anti-PD-L1 antibody.

h. Claims 10 and 20: the Anti-PD-1 Antibody Is Nivolumab

215. Claims 10 and 20 depend from claims 2 and 1, respectively, and recite “wherein the anti-PD-1 antibody is nivolumab.”

216. Postow–NCT109 satisfies claims 10 and 20 because Postow discloses the anti-PD1 antibody “nivolumab” (EX1005 at p. 2006), the same anti-PD1 antibody NCT-109 disclosed (EX1007 at 5), thus rendering claims 10 and 20 obvious.

i. Claim 13: the Anti-CTLA-4 Antibody Is Ipilimumab

217. Claim 13 depends from claim 2 and further recites “wherein the anti-CTLA-4 antibody is ipilimumab.”

218. Postow–NCT109 satisfies claim 13, thus rendering it obvious because Postow discloses the anti-CTLA-4 antibody “ipilimumab.” EX1005 at p. 2006.

j. Claims 14, 15, and 19: the Anti-CTLA-4 Antibody Is from 0.1 mg/kg to 10.0 mg/kg or 3 mg/kg

219. Claim 14 depends from claim 2 and further recites: “wherein the dose of the anti-CTLA-4 antibody is from 0.1 mg/kg to 10.0 mg/kg.” Claim 15 depends from claim 14 and further recites: “wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.” Claim 19 depends from claim 1 and further recites: “wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.”

220. Postow–NCT109 satisfies claims 14, 15, and 19, thus rendering them obvious because Postow discloses administering 3 mg/kg of the anti-CTLA-4 antibody ipilimumab – exactly the dose claimed by claims 15 and 19 and within the 0.1 mg/kg to 10 mg/kg range claimed by claim 14. EX1005 at p. 2006.

221. The combined references of Postow and NCT-109 disclose each and every limitation of Challenged Claims 1-6, 9-10, 13-15, and 19-20 and as discussed in Sections X.C.1.b-d, a POSA would have had reason to combine such disclosures and a reasonable expectation of arriving at the claimed methods, thus rendering these Challenged Claims obvious.

D. GROUND 3B: Postow and NCT-109 Render Obvious Claims 11 and 17

222. Claims 11 and 17 are discussed separately in Ground 3B because I was not asked to and did not render an opinion regarding whether claims 11 and 17 are entitled to a April 28, 2015 priority date. *See* Section VI.E.² Nonetheless, claims 11 and 17 were obvious as of April 28, 2015.

223. Claims 11 and 17 depend from claims 2 and 1, respectively, which are obvious over Postow-NCT109 for the same reasons I set forth in Ground 3A.

224. Claims 11 and 17 each recite “the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.” As explained above in Section X.A.1.c, POSAs would have administered 240 mg nivolumab once every two weeks instead of the 3 mg/kg every two weeks as disclosed by Postow to achieve the “numerous advantages” of flat dosing as disclosed by Wang. *See also* my discussion above in Section X.A.1.b. NCT-109 specifically discloses administering a flat dose of “**240 mg**” nivolumab “**every 2 weeks**” (EX1007 at 5), including to “melanoma subjects” “after receiving CTLA-4 and anti-PD-1 or PD L-1 antibody therapy” (EX1007 at 6). In view of these disclosures and the reasons

² While the '973 Provisional discloses a 240 mg dose of nivolumab, as explained above in Section VI.E, Postow was publicly accessible even before the '973 Provisional was filed.

a POSA would have to make such modifications and to reasonably expect such to succeed, as discussed in Section X.A.1.b above, claims 11 and 17 are obvious.

Accordingly, claims 11 and 17 are obvious over Postow-NCT109.

E. GROUND 3C: Postow and NCT-109 Render Obvious Claims 12 and 18

225. Claims 12 and 18 depend from claims 2 and 1, respectively, which are obvious over Postow-NCT109 for the reasons set forth in Ground 1A. Claims 12 and 18 each recite “the dose of the anti-PD-1 antibody in (b) [i.e., the flat dose monotherapy] is about 480 mg administered once every four weeks.”

226. Postow-NCT109 renders obvious claims 12 and 18 at least because a POSA would have been motivated to modify Postow-NCT109 to obtain the 480 mg administered once every four weeks dosing. As explained in Section X.A.3.a, above, POSAs would have administered 480 mg nivolumab once every four weeks instead of the 3 mg/kg every two weeks as disclosed by Postow to achieve the “numerous advantages” of flat dosing as disclosed by Wang. *See also* Section X.A.1.b. Administering 480 mg nivolumab once every four weeks would have been particularly convenient for patients, requiring them to come in half as frequently for infusions.

227. POSAs would have had at least a reasonable expectation that the 480 mg dose once every four weeks would have had comparable efficacy and tolerability to 240 mg once every two weeks (as disclosed in NCT-109) and

likewise 3 mg/kg once every two weeks (as disclosed in Postow) for the same reasons described for Ground 1C (*see* Section X.A.3.a), including because of nivolumab’s wide therapeutic window and long-lasting effects. EX1009 at 3171 (“PD-1 occupancy appeared to be *dose-independent*” and “mean plateau occupancy of 72%” was observed “*≥ 57 days ... after one infusion.*”). Thus, POSAs would have expected that one infusion of 480 mg nivolumab would produce a sufficient concentration of nivolumab to achieve efficacy for over 57 days – about eight weeks. Consequently, POSAs would have expected 480 mg nivolumab every four weeks to have substantially the same efficacy as 3 mg/kg nivolumab every two weeks (i.e., 240 mg for an average 80 kg patient—consistent with NCT-109) because Brahmer taught that nivolumab was dose-independent and effective much longer – up to eight weeks. EX1009 at 3171.

228. Dr. Shah’s pharmacokinetic modeling (as discussed in Section X.A.3.a) further confirms a POSA’s reasonable expectation of success in implementing NCT505-NCT109 while administering 480 mg nivolumab every four weeks (rather than 240 mg nivolumab every two weeks) for the nivolumab monotherapy.

F. GROUND 4: Postow, NCT-109, and Cogswell Render Obvious Claims 5-9 and 16

229. Postow discloses measuring PD-L1 expression in a patient’s melanoma tumor. EX1005 at p. 2008 (disclosing assessing the “expression of PD-

L1 on the surface of tumor cells” “in pretreatment tumor samples”). Cogswell provides additional details regarding measuring PD-L1 expression on tumor cell surfaces. EX1015 at 125:22-33. There is nothing inventive in further requiring the use of a standard prior art test to identify a PD-L1-negative melanoma tumor, or in supplementing Postow-NCT-109’s immunotherapy with an anti-cancer agent (as also disclosed in Cogswell)—rendering claims 5-9 obvious.

1. Reason to Combine

230. Postow discloses a specific assay developed by “Dako” for measuring PD-L1 expression. EX1005 at p. 2008. POSAs would have looked to Cogswell for further details to run the Dako test. EX1015 at 125:23-25 (disclosing “pre-treatment PD-L1 expression was measured by IHC in FFPE tumor specimens using the rabbit anti-PD-L1 mAb, 28-8, and an automated assay *developed by Dako.*”). POSAs would have thus been motivated to turn to Cogswell when performing the testing disclosed by Postow.

2. Reasonable Expectation of Success

231. POSAs would have had at least a reasonable expectation of successfully combining Cogswell with Postow and NCT-109 (hereinafter “Postow–NCT109–Cogswell”) because Postow identifies the Dako test by name, thus indicating that the test was suitable for the intended purpose. EX1005 at p. 2008. POSAs would have thus had at least a reasonable expectation that PD-L1

testing disclosed by Cogswell would successfully measure the PD-L1 of the melanoma tumors Postow disclosed measuring.

3. Claim-by-Claim Analysis

232. Postow–NCT109–Cogswell discloses every element of claims 5-9 and 16, rendering those claims obvious.

a. Claim 5: Providing a Sample of Tumor Cells

233. Claim 5 depends from claim 4 and further recites: “wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.”

234. Postow–NCT109–Cogswell satisfies claim 5, thus rendering it obvious. Specifically, Postow–NCT109–Cogswell satisfies claim 4, from which claim 5 depends for the same reasons discussed above in Ground 3A. *See my discussion above in Section X.C.2.e.* Postow–NCT109–Cogswell also satisfies claim 5 based on Postow’s disclosure of obtaining a sample of tumor cells. EX1005 at p. 2008. For example, Postow discloses that “the expression of PD-L1 on the surface of tumor cells was assessed in pretreatment tumor samples”. EX1005 at p. 2008. Moreover, Cogswell discloses a test to assess “the proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface exceeds a predetermined threshold level.” EX1015 at Abstract. POSAs

would thus have understood Cogswell to disclose providing a test tissue sample of the tumor cells obtained from the patient as recited in claim 5, thus rendering claim 5 obvious over Postow–NCT109–Cogswell.

b. Claim 6: Assessing the Portion of the Cells that Express PD-L1 on the Cell Surface

235. Claim 6 depends from claim 5 and further recites: “wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.”

236. Postow–NCT109–Cogswell satisfies claim 6, thus rendering it obvious. Cogswell discloses measuring “the *proportion of cells in a test tissue sample from the patient that express PD-L1 on the cell surface*” as well. EX1015 at Abstract. In addition, Postow discloses a “tumor was considered to be PD-L1–positive if *at least 5%* of tumor cells showed *cell-surface* PD-L1 staining” as well. EX1005 at p. 2008. As discussed in Section X.C.2.f, POSAs would have understood that the “at least 5%” threshold meant assessing the proportion of cells in the test tissue sample that express PD-L1 as recited in claim 6 because a percentage is a proportion, and the proportion of cells that express PD-L1 would need to be determined to evaluate whether the “at least 5%” threshold was met. For at least these reasons, a POSA would have had reason to combine these disclosures to arrive at the method of claim 6 with a reasonable expectation of success.

c. Claim 7: IHC Assay on a FFPE Sample

237. Claim 7 depends from claim 6 and further recites: “wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.”

238. Postow–NCT109–Cogswell satisfies claim 7, thus rendering it obvious. Specifically, Cogswell discloses that the “[a]nti-PD-L1 Abs of the invention also include isolated Abs selected for their ability to bind to PD-L1 in *formalin-fixed, paraffin-embedded (FFPE) tissue specimens*” and that “pre-treatment PD-L1 expression was measured by *IHC in FFPE tumor specimens* using the rabbit anti-PD-L1 mAb, 28-8, and an *automated assay* developed by Dako”. EX1015 at 3:25-26, 125:23-25. A POSA would have reason to combine this teaching with Postow and NCT-109 to arrive at the method of claim 7 with a reasonable expectation of success, thus rendering claim 7 obvious. *See* Sections X.F.1-2.

d. Claim 8: the Anti-PD-L1 mAb Has a Heavy Variable Region Comprising the Amino Acids in SEQ ID NO: 1 and a Light Variable Region Comprising the Amino Acids in SEQ ID NO: 2

239. Claim 8 depends from claim 7 and further recites: “wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID

NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2.”

240. Postow–NCT109–Cogswell satisfies claim 8, thus rendering it obvious. Specifically, Cogswell discloses that “[t]he clone that produced the most robust detection specifically of membranous PD-L1, rabbit clone 28-8, was selected for the IHC assays” and that “[t]he sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively.” EX1015 at 35:9-12; EX1027. Cogswell’s SEQ ID NOs. 35 and 36 are identical to the ’113 patent’s SEQ ID NO: 1 and SEQ ID NO: 2. *See* my discussion above in Sections IX.F, X.B.3.d; *compare* EX1015 at 133 (defining SEQ ID NO: 35 as “V_H amino acid sequence of 28-8” and SEQ ID NO: 36 as “V_L amino acid sequence of 28-8”) *with* EX1001 at 38:45-65 (defining SEQ ID NO: 1 as “V_H amino acid sequence of 28-8 (*Oryctolagus cuniculus*)” and SEQ ID NO: 2 as “V_L amino acid sequence of 28-8 (*Oryctolagus cuniculus*)”).

241. A POSA would have reason to combine this teaching with Postow and NCT-109 to arrive at the method of claim 8 with a reasonable expectation of success, thus rendering claim 8 obvious. *See* Section X.F.1-2.

e. Claim 9: Less Than About 5% of Tumor Cells Show Binding to an Anti-PD-L1 Antibody

242. Claim 9 depends from claim 2 and further recites: “wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.”

243. Postow–NCT109–Cogswell satisfies claim 9, thus rendering it obvious. Cogswell discloses “*PD-L1 positivity was defined per specimen by a 5% expression threshold.*” EX1015 at 111:16-18. POSAs would thus have understood Cogswell to disclose a threshold of less than 5% of tumor cells showing binding to an anti-PD-L1 antibody as being PD-L1-negative. In addition, Postow discloses that a “tumor was considered to be PD-L1–*positive* if *at least 5%* of tumor cells showed *cell-surface* PD-L1 staining” and Postow discloses at least 69 patients “in the combination group” “with PD-L1-negative tumors.” EX1005 at p. 2009. POSAs would have understood that meant a PD-L1–*negative* tumor would have less than 5% of tumor cells showing binding to the anti-PD-L1 antibody used in the assay as required by claim 9. A POSA would understand that at least Postow’s identified patients as PD-L1 negative based upon the patients having less than about 5% of tumor cells showed *cell-surface* PD-L1 staining. A POSA would have reason to combine this teaching with Postow and NCT-109 to arrive at the method of claim 9 with a reasonable expectation of success, thus rendering claim 9 obvious. *See* Section X.F.1-2.

f. Claim 16: Anti-Cancer Agent

244. Claim 16 depends from claim 2 and recites “further comprising administering an anti-cancer agent.” Postow-NCT-109 discloses each and every element of claim 2, as explained in Ground 3A. *See* my discussion above in Section X.C.2.b. Cogswell further discloses that a “combined PD-1 and CTLA-4 blockade may also be further combined with standard cancer treatments,” such as “chemotherapeutic regimes.” EX1015 at 63:25-27. Cogswell further states that “Abs may be used alone or in combination.... either or both of these Abs may be used in conjunction with other immunogenic and/or anti-cancer agents.” EX1015 at 40:5-8. POSAs would have been motivated to administer chemotherapy in addition to the administration of the nivolumab and ipilimumab according to Postow–NCT109 to “increase[e] levels of tumor antigen in the antigen presentation pathway,” resulting in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1.

245. POSAs would have had at least a reasonable expectation that such additional anti-cancer agents would be at least additive because Cogswell discloses that, in fact, such additional anti-cancer agents resulted in “synergy with a combined PD-1 and CTLA-4 blockade.” EX1015 at 63:29-64:1. POSAs would have reason to further administer an anti-cancer agent with the therapies disclosed

in Postow and NCT-109 and would have had a reasonable expectation of success in doing so, thus rendering claim 16 obvious.

XI. SECONDARY CONSIDERATIONS

246. I was asked to review the patent and the prosecution history to determine whether either reflects the presence of unexpected results or other alleged secondary considerations (discussed above in Section V.E.2, and in paragraph 32) as to the Challenged Claims. I found no such evidence.

247. I note that the Challenged Claims require administering anti-PD-1 monotherapy as a *flat* dose, whereas the specification's data uniformly concerned *weight-based* doses. EX1001 at 27:2-12.

248. Moreover, nothing in the patent or the prosecution history ever ascribes any significance to the specific dosages listed in the claims.

249. The '113 Patent instead focuses on a showing "that for PD-L1 negative tumors, a combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody is more suitable than a monotherapy of either an anti-PD-1 antibody or an anti-CTLA-4 antibody." EX1001 at 10:59-63.

250. But the prior art disclosed such "combination therapy"—including for "PD-L1 negative" tumors—and highlighted its "unique features compared to either [anti-PD-1 or anti-CTLA-4] monotherapy." *E.g.*, EX1028. For example, NCT-505 concerned such combination therapy and included PD-L1 negative tumors.

EX1014. Postow later confirmed that such combination therapy yielded a “significantly greater” response rate than anti-CTLA-4 monotherapy—including in “PD-L1 negative tumors.” EX1005 at p. 2006, 2009.

251. My review of the patent and prosecution history thus confirmed that Patent Owner provided no evidence of secondary considerations as to the Challenged Claims.

* * *

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 that the foregoing is true and correct.

Dated: 2-27-25

Brent Hanks, M.D., Ph.D.

LISTING OF CHALLENGED CLAIMS

Ref.	Claim Limitation
1[pre]	A method for treating a melanoma tumor in a human patient in need thereof comprising:
1(i)	(i) identifying a patient having a PD-L1-negative melanoma tumor; and
1(ii)(a)	(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
1(ii)(b)	(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.
2[pre]	A method for treating a melanoma tumor in a human patient in need thereof comprising administering to the patient:

Ref.	Claim Limitation
2(a)	(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
2(b)	(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.
3	The method of claim 2, wherein the patient is characterized by (i) extended progression-free survival for over 8 months following the administration, (ii) tumor size reduction at least about 10% compared to the tumor size prior to the administration, or (iii) both (i) and (ii).
4	The method of claim 2, further comprising measuring a PD-L1 expression on the melanoma tumor prior to the administration.
5	The method of claim 4, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.

Ref.	Claim Limitation
6	The method of claim 5, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.
7	The method of claim 6, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.
8	The method of claim 7, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2.
9	The method of claim 2, wherein less than about 5% of tumor cells show binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.
10	The method of claim 2, wherein the anti-PD-1 antibody is nivolumab.

Ref.	Claim Limitation
11	The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.
12	The method of claim 2, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
13	The method of claim 2, wherein the anti-CTLA-4 antibody is ipilimumab.
14	The method of claim 2, wherein the dose of the anti-CTLA-4 antibody is from 0.1 mg/kg to 10.0 mg/kg.
15	The method of claim 14, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.
16	The method of claim 2, further comprising administering an anti-cancer agent.
17	The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 240 mg administered once every two weeks.

Ref.	Claim Limitation
18	The method of claim 1, wherein the dose of the anti-PD-1 antibody in (b) is about 480 mg administered once every four weeks.
19	The method of claim 1, wherein the dose of the anti-CTLA-4 antibody is 3 mg/kg.
20	The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.

APPENDIX A - LISTING OF MATERIALS CONSIDERED

Exhibit	Description
1001	U.S. Patent No. 10,174,113 (“113 Patent”)
1002	Prosecution History of U.S. Patent No. 10,174,113
1005	Postow et al., Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma., <i>N Engl J Med.</i> 2015 May 21; 372(21):2006-17. (“Postow”)
1007	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) (“NCT-109”)
1008	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. (“Wang”)
1009	Brahmer et al., Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. <i>J Clin Oncology.</i> 2010 Jul 1; 28(19):3167–3175. (“Brahmer”)
1011	Topalian et al., Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. <i>N Engl J Med.</i> 2012 Jun 28; 366(26):2443-54. (“Topalian”)
1013	NCT02713867 Version 2, Brief Title: “A Dose Frequency Optimization, Trial of Nivolumab 240 mg Every 2 Weeks vs Nivolumab 480 mg Every 4 Weeks in Subjects With Advanced or Metastatic Non-small Cell Lung Cancer Who Received 4 Months of Nivolumab at 3 mg/ kg or 240 mg Every 2 Weeks” (Last Update Posted to clinicaltrials.gov: March 22, 2016) (“NCT-867”)
1014	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) (“NCT-505”)
1015	International Patent Publication No. WO 2013/173223 A1 (“Cogswell”)

Exhibit	Description
1018	U.S. Provisional Patent Application No. 62/153,973 (filed April 28, 2015) (“973 Provisional”)
1019	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary
1021	Zalevsky et al., Enhanced Antibody Half-Life Improves in Vivo Activity. <i>Nat Biotechnol.</i> 2010 Feb; 28(2):157-9. (“Zalevsky”)
1022	Weber J., Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. <i>Oncologist.</i> 2007 Jul; 12(7):864-72 (“Weber”)
1025	Philips et al., Therapeutic Uses of Anti-PD-1 and Anti-PD-L1 Antibodies. <i>Int Immunol.</i> 2015 Jan; 27(1):39-46. doi: 10.1093/intimm/dxu095. Epub 2014 Oct 16. (“Philips”)
1027	Sequence Listing of International Patent Publication No. WO 2013/173223 A1 (Nov. 21, 2013) (“Cogswell”)
1028	Callahan et al., Peripheral and Tumor Immune Correlates in Patients with Advanced Melanoma Treated with Combination Nivolumab (Anti-PD-1, BMS-936558, ONO-4538) and Ipilimumab. 2013 ASCO Annual Meeting (May 20, 2013) (Abstract) (“Callahan”)
1029	Declaration of Dr. Dhaval Shah
1030	Curriculum Vitae of Dr. Dhaval Shah
1033	Mathijssen et al., Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults. <i>Oncologist.</i> 2007 Aug; 12(8):913-23. (“Mathijssen”)
1034	Bai et al., A Guide to Rational Dosing of Monoclonal Antibodies. <i>Clin Pharmacokinet.</i> 2012 Feb 1; 51(2):119-35. (“Bai”)
1035	Feng et al., Model-based Clinical Pharmacology Profiling of Ipilimumab in Patients with Advanced Melanoma. <i>Br J Clin Pharmacol.</i> 2014 Jul; 78(1):106-17. (“Feng”)

Exhibit	Description
1036	Mould et al., Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies: Concepts and Lessons for Drug Development. <i>BioDrugs</i> . 2010 Feb 1; 24(1):23-39. (“Mould”)
1039	Eisenhauer et al., New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). <i>Eur J Cancer</i> . 2009 Jan; 45(2):228-47. (“Eisenhauer”)