

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. IPR2025-00601
Patent No. 9,856,320

DECLARATION OF PAUL ANDREW ANTONY, M.D.

Amgen Exhibit 1003 Amgen v. BMS

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	SUMMARY OF OPINIONS.....	2
III.	PERSONAL AND PROFESSIONAL BACKGROUND	2
IV.	MATERIALS REVIEWED AND CONSIDERED	7
V.	MY UNDERSTANDING OF APPLICABLE LEGAL PRINCIPLES	7
	A. Burden of Proof	8
	B. Person of Ordinary Skill in the Art (POSA)	8
	C. Interpretation of Claims.....	9
	D. Prior Art.....	9
	E. Patentability	9
VI.	PERSON OF ORDINARY SKILL IN THE ART (“POSA”).....	12
VII.	BACKGROUND OF THE ’320 PATENT	14
	A. Technical Background/Overview.....	14
	B. Clinical History Background.....	20
	C. Known Dosing and Safety Background for Anti-PD-1 and Anti-CTLA-4	22
	1. Toxicity Associated with Extended Dosing of Anti-CTLA-4	23
	2. Anti-PD-1 Exhibited a More Tolerable Safety Profile	25
	D. The Challenged Claims of the ’320 patent.....	26
	E. Prosecution History of the ’320 Patent.....	34
VIII.	CLAIM INTERPRETATION	37
IX.	PRIOR ART TO THE ’320 PATENT.....	37
	A. NCT 231 (EX1005)	38
	B. Korman (EX1006)	41
	C. Wolchok (EX1007).....	44
	D. Sznol (EX1009)	45

X.	THE TREATMENT METHODS RECITED IN THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS TO A POSA IN VIEW OF THE PRIOR ART AS OF MAY 2012	45
A.	Ground 1: NCT-231 in View of Korman, and In Further View of Wolchok Render Obvious Claims 1-4, 6-12 and 14-17.....	46
1.	NCT 231 (EX1005).....	47
2.	Korman (EX1006).....	49
3.	Wolchok (EX1007)	53
4.	Reason Why A POSA Would Combine The Teachings of NCT 231, Korman, and Wolchok	54
5.	Reasonable Expectation of Success	66
6.	Claim-by-Claim Analysis.....	69
B.	GROUND 2: Korman in View of Wolchok, and in further View of Sznol Render Obvious Claims 5, 13, and 18-22.	95
1.	Reason to Modify Korman with the Teachings of Wolchok and Sznol.....	97
2.	Reasonable Expectation of Success	100
3.	Claim-By-Claim Analysis.....	101
XI.	SECONDARY CONSIDERATIONS DO NOT OVERCOME A FINDING OF OBVIOUSNESS.	114
XII.	CONCLUSION.....	116
	APPENDIX A.....	118

I, Paul Andrew Antony, MD, declare:

I. INTRODUCTION

1. I have been retained by counsel to discuss the scope and content of prior art as it would have been understood as a person of ordinary skill in the art (“POSA”) as such relates to the above-captioned inter partes review (“IPR”) proceeding regarding U.S. Patent No. 9,856,320 (“the ’320 patent”). In connection with my analysis, I have reviewed the ’320 patent, its file history, and the documents listed in Appendix A to this Declaration. I have been asked to provide a declaration regarding the scope and content of the prior art applied in the above mentioned IPR.

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, filed herewith as EX1004.

3. This declaration is based on information currently available to me. I declare that I have personal knowledge of the facts and opinions set forth in this declaration and believe them to be true. If called upon to do so, I would testify competently thereto.

4. I am being compensated at my standard 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. I have no financial interest in 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 the scope and content of the prior art and whether claims 1-22 of the '320 patent would have been obvious to a POSA in light of the prior-art references identified in the Petition. For reasons provided below, it is my opinion that each of claims 1-22 would have been obvious to a POSA as of the earliest claimed priority date of that patent (discussed in more detail below).

Ground Number and Reference(s)		Claims	Basis
1	NCT 231 in view of Korman and Wolchok	1-4, 6-12, 14-17	35 U.S.C. § 103 (pre-AIA)
2	Korman in view of Wolchok and Sznol	5, 13, 18-22	35 U.S.C. § 103 (pre-AIA)

III. PERSONAL AND PROFESSIONAL BACKGROUND

6. I have over three decades of research experience in cancer and immunology. In 2000, I received a MD, with a Distinction in Research, from the University of Michigan Medical School in Ann Arbor, Michigan.

7. From 2000-2006, I was a Fellow in Immunotherapy of Cancer at the National Cancer Institute (NCI) of the National Institutes of Health in Bethesda, Maryland, working closely with Steve Rosenberg, MD, PhD, and Nick Restifo, MD, both pioneers in immunotherapy of cancer. I also worked closely with Polly Matzinger, PhD at the National Institute of Allergy and Infectious Diseases (NIAID), who discovered danger signals and had discussions with Ron Schwartz, discoverer of co-signaling on T cells, i.e. B7-1, B7-2, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and CD28, and his post doc, Nevil Singh. While at NCI, I designed immunotherapies for cancer, including cell therapies such as T cell receptors (TCRs), chimeric antigen receptors (CARs) as well as antibody therapies such as CTLA-4 antibodies for preclinical studies that lead to human trials. During this time, I worked with and trained several notable individuals who continue to contribute to the immunotherapy of cancer today including Chris Klebanoff, MD, at Memorial Sloan Kettering, Chris Hendricks, MD, at Rutgers, Steve Finkelstein, MD, at Moffitt Cancer Center, Mark Theoret, MD, at the FDA, and several others.

8. I also participated in the discussion and implementation of clinical trials for a combination therapy including CTLA-4 antibodies and a melanoma antigen glycoprotein 100 (gp100) vaccine. Additionally, I assisted with the design and participated in a Phase II clinical trial for cancer therapy (metastatic

melanoma) employing interleukin-2 (IL-2) following lymphodepleting chemotherapy and reinfusion of autologous lymphocytes depleted of T regulatory lymphocytes. Lastly, I participated in several yearly immunotherapy meetings such as Society for Immunotherapy of Cancer (SITC), the American Association of Immunologists (AAI), the American Association for Cancer Research (AACR), and KEYSTONE (The Keystone Symposia on Molecular and Cellular Biology), presenting data and discussing therapies with other notable scientists.

9. From 2006-2020, I held various positions at the Johns Hopkins University School of Medicine, Department of Oncology, and University of Maryland School of Medicine, Department of Pathology and Department of Microbiology and Immunology, where I was an Adjunct and Assistant Professor, respectively.

10. During 2006-2008, my research at the Johns Hopkins University School of Medicine was focused on the design of T cell immunotherapies for cancer as well as the development of programmed cell death protein 1 (PD-1) therapies in mouse models for use in human cancer patients.

11. From 2008-2020, I established an immunotherapy laboratory and hired several people to join my lab. My research projects at the University of Maryland School of Medicine included training individuals in cancer immunotherapy and experimenting with new immunotherapies for cancer. I

worked extensively on the development of T cell-based immunotherapies for cancer and immune checkpoint therapies, including combination therapies. In particular, I advanced programmed death-ligand 1 (PD-L1) and lymphocyte-activation gene 3 (LAG-3) therapies for relapsing cancer and examined the efficacy of combination therapies such as with PD-1, PD-L1, CTLA-4, and LAG-3 antibodies. There, I worked closely with Scott Strome, MD (my mentor) who was a co-discoverer of the checkpoint molecule, B7-H1 also known as PD-L1. We further advanced combination therapies in several publications.

12. Throughout my career, I have trained and worked with several notable PhD and MD candidates and individuals, undergraduates, and postdoctoral fellows in Immunotherapy of Cancer and advanced immunology as mentioned above, taught basic and advanced immunology, stem cell biology, and cancer immunotherapy, served as a reviewer for many journals, including Immunity, the Journal for ImmunoTherapy of Cancer (JITC), Journal of Experimental Medicine (JEM), Nature Immunology, and Journal of Immunology, received over 2.5 million in funding on several grants that were ranked number 1 including the American Cancer Society, and the Melanoma Research Foundation, as well as numerous awards for my work (The Cynthia Chambers Award, a former postdoc of James Allison), and published over 35 peer reviewed papers on T cell therapies and checkpoint inhibitors, some cited over 1000 times and one

including a collaboration with James Allison, PhD, who discovered CTLA-4 and developed ipilimumab. Some of these papers include:

- Goding SR, Wilson KA, Rosinsky C, **Antony PA**. PD-L1-Independent Mechanisms Control the Resistance of Melanoma to CD4+ T Cell Adoptive Immunotherapy. *J Immunol*. 2018 May 1;200(9):3304-3311. doi: 10.4049/jimmunol.1701617. Epub 2018 Mar 30. PubMed PMID: 29602773.
- Church SE, Jensen SM, **Antony PA**, Restifo NP, Fox BA. Tumor-specific CD4+ T cells maintain effector and memory tumor-specific CD8+ T cells. *Eur J Immunol*. 2014 Jan;44(1):69-79. doi: 10.1002/eji.201343718. Epub 2013 Nov 21. PubMed PMID: 24114780; PubMed Central PMCID: PMC4283993.
- Goding SR, Wilson KA, **Antony PA**. Combination of adoptive cell transfer, anti-PD-L1 and anti-LAG-3 antibodies for the treatment of recurrent tumors: Better with more. *Oncoimmunology*. 2013 August; 2(8).
- Goding SR, Wilson KA, Xie Y, Harris KM, Baxi A, Akpinarli A, Fulton A, Tamada K, Strome SE, **Antony PA**. Restoring immune function of tumor-specific CD4+ T cells during recurrence of melanoma. *J Immunol*. 2013 May 1;190(9):4899-909. doi: 10.4049/jimmunol.1300271. Epub 2013 Mar 27. PubMed PMID: 23536636; PubMed Central PMCID: PMC3633733.
- Xie Y, Akpinarli A, Maris C, Hipkiss EL, Lane M, Kwon EK, Muranski P, Restifo NP, **Antony PA**. Naive tumor-specific CD4(+) T cells differentiated in vivo eradicate established melanoma. *J Exp Med*. 2010 Mar 15;207(3):651-67. doi: 10.1084/jem.20091921. Epub 2010 Feb 15. PubMed PMID: 20156973; PubMed Central PMCID: PMC2839147.
- Quezada SA, Simpson TR, Peggs KS, Merghoub T, Vider J, Fan X, Blasberg R, Yagita H, Muranski P, **Antony PA**, Restifo NP, Allison JP. Tumor-reactive CD4(+) T cells develop cytotoxic activity and eradicate large established melanoma after transfer into lymphopenic hosts. *J Exp Med*. 2010 Mar 15;207(3):637-50. doi: 10.1084/jem.20091918. Epub 2010 Feb 15. PubMed PMID: 20156971; PubMed Central PMCID: PMC2839156.

13. Presently, I work in immunotherapy consulting for Gerson Lehrman Group, Thirdbridge, First Thought, and Guidepoint Consulting Group as well as teach for Johns Hopkins University on occasion.

IV. MATERIALS REVIEWED AND CONSIDERED

14. 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 VI below. In forming my opinions, I have studied and considered the materials identified Appendix A.

15. 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 or page number added by the exhibit label.

V. MY UNDERSTANDING OF APPLICABLE LEGAL PRINCIPLES

16. 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 patentability 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

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

18. I understand that, in this proceeding, Petitioner has the burden of proving that the challenged claims of the ’320 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)

19. 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 pertinent prior art and the conventional wisdom in the art and is a person of ordinary creativity. I have applied this standard throughout my declaration.

20. 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

21. 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. I have applied this standard in preparing the opinions in this declaration.

D. Prior Art

22. 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.

E. Patentability

23. 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.

24. 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.

25. 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.” To my knowledge, the Patent Owner has not asserted any such secondary considerations with respect to the ’320 patent.

26. 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 fashion proposed.

27. 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;

- and the normal desire of scientists or artisans to improve upon what is already generally known which provides the motivation to determine where in a previously disclosed set of ranges is the optimum combination.

28. I understand that for a prior-art reference, or a combination of references, to render a claimed invention obvious, one of ordinary skill in the art at the time the invention was made must have expected a reasonable chance of success in applying the teachings of the references to arrive at the claimed invention. Certainty and absolute predictability are not required to establish a reasonable expectation of success.

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

29. The ’320 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 by early 2012. I use this timeframe because the face of the ’320 patent indicates an earliest claimed priority date of May 15, 2012. 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 ’320 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 May 15, 2012 timeframe, even if I do not say so specifically in each case.

30. In my opinion, a person of ordinary skill in the art in the May 15, 2012, timeframe would have a Ph.D. degree in immunology or a related field (for example, biochemistry), or alternatively a M.D. with a particular focus on cancer immunotherapy, plus at least two years of experience in the field of cancer immunotherapy, including experience with cancer treatments. The levels of education, experience and knowledge described above can trade off against one another. POSAs would also have either been (1) skilled in pharmacokinetics or (2) able to communicate as part of a team with pharmacokinetics experts if necessary. This person would have been capable of understanding and applying the teachings of the '320 patent and the prior-art references discussed in this declaration—including understanding literature regarding clinical trials for cancer.

31. By 2012, I held a MD and had 20 years of research experience, including 8 years of cancer immunotherapy and immunology research at the University of Michigan, a 6 year fellowship in Immunotherapy of Cancer at the National Cancer Institute of the National Institutes of Health and an additional 6 years of research in immunology at the National Institute of Allergy and Infectious Disease, Johns Hopkins University, and University of Maryland School of Medicine. Specifically, my experience prior to 2012 involved basic and

translational research for immunotherapies, including immune checkpoint therapies employing anti-CTLA-4 antibodies and anti-PD-1 or anti-PDL-1 antibodies for cancer, and the participation in the design of clinical trials.

Therefore, I was a person of more than ordinary skill in the art during the relevant timeframe. However, I worked with many people who fit the characteristics of the POSA, for example, I have supervised many POSAs through my research and clinical trial work, 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.

VII. BACKGROUND OF THE '320 PATENT

A. Technical Background/Overview

32. The '320 patent concerns methods of treating cancer by administering two therapeutic antibodies—anti-PD-1 and anti-CTLA-4—known in the art as “immune checkpoint inhibitors.” Immune checkpoint inhibitors work by blocking immune checkpoint proteins from binding with their partner proteins (on a T cell, for example). When immune checkpoint proteins and partner proteins bind together, they send an “off” signal to the T cells. This can prevent the immune system from destroying the cancer cells. Checkpoint *inhibitors* prevent the “off” signal from being sent, allowing the T-cells to kill the cancer.

33. The study of anti-PD-1 and anti-CTLA-4 individually as cancer therapies dates back to the early 2000's, when the first anti-CTLA-4 antibody clinical trial was initiated in 2000 (EX1036, 4713) and subsequent trials commenced several years later. EX1011, 1, EX1012, 1. Anti-CTLA-4 antibody therapy was ultimately approved by the FDA as Ipilimumab in 2011. EX1008, 1; EX1018, 1 ("YERVOY 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses.").

34. Similarly, clinical trials studying anti-PD-1 began as early as 2007. EX1013, 1. In 2008, clinical trial NCT00730639 initiated the Phase 1 study of the anti-PD1 antibody nivolumab at bi-weekly dosing in subjects with advanced or recurrent malignancies. EX1014, 1, 4. Success from this trial was reported in Sznol. EX1009, 205s ("MDX-1106 [i.e., nivolumab] administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.").

35. Additionally, concurrent administration of these antibodies for the treatment of cancer was published as early as 2006, with the report of promising animal data administering both antibodies (EX1006, 66, 94), and by 2009, when the first clinical trial was initiated to evaluate concurrent anti-PD-1 and anti-CTLA-4 therapy in humans. EX1005, 1, 4. By 2012, therefore, POSAs were familiar with both the varied dosing numbers, frequencies, and concentrations tested for each antibody as a monotherapy, as well the various dosing options

being studied for concurrent treatment with anti-PD-1 and anti-CTLA-4 antibodies.

36. Specifically, by May of 2012, the NCT01024231 (CA209-004) clinical trial was underway whereby the protocol called for the administration of (1) an induction phase of anti-PD-1 and anti-CTLA-4 antibodies together followed by anti-PD-1 alone, which was then followed by (2) a maintenance phase of both antibodies again. EX1005 (NCT01024231, Version 3: “Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted to clinicaltrials.gov: January 5, 2010) (NCT 231), 4.

37. Nearly six years prior to 2012, Alan Korman had already published a patent application describing the use of anti-PD-1 and anti-CTLA-4 check-point inhibitor antibodies in combination for the treatment of cancer in humans, along with data demonstrating synergistic effects of this combination in animal models. Korman disclosed various dosing options—both amounts and frequencies—for such administration. EX1006 (WO 2006/121168, published Nov. 16, 2006) (Korman).

38. For example, Korman disclosed:

- Ranges, specific, and preferred dosing amounts for anti-PD-1 antibodies, with at least one example provided in an induction-maintenance dosing format. EX1006, 55 (“Preferred dosage

regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight...via intravenous administration, with the antibody being given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months.”).

- The then “known dose” of anti-CTLA-4 antibodies (i.e., 3 mg/kg). EX1006, 20.
- The *simultaneous* administration of anti-PD-1 and anti-CTLA-4 antibodies per the dosing ranges disclosed. EX1006, 56.

39. Moreover, in 2010, Sznol et al. (EX1009, (*J. Clin. Oncology* Vol. 28, No. 15, May 20, 2010) (Sznol)) had published safety and efficacy results for dosing anti-PD-1 antibodies bi-weekly (i.e., every two weeks).

40. And by 2012, anti-CTLA-4 monotherapy had been studied and was *already approved* by the FDA for treatment of cancer in humans and had been demonstrated safe and efficacious at the regimen of 3 mg/kg “every 3 weeks for four cycles.” EX1007 (Wolchok et al., *Lancet Oncol.* 2010; 11:155–64) (“Wolchok”), 155 (abstract); EX1008, 1.

41. Thus, by 2012, the concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of cancer had been described in a variety of printed publications, including in published patent applications, clinical trial protocols, and peer-reviewed scientific papers. EX1006, 56 (“[T]wo or more

monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated.”); EX1005, 4 (“The purpose of this study is to assess the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma.”); EX1030, 4279 (“Our preclinical data in the B16 melanoma model strongly suggest that combining these agents [anti-PD-1 and anti-CTLA-4 antibodies] may have synergistic effects in driving tumor rejection.”).

42. In addition, and as I discuss more fully below, by 2012 it was well-understood by POSAs that toxicity and increased risk of immune-related adverse events were associated with treatment with anti-CTLA-4 antibodies relative to anti-PD-1. By contrast, anti-PD-1 antibodies were known to exhibit less relative toxicity and were tolerated for longer dosing periods.

43. This was also predicted by the distinct phenotypes of *Ctla4*-knockout mice versus *Pdl*-knockout mice. EX1022, 260; *see* EX1015, 9543-44, 9550. *Ctla4*-knockout mice had severe lymphoproliferative disease at birth and autoimmunity whereas *Pdl*-knockout mice had much less severe autoimmunity that appeared later in development. *See* EX1022, 260; EX1037, 3168, 3172.

Notably, polymorphisms of CTLA-4 and PD-1 are associated with various autoimmune conditions. *E.g.*, EX1016, 816-18; EX1010, 170.

44. Thus, while adverse events were associated with anti-PD-1 antibody administration, the frequency of immune-related toxicities from anti-PD1 treatment was understood to be less severe than with anti-CTLA4 administration as shown by research studies and at least one phase I clinical trial before 2012. *See, e.g.*, EX1022, 260; EX1037, 3167-69, 3172. Occurrence of immune related adverse events were also as predicted from the mechanisms of action of each molecule and their respective distribution throughout the body in various tissues, for instance CTLA-4 is expressed by naïve T cells, whereas PD-1 is expressed by activated and exhausted memory T cells. EX1022, 258; EX1037, 3168. Thus, in combination, the frequency of immune related adverse events would be expected to increase due to increased T cell activation. *See, e.g.*, EX1022, 257-58; EX1037, 3167-69; EX1006, 60, 62, 66; *See generally*, EX1015. Finally, these distinct mechanisms of action also contribute to the distinct timing of each pathway in its impact on T-cell activity. EX1010, 178 (“CTLA-4 is important for limiting T-cell activity for cells early during the immune responses. PD-1, on the other hand, limits T-cell activity in peripheral tissues and may be the last chance to prevent T-cell destruction of self-tissue resulting in autoimmunity.”) This full body of knowledge would have informed a POSA’s decisions in developing a

method of treating cancer with concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies.

B. Clinical History Background

45. By way of the nomenclature I use in this Declaration and as it is used in the prior art cited herein, various names and designations are given to anti-PD-1 antibodies including, “nivolumab,” “Opdivo,” “BMS-936558,” “MDX1106-4,” and “ONO-4538.”

46. In addition, various names and designations are given to anti-CTLA-4 antibodies including, “ipilimumab,” “Yervoy,” “BMS-734016,” “MDX-010,” and “MDX-101.”

47. The first clinical trials for anti-CTLA-4 as a monotherapy were initiated in the early 2000’s and that drug was then approved for administration to humans (as ipilimumab) in 2011 for the therapy of advanced melanoma. EX1012 (NCT00729950), 1; EX1017 (NCT00094653), 1; EX1008, 1. Other trials studied administration of anti-CTLA-4 antibodies for the treatment of other types of cancer such as prostate cancer. EX1011 (NCT00323882), 2.

48. Clinical trials studying anti-PD-1 began as early as 2007. For example, clinical trial NCT00441337 was initiated in 2007 to study the anti-PD-1 antibody, nivolumab, in patients with selected refractory or relapsed malignancies. EX1013 (NCT00441337), 1-2.

49. In 2008, clinical trial NCT00730639 initiated the Phase 1 study of nivolumab at bi-weekly dosing of 1, 3, and 10 mg/kg in subjects with advanced or recurrent malignancies. EX1014 (NCT00730639), 1, 4. Success from this trial was reported in Sznol, M., et al., which reported, “MDX-1106 [i.e., nivolumab] administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.” EX1009, 205s (2506; conclusions). A POSA in 2012 would have understood the phrase “biweekly” to mean, or at the very least suggest, “once every 2 weeks.”

50. By December of 2009, clinical trials were initiated to study the concurrent dosing of anti-PD-1 and anti-CTLA-4 antibodies. For example, NCT 231 commenced on December 14, 2009 to “assess the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma.” EX1005, 4.

51. In the January 5, 2010 posting of NCT 231, five cohorts of patients were given anti-CTLA-4 and anti-PD-1 therapies at different concentrations and on a schedule where both drugs were administered together every three weeks for 4 doses, followed by administration of anti-PD-1 alone every 3 weeks for 4 doses, followed by a maintenance dosing of both antibodies again every 12 weeks for 8 doses, a total of 84 weeks. EX1005, 4. In 2012, a POSA would have understood

an “every 12 week” dosing interval to be equivalent to, or at least to suggest, an “every three months” dosing interval or a “once a quarter” dosing interval.

52. Though nomenclature varies and the specific terms “induction” and “maintenance” are not always used to describe dosing phases, many studies of anti-CTLA-4 and/or anti-PD-1 dating back to at least as early as 2011 utilized “induction-maintenance” dosing formats. In these dosing formats an initial (or “induction”) dose at a particular frequency, number, and concentration of the drug is administered to a patient with the goal of eliciting a therapeutic response. After that therapeutic regimen concludes, an ongoing (“maintenance”) dose is administered (often at a lower concentration and/or less frequently) in order to maintain some therapeutic effect longer-term (while avoiding potential toxicities with higher concentrations or high-frequency dosing). EX1007, 155; EX1006, 55. In several prior art studies of combination therapies involving anti-PD-1 and anti-CTLA-4, an “induction” phase of therapy included both an initial phase of a combined therapy followed by a phase of one of the previously combined drugs alone. EX1005, 4; EX1039, 2518-19.

C. Known Dosing and Safety Background for Anti-PD-1 and Anti-CTLA-4

53. Given the extensive study of these antibodies (anti-PD-1 and anti-CTLA-4) prior to their first concurrent use as a cancer therapy in clinical trials, important knowledge was uncovered about the safety and efficacy profiles for

each. As I discuss below, this information contributed to dosing strategies for the concurrent therapy and its study over the decade following the launch of the NCT 231 clinical trial.

1. Toxicity Associated with Extended Dosing of Anti-CTLA-4

54. By 2012, the U.S. Food and Drug Administration had approved ipilimumab injection for the treatment of unresectable or metastatic melanoma based on a randomized (3:1:1), double-blind, double-dummy clinical trial (MDX010-20) in patients with unresectable or metastatic melanoma who had received at least one prior systemic treatment for melanoma. EX1008, 1. Based on that clinical study, the approved dose and schedule for ipilimumab was 3 mg/kg as an intravenous infusion every three weeks for a total of four doses. *Id.*; *see also*, EX1018 (Yervoy label 2011), 1 (“The recommended dose of YERVOY [Ipilimumab] is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses.”).

55. A schedule of dosing every 3 weeks was adopted in several early studies of anti-CTLA-4 antibodies (EX1011, 3; EX1012, 2); however, evidence of a unique toxicity profile emerged from these trials such that a POSA would have recognized by 2012 that anti-CTLA-4 treatment at increasingly higher doses or longer courses was found to induce immune-related adverse events (irAEs). EX1019, 29 (abstract), 34 (“[T]he cases we present demonstrate the importance of

monitoring for autoimmune hypophysitis and hypopituitarism in subjects with prostate cancer being treated with antiCTLA-4 antibody therapy.”), 35 (“The cases we present demonstrate the clinical course of autoimmune hypophysitis and consequent hypopituitarism after treatment with ipilimumab and highlight the possible role of CTLA-4 blockade in its pathogenesis.”); EX1020, 499 (Abstract) (“Inhibition of CTLA-4 characteristically induces well-identified side effects for which the definition “immune-related adverse events” (irAEs) has been proposed. IrAEs mainly include colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies; uveitis, nephritis, and inflammatory myopathy also have been reported occasionally.”); EX1021, 865 (“In this article, I briefly describe findings from several ongoing and completed trials with ipilimumab...and present several cases that highlight the kinetics of antitumor responses and the relationship to IRAEs in patients receiving the CTLA-4 antibody ipilimumab.”).

56. In addition, studies such as reported in Wolchok demonstrated the difficulty faced by clinical trial administrators to keep patients on anti-CTLA-4 immunotherapy for extended periods of time given the challenging adverse reactions and toxicity profile of that drug. For each dosage arm of the study discussed in Wolchok, only a small fraction of patients even received the maintenance dosing. EX1007, 157, Fig. 1 (“Trial Profile,” showing significant

participant loss in progression from induction to maintenance dosing of anti-CTLA-4).

2. Anti-PD-1 Exhibited a More Tolerable Safety Profile

57. It was also understood by POSAs by 2012, however, that treatment with anti-PD-1 antibody therapy was less toxic than treatment with anti-CTLA-4 antibody therapy, comparatively. *See* EX1022, 260 (“Furthermore, the relatively mild phenotypes of *Pdl1* (also known as *Pdcd1*), *Pdl1* (also known as *Cd274* and *Pdcd1lg1*) and *Pdl2* (also known as *Cd273* and *Pdcd1lg2*) knockout mice suggest that blockade of this pathway would result in less collateral immune toxicity than for CTLA-4 blockade, which seems to be the case in clinical trials.”); EX1037, 3172 (“While both anti-PD-1 and anti-CTLA-4 therapies are associated with irAEs, as predicted by preclinical models and consistent with the physiologic roles of these molecules, these toxicities appear to be less frequent and milder in patients receiving anti-PD-1.”); EX1044, 514 (describing a “milder toxicity profile for anti-PD1 mAb as compared to that of anti-CTLA-4 mAb”); EX1042, 245 (same). As noted above, this difference was predicted by the distinct phenotypes of *Ctla4*-knockout mice versus *Pdl1*-knockout mice. EX1022, 260.

58. Treatment with anti-CTLA-4 antibodies in several clinical trials as mentioned above in paragraphs 54-56 produced substantial immune mediated toxicities (grade 3-4 adverse events) in ranges from 25-30% of patients, but

treatment with anti-PD-1 antibodies produced much less severe immune related toxicities and in fewer patients, about 14% grade 3-4 drug related adverse events. As predicted from genetic mutations in mice and the relative distribution of the CTLA-4 and PD-1/PD-L1 molecules and their respective non-redundant mechanisms of action, toxicity from therapy with anti-PD-1 was lower than that from therapy with anti-CTLA-4. PD-1 toxicity was also seen in different organs than that of anti-CTLA-4 (with colitis being most common with anti-CTLA-4 and pneumonitis being most common with anti- PD-1). However, although less, toxicity with anti-PD-1 antibodies could be severe especially for pneumonitis and guidelines to mitigate these irAEs were implemented in several clinical trials.

D. The Challenged Claims of the '320 patent

59. I understand that the '320 patent claims an earliest possible priority date of May 15, 2012. I further understand that the '320 patent contains two independent (1 and 5) and twenty dependent claims which recite methods of treating cancer generally—and certain types of cancer specifically—by administering anti-PD-1 and anti-CTLA-4 antibodies at various dose amounts, frequencies, and concentrations. EX1001, claims. I note that while certain of my discussion of the prior art notes the demonstration of safe and effective treatment with anti-PD-1 and/or anti-CTLA antibodies, none of the challenged claims recite

or require any particular level of efficacy and dependent claim 7 only broadly recites a host of possible outcomes, including maintenance of stable disease.

60. These claims are reproduced below:

Claim 1
[1Pre] A method of treating a human subject afflicted with a cancer comprising administering to the subject:
[1A] (a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) (“anti-PD-1 antibody”); and (b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (“anti-CTLA-4 antibody”);
[1B] (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses; followed by ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses; and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages:

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

Claim 2

The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.

Claim 3

The method of claim 1, wherein the anti-CTLA-4 antibody is ipilimumab.

Claim 4

The method of claim 1, wherein the anti-CTLA-4 antibody is administered during the induction dosing schedule once every 3 weeks for a total of 4 doses.

Claim 5

[5Pre] A method of treating a human subject afflicted with a cancer comprising

[5A] administering to the subject 1 mg/kg of an anti-PD-1 antibody and 3 mg/kg of an anti-CTLA-4 antibody every 3 weeks for 4 doses,

[5B] followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.

Claim 6

The method of claim 1, wherein the administering comprises:

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

Claim 7

The method of claim 1, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.

Claim 8

The method of claim 1, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, cutaneous or intraocular malignant melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, colorectal cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration-resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.

Claim 9

The method of claim 8, wherein the hematologic malignancy is selected from multiple myeloma, B-cell lymphoma, Hodgkin lymphoma/primary mediastinal B-cell lymphoma, non-Hodgkin's lymphomas, acute myeloid lymphoma, chronic myelogenous leukemia, chronic lymphoid leukemia, lymphocytic lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, acute lymphoblastic leukemia, mycosis fungoides, anaplastic large cell lymphoma, T-cell lymphoma, and precursor T-lymphoblastic lymphoma.

Claim 10

The method of claim 1, wherein the cancer is the cancer is an advanced, recurring, metastatic, and/or refractory cancer.

Claim 11

The method of claim 1, wherein the treatment is further combined with one of more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.

Claim 12

The method of claim 1, wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the maintenance dosing schedule at the following dosages:

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

Claim 13

The method of claim 5, wherein the anti-PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg.

Claim 14

The method of claim 1, wherein 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.

Claim 15

The method of claim 1, wherein 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.

Claim 16

The method of claim 1, wherein 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.

Claim 17

The method of claim 1, wherein 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.

Claim 18

The method of claim 5, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.

Claim 19

The method of claim 5, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, colorectal cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration-resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.

Claim 20

The method of claim 5, wherein the cancer is melanoma.

Claim 21

The method of claim 5, wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.

Claim 22

The method of claim 5, wherein the treatment is further combined with one of more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.

E. Prosecution History of the '320 Patent

61. I have reviewed the back and forth correspondence between the United States Patent and Trademark Office (USPTO) and the Patent Owner that led to the allowance of the challenged claims. This record of correspondence is provided with this declaration as Exhibit 1002. I understand that this is called the “prosecution history” of the '320 patent. I understand that the '320 patent was filed as U.S. Application No. 14/400,667 (the '667 Application). I further understand that the originally-filed claims of the '667 Application included claim 14, reproduced below:

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

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

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

each antibody being administered in a dosage ranging from 0.1 to 20.0 mg/kg body weight in a concurrent regiment comprising:

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

at least once every 2, 3 or 4 weeks, or at least once a month,
for 2, 4, 6, 8 or 12 doses; followed by

(ii) a maintenance dosing schedule comprising combined
administration of the anti-PD-1 and anti-CTLA-4 antibodies at
a dosing frequency of at least once every 8, 12 or 16 weeks, or
at least once a quarter, for at least 4, 6, 8, 10, 12 or 16 doses.

EX1002, 315-16.

63. I understand that during prosecution, the Examiner issued a Non-Final Rejection arguing that then-pending claim 14 (shown above) as well as claims 15 and 22-35 were not patentable because they were fully disclosed in (anticipated by) the clinical trial protocol from NCT01024231 (available at clinicaltrials.gov, as accessed on April 27, 2017), citing a version from April 27, 2017. EX1002, 192-193.

64. In addition to finding that the dosing structure and dosing frequencies overlapped between the pending claims and those recited in the NCT0102423 trial, the Examiner found that in the pending claims, “the antibody doses are 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg” while in the NCT01024231 trial, version from April 27, 2017, “the doses are 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg.” EX1002, 193. In view of this, the Examiner found that the regimen of NCT01024231 (combination BMS-936558 and

ipilimumab) was within the scope of the then-pending claims and anticipated them. EX1002, 193.

65. I understand that in an August 2, 2017 response, Patent Owner asserted that the April 27, 2017 version of NCT01024231 relied on by the Examiner was not prior art to the pending claims. EX1002, 51-52. However, Patent Owner provided the Examiner an earlier published version of that trial dated April 30, 2012 and changed, or amended, the then-pending claims by adding the dosing amount options ((a) through (m)) found in claim 15 to claim 14 and cancelled claim 15. EX1002, 44-45, 52.

66. I understand that Patent Owner also amended claim 28 (later issuing as claim 5) to recite “every 3 weeks for 4 doses, followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.” EX1002, 46.

67. I understand that Patent Owner argued that the “version of NCT01024231 available on April 30, 2012 fails to disclose the specific doses of anti-PD-1 antibody and the anti-CTLA-4 antibody recited in claim 14 and the specific dosing schedule recited in claim 28.” EX1002 52-53.

68. I understand that on August 24, 2017, the Examiner issued a Notice of Allowance without further explanation. EX1002, 28-34.

69. As discussed below, the NCT-231 reference relied upon in this Petition presents different intervention cohorts at different concentrations of dosing than the April 30, 2012 version (Version 58) of this protocol considered by the Examiner. *Compare* EX1005, 4, *with* EX1031, 4-5 (Cohorts 2 and 3 from NCT-231 (EX1005, 4) studied 0.3 mg/kg anti-PD-1; 10 mg/kg anti-CTLA and 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4, respectively. These two cohorts were *not* included in the April 27, 2017 version of NCT-231 (EX1031, 4-5). Similarly, Cohorts 2, 3, 6, and 7 from the April 27, 2017 version to NCT-231 (EX1031, 4-5) were *not* included in NCT-231 (EX1005, 4)).

VIII. CLAIM INTERPRETATION

70. I understand that determining whether a claimed invention is novel and non-obvious requires comparing the prior art to the claim. I have interpreted claim terms in accordance with their ordinary and customary meaning as understood by a POSA in light of the specification and prosecution history of the '320 patent.

IX. PRIOR ART TO THE '320 PATENT

71. I have been informed and understand that all of the references applied herein are indisputable prior art to the '320 patent because they were publicly available more than one year before the '320 patent's earliest claimed priority date

of May 15, 2012 (i.e., the date of the provisional application to which the '320 patent claims priority).

A. NCT 231 (EX1005)

72. NCT 231 is a clinical trial protocol, entitled “Dose-Escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects with Unresectable Stage III or Stage IV Malignant Melanoma.” I understand based on my own utilization and searching of the clinicaltrials.gov website that Version 3 of this clinical trial protocol was posted to ClinicalTrials.gov on January 5, 2010. EX1005. The website, www.clinicaltrials.gov, is run by the NIH and publicizes clinical studies in a searchable and easy to understand manner in order to keep physicians and patients apprised of ongoing clinical studies. Based on my experience, www.clinicaltrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical studies. An interested member of the public such as a researcher or a person of ordinary skill in this field would have considered the posting dates cited at clinicaltrials.gov to be trustworthy and authoritative, and would have understood that EX1005 was published online and accessible by searching, and so was in the prior art, by the relevant date.

73. Further, such interested person could have used clinicaltrials.gov to understand the state of the art, including, for example, in order to be able to

potentially recommend clinical studies to patients. Further, based on my experience, the website was indexed and searchable by subject matter. For example, ClinicalTrials.gov offered a “Basic Search” and an “Advanced Search” option for browsing its database. Keyword searching was available using “Basic Search” based on, e.g., the name of a medical condition, intervention, or the location of a clinical trial. In addition, “Advanced Search” allowed for filtering search results by more categories, such as, conditions, interventions, outcome measures, sponsors, study IDs, etc.

74. In order to access NCT-231, an interested member of the public, such as a researcher or clinician, could type the clinical trial number into the “Other Terms” search function, or could input search terms such as “ipilimumab” and “BMS-936558” to find various trials involving these antibodies. After finding the NCT-231 trial, such interested person could click on the associated link and navigate to the “Record History” tab, where all of the study record versions are listed by ascending date. An interested member of the public could click on the date associated with Version 3 (2010-01-04) to access this version and view the various study arms and cohorts. Version 3 of NCT-231 bears a “Last update posted” date of 2010-01-05 [Estimated]. I understand that this date indicates when the updated version would have been posted to clinicaltrials.gov and is accurate within a few days of the date indicated.

75. The “Brief Summary” section of NCT 231 summarizes that “[t]he purpose of this study is to assess the safety and tolerability of treatment with BMS-936558 (MDX-1106) in combination with ipilimumab in subjects with unresectable Stage III or Stage IV malignant melanoma.” EX1005, 4.

76. The “Assigned Interventions” section of NCT 231 (EX1005, 4) describes the dosing structure of the clinical trial as follows:

Drug: BMS-936558 (MDX1106-04)

- Solution, IV, 60 min infusion, q3 weeks for 21 weeks in induction and q12 weeks for 84 weeks in maintenance

Drug: Ipilimumab

- Solution, IV, 90 minute infusion, q3 weeks for 9 weeks in induction and q12 weeks for 84 weeks in maintenance.

77. I have graphically depicted this dosing structure as follows:

Weeks	Ipilimumab once every 3 weeks (4 doses)								Ipilimumab once every 12 weeks (8 doses)							
	↓	↓	↓	↓					↓	↓	↓	↓	↓	↓	↓	↓
	0	3	6	9	12	15	18	21	24	36	48	60	72	84	96	108
	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
	Nivolumab once every 3 weeks (8 doses)								Nivolumab once every 12 weeks (8 doses)							

This graphic simply depicts the information contained in NCT-231 and is helpful to understand exactly when each dose was administered per the intervals recited in that protocol. A similar graphic appears in the Supplementary Materials to

Wolchok et al., “Nivolumab plus Ipilimumab in Advanced Melanoma,” *NEJM*, 369, 2, July 11, 2013 (EX1027, EX1061, 3). While the publication of this graphic post-dates the May 15, 2012 earliest claimed priority date that I reference in this declaration for purposes of assessing prior art, the information in the Wolchok Supplementary Materials merely confirms the graphical depiction that a POSA would have created based on the information actually recited in NCT 231.

78. The five cohorts studied as of the January 5, 2010 NCT 231 (version 3) protocol tested the following antibody concentrations:

- C1: BMS-936558 (MDX1106-04) at 0.3 mg/kg; Ipilimumab at 3 mg/kg
- C2: BMS-936558 (MDX1106-04) at 0.3 mg/kg; Ipilimumab at 10 mg/kg
- C3: BMS-936558 (MDX1106-04) at 1 mg/kg; Ipilimumab at 10 mg/kg
- C4: BMS-936558 (MDX1106-04) at 3 mg/kg; Ipilimumab at 10 mg/kg
- C5: BMS-936558 (MDX1106-04) at 10 mg/kg; Ipilimumab at 10 mg/kg

EX1005, 4.

B. Korman (EX1006)

79. I have been informed that Korman (WO 2006/121168) is a patent publication that published on November 16, 2006, nearly 6 years before the May 15, 2012 earliest claimed priority date of the '320 patent. Korman disclosed concurrent administration of anti-CTLA-4 and anti-PD-1 for the treatment of cancer in humans. EX1006 (Korman), Abstract (“The present invention further

provides methods for using a combination immunotherapy, such as the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat hyperproliferative disease, such as cancer.”), 16, 66.

80. By 2012 it was well known—and discussed in Korman and elsewhere—that anti-PD-1 and anti-CTLA-4 therapies could be (and were) administered together *and* that such concurrent administration exhibited synergistic effects in treating cancer in animal models. EX1006, 66 (“In addition, the results of Examples 14, 16 and 18 show that the combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody had a significant (synergistic) effect on tumor growth even at sub-optimal therapeutic doses as compared to treatment with either antibody alone (i.e., the combination therapy was surprisingly more effective at subtherapeutic doses than either monotherapy”), 94-95 (“Together these data indicate that the combination therapy comprising anti-PD-1 and anti-CTLA-4 antibodies is substantially more effective than treatment with either antibody alone. In addition, surprisingly the dose of each antibody can be reduced without affecting the synergistic efficacy of this combination of immunostimulatory therapeutic antibodies. The combination therapy still seems to be effective even when the tumor mass is more mature (i.e., larger).”), 98; EX1030, 4276 (left col.), 4278-4279; EX1045, 1.

81. Korman also provides extensive dosing information for anti-PD-1 antibodies:

Pharmaceutical compositions of the invention also can be administered in combination therapy, *i.e.*, combined with other agents. For example, the combination therapy can include an anti-PD-1 antibody of the present invention combined with at least one other ... agent...For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example, dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months. Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration, with the antibody being given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) every three weeks. EX1006, 55.

82. Korman also recites “3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody” (EX1006, 20) and indicates that anti-PD-1 and anti-CTLA-4 can be administered simultaneously per the disclosed dosages. EX1006, 56 (“In certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated.”).

C. Wolchok (EX1007)

83. Wolchok, a publication from February of 2010, describes the results of a Phase II, randomized, double-blind clinical trial on anti-CTLA-4 antibody therapy (Ipilimumab monotherapy) in patients with pretreated advanced melanoma. EX1007, 155 (abstract). Wolchok discloses the treatment arm of this study as receiving “a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months.” EX1007, 155.

84. By March 25, 2011, following on Wolchok’s results, anti-CTLA-4 antibodies as a monotherapy was approved for human use by the FDA at a dose of 3 mg/kg given every three weeks for four doses. EX1008, 1; EX1018, 1, (“Dosage and Administration,” indicating the approved dose is “3 mg/kg

administered intravenously over 90 minutes every 3 weeks for a total of four doses”).

D. Sznol (EX1009)

85. Sznol is a Meeting Abstract from the 2010 ASCO Annual Meeting, published in the *Journal of Clinical Oncology* on May 20, 2010. Sznol describes the results of a multicenter trial evaluating the safety, antitumor activity, pharmacokinetics (PK), and immunological correlates of extended biweekly dosing of the anti-PD-1 antibody, MDX-1106. EX1009, 205s.

86. Sznol studied “biweekly MDX-1106 dosing at 1, 3, or 10 mg/kg IV” in patients who had “treatment refractory metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma (MEL), or prostate cancer (CRPC), and no history of autoimmune disease.” EX1009, 205s.

87. Sznol reported that “MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.” EX1009, 205s.

X. THE TREATMENT METHODS RECITED IN THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS TO A POSA IN VIEW OF THE PRIOR ART AS OF MAY 2012

88. I have been asked to provide my opinion on claims 1-22 of the '320 patent in light of the prior-art references available as of May 15, 2012. For the reasons explained below, it is my opinion that each of the methods of treatment

recited in claims 1-22 would have been obvious to a POSA in view of the scope and content of the prior art available to POSAs as of May 15, 2012.

A. **Ground 1: NCT-231 in View of Korman, and In Further View of Wolchok Render Obvious Claims 1-4, 6-12 and 14-17.**

89. Challenged Claim 1 recites a method of treating a human subject afflicted with cancer by administering, in an induction phase, anti-PD-1 and anti-CTLA-4 antibodies at various options of dose numbers and frequencies and various options of dose concentrations ((a) through (m)), followed by administering the anti-PD-1 antibody alone at various options of dose numbers and frequencies, followed by administering, in a maintenance phase, the two antibodies again at various options of dose numbers and frequencies. EX1001, cl. 1. Dependent claims 2-4, 6-12, and 14-17 recite specific type of antibodies administered, additional dosing limitations, treatment outcomes, types of cancer, and additional therapies to combine with the antibodies of claim 1. EX1001, cls. 2-4, 6-12, 14-17. Aside from claim 7's recitation of various options of outcomes, including maintenance of stable disease, none of these claims require any particular level of efficacy.

90. In my opinion, these claims would have been obvious to a POSA by May 15, 2012 over the 2010 published protocol of NCT-231 disclosing anti-PD-1 plus anti-CTLA-4 combination therapy dosed *in the precise structure* claimed

(NCT 231), in view of prior art references (Korman and Wolchok) disclosing the claimed dosing concentrations, specifically, and ranges understood by a POSA to be encompassing such concentrations, of each antibody.

91. Given these explicit dosing disclosures and the standard approach of POSAs to study a variety of concentration options and optimize antibody dosing to maximize therapeutic efficacy while minimizing toxic effects, a POSA would have had reason to combine the teachings of these references to arrive at a dosing regimen falling within the scope of challenged claim 1.

92. Moreover, given the known success with similar dosing concentrations for each antibody administered alone, the demonstrated positive results of this combination in animal models, and the known reliability of an iterative approach to selecting dosing concentrations, such a POSA would have had a reasonable expectation that implementing the NCT-231 protocol with dosing concentrations disclosed in Korman and Wolchok would yield a method of treating cancer.

1. NCT 231 (EX1005)

93. As I noted above, NCT 231 is Version 3 of a clinical trial protocol posted to clinicaltrials.gov on January 5, 2010 in which the concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies was tested as a cancer

therapeutic in humans. EX1005, 1-2. The dosing structure studied in NCT 231 across the five experimental cohorts is described as:

- Drug: BMS-936558 (MD1106-04)
 - administered every 3 weeks, for 21 weeks in induction and every 12 weeks for 84 weeks in maintenance, and
- Drug: Ipilimumab
 - administered every 3 weeks for 9 weeks in induction and every 12 weeks for 84 weeks in maintenance.

94. This structure equates to an induction phase of 4 doses of combination therapy given every 3 weeks, followed by 4 doses of anti-PD-1 alone given every 3 weeks, followed by a maintenance phase of 8 doses of combination therapy given every 12 weeks. EX1005, 4.

95. As noted above, I have graphically depicted this dosing regimen as follows:

		Ipilimumab once every 3 weeks (4 doses)								Ipilimumab once every 12 weeks (8 doses)							
		↓	↓	↓	↓					↓	↓	↓	↓	↓	↓	↓	↓
Weeks		0	3	6	9	12	15	18	21	24	36	48	60	72	84	96	108
		↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
		Nivolumab once every 3 weeks (8 doses)								Nivolumab once every 12 weeks (8 doses)							

This dosing structure—an induction phase of anti-PD-1 and anti-CTLA-4 followed by anti-PD-1 alone, followed by a maintenance phase of the two

antibodies—falls squarely within the scope of options presented in claim 1 where both anti-PD-1 and anti-CTLA-4 antibodies are given once every three weeks for four doses, anti-PD-1 is given alone once every three weeks for four doses, and then both antibodies are given again once every 12 weeks for 8 doses.

96. NCT-231 describes five cohorts receiving the following antibody concentrations:

C1: BMS-936558 at 0.3 mg/kg; Ipilimumab at 3 mg/kg

C2: BMS-936558 at 0.3 mg/kg; Ipilimumab at 10 mg/kg

C3: BMS-936558 at 1 mg/kg; Ipilimumab at 10 mg/kg

C4: BMS-936558 at 3 mg/kg; Ipilimumab at 10 mg/kg

C5: BMS-936558 at 10 mg/kg; Ipilimumab at 10 mg/kg

EX1005, 4.

97. NCT 231 thus discloses various dosing concentration options for both anti-PD-1 antibodies (0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg) and anti-CTLA-4 antibodies (3 mg/kg) that overlap with those recited in options (a) through (m) of the challenged claims. EX1005, 4.

2. Korman (EX1006)

98. Claim 1 recites a number of dosing concentration options (i.e., options (a) through (m)) to be used with the induction/maintenance dosing format

discussed above. All of these options were already explicitly disclosed in Korman (or in the combination of Korman and Wolchok as discussed further below).

99. For example, Korman discloses concentration option (b): (b) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody. Korman teaches, as to the antibody of the invention, such as anti-PD-1 antibody, “[f]or example dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, **5 mg/kg** body weight or 10 mg/kg body weight.” EX1006, 55. Korman also explicitly discloses, “3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 20 (as confirmed by Wolchok and the 2011 FDA approval of the antibody for cancer therapy (EX1007, 155; EX1008, 1)). Korman similarly discloses option (c): 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody. EX1006, 55, 20.

100. Additionally, Korman discloses option (f): 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody. Korman recites that “preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight.” EX1006, 55. Korman also discloses that anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and links this to the combination of anti-PD-1 and anti-CTLA-4 antibodies: “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously,

in which case the dosage of each antibody falls within the ranges indicated.”

EX1006, 55-56. A POSA would have recognized Korman to disclose a “preferred” 1 mg/kg dose of both anti-PD-1 and anti-CTLA-4 antibodies, corresponding to claim 1, (f).

101. In similar fashion, Korman discloses option (g): 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody, 3 mg/kg being the other “preferred” and disclosed dose of anti-PD-1 antibody. EX1006, 55-56.

102. In addition, Korman discloses the specific concentrations (and a range encompassing such concentrations) for claimed options (h) (5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), (i) (10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), and (m) (5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody). Korman recites concentrations for anti-PD-1 of “1 mg/kg...5 mg/kg body weight or 10 mg/kg body weight” and concentrations falling within the range 1-10 mg/kg. EX1006, 55. And, again, Korman teaches that “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.

103. Korman likewise discloses the low dose of 0.3 mg/kg for anti-PD-1 as recited in claim 1 dosing option (k) (0.3 mg/kg anti-PD-1 antibody and 0.3

mg/kg of anti-CTLA-4 antibody) and (e) (0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody). EX1006, 55 (“[f]or example dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.”), 56 (“[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.”).

104. Finally, Korman discloses the dosing concentration range of 0.01 mg/kg to 5 mg/kg for anti-PD-1 antibodies, which encompasses the anti-PD-1 antibody concentrations recited in claim 1 options (a) (0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody), (d) (0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody) and (j) (0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody) and (l) (0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody). EX1006, 55. And, again, Korman teaches that “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.

3. Wolchok (EX1007)

105. Wolchok discloses a number of safe and effective dose concentrations for anti-CTLA-4 including 10 mg/kg, 3 mg/kg, and 0.3 mg/kg. EX1007, 155 (abstract). These concentration options are recited in claim 1's anti-CTLA-4 dosing options of (b) and (c). As such, when combined with the dosing disclosures discussed above, Korman and Wolchok disclose the dosing concentration of options (b) and (c).

106. Korman and Wolchok together also explicitly disclose option (k) of claim 1's dosing concentrations for induction dosing: (k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA antibody. Korman teaches, with respect to anti-PD-1 antibodies, "[f]or example dosages can be 0.3 mg/kg body weight." EX1006, 55. And Wolchok teaches, with respect to anti-CTLA-4 antibodies, "[p]atients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months." EX1007, 155 (Abstract).

107. Similarly, Korman and Wolchok together recite the dosing concentration options of (a) (0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody), (b) (5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody), and (c) (10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4

antibody), for the reasons discussed in paragraphs 102, 104 and 106 regarding Korman’s disclosures of 0.1 mg/kg, 5 mg/kg and 10 mg/kg for anti-PD-1 antibodies (or ranges overlapping the same) and the 3 mg/kg disclosure of anti-CTLA-4 antibodies as recited in Wolchok.

4. Reason Why A POSA Would Combine The Teachings of NCT 231, Korman, and Wolchok

108. A POSA would have had several reasons—discussed below—to combine the dosing concentrations disclosed in NCT 231, Korman, and Wolchok to arrive at any one of the broadly claimed dosing concentrations listed in limitations ((a) through (m)) for use in the induction-maintenance dosing structure of NCT 231. A POSA would have understood that NCT 231’s disclosure of “BMS-936558” to be referring to the same antibodies as Korman’s disclosure of “anti-PD-1 antibodies” and NCT 231’s and Wolchok’s disclosure of “ipilimumab” to be referring to the same antibodies as Korman’s disclosure of anti-CTLA-4 antibodies. *See* paragraphs 45, 46. In addition, a POSA would have reasonably expected success in applying these concentrations to the dosing structure disclosed in NCT 231. I refer to these combined teachings as “NCT231-Korman-Wolchok”.

a. Knowledge-Based and Iterative Strategies For Studying Dose Concentration Options Would Have Provided a POSA With Reason to Combine The Teachings of NCT-231, Korman, and Wolchok To Generate Dosing Schedules For Concurrent Anti-PD-1 and Anti-CTLA-4 Therapy

109. By 2012, the oncology field understood that combinations of two or more immunotherapies could provide safe and effective treatments for otherwise incurable cancers, particularly in situations where both antibodies demonstrated success as a monotherapy and were shown safe and efficacious as a combination in animal models. EX1032, 1222-23, 1225-26; EX1045, 1; EX1006, 66. It was known by 2011 that the “[d]evelopment considerations for combination therapies” include the state of existing knowledge about “dose, efficacy, and toxicity” of the proposed compounds. EX1032, 1223-24 (Table 1).

Table 1. Development considerations for combination therapies

Drug development		Drug B	
		Early	Late
Drug A	Early	Combination opportunity is theoretical	Dose, efficacy, and toxicity of at least one compound is well defined
	Late	Dose, efficacy, and toxicity of at least one compound is well defined	Combination opportunity on the basis of a solid understanding of the dose, efficacy, and toxicity of each agent as a monotherapy

110. The prior art also posited that for a combination of two drugs which are both active independently, but expected to be more effective than either agent alone (as was known to be the case for anti-PD-1 in combination with anti-CTLA-4 (EX1006, 94; EX1030, 4279)), a POSA could administer each drug at its full dose. EX1032, 1224 (“A phase I dose-seeking trial should ideally be designed

around a testable hypothesis. For example, 1) both drugs can be given at full dose”).

111. Moreover, POSAs understood that “combinatorial strategies will always be easier to develop when one of the components is already approved as a single agent” and as such provided a dosing starting point from which to build a combined regimen. EX1032, 1225.

112. After starting with a “testable hypothesis” such as the known, full, subtherapeutic, or approved dosing concentrations for each antibody, it was also common in this field to test incrementally higher or lower concentrations within a reasonable range to optimize a combination therapy. EX1040, 709 (“‘[U]p-and-down’ designs [] allow dose escalation and de-escalation...The general principle of this design is to escalate or de-escalate the dose with diminishing fractions of the preceding dose depending on the absence or presence of severe toxicity in the previous cohort of treated patients.”).

113. Before 2012, it was known that the designing of dosing regimens for the study of anti-CTLA-4 and anti-PD-1 combination therapy had to account for complexities arising from the antibodies’ distinct mechanisms of action. *See* EX1040, 713, 715. Also factored in were the nonoverlapping toxicity profiles of each antibody, and the risk of heightened immune-related adverse events, especially with anti-CTLA-4. *Id.* In view of these factors, careful selection of

dose-escalation strategies for the combined administration of both antibodies was required. *Id.* Approaches such as alternating or simultaneous escalation or escalating one agent while holding the other at a fixed dose, were considered to navigate the complexities and safely approach the maximum tolerated doses of each agent. *Id.*, 715-16. These strategies were informed by preclinical data, published literature on existing doses and outcomes, existing treatment standards, and the design of future randomized trials to optimize the therapeutic potential of combining anti-CTLA-4 and anti-PD-1 therapies. *Id.*

114. In view of the aforementioned dosing principles for combination therapies, the many disclosed dosing options and ranges (particularly those already disclosed, studied, or approved for these checkpoint antibodies), a POSA would have had reason to apply existing knowledge to combine known, tested, and/or approved concentrations for each antibody as discussed in subsections (b) and (e), below.

115. Additionally, a POSA would have engaged in standard iteration to “improve upon what is already generally known” by adjusting dosing concentrations within disclosed concentration ranges in assembling a dosing protocol according to the structure of NCT-231 for an anti-PD-1 plus anti-CTLA-4 therapy as discussed in section (c), (d), (e), and (f), below.

116. Indeed, this would have been little more than the routine application of a well-known problem-solving strategy, particularly given a POSAs desire to maximize efficacy and in view of the already existing evidence of success with anti-CTLA-4 and anti-PD-1 alone and in combination.

117. Moreover, as discussed in section XI., below, my understanding is that Patent Owner has provided no evidence demonstrating that any of the particular claimed dosing schemes exhibit some critical or unexpected results relative to what was already known in the prior art.

b. Claim 1 Concentration Options (b) and (c)

118. With respect to options (b)—5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody—and (c)—10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody—a POSA seeking safe and effective concentrations amounts would have had reason to utilize the explicitly disclosed concentration options for anti-PD-1 and anti-CTLA-4 found in Korman and Wolchok in the induction-maintenance dosing format of NCT 231.

119. For example, Korman offers incremental dosing options for anti-PD-1 that overlap with the options already tested for this antibody when dosed alone (i.e., Korman discloses “0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight” which overlap with

the increments already demonstrated safe and efficacious for anti-PD-1 alone “1, 3, or 10 mg/kg”). EX1009, 205s.

120. For anti-PD-1, a POSA would have reason to select the 5 mg/kg option explicitly disclosed in Korman because it is an incremental option between the 3 mg/kg and 10 mg/kg options which had already been tested and shown to be safe and efficacious. EX1009, 205s.

121. Similarly, a POSA would have had reason to select the 10 mg/kg option explicitly disclosed in Korman because it was a known dose and had already been shown safe and effective in a study of anti-PD-1 alone. EX1009, 205s.

122. Confirming the reasonableness of this selection, in particular, a 10 mg/kg dose of anti-PD-1 was also already being tested in the NCT-231 clinical trial of the concurrent anti-PD-1 plus anti-CTLA-4 antibody therapy more than two years before May of 2012. EX1005, 4 (cohort arm 5).

123. Likewise, for anti-CTLA-4, Korman indicates that 3 mg/kg of anti-CTLA-4 antibody was the “known dose” at the time (as confirmed by Wolchok and the 2011 FDA approval of the antibody for cancer therapy (EX1007, 155; EX1008, 1), and a POSA would have reason to start with or select already-known and familiar dosing options when seeking optimal therapeutic efficacy at tolerable toxicity. Likewise, a 3 mg/kg dose of anti-CTLA-4 was already being tested in a

clinical trial more than two years before May 15, 2012. EX1005, 4 (cohort arm 1).

124. For at least these reasons, a POSA would have reason to select 5 and 10 mg/kg of anti-PD-1 antibody to administer with the already known dose of 3 mg/kg of anti-CTLA-4 to arrive at claimed options (b) and (c).

c. Claim 1 Concentration Options (f) and (g)

125. With respect to option (f)—1 mg/kg anti-PD-1 antibody with 1 mg/kg of anti CTLA-4 antibody—a POSA would have had reason to select a concentration of 1 mg/kg for both antibodies given the explicit disclosure in Korman that 1 mg/kg was a “preferred” dosing concentration for this drug (both specifically and at the lower bound of the disclosed range 1-10 mg/kg) and because Korman indicated specifically that when anti-PD-1 and anti-CTLA-4 are “administered simultaneously”... “the dosage of each antibody falls within the ranges indicated.” EX1006, 56. Likewise, a 1 mg/kg dose of anti-PD-1 was also already being tested in a clinical trial of the concurrent anti-PD-1 plus anti-CTLA-4 antibody therapy more than two years before May 15, 2012. EX1005, 4 (cohort arm 3).

126. For similar reasons, a POSA would have reason to select the other “preferred” dosing concentration for anti-PD-1 (3 mg/kg) and likewise followed Korman’s guidance that such dose could be paired with anti-CTLA-4 antibody

where the dose of anti-CTLA-4 antibody falls within the range indicated (i.e., 1-10 mg/kg) to arrive at concentration option (g)—3 mg/kg anti-PD-1 antibody with 1 mg/kg of anti CTLA-4 antibody. Likewise, a 3 mg/kg dose of anti-PD-1 was also already being tested in a clinical trial of the concurrent anti-PD-1 plus anti-CTLA-4 antibody therapy more than two years before May 15, 2012. EX1005, 4 (cohort arm 4).

127. In my opinion, a POSA would have had reason to select the “preferred” dosing concentrations of 1 mg/kg or 3 mg/kg for anti-PD-1 as specifically disclosed and as falling within the disclosed range, and then would have followed Korman’s guidance that when dosing anti-PD-1 with anti-CTLA-4, both dosages could fall within the ranges indicated.

d. Claim 1 Concentration Options (h), (i), and (m)

128. With respect to claim options (h) (5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), (i) (10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody), and (m) (5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody), a POSA would have reason to select the specific recited concentrations from the listed options of anti-PD-1 (0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, **5 mg/kg body weight or 10 mg/kg body weight**), each of which was also a potentially optimal value falling within the disclosed 1-10 mg/kg range and would have then reasonably followed Korman’s

guidance that when “two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.”

EX1006, 56. Likewise, a 10 mg/kg dose of anti-PD-1 was also already being tested in a clinical trial of the concurrent anti-PD-1 plus anti-CTLA-4 antibody therapy more than two years before May 15, 2012. EX1005, 4 (cohort arm 5).

129. Because it was a well-known strategy to test iteratively higher and lower concentrations falling around previously known and tested concentrations and falling within disclosed concentration ranges (*see* Section X.A.4.a, above), a POSA would have reasonably selected and tested various incremental doses within Korman’s disclosed ranges (i.e., 1-10 mg/kg, and 0.01-5 mg/kg).

e. Claim 1 Concentration Option (k)

130. With respect to option (k) (0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody), a POSA would have had reason to and would have explored the low effective doses disclosed in the prior art (e.g., 0.3 mg/kg, as disclosed in both Korman and NCT 231 (as to anti-PD-1) and Wolchok (as to anti-CTLA-4) so as to maximize efficacy while reducing harmful side effects.

131. A POSA would have had further reason to investigate these lower doses in view of Korman’s own touting of the effectiveness of this combination therapy when anti-CTLA-4 is administered at a subtherapeutic dose (e.g., below 3

mg/kg). EX1006, 66, 94. In addition, as discussed in Section X.A.4.a, incremental escalation and de-escalation from known concentrations was a reasonable strategy for arriving at dosing schemes for this combination of antibodies and provided POSAs with reason to try these slightly higher and lower concentrations.

132. Moreover, a 0.3 mg/kg dose of anti-PD-1 was also already being tested in NCT-231. EX1005, 4 (cohort arm 2).

133. For similar reasons, a POSA would have reason to try the slightly higher dose concentration of 1 mg/kg for anti-CTLA-4 as recited in claimed option (e) (0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody) with the 0.3 mg/kg dose of anti-PD-1 as both concentrations fall within Korman's disclosed range of 0.01 to 5 mg/kg and because Korman indicated specifically that when anti-PD-1 and anti-CTLA-4 are "administered simultaneously" "the dosage of each antibody falls within the ranges indicated." EX1006, 56.

134. In view of these reasons to try a lower dose and Korman's suggestion that such would be successful, options (k) and (e) of claim 1 would have been obvious dosing options to a POSA as of May 15, 2012.

f. Claim 1 Concentration Options (a), (d), (j), and (l)

135. With respect to concentration options (a) (0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody), (d) (0.1 mg/kg anti-PD-1

antibody and 1 mg/kg of anti-CTLA-4 antibody) and (j) (0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody) and (l) (0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of anti-CTLA-4 antibody), Korman discloses the dosing concentration range of 0.01 mg/kg to 5 mg/kg for anti-PD-1 antibodies, which encompasses each of these anti-PD-1 antibody concentrations. EX1006, 55. And, again, Korman teaches that “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56. Additionally, for concentration option (a), both Korman and Wolchok disclose 3 mg/kg of CTLA-4 antibody. EX1006, 56; EX1007, abstract.

136. For the reasons set forth in Section X.A.4.a., above, a POSA would have reason to study various options within the disclosed 0.01 to 5 mg/kg range and to optimize results towards an effective concentration combination option for anti-PD-1 and anti-CTLA-4 antibodies. Moreover, as discussed above, a POSA would have reason to study low, subtherapeutic doses such as 0.1 mg/kg in view of Korman’s discussion of success with the same. EX1006, 66, 93-4.

137. As discussed at length, above, many various concentration increments were already being tested for anti-PD-1 and anti-CTLA-4 antibodies (alone and together) in the prior art. EX1007, 155; EX1009, 205s, EX1005, 4.

138. This confirms the rationale that various combinations of incremental concentrations between 0.1 mg/kg and 10 mg/kg for anti-PD-1 and anti-CTLA-4 antibodies in a concurrent regimen would have been obvious as the product of routine optimization of concentrations falling within a disclosed range (Korman).

139. A POSA would have recognized that the dosing concentration options of claim 1 ((a) through (m)) were nothing more than routine selections in view of disclosed concentrations, concentrations that were already being tested or had been tested for each of anti-PD-1 and anti-CTLA-4 antibodies, and disclosed concentration ranges. A POSA would have also recognized that these routine selections were nothing more than methodical experimentation for choosing the right antibody concentration for a combination regimen to minimize toxicity and maximize efficacy as discussed in the FDA guidance at the time and other publications on phase I clinical trial design.

140. In sum, a POSA would have had reason to select any one of the claimed dosing options ((a) through (m)) by adopting the explicit (often “preferred”) disclosed concentrations in Korman (confirmed by Wolchok and the FDA approval of ipilimumab or Sznol), Wolchok, or NCT-231, or by starting with low effective doses, and/or by routine experimentation of various dose options within the disclosed ranges of 1-10 mg/kg or 0.01-5 mg/kg for either of anti-PD-1 or anti-CTLA-4 antibodies.

5. Reasonable Expectation of Success

141. In view of the extensive prior art guidance relating to dosing concentrations for anti-PD-1 and anti-CTLA-4 administered alone (e.g., EX1007, 155; EX1009, 205s), and in view of an ongoing clinical trial testing various dosing concentrations in the same induction-maintenance structure as the challenged claims (EX1005, 4), and in view of explicit disclosure of the claimed dosing concentrations for the concurrent administration of the two antibodies together (EX1006, 55-56), and in view of evidence of success in animal models of such combination (EX1030, 4279; EX1045, 1), a POSA would have reasonably expected success in applying any one or more of the recited dosing concentration combinations (corresponding to (a) through (m)) to the dosing structure of NCT 231.

142. A POSA would have understood that dosing selections for combinations of drugs is a matter of balancing safety and efficacy within certain known constraints and considerations as discussed in the FDA guidance at the time and other literature related to phase I clinical trial design. EX1040.

143. As I discuss in Section X.A.4.a, above, many dosing decisions for combination therapies start with information about dosing concentrations that were already known to be safe and efficacious in humans for each drug alone based on prior disclosures and studies.

144. Studies reported in Sznol and Wolchok provided baseline information about anti-PD-1 and anti-CTLA-4 dosing concentrations when each was given alone. EX1007, 155; EX1009, 205s.

145. Such information would be bolstered by disclosure of concurrent administration of the two antibodies (EX1005, 4) and evidence of relative safety and efficacy for the combination therapy in animal models. EX1006, 97 (“This study indicates that, in a murine tumor model, treatment with the combination of CTLA-4 antibody and PD-1 antibody has a significantly greater effect on tumor growth than either antibody alone, even when a tumor is already well established.”); EX1030, 4276; EX1045, 1.

146. From there, researchers typically iterate the testing of various combination doses from such known concentrations (administering incrementally higher or lower concentrations as desired). *See generally* EX1040.

147. In this way, researchers can reasonably expect gradual increases or decreases in efficacy depending on incrementally different concentrations, without severe swings in toxicity. This iterative approach is confirmed by the fact that the particular concentrations of these two antibodies specifically were themselves varied and optimized within the context of the NCT 231 study. EX1005, 4.

148. For example, the five cohorts studied as of the January 5, 2010 NCT 231 (version 3) protocol tested the following concentrations:

- C1: BMS0936558 (MDX1106-040) at 0.3 mg/kg; Ipilimumab at 3 mg/kg
- C2: BMS0936558 (MDX1106-040) at 0.3 mg/kg; Ipilimumab at 10 mg/kg
- C3: BMS0936558 (MDX1106-040) at 1 mg/kg; Ipilimumab at 10 mg/kg
- C4: BMS0936558 (MDX1106-040) at 3 mg/kg; Ipilimumab at 10 mg/kg
- C5: BMS0936558 (MDX1106-040) at 10 mg/kg; Ipilimumab at 10 mg/kg

EX1005, 4.

149. Subsequently, these studied concentrations were modified by 2012 such that the April 30, 2012 (Version 58) cohorts examined the following concentrations (adding in new intermediate concentrations C2, C3 and anti-PD-1 alone concentrations C6, and C7):

- C1: BMS0936558 (MDX1106-040) at 0.3 mg/kg; Ipilimumab at 3 mg/kg
- C2: BMS0936558 (MDX1106-040) at 1 mg/kg; Ipilimumab at 3 mg/kg
- C3: BMS0936558 (MDX1106-040) at 3 mg/kg; Ipilimumab at 3 mg/kg
- C4: BMS0936558 (MDX1106-040) at 3 mg/kg; Ipilimumab at 10 mg/kg
- C5: BMS0936558 (MDX1106-040) at 10 mg/kg; Ipilimumab at 10 mg/kg
- C6: BMS0936558 (MDX1106-040) alone at 1 mg/kg
- C7: BMS0936558 (MDX1106-040) alone at 3 mg/kg

EX1031 (April, 2012 version of NCT 01024231 protocol, Version 58), 3.

150. The title of NCT 231 itself is “***Dose-escalation Study...***” Thus it was clearly within the reasonable expectation of a POSA during this time (in the

context of these two antibodies specifically, and particularly in view of the prior art success of these antibodies) that modifying and utilizing incrementally higher concentrations, typically trying increasing increments based on the log function of a given concentration (i.e., 1, 10), or based on tenths of a given dose (0.1, 1, and 0.3, 3), or doubling of doses (5,10) would successfully yield dosing concentrations to treat cancer, as claimed.

151. For at least these reasons, a POSA would have had both reason to select any one of a number of the explicitly disclosed—some “preferred”—options set forth in Korman and Wolchok (or select incremental concentration levels within disclosed concentration ranges) and utilize these with the intervention cohorts of NCT-231 and would have reasonably expected such to yield a method for treating cancer as recited in the challenged claims.

6. Claim-by-Claim Analysis

a. Independent Claim 1

i. [1Pre] “A method of treating a human subject afflicted with a cancer comprising administering to the subject:”

152. I have been informed that the first phrase of challenged claim 1 is called the “preamble,” and it may not serve to limit claim 1 in any particular way.

153. To the extent claim 1’s preamble is limiting, however, it is my opinion that NCT231-Korman-Wolchok satisfies it because the NCT231-Korman-

Wolchok method as detailed in above in Sections X.A.1-X.A.5 entails treating cancer—consistent with the teachings of all three prior art references.

154. NCT 231 is a clinical trial evaluating concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of cancer (“Unresectable Stage III or Stage IV Malignant Melanoma”). EX1005, 3.

155. Additionally, Korman discloses the use of anti-PD-1 and anti-PD-1 concurrent with anti-CTLA-4 for the treatment of cancer. EX1006, abstract.

156. And Wolchok provides dosing information and study results for the use of anti-CTLA-4 antibodies for the treatment of cancer (“stage III (unresectable) or stage IV melanoma”). EX1007, 155 (methods).

- ii. **[1A] “(a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1) (“anti-PD-1 antibody”); and (b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (“anti-CTLA-4 antibody”)”**

157. It is my opinion that NCT231-Korman-Wolchok satisfies limitation [1A] because it entails the concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies as detailed above in Sections X.A.1-X.A.5.

158. In particular, the method of NCT231-Korman-Wolchok entails the concurrent administration of both anti-PD-1 and anti-CTLA as disclosed and tested in NCT 231 (EX1005, 4) and the disclosure of simultaneous administration

of anti-PD-1 and anti-CTLA-4 antibodies for the treatment of cancer, as described in Korman. EX1006, 55-56.

- iii. **[1B] “(i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 2, 3 or 4 weeks, or once a month, for 2, 4, 6, 8, 10, or 12 doses; followed by (ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses;”**

159. It is my opinion that NCT231-Korman-Wolchok satisfies limitation [1B] because this method involves concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies on a dosing schedule that falls within the options set forth in limitation [1B] as detailed above in Sections X.A.1 and 4.

160. Specifically, the clinical trial protocol described in NCT 231 discloses an induction phase of 4 doses of combination therapy given every 3 weeks, followed by 4 doses of anti-PD-1 alone given every 3 weeks, followed by a maintenance phase of 8 doses of combination therapy given every 12 weeks. EX1005, 4. The dosing structure of the NCT231-Korman-Wolchok method thus falls within the scope of dosing numbers and frequencies disclosed in limitation [1B]. EX1005, 4.

- iv. [1C] “and wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the induction dosing schedule at the following dosages: (a) [through (m)].

161. It is my opinion that NCT231-Korman-Wolchok satisfies limitation [1C] because it entails selecting any one of the claimed concentrations for anti-PD-1 and anti-CTLA-4 antibodies ((a) through (m)), each of which are disclosed (or fall within disclosed ranges) in Korman and Wolchok, and were already being tested in NCT 231. Section X.A.1-5.

162. For clarity, I have summarized the prior art disclosures applicable to the relevant concentration options from challenged claim 1:

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody	“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55. Korman also discloses, “3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 56.	“217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.	Cohort Arm 1 0.3 mg/kg anti-PD-1; 3 mg/kg anti-CTLA-4
(b) 5 mg/kg anti-PD-1	“[f]or example dosages [of anti-PD-1] can be 0.3	“217 patients with previously treated	Cohort Arm 1 0.3 mg/kg

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
antibody and 3 mg/kg of anti-CTLA-4 antibody;	mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55. Korman also discloses, “ 3 mg/kg , i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 56.	stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72) , or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.	anti-PD-1; 3 mg/kg anti-CTLA-4
(c) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight .” EX1006, 55. Korman also discloses, “ 3 mg/kg , i.e., the known dose of anti-CTLA-4 antibody.” EX1006, 56.	“217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72) , or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.	Cohort Arm 5 10 mg/kg anti-PD-1 ; 10 mg/kg anti-CTLA-4 Cohort Arm 1 0.3 mg/kg anti-PD-1; 3 mg/kg anti-CTLA-4
(d) 0.1 mg/kg anti-PD-1 antibody	“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more		

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
and 1 mg/kg of anti-CTLA-4 antibody;	usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55. And “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(e) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55. “For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg,		Cohort Arm 1 0.3 mg/kg anti-PD-1 ; 3 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
	of the host body weight.” EX1006, 55. And “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(f) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	“Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight.” EX1006, 55. Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are		Cohort Arm 3 1 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
	administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(g) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	“Preferred dosage regimens for an anti-PD-1 antibody of the invention include...3 mg/kg body weight.” EX1006, 55. Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		Cohort Arm 4 3 mg/kg anti-PD-1 ; 10 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
(h) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55. Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(i) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10		Cohort Arm 5 10 mg/kg anti-PD-1; 10 mg/kg anti-CTLA-4

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
anti-CTLA-4 antibody;	<i>mg/kg body weight.</i>” EX1006, 55. Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(j) 0.1 mg/kg anti-PD-1 antibody and 0.1 mg/kg of anti-CTLA-4 antibody;	“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55. And “[i]n certain embodiments, two or more monoclonal		

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
	antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(k) 0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody;	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight , 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55.	“217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction).” EX1007, abstract.	Cohort Arm 1 0.3 mg/kg anti-PD-1 ; 3 mg/kg anti-CTLA-4
(l) 0.5 mg/kg anti-PD-1 antibody and 0.5 mg/kg of	“For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg and more usually 0.01 to 5 mg/kg, of the host body weight.” EX1006, 55.		

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
anti-CTLA-4 antibody;	And “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		
(m) 5 mg/kg anti-PD-1 antibody and 5 mg/kg of anti-CTLA-4 antibody.	“[f]or example dosages [of anti-PD-1] can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight.” EX1006, 55. Anti-PD-1 antibody can be dosed “within the range of 1-10 mg/kg” and “[i]n certain embodiments, two or more monoclonal antibodies with different binding specificities (e.g., anti-PD-1 and anti-		

Claim 1	Korman	Wolchok	NCT 231 (EX1005, 4)
	CTLA-4) are administered simultaneously, in which case the dosage of each antibody falls within the ranges indicated.” EX1006, 55-56.		

163. In my opinion, a POSA would have understood that dosing concentrations corresponding to options (a) through (m) would be reasonable concentrations to select for use in the protocol of NCT 231 in view of Korman’s disclosure of many of these concentrations (several as “preferred”), in view of Korman’s disclosure of ranges encompassing each of these concentrations, in view of the variety of similar concentrations already being tested in NCT 231, and in furtherance of well-known iterative dosing principles designed to find optimal concentration values within disclosed ranges.

164. Moreover, in my opinion, a POSA would have reasonably expected success in applying these disclosed concentrations to the dosing structure of NCT 231 in view of the foregoing prior art knowledge and the understanding that many such doses were already known to be safe and effective for each antibody.

b. Claim 2: “The method of claim 1, wherein the anti-PD-1 antibody is nivolumab.”

165. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method because as discussed above in Sections X.A.1-X.A.5, the NCT 231 clinical trial protocol entails the administration of BMS-936558 (MD1106-04) (also known as nivolumab) as the anti-PD-1 antibody. EX1005, 3.

166. In addition, Korman discloses, “Figure 4A shows the nucleotide sequence (SEQ ID NO: 60) and amino acid sequence (SEQ ID NO: 4) of the heavy chain variable region of the 5C4 human monoclonal antibody . . . Figure 4B shows the nucleotide sequence (SEQ ID NO: 67) and amino acid sequence (SEQ ID NO: 11) of the light chain variable region of the 5C4 human monoclonal antibody.” EX1006, 10-11.

167. I have confirmed by BLAST alignment and literature sources that the 5C4 human monoclonal antibody sequence disclosed in Korman is a human monoclonal antibody fragment that describes the partial sequences of the VH and VL chains used by the antibody designated as nivolumab, which is an anti-PD1 antibody. These sequences are unique to each antibody, like a fingerprint, and thus indicate that this is the nucleotide sequence to the antibody to Nivolumab.

c. Claim 3: “The method of claim 1, wherein the anti-CTLA-4 antibody is ipilimumab.”

168. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method because as discussed above Section X.A.1, the NCT 231 clinical trial protocol explicitly entails the administration of “ipilimumab.” EX1005, 3. And Korman discloses, “In certain embodiments, the anti-CTLA-4 antibody is human sequence monoclonal antibody 10D1 and the anti PD-1 antibody is human sequence monoclonal antibody, such as 17D8, 2D3, 4H1, 5C4, and 4A11.” EX1006, 66.

169. I have confirmed by BLAST alignment and multiple literature sources that the 10D1 human monoclonal antibody disclosed in Korman is ipilimumab, which is also known as MDX-010 or MDX-101.

d. Additional Dosing Limitations

170. Claims 4, 6, 12, and 14-17 disclose additional details of the dosing intervals or concentrations recited in independent claim 1. It is my opinion that NCT231-Korman-Wolchok render obvious each of these variations on the method of claim 1 for the same reasons discussed above regarding claim 1 and for the additional reasons discussed below with respect to the specific claim limitations.

i. Claim 4

171. Claim 4 depends from claim 1 but recites “wherein the anti-CTLA-4 antibody is administered during the induction dosing schedule once every 3 weeks

for a total of 4 doses.” It is my opinion that NCT231-Korman-Wolchok renders obvious the method of claim 4 for the same reasons discussed above regarding the dosing numbers and frequencies recited in claim 1 (Sections X.A.1 and X.A.6.a.iii) because this method entails administering an anti-CTLA-4 antibody (ipilimumab) during the induction dosing schedule once every three weeks, for a total of four doses. EX1005, 4; EX1007, 155; Section X.A.6.c.

ii. Claim 6

172. Claim 6 depends from claim 1 but further recites, “wherein the administering comprises: (i) an induction dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 3 weeks for 4 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once every 3 weeks for 4 doses; followed by (ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 2 to 12 weeks for up to 8 doses.”

173. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a dosing schedule (NCT 231) falling precisely within this claim (as discussed in Section X.A.1, above) and whereby the maintenance dosing frequency disclosed in NCT 231 is once every 12 weeks for 8 doses. EX1005, 4.

iii. Claim 12

174. Claim 12 depends from claim 1 but further recites, “wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are administered in the maintenance dosing schedule” at the same (a) through (m) concentrations recited in claim 1.

175. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails the selection of any one of the concentrations explicitly disclosed in Korman and Wolchok and which would have been combined by a POSA for the reasons discussed above at Sections X.A.2-X.A.5.

176. A POSA would have further recognized such concentration options to be equally applicable to maintenance doses as they are for induction doses and would have reason to administer similar concentrations for therapeutic consistency, maintaining safety, limiting toxicity, and convenience. Confirming this, NCT 231 includes concentration information for each cohort, where the concentrations given do not change between induction and maintenance dosing. EX1005, 4.

177. In addition, Korman discloses a specific dose for anti-PD-1 given in an induction-maintenance dosing structure, with no distinction in concentration between the induction and maintenance dose. EX1006, 55 (“Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight...via intravenous administration, with the antibody being

given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months.”). Korman also instructs that anti-PD-1 and anti-CTLA-4 can be given simultaneously per such dosing structure. EX1006, 56. Such disclosure of “1 mg/kg” for both antibodies in a maintenance regimen satisfies dosing option (f) of claim 12.

178. Korman also discloses 0.3 mg/kg as a concentration option for anti-PD-1, while Wolchok discloses administration of anti CTLA-4 antibodies at 10, 3, or 0.3 mg/kg *in a maintenance dosing schedule*. EX1006, 55; EX1007, 155 (“either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0.3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months.”).

179. In view of these maintenance dosing disclosures and as discussed in sections X.A.4.e., above, a POSA would have had a reason to assemble the dosing concentration disclosures of Korman and Wolchok to arrive at the concentration option (k) (0.3 mg/kg anti-PD-1 antibody and 0.3 mg/kg of anti-CTLA-4 antibody) and would have selected this as a maintenance concentration as this would have been a reasonable sub-therapeutic dose from which to study incrementally higher concentrations while minimizing safety and toxicity concerns.

iv. Claim 14

180. Claim 14 depends from claim 1 but further recites “wherein 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.”

181. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT 231. EX1005, 4, Section X.A.1 and X.A.6.a.iii., above.

182. In addition, as discussed above in Sections X.A.2-4b., 5, and 6.a.iv, administration of 5 mg/kg of the anti-PD-1 antibody and 3 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (b), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT 231.

v. Claim 15

183. Claim 15 depends from claim 1 but further recites, “wherein 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.”

184. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT 231. *See* EX1005, 4, Section X.A.1 and A.6.a.iii., above. In addition, as discussed above in Sections X.A.2-4.c., 5, and 6.a.iv., administration of 1 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (f), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT 231.

vi. Claim 16

185. Claim 16 depends from claim 1 but further recites, “wherein 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.”

186. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT 231. EX1005, 4, Section X.A.1 and A.6.a.iii. above. In addition, as discussed above in Sections X.A.2-4.c., 5, and 6.a.iv, administration of 3 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (g),

would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT 231.

vii. Claim 17

187. Claim 17 depends from claim 1 but further recites, “wherein 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.”

188. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails an induction dosing of anti-PD-1 and anti-CTLA-4 administered every three weeks for four doses as recited in NCT 231. EX1005, 4 and Section X.A.1 and A.6.a.iii. above. In addition, as discussed in Sections X.A.2-4.d., 5, and 6.a.iv, above, administration of 5 mg/kg of the anti-PD-1 antibody and 1 mg/kg of the anti-CTLA-4 antibody, which corresponds to claim 1, option (h), would have been an obvious concentration selection for administration of the antibodies in the induction phase of the format of NCT 231.

e. Types of Cancer and Disease Manifestation

189. Claims 7-11 depend from claim 1 but recite broad options of treatment outcomes and types of cancer to be treated with the method of the challenged claims. It is my opinion that NCT231-Korman-Wolchok render obvious each of these methods for the same reasons discussed above regarding

claim 1 and for the additional reasons discussed below with respect to the specific limitations of claim 1's method recited in these claims.

i. Claim 7

190. Claim 7 depends from claim 1 but further recites, “wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.”

191. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment of cancer resulting in reduction of tumor growth, for example. Korman discloses that “the combination treatment of anti-CTLA-4 antibody and anti-PD-1 antibody showed an unexpected, significantly greater effect on reducing tumor growth as compared to treatment with either antibody alone (see, e.g., Figures 21D, 24D, 30F and 33H-J).” EX1006, 66.

192. While Korman's results were in animal studies, a POSA would have reasonably expected a similar response in humans, or at the very least no change, as both checkpoints (anti-CTLA-4, and anti-PD-1) were understood to involve enhanced activation of human T cells in vitro, had similar sequence, message expression, gene structure, and chromosomal location as in mice, and patients with single nucleotide polymorphisms in these genes manifested various

autoimmune type syndromes. See paragraph 43, above. Furthermore, Tumor Infiltrating Lymphocytes from cancer patients expressed PD-1, and tumors expressed PD-L1 [B7-H1], thus it was reasonable that these pathways would be involved in immune evasion in humans as well. *See* Sections X.A.4-5.

193. In addition, by 2012 both anti-PD-1 and anti-CTLA-4 had demonstrated positive results in humans for outcomes such as “complete or partial response” or “objective tumor response” when administered alone, which would have provided a POSA a reasonable expectation of success for the NCT231-Korman-Wolchok method dosed at similar concentrations. EX1009, 205s (For bi-weekly dosing of MDX-1106, “As of Dec 2009, 6/16 (37.5%) evaluable pts had objective tumor responses, including 3 at 1 mg/kg (RCC/CR, RCC/PR, MEL/PR), 2 at 3 mg/kg (NSCLC/PR, MEL/PR) and one at 10 mg/kg (MEL/PR).”). EX1007, 155 (“[O]verall response rate (the proportion of patients with a complete or partial response...was 11.1% (95% CI 4.9–20.7) for 10 mg/kg, 4.2% (0.9–11.7) for 3 mg/kg, and 0% (0.0–4.9) for 0.3 mg/kg (p=0.0015; trend test).”).

194. In view of this information, a POSA would have reasonably expected at least some degree of similar response in humans, or at the very least would have reasonably expected the maintenance of stable disease. *See* section X.A.5, above.

ii. Claim 8

195. Claim 8 depends from claim 1, but further recites, “wherein the cancer is selected from liver cancer, hepatocellular carcinoma . . . cutaneous or intraocular malignant melanoma . . . non-Hodgkin’s lymphoma . . . and a hematologic malignancy.”

196. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment of several cancers, including several that fall within or overlap with those recited in claim 8 including melanoma and non-Hodgkin’s lymphoma. EX1006, 68. Both NCT 231 and Wolchok studied patients with “stage III (unresectable) or stage IV melanoma.” EX1007, 155; EX1005, 4. A POSA would have understood malignant melanoma to include stage III or stage IV melanoma.

197. Korman also discloses use of “blockade of PD-1 and CTLA-4” as treatment against various cancers including melanoma (e.g., metastatic malignant melanoma), lung cancer, and non-Hodgkin’s lymphoma, among others. EX1006, 68.

198. A POSA would have reason to enlist the method of NCT231-Korman-Wolchok to treat, for example, melanoma, non-Hodgkin’s lymphoma, or lung cancer, given Korman’s teaching and the existence of studies (Wolchok and NCT 231, for example) treating the disease with anti-CTLA-4 alone or in

combination with anti-PD-1, and would have reasonably expected success in combining such teachings.

iii. Claim 9

199. Claim 9 depends from claim 1 but further recites, “wherein the hematologic malignancy is selected from multiple myeloma, B-cell lymphoma, Hodgkin lymphoma/primary mediastinal B-cell lymphoma, non-Hodgkin's lymphomas. . . and precursor T-lymphoblastic lymphoma.”

200. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment of several cancers, including Hodgkin’s lymphoma and non-Hodgkin’s lymphoma. EX1006, 68. Given this disclosure, a POSA would have reason to enlist the method of NCT231-Korman-Wolchok to treat, for example, at least non-Hodgkin’s lymphoma and similar diseases, and would have reasonably expected success in combining those teachings.

iv. Claim 10

201. Claim 10 depends from claim 1 but further recites, “wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.”

202. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment of several cancers including metastatic cancer. EX1006, 60 (“The present invention is also useful for

treatment of metastatic cancers, especially metastatic cancers that express PD-L1.”), 68; EX1007, 155 (background, studying patients with advanced melanoma).

203. Given this disclosure, a POSA would have reason to enlist the method of NCT231-Korman-Wolchok to treat, for example, metastatic cancer, and would have reasonably expected success in combining those teachings.

v. Claim 11

204. Claim 11 depends from claim 1 but further recites, “wherein the treatment is further combined with one of more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.”

205. It is my opinion that NCT231-Korman-Wolchok renders obvious this claimed method as it entails a method of treatment whereby the claimed antibodies are administered with other known cancer therapies. For example, Korman discloses these precise therapeutic additions. EX1006, 70 (“A combined PD-1 and CTLA-4 blockade may also be further combined with standard cancer treatments. For example, a combined PD-1 and CTLA-4 blockade may be effectively combined with chemotherapeutic regimes.”). Korman also provides a mechanistic explanation regarding the motivation to layer on such additional therapies—“The scientific rationale behind the combined use of PD-1 and CTLA-4 blockade with chemotherapy is that cell death, which is a consequence of the

cytotoxic action of most chemotherapeutic compounds, should result in increased levels of tumor antigen in the antigen presentation pathway.” EX1006, 70.

206. Given this disclosure, a POSA would have reason to further add existing cancer therapies such as chemotherapy to the method of NCT231-Korman-Wolchok to treat cancer and would have reasonably expected success in combining such teachings.

* * *

207. For at least the foregoing reasons, it is my opinion that challenged claims 1-4, 6-12, and 14-17 are obvious over NCT231-Korman-Wolchok.

B. GROUND 2: Korman in View of Wolchok, and in further View of Sznol Render Obvious Claims 5, 13, and 18-22.

208. Challenged claim 5 states as follows:

[5Pre] 5. A method of treating a human subject afflicted with a cancer comprising

[5A] administering to the subject 1 mg/kg of an anti-PD-1 antibody and 3 mg/kg of an anti-CTLA-4 antibody

[5B] every 3 weeks for 4 doses,

[5C] followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.

209. By 2012, all of the features of challenged claim 5 were known.

Korman had—nearly six years earlier—provided explicit dosing disclosures for

both anti-PD-1 antibodies, anti-CTLA-4 antibodies, and their concurrent use.

EX1006, 55 (“Preferred dosage regimens for an anti-PD-1 antibody of the invention include **1 mg/kg** body weight...using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) **every three weeks**; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks”); EX1006, 20 (“**3 mg/kg**, *i.e.*, the known dose of anti-CTLA-4 antibody.”); EX1006, 56 (“In certain embodiments, two or more monoclonal antibodies with different binding specificities (*e.g.*, anti-PD-1 and anti-CTLA-4) are administered simultaneously, in which case ***the dosage of each antibody administered falls within the ranges indicated.***”).

210. Moreover, Wolchok disclosed and reported the results of a study on what would become the approved dosing schedule for anti-CTLA-4 therapy at a concentration of 3 mg/kg “once every three weeks for four cycles.” EX1007, 155 (abstract); EX1008, 1.

211. And by 2010, prior art reference Sznol reported that biweekly anti-PD-1 monotherapy had been demonstrated safe and effective at a dose of 1, 3, or 10 mg/kg administered bi-weekly. EX1009, 205s.

212. As I discuss below, a POSA would have had a reason to combine these prior art teachings to arrive at the method of claim 5 and its dependent

claims and would have reasonably expected to arrive at a method for the treatment of cancer.

1. Reason to Modify Korman with the Teachings of Wolchok and Sznol

a. Combination dosing number and frequency

213. Korman discloses that a “preferred dosage regimen” for anti-PD-1 would be “every three weeks” while Wolchok discloses the effective treatment of melanoma with anti-CTLA-4 antibody at a dosing frequency of “every three weeks for four cycles.” EX1007, 155 (methods).

214. Korman also discloses the treatment of cancer using simultaneous administration of anti-PD-1 and anti-CTLA-1. EX1006, 56. In deciding at what frequency to administer Korman’s concurrent therapy, a POSA would have recognized that both Korman and Wolchok disclose an “every three week” regimen. EX1006, 55. And a POSA would have deemed this frequency reasonable to use given Wolchok’s success with such frequency for the relatively more toxic antibody, anti-CTLA-4. *See* § VII.C, above.

215. By May of 2012 it was also clear that anti-CTLA-4 antibodies generated significant immune-related adverse events. *See* Exs. 1019, 29 (abstract) 1020, 499; 1021, 865; EX1007, 157, Fig. 1 (“Trial Profile,” showing significant participant loss in progression from induction to maintenance dosing of anti-CTLA-4).

216. By contrast, a POSA would have been aware of “a milder toxicity profile for anti-PD-1 than for anti-CTLA-4.” EX1042, 245, right col.; EX1044, 512, 514; EX1037, 3172; *See* § VII.C.1-2, above. With this information, a POSA would have been cautious with the administration of anti-CTLA-4 and chosen a frequency for any combination therapy involving this drug that was already demonstrated safe and effective. A POSA dosing a concurrent therapy including anti-CTLA-4 would reasonably have followed Korman and Wolchok’s frequency disclosure of “every three weeks” limited by Wolchok’s number of doses, “for four cycles.” EX1007, 155.

b. Subsequent Dosing of Anti-PD-1 Alone

217. In view of the less severe toxicity profile for anti-PD-1 antibodies and the sequentially later mechanistic action of anti-PD-1 relative to anti-CTLA-4 in blocking the T-cell “off signal” to kill cancer cells, a POSA would have desired to extend the therapeutic benefit of the combination drug by continuing patients on anti-PD-1 antibodies subsequent to the concurrent therapy. EX1010, 178 (“CTLA-4 is important for limiting T-cell activity for cells early during the immune responses. PD-1, on the other hand, limits T-cell activity in peripheral tissues and may be the last chance to prevent T-cell destruction of self-tissue resulting in autoimmunity.”).

218. A POSA would therefore have had reason to continue administering anti-PD-1 antibody as a monotherapy even after completion of the combination and would have looked to existing reports of success with anti-PD-1 as a monotherapy, such as the bi-weekly dosing reported by Sznol. EX1009, 205s (“As of Dec 2009, 6/16 (37.5%) evaluable pts had objective tumor responses, including 3 at 1 mg/kg (RCC/CR, RCC/PR, MEL/PR)...conclusions: MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.”). Korman also discloses bi-weekly dosing for anti-PD-1. EX1006, 55 (“An exemplary treatment regime entails administration once per week, *once every two weeks*.”).

c. Dosing concentrations

219. A POSA implementing the concurrent antibody therapy of Korman would have reason to dose anti-PD-1 at a concentration of 1 mg/kg given its designation by Korman as “preferred” (EX1006, 55-56) and its demonstrated success in Sznol at reducing melanoma tumors (3 patients with objective tumor responses at 1 mg/kg). EX1009, 205s (results).

220. Such POSA would have also had reason to dose anti-CTLA-4 at the “known” (EX1006, 22), “stud[ied]” (EX1007, 155), and “approved” and “recommended” (EX1008, 1) 3 mg/kg concentration disclosed in both Korman and Wolchok. A POSA would have reason to look to these disclosures in view of

the standard approach in the field of dosing cancer immunotherapies of starting with what had been disclosed, known, studied, and reported safe and efficacious. EX1032, 1224 (right col.). Such approach would have provided a POSA with reason to settle on concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies at 1 mg/kg of the former and 3 mg/kg of the latter.

221. In sum, a POSA would have reason to administer anti-PD-1 and anti-CTLA-4 concurrently and every three weeks as disclosed in Korman, at 1 mg/kg anti-PD-1 (Korman) and 3 mg/kg of anti-CTLA-4 (Korman and Wolchok), in a manner consistent with the approved dosing scheme for anti-CTLA-4 (i.e., every three weeks for four cycles) (Wolchok), and would have looked to avoid harmful toxicity and seek the additional therapeutic benefit from an extended dose of anti-PD-1 alone at its known, safe, and effective bi-weekly frequency as reported in Sznol.

222. I refer to these teachings, combined for the reasons discussed above, as “Korman-Wolchok-Sznol.”

2. Reasonable Expectation of Success

223. A POSA would have had a reasonable expectation of success in developing a method to treat cancer by administering anti-PD-1 and anti-CTLA-4 antibodies concurrently as disclosed in Korman at the dosing numbers,

frequencies, and concentrations disclosed in Korman, Wolchok, and Sznol, and then by administering anti-PD-1 alone biweekly as taught in Sznol.

224. Such reasonable expectation would exist for the same reasons disclosed above regarding the combination of NCT 231 and Korman and Wolchok and would include: the existing safety and efficacy demonstrated with anti-PD-1 alone at a concentration of 1 mg/kg (EX1009, 205s), the existing safety and efficacy of anti-CTLA-4 alone at a concentration of 3 mg/kg given every three weeks for four doses (EX1007, 155; EX1008, 1), the disclosure of administering anti-PD-1 and anti-CTLA-4 concurrently and the demonstrated efficacy of such concurrent administration in animal models (EX1006, EX1030, EX1045), and the known safety and toxicity profiles of each antibody as discussed at length above in Section VII.C. This body of knowledge would have given a POSA a reasonable expectation of success in administering 1 mg/kg of anti-PD-1 and 3 mg/kg of anti-CTLA-4 together every three weeks for four cycles, followed by administering anti-PD-1 alone, bi-weekly.

3. Claim-By-Claim Analysis

a. Independent Claim 5

i. [5Pre] “A method of treating a human subject afflicted with a cancer comprising”

225. I have been informed that the first phrase of challenged claim 5 is called the “preamble” and it may not serve to limit claim 5 in any particular way.

226. To the extent claim's preamble is limiting, however, it is my opinion that Korman-Wolchok-Sznol satisfies it because the Korman-Wolchok-Sznol method as detailed above in Sections IX.B-D., X.A.2-3, and X.B.1-2. above entails treating human cancer patients.

227. Korman discloses the use of anti-PD-1 antibodies concurrent with anti-CTLA-4 antibodies for the treatment of cancer. EX1006, 1 (Abstract).

228. Wolchok provides dosing information and study results for the use of anti-CTLA-4 antibodies for the treatment of cancer ("stage III (unresectable) or stage IV melanoma"). EX1007, 155 (methods).

229. Sznol studies treatment with anti-PD-1 in patients with "advance refractory malignancies." EX1009, 205s (Title).

230. A POSA would have had a reason to apply the various treatment details of each cancer-treatment-focused prior art reference in developing a concurrent therapy using these two antibodies that would account for the safety and toxicity profiles of each and would have reasonably expected success in doing so. This is consistent with my discussion above at Sections X.B.1-2.

ii. [5A] "administering to the subject 1 mg/kg of an anti-PD-1 antibody,"

231. It is my opinion that Korman-Wolchok-Sznol satisfies limitation [5A] because it entails administering anti-PD-1 antibody at a concentration of 1 mg/kg, consistent with the teachings of both Korman (which discloses this

concentration as “preferred” for anti-PD-1) and Sznol (which demonstrates safe and effective results of treatment of refractory cancers with 1 mg/kg of anti-PD-1). EX1006, 55; EX1009, 205s.

iii. [5B] “And 3 mg/kg of an anti-CTLA-4 antibody”

232. It is my opinion that Korman-Wolchok-Sznol satisfies limitation [5B] because it entails administering anti-CTLA-4 antibody at a concentration of 3 mg/kg, consistent with the teachings of both Korman (which discloses this as the “known” concentration for anti-CTLA-4 (EX1006, 20)) and Wolchok (which demonstrates safe and effective Phase II trial results of treatment of metastatic melanoma with 3 mg/kg of anti-CTLA-4). EX1007, 155 (methods). Ipilimumab was also approved by the FDA in 2011 at this concentration. EX1008, 1.

233. A POSA would thus have had reason to select a safe and effective concentration of anti-CTLA-4 in Korman’s concurrent administration based on *existing data* about the antibody’s safety and effectiveness and so would have relied on these existing prior art disclosures to select 3 mg/kg. This is consistent with my discussion above at Sections X.B.1-2.

iv. [5C] “Every 3 weeks for 4 doses,”

234. It is my opinion that Korman-Wolchok-Sznol satisfies limitation [5C] because it entails administering anti-PD-1 antibody and anti-CTLA-4 antibody together every three weeks for four doses (or cycles).

235. Korman describes administering anti-PD-1 antibody on an “every three weeks” schedule and instructs that anti-PD-1 and anti-CTLA-4 can be given together (simultaneously) such that anti-CTLA-4 would also be given “every three weeks.” EX1006, 55-56.

236. Additionally, Wolchok discloses the later-approved dosing regimen for anti-CTLA-4 at “every 3 weeks *for four cycles*,” and in view of the greater toxicity concerns relating to the length of administration of anti-CTLA-4 (as I discuss above in Section 52), a POSA would have applied Wolchok’s four cycle dosing number to the “every three week” dosing frequency of Korman for a combination therapy involving anti-CTLA-4. EX1007, 155; EX1008, 1.

237. A POSA would have thus had reason to give anti-CTLA-4 antibody therapy—and would have understood from Korman and Wolchok that concurrent anti-PD-1 and anti-CTLA-4 therapy could reasonably be given—every three weeks for four doses. This is consistent with my discussion above at Section X.B.1-2.

- v. **[5D] “followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.”**

238. It is my opinion that Korman-Wolchok-Sznol satisfies limitation [5D] because it entails the application of knowledge about the safety and toxicity of each of these antibodies to administer anti-PD-1 monotherapy following the

four cycles of combination therapy (four cycles being the disclosed and studied dose number for anti-CTLA-4). EX1007, 155; EX1008, 1.

239. As I discuss above in Sections VII.C., and X.B.1-2, a POSA would have recognized that anti-CTLA-4 therapy was associated with increased risk of toxicity and adverse immune-related events, particularly after repeated doses of the antibody, such that patients undergoing clinical trials with this drug were likely to drop off or out of clinical trials entirely after a certain length of dosing. EX1019, 29 (abstract); EX1020, 499; 1021, 865; EX1007, 157, Fig. 1. As such, the four cycles of every 3 weeks dosing studied in Wolchok (and ultimately approved in 2011) would have been viewed by POSAs to be a reasonable number and frequency for doses of this antibody.

240. This understanding of the limitations of anti-CTLA-4 antibody administration, combined with the desire to balance therapeutic efficacy with toxicity and patient tolerance and in recognition of the temporal nature of each antibody's mechanism of action (EX1010, 178), would have provided POSAs with reason to follow the concurrent therapy with a phase of anti-PD-1 monotherapy.

241. Because Sznol disclosed safe and effective bi-weekly dosing of anti-PD-1 in humans, a POSA would have had reason to apply these existing results to dose anti-PD-1 monotherapy bi-weekly. Given the evidence of safety and

efficacy already known to be associated with bi-weekly dosing of anti-PD-1 (EX1009, 205s), a POSA would have reasonable expected success in combining these dosing teachings.

242. For the foregoing reasons, it is my opinion that challenged claim 5 is obvious over Korman-Wolchok-Sznol.

b. Claim 13

243. Claim 13 depends from claim 5 but further recites, “wherein the anti-PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg.”

244. It is my opinion that Korman-Wolchok-Sznol renders obvious this claimed method because it entails administering anti-PD-1 alone bi-weekly and at a dose of 3 mg/kg. As discussed above, Sznol reported safe and effective results of dosing anti-PD-1 alone bi-weekly at this precise dose (3 mg/kg) and a POSA would have looked to this existing information in selecting the precise concentration of an anti-PD-1 monotherapy following concurrent administration of anti-PD-1 and anti-CTLA-4. EX1009, 205s (methods). Korman likewise discloses the administration of anti-PD-1 at a dose of 3 mg/kg. EX1006, 55.

c. Claim 18

245. Claim 18 depends from claim 1 but further recites, “wherein the treatment provides a reduction in tumor size, reduction in tumor growth,

elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.” It is my opinion that Korman-Wolchok-Sznol renders obvious this claimed method for the same reasons I discuss above at Section X.A.6.e.i, regarding claim 7.

d. Claim 19

246. Claim 19 depends from claim 5 but lists types of cancer which can be treated by the claimed method, including melanoma.

247. It is my opinion that Korman-Wolchok-Sznol renders obvious this claimed method because it entails the treatment of melanoma, and more specifically, all three prior art references contributing to the Korman-Wolchok-Sznol method involve the treatment of melanoma.

248. Korman discloses the treatment of melanoma with concurrent anti-PD-1 and anti-CTLA-4 therapy. EX1006, 68. Wolchok studied patients with “stage III (unresectable) or stage IV melanoma.” EX1007, 155 (abstract). And Sznol evaluated patients who “had treatment refractory metastatic...melanoma.” EX1009, 205s (methods). In light of these disclosures, a POSA would have reason to use the Korman-Wolchok-Sznol method to treat melanoma and would have reasonably expected success in combining such teachings.

e. Claim 20

249. Claim 20 depends from claim 5 but further recites, “wherein the cancer is melanoma.” It is my opinion that Korman-Wolchok-Sznol renders this claimed method obvious for the same reasons I discuss above at Section X.B.3.d, regarding claim 19.

f. Claim 21

250. Claim 21 depends from claim 5 but further recites, “wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.”

251. It is my opinion that Korman-Wolchok-Sznol renders obvious this claimed method because it entails the treatment of advanced and/or metastatic and/or refractory melanoma, and more specifically, all three prior art references contributing to the Korman-Wolchok-Sznol method involve the treatment of either advanced and/or metastatic and/or refractory melanoma.

252. Korman discloses the treatment of “metastatic malignant” melanoma with concurrent anti-PD-1 and anti-CTLA-4 therapy. EX1006, 68. Wolchok studied patients with “advanced melanoma.” EX1007, 155 (background).

253. And Sznol evaluated patients who “had treatment refractory metastatic...melanoma.” EX1009, 205s (methods). In light of the focus of these references, a POSA would have reason to use the Korman-Wolchok-Sznol method

to treat advanced and/or metastatic and/or refractory melanoma and would have reasonably expected success in combining these teachings.

g. Claim 22

254. Claim 22 depends from claim 1 but further recites, “wherein the treatment is further combined with one of more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.” It is my opinion that Korman-Wolchok-Sznol renders this claimed method obvious for the same reasons discussed above at Section X.A.6.e.v, regarding claim 11.

* * *

255. For the foregoing reasons, it is my opinion that claims 5, 13, and 18-22 are obvious over Korman-Wolchok-Sznol.

256. For clarity, I have summarized the prior art disclosures applicable to the relevant concentration options from challenged claims 5 and 13.

Claim 5	Korman	Wolchok	Sznol
[5A] administering to the subject 1 mg/kg of an anti-PD-1 antibody	“Preferred dosage regimens for an anti-PD-1 antibody of the invention include <i>1 mg/kg body weight.</i> ” EX1006, 55.		“Escalation of biweekly MDX-1106 dosing at <i>1</i> , <i>3</i> , or <i>10 mg/kg</i> IV was studied.” “Results:...Preliminary PK estimates of trough/peak

Claim 5	Korman	Wolchok	Sznol
	“For administration of the antibody, <i>the dosage ranges from</i> about 0.0001 to 100 mg/kg and <i>more usually 0.01 to 5 mg/kg, of the host body weight...</i> or within the range of 1-10 mg/kg.” EX1006, 55.		antibody levels after 2 cycles are ~ 25/40, 50/110, 150/300 ug/ml for <i>1, 3, and 10 mg/kg</i>, respectively.” “MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg. EX1009, 205s.
[5B] and 3 mg/kg of an anti-CTLA-4 antibody	Korman discloses, “<i>3 mg/kg, i.e., the known dose of anti-CTLA-4 antibody.</i>” EX1006, 20.	“217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), <i>3 mg/kg (n=72)</i>, or 0.3 mg/kg (n=72) <i>every 3 weeks for four cycles (induction).</i>”	

Claim 5	Korman	Wolchok	Sznol
		EX1007 (methods).	
[5C] every 3 weeks for 4 doses,	“Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration, with the antibody being given using one of the following dosing schedules...(ii) every three weeks....In certain embodiments, two or more monoclonal antibodies with different binding specifics (<i>e.g., anti-PD-1 and anti-CTLA-4</i>) are administered simultaneously, in which case the dosage of each antibody	In view of the greater toxicity concerns relating to the length of administration of anti-CTLA-4, a POSA would have applied Wolchok’s four cycle dosing number (“every 3 weeks for four cycles”) to the “every three week” dosing frequency of Korman for a combination therapy involving anti-CTLA-4. EX1007, 155 (methods).	

Claim 5	Korman	Wolchok	Sznol
	<i>administered falls within the ranges indicated.”</i> EX1006, 55-56.		
[5D] followed by subsequently administering the anti-PD-1 antibody alone at a dosing frequency of once every 2 weeks.			Because Sznol discloses safe and effective bi-weekly dosing of anti-PD-1 in humans (“ MDX-1106 [(a fully human IgG4 PD-1 blocking antibody)] administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg.”), and because anti-PD-1 exhibits lower toxicity relative to anti-CTLA-4, a POSA would have reason to apply these existing results of Sznol to administer biweekly anti-PD-1 monotherapy following the combined administration. EX1009, 205s;

Claim 5	Korman	Wolchok	Sznol
			<i>see also</i> Section VII.C. and X.B.1, 2.

Claim 13	Korman	Wolchok	Sznol
The method of claim 5, wherein the anti-PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg.	“Preferred dosage regimens for an anti-PD-1 antibody of the invention include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration....” EX1006, 55. “For administration of the antibody, <i>the dosage ranges from</i> about 0.0001 to 100 mg/kg and <i>more usually 0.01 to 5 mg/kg, of the host body weight</i>...or within the range of 1-10 mg/kg.” EX1006, 55.		Because Sznol discloses safe and effective bi-weekly dosing of anti-PD-1 in humans (“<i>MDX-1106 [(a fully human IgG4 PD-1 blocking antibody)] administered biweekly</i> is well tolerated and has antitumor activity at 1-10 mg/kg.”), and because Sznol reported safe and effective results of dosing anti-PD-1 alone bi-weekly at 3 mg/kg (“Escalation of biweekly MDX-1106 dosing at 1, 3, or 10 mg/kg IV was studied.”), and because anti-PD-1 exhibits

Claim 13	Korman	Wolchok	Sznol
			lower toxicity relative to anti-CTLA-4, a POSA would have reason to apply these existing results of Sznol to administer biweekly anti-PD-1 monotherapy at 3 mg/kg following the combined administration. EX1009, 205s; <i>see also</i> Section VII.C. and X.B.1, 2.

XI. SECONDARY CONSIDERATIONS DO NOT OVERCOME A FINDING OF OBVIOUSNESS.

257. As I noted above at ¶25, I have been informed that certain objective factors, sometimes referred to as “secondary considerations”—if present—can outweigh a finding of obviousness. To my knowledge, the Patent Owner has not asserted any such secondary considerations with respect to the ’320 patent and there was no discussion of such secondary considerations during the back-and-forth with the Examiner at the USPTO that led to the ’320 patent. *See generally*, EX1002.

258. I have, however, reviewed some of the statements that the Patent Owner made during prosecution of related claims with similar dosing limitations in Europe (EX1023, 1034). In that proceeding, Patent Owner argued that Table 10 of the '320 patent evidences surprising or unexpected results with respect to cohort 2 and 2a (EX1025, 1-2) or cohort 2. EX1035, 2.

259. However, the dosing regimen of cohort 2 does not align with any dosing regimen recited in any challenged claim. *Compare* EX1001, Table 10, *with* EX1001, cls. 1-22. And the data in Table 10 arose from a “concurrent regimen” structure that was distinct from and irrelevant to the dosing regimen of claim 5 or any of its dependent claims. EX1001, 87:4-16. There is no data in the '320 patent relating to claim 5's dosing regimen at all, let alone data demonstrating unexpected results of such regimen. EX1001, 87:4-16. I understand that alleged evidence of unexpected results must correspond to what is actually claimed.

260. Moreover, Patent Owner's arguments regarding the unexpected results of cohort 2 and 2a were rejected by the Examining Division in Europe, leading to Patent Owner's withdrawal of such claims. EX1026, 2-3; EX1033, 1.

261. In any case, it is my opinion that the data presented in Table 10 fails to establish unexpected results across the full scope of claim 1 and its dependent claims. Instead, Patent Owner admitted that certain unclaimed cohorts performed

better than the single cohort from Table 10 that falls within the scope of any challenged claim (cohort 2a, corresponding to claimed option (g)). EX1035, 2 (“[t]he data in Table 10 clearly show that the dosing regimen of *Cohort 2 has superior effects as compared to those of cohorts 1, 2a, and 3.*”).

262. Moreover, there is no evidence that any of the concentration regimens recited in Table 10 of the ’320 patent demonstrate any difference *in kind* relative to the prior art in objective response rate or 80% tumor reduction at 12 weeks (as opposed to a difference of degree).

263. To the contrary, the prior art was already well aware of and fully expected additive (and synergistic) benefits to combining these antibodies. EX1006, 66; EX1045, 1.

264. In my opinion, there is no evidence of secondary considerations that would overcome the foregoing explanation for why challenged claims 1-22 would have been obvious to a POSA over the prior art as of May 15, 2012.

XII. CONCLUSION

265. In conclusion, it is my opinion that challenged claims 1-22 are obvious over the prior art as of May 15, 2012.

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: ____ 28 February 2025 _____

_____/Paul Andrew Antony/____

Dr. Paul Andrew Antony

APPENDIX A

Exhibit	Description
1001	U.S. Patent No. 9,856,320
1002	Prosecution History of U.S. Patent No. 9,856,320
1005	NCT01024231 Version 3, Brief Title: “Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted to clinicaltrials.gov: January 5, 2010).
1006	International Patent Publication No. WO 2006/121168
1007	Wolchok et al., Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomized, double-blind, multicentre, phase 2, dose-ranging study. <i>Lancet Oncol.</i> 2010 Feb; 11(2):155–64.
1008	March 25, 2011 Bristol Myers Squibb Press Release announcing Ipilimumab FDA Approval, “FDA Approves YERVOY™ (ipilimumab) for the Treatment of Patients with Newly Diagnosed or Previously-Treated Unresectable or Metastatic Melanoma, the Deadliest Form of Skin Cancer.”
1009	Sznol et al., Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1 BMS-936558/ONO4538) in patients with advanced refractory malignancies. <i>J Clin Oncology.</i> 2010 May 20; 28(15).
1010	Fife et al., Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways.” <i>Immunol Rev.</i> 2008 Aug; 224:166–182.
1011	NCT00323882 Version 1, Brief Title: “Phase I/II, Open-Label, Dose-Escalation Study of MDX-010 in Patients With Metastatic Hormone-Refractory Prostate Cancer” (Last Update Posted to clinicaltrials.gov: May 10, 2006).
1012	NCT00729950 Version 1, Brief Title: “Study of MDX-010 in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted to clinicaltrials.gov: August 8, 2008).
1013	NCT00441337 Version 1, Brief Title: “Safety and PK Study of MDX-1106 in Patients With Selected Refractory or Relapsed Malignancies” (Last Update Posted to clinicaltrials.gov: February 28, 2007).
1014	NCT00730639 Version 1, Brief Title: “A Phase 1b Study of MDX-1106 in Subjects With Advanced or Recurrent Malignancies” (Last Update Posted to clinicaltrials.gov: August 8, 2008).
1015	Parry et al., CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. <i>Mol Cell Biol.</i> 2005 Nov; 25(21):9543-53.

1016	Okazaki et al., PD-1 and PD-1 ligands: from discovery to clinical application. <i>Int Immunol</i> . 2007 Jul; 19(7):813-24.
1017	NCT00094653 Version 1, Brief Title: “MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients with Melanoma” (Last Update Posted to clinicaltrials.gov: June 24, 2005).
1018	YERVOY FDA Approved label and prescribing information, March 2011
1019	Dillard et al., Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. <i>Pituitary</i> . 2010; 13(1):29-38.
1020	Giacomo et al., The Emerging Toxicity Profiles of Anti-CTLA-4 Antibodies Across Clinical Indications. <i>Semin Oncol</i> . 2010 Oct; 37(5):499-507.
1021	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.
1022	Pardoll D., The blockade of immune checkpoints in cancer immunotherapy. <i>Nat Rev Cancer</i> . 2012 Mar 22; 12(4):252-64.
1023	European Patent Application No. 17189595.6, Amended Claims, dated October 18, 2018.
1025	European Patent Application No. 17189595.6, Reply to Communication from the Examining Division, dated April 16, 2020.
1026	European Patent Application No. 17189595.6, Annex to the Communication, dated April 11, 2022.
1027	Wolchok et al., Nivolumab plus Ipilimumab in Advanced Melanoma. <i>N Engl J Med</i> . 2013 Jun 2; 369(2):122-33.
1030	Curran et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. <i>Proc Natl Acad Sci USA</i> . 2010 Mar 2; 107(9):4275–4280.
1031	NCT01024231, Version 58, Brief Title: “Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma” (Last Update Posted to clinicaltrials.gov: May 1, 2012).
1032	Humphrey et al., Opportunities and Challenges in the Development of Experimental Drug Combinations for Cancer. <i>J Natl Cancer Inst</i> . 2011 Aug 17; 103(16):1222–1226.

1033	European Patent Application No. 17189595.6, Notice of Withdrawal. (Sept. 20, 2022)
1034	European Patent Application No. 22196038.8 Amended claims filed after receipt of (European) search report. (Oct. 18, 2023)
1035	European Patent Application No. 22196038.8 – Letter accompanying amendments received before examination (Oct. 18, 2023)
1036	Hodi et al., Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. <i>Proc Nat’l Acad Sci USA</i> . 2003 Apr 15; 100(8):4712–4717.
1037	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
1039	Wolchok, J.D., et al., Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. <i>N Engl J Med</i> . 2011 Jun 30; 346(26):2517-1526.
1040	Tourneau et al., Dose escalation methods in Phase 1 cancer clinical trials. <i>J Natl Cancer Inst</i> . 2009 May 20; 101(10):708–720.
1042	Simeone et al., Immunomodulating antibodies in the treatment of metastatic melanoma: The experience with anti-CTLA-4, anti-CD137, and anti-PD1. <i>J Immunotoxicol</i> . 2012 Jul-Sep; 9(3):241-7.
1044	Ascierto et al., Clinical Experiences with Anti-CD137 and Anti-PD1 Therapeutic Antibodies. <i>Semin Oncol</i> . 2010 Oct; 37(5):508-16.
1045	Korman et al., Activity of Anti-PD-1 in murine tumor models: Role of ‘host’ PD-L1 and synergistic effect of anti-PD-1 and anti-CTLA-4. <i>J Immunology</i> . 2007 Apr; 178(1_Supplement):S82 (abstract). DOI:10.4049/jimmunol.178.Supp.48.37
1061	Wolchok et al., Supplementary Appendix. Nivolumab plus Ipilimumab in Advanced Melanoma. <i>N Engl J Med</i> . 2013 Jul 11; 369(2):122-33