

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. IPR2025-00603
Patent No. 11,332,529

DECLARATION OF DR. ARTA MONIR MONJAZEB

Amgen Exhibit 1003 Amgen v. BMS

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I, Dr. Arta Monir Monjazez, M.D., Ph.D., declare:

I. INTRODUCTION

1. I have been retained by counsel to render certain opinions as an expert witness for the above-captioned inter partes review (“IPR”) proceeding regarding U.S. Patent No. 11,332,529 (“the ’529 patent”). In connection with my analysis, I have reviewed the ’529 patent (EX1001), its file history (EX1002), and the additional documents listed in Appendix A to this Declaration. I have been asked to provide a declaration regarding my opinions on the validity of claims 1-18 (the “Challenged Claims”) of the ’529 patent.

2. This declaration sets forth the opinions I have formed in this IPR and provides the bases and reasons for those opinions. I have summarized my educational background, professional experience, and publications herein and have attached my complete curriculum vitae, 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 validity of claims 1-18 of the '529 patent ("Challenged Claims") in light of the prior-art references identified in the Petition. For reasons exemplified below, it is my opinion that each of claims 1-18 was anticipated, or would have been obvious to a POSA, as set forth in the table below. The table refers to short-form names (e.g., "NCT-188"), which I define in Section VIII below when discussing the prior art.

Ground Number and Reference(s)		Claim(s)	Basis
1A	NCT-188	1 and 4-14	§102
1B	NCT-188 and Zhang	2-3	§103
1C	NCT-188 and NCT-109	15-18	§103
2A	NCT-188, Postow, and Xiao	1 and 4-14	§103
2B	NCT-188, Zhang, Postow, and Xiao	2-3	§103
2C	NCT-188, NCT-109, Postow, and Xiao	15-18	§103
3A	Le, Xiao, and Hammers	1 and 4-14	§103
3B	Le, Xiao, Hammers, and Zhang	2-3	§103
3C	Le, Xiao, Hammers, and NCT-109	15-18	§103

III. PERSONAL AND PROFESSIONAL BACKGROUND

6. A description of my professional background and qualifications is provided below. An additional account of my work experience and qualifications is included in my curriculum vitae, which is identified as EX1004.

7. I am a Professor of Radiation Oncology at the UC Davis Comprehensive Cancer Center and a clinician scientist leading the clinical care of patients, a high-powered basic science research enterprise, and cutting-edge human clinical trials. Throughout my career, I have served in leadership roles in radiation oncology and cancer immunotherapy on an institutional and national level including: PI (principal investigator) of an R01 funded basic science research laboratory; heading GI and sarcoma radiotherapy at UC Davis; Director of the Cancer Immunology and Energetics Program at UC Davis Comprehensive Cancer Center; Director of Radiobiology for the UC Davis Department of Radiation Oncology; Co-Chair of NRG Oncology Immunotherapy Committee Co-Chair; and PI of institutional investigator initiated trials and national clinical trials.

8. In the clinic, I specialize in the treatment of gastrointestinal malignancies and sarcomas, including colorectal cancer. I hold national leadership positions and have published extensively on the management of these diseases. I have been certified in Radiation Oncology by the American Board of Radiology since May 2011.

9. My research has two major themes. The first focuses on understanding mechanisms of resistance to cancer immunotherapy and exploring combinatorial strategies, including combined radiotherapy and immunotherapy, to overcome resistance. The second is understanding how aging and obesity affect inflammation and immunity in the context of cancer development, progression, and therapy. My research is translational in nature spanning from basic mechanistic studies to murine models to large animal companion canine clinical trials and human clinical trials.

10. I am uniquely trained for this line of research with an honors thesis in Immunology at the University of California, Berkeley, a PhD in Cancer Biology and Inflammation, a Holman pathway research fellowship in cancer immunology, board certification as a radiation oncologist, and training through the UC Davis K12 program in translational cancer immunotherapy.

11. I graduated from the University of California at Berkeley with a B.A. in Molecular and Cell Biology, with Honors in Immunology in May 1997. I then completed my M.D. (2005) and Ph.D. (2003) at Wake Forest University School of Medicine.

12. I interned at the Harbor – UCLA Medical Center during 2005-2006. I completed a residency at the Wake Forest University Baptist Medical Center,

Department of Radiation Oncology from 2006-2010 and was Chief Resident from 2009-2010.

13. Since 2010, I have been affiliated with the UC Davis Comprehensive Cancer Center in the Department of Radiation Oncology and Laboratory of Cancer Immunology, as an Assistant Professor (2010-2015), Associate Professor (2015-2021), and Professor (2021-present). I have also held other positions at UC Davis simultaneously. From 2016-2021, I was a CCSG (Comprehensive Cancer Center Support Grant) Staff Investigator in Immunotherapy. From 2021 to present, I have been the Director of the Cancer Immunology and Energetics Program. From 2024 to present, I have been the Director of Radiation Biology.

14. My work has been recognized by a number of honors, awards, and appointments, including: NIH Association for Clinical and Translational Science – Outstanding Abstract Award (2013); NCI NRG Oncology Committee on Immunotherapy and Immunomodulation (2014-2019 and as chair from 2019-2022); NCI PD-L1 Development Project Team Member (2015-present); CTEP Clinical Trial Design and Immuno-oncology Agent Working Group (2016-present); and Oettinger Memorial Award for Outstanding Cancer Research (2022) ; NCI – Gastrointestinal Malignancy Working Group (2017-present), and NCI – NRG Oncology Developmental Therapeutics Committee (2018-present).

15. I have led or co-led numerous clinical trials. As an example, these include: a Phase I/II trial of Intralesional IL-2 and Pembrolizumab in patients with primary or acquired resistance to PD-1/PD-L1 checkpoint inhibitors (2018-2025); a Pilot Study of MPDL3280A plus Stereotactic Ablative Radiotherapy (SAR) in Non-Small Cell Lung Cancer (2015-2023); a Phase 2 Study of MEDI4736 (durvalumab) and Tremelimumab Alone or in Combination with High or Low-Dose Radiation in Metastatic Colorectal and NSCLC (2017-2019); a Phase II Trial of TG4010 plus Nivolumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) who have Progressed after One Line of Systemic Therapy (2016-2019), and a randomized Phase III trial of SABR +/- atezolizumab for early stage medically inoperable NSCLC (2020-Present).

16. I regularly teach courses including Cancer Immunology – (IMM 203); Cancer Nutrition – (Nutrition 116B); Radiation Oncology; Radiation Biology; and Interdisciplinary Study of Gastrointestinal Cancer. I regularly mentor undergraduate students, graduate students, medical students, and residents.

17. I have published over 100 articles in peer-reviewed journals, in addition to numerous abstracts, all of which are set forth in my curriculum vitae. Of particular relevance are a series of abstracts and articles related to the above-noted Phase 2 Study of MEDI4736 (durvalumab) and Tremelimumab Alone or in

Combination with High or Low-Dose Radiation in Metastatic Colorectal and NSCLC:

- **A Monjaze**, A Giobbie-Hurder, A Lako, AA Tesfaye, A Stroiney, RD Gentzler, S Jabbour, OB Alese, OE Rahma, JM Cleary, E Sharon, D Raben, HJ Mamon, H Streicher, HX Chen, M Ahmed, E Gjini, S Rodig, FS Hodi, JD Schoenfeld, “Analysis of colorectal cancer patients treated on ETCTN 10021: A multicenter randomized trial of combined PD-L1 and CTLA-4 inhibition with targeted low-dose or hypofractionated radiotherapy,” *Journal of Clinical Oncology* 37 (8), 49-49 (March 2019).
- **A Monjaze**, A Giobbie-Hurder, A Lako, M Awad, R Gentzler, C Lee, J Hubbard, J Abbruzzese, S Jabbour, N Uboha, K Stephans, J Johnson, H Park, L Villaruz, K Kao, E Sharon, D Raben, R Mak, H Streicher, H Chen, M Ahmed, S Rodig, FS Hodi, J Schoenfeld, “A randomized multi-center phase 2 study of combined PD-L1/CTLA-4 inhibition with or without radiation in non-small cell lung cancer patients who progressed on PD-(L) 1 directed therapy: ETCTN 10021,” *JITC* (7) (Nov. 6, 2019).
- **Monjaze AM**, Giobbie-Hurder A, Lako A, Thrash EM, Brennick RC, Kao KZ, Manuszak C, Gentzler RD, Tesfaye A, Jabbour SK, Alese OB, Rahma OE, Cleary JM, Sharon E, Mamon HJ, Cho M, Streicher H, Chen HX, Ahmed MM, Mariño-Enríquez A, Kim-Schulze S, Gnjjatic S, Maverakis E, Marusina AI,

Merleev AA, Severgnini M, Pfaff KL, Lindsay J, Weirather JL, Ranasinghe S, Spektor A, Rodig SJ, Hodi FS, Schoenfeld JD, “A Multicenter Randomized Phase 2 Trial of Combined PD-L1 and CTLA-4 Inhibition with Targeted Low-Dose or Hypofractionated Radiation for Patients with Metastatic Colorectal Cancer,” Clin Cancer Res. 27(9):2470-2480 (May 1, 2021).

- Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, Kao KZ; Lako A, Tsuji J, Liu Y, Brennick RC, Gentzler R, Lee C, Hubbard J, Abbruzzese JL, Jabbour SK, Uboha N, Stephans K, Johnson JM, Park H, Villaruz LC, Sharon E, Streicher H, Ahmed M, Lyon H, Cibuskis C, Lennon N, Jhaveri A, Yang L, Altreuter J, Gunasti L, Weirather JL, Mak RH, Awad MM, Rodig SJ, Chen HX, Wu CJ, **Monjazebe AM***, Hodi FS., “Durvalumab, tremelimumab alone or in combination with low-dose or hypofractionated targeted radiotherapy in metastatic non-small cell lung cancer refractory to prior PD-1 therapy: a multicentre, open-label, randomized, phase 2 trial,” Lancet Oncology, 23(2):279-291 (Jan 13, 2022).

18. My curriculum vitae is provided as EX1004.

IV. MATERIALS REVIEWED AND CONSIDERED

19. 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.

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

V. UNDERSTANDING OF THE APPLICABLE LEGAL STANDARDS

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

A. Burden of Proof

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

23. I understand that, in this proceeding, Petitioner has the burden of proving that the challenged claims of the '529 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”)

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

25. 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

26. I understand that, in IPR proceedings, claim terms in a patent are given their ordinary and customary meaning as understood by a POSA in the

context of the entire patent and the prosecution history pertaining to the patent. If the specification provides a special definition for a claim term that differs from the meaning the term would otherwise possess, the specification's special definition controls. I have applied these standards in preparing the opinions in this declaration.

D. Prior Art

27. 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.

28. I understand that the prior art available in an IPR includes printed publications published before the effective filing date of the claimed invention. I understand that a reference qualifies as a "printed publication" if it was publicly accessible as of the effective filing date, meaning that the reference was disseminated or otherwise made available such that a POSA, exercising reasonable diligence, would have been able to access it. For publication via the Internet, factors that may be relevant to public accessibility include whether the website is searchable or indexed and whether the reference was published on a website well known to POSAs. I understand that it is not necessary to show that a reference was actually retrieved or read.

E. Validity of a Patent

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

1. Anticipation

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

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

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

2. Obviousness

33. 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.

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

- the scope and content of the prior art;
- the differences between the prior art and the claims at issue;
- the knowledge of a person of ordinary skill in the pertinent art; and
- if present, objective factors indicative of non-obviousness, sometimes referred to as “secondary considerations.” These include evidence: that the alleged invention found commercial success for reasons causally related to the alleged invention; that the technical direction followed by those skilled in the art taught away from the approach of

the alleged invention; of long-felt but unsatisfied need for the alleged invention; that the alleged invention achieves results that are unexpected to those skilled in the art; that the alleged invention rapidly replaced prior-art devices in the industry; competitors copied the alleged invention; that those skilled in the art unsuccessfully attempted to make the invention; that the industry acquiesced to the patent's validity by taking licenses or not infringing; of skepticism, disbelief in or incredulity on the part of those skilled in the art that the patentee's approach worked; and of recognition of alleged invention by technically competent peers. To my knowledge, the Patent Owner has not asserted any such secondary considerations with respect to the '529 patent.

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

36. 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.

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

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

38. The ’529 patent involves technology in the field of cancer immunology. I have been asked to provide my opinions as to the state of the art in this field as of early 2016—that is, before the June 3, 2016 filing date of the provisional application referenced on the face of the ’529 patent. 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 ’529 patent or its description, the manner in which a POSA would have understood the prior art, or what a POSA would have been led to do based on the prior art, I am referencing the early 2016 timeframe, unless I state differently.

39. In my opinion, a person of ordinary skill in the art in early 2016 (“POSA”) would have a Ph.D. degree in immunology or a related field (for example, biochemistry), or alternatively a M.D. with a particular focus on the field of cancer immunotherapy, and at least two years of experience in the field of cancer immunotherapy, including experience with colorectal cancer treatments. The levels of education, experience, and knowledge described above can trade off against one another. A POSA would also have either been skilled in pharmacokinetics or able to communicate as part of a team with pharmacokinetics experts if necessary. A POSA would also have been capable of understanding and applying the teachings of the ’529 patent and the prior-art references discussed in this declaration—including understanding literature regarding clinical trials for colorectal cancer and cancer immunotherapy.

40. By June 2016, I had completed my M.D. and Ph.D. degrees, had completed my residency and fellowship, and had about six years of post-residency experience in oncology, including immunotherapy for the treatment of colorectal cancer, including my residency and my position in the Department of Radiation Oncology and the Laboratory of Cancer Immunology at UC Davis Comprehensive Cancer center. Thus, I had at least the level of education and experience of a POSA as of 2016. I have also supervised and collaborated with many people who fit the characteristics of the POSA, and I am familiar with their level of skill.

When developing the opinions set forth in this declaration, I assumed the perspective of a POSA, as set forth above.

VII. BACKGROUND OF THE '529 PATENT

A. The '529 Patent Claims

41. The '529 Patent consists of one independent claim (claim 1) and seventeen dependent claims (claims 2-18). The complete text of claims 1-18 is included in the Claim Listing at the end of this declaration (starting on page 120).

1. Independent Claim 1

42. Independent claim 1 is directed to:

A method of treating a subject afflicted with a tumor derived from a colorectal cancer, comprising administering to the subject:

(i) an anti-PD-1 antibody, and

(ii) an anti-CTLA-4 antibody;

wherein the tumor is a colon cancer or a rectal cancer; and

wherein the tumor exhibits a high degree of microsatellite instability (MSI-H).

43. As evident from the claim language, claim 1 does not include any particular safety and/or efficacy requirement.

44. While the '529 Patent indicates that “[t]here remains a need for therapies with an acceptable safety profile and high efficacy that enhance antitumor immune responses compared to monotherapy and other immunotherapy

combinations” (EX1001 at 2:16-19), no such language appears in claim 1 itself. I understand that it is improper to import limitations from the patent specification into a patent claim if the claim itself does not recite such requirements.

2. Dependent Claims 2-18

45. Dependent claims 2-18 refer back (whether directly or indirectly—that is, via other dependent claims) to independent claim 1 and specify additional requirements for practicing the methods specified by those dependent claims. For example, as discussed immediately below, dependent claim 2 refers to the “method of claim 1” while specifying that the tumor exhibit one or more characteristics beyond the baseline requirements of claim 1. Dependent claim 3 in turn refers to the “method of claim 2” and specifies additional requirements that further limit the scope of what claim 3 covers.

a. Dependent Claims 2-3: Characteristics of the Tumor

46. Dependent claim 2 depends from independent claim 1 and requires that the tumor exhibit “one or more characteristics selected from the group consisting of:

- (a) the tumor comprises a germline alteration in at least two DNA mismatch repair genes (MMR) genes;
- (b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
- (c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and

(d) any combination thereof.”

I understand that as a matter of patent law, claim 2 is invalid in view of a method that anticipates or renders obvious the steps of claim 1 (as noted in the preceding paragraph) and involves treating a tumor that satisfies any one of the characteristics recited in claim 2. For example, claim 2 could be anticipated or rendered obvious by performing the method of claim 1 to treat a colon cancer or rectal cancer tumor in which “at least one protein encoded by DNA [mismatch repair] genes is not detected in the tumor” (i.e., consistent with the characteristic recited in scenario (c) above)—regardless whether the tumor also comprises a germline alteration in at least two DNA mismatch repair genes (MMR) genes (per scenario (a)) and/or a germline alteration in at least 30% of five or more MMR genes (per scenario (b)).

47. Dependent claim 3 depends from dependent claim 2 and further specifies that “the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.”

b. Dependent Claim 4: Survival of At Least About One Month

48. Claim 4 depends from claim 1 and specifies that “the subject exhibits a progression-free survival of at least about one month after the administration” or “the subject exhibits an overall survival of at least about one month after the administration.” Overall survival refers to the length of time “patients diagnosed

with the disease are still alive.” EX1023 (defining “overall survival”). Given that any patient exhibiting a “progression-free survival of at least about one month” would necessarily still be alive at the time (i.e., one month after treatment), claim 4 merely recites that a patient receiving the treatment specified in claim 1 remain alive approximately one month after treatment.

c. Dependent Claims 5-18: Required Dosages and/or Particular Antibodies

49. Dependent claims 5-18 impose additional requirements on the claimed method of treatment by: (a) specifying the identity of the anti-PD-1 antibody and/or the anti-CTLA-4 antibody, (b) specifying certain dosage requirements for the anti-PD-1 antibody and/or the anti-CTLA-4 antibody during the combination therapy; and/or (c) requiring that the combination therapy be followed by an anti-PD-1 antibody monotherapy. In the drug therapy context, “monotherapy” refers to administration of a single drug. See EX1015 (“In drug therapy, monotherapy refers to the use of a single drug to treat a disease or condition.”); EX1036 (defining monotherapy as “the use of a single drug to treat a particular disorder or disease”).

50. Claim 5 requires that the anti-PD-1 antibody is nivolumab or pembrolizumab. Claim 7 specifies that the anti-CTLA-4 antibody is ipilimumab or tremelimumab.

51. Claims 6, 8-9, and 11 specify dosing of the anti-CTLA-4 antibody, the anti-PD-1 antibody, or both.

52. Claims 10 and 12 specify that “the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by anti-PD-1 antibody monotherapy.” Claims 13-16 recite dosing of the anti-PD-1 antibody monotherapy. Claims 17-18 specify that the anti-PD-1 antibody is nivolumab and the anti-CTLA-4 antibody is ipilimumab, respectively.

B. Technical Background

1. Immune Checkpoint Inhibitors

53. “Anti-PD-1” antibodies and “anti-CTLA-4” antibodies are two types of therapeutic antibodies known in the art as “immune checkpoint inhibitors” because they target proteins known as immune checkpoints. Immune checkpoints normally down-regulate the immune system upon binding with their ligand proteins. Immune checkpoint proteins are often present on immune cells such as T-cells—sending an “off” signal to the T-cells and preventing them from attacking healthy cells indiscriminately. Examples of immune checkpoints include the programmed death 1 (“PD-1”) protein, the programmed death-ligand 1 (“PD-L1”) protein, and the cytotoxic T-lymphocyte–associated antigen 4 (“CTLA-4”) protein. PD-1 is generally found on immune cells. PD-L1 is a ligand that binds PD-1 and is found on immune cells and other cells, including on tumor cells.

54. POSAs have long recognized that certain cancers express immune checkpoint proteins or their ligands—thereby suppressing the immune system and thwarting a robust anti-tumor immune response. Long before the earliest possible effective filing date of June 3, 2016, POSAs were therefore investigating the use of “checkpoint inhibitors” such as anti-PD-1 antibodies and anti-CTLA-4 antibodies to treat various types of cancer. Anti-PD-1 antibodies target the PD-1 checkpoint protein, while anti-CTLA-4 antibodies target the CTLA-4 checkpoint protein.

55. Multiple anti-PD-1 antibodies had received FDA approval years before the ’529 Patent’s earliest possible effective filing date of June 3, 2016.

56. For example, the anti-PD-1 antibody nivolumab was first approved in 2014 for the treatment of melanoma and commercialized by Bristol-Myers Squibb under the Opdivo® brand name. EX1020 at 180 (“On December 22, 2014, the FDA approved nivolumab (Opdivo; Bristol-Myers Squibb) for the treatment of patients with unresectable or metastatic melanoma....”). As the ’529 Patent acknowledges, nivolumab was the subject of earlier patents such as U.S. Patent No. 8,008,449 (EX1044). *See* EX1001 at 18:63-19:3.

57. Pembrolizumab was likewise first approved in 2014 for the treatment of melanoma and commercialized by Merck under the KEYTRUDA® brand name. As the ’529 Patent acknowledges, pembrolizumab was the subject of earlier patents such as U.S. Patent No. 8,900,587 (EX1045). *See* EX1001 at 19:24-25.

58. In addition, the anti-CTLA-4 antibody ipilimumab was first approved in 2011 for the treatment of melanoma and commercialized by Bristol-Myers Squibb under the brand name Yervoy®. EX1021 at 6958. As the '529 Patent acknowledges, ipilimumab was the subject of earlier patents such as U.S. Patent No. 6,984,720 (EX1046). *See* EX1001 at 22:29-32.

59. POSAs also considered the possibility of treating cancer using an anti-PD-1 antibody such as nivolumab together with an anti-CTLA-4 antibody such as ipilimumab. Indeed, when disclosing nivolumab, U.S. Patent No. 8,008,449 (EX1044) taught that the invention included “the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer.” EX1044 at 1:35-38. Similarly, when disclosing pembrolizumab, U.S. Patent No. 8,900,587 (EX1045) taught that the invention included “an anti-PD-1 antibody...combined with anti-CTLA-4.” EX1045 at 9:52-55.

60. In a 2013 article published in the New England Journal of Medicine, Wolchok disclosed promising clinical study results using nivolumab together with ipilimumab to treat patients with advanced melanoma. EX1013. In particular, Wolchok disclosed that the concurrent therapy “had a manageable safety profile” and “provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients.” EX1013 at 122. Wolchok had initiated the clinical study

given promising preclinical data and evidence that “CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity.” EX1013 at 123; *see also* EX1013 at 130 (noting that “immunologic checkpoints are nonredundant” and Wolchok had accordingly “hypothesized that a combined blockade of CTLA-4 and PD-1 could produce greater antitumor activity than either single agent.”).

Similarly, in an article published online May 31, 2015 in the New England Journal of Medicine, Larkin reported results for a “randomized, double-blind, phase 3 study” in which “nivolumab alone or nivolumab plus ipilimumab was compared with ipilimumab alone in patients with metastatic melanoma.” EX1011 at 23.

Larkin showed that “the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone.” EX1011 at 31.

2. Microsatellite Instability

61. Microsatellite instability (MSI) refers to a clonal change in the number of repeated DNA nucleotide units in microsatellites, which are stretches of DNA sequence—either mononucleotides or units of two or more nucleotides—repeated in the genome. EX1039 at 3380. It arises in tumors in which the normal DNA mismatch repair (MMR) system is not functioning properly because one or more mismatch repair genes are deactivated. EX1039 at 3380. The MMR system normally “targets base-base mismatches and insertion-deletion mismatches that

arise as a result of DNA replication errors.” EX1006 at 13. Microsatellites in particular are prone to such errors given their repetitive pattern. EX1006 at 13. Accordingly, “[a] hallmark of MMR-deficient cells is instability (replication errors) at microsatellite regions.” EX1006 at 13.

62. Colorectal cancer exhibiting a high degree of microsatellite instability (i.e., “MSI-H”) had been recognized as a distinct form of colorectal cancer well before the ’529 Patent’s earliest possible effective filing date of June 3, 2016. For example, a 2001 article noted that “[t]he presence of MSI defines a subset of colorectal carcinomas with special molecular etiology and characteristic clinical, pathologic features, inclusive of increased survival.” EX1028 at 2417. A subsequent 2013 article noted that “approximately 15% of CRCs [i.e., colorectal cancers] display MSI due to germline mutations, epigenetic silencing of MMR gene or a combination of these factors.” EX1006 (Zhang) at 12.

63. The ’529 Patent’s “Background of the Disclosure” section notes that certain colorectal cancers were “associated with a high degree of microsatellite instability (MSI-H), which results from impaired DNA mismatch repair” and that “[i]n particular, patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC) (~5% of patients) are less likely to benefit from conventional chemotherapy than patients with proficient MMR (pMMR) mCRC.” EX1001 at 2:2-9. This was well known

prior to the provisional application's June 3, 2016 filing date, as reflected in articles such as those discussed above.

64. The '529 Patent's "Background of the Disclosure" section also notes that "dMMR-MSI-H CRC is associated with a high mutational burden and is particularly susceptible to immune checkpoint inhibitor blockade." EX1001 at 2:10-12. This was also well known prior to the provisional application's June 3, 2016 filing date as reflected in the prior art discussed herein.

VIII. PRIOR ART TO THE '529 PATENT

65. As explained below, all of the references discussed herein were publicly available more than one year before the '529 Patent's earliest possible effective filing date of June 3, 2016 (which I understand is the date of the provisional application to which the '529 Patent claims priority). Accordingly, I understand that all of the references constitute prior art to the '529 Patent and may be considered when assessing whether claims 1-18 are anticipated and/or would have been obvious in view of the prior art.

A. NCT-188 (EX1005)

66. NCT02060188 (hereinafter "NCT-188") is Version 1 of a clinical trial protocol, with the Brief Title "A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)."

EX1005 at 4. The “Last Update Posted” date for Version 1 on ClinicalTrials.gov was February 11, 2014. EX1005 at 4.

67. POSAs understood that the purpose of ClinicalTrials.gov is to provide the public access to clinical trial information, like NCT-188, as widely and promptly as possible.

68. NCT-188 (Version 1) bears a “Last Update Posted” date of February 11, 2014. The “Last Update Posted” date is “[t]he most recent date on which changes to a study record were made available on ClinicalTrials.gov.” EX1018 at 10. By early 2016, POSAs were aware that clinical trial protocols like NCT-188 were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. POSAs routinely use ClinicalTrials.gov as a source of clinical trial information and in particular as a means to readily search for trials of interest. Clinicaltrials.gov had search functionality that facilitated such queries. For example, a POSA could have readily located NCT-188 on ClinicalTrials.gov by searching for key terms such as colon cancer or colorectal cancer, MSI-H, nivolumab, or ipilimumab. Specifically, a POSA interested in learning about new clinical trials directed to colon or colorectal cancer could readily locate NCT-188 by searching those terms on ClinicalTrials.gov. Accordingly, the “Last Update Posted” date for NCT-188 demonstrates that it was publicly available as of February 11, 2014.

B. Zhang (EX1006)

69. Zhang is an article entitled “Era of Universal Testing of Microsatellite Instability in Colorectal Cancer.” It was published on February 15, 2013, in the World Journal of Gastrointestinal Oncology—a journal that was readily accessible to a POSA more than one year prior to the ’529 Patent’s earliest possible effective filing date of June 3, 2016 (i.e., the date of the provisional application to which the ’529 Patent claims priority). Accordingly, Zhang would have been accessible to POSAs by the effective filing date.

C. NCT-109 (EX1007)

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

71. As discussed above in Section VIII.A, ClinicalTrials.gov publicizes clinical trial protocols and NCT-109’s “Last Update Posted” date demonstrates that it was publicly available as of October 23, 2013. POSAs knew that clinical trial protocols like NCT-109 were posted to ClinicalTrials.gov and would have been familiar with searching for and accessing such information. As discussed, ClinicalTrials.gov was a well-known, readily-searchable source of clinical trial information as of early 2016. For example, a POSA would have readily located

NCT-109 by searching for key terms like nivolumab, anti-PD-1, immunotherapy, or solid tumor. Specifically, a POSA interested in dosing of nivolumab would have readily located NCT-109 on ClinicalTrials.gov by searching for nivolumab. Accordingly, the “Last Update Posted” date for NCT-109 demonstrates that it was publicly available as of October 23, 2013.

D. Le (EX1008)

72. Le is an article entitled “PD-1 Blockade in Tumors with Mismatch-Repair Deficiency” (EX1008) and published in the New England Journal of Medicine (NEJM). The NEJM was well-known to POSAs as of early 2016. Le was published online at NEJM.org on “May 30, 2015.” EX1008 at 2509. Further, the Internet Archive (also known as the “Wayback Machine”) archived Le on June 2, 2015. EX1019 at 7. Le also has an associated appendix (EX1032) and protocol (EX1040), which POSAs would have considered together with Le itself.

73. At the time of Le’s May 30, 2015 online publication, POSAs were aware that many journals published online and kept abreast of developments of interest by reading articles posted on journal websites and by receiving regular email notifications from such journals immediately upon the publication of a new issue which includes the table of contents listing the newly published articles. The New England Journal of Medicine is (and was, in early 2016) a leading medical journal, and POSAs would have routinely consulted that journal’s website to stay

abreast concerning developments in the treatment of colorectal cancer.

Additionally, the website of the New England Journal of Medicine was searchable—*see* EX1019 at 7 (showing search bar for search by “Keyword, Title, Author, or Citation”)—and external search engine website searches would also return NEJM articles. Accordingly, as of the date of its online posting (May 30, 2015), Le would have been accessible to POSAs. This is confirmed by Kroemer (EX1047)—a July 2015 article published in an unrelated journal by a group of researchers that did not overlap at all with the list of authors in Le. Kroemer was submitted on June 1, 2015 (i.e., the first day after Le was published online) and cites Le for the proposition that “patients with mismatch repair-deficient CRC lesions obtain clinical benefits from the administration of a PD-1 targeting mAb” (EX1047). As the citation in Kroemer illustrates, it was routine for colorectal cancer researchers to access NEJM articles immediately after they became publicly accessible, and Le specifically was accessed within a day of its publication.

E. Postow (EX1031)

74. Postow is an article entitled “Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma” (EX1031) and published in the New England Journal of Medicine. As discussed above in Section VIII.D, the New England Journal of Medicine was well-known to POSAs as of early 2016. Postow was published online at NEJM.org on April 20, 2015. EX1031 at 1.

75. At the time of Postow’s April 20, 2015 online publication, POSAs were aware that many journals published online and kept abreast of developments of interest by reading articles posted on journal websites. The New England Journal of Medicine is (and was, in early 2016) a leading medical journal, and POSAs would have routinely consulted that journal’s website to stay abreast concerning developments in the treatment of colorectal cancer. Additionally, the website of the New England Journal of Medicine was searchable—see EX1019 at 7 (showing search bar for search by “Keyword, Title, Author, or Citation”)—and external search engine website searches would also return NEJM articles. Accordingly, as of the date of its online posting (April 20, 2015), Postow would have been accessible to POSAs. This is confirmed by Larkin (EX1011)—a May 31, 2015, article published online at NEJM.org. EX1011 at 34 (footnote 13). Larkin cites Postow to report “[t]he results of a phase 2 study that compared combined nivolumab and ipilimumab with ipilimumab alone in patients with *BRAF* wild-type melanoma.” EX1011 at 24. As the citation in Larkin illustrates, it was routine for researchers to access NEJM articles immediately after they became publicly accessible.

F. Hammers (EX1009)

76. Hammers is an abstract for a poster presentation at the Annual Meeting of the American Society of Clinical Oncology (ASCO), which occurred

May 29-June 2, 2015, entitled “Expanded Cohort Results from CheckMate 016: A Phase I Study of Nivolumab in Combination with Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC)” and published on May 20, 2015 in the Journal of Clinical Oncology. EX1009 at page 251s. The Journal of Clinical Oncology is a medical journal that was established more than a year before the ’529 Patent’s earliest possible effective filing date of June 3, 2016 (i.e., the date of the provisional application to which the ’529 Patent claims priority) and it was well-known in early 2016. Accordingly, Hammers would have been accessible to POSAs by the effective filing date. The disclosure in Hammers would also have been accessible to POSAs at the ASCO Annual Meeting, which occurred May 29-June 2, 2015, as shown at EX1009 at Title Page. ASCO is a leading organization for oncologists. By being presented at the ASCO Annual Meeting, the disclosure in Hammers would have been presented directly to oncologists (including numerous POSAs) specializing in gastrointestinal cancers.

G. Xiao (EX1010)

77. Xiao is an article entitled “The Microsatellite Instable Subset of Colorectal Cancer is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy” and published on January 15, 2015 in Cancer Discovery. Cancer Discovery is a medical journal that was established more than a year before the ’529 Patent’s earliest possible effective filing date of June 3, 2016 (i.e., the date of

the provisional application to which the '529 Patent claims priority) and it was well-known in early 2016. Accordingly, Xiao would have been accessible to POSAs by the effective filing date.

IX. DETAILED ANALYSIS OF THE CHALLENGED CLAIMS

78. My analysis below is divided into two parts. The first part concerns grounds 1A through 1C and 2A through 2C related to NCT-188—that is, a BMS clinical study protocol posted on February 11, 2014. The second part concerns grounds 3A through 3C related to Le, Xiao, and Hammers.

A. Grounds Related to NCT-188 (Grounds 1A-1C and 2A-2C)

1. GROUND 1A: NCT-188 Anticipates Claims 1 and 4-14

79. NCT-188 anticipates independent claim 1 and dependent claims 4-14 because NCT-188 discloses all elements of these claims—including the same active pharmaceutical ingredients (i.e., antibodies), the same MSI-H colorectal cancer tumors, and the same dosages.

80. NCT-188's disclosures consistently track, and are in all relevant respects identical to, the disclosures of the '529 Patent. While the '529 Patent discloses results of the treatment protocol and NCT-188 does not, there are multiple reasons why this did not impact my analysis.

81. First, independent claim 1 and dependent claims 5-14 do not require any particular result. Claim 1 is directed to “treating a subject,” and the '529 Patent defines “[t]reatment” as “refer[ring] to any type of intervention or process

performed on, or the administration of an active agent to, the subject with the *objective* of” reversing or alleviating a disease or its symptoms. EX1001 at 11:6-12. The specification consistently ties forms of “treat” to administration (rather than any particular result) while distinguishing “response” to treatment from treatment itself. *See, e.g.*, EX1001 at 2:38 (“the administering treats the colorectal cancer”); 4:67 (same); 6:21-27 (“the subject exhibits a complete response or partial response to treatment...”). In other words, a subject is “treated” whether or not the treatment is successful. *See* EX1001 at 11:6-12 (“*objective of* reversing, alleviating,” etc.). The ’529 Patent’s usage is consistent with the ordinary meaning of “treating” to POSAs, and POSAs would have understood that “treating a subject” does not require any particular result of that treatment.

82. Second, I have been informed that in the context of a claimed treatment method, an earlier disclosure that proposes the administration of the treatment method (without showing the results of doing so on patients) can anticipate the claimed method. Thus, I understand the ’529 Patent’s disclosure of results ostensibly yielded by a protocol reflecting the claimed treatment method do not impact whether the treatment method as claimed is anticipated.

a. NCT-188 (EX1005)

83. The Official Title of NCT-188 (Version 1) is “A Phase 2 Clinical Trial of Nivolumab and *Nivolumab Plus Ipilimumab* in Recurrent and Metastatic

Microsatellite High (MSI-H) Colon Cancer.” EX1005 at 4. NCT-188 discloses treating patients with MSI-H colon cancer with nivolumab and ipilimumab, followed by nivolumab monotherapy, and states that “[t]he purpose of this study is to examine if *Nivolumab* alone or *in combination with Ipilimumab* will demonstrate a meaningful objective response rate in patients with recurrent and metastatic *colon cancer* who also have *a specific biomarker in their tumors.*” EX1005 at 4.

84. NCT-188 describes identifying tumors by MSI status, with the study designed to identify the response rate “in all MSI-High subjects.” EX1005 at 4-5.

85. NCT-188 discloses four different arms involving the co-administration of nivolumab and ipilimumab. EX1005 at 5. In each case, the initial phase of treatment involved co-administration every three weeks for four doses. EX1005 at 5. During this phase, the arms featured the following dosages:

Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)
-1	0.3	1
1	1	1
2a	1	3
2b	3	1

EX1005 at 5.

86. NCT-188 further discloses that each of these co-administration study arms (*i.e.*, involving treatment that administered both nivolumab and ipilimumab) included a subsequent phase in which patients received an anti-PD-1 monotherapy,

i.e., administering nivolumab alone. EX1005 at 5 (“...followed by Nivolumab 3mg/Kg IV every 2 weeks until disease progression”). The table below summarizes the NCT-188 disclosure’s teachings as a whole concerning the co-administration study arms:

	Initial Co-Administration Phase (once every three weeks for four doses)		Subsequent Monotherapy Phase (once every two weeks until disease progression)
Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)	Nivolumab (mg/kg)
-1	0.3	1	3
1	1	1	3
2a	3	3	3
2b	3	1	3

EX1005 at 5. I note that NCT-188 also discloses a nivolumab monotherapy arm (*i.e.*, treating patients with nivolumab alone, without any initial co-administration), which is not included in the above table. This arm is immaterial to the anticipation analysis I provide herein, which focuses on NCT-188’s disclosures related to the co-administration of nivolumab and ipilimumab.

b. NCT-188 is Enabling

87. I have been informed and understand that anticipation does not require actual performance of suggestions in a disclosure, but instead only requires that those suggestions be enabling to one of skill in the art. NCT-188 provides such an

enabling disclosure because POSAs could readily practice the disclosed treatment methods without undue experimentation. Anti-PD-1 antibodies such as nivolumab and anti-CTLA-4 antibodies such as ipilimumab were readily available to POSAs as of NCT-188's February 2014 posting date and continued to be available from that point through to the '529 Patent's earliest possible effective filing date of June 3, 2016 (i.e., the date of the provisional application to which the '529 Patent claims priority). Using such antibodies to treat colorectal cancer patients at the dosage levels and frequencies disclosed in NCT-188 (and later recited in the '529 Patent's dependent claims) would have been well within POSAs' capabilities. Moreover, while none of the challenged claims require testing a subject's colorectal cancer to confirm MSI-H status, such testing likewise could be performed commercially and was well within POSAs' capabilities.

88. I also note that the level of detail disclosed in NCT-188 is comparable to the treatment disclosed in the '529 Patent. For example, NCT-188's "Dose Level 2b" discloses the same inclusion criteria (i.e., patients with MSI-H colorectal cancer) and the same treatment parameters for such patients (i.e., "Nivolumab 3mg/Kg IV combined with Ipilimumab 1 mg/Kg IV every 3 weeks for 4 doses followed by Nivolumab 3mg/Kg IV every 2 weeks") later disclosed in the '529 Patent.

89. I have been informed that proof of efficacy is not required for prior art references to be enabling. Nevertheless, I note that other prior art references indicated to a POSA that the nivolumab/ipilimumab treatment disclosed in NCT-188 was efficacious. For example, Lipson (EX1037) reports that nivolumab achieved a “[d]urable complete response in [MSI-H] colorectal cancer.” EX1037 at 463-464. While Lipson refers to “BMS-936558” rather than nivolumab by name, the ’529 Patent acknowledges that BMS-936558 was an earlier designation for nivolumab. EX1001 at 1:52. In addition, Duraiswamy (EX1053) reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model. EX1053 at 3595. Specifically, Duraiswamy found that “[b]lockade of either PD-1 or CTLA-4 pathways enhanced effector T cell infiltration” into tumors, but that “simultaneous blockade of both pathways had synergistic effects in activation of tumor antigen specific CD8+ and CD4+ effector T cells.” EX1053 at 3599-3600. By increasing activation of effector T cells, the combination would have greater antitumor immune response. EX1053 at 3591 (“blocking of PD-1 and CTLA-4 can modulate Treg functions and enhance antitumor responses.”).

c. Claim-by-Claim Analysis

i. Independent Claim 1

90. NCT-188 anticipates claim 1 of the ’529 Patent because it discloses all claimed steps of the method recited in claim 1.

(1) [1.PRE] “A method of treating a subject afflicted with a tumor derived from a colorectal cancer...”

91. To the extent the preamble of claim 1 is limiting, NCT-188 satisfies it because NCT-188 discloses “[a] method of treating a subject afflicted with a tumor derived from a colorectal cancer.” NCT-188 is specifically directed to “[a] Phase 2 Clinical Trial...in...Colon Cancer” (EX1005 at 4) and POSAs would therefore understand that it is describing a method of treating patients with tumors derived from a particular type of colorectal cancer. NCT-188 further discloses that its patients must have “[h]istologically confirmed colorectal cancer” including “[m]easurable disease by CT or MRI” with ongoing “[t]umor imaging assessments” of the patients. EX1005 at 5.

92. Even if “treating” were interpreted to require efficacy (despite the plain language in the specification to the contrary, as I discussed above in paragraph 81), NCT-188 would satisfy such a requirement because NCT-188’s disclosures mirror those in the ’529 Patent (as I noted above in paragraphs 80 and 88). Where the claim steps are the same as in the prior art (as they are here), I understand that as a legal matter the efficacy of those claimed steps is considered to be inherent in carrying out the claimed steps, because the efficacy inevitably flows from the treatment. POSAs understood that performing the identical administration set forth in NCT-188 and the ’529 Patent would necessarily give the

same result—they are the same treatment. Put another way, claim 1 of the '529 Patent does not recite any steps above or beyond those disclosed in NCT-188 to achieve the supposedly required efficacy.

**(2) [1.A] “administering to the subject:
(i) an anti-PD-1 antibody, and
(ii) an anti-CTLA-4 antibody”**

93. NCT-188 satisfies limitation [1.A] because it discloses “administering to the subject: (i) an anti-PD-1 antibody, and (ii) an anti-CTLA-4 antibody.” In particular, it discloses administering an anti-PD-1 antibody in the form of nivolumab together with an anti-CTLA-4 antibody in the form of ipilimumab. EX1005 at 4 (“A Study of...Nivolumab Plus Ipilimumab”); 5 (dosing information including “Nivolumab 3 mg/[k]g IV combined with Ipilimumab 1 mg/[k]g IV every 3 weeks for 4 doses”).

94. A POSA would have understood that nivolumab is an anti-PD-1 antibody. *See* EX1020 at 180. This understanding is also corroborated in earlier patents such as U.S. Patent No. 8,008,449. EX1044. Before June 3, 2015, nivolumab had already been approved by the FDA for treating two different cancers: advanced melanoma and lung cancer. EX1020 at 180, 183. After June 3, 2015, but before June 3, 2016, the FDA approved nivolumab for five more indications: wild-type melanoma (with ipilimumab) (Oct. 1, 2015); advanced lung cancer (Oct. 9, 2015); metastatic renal cell carcinoma (Nov. 23, 2015);

unresectable or metastatic melanoma (with ipilimumab) (Jan. 23, 2016); and Hodgkin lymphoma (May 17, 2016).

95. A POSA would have understood that ipilimumab is an anti-CTLA-4 antibody. *See* EX1021 at 6958. This understanding is also corroborated in earlier patents such as U.S. Patent No. 6,984,720. EX1046. Before June 3, 2015, ipilimumab had already been approved by the FDA for treating melanoma. EX1021 at 6958. After June 3, 2015, but before June 3, 2016, the FDA approved nivolumab for three more indications: wild-type melanoma (with nivolumab) (Oct. 1, 2015); melanoma, after surgery (Oct. 28, 2015); and unresectable or metastatic melanoma (with nivolumab) (Jan. 23, 2016).

(3) [1.B] “the tumor is a colon cancer or a rectal cancer”

96. NCT-188 satisfies limitation [1.B] because it discloses a method of treating a cancer tumor in which “the tumor is a colon cancer or a rectal cancer.” EX1005 at 4 (“Phase 2 Clinical Trial ...in Recurrent and Metastatic Microsatellite High (MSI-H) *Colon Cancer*”); 5 (patients must have “[h]istologically confirmed colorectal cancer” and “[m]easurable disease by CT or MRI”).

97. POSAs would have understood that colorectal cancer encompasses colon cancer and rectal cancer. This is also consistent with the ordinary meaning of “colorectal” as “relating to or affecting the colon and rectum.” EX1022 Merriam-Webster Dictionary (definition of colorectal). Accordingly, POSAs

would have understood that NCT-188 is directed to treatment of colon cancer or rectal cancer tumors.

(4) [1.C] “the tumor exhibits a high degree of microsatellite instability (MSI-H)”

98. NCT-188 satisfies limitation [1.C] because it discloses a method of treating a tumor that “exhibits a high degree of microsatellite instability (MSI-H).” In particular, NCT-188 discloses that the cancer is “Microsatellite High (MSI-H) Colon Cancer.” EX1005 at 4. NCT-188 identifies the response rate “in all MSI-High subjects” as one of its primary outcome measures. EX1005 at 5. Accordingly, POSAs would have understood that NCT-188 is directed to treatment of tumors exhibiting a high degree of microsatellite instability.

99. Neither limitation [1.C] nor any other aspect of claim 1 requires testing the tumor to identify whether it exhibits MSI-H. However, even if limitation [1.C] were interpreted to require a testing step, NCT-188 discloses “[t]esting for MSI Status” as an inclusion criterion. EX1005 at 5. Accordingly, POSAs would have understood that NCT-188 is directed to methods of treatment in which colorectal cancer patients are first tested to see whether their tumors exhibit a high degree of microsatellite instability, and then treated with the disclosed method only if their tumors exhibit a high degree of microsatellite instability.

ii. Dependent Claim 4: Survival of At Least About One Month Following Treatment

100. NCT-188 also anticipates claim 4 of the '529 Patent.

101. Claim 4 depends from claim 1 and requires that, after administration, the subject either “exhibit[] a progression-free survival of at least about one month” or “exhibit[] an overall survival of at least about one month.”

102. Overall survival refers to the length of time “patients diagnosed with the disease are still alive.” EX1023 (defining “overall survival”). Given that any patient exhibiting a “progression-free survival of at least about one month” would necessarily still be alive one month after treatment, claim 4 reduces to the recitation that a patient receiving the treatment specified in claim 1 remain alive approximately one month after treatment.

103. POSAs would have understood that this additional recitation in claim 4 states an intended effect of the recited steps in claim 1. In particular, nothing in claim 4 specifies any additional steps to take above and beyond those already recited in claim 1. In other words, there is no difference in the treatment specific to claim 4 or to meeting these limitations of claim 4 that differentiate claim 4 from claim 1. A POSA would instead perform the same administration of treatment that is set out in claim 1 and then evaluate whether the patient survives at least one month—i.e., achieves the intended effect.

104. I have been informed that a statement of intended effect is generally non-limiting. As discussed above, the phrases “exhibit[] a progression-free survival of at least about one month” and “exhibit[] an overall survival of at least about one month” are such statements of intended effect. Aside from these statements of intended effect, claim 4 is identical to independent claim 1 and does not “require any additional required structure or condition.” Accordingly, in the context of this particular case, POSAs would have understood that the entire wherein clause in claim 4 is merely a “non-limiting statement...of intended effect.”

105. Indeed, aside from disclosing the co-administration of “3 mg/kg nivolumab+1 mg/kg ipilimumab” (which is identical to the treatment regime of “Dose Level 2b” as disclosed in NCT-188), the ’529 Patent does not disclose any other pertinent treatment parameters. Nor does the ’529 Patent otherwise disclose any other difference between the patients who fell above (versus below) “[t]he median time from the first dose to death or the last known alive date” of “8.7 months.” EX1001 at 36:62-63.

106. In any event, even if claim 4’s wherein clause did ostensibly limit the claim, it would not render the claim patentable over NCT-188. I have been informed that an applicant is not entitled to a patent for merely disclosing the results of carrying out a process that was previously disclosed, where those results are inherent in, that is, the natural result flowing from, performing the process.

NCT-188’s Dose Level 2b entails the same process as that disclosed in the ’529 Patent and is directed to the same purpose—namely, treating MSI-H colorectal cancer.

107. I also note that achieving one-month overall survival is generally a very achievable milestone for most colorectal cancer patients. When considering MSI-H colorectal patients as a group (and even those with stage IV metastatic cancer in particular), POSAs would expect most patients to survive at least one month from diagnosis with conventional therapy or even with no therapy. For example, before the earliest possible effective filing date of June 3, 2016, colorectal cancer patients receiving other therapies exhibited mean survival of 5.13 years (colon cancer) and 4.67 years (rectal cancer) from diagnosis. EX1034 at 605. Moreover, MSI-H colorectal carcinomas were known to be associated with “increased survival” as compared to MSI-stable carcinomas. EX1028 at 2417; *see also* EX1006 at 15 (“Studies have shown that MSI CRCs carry a better prognosis compared to those with MSS CRCs.”). I also note that the ’529 Patent is not limited to later-stage patients.

iii. Dependent Claims 5-14: Specific Antibody and/or Dosage Requirements

108. NCT-188 anticipates claims 5-14 of the ’529 Patent because it discloses the additional limitations recited in all of those dependent claims.

(1) Claim 5: Anti-PD-1 Antibody is Nivolumab or Pembrolizumab

109. NCT-188 satisfies the additional limitation of claim 5 because it discloses a method of treatment in which “the anti-PD-1 antibody is nivolumab or pembrolizumab”—specifically, treatment using nivolumab. EX1005 at 4 (“A Study of...*Nivolumab* Plus Ipilimumab...”), 5 (dosages with nivolumab).

(2) Claim 6: Anti-CTLA-4 Antibody Dosage

110. NCT-188 satisfies the additional limitations of claim 6 because it discloses a method of treatment in which “the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.”

111. In particular, NCT-188 discloses treatment methods involving administration of ipilimumab (which POSAs would understand to be an anti-CTLA-4 antibody) at doses of 1 mg/kg IV every 3 weeks and 3 mg/kg IV every 3 weeks. EX1005 at 5. Accordingly, POSAs would understand that NCT-188 discloses multiple dosages within the range of 0.1 mg/kg to 10.0 mg/kg with a frequency of every 3 weeks, as recited in claim 6.

(3) Claim 7: Anti-CTLA-4 Antibody is Ipilimumab or Tremelimumab

112. NCT-188 satisfies the additional limitation of claim 7 because it discloses a method of treatment in which “the anti-CTLA-4 antibody is ipilimumab or tremelimumab.”

113. In particular, NCT-188 satisfies this limitation by disclosing dosing with ipilimumab (an anti-CTLA-4 antibody). EX1005 at 4 (“A Study of ...Nivolumab Plus *Ipilimumab*”), 5 (describing dosing with ipilimumab).

(4) Claim 8: Anti-PD-1 Antibody Dosage

114. NCT-188 satisfies the additional limitations of claim 8 because it discloses a method of treatment in which “the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.” NCT-188 discloses treatment methods involving the use of nivolumab (which POSAs would understand to be an anti-PD-1 antibody) at doses of 0.3 mg/kg IV every 3 weeks, 1 mg/kg IV every 3 weeks, and 3 mg/kg IV every 3 weeks. EX1005 at 5. Accordingly, NCT-188 discloses multiple dosages within the range of 0.1 mg/kg to 10.0 mg/kg and a frequency of every 3 weeks, as recited in claim 8.

(5) Claim 9: Anti-PD-1 and Anti-CTLA-4 Dosages

115. NCT-188 satisfies the additional limitation of claim 9 because it discloses multiple treatment arms in which the dosages of anti-PD-1 and anti-CTLA-4 antibodies satisfies at least one of the four recited scenarios separated by an “or.” Any one of those disclosed arms therefore suffices to satisfy the limitation. I have been informed that a claim covering more than one alternative

structure or composition is anticipated if any one of them was disclosed in the prior art.

116. In particular, NCT-188 discloses three of the four alternatives recited in claim 9, as shown below.

Claim 9 option	anti-PD-1 antibody (mg/kg) (e.g., nivolumab)	anti-CTLA-4 antibody (mg/kg) (e.g., ipilimumab)	Arm designation in NCT-188
(i)	1	1	Dose Level 1
(ii)	1	3	Dose Level 2a
(iii)	3	1	Dose Level 2b
(iv)	3	3	

117. NCT-188’s disclosures of dose levels 1, 2a, and 2b therefore each separately anticipates claim 9.

(6) Claim 10: Subsequent Anti-PD-1 Monotherapy

118. Claim 10 depends from claim 9 and further requires “the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.”

119. NCT-188 satisfies the additional limitations of claim 10 because it satisfies claim 9 (as discussed above) and further discloses that each arm of the study (i.e., featuring the combination therapy of nivolumab and ipilimumab) was followed by an anti-PD-1 monotherapy—specifically, administering “Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression.” EX1005 at 5. NCT-188’s disclosures of dose levels 1, 2a, and 2b therefore each separately anticipates claim

10. A POSA would understand based on NCT-188 that the disclosure of the nivolumab monotherapy applied to each arm of the study.

(7) Claim 11: Anti-PD-1 and Anti-CTLA-4 Dosages and Duration.

120. Claim 11 depends from claim 1 and recites “wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once about every 3 weeks for a total of 12 weeks.”

121. NCT-188 satisfies this limitation because it discloses “Dose Level 2b: Nivolumab [an anti-PD-1 antibody] *3 mg/[k]g* IV combined with Ipilimumab [an anti-CTLA-4 antibody] *1 mg/[k]g* IV every *3 weeks for 4 doses...*” EX1005 at 5. Accordingly, the dosage is the same and the period of time every 3 weeks for 4 doses corresponds to a total of 12 weeks.

(8) Claim 12: Combination of Claims 10 and 11

122. Claim 12 depends from claim 11 and is otherwise identical to claim 10 in that it requires the “administration of the anti-PD-1 antibody and the anti-CTLA antibody” be “followed by an anti-PD-1 antibody monotherapy.” NCT-188 anticipates claim 12 for the same reasons I noted above in connection with claims 10 and 11. POSAs would understand that NCT-188’s disclosure of subsequent anti-PD-1 monotherapy—specifically, administering “Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression”—was applicable to all of NCT-188’s

arms, including Dose Level 2b (i.e., the dosage level that anticipates claim 11 as discussed immediately above).

**(9) Claim 13: Anti-PD-1 Monotherapy
Administered Once About Every Two Weeks**

123. Claim 13 depends from claim 12 and recites “the anti-PD-1 antibody monotherapy is administered once about every 2 weeks.”

124. NCT-188 satisfies this limitation by disclosing that the anti-PD-1 antibody monotherapy provided after the combination therapy phase is administered every 2 weeks. EX1005 at 5 (“followed by Nivolumab 3mg/Kg IV every 2 weeks until disease progression”).

**(10) Claim 14: Anti-PD-1 Monotherapy of 3 mg/kg
Administered Once About Every Two Weeks**

125. Claim 14 depends from claim 12 and recites “the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks.”

126. NCT-188 satisfies this limitation by disclosing that the anti-PD-1 antibody monotherapy is administered at a dose of 3 mg/kg once every 2 weeks. EX1005 at 5 (“followed by Nivolumab 3mg/Kg IV every 2 weeks until disease progression”).

**2. GROUND 1B: NCT-188 and Zhang Render Obvious
Claims 2-3**

127. Dependent Challenged Claims 2-3 recite characteristics of the colon or rectal cancer tumor treated pursuant to claim 1's immunotherapy method.

Those characteristics specify well-known details concerning MSI-H status, which is already expressly recited in claim 1. As discussed in Section VII.B.2 above, MSI-H tumors arise from losses of function in a patient's MMR (i.e., mismatch repair) system. EX1039 at 3380.

128. Claim 2 depends from claim 1 and recites several characteristics in the alternative, any one of which suffices to practice the claimed method. One of those characteristics is that "at least one protein encoded by DNA MMR genes is not detected in the tumor." EX1001 at 37:36-45. The absence of one or more MMR proteins is consistent with MSI-H status.

129. Claim 3 depends from claim 2 and specifies that the "DNA MMR genes" may be "any combination" of five genes—including MSH2, MLH1, MSH6, PMS2, and PMS1. EX1001 at 37:46-48. All five of the recited genes were well known to POSAs as related to MMR. *E.g.*, EX1006 at 13 (citing MSH2, MLH1, MSH6, PMS2, and PMS1); *see also* EX1024 at 200 ("The vast majority of hereditary non-polyposis colorectal cancer (HNPCC) patients will have microsatellite high (MSI-H) tumors. HNPCC is an autosomal-dominant condition that accounts for approximately 2-3% of all colorectal carcinomas. In most cases,

the genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1.”); *see also* EX1025 at 98 (similar—referring separately to “MMR proteins MLH1, MSH2, MSH6, and PMS2).”

130. As discussed further below, the characteristics specified in claims 2 and 3 are disclosed in prior art references such as Zhang (EX1006). While they are not expressly recited in the above-discussed NCT-188 disclosure concerning MSI-H colorectal cancer treatment more generally, there was nothing inventive about using NCT-188’s disclosures to treat MSI-H colorectal cancer having the particular characteristics recited in claims 2 and 3.

a. Zhang (EX1006)

131. Zhang is a 2013 article in the World Journal of Gastrointestinal Oncology that is entitled “Era of universal testing of microsatellite instability in colorectal cancer.” EX1006. Zhang explains that, as of 2013, “[i]ncreased emphasis has been placed on the importance of MSI testing for all newly diagnosed individuals with [colorectal cancers].” EX1006 at 12 (Abstract); *see also* EX1006 at 13 (“Increased emphasis has been placed on the importance of MSI testing for all newly diagnosed individuals with CRCs.”).

132. Zhang discloses that “MSI is detected indirectly by ***demonstrating absence of expression of MMR proteins*** by immunohistochemical staining (IHC),

or more directly by polymerase chain reaction (PCR)-based amplification of specific microsatellite repeats.” EX1006 at 14. Further, Zhang discloses that “[t]he principle of using IHC of MMR proteins to indirectly indicate the presence of MSI is that the absence of one or more of the MMR proteins can cause MSI.” EX1006 at 14. Zhang also emphasizes that both IHC and PCR-based approaches “show high sensitivity and specificity in detecting MSI.” EX1006 at 12 (Abstract).

b. Reason to Combine NCT-188 and Zhang

133. As discussed above in Section IX.A.1.a, NCT-188 discloses treating MSI-H colorectal cancer tumors and specifically discloses “[t]esting for MSI Status” as one of the “Inclusion Criteria.” EX1005 at 5. Given that criterion, POSAs implementing NCT-188 would have reason to test prospective patients to detect MSI-H status and therefore practice NCT-188 according to its Inclusion Criteria and to achieve NCT-188’s “primary outcome measure[]” of determining the “[o]bjective response rate (ORR) in all MSI-High subjects.” EX1005 at 5. Zhang discloses criteria to identify MSI-H status.

134. POSAs would have had reason to consider Zhang because it is expressly directed to colorectal cancer and was published in a journal about “Gastrointestinal Oncology.” In particular, Zhang teaches the desirability of “MSI testing for all newly diagnosed individuals with CRC” (i.e., colorectal cancer). EX1006 at 12. Accordingly, POSAs would have been motivated to use the MSI-H

criteria of Zhang to further define MSI-H status as disclosed in NCT-188 when “[t]esting for MSI Status” as NCT-188 discloses prior to treating patients for colorectal cancer.

135. POSAs also would have had reason to implement NCT-188 using Zhang’s methodology of “*demonstrating absence of expression of MMR proteins* by immunohistochemical staining (IHC)” (EX1006 at 14) because such staining was a well-known methodology that could be readily implemented without special equipment and/or the need for genetic testing. For example, Zhang explains that “[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system.” EX1006 at 14.

136. For the remainder of this declaration, I will use the term “NCT-188-Zhang” to refer to NCT-188 implemented using Zhang’s disclosed method of “*demonstrating absence of expression of MMR proteins*” to determine MSI-H status—including the use of commercially available antibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 as disclosed in Zhang.

c. Reasonable Expectation of Success

137. A POSA would have had a reasonable expectation of success in combining NCT-188 and Zhang given that Zhang’s immunohistochemical staining methodology for detecting MSI status was a well-known and reliable technique

that could be implemented using readily available equipment and reagents—including the commercially available antibodies noted in Zhang. Zhang itself discloses that “universal testing for MSI” using immunohistochemical staining was “cost effective, sensitive, specific and is getting widely accepted.” EX1006 at 17.

d. Claim-by-Claim Analysis of NCT-188-Zhang

i. Claim 2

138. Claim 2 depends from claim 1 and recites that the tumor meets one or more of three characteristics, one of which is that “at least one protein encoded by DNA MMR genes is not detected in the tumor.”

139. NCT-188-Zhang renders obvious claim 2 because the combination involves implementing NCT-188’s inclusion criteria of “testing for MSI status” based on Zhang’s disclosure of detecting MSI via “immunohistochemical staining (IHC).” EX1006 at 14.

140. In particular, Zhang’s disclosed IHC method involves testing the tumor to determine if it “indicate[s] the presence of MSI” via “*the absence of one or more of the MMR proteins.*” EX1006 at 14. POSAs would understand from Zhang that “one or more of the MMR proteins” means “at least one protein encoded by DNA MMR genes.” Indeed, Zhang describes the eukaryotic MMR system and notes the role of particular MMR genes. Id. at 13. Accordingly, POSAs would have understood that detection of MSI positive colon or rectal

cancer pursuant to NCT-188-Zhang entails the determination that “at least one protein encoded by DNA MMR genes is not detected in the tumor.”

ii. Claim 3

141. Claim 3 depends from claim 2 and recites that “the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.”

142. NCT-188-Zhang renders obvious claim 3 because Zhang teaches identifying MSI status using immunohistochemical staining “of MMR proteins to indirectly indicate the presence of MSI” through the “absence of one or more of the MMR proteins.” EX1006 at 14. Zhang explains that “[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system.” EX1006 at 14. As explained above in Section IX.A.2.b, the NCT-188-Zhang combination entails the use of the commercially available antibodies disclosed in Zhang—including those indicating the presence or absence of MLH1, PMS2, MSH2 and MSH6. Accordingly, NCT-188-Zhang involves the treatment of patients in which the “DNA MMR genes” of claim 2 include MLH1, PMS2, MSH2, and MSH6. That group of genes satisfies the additional requirement of claim 3 because it includes “*MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.*”

3. GROUND 1C: NCT-188 and NCT-109 Render Obvious Claims 15-18

143. Claims 15-18 depend directly or indirectly from dependent claim 12 and require that the “anti-PD-1 antibody monotherapy” required by claim be administered as a “flat dose,” meaning that all patients receive the same dose “without correction for body size or other (pharmacological) parameters.” EX1029 at 918; *see also* ’529 Patent, at 13:34-42 (explaining that a “flat dose” is “a dose that is administered to a patient without regard for the weight or body surface area (BSA) of the patient”). “Flat” dosing as referenced in the ’529 Patent is also commonly described as “flat-fixed” dosing or simply “fixed” dosing. See, e.g., EX1029 at 918 (“Flat-fixed dosing refers to dosing strategies without correction for body size or other (pharmacological) parameters.”); EX1055 at 119 (discussing “body weight-independent (fixed) dosing regimens” and contrasting with “body weight-based” approaches.” “Fixed” dosing was well-known and well-documented prior to the provisional application’s June 3, 2016 filing date. See, for example, the Wang (EX1030), Mathijssen (EX1029), Bai (EX1055) references discussed further below, which all disclose examples of “fixed” doses.

144. Such flat dosing was a well-known technique—including in the context of anti-PD-1 antibody cancer treatments, as disclosed in the NCT-109 reference discussed further below. Moreover, as discussed further below, such flat dosing was recommended in the medical literature as offering numerous

advantages over the alternative approach of dosing patients depending on their weight.

145. I note that the '529 Patent itself defines “fixed dose” differently—that is, when “two or more different antibodies... are present in the composition in particular (fixed) ratios with each other.” '529 Patent, at 13:8-33. However, this definition does not impact how a POSA would have understood the prior art discussed herein.

a. NCT-109 (EX1007)

146. The Official Title of NCT-109 (Version 1) is “A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors.” EX1007 at 4.

147. NCT-109 discloses administration of flat doses of nivolumab, with arms designated Parts B and C including dosages of 80 and 240 mg of nivolumab. EX1007 at 5. Nivolumab is identified as BMS-936558 in NCT-109, as is confirmed by the Official Title, which states “A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination

With Anti-PD-1 Monoclonal Antibody (*Nivolumab*, *BMS-936558*) in Advanced Solid Tumors.” EX1007 at 4.

b. Reason to Combine NCT-188 and NCT-109

148. As discussed above in Section IX.A.1.c.iii(6) (concerning dependent claim 10), POSAs would have understood that NCT-188 discloses anti-PD-1 antibody monotherapy at a weight-based dose of 3 mg/kg after conclusion of the combination therapy administering both anti-PD-L1 and anti-CTLA-4. *See* EX1005 at 5 (“...followed by Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression”).

149. POSAs would have recognized that flat dosing offers advantages over the weight-based dosing for the nivolumab monotherapy as disclosed in NCT-188. For example, a 2009 article by Wang, et al., about flat dosing in the context of monoclonal antibodies explains that flat dosing offered “numerous advantages over body size–based dosing” including greater convenience and lower costs:

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

EX1030 at 1023.

150. In view of these advantages, Wang concluded (and a POSA would have known) that “when there is no advantage of one dosing approach over another from a PK [i.e., pharmacokinetic] and PD [pharmacodynamic] perspective, *fixed dosing is the approach of choice*.” EX1030 at 1023. As discussed above in paragraph 143, “fixed” dosing is another term for “flat dose” (i.e., not based on patient weight). A POSA would have understood that Wang’s teaching was applicable to the nivolumab monotherapy phase of NCT-188 because weight-based dosing of nivolumab alone did not offer any advantage from a PK or PD-related perspective (particularly given nivolumab’s wide therapeutic window as discussed herein) and likewise did not offer any particular practical benefit. By contrast, in NCT-188’s initial phase of administering nivolumab together with ipilimumab, weight-based dosing offered certain practical benefits. As compared to nivolumab, ipilimumab was understood to have a less forgiving safety profile, such that a POSA may have had reason to prefer weight-base dosing for ipilimumab. *See, e.g.*, EX1066 at 930 (reviewing previous clinical trials: “Overall, nivolumab and pembrolizumab appear to be better tolerated than ipilimumab.”) And if ipilimumab was to be administered via weight-based dosing, convenience and safety offered a reason to administer nivolumab via weight-based dosing as well—consistent with NCT-188’s disclosure. Put differently, a POSA would have had

reason to practice NCT-188's nivolumab monotherapy phase via flat dosing even while practicing NCT-188's earlier co-therapy phase using weight-based dosing for both nivolumab and ipilimumab.

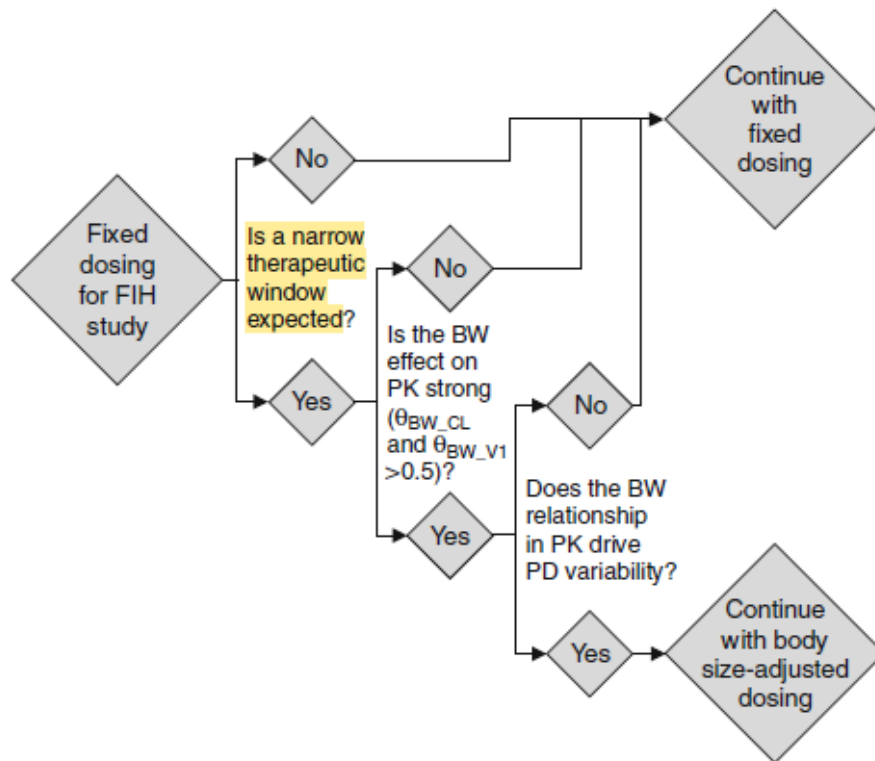
151. Other prior art confirms Wang's recommendations and further confirms that a POSA would have had reason to practice NCT-188's nivolumab monotherapy phase using a flat dose of nivolumab rather than a weight-based dose. For example, Mathijssen notes that flat-dosing provides advantages in the context of "anticancer drugs" including "positive economic implications"; "safety implications, because fewer errors will be made in calculation, preparing, and administering the proper individual dose"; better "patient adherence" and avoidance of "false feeling of being precise" from size-based dosing, and thus may be preferred to size-based dosing unless the therapeutic agent exhibits "a narrow therapeutic window and high interindividual variability in exposure." EX1029 at 918.

152. Bai likewise teaches that most monoclonal antibodies have "a relatively large therapeutic window" and "fixed dosing is recommended" as "the first option in first-in-human studies" given the "many practical advantages" that flat dosing provides. EX1055 at 119, 133. Moreover, it was known that nivolumab had a wide therapeutic window. EX1050 (Brahmer) at 3169, 3171. While Brahmer refers to "BMS-936558" and "MDX-1106" rather than nivolumab

by name, the '529 Patent acknowledges that BMS-936558 and MDX-1106 were earlier designations for nivolumab. EX1001 at 1:52-53.

153. I have been informed that the motivation to combine elements may be derived from any need or problem known in the field. As Wang, Mathijssen, and Bai demonstrate, POSAs would have recognized that flat dosing potentially offered multiple advantages over weight-based dosing when implementing NCT-188's anti-PD-1 monotherapy step.

154. Accordingly, POSAs would have had reason to practice NCT-188's nivolumab monotherapy step using a flat dose of nivolumab rather than the weight-based dose disclosed in NCT-188. Nivolumab is a monoclonal antibody (i.e., the subject of Wang's recommendation concerning fixed dosing) and likewise an anticancer drug (i.e., the subject of Mathijssen's recommendation concerning fixed dosing). Further, Bai emphasizes how fixed dosing is desirable for monoclonal antibody therapies except in cases where a narrow therapeutic window was expected. EX1055 at 133:



Further, nivolumab was a monoclonal antibody already known to have a *wide* therapeutic window. EX1050 (Brahmer) at 3169, 3171.

155. More specifically, POSAs would have had reason to select a flat dosage of 240 mg of nivolumab—consistent with one of the dosages expressly disclosed in NCT-109—given Wang’s disclosure that when bodyweight-based dosing has been used previously, “[t]he dose of fixed dosing approach [is] set to the dose that would be given to a subject with median [bodyweight] by [bodyweight]-based dosing.” EX1030 at 1014. Under that approach, NCT-188’s disclosure of 3 mg/kg nivolumab dosing for the monotherapy nivolumab phase translates to 240 mg nivolumab from the simple conversion of multiplying NCT-188’s 3 mg/kg by the approximate 80 kg weight of an average subject participating

in, for example, a study of ipilimumab in patients with advanced melanoma. *See* EX1041 at 108 (reporting mean body weight of 80.11 kg). And such 240 mg nivolumab corresponds to the flat dose of nivolumab expressly disclosed in NCT-109. While NCT-109’s disclosure concerns a flat dose of nivolumab together with a flat dose of an anti-LAG-3 antibody (rather than a flat dose of nivolumab as a monotherapy), the operative teaching in NCT-109 from a POSA’s perspective would simply have been that nivolumab had been recognized as suitable for flat dosing—including 240 mg flat doses.

156. For the remainder of this declaration, I will use the term “NCT-188-NCT-109” to refer to practicing NCT-188 with a 240 mg flat dose of nivolumab for the nivolumab monotherapy phase. Aside from substituting the 240 mg flat dose of nivolumab in place of the 3 mg/kg weight-based dose for the nivolumab monotherapy phase, NCT-188-NCT-109 is identical to NCT-188 and in particular does not alter anything about NCT-188’s initial co-administration of nivolumab together with ipilimumab. NCT-188-NCT-109 therefore satisfies dependent claim 12 (from which dependent claims 15-18 depend) for the same reasons detailed in above in Section IX.A.1.c.iii(8).

c. Reasonable Expectation of Success

157. POSAs would have had a reasonable expectation of success when practicing NCT-188 with a 240 mg flat dose of nivolumab once every two weeks

for the nivolumab monotherapy phase (i.e., in place of the 3 mg/kg nivolumab once every two weeks as disclosed in NCT-188 for the nivolumab monotherapy phase) given that it reflects the amount of nivolumab specified by NCT-188 for a patient of average weight (i.e., 80 kg).

158. 240 mg flat dosing of nivolumab was also a well-established dosing strategy for a variety of different tumor types. For example, a patent application filed in May 2015 disclosed using a 240 mg flat dose of nivolumab in the treatment of lung cancer. EX1043 at ¶¶ [0002], [0096], [0187]. Moreover, a previous dose escalation study had reported that nivolumab was tolerated at dosages up to 10 mg/kg across multiple cancer types. EX1049 at 2445. Such reports further confirmed the safety of a 240 mg flat dose even for lightweight patients. For example, 240 mg nivolumab corresponds to less than 7 mg/kg even for an 80 pound (36 kg) patient. Such earlier teachings confirm that POSAs would have had a reasonable expectation of success when using this technique to implement the nivolumab monotherapy phase of NCT-188.

d. Claim-by-Claim Analysis

i. Claim 15: Anti-PD-1 Antibody Monotherapy Administered as a Flat Dose

159. NCT-188-NCT-109 satisfies claim 15 because “the anti-PD-1 antibody monotherapy is administered as a flat dose”—specifically, a 240 mg flat

dose of the anti-PD-1 antibody nivolumab—as detailed above in Section IX.A.3.b.

Accordingly, NCT-188 in view of NCT-109 renders claim 15 obvious.

ii. Claim 16: Anti-PD-1 Antibody Monotherapy Administered as a Flat Dose of About 240 mg Once About Every 2 Weeks

160. NCT-188-NCT-109 satisfies claim 16 because “the anti-PD-1 antibody monotherapy is administered at a flat dose of about 240 mg once about every 2 weeks” as detailed above in Section IX.A.3.b. Accordingly, NCT-188 in view of NCT-109 renders claim 16 obvious.

161. Moreover, as I explained in Section IX.A.3.b, a 240 mg flat dose of nivolumab merely corresponds to the amount of nivolumab that would be administered to an 80 kg patient—consistent with the average weight of patients in, for example, an ipilimumab study (EX1041) under the letter of NCT-188’s teaching of a 3 mg/kg weight-based dose of nivolumab once every two weeks. There was nothing inventive about following NCT-188’s teachings as applicable to a patient of average weight.

iii. Claim 17: Anti-PD-1 Antibody is Nivolumab

162. NCT-188-NCT-109 satisfies claim 17 because it satisfies claim 16 (as detailed immediately above) and further because the anti-PD-1 antibody used is nivolumab—consistent with the disclosures in both NCT-188 and NCT-109. *See* EX1005 at 5 (“followed by Nivolumab 3 mg/[k]g IV every 2 weeks until disease progression”); EX1007 at 5 (dosages with nivolumab).

iv. Claim 18: Anti-CTLA-4 Antibody is Ipilimumab

163. NCT-188-NCT-109 satisfies claim 18 because it satisfies claim 17 (as detailed immediately above) and further because the anti-CTLA-4 antibody used in the combination therapy phase of the treatment is ipilimumab—consistent with the disclosure in NCT-188. *See* EX1005 at 4 (“A Study of ...Nivolumab Plus Ipilimumab”), 5 (describing dosing with ipilimumab). The combination therapy disclosures in NCT-188 are not impacted by the substitution of NCT-109’s 240 mg flag dosing of nivolumab for the subsequent weight-based anti-PD-1 monotherapy phase disclosed in NCT-188.

4. GROUNDS 2A-2C (Addition of Postow and Xiao to Grounds 1A-1C)

164. As I discussed for Ground 1A (Section IX.A.1), NCT-188 is enabling (Section IX.A.1.b) and anticipates claims 1 and 4-14 (Section IX.A.1.c). However, even if PO disputed NCT-188’s enablement and/or argued that the claims require some efficacy not disclosed by or inherent from NCT-188, it is my opinion that in any event all claims of the ’529 patent would have been obvious in view of the references discussed in Grounds 1A-1C together with Postow and Xiao. Grounds 2A-2C below discuss the obviousness of the claims discussed in Grounds 1A-1C when considered in combination with the teachings of Postow and Xiao.

165. Postow (EX1031) discloses the same dosage schedule as NCT-188’s Dose Level 2a (i.e., 1 mg/kg nivolumab and 3 mg/kg ipilimumab every three

weeks for four doses, followed by 3 mg/kg nivolumab monotherapy every two weeks) and further discloses that such treatment resulted in “durable responses.” EX1031 at 1-5. Postow specifically discloses that such treatment—with doses including nivolumab *and* ipilimumab—resulted in “substantially higher objective response rate, longer progression-free survival, and higher rates of complete responses than ipilimumab monotherapy.” *Id.* Postow’s findings are corroborated by, for example, Larkin (EX1011), which reported that the “combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone.” EX1011 at 31. Wolchok had likewise reported that while “not formally compared in [Wolchok’s] study, concurrent treatment with nivolumab and ipilimumab was associated with rates of objective responses that exceeded the previously reported results with either nivolumab or ipilimumab alone.” EX1013 at 131.

166. Furthermore, while Postow’s clinical results were reported for melanoma patients, Xiao (EX1010) specifically referenced anti-PD-1 *colorectal cancer* clinical trials such as NCT-188 and emphasized that “[c]ombinations with IDO, LAG-3, CTLA-4, and other checkpoints will likely follow.” EX1010 at 18.

167. In view of these express teachings in Postow and Xiao, POSAs would have reasonably expected NCT-188’s disclosures—including but not limited NCT-188’s disclosures regarding Dose Level 2a—to be efficacious for colorectal cancer

and thus would have had reason to implement NCT-188 to maximize the likelihood of such efficacy in the context of colorectal cancer. Indeed, other teachings in the prior art corroborate that POSAs had a high level of skill in the art and would have reasonably expected NCT-188 to be efficacious for colorectal cancer. For example, POSAs would have been aware of Lipson (EX1037), which reported that even nivolumab (i.e., BMS-936558, as the '529 Patent acknowledges, EX1001 at 1:52) alone achieved a “[d]urable complete response in [MSI-H] colorectal cancer.” EX1037 at 463-464.

168. Additionally, POSAs would have been aware of the synergistic effects of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model. For example, as I noted above in paragraph 89, Duraiswamy (EX1053) reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model (EX1053 at 3595), and found that “[b]lockade of either PD-1 or CTLA-4 pathways enhanced effector T cell infiltration” into tumors, but that “simultaneous blockade of both pathways had synergistic effects in activation of tumor antigen specific CD8⁺ and CD4⁺ effector T cells” (*id.* at 3599-3600), which yielded a greater antitumor immune response (*id.* at 3591).

a. GROUND 2A: NCT-188, Postow, and Xiao Render Obvious Claims 1 and 4-14

169. As discussed in Ground 1A (Section IX.A.1), it is my opinion that NCT-188 anticipates claims 1 and 4-14. To the extent NCT-188 is found not to anticipate claims 1 and 4-14, those claims are at the very least *obvious* over NCT-188 (as detailed in Ground 1A) in view of Postow and Xiao for the reasons discussed above in Section IX.A.4.

170. Also, dependent claim 4—which is the only claim that recites clinical results—is obvious over NCT-188 in view of Postow and Xiao *even if* claim 4 were found to require some efficacy that is not inherent—which I understand it would not be, as I discussed above in Section IX.A.1.c.ii, in paragraphs 103-107.

171. Claim 4’s recited efficacy would have been obvious to a POSA in view of the prior art because a POSA would have had reason to take steps consistent with medical best practices to maximize the likelihood of patients surviving at least one month following treatment, and further would have reasonably expected patients undergoing the combination therapy to survive at least one month as recited in claim 4. The medical literature already predicted “the use of effective immunotherapy for treatment of colorectal cancer in the near future.” EX1038 at 3738. Additionally, NCT-188’s dosing and assessment schedules themselves confirm that more than one month survival of the treated patients was expected, as demonstrated by the fact that the combination treatment

itself continued for more than one month, e.g., 9 weeks after initial dose—*see* EX1005 at 5 (combination treatment “every 3 weeks for 4 doses”; i.e., 9 weeks from initial dose)—and tumor imaging and assessment also continued for more than one month, for example, for “at least 6 months after ... first dose.” *See* EX1005 at 5 (“Tumor imaging assessments will occur every 6 weeks from the date of first dose (+/-1 wk) for the first 24 weeks, then every 12 wks (+/-1 wk) thereafter...”; “The final analysis of the primary endpoint will occur at least 6 months after the last enrolled subject’s first dose...”).

**b. GROUND 2B: NCT-188, Zhang, Postow, and Xiao
Render Obvious Claims 2-3**

172. As discussed in Ground 1B (Section IX.A.2), it is my opinion that claims 2-3 are obvious over NCT-188 and Zhang. To the extent claims 2-3 are found not to be rendered obvious by NCT-188 and Zhang, those claims are at the very least obvious over NCT-188 and Zhang (as detailed in Ground 1B) in further view of Postow and Xiao for the reasons discussed above in Section IX.A.4. Indeed Xiao specifically discusses MSI-H (i.e., MSI) colorectal cancer and discusses how it can result from “mutation of DNA mismatch repair genes,” which Zhang details. EX1010 at 16.

**c. GROUND 2C: NCT-188, NCT-109, Postow, and Xiao
Render Obvious Claims 15-18**

173. As discussed in Ground 1C (Section IX.A.3), it is my opinion that claims 15-18 are obvious over NCT-188 and NCT-109. To the extent claims 15-18 are found not to be rendered obvious by NCT-188 and NCT-109, those claims are at the very least obvious over NCT-188 and NCT-109 (as detailed in Ground 1C) in further view of Postow and Xiao for the reasons discussed above in Section IX.A.4. Indeed, Xiao specifically identifies LAG-3 (along with PD-1 and CTLA-4) as among the checkpoint molecules expressed in MSI colorectal cancer (*e.g.*, EX1010 at 16), and NCT-109 concerns a clinical trial testing the effectiveness of anti-LAG-3 antibodies with or without anti-PD-1 (*e.g.*, EX1007 at 4).

B. Grounds Related to Le, Xiao, and Hammers

174. Le in view of Xiao and Hammers (“Le-Xiao-Hammers”) renders obvious claims 1 and 4-14.

**1. GROUND 3A: Le in View of Xiao and Hammers Renders
Obvious Claims 1 and 4-14**

a. Le (EX1008)

175. Le describes results of a phase 2 study “evaluat[ing] the clinical activity of pembrolizumab, an [anti-PD-1] immune checkpoint inhibitor” in 41 patients across three cohorts:

- the first—cohort A—including patients with mismatch repair-
deficient [*i.e.*, MSI-H] colorectal adenocarcinomas;

- the second—cohort B—including patients with mismatch repair-*proficient* colorectal adenocarcinomas; and
- the third—cohort C—including patients with other types of cancers that were mismatch repair-*deficient*.

EX1008 at 2509-10. POSAs would have understood that Le’s cohort A (i.e., patients with mismatch repair-*deficient* colorectal adenocarcinomas) corresponds to patients with MSI-H colorectal cancer as recited in claim 1 of the ’529 Patent.

“Cells with deficient DNA mismatch repair develop microsatellite instability.”

EX1028 at 2417; *see also* EX1026 at 1043 (“The tumor phenotype associated with either hereditary or acquired loss of DNA mismatch repair competency is called microsatellite instability (MSI).”); EX1027 at 5248 (“MSI is caused by a failure of the DNA MMR system to repair errors that occur during the replication of DNA ...”).

176. Le reported markedly better results when using pembrolizumab to treat cohort A (i.e., MSI-H colorectal cancer patients) as compared to cohort B (i.e., microsatellite stable (“MSS”) colorectal cancer patients). EX1008 at 2513.

	MSS Colorectal Cancer (Cohort B)	MSI-H Colorectal Cancer (Cohort A)
Objective Response Rate	0%	40%
Progression-Free	11%	78%

	MSS Colorectal Cancer (Cohort B)	MSI-H Colorectal Cancer (Cohort A)
Survival Rate		
Disease Control Rate	11%	90%

EX1008 at 2514. In particular, Le found that the immune-related objective response rate and the immune-related progression-free survival rate at 20 weeks in MSS colorectal cancer patients were 0% and 11%, respectively. EX1008 at 2513. These figures increased to 40% and 78%, respectively, in MSI-H colorectal cancer patients. EX1008 at 2513. Le also found a disease control rate of only 11% for MSS colorectal patients, compared to 90% for MSI-H colorectal cancer patients. EX1008 at 2513. Further, Le disclosed that “among the patients with mismatch repair-proficient cancers (cohort B), the median progression-free survival was only 2.2 months... and the median overall survival was 5.0 months,” whereas for MSI-H colorectal cancer patients (cohort A) neither survival criteria was reached. EX1008 at 2514.

177. Based on these results, Le concluded that “mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors.” EX1008 at 2516. The results supported Le’s hypothesis to this effect (EX1008 at 2516), which Le had based on an earlier study reporting that of “33 patients with colorectal cancer” “only 1 of [the] 33” had responded to anti-PD-1

antibody treatment (EX1008 at 2510). Despite that low percentage, the colorectal cancer tumor of the single responsive patient “was mismatch repair-deficient.” EX1008 at 2510 (citing EX1037). In support of the statement that of “33 patients with colorectal cancer” “only 1 of [the] 33” had responded to anti-PD-1 antibody treatment, Le cites Topalian (EX1049) and Brahmer (EX1050). EX1008 at 2510 (citing endnotes 10 and 12). Topalian identifies “7 [patients] with colorectal cancer” (EX1049 at 2449) and states that “[n]o objective responses were observed in patients with colorectal ... cancer” (EX1049 at 2446). Brahmer identifies 14 patients with colorectal cancer tumors (EX1050 at 3169 at Table 1) and states that “[o]ne patient with [colorectal cancer] ... achieved a [complete response]” (EX1050 at 3169). Thus, Topalian and Brahmer account for 21 colorectal cancer patients including one with a response. It is not clear what additional 12 patients Le may have considered to reach a total of 33. However, the total number of patients does not change Le’s conclusion based on the fact that the one responsive patient was mismatch repair-deficient. EX1008 at 2510 (citing EX1037); EX1037 at 463 (describing “[d]urable complete response in colorectal cancer” for MSI-H patient).

178. While not necessary to my analysis, I note that one of my own articles (EX1057) cited Le as evidence that “immune checkpoint inhibition has led to significant clinical benefit in patients with microsatellite instable colorectal

cancer.” EX1057 at 2470 & n.1. Indeed, given Le’s data confirming the efficacy of anti-PD-1 antibodies for treatment of MSI-H colorectal cancer, the subsequent study described in my article assessed whether anti-PD-1 and anti-CTLA-4 antibodies together with radiation would be effective in treating **MSS** colorectal cancer. This subsequent study focused on MSS colorectal cancer rather than MSI-H colorectal cancer given evidence (including Le) that immunotherapies were effective in treating MSI-H colorectal cancer. Once Le’s data was in hand, focus turned to whether immunotherapies coupled with other treatment modalities could be effective in MSS colorectal cancer.

b. Xiao (EX1010)

179. Xiao is a January 2015 article entitled “The Microsatellite Instable Subset of Colorectal Cancer is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy.” EX1010. Reviewing earlier work, Xiao highlights how anti-PD-1 therapies could be combined with antibodies targeting other checkpoints such as CTLA-4 to treat MSI-H colorectal cancer. EX1010 at 16.

180. Specifically, Xiao summarizes an earlier study and notes how it determined that “compared with [microsatellite stable] tumors, [microsatellite instable] tumors highly upregulate expression of multiple immune checkpoints, including programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated

antigen 4 (CTLA-4).” EX1010 at 16. Xiao identified PD-1 and CTLA-4 as two of the checkpoints upregulated in MSI-H colorectal cancer tumors. EX1010 at 16.

181. Xiao also notes that all of these upregulated checkpoints—including PD-1 and CTLA-4—were “currently being targeted clinically with inhibitors.” EX1010 at 18. More specifically, Xiao stated that “[t]he FDA approved a CTLA-4 monoclonal antibody (mAb; ipil[i]mumab) in 2010 and a PD-1 mAb (pembrolizumab) in 2014 for melanoma treatment.” EX1010 at 18.

182. Xiao also reported that “two clinical trials have been initiated to test PD-1 blockage in patients with MSI colorectal cancer” and stated that “[c]ombinations with IDO, LAG-3, **CTLA-4**, and other checkpoints will likely follow.” EX1010 at 18. POSAs would have recognized that Le (EX1008) reflected the results of one of those two trials referenced in Xiao. Indeed, the relevant sentence in Xiao cites Llosa (EX1014), which is entitled “The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints” and had predicted that “MSI tumors will respond to checkpoint blockade with agents such as anti-PD-1 or anti-PD-L1 antibodies, whereas MSS tumors will be much less responsive” (EX1014 at 49). Llosa further disclosed that “based on these findings, two clinical trials testing anti-PD-1 antibodies in patients selected based on MSI have been initiated (NCT01876511 and NCT02060188).” EX1014 at 49. Le discloses that it reflects

the results of NCT01876511. *See* EX1008 at 2509 (“This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others; *ClinicalTrials.gov* number, NCT01876511.)”).

c. Hammers (EX1009)

183. Hammers is a published poster abstract describing “[a] phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma.” EX1009 at 251s. Hammers reports that patients received either (i) 3 mg/kg nivolumab + 1 mg/kg ipilimumab; (ii) 1 mg/kg nivolumab and 3 mg/kg ipilimumab, or (iii) 3 mg/kg nivolumab and 3 mg/kg ipilimumab, each administered once every three weeks for four doses and followed by 3 mg/kg nivolumab every two weeks until disease progression or toxicity. EX1009 at 251s.

	First Phase: Combination therapy once every 3 weeks for 4 doses		Second Phase: Monotherapy every 2 weeks until progression or toxicity
Arm	Nivolumab (mg/kg)	Ipilimumab (mg/kg)	Nivolumab (mg/kg)
(i) N3+I1	3	1	3
(ii) N1+I3	1	3	3
(iii) N3+I3	3	3	3

184. Hammers reported that arm (iii) “showed early toxicity and did not proceed to expansion” but that the other two arms were expanded and that results of the study “confirm[ed] initial safety findings and promising antitumor activity

for [nivolumab] + [ipilimumab] in [patients] with [metastatic renal cell carcinoma].” EX1009 at 251s. Hammers reported that the results “appear encouraging and support further development of this combination.” EX1009 at 251s.

d. Reason to Combine Le, Xiao, and Hammers

185. Given the positive results reported in Le concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer patients (EX1008 at 2512-2515), Xiao’s teaching that “[c]ombinations” with other checkpoints such as CTLA-4 “will likely follow” (EX1010 at 18) would have motivated POSAs to treat MSI-H colorectal cancer patients (as disclosed in Le) using the particular therapeutic regimes disclosed in Hammers—including (1) the combination of anti-PD-1 and anti-CTLA-4 antibodies followed by (2) anti-PD-1 monotherapy. For the remainder of this declaration, I will use the term “Le-Xiao-Hammers” to refer to this combination, which is described in further detail below.

i. Given the Favorable Results Disclosed in Le, Xiao Would Have Motivated a POSA to Combine Anti-PD-1 and Anti-CTLA-4 Antibodies to Treat MSI-H Colorectal Cancer

186. There are multiple reasons why POSAs considering how to leverage the favorable results Le discloses concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer would have looked to Xiao’s teachings concerning combined anti-PD-1 and anti-CTLA-4 antibody therapy.

187. For one, Xiao indicates that “two clinical trials have been initiated to test PD-1 blockade in patients with MSI colorectal cancer” and “[c]ombinations with IDO, LAG-3, CTLA-4, and other checkpoints will likely follow.” EX1010 at 18. Xiao cites to a separate reference (Llosa, EX1014) confirming that one of those two clinical trials was NCT01876511—the same trial whose results Le subsequently disclosed. EX1010 at 18 (reference 3: “Llosa NJ, Cruise M, Tam A, Wick EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015;5: 43–51”); EX1014 at 49 (“Indeed, based on these findings, two clinical trials testing anti-PD-1 antibodies in patients selected based on MSI have been initiated (*NCT01876511* and NCT02060188).”); EX1008 at 2509 (“This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others; ClinicalTrials.gov number, *NCT01876511*).”)

188. The fact that Le reports positive results concerning one of the “two clinical trials” referenced in Xiao “to test PD-1 blockade in patients with MSI colorectal cancer” (EX1010 at 18) would have naturally prompted POSAs to look to Xiao in particular for teachings concerning desirable next steps following the successful completion of the NCT01876511 study. Indeed, subsequently published

references such as Kroemer (submitted almost immediately after Le's online publication) recognized Le's successful result with respect to MSI-H colorectal cancer patients. EX1047 at 1 (citing Le: "[P]atients with mismatch repair-deficient CRC lesions obtain clinical benefits from the administration of a PD-1-targeting mAb."). Further, POSAs would have understood Xiao as disclosing that such next steps following Le's success would likely include combinations with anti-CTLA-4 antibodies. While Xiao also refers to other checkpoints such as "IDO" and "LAG-3," POSAs would have understood that Xiao highlights CTLA-4 given Xiao's teaching that ipilimumab had previously been approved by the FDA. EX1010 at 18. Other prior art also emphasized combining an anti-CTLA-4 antibody with an anti-PD-1 antibody in a combination therapy. *See* EX1044 at 1:37-38 (disclosing "combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer"); EX1045 at 9:52-55 (disclosing "an anti-PD-1 antibody...combined with anti-CTLA-4"); EX1054 (article entitled "CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy," noting that anti-CTLA antibody ipilimumab had been approved by FDA and that anti-CTLA therapy was being tested together with anti-PD-1 therapy).

189. In addition, POSAs would have recognized that Le and Xiao are complementary and directed to the same problem of understanding why anti-PD-1

antibodies had shown limited efficacy in treating colorectal cancer despite their overall successful track record in treating various other types of cancers:

Discussion in Le (EX1008 at 2510)	Discussion in Xiao (EX1010 at 18)
Blockade of this pathway with antibodies to PD-1 or its ligands has led to remarkable clinical responses in patients with many different types of cancer, including melanomas, non-small-cell lung cancer, renal-cell carcinoma, bladder cancer, and Hodgkin's lymphoma...In reports of the effects of PD-1 blockade in human tumors, only 1 of 33 patients with colorectal cancer had a response to this treatment, in contrast to substantial fractions of patients with melanomas, renal-cell cancers, and lung tumors who have a response.	Anti-PD-1 and anti-PD-L1 antibodies have demonstrated significantly durable efficacy in patients with melanoma, renal cancer, and non-small cell lung cancer. However, colorectal cancer appeared to be a poor responder to antibody blockade of PD-1 or PD-L1 in clinical trials.

190. Le highlights how “mismatch-repair deficiency occurs in a small fraction of advanced colorectal cancers”—prompting Le’s hypothesis (confirmed by Le’s data) “that mismatch repair-deficient tumors are more responsive to PD-1 blockade than are mismatch repair-proficient tumors.” EX1008 at 2510. Similarly, Xiao notes that “[m]icrosatellite instable (MSI) colorectal cancer comprises approximately 15% of sporadic colorectal cancer” (EX1010 at 16) and further that “most MSI colorectal cancers typically present with lower-stage disease than MSS colorectal cancers,” such that “the MSI subtype represents only 5% to 6% of the stage IV colorectal cancer population” and accordingly it was “likely there were few MSI patients in PD-1 and PD-L1 clinical trials” (EX1010 at 18). POSAs would have recognized that Xiao’s inference was in accord with Le’s determination in particular that while “only 1 of 33 patients with colorectal cancer” treated in a PD-1 clinical trial “had a response to this treatment,” that patient’s tumor “was mismatch repair deficient.” EX1008 at 2510. This consistency reinforces why a POSA would have looked to Xiao’s teachings (and in particular the combination of anti-PD-1 and anti-CTLA-4 antibodies) when considering how to leverage Le’s favorable results.

**ii. Hammers Discloses a Particular Combination
Therapy of Anti-PD-1 and Anti-CTLA Antibodies
To Which a POSA Would Have Looked Given The
Teachings in Le and Xiao**

191. Given the combined teachings of Le and Xiao and indicating that it would be desirable to treat MSI-H colorectal cancer patients using a combination therapy involving both anti-PD-1 and anti-CTLA-4 antibodies, POSAs would have had reason to look to Hammers in particular for the details of such combination therapy because Hammers discloses favorable results using anti-PD-1 and anti-CTLA-4 antibodies to treat renal-cell carcinoma. EX1009 at 251s (“nivolumab [i.e., an anti-PD-1 antibody] in combination with ipilimumab [i.e., an anti-CTLA antibody] in metastatic renal cell carcinoma”).

192. Renal-cell carcinoma is one of the types of cancer for which Le taught anti-PD-1 antibodies had shown “remarkable clinical responses,” with the “expression of PD-1 ligands...on the surface of tumor cells” being a significant “predictive biomarker of response to PD-1 blockade.” EX1008 at 2510. Given this teaching and Le’s determination that the objective response rate when treating MSI-H colorectal cancer using anti-PD-1 antibodies was comparable to that when treating other types of MSI-H cancers using anti-PD-1 antibodies (EX1008 at 2513), POSAs would have looked to the Hammers protocol as a suitable guide for implementing Xiao’s suggestion of combination therapy for MSI-H colorectal cancer.

193. Indeed, POSAs often consider therapies that have been successful in one cancer (such as renal cancer) for use with another cancer (such as colorectal cancer). This is particularly common when both cancers are of the same type. Here, for example, both renal cancer and colorectal cancer present as solid tumors.

194. Either of the two expanded arms of Hammers (i.e., featuring either 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab or 1 mg/kg of nivolumab and 3 mg/kg of ipilimumab) would have been obvious to implement in view of the positive results disclosed in Hammers for such combination therapies.

195. This combined method—involving testing colorectal cancer patients to determine whether their tumors were MSI-H (as disclosed in Le) and then treating such patients using a combination therapy incorporating both anti-PD-1 and anti-CTLA-4 antibodies (as suggested by Xiao) with the particular protocol disclosed by Hammers—is the combination I reference herein as “Le-Xiao-Hammers.”

e. Reasonable Expectation of Success

196. A POSA would have had a reasonable expectation of success when implementing Le-Xiao-Hammers given:

- (1) the favorable clinical results disclosed in Le as well as Lipson (EX1037, and referenced in Le) concerning the use of anti-PD-1 antibodies to treat MSI-H colorectal cancer; coupled with

(2) the favorable clinical results in Hammers as well as numerous other prior art references teaching the benefits of combined anti-PD-1 and anti-CTLA-4 antibody therapy as compared to monotherapy alone for various different types of cancer.

197. Based on Le and Lipson, POSAs would have had a reasonable expectation of success when using anti-PD-1 immunotherapy to treat MSI-H colorectal cancer. Indeed, the results disclosed in Le and Lipson tracked other prior art teachings that MSI-H colorectal cancers were “good candidates for immunotherapy.” EX1038 at 3740-41. Lipson, in particular, provided a reasonable expectation of success in using nivolumab (i.e., the anti-PD-1 antibody disclosed in Hammer) in place of the different anti-PD-1 antibody used for Le’s study) given that Lipson reports that nivolumab achieved a “[d]urable complete response in [MSI-H] colorectal cancer.” EX1037 at 463-464.

198. Further, based on Hammers and other medical literature, POSAs would have had a reasonable expectation that the combination of anti-PD-1 and anti-CTLA immunotherapy would also effectively treat MSI-H colorectal cancer and indeed achieve even better results than those observed with anti-PD-1 immunotherapy alone. For example, Curran encouraged POSAs to use the combination, explaining that “the CTLA-4 and PD-1 inhibitory pathways appeared to be nonredundant” (EX1012 at 4275) and the “combination blockade ... leads to

synergistic levels of tumor rejection” (EX1012 at 4278). Similarly, Larkin found that “the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone.” EX1011 at 31. Further, in the specific context of colorectal cancer, Duraiswamy (EX1053) reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy had been reported in a colon carcinoma mouse model. EX1053 at 3595, 3599-3600.

199. An earlier patent directed to nivolumab itself (EX1044) would have further reinforced that reasonable expectation of success to POSAs given the patent’s explicit teaching that the invention concerned “the use of anti-PD-1 antibodies and the use of combination immunotherapy, including the combination of anti-CTLA-4 and anti-PD-1 antibodies, to treat cancer and/or to decrease the incidence or magnitude of adverse events related to treatment with such antibodies individually.” EX1044 at 1:35-40.

f. Claim-by-Claim Analysis

200. Le-Xiao-Hammers discloses every element of independent claim 1 as well as dependent claims 4 and 5-14, thus rendering them obvious.

i. Independent Claim 1

(1) [1.Pre] “A method of treating a subject afflicted with a tumor derived from a colorectal cancer...”

201. To the extent claim 1’s preamble is limiting, Le-Xiao-Hammers satisfies it because the Le-Hammers-Xiao method as detailed above in Section IX.B.1.d entails treating colorectal cancer—consistent with the teachings in both Le and Xiao. Le is directed to methods of treating subjects afflicted with a tumor derived from a colorectal cancer. *See* EX1008 at 2509-2510. Additionally, Xiao discloses treating colorectal cancer patients. EX1010 at Summary. Specifically, Xiao concludes that “the [microsatellite instable] subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy.” EX1010 at Summary. Xiao also reports that “two clinical trials have been initiated ...in patients with MSI colorectal cancer.” EX1010 at 18. The results of one of those studies were later reported in Le itself, as discussed in paragraphs 182 and 187-188 above.

**(2) [1.A] “administering to the subject:
(i) an anti-PD-1 antibody, and
(ii) an anti-CTLA-4 antibody”**

202. Le-Xiao-Hammers satisfies limitation [1.A] because it entails administering both an anti-PD-1 antibody and an anti-CTLA-4 antibody as discussed above in Section IX.B.1.d—consistent with the teachings in both Xiao and Hammers as well as related disclosures in Le. Xiao references then-ongoing

clinical trials “test[ing] PD-1 blockade in patients with MSI colorectal cancer” (one of which was the trial for which Le subsequently reported favorable results) and suggests that a combination with CTLA-4 would “likely follow.” EX1010 at 18. And Hammers discloses administering an anti-PD-1 antibody (nivolumab) and an anti-CTLA-4 antibody (ipilimumab) when treating a different type of cancer (i.e., renal cell carcinoma) expressly referenced in both Le and Xiao. EX1009.

(3) [1.B] “the tumor is a colon cancer or a rectal cancer”

203. Le-Xiao-Hammers satisfies limitation [1.B] because it entails treating colon or rectal cancer patients as discussed above in Section IX.B.1.d—consistent with the teachings in both Le and Xiao. Le is directed to treating colon or rectal cancer. EX1008 at 2509-2510 (discussing cohorts A and B including patients with colorectal adenocarcinomas). Similarly, Xiao is directed to treating colorectal cancer tumors. EX1010 at summary, 1.

204. “Colorectal” means “relating to or affecting the colon and rectum.” EX1022 (defining colorectal). POSAs would understand that both Le and Xiao are directed specifically to treating colon cancer or rectal colon or rectal adenocarcinoma—a particular type of colorectal cancer.

**(4) [1.C] “the tumor exhibits a high degree of
microsatellite instability (MSI-H)”**

205. Le-Xiao-Hammers satisfies limitation [1.C] because it entails treating MSI-H colon or rectal cancer tumors as discussed above in Section IX.B.1.d—consistent with the teachings in both Le and Xiao.

206. Le describes evaluating treatment of patients with mismatch repair-deficient colorectal cancers as compared to mismatch repair-proficient colorectal cancers. EX1008 at 2509. POSAs would have understood that mismatch repair deficient corresponds to MSI-H, and mismatch repair proficient corresponds to MSS. Specifically, Le explains that it identified mismatch-repair status based on microsatellite instability. EX1008 at 2512; *see also* EX1032 at 5 (Appendix 1 to Le, disclosing assessment of MSI status using five microsatellites to determine mismatch repair status).

207. Xiao discloses that “[microsatellite instable] tumors highly upregulate expression of multiple immune checkpoints.” EX1010 at 16. Xiao concludes that “the [microsatellite instable] subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy.” EX1010 at Summary.

**ii. Dependent Claim 4: Survival of At Least About
One Month Following Treatment**

208. Le-Xiao-Hammers renders obvious claim 4 for at least two separate and independent reasons.

209. First, as detailed above in Section IX.A.1.c.ii (explaining why NCT-188 anticipates claim 4), claim 4’s “wherein” clause—that is, the recitation that after administration, the subject either “exhibit a progression-free survival of at least about one month” or “exhibit an overall survival of at least about one month”—recites a non-limiting statement of intended effect.

210. Second, even if the wherein clause were deemed to limit claim 4 in some form, it would still be inherent in Le-Xiao-Hammers given that the recited outcome (i.e., patient survival of at least one month) is the natural result of administering 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab as disclosed in Hammers. I have been informed that inherency may satisfy a claim limitation in an obviousness analysis. Here, the result would be inherent because Le reported that median overall and progression-free survival were not reached after twelve months for patients receiving anti-PD-1 therapy alone, meaning that at the time of analysis, greater than half of the patients were still alive and without evidence of disease progression. EX1008 at Fig. 2. In other words, at least half of the patients exhibited overall and progression free survival of at least 12 months, significantly more than claim 4’s one month survival. Accordingly, at least this result would be inherent in the combination therapy. *See* Sections IX.B.1.d, IX.B.1.e.

211. Alternatively, a POSA would find these results obvious, with at least a reasonable expectation of success, based on the clinical results disclosed in Le,

Lipson, and Hammers. Specifically, disclosures in Le concerning the success of anti-PD-1 antibody therapy in treating MSI-H colorectal cancer, the disclosure in Lipson reporting “[d]urable complete response in [MSI-H] colorectal cancer” treated with nivolumab in particular (EX1037 at 473), and the disclosure in Hammers concerning the improved performance of nivolumab together with ipilimumab.

212. Such inherency is confirmed by the ’529 Patent’s disclosures concerning the effect of administering 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab to patients with MSI-H colorectal cancer. *See* EX1001 at 36:59-37:7; Figs. 12A, 12B. And beyond these dosages, the ’529 Patent does not disclose any additional manipulative steps to increase the likelihood of patient survival. Accordingly, the ’529 Patent’s specification itself confirms that the natural result of administering Hammers’ disclosed dosages—that is, 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab—to MSI-H colorectal cancer patients is that such patients survive at least one month following treatment.

iii. Claims 5-14: Specific Antibody and/or Dosage Requirements

213. Le-Xiao-Hammers renders dependent claims 5-14 obvious because, as discussed above in Section IX.B.1.d, it would have been obvious in view of these references to treat MSI-H colorectal cancer patients by administering an anti-PD-1 antibody and an anti-CTLA-4 antibody (thereby rendering independent claim 1

obvious, as detailed in Section IX.B.f.i) and in particular to use the treatment regime disclosed in Hammers of (1) 3 mg/kg of nivolumab and 1 mg/kg of ipilimumab once every three weeks for four doses followed by (2) 3 mg/kg of nivolumab once every two weeks. Those parameters satisfy all additional requirements of claims 5-14 as discussed further below.

(1) Claim 5

214. Claim 5 depends from claim 1 and recites “the anti-PD-1 antibody is nivolumab or pembrolizumab.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering nivolumab as the anti-PD-1 antibody. EX1009 at 251s.

(2) Claim 6

215. Claim 6 depends from claim 1 and recites “the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering ipilimumab (i.e., an anti-CTLA-4 antibody) at a dose of 1 mg/kg once every three weeks. EX1009 at 251s.

(3) Claim 7

216. Claim 7 depends from claim 1 and recites “the anti-CTLA-4 antibody is ipilimumab or tremelimumab.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering ipilimumab (i.e., an anti-CTLA-4 antibody). EX1009 at 251s.

(4) Claim 8

217. Claim 8 depends from claim 1 and recites “the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering nivolumab (i.e., an anti-PD-1 antibody) at a dose of 3 mg/kg once every three weeks. EX1009 at 251s.

(5) Claim 9

218. Claim 9 depends from claim 1 and recites four different treatment regimes in the alternative, one of which requires administering 3 mg/kg of an anti-PD-1 antibody and 1 mg/kg of an anti-CTLA-4 antibody. Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering nivolumab (i.e.,

an anti-PD-1 antibody) at a dose of 3 mg/kg and ipilimumab (i.e., an anti-CTLA-4 antibody) at a dose of 1 mg/kg. EX1009 at 251s.

(6) Claim 10

219. Claim 10 depends from claim 9 and recites “the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.” In the drug therapy context, “monotherapy” refers to administration of a single drug. *See* EX1015 (“In drug therapy, monotherapy refers to the use of a single drug to treat a disease or condition.”); EX1036 (defining monotherapy as “the use of a single drug to treat a particular disorder or disease”).

220. Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails a combination therapy administering nivolumab (i.e., an anti-PD-1 antibody) together with ipilimumab (i.e., an anti-CTLA-4 antibody) satisfying claim 9 (as detailed immediately above) followed by a monotherapy stage administering nivolumab alone. EX1009 at 251s.

(7) Claim 11

221. Claim 11 depends from claim 1 and recites “wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once

about every 3 weeks for a total of 12 weeks.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime entails administering nivolumab (i.e., an anti-PD-1 antibody) at a dose of 3 mg/kg and ipilimumab (i.e., an anti-CTLA-4 antibody) at a dose of 1 mg/kg once every 3 weeks for 4 doses (i.e., a total of 12 weeks).

EX1009 at 251s.

(8) Claim 12

222. Claim 12 depends from claim 11 and is otherwise identical to claim 10 in that it recites the same “anti-PD-1 antibody monotherapy.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime satisfies claim 11 and also includes a subsequent anti-PD-1 antibody monotherapy phase as discussed above in connection with claim 10.

(9) Claim 13

223. Claim 13 depends from claim 12 and recites “the anti-PD-1 antibody monotherapy is administered once about every 2 weeks.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime satisfies claim 12 and further because the anti-PD-1 antibody monotherapy is administered once every 2 weeks. EX1009

at 251s (“Q2W”). A POSA would understand that “Q2W” is shorthand for administering treatment once every two weeks.

(10) Claim 14

224. Claim 14 depends from claim 12 and recites “the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks.” Le-Xiao-Hammers renders obvious the claimed method with this additional limitation because the above-discussed Hammers treatment regime satisfies claim 12 and further because the anti-PD-1 antibody monotherapy is administered at a dosage of 3 mg/kg nivolumab once every 2 weeks. EX1009 at 251s (“N 3 mg/kg IV Q2W”). A POSA would understand that “N” is shorthand for nivolumab and further that “Q2W” is shorthand for administering treatment once every two weeks.

225. For the foregoing reasons, claims 4-14 are obvious over Le-Hammers-Xiao.

2. GROUND 3B: Le, Xiao, Hammers, and Zhang Render Obvious Claims 2-3

226. Le in view of Xiao and Hammers and further in view of Zhang (“Le-Xiao-Hammers-Zhang”) renders obvious dependent claims 2 and 3.

a. Reason to Combine Zhang With Le-Xiao-Hammers

227. As discussed in Section IX.B.1.d, the Le-Xiao-Hammers method entails treating MSI-H colorectal cancer tumors—consistent with Xiao’s teaching

“that the MSI subset of colorectal cancer is a particularly good candidate for checkpoint immunotherapy” (EX1010 at 16) and Le’s report that “mismatch repair status predicted clinical benefit” of such checkpoint immunotherapy” (EX1008 at 2509). Given these teachings and the corresponding purpose of the method that would have been obvious from Le in view of Xiao and Hammers (that is, to treat patients with MSI-H colorectal cancer), POSAs implementing such method would have tested patients presenting with colorectal cancer to determine whether their tumors were mismatch repair deficient (i.e., MSI-H) or proficient.

228. Zhang discloses such criteria to identify MSI-H status. Moreover, Zhang would commend itself to the attention of a POSA because it is expressly directed to colorectal cancer and was published in a journal about “Gastrointestinal Oncology.” In particular, Zhang teaches the desirability of “MSI testing for all newly diagnosed individuals with CRC” (i.e., colorectal cancer). EX1006 at 12. Accordingly, POSAs would have been motivated to use the MSI-H criteria of Zhang to determine whether colorectal cancer patients would be likely to benefit from the method of treatment rendered obvious by Le-Xiao-Hammers.

229. In particular, a POSA would have had reason to implement Le-Xiao-Hammers using Zhang’s methodology of “***demonstrating absence of expression of MMR proteins*** by immunohistochemical staining (IHC)” (EX1006 at 14) because such staining was a well-known methodology that could be readily implemented

without special equipment and/or the need for genetic testing. *See also* EX1006 at 14 (noting that “[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be used to provide information of functionality of the MMR system”). For the remainder of this declaration, I will use the term “Le-Xiao-Hammers-Zhang” to refer to Le-Xiao-Hammers implemented using Zhang’s disclosed method of “*demonstrating absence of expression of MMR proteins*” to determine MSI-H status—including the use of commercially available antibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 as disclosed in Zhang.

b. Reasonable Expectation of Success

230. A POSA would have had a reasonable expectation of success in combining Le-Xiao-Hammers and Zhang given that Zhang’s immunohistochemical staining methodology for detecting MSI status was itself a well-known and reliable technique that could be implemented using readily available equipment. The fact that Le’s protocol—made publicly available at the same time as Le itself—recognized “immunohistochemistry” as a basis “for determining MSI” (EX1040 at 16)—further confirms a POSA’s reasonable expectation that Zhang’s immunohistochemical staining methodology would be suitable for the Le-Xiao-Hammers method.

c. Claim-by-Claim Analysis

i. Claim 2

231. Le-Xiao-Hammers-Zhang renders claim 2 obvious given that Le-Xiao-Hammers-Zhang incorporates Zhang's disclosure of detecting MSI via "immunohistochemical staining (IHC)" (EX1006 at 14).

232. In particular, Zhang's disclosed IHC method involves testing the tumor to determine if it "indicate[s] the presence of MSI" via "*the absence of one or more of the MMR proteins.*" EX1006 at 14. POSAs would understand from Zhang that "one or more of the MMR proteins" means "at least one protein encoded by DNA MMR genes." Indeed, Zhang describes the eukaryotic MMR system and notes the role of particular MMR genes. EX1006 at 13-14. Accordingly, POSAs would understand that detection of MSI positive colon or rectal cancer pursuant to Le-Xiao-Hammers entails the determination that "at least one protein encoded by DNA MMR genes is not detected in the tumor."

ii. Claim 3

233. Le-Xiao-Hammers-Zhang renders claim 3 obvious given that Le-Xiao-Hammers-Zhang incorporates Zhang's disclosed technique of identifying MSI status using immunohistochemical staining "of MMR proteins to indirectly indicate the presence of MSI" through the "absence of one or more of the MMR proteins." EX1006 at 14. Zhang explains that "[a]ntibodies against MMR proteins such as MLH1, PMS2, MSH2 and MSH6 are commercially available and can be

used to provide information of functionality of the MMR system.” EX1006 at 14. In particular, as explained in Section IX.B.2.a, the Le-Xiao-Hammers-Zhang combination entails the use of the commercially available antibodies disclosed in Zhang—including those indicating the presence or absence of MLH1, PMS2, MSH2 and MSH6. Accordingly, NCT-188-Zhang involves treating patients in which the “DNA MMR genes” of claim 2 include MLH1, PMS2, MSH2 and MSH6. That group satisfies the additional requirement of claim 3 because it includes “MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.”

3. GROUND 3C: Le, Hammers, Xiao, and NCT-109 Render Obvious Claims 15-18

234. Le in view of Hammers and Xiao and further in view of NCT-109 (“Le-Hammers-Xiao-NCT-109”) renders obvious claims 15-18.

a. Reason to Combine NCT-109 With Le-Xiao-Hammers

235. Consistent with the protocol disclosed in Hammers, Le-Xiao-Hammers as explained above in Section IX.B.1.d entails anti-PD-1 antibody monotherapy at a weight-based dose of 3 mg/kg following completion of the anti-PD-1 and anti-CTLA-1 antibody combination therapy. *See* EX1009 at 251s (“then [nivolumab] 3 mg/kg IV Q2W until progression or toxicity”). Given the advantages of flat dosing over weight-based dosing as detailed in Section IX.A.3.b concerning the combination of NCT-188 and NCT-109, a POSA would have had

reason to modify Le-Xiao-Hammers in view of NCT-109 (disclosing flat dosing with nivolumab), for those same reasons discussed in Section IX.A.3.b. For the remainder of this declaration, I will use the term “Le-Xiao-Hammers-NCT-109” to refer to Le-Xiao-Hammers implemented using flat dosing for the monotherapy (as opposed to the weight-based dosing disclosed in Hammers).

b. Reasonable Expectation of Success

236. A POSA would have had a reasonable expectation of success in combining Le-Xiao-Hammers and NCT-109 for the same reasons detailed above in Section IX.A.3.b concerning the combination of NCT-188 and NCT-109. In particular, a POSA would have had a reasonable expectation of success when practicing Le-Xiao-Hammers with a 240 mg flat dose of nivolumab once every two weeks for the nivolumab monotherapy phase (i.e., in place of the 3 mg/kg nivolumab once every two weeks as disclosed in Hammers for the monotherapy phase) given that it reflects the amount of nivolumab specified by Hammers for a patient having 80 kg body weight—consistent with the average weight of patients in other immunotherapy studies. *See* EX1041 at 108 (reporting mean body weight of 80.11 kg).

c. Claim-by-Claim Analysis

i. Claim 15

237. Le-Hammers-Xiao-NCT-109 renders claim 15 obvious for substantially the same reasons as NCT-188-NCT-109, discussed in Section IX.A.3.d.i.

ii. Claim 16

238. Le-Hammers-Xiao-NCT-109 renders claim 16 obvious for substantially the same reasons as NCT-188-NCT-109, discussed in Section IX.A.3.d.ii.

iii. Claim 17

239. Le-Hammers-Xiao-NCT-109 renders claim 17 obvious for substantially the same reasons as NCT-188-NCT-109, discussed in Section IX.A.3.d.iii.

iv. Claim 18

240. Le-Hammers-Xiao-NCT-109 renders claim 18 obvious for substantially the same reasons as NCT-188- NCT-109, discussed in Section IX.A.3.d.iv.

X. SECONDARY CONSIDERATIONS DO NOT RENDER THE CHALLENGED CLAIMS PATENTABLE

241. I have been informed that secondary considerations (as discussed above in paragraph 34) are not relevant to anticipation (i.e., the legal basis for Ground 1A).

242. I have also been informed that PO did not assert any unexpected results or other ostensible secondary considerations potentially relevant to Grounds 1B-1C, 2A-2C, or 3A-3C during prosecution of the application leading to the '529 Patent.

243. In addition, I note that Grounds 2B-2C and 3B-3C relate exclusively to Challenged Claims 2-3 and 15-18, for which the '529 Patent lacks corresponding data.

244. While the specification discloses certain results concerning MSI-H colorectal cancer generally, it never specifies whether any such results concern tumors satisfying any of the specific MSI-H characteristics recited in Challenged Claims 2-3 (i.e., the subject of Grounds 2 and 5). Nothing in the '529 Patent suggests any reason why the treatment method of claim 1 is particularly beneficial when applied to colorectal cancers satisfying the additional criteria specified in claim 2—much less the further criteria specified in claim 3. I note that “Example 1” refers to the determination of MSI-H status based on (1) PCR testing indicating whether “two or more markers showed instability out of 5 loci tested or if at least 30% of the markers showed instability when 5 or more loci were tested” and/or (2) IHC testing to determine “if there was a loss of one or more markers.” EX1001 at 27:58-65. However, such disclosures do not align with claims 2 and 3 given that the claims refer to MMR genes rather than markers. *See, e.g.*, EX1024 at 200

(referring separately to “the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1” and “markers, including mononucleotide repeats such as BAT25, BAT26, and BAT40 and the dinucleotide repeats D5S346, D2S123, and D17S250”); *see also* EX1025 at 98 (similar—referring separately to “MMR proteins MLH1, MSH2, MSH6, and PMS2” and “microsatellite markers (Bethesda panel), including two for mononucleotide repeats (BAT26 and BAT25) and three for dinucleotide repeats (D2S123, D5S346, and D17S250),” while also noting that colorectal cancer “is defined as MSI-H if two or more of the five markers show instability (or >30% of unstable markers if a larger panel is used).”).

245. Likewise, the specification does not disclose any results concerning treatments involving flat dosing of the anti-PD-1 antibody monotherapy as required by Challenged Claims 15-18 (i.e., the subject of Grounds 3 and 6). Nor does the specification otherwise suggest any reason why the additional limitations of claims 15-18 were significant. For example, the specification discloses the concept of flat dosing generally (as required by claims 15-18) and 240 mg specifically (as required by claim 16) as part of a longer list of undifferentiated options—in other words, a “laundry list.” EX1001 at 23:26-44:

In some embodiments, the anti-PD-1 antibody is administered at a weight-based dose. For administration of an anti-PD-I antibody, the dosage can range from at least about 0.01 to at least about 20 mg/kg, from at least about 0.1 to at least about 10 mg/kg, of the subject's body

weight. For example, dosages can be at least about 0.1 mg/kg, at least about 0.3 mg/kg, at least about 1 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 5 mg/kg, or at least about 10 mg/kg body weight. In certain embodiments, the dosage of the anti-PD-1 antibody is 3 mg/kg body weight. In certain embodiments, an anti PD-1 antibody is administered at a flat dose. In certain embodiments, the flat dose of the anti-PD-1 antibody is a dose (e.g., flat dose) of at least about 100-300 mg, such as, at least about 200-300 mg, at least about 220-260 mg, at least about 230-250 mg or at least about 240 mg, such as at least about 60 mg, at least about 80 mg, at least about 100 mg, at least about 120 mg, at least about 140 mg, at least about 160 mg, at least about 180 mg, at least about 200 mg, at least about 220 mg, at least about 240 mg, at least about 260 mg, at least about 280 mg or at least about 300 mg.”

See also EX1001 at 2:66-3:9:

In embodiments, the anti-PD-1 antibody is administered at a flat dose of at least about 200 mg, at least about 220 mg, at least about 240 mg, at least about 260 mg, at least about 280 mg, at least about 300 mg, at least about 320 mg, at least about 340 mg, at least about 360 mg, at least about 380 mg, at least about 400 mg, at least about 420 mg, at least about 440 mg, at least about 460 mg, at least about 480 mg, at least about 500 mg, at least about 550 mg, at least about 600 mg, at least about 650 mg, at least 700 mg, at least 750 mg, or at least 800 mg.

Nothing in the '529 Patent suggests any particular reason why flat dosing of the anti-PD-1 antibody worked differently or better than weight-based

dosing—much less why there was any particular significance to a 240 mg flat dose as compared to the numerous other options also disclosed.

246. Finally, to the extent PO may allege any data in the '529 Patent is relevant to Grounds 2A or 3A, such results would have been expected in view of the prior art. Anti-PD-1 antibodies were known to be effective in treating MSI-H colorectal cancer. EX1008 (Le) at 2514 (reporting that “median progression-free survival and median overall survival were not reached” for MSI-H colorectal cancer patients treated with pembrolizumab); EX1037 at 463 (reporting “Durable complete response in [MSI-H] colorectal cancer” treated with nivolumab). The statement that median progression-free survival and median overall survival were “not reached” in Le (EX1008 at 2514) means that at the time of analysis, greater than half of the patients were still alive and without evidence of disease progression. Based on the Kaplan-Meier estimates it would be expected that at one year after starting therapy over half of the MSI-H patients would still be alive and without evidence of cancer progression.

247. Earlier literature had also disclosed synergistic effects against some tumors when combining anti-PD-1 and anti-CTLA-4 antibodies.

248. For example, Larkin (EX1011) reported results for a “randomized, double-blind, phase 3 study” in which “nivolumab alone or nivolumab plus ipilimumab was compared with ipilimumab alone in patients with metastatic

melanoma.” EX1011 at 23. Larkin reported that “the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone.” EX1011 at 31.

249. Wolchok (EX1013) likewise reported clinical “data suggest[ing] that rapid responses of a greater magnitude may be achieved in [melanoma] patients treated with the combination of nivolumab and ipilimumab, as compared with the previous experience with either agent alone.” EX1013 at 131; *see also id.* at 122 (“Concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients.”); *id.* at 132 (“More rapid and deeper clinical tumor responses were observed in patients treated with the combination therapy, as compared with the previous experience with either agent alone.”). Wolchok’s results were consistent with Wolchok’s hypothesis “that a combined blockade of CTLA-4 and PD-1 could produce greater antitumor activity than either single agent.” *Id.* at 130.

250. Postow (EX1031) similarly reported “[t]he results of a phase 2 study that compared combined nivolumab and ipilimumab with ipilimumab alone in patients with *BRAF* wild-type melanoma” (EX1011 at 24), reporting that treatment involving combined nivolumab and ipilimumab resulted in “durable

responses” characterized by “substantially higher objective response rate, longer progression-free survival, and higher rates of complete responses than ipilimumab monotherapy.” EX1031 at 1-5.

251. Separately, with respect to the treatment of small cell lung cancer, Antonia (EX1052) reported an overall response rate of 15% for nivolumab alone and 25% for the combination of nivolumab and ipilimumab. EX1052.

252. Such clinical reports were consistent with preclinical data and related analysis indicating that anti-PD-1 and anti-CTLA-4 antibodies together had synergistic effects above and beyond those either antibody had individually. Indeed, Wolchok cited such preclinical data when explaining the rationale for conducting the above-discussed trial concerning “combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma.” EX1013 at 123 (“In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.”). Wolchok further stressed that “CTLA-4 and PD-1 appear to play *complementary roles* in regulating adaptive immunity.” EX1013 at 123.

253. For instance, Curran—one of the references cited by Wolchok in this discussion (reference 6 in EX1013 at 123)—reported that “in the context of Fvax vaccination, combination blockade of the CTLA-4 and PD-1 negative

costimulatory receptors leads to synergistic levels of tumor rejection.” EX1012 at 4278. Curran further observed that:

In clinical trials, antibodies that block CTLA-4 have shown efficacy in treating advanced melanoma and prostate cancer but at the price of autoimmune complications that are often severe. Human studies of α PD-1 and α PD-L1 antibodies are at a much earlier stage yet suggest that these agents may be efficacious while engendering fewer autoimmune complications (27). ***Our preclinical data in the B16 melanoma model strongly suggest that combining these agents may have synergistic effects in driving tumor rejection.*** Although combining multiple coinhibitory blocking antibodies in the clinic should be approached with great caution, our studies suggest that blocking a single inhibitory receptor only leads to up-regulation of the unblocked pathway. ***To allow tumor-infiltrating T cells the capacity to expand, kill, and produce inflammatory cytokines within the tumor micro- environment appears to require simultaneous blockade of multiple negative costimulatory receptors.***

EX1012 at 4279-4280 (emphasis added).

254. In addition, Duraiswamy (EX1053) reported a synergistic effect of anti-PD-1 and anti-CTLA-4 combination therapy had been reported specifically in a colon carcinoma mouse model. EX1053 at 3595. Specifically, Duraiswamy found that “[b]lockade of either PD-1 or CTLA-4 pathways enhanced effector T cell infiltration” into tumors, but that “simultaneous blockade of both pathways had synergistic effects in activation of tumor antigen specific CD8+ and CD4+

effector T cells.” EX1053 at 3599-3600. By increasing activation of effector T cells, the combination would have greater antitumor immune response. EX1053 at 3591 (“blocking of PD-1 and CTLA-4 can modulate Treg functions and enhance antitumor responses”).

255. Similarly, Callahan (EX1054) cited Curran when noting “[p]reclinical studies suggest[ing] that CTLA-4 and PD-1 or PD-L1-blocking antibodies may be combined to achieve superior antitumor activity.” EX1054 at 49 (citing Curran (reference no. 106). Callahan taught that CTLA-4 and PD-1 had “nonredundant functions,” thus “support[ing] the concept that combined blockade could have favorable clinical activity.” EX1054 at 49; *see also id.* at 41-42 (explaining that anti-PD-1 and anti-CTLA-4 antibodies each had “a nonredundant role in modulating immune responses,” such that “combined blockade of both [relevant] pathways may achieve superior antitumor activity”).

256. Relatedly, Callahan specifically mentioned “colorectal tumors” when noting instances in which “activity was seen” when combining CTLA-4 with other agents even though “CTLA-4 blockade was not active in the monotherapy setting.” EX1054 at 48. And while Callahan also noted one clinical trial of nivolumab (i.e., BMS-936559) in which no objective responses were seen in colorectal cancer patients (*id.*), a POSA would have been aware that subsequent reports from Lipson (EX1037 at 463-464) and Le (EX1008 at 2512-2515) indicating that anti-PD-1

antibodies—nivolumab in the case of Lipson and pembrolizumab in the case of Le—*were* effective in treating MSI-H colorectal cancers. For example, Lipson reports that nivolumab achieved a “[d]urable complete response in [MSI-H] colorectal cancer.” EX1037 at 463-464.

257. Callahan, Larkin, Wolchok, Postow, Antonia, Curran, and Duraiswamy likewise provide context for Xiao’s teaching that combinations of PD-1 with other checkpoints such as CTLA-4 would “likely follow” the two then-pending clinical trials (including that subsequently reported in Le) related to the use of “PD-1 blockade in patients with MSI colorectal cancer.” EX1010 at 18. As previously discussed in connection with Grounds 4-6, Xiao’s teaching would have motivated a POSA familiar with Le’s favorable results to treat MSI-H colorectal cancer patients with a combination of nivolumab and ipilimumab—including the particular dosages disclosed in Hammers. Given this existing literature, there was nothing surprising or unexpected about the ’529 Patent’s disclosed results.

258. I am aware that the ’529 Patent’s prosecution history (EX1002) includes a search report and related written opinion in which the European Patent Office suggested that:

[T]he particular combination of the therapeutic regime involving the combined administration of 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered according to the dosing schedule of the application to patients with metastatic colorectal cancer with high

microsatellite instability, appears to result in the surprising result of prolonged progression free survival compared to those patient[s] receiving nivolumab monotherapy which is considered to involve an inventive step according to Article 33(3) PCT.

EX1002 at 111. Relatedly, the opinion states that:

The subject-matter of [originally filed PCT] claims 8 to 15 differ from the prior art as the treatment of a subject afflicted with a tumor derived from a colorectal cancer, wherein the tumor exhibits a high degree of microsatellite instability (“MSI-H”) using an anti-PD-1 antibody (nivolumab) combined with the administration of an anti-CTLA-4 antibody (ipilimumab) is not disclosed in the state of the art.

The effect of said difference is shown in the description page 47, Figure 6 and Table 7, where 45.9% of patients receiving 3 mg/kg nivolumab monotherapy exhibited progression-free survival at 6 months, while **66.6% of patients receiving 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab exhibited progression-free survival at 6 months.**

Table 8 shows that 75.0% of patients receiving 3 mg/kg nivolumab monotherapy exhibited progression-free survival at 6 months, while **85.1% of patients receiving 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab exhibited progression-free survival at 6 months.** At 9 months, 65.6% of patients receiving 3 mg/kg nivolumab monotherapy exhibited progression-free survival, while **85.1% of patients receiving 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab exhibited progression free survival.**

EX1002 at 109.

259. However, there are multiple omissions and oversights that undermine this conclusion.

260. For one, the opinion neglects that the NCT-188 protocol (EX1005) expressly disclosed treating metastatic colorectal cancer with high microsatellite instability using a combination of 3 mg/kg nivolumab with 1 mg/kg ipilimumab administered according to the dosing schedule recited in the '529 Patent. Indeed, as discussed in connection with Ground 1 in Section IX.A.1 above, NCT-188 anticipates claims 1 and 4-14 of the '529 Patent.

261. While the opinion refers to NCT-188 (referenced as “D3”), it describes the study as merely concerning “a Phase 2 clinical trial investigating the treatment of the *anti-PD-1 antibody nivolumab* on patients with microsatellite unstable colorectal cancer.” EX1002 at 109. However, as discussed in Section IX.A.1, NCT-188 actually described treating microsatellite unstable colorectal cancer using a *combination* of the anti-PD-1 antibody nivolumab with the anti-CTLA antibody ipilimumab—including an arm involving dosages of 3 mg/kg nivolumab and 1 mg/kg ipilimumab. In view of the fact that the opinion appears to have overlooked NCT-188’s disclosure of combination therapy, I do not find the opinion’s conclusions about differences between NCT-188 and the PCT application’s disclosures to be persuasive. The opinion also neglected that NCT-

188 disclosed the exact combination of 3 mg/kg nivolumab and 1 mg/kg ipilimumab, as discussed in Ground 1. The corresponding result associated with administering the treatment set forth in NCT-188 was likewise predictable. Finally, as noted above, I understand that as a legal matter alleged unexpected results are irrelevant to anticipation.

262. Separately, as discussed above, numerous other prior art references—including Callahan, Larkin, Wolchok, Postow, Antonia, Curran, and Duraiswamy—taught that anti-PD-1 and anti-CTLA-4 antibodies had synergistic effects. Larkin, Wolchok, and Antonia likewise reported that the combination of anti-PD-1 and anti-CTLA-4 antibodies achieved better results than anti-PD-1 antibodies alone. For example, in connection with metastatic melanoma, Larkin reported that “the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher rate of response than did nivolumab alone.” EX1011 at 31. And while Larkin concerned metastatic melanoma, POSAs would have expected comparable results for MSI-H colorectal cancer, especially given the prior art’s promising clinical results—for example, in Lipson—for treatment of MSI-H colorectal cancer with nivolumab alone. *E.g.*, EX1037 at 463-464.

263. Thus, even setting aside NCT-188, there was nothing surprising or unexpected about the ’529 Patent specification’s report that the combination of 3

mg/kg nivolumab in combination with 1 mg/kg ipilimumab prolonged progression free survival of MSI-H colorectal cancer patients as compared to those patients receiving nivolumab monotherapy. Instead, such improved results are consistent with the many teachings in the prior art that anti-PD-1 and anti-CTLA-4 antibodies had synergistic effects. Relatedly, I note that the opinion and corresponding search report never reference Callahan, Larkin, Wolchok, Antonia, or Curran. EX1002 at 98-114. Furthermore, while the opinion briefly mentions Duraiswamy (referenced as “D8”) (EX1002 at 108) it never acknowledges Duraiswamy’s teaching that “simultaneous blockade of both [PD-1 or CTLA-4] pathways had synergistic effects” (EX1053 at 3600). Instead, the opinion merely references the “dual blockade,” without acknowledging the “synergistic effects” taught in Duraiswamy. EX1002 at 110.

264. Even aside from these multiple oversights, the opinion does not undertake any statistical analysis to establish the significance of the ostensible improvement in progression free survival times—notwithstanding the small sample sizes reflected in the cited table (i.e., Table 6) and figures (i.e., Figures 7 and 8). I recognize that the Larkin, Wolchok, and Antonia references (i.e., all disclosing improved results of combined anti-PD-1 and anti-CTLA-4 treatment as compared to anti-PD-1 monotherapy) likewise involve small sample sizes and note the desirability of follow-up analysis. The point, however, is that the data in the ’529

Patent is comparable to that in the prior art. It does not reflect surprising or unexpected results.

265. On the contrary, a POSA would have expected at least some level of improved efficacy in treating MSI-H colorectal cancer with a combination of anti-PD-1 and anti-CTLA-4 antibodies as compared to treatment using anti-PD-1 antibodies alone.

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: February 28, 2025

A handwritten signature in dark ink, appearing to be 'Arta Monir Monjaze', with a stylized, flowing script.

Arta Monir Monjaze, MD, PhD

CLAIM LISTING

Claim 1
1. A method of treating a subject afflicted with a tumor derived from a colorectal cancer, comprising
administering to the subject:
(i) an anti-PD-1 antibody, and
(ii) an anti-CTLA-4 antibody;
wherein the tumor is a colon cancer or a rectal cancer; and
wherein the tumor exhibits a high degree of microsatellite instability (MSI-H).
Claim 2
2. The method of claim 1, wherein the tumor exhibits one or more characteristics selected from the group consisting of:
(a) the tumor comprises a germline alteration in at least two DNA mismatch repair genes (MMR genes);
(b) the tumor comprises a germline alteration in at least 30% of five or more MMR genes;
(c) at least one protein encoded by DNA MMR genes is not detected in the tumor; and
(d) any combination thereof.
Claim 3
3. The method of claim 2, wherein the DNA MMR genes comprise MSH2, MLH1, MSH6, PMS2, PMS1, or any combination thereof.
Claim 4
4. The method of claim 1, wherein:
(i) the subject exhibits a progression-free survival of at least about one month after the administration, or
(ii) the subject exhibits an overall survival of at least about one month after the administration.
Claim 5
5. The method of claim 1, wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.
Claim 6

6. The method of claim 1, wherein the anti-CTLA-4 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.
Claim 7
7. The method of claim 1, wherein the anti-CTLA-4 antibody is ipilimumab or tremelimumab.
Claim 8
8. The method of claim 1, wherein the anti-PD-1 antibody is administered at a dose ranging from at least about 0.1 mg/kg to at least about 10.0 mg/kg body weight once about every 1, 2, 3, or 4 weeks.
Claim 9
9. The method of claim 1, wherein:
(i) the anti-PD-1 antibody is administered at a dose of about 1 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight;
(ii) the anti-PD-1 antibody is administered at a dose of about 1 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 3 mg/kg body weight;
(iii) the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight; or
(iv) the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 3 mg/kg body weight.
Claim 10
10. The method of claim 9, wherein the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.
Claim 11
11. The method of claim 1, wherein the anti-PD-1 antibody is administered at a dose of about 3 mg/kg body weight and the anti-CTLA-4 antibody is administered at a dose of about 1 mg/kg body weight once about every 3 weeks for a total of 12 weeks.
Claim 12

12. The method of claim 11, wherein the administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody is followed by an anti-PD-1 antibody monotherapy.
Claim 13
13. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered once about every 2 weeks.
Claim 14
14. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered at a dose of about 3 mg/kg once about every 2 weeks.
Claim 15
15. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered as a flat dose.
Claim 16
16. The method of claim 12, wherein the anti-PD-1 antibody monotherapy is administered at a flat dose of about 240 mg once about every 2 weeks.
Claim 17
17. The method of claim 16, wherein the anti-PD-1 antibody is nivolumab.
Claim 18
18. The method of claim 17, wherein the anti-CTLA-4 antibody is ipilimumab.

APPENDIX A - LISTING OF MATERIALS CONSIDERED

Exhibit	Description
1001	U.S. Patent No. 11,332,529 (“’529 Patent”)
1002	Prosecution History of U.S. Patent No. 11,332,529
1005	NCT02060188 Version 1, Brief Title: “A Study of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Colon Cancer (CheckMate 142)” (Last Update Posted to clinicaltrials.gov: February 11, 2014) (“NCT-188”)
1006	Zhang et al., Era of Universal Testing of Microsatellite Instability in Colorectal Cancer. <i>World J Gastrointest Oncol.</i> 2013 Feb 15;5(2):12-9. (“Zhang”)
1007	NCT01968109 Version 1, Brief Title: “Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors” (Last Update Posted to clinicaltrials.gov: October 23, 2013) (“NCT-109”)
1008	Le et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. <i>N Engl J Med.</i> 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30. (“Le”)
1009	Hammers et al., Expanded Cohort Results from CheckMate 016: A Phase I Study of Nivolumab in Combination with Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC). <i>J Clin Oncol.</i> , 33:15_suppl, May 20, 2015 (“Hammers”)
1010	Xiao et al., The Microsatellite Instable Subset of Colorectal Cancer Is a Particularly Good Candidate for Checkpoint Blockade Immunotherapy. <i>Cancer Discov.</i> 2015 Jan; 5(1):16-8. (“Xiao”)
1011	Larkin et al., Combined Nivolumab and Ipilimumab or Monotherapy in Previously Untreated Melanoma. <i>N Engl J Med.</i> 2015 Jul 2; 373(1):23-34. doi: 10.1056/NEJMoa1504030. Epub 2015 May 31. (“Larkin”)
1012	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 U S A.</i> 2010 Mar 2; 107(9):4275-80. (“Curran”)
1013	Wolchok et al., Nivolumab plus Ipilimumab in Advanced Melanoma. <i>N Engl J Med.</i> 2013 Jun 2; 369(2):122-33.
1014	Llosa et al., The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints., <i>Cancer Discov.</i> 2015 Jan; 5(1):43-51.doi: 10.1158/2159-8290.CD-14-0863. Epub 2014 Oct 30. (“Llosa”)

1015	National Cancer Institute, “Monotherapy,” in Dictionary of Cancer Terms, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/monotherapy
1018	U.S. National Library of Medicine, National Institutes of Health, ClinicalTrials.gov, Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary
1019	Affidavit of Nathaniel E. Frank-White with Exhibit A attaching online versions of Le (EX1008) dated June 2, 2015 and Larkin (EX1011) dated June 3, 2015.
1020	Raedler et al., Opdivo (Nivolumab): Second PD-1 Inhibitor Receives FDA Approval for Unresectable or Metastatic Melanoma. <i>Am Health Drug Benefits</i> . 2015 Mar; 8(Spec Feature):180-3. (“Raedler”)
1021	Lipson et al., Ipilimumab: An Anti-CTLA-4 Antibody. <i>Clin Cancer Res</i> . 2011 Nov 15; 17(22):6958-62. (“Lipson-2011”)
1022	Merriam-Webster Collegiate Dictionary, “Colorectal”
1023	National Cancer Institute, Dictionary of Cancer Terms, “overall survival”, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival
1024	Pawlik et al., “Colorectal Carcinogenesis: MSI-H versus MSI-L. <i>Dis Markers</i> . 2004; 20(4-5):199-206 (“Pawlik”)
1025	de’Angelis et al., Microsatellite Instability in Colorectal Cancer. <i>Acta Biomed</i> . 2018 Dec 17; 89(9-S):97-101. (“de’Angelis”)
1026	Lindor et al., Immunohistochemistry versus Microsatellite Instability Testing in Phenotyping Colorectal Tumors. <i>J Clin Oncol</i> . 2002 Feb 15; 20(4):1043-8. (“Lindor”)
1027	Boland et al., A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. <i>Cancer Res</i> . 1998 Nov 15; 58(22):5248-57. (“Boland”)
1028	Smyrk et al., Tumor-Infiltrating Lymphocytes Are a Marker for Microsatellite Instability in Colorectal Carcinoma. <i>Cancer</i> . 2001 Jun 15; 91(12):2417-22. (“Smyrk”)
1029	Mathijssen et al., Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults. <i>Oncologist</i> . 2007 Aug; 12(8):913-23. (“Mathijssen”)
1030	Wang et al., Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. <i>J Clin Pharmacol</i> . 2009 Sep; 49(9):1012-24. (“Wang”)

1031	Postow et al., Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma., <i>N Engl J Med.</i> 2015 May 21; 372(21):2006-17. (“Postow”)
1032	Le et al., <i>Supplementary Appendix 1</i> . PD-1 Blockade in Tumors with Mismatch-Repair Deficiency,” <i>N Engl J Med.</i> 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30
1034	van Eeghen et al., Impact of age and comorbidity on survival in colorectal cancer. <i>J Gastrointest Oncol.</i> 2015 Dec; 6(6):605-12. (“van Eeghen”)
1036	Merriam-Webster Medical Dictionary, “monotherapy”
1037	Lipson et al., Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody. <i>Clin Cancer Res.</i> 2013 Jan 15;19(2):462-8. (“Lipson-2013”)
1038	Pernot et al., Colorectal Cancer and Immunity: What We Know and Perspectives. <i>World J Gastroenterol.</i> 2014 Apr 14; 20(14):3738-50. (“Pernot”)
1039	de la Chapelle et al., Clinical Relevance of Microsatellite Instability in Colorectal Cancer. <i>J Clin Oncol.</i> 2010 Jul 10; 28(20):3380–3387. Chapelle”)
1040	Le et al., <i>Protocol</i> . PD-1 Blockade in Tumors with Mismatch-Repair Deficiency,” <i>N Engl J Med.</i> 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596. Epub 2015 May 30
1041	Feng et al., Model-based Clinical Pharmacology Profiling of Ipilimumab in Patients with Advanced Melanoma. <i>Br J Clin Pharmacol.</i> 2014 Jan 17; 78(1):106-17. (“Feng”)
1043	U.S. Patent Application Publication No. 2017/0158776A1
1044	U.S. Patent No. 8,008,449
1045	U.S. Patent No. 8,900,587
1046	U.S. Patent No. 6,984,720
1047	Kroemer et al., Colorectal Cancer: The First Neoplasia Found to be under Immunosurveillance and the Last One to Respond to Immunotherapy? <i>OncoImmunology.</i> 2015 Jun 5; 4(7):e1058597. (“Kroemer”)
1049	Topalian et al., Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. <i>N Engl J Med.</i> 2012 Jun 28; 366(26):2443-54. (“Topalian”)

1050	Brahmer et al., Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. <i>J Clin Oncology</i> . 2010 Jul 1; 28(19):3167–3175 (“Brahmer”)
1052	Antonia et al., Phase I/II Study of Nivolumab With or Without Ipilimumab for Treatment of Recurrent Small Cell Lung Cancer (SCLC): CA209-032., <i>J Clin Oncology</i> . 2015 May 20; 33(15S) (“Antonia”)
1053	Duraismamy et al., Dual blockade of PD-1 and CTLA-4 Combined With Tumor Vaccine Effectively Restores T cell Rejection Function in Tumors. <i>Cancer Res</i> . 2013 Jun 15; 73(12):3591-603. (“Duraismamy”)
1054	Callahan et al., At the Bedside: CTLA-4- and PD-1-Blocking Antibodies in Cancer Immunotherapy. <i>J Leukoc Biol</i> . 2013 Jul; 94(1): 41–53. (“Callahan”)
1055	Bai et al., A Guide to Rational Dosing of Monoclonal Antibodies. <i>Clin Pharmacokinet</i> . 2012 Feb 1; 51(2):119-35. (“Bai”)
1057	Monjazebe et al., A Randomized Trial of Combined PD-L1 and CTLA-4 Inhibition with Targeted Low-Dose or Hypofractionated Radiation for Patients with Metastatic Colorectal Cancer. <i>Clin Cancer Res</i> . 2021 May 1; 27(9):2470–2480. (“Monjazebe”)
1066	Barbee et al., Current Status and Future Directions of the Immune Checkpoint Inhibitors Ipilimumab, Pembrolizumab, and Nivolumab in Oncology. <i>Annals of Pharmacotherapy</i> . 2015, 49(8):907–937. (“Barbee”)