

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ZYDUS PHARMACEUTICALS (USA) INC., ZYDUS LIFESCIENCES
LIMITED, ZYDUS LIFESCIENCES GLOBAL FZE, AND FORMYCON AG,

Petitioner

v.

MERCK SHARP & DOHME LLC and AGILENT TECHNOLOGIES, INC.,
Patent Owner

PGR2027-00003

Patent No. 12,529,702

Title: SCORING METHODS FOR ANTI-PD THERAPY ELIGIBILITY AND
COMPOSITIONS FOR PERFORMING SAME

**DECLARATION OF JONATHAN BRAUN, M.D., Ph.D.,
IN SUPPORT OF ZYDUS'S PETITION FOR
POST-GRANT REVIEW OF U.S. PATENT NO. 12,529,702**

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I, Jonathan Braun, declare and state as follows:

I. INTRODUCTION AND SUMMARY

1. I have been retained by Zydus Pharmaceuticals (USA) Inc., Zydus Lifesciences Limited, Zydus Lifesciences Global FZE, and Formycon AG (collectively “Petitioner”) as a technical expert in connection with the above-identified proceeding. I have been asked to provide my opinions regarding whether claims 1-21 of U.S. Patent No. 12,529,702 (“*US702*”, EX1001) are invalid (a) for covering patent ineligible subject matter under 35 U.S.C. §101, (b) for failing to enable the full scope of the claimed subject matter under 35 U.S.C. §112, and (c) because they would have been obvious to a person of ordinary skill in the art (“*POSA*”) under 35 U.S.C. §103.

2. *US702* relates to a method of using a diagnostic score to determine whether a subject with a malignancy is eligible for treatment with an anti-PD therapeutic agent.

3. I understand that my declaration will be submitted in support of Petitioner’s Petition for Post-Grant Review of *US702*, against Merck Sharpe & Dohme LLC and Agilent Technologies, Inc. (collectively, “Merck” or “Patent Owner”).

4. My opinions in this declaration are based on my review of *US702*, the relevant prior art that I have identified and of which I have been informed, other

documents referred to in this declaration, and my many years of experience as a histopathologist and evaluating histopathological and predictive methodologies, including during the relevant time period for the questions I have been asked to consider. I also served as co-investigator of Diversity and Determinants of the Immune-Inflammatory Response to SARS-CoV-2 (U54 CA260591), a 15,000 subject clinical trial in which I led the clinical trial's histopathologic and predictive methodology studies (corresponding to those relevant to *US702*). The opinions I offer are made to a reasonable degree of scientific certainty.

5. Petitioner retained me through IMS Legal Strategies at a consulting rate of \$1005 per hour. I am also being reimbursed for reasonable travel expenses related to my consultation. I do not have a personal or financial interest in the outcome of this proceeding, nor is my compensation affected by its outcome.

II. BACKGROUND AND QUALIFICATIONS

6. My qualifications as an expert in this field are established by my curriculum vitae (EX1003) and the experience and publications cited therein.

7. I have been an Emeritus Professor at the University of California, Los Angeles (UCLA) since 2019. I was a Professor and Enterprise Operations Director, IBDI, at Cedars Sinai Medical Center from 2019 to 2024, and before that, a Professor and Chair of Pathology and Laboratory Medicine at the UCLA David Geffen School of Medicine in Los Angeles, California from 1994 to 2018. In

addition, I served from 1991 to 2018 as the Co-Director and Director of the Tumor Immunology Program for the UCLA Jonsson Comprehensive Cancer Center.

8. I received my undergraduate degree from Stanford University in 1975. I earned my Ph.D. (Immunology) and M.D. from Harvard University and Harvard Medical School in 1980 and 1981. I completed a pathology residency at Brigham and Women's Hospital of Boston and Harvard Medical School between 1981 and 1985. Concurrently, I completed postdoctoral studies in molecular biology (with David Baltimore) at Massachusetts Institute of Technology and the Whitehead Institute in 1984 and 1985.

9. I joined the faculty of the Department of Pathology and Laboratory Medicine at the UCLA School of Medicine in 1985, and was appointed permanent Department Chair and full professor in 1995, positions I held until 2018. During this period, I also served in a joint appointment with the UCLA Department of Molecular and Medical Pharmacology (2006-2015), and as the Co-Director to Director (Assistant Vice Chancellor) of the UCLA Clinical and Translational Sciences Institute.

10. I have devoted my career to academic clinical practice and scientific research. My clinical practice includes my roles as clinical service chief and executive leadership of Pathology and Clinical Laboratory services of the UCLA Health System. During my 23 years as service chief and in executive leadership,

these services were the largest in the Western United States, with an ongoing medical staff of more than 100 pathologists and laboratory medicine clinicians under my direction. These services annually performed over 150,000 clinical cases involving histopathologic analysis, of which over 100,000 were cancer diagnosis and analysis for treatment planning, regularly including PD-L1 assessment by histopathology and predictive analysis.

11. My research concerns the immunology and microbiome biology of chronic inflammatory disease and cancer. My reports on this research include 530 articles and chapters, of which 228 were peer-reviewed scientific studies. My studies devoted to histopathology and predictive methodologies included seventeen for endometrial or ovarian adenocarcinoma (for example, Kiyohara, *Oncogene*. 2017 Oct 19;36(42):5793-5807); thirteen for colonic adenocarcinoma (for example, Bergstrom *Gastroenterology* 2016. 151:152-64; Bergstrom 2020. *Science* Oct 23;370(6515):467-72); thirteen for lymphoma or leukemia (for example, de Vos, *Lab Invest*. 2003 Feb;83(2):271-85); four for breast adenocarcinoma (for example, Fu, *Mol Cancer Ther*. 2014 Apr;13(4):902-15); two for melanoma (for example, Moriceau, *Cancer Cell*. 2015. Feb 9; 27(2):240-56); two for glioblastoma (for example, Fu, *J Biol Chem*. 2014 May 16; 289(20):13974-85); and two for directed PD-L1 manipulation (for example, *PLoS One*. 2012. 7(4):e32588).

12. I have also earned numerous professional awards and honors in the field of immunology. For instance, in 2001, I was appointed Fellow of the American Association for the Advancement of Science; in 2009, I served as President of the Federation of Clinical Immunology Societies; and in 2008, I served as President of the Clinical Immunology Society. In 2016, I was selected to give the annual Georgia Health Sciences University Presidential Lecture on immunity and cancer. In 2018, I was selected for three of the outstanding national honors for intellectual achievement and leadership in pathology, based on my work on immunity and cancer. These were the annual James Kangos Lecture at UPMC, the annual Ramzi Cotran Lecture at Brigham and Women's Hospital, and the Charles M. Mansbach, II, MD, Memorial Lecture for the American Gastroenterological Association.

13. Among my many professional memberships are the American Association of Immunologists, American Society of Investigative Pathology, Clinical Immunology Society, Association for Pathology Chairs, College of American Pathologists, and Association for Pathology Informatics. Of my memberships, these are particularly pertinent because (a) they include the professional peer groups involved in scientific development, scientific and clinical validation, and clinical use of PD-L1 assessment in cancer and (b) they are

memberships conferred only by *merit and election* by national or international professional peers in these societies.

14. Throughout my career, I have continually served as a member of advisory committees and study sections for organizations that play leading national roles in the prioritization and funding of research for immunology and cancer research and clinical innovation. Among them are my grant review committee roles for the NIH, including service on 28 study sections spanning from 1987 to 2024. I have also served as a member of the following study sections: REP Chair, Cooperative Prostate Cancer Tissue Resource (CPCTR) (2001-2004); Co-chair, Digestive Diseases and Nutrition C Subcommittee (2008-2013); NIH Director's Opportunity in Immunology (2010); Chair, Immune Defense Mechanisms at the Mucosa (2011); NIH Director's New Innovator Award (2012); Development, Differentiation, Modulation of Immune Responses (2014); Cellular and Molecular Immunology B (2015, 2016); and Board of Scientific Counselors, NIAID Division of Intramural Research (2019).

15. I have served on many editorial boards of leading scientific and medical journals, including the following two that publish research studies concerning immune mechanisms and therapeutic utility of immune targets for cancer (including PD-L1): Clinical Immunology (section editor, 2001-2010;

editorial board, 2011-2014) and Gastroenterology (associate editor, 2008-2016). I note that Gastroenterology is the world's leading journal for gastroenterology.

16. My UCLA advisory board roles for cancer translational and clinical research funding included the UCLA Jonsson Comprehensive Cancer Center Seed Grant Committee (1995-2016; 2010-2016 as Chair), and the UCLA Genitourinary Cancer SPORE Internal Advisory Board (2002-2021).

17. My research has been continually funded from 1986 to 2024 by the NIH, as well as many other organizations. With regard to the topics of *US702*, I highlight these research projects: Tumor Immunology Program (NCI Comprehensive Cancer Center Core Grant, 2009-2019); Immune mechanisms of pathogenesis and protection for Crohn's disease and risk of adenocarcinoma (1991-2015); Role of Intestinal O-glycans in intestinal inflammation and colonic adenocarcinoma (2010-2024); Mechanisms of intestinal inflammation-associated systemic genotoxicity, (NIH/NIAID 2005-2010); The UCLA Center for In Vivo Imaging in Cancer Biology (NIH/NCI 2001-2003, 2005-2010); Index and retrieval of pathology specimens (Shared Pathology Informatics Network (NIH/NCI 2001-2006); Identification of genes affecting host-tumor interaction in B cell lymphoma (NIH/NCI 1986-1999); Targeting EMP2 for endometrial adenocarcinoma immunotherapy, Jonsson Comprehensive Cancer Center (2007-2009); and Scholar award, Blood Cancer United (1986-1991).

18. I am a named inventor on 24 issued U.S. and foreign patents, including the following: U.S. Patent No. 9,110,064 (Methods for Diagnosis and Treatment of Endometrial Cancer); U.S. Patent No. 9,624,304 (Antibodies Which Bind Epithelial Membrane Protein 2 (EMP2)); and U.S. Patent No. 11,053,310 (Antibodies for the Treatment of Cancers).

III. LEGAL BACKGROUND

19. I do not hold any legal qualifications; however, Petitioner's counsel has informed me of a number of legal principles to consider when formulating my opinions relating to the validity of *US702*. These principles are set forth below.

A. Claim Construction

20. I understand that in post-grant review ("PGR") proceedings, the terms in a patent claim are generally given their ordinary and customary meaning as understood by a POSA in the context of the entire patent disclosure. If, however, an inventor defines a claim term in the patent disclosure, then the inventor's definition applies. If the inventor chooses to define a claim term, however, the inventor must do so with reasonable clarity, deliberateness, and precision.

21. I further understand that claims can be "independent" or "dependent." An independent claim does not refer to or incorporate the elements of any other claim. A dependent claim refers to another claim and includes all of its limitations,

while also adding additional limitation(s). *US702* has one independent claim, claim 1, with the remaining claims depending directly or indirectly on claim 1.

B. Burden of Proof

22. I understand that in a PGR, a claim is not patentable if a “preponderance of the evidence” establishes that the claim is invalid.

23. I understand that “a preponderance of the evidence” means “more likely than not.”

C. Prior Art and Earliest Possible Effective Filing Date

24. I was asked to assume that the earliest possible effective filing date of *US702* is April 1, 2016. I have been asked to assume that any printed publication published prior to April 1, 2016 (*i.e.*, what I have been asked to assume is the earliest possible effective filing date for these patents) should be considered “prior art.”

25. I further understand that a document is considered a “printed publication” if it was published or otherwise made available such that a POSA exercising reasonable diligence could have located it.

D. Patent Eligible Subject Matter

26. I have been informed that laws of nature, natural phenomena, abstract ideas, and mental steps are not patentable under the Patent Act, 35 U.S.C. §101, which is referred to as Section 101. I have also been informed that a two-step approach can be used to resolve questions relating to what is or is not patent-

eligible subject matter. The first step is to determine whether the claim at issue is directed to a “patent-ineligible concept,” such as a law of nature, abstract idea, or mental step. If the claim is directed to a “patent-ineligible concept,” the second step is to identify “what else” is claimed so as to determine whether the claim provides an inventive concept that amounts to significantly more than the patent-ineligible concept. If a claim does not provide such an inventive concept, then it is invalid under Section 101.

27. I have been informed that a law of nature refers to universal truths and natural forces that exist in the world, like a natural correlation that exists independently of human action. As an example, I have been informed that the relationship between a patient’s physical state, such as the concentration of a metabolite in a patient’s blood, and drug efficacy or the likelihood that a drug will prove ineffective or cause harm, is a law of nature.

28. I have been informed that an idea, in and of itself, is not patentable, and understand that an abstract idea is a concept that has no reference to material objects or specific examples. In other words, it is not concrete.

29. I have been informed that mathematical principles, formulas, or calculations are generally viewed as abstract ideas and claims directed to them are not patent eligible.

30. I have been informed that a mental step is a step that can be conducted in the mind of an individual. I have also been informed that a doctor determining a treatment for a patient is an example of a mental step.

31. I have been informed that the addition of well understood, routine, or conventional subject matter or activities are not enough to supply an inventive concept that transforms patent-ineligible subject matter into a patentable invention.

E. Obviousness

32. I have been informed by counsel that, for a patent claim to be patentable, it must be “non-obvious” over the prior art.

33. I understand that a patent claim is obvious if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. For purposes of my analysis, I have been asked to assume a date of invention of April 1, 2016, for *US702*.

34. I understand that when assessing whether a claim is obvious, I should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between what is claimed and the prior art; and (4) any evidence of “secondary considerations” that may indicate that the claims are not obvious.

35. I understand that a claimed invention may be obvious when, for example, there is some teaching, suggestion, or motivation that would have led a POSA to modify a prior art reference or to combine prior art teachings to arrive at the claimed invention.

36. I also understand that in combining or modifying prior art references to arrive at the claimed invention, the POSA must have a reasonable expectation of success, given their general knowledge and what has been disclosed in the prior art. I understand that this success need only be reasonably expected and does not need to be guaranteed or proven.

37. I understand further that if a member of a genus, that is, a species, is obvious, then the genus is also obvious.

38. I have been informed that if a claim recites selecting an element from a listed group of elements, such as selecting a therapeutic agent from a listed group of therapeutic agents, then if the prior art renders the claim obvious for any single listed element, the claim is rendered obvious. Put another way, I have been informed that if the claim would be obvious with respect to only one listed element, then the claim as a whole is rendered obvious.

39. I understand that evidence of “secondary considerations” may weigh against a finding that a claimed invention would have been obvious. Such secondary evidence may include: (1) commercial success of a product due to the

merits of what is provided in the patent claim; (2) a long-felt but unsolved need for the solution provided by the patent claim; (3) unsuccessful attempts by others to find the solution provided; or (4) unexpected results of the claimed invention compared to the closest prior art. I understand such “secondary considerations” of non-obviousness must have a “nexus” to the claimed invention over what was known in the prior art.

F. Enablement

40. I have been informed that a patent must enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation, and that this is known as the enablement requirement.

41. I also understand that the enablement requirement is met only when a POSA, after reading the patent specification, could make and use/practice the claimed invention without undue experimentation.

42. I have been informed that a claimed invention is not enabled if the specification does not teach those of ordinary skill in the art how to make and use the full scope of the invention without undue experimentation.

43. I have been informed that the full scope of the claimed invention must be enabled, meaning that the specification must teach a POSA how to make and use the claimed invention as broadly as it is claimed.

44. I have been informed that the assessment of undue experimentation is based on the state of the art as of the earliest effective filing date of *US702*.

45. I also understand that one can assess whether undue experimentation is required based on the following nonexclusive list of factors that are known as the *Wands* factors: (1) the breadth of the claims; (2) the amount of direction or guidance presented in the disclosure; (3) the presence or absence of working examples in the disclosure; (4) the nature of the invention; (5) the predictability or unpredictability of the art; (6) the state of the prior art; (7) the relative skill of those in the art; and (8) the quantity of experimentation necessary. I have also been informed that the enablement analysis is case-specific and fact-specific, and that all eight factors need not be analyzed in every case.

46. I have been informed that a “working” example is an example that reports work that was actually performed or experiments that were conducted and yielded actual results, and that a “prophetic” example is an example that describes predicted experimental results. I have also been informed that when describing a “working” example, the past tense is used, and that when describing a “prophetic” example, the present or future tense is used.

47. I have been informed that to determine whether there is a reasonable correlation between the scope of the claims and the scope of enablement, the degree of predictability of the relevant art needs to be considered. I have been

informed that chemical and physiological inventions, unlike mechanical and electrical inventions, are often considered “unpredictable” arts because a slight variation can yield an unpredictable result or may not function at all.

48. I have been informed that in unpredictable arts, there must be some quantum of data or reasoning that supports the inventor’s contention that a therapy operates as claimed, and that while every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

49. I have been informed that the specification need not teach what is well known in the art.

50. I have been informed that the determination of non-enablement must be based on the evidence as a whole.

G. The POSA

51. I understand that claim construction, patent eligible subject matter, obviousness, and enablement must be judged from the perspective of the POSA to which the patent is directed. I understand that the POSA is a hypothetical person that is presumed to have knowledge of all of the relevant prior art.

52. I understand that in determining who a POSA is, the following may be considered: (1) the educational level of the inventor(s); (2) the type of problems

encountered in the relevant technical field; (3) prior-art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field.

53. *US702* concerns methods of using a diagnostic score to determine whether a subject with a malignancy is eligible for treatment with an anti-PD therapeutic agent. Based on my extensive experience in histology, oncology, and the PD-1/PD-L1 axis specifically, I believe the POSA would have been a medical doctor and/or clinical researcher with an M.D and/or Ph.D. and would have had significant experience in one or more of the fields of histology, immunohistochemistry, and oncology. The POSA also would have collaborated with others having such education and/or experience, including scientists skilled in related fields, such as pathology, molecular biology, and immunology.

54. Even if a different definition of POSA is adopted, that POSA would have had access to individuals skilled in histology, immunohistochemistry, oncology, and immunology.

IV. SCIENTIFIC BACKGROUND

55. *US702* concerns methods of using a diagnostic score based on semi-quantification of PD-L1⁺ cells to determine the eligibility of a subject with a malignancy (cancer) for treatment with an anti-PD therapeutic agent. As discussed below, by the earliest possible effective filing date, (a) anti-PD therapies were

approved for cancer treatment; (b) researchers were already evaluating PD-L1⁺ cells, particularly tumor cells and mononuclear inflammatory cells in the tumor microenvironment (MICs) as a means for predicting whether a patient would benefit from anti-PD therapy; and (c) techniques for quantifying PD-L1⁺ cells were routine and conventional and had been used for decades.

A. Anti-PD Therapy, a Form of Immunotherapy that Targets the PD-1/PD-L1 Axis, Was Being Used for Cancer Treatment at the Time of Invention

1. Cancer and Immunotherapy

56. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

57. Cancer can occur almost anywhere in the body. When cancer cells grow and multiply, they can form lumps of tissue called tumors. Some cancers, such as cancers of the blood, do not form solid tumors.

58. Cancer cells arise from alterations in cells that may change DNA sequences or how genes are expressed. EX1017, 563. The accumulated alterations distinguish cancer cells from normal cells and can allow the immune system to recognize the cancer cells as foreign. EX1017, 563. However, as explained below, many cancer cells express proteins that suppress the cancer-killing action of the immune system.

59. Over time, cancer treatments have moved from blunt, non-specific, and systemic approaches, like hormone therapy, radiation, and chemotherapy, to more precise and targeted therapies. For example, in 1998, the U.S. Food and Drug Administration (“FDA”) approved trastuzumab, a monoclonal antibody that blocks the HER-2 protein associated with the growth of some breast cancers.

EX1026.

60. Beginning in the 1980s, scientists began learning more about how the immune system fights cancer. This research led to the development of immunotherapies, which generally work with the body’s immune system to fight disease. For cancer, immunotherapy helps the immune system find and attack cancer cells by stimulating or boosting the immune system or allowing it to better recognize cancer cells. Interferon-alpha was an early immunotherapy that slowed the growth of cancer cells. EX1028, 735.

2. Use of Immunotherapy To Target the PD-1/PD-L1 Immune Checkpoints Had Been Extensively Studied

61. By 2016, checkpoint inhibitors, another type of immunotherapy, were being used to treat cancer.

62. Cytotoxic T-cells typically identify and destroy abnormal cells, including cancer cells. The immune system has “checkpoints” to help prevent T-cells from attacking healthy cells. These checkpoints act through proteins on the surface of cytotoxic T-cells that, when bound to partner proteins on another cell,

send an “off” signal to the T-cell, preventing it from destroying the cell to which it is bound. EX1077, 252.

63. Some cancer cells express partner proteins that can bind to checkpoint proteins on the surface of T-cells and send the “off” signal, thereby preventing the T-cell/immune system from killing the cancer cell. *Id.*

64. Checkpoint inhibitors can bind to a checkpoint protein on the T-cell or its partner protein on the cancer cell, preventing binding of the two proteins. Doing so prevents the “off” signal and allows the T-cells to continue killing cancer cells. *Id.*

65. One immune checkpoint that was extensively studied was the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis, knowledge of which led to developing anti-PD therapies that target the checkpoint protein PD-1 or its partner protein PD-L1.

66. As *Herbst* explained, PD-L1, also called B7-H1 or CD274, is expressed on many cancer and immune cells and “plays an important part in blocking the ‘cancer immunity cycle’ by binding programmed death-1 (PD-1) and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation [the immune system]. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators, and restricts tumour cell killing.” EX1017, 563 (citations omitted); *see also* EX1056, 848 (“Tumor

cells have co-opted this PD-1/PD-L1 regulatory mechanism, designed to protect normal mucosa from autoimmune attack, and instead overexpress PD-L1 to avoid immunologic surveillance to facilitate cancer growth.”).

67. As of 2016, the goal of blocking the PD-L1/PD-1 axis with anti-PD therapeutics was to enhance or reinvigorate the immune system’s anti-cancer activity in patients whose tumor cells expressed PD-L1. EX1017, 563. In fact, as discussed further below, it was known that PD-L1 expression in some tumor cells correlated to a patient’s response to an anti-PD therapy. *See, e.g.*, Paragraphs 102-10.

3. By 2016, Anti-PD Therapies Pembrolizumab and Nivolumab Were Approved and Others Were Being Developed

68. The knowledge of the role of the PD-1/PD-L1 axis/checkpoint with respect to blocking the immune response, and that targeting PD-1 would block interaction of PD-1 and PD-L1, led to the development of multiple anti-PD therapies/checkpoint inhibitors, such as pembrolizumab, nivolumab, and others. Further details regarding pembrolizumab and nivolumab, both approved before the earliest possible effective filing date, are below. *See* Paragraphs 69-75.

69. **Pembrolizumab:** In September 2014, pembrolizumab (brand name Keytruda and previously known as MK-3475 and lambrolizumab), became the first approved PD-1 inhibitor when the FDA approved it for treating patients with

advanced or unresectable melanoma. EX1030, 96. Keytruda was indicated “for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.” EX1019, 1. Pembrolizumab “was approved under the accelerated approval program based on surrogate end points of confirmed overall response rate (ORR) and duration of response.” EX1030, 96.

70. Pembrolizumab is “a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.” EX1019, 9-10. *Keytruda 2014PI* further states: “In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.” *Id.*

71. The 2014 label for Keytruda (pembrolizumab) described the mechanism of action of pembrolizumab, which targets PD-1, as follows:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

EX1019, 9-10.

72. **Nivolumab:** Nivolumab (brand name Opdivo) is another PD-1 inhibitor. In December 2014, FDA approved nivolumab “for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.” EX1020, 1, 2; EX1021.

73. Nivolumab is “a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.” EX1020, 12-13.

74. Nivolumab, like pembrolizumab, received accelerated approval for unresectable or metastatic melanoma. EX1021.

75. The 2014 label for Opdivo described the mechanism of action of nivolumab as follows:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

EX1020, 12-13.

76. Other anti-PD therapies, such as Roche's MPDL3280A, were also being developed. MPDL3280A is a high-affinity human monoclonal immunoglobulin-G1 (IgG1) antibody that specifically binds to PD-L1. EX1017, 563.

77. *Herbst* reported administering MPDL3280A to subjects with non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma and other tumors (including colorectal cancer, gastric cancer, and head and neck squamous cell carcinoma). *Id.*

78. *Herbst* found an association between response and the expression of PD-L1 in pretreatment samples. The association of response to PD-L1 expression in tumor-infiltrating immune cells was statistically significant, while the association of response to PD-L1 expression in tumor cells was not. EX1017, 564-65.

B. It Was Known that PD-L1 Expression in Tumor Cells and MICs Could Impact Patient Response and Could Be Used To Identify Patients Who Might Benefit Most from Anti-PD Therapy

1. It Was Known that Tumor Cells Expression of PD-L1 Could Downregulate Immune Response

79. Many prior art studies had shown that tumor cells expressing PD-L1 could block immune response. For example, *Gadiot* reported that "tumor cell-expressed PD-L1 can induce inhibition or apoptosis of tumor-specific T cells." EX1014, 2193. *Topalian* reported that, of 25 patients whose tumor cells expressed

PD-L1, “9 (36%) had an objective response [to anti-PD therapy]” and that “[n]one of the 17 patients with PD-L1-negative tumors had an objective response.”

EX1042, 2449-50. *Muenst 2014* reported that in breast cancer cases, tumor cell expression of PD-L1 resulted in significantly worse overall survival and that when adjusted for age, grade, tumor size, lymph node status, and intrinsic subtype, the expression of PD-L1 was an independent negative prognostic factor for overall survival. EX1016, 19-20.

80. As explained below, it was also known that the local tumor microenvironment, including tumor cells and tumor infiltrating immune cells and the surrounding stroma, were key sites for assessing PD-L1 expression to predict clinical response to anti-PD therapies. *See* Paragraphs 81-90.

2. It Was Known that PD-L1 Expression in Immune Cell Infiltrates Could Also Suppress Immune Response

81. It was known in the prior art that PD-L1 expression in immune cell infiltrates called mononuclear inflammatory cells (MICs), like PD-L1 expression on tumor cells, could suppress the immune response against cancer cells. EX1058, 1327; EX1013, 7. MICs could be found in the tumor nest (an aggregation of tumor cells without intervening stroma or non-malignant cells) or in the adjacent supporting stroma (the connective tissue and extracellular framework surrounding and supporting the tumor). EX1060, 229.

82. As used in the prior art (and *US702*), mononuclear inflammatory cells refer to hemopoietic-derived cells with a morphologically single nucleus (“mononuclear”) that participate in immune and inflammatory responses. MICs include monocytes, macrophages, dendritic cells, and lymphocytes that have infiltrated body tissues in response to a range of diseases including cancer. EX1069, 656; EX1013, 3; EX1060, 229.

83. The prior art used various terms when referring to MICs. For example, as explained above, *Taube 2012* taught quantification of infiltrating host inflammatory cells, including tumor infiltrating lymphocytes (TILs) and associated macrophages/histiocytes. EX1013, 3. The term “infiltrating lymphocytes,” such as used in *Thompson* (EX1032), is simply an abbreviated term for TILs because “infiltrating” pertains to tumor infiltration.

84. TILs and macrophages are typically in close microscopic association when found in tumor and tumor stroma. In addition to this close association, they often overlap in H&E morphology and PD-L1 staining. For example, *Savas* taught that “[b]oth stromal and intratumoural TILs comprise a complex mixture of different lymphocyte subtypes, dominated by T cells, with lesser proportions of B cells, NK cells and macrophages.” EX1060, 229. And *Taube 2012* stated: “Membranous B7-H1 expression was also observed in the TILs and associated macrophages.” EX1013, 4.

85. Other published reports quantitating MICs also use terms reflecting this overlap of lymphocytes and macrophages, such as “tumor-infiltrating immune cells”/TIICs (EX1027, 5066; EX1031, 987), or “tumor infiltrating mononuclear cells”/TIMCs (EX1023, 812).

3. It Was Understood That PD-L1 Negative MICs Played an Important Role in the Immune Response

86. It was also known that the presence of MICs, including PD-L1 negative (PD-L1⁻) immune cells, often correlated with better overall response. For example, *Tumeh* reported the following:

T-cell infiltrates have been found to have predictive value with respect to the natural history of primary cancers. We build on this and report that the baseline density and location of T cells in metastatic melanomas have predictive value in the treatment outcome of patients receiving therapies that block the PD-1/PD-L1 axis. Releasing the PD-1 immune checkpoint results in clinically relevant antitumour activity when there is a greater density of pre-existing tumour-antigen-restricted CD8⁺ T cells that are negatively regulated by PD-1/PD-L1 interactions.

EX1033, 571 (footnotes omitted).

87. Other references taught that in breast cancer patients, TILs/MICs were more often seen in hormone receptor negative tumors and were linked with longer event-free survival. EX1067, e29288-1; EX1066, 989.

88. *Lu* taught that “frequencies of T-bet⁺ and CD8⁺ lymphocytes within tumor tissues are positively associated with cancer patient survival” in esophageal and gastric cancer tissues. EX1034, 270.

89. *Santojemima* taught that, in general, PD-L1⁺ tumor infiltrating immune cells can help fight cancer. EX1035, 807 (“The accumulation of tumor infiltrating lymphocytes in ovarian cancer is prognostic for increased survival”).

90. The prior art also taught that PD-L1 expression in tumors is associated with increased levels of MICs and better outcomes in a variety of cancers, including lung cancer, colon carcinoma, and melanoma. EX1067, e29288-1.

4. Quantification of PD-L1 Positive Tumor Cells and MICs Was Routine and Conventional

91. Because it was known that PD-L1 positive (PD-L1⁺) tumor cells and MICs could suppress the immune response, researchers quantified the level of PD-L1 expression in tumor cells and/or infiltrating immune cells.

92. For example, *Taube 2012* describes evaluating PD-L1 expression using immunohistochemistry (“IHC”) in tumor cells and in tumor-infiltrating immune cells including lymphocytes (“TILs”), using human tissue samples from melanocytic lesions. EX1013, 2 (“Here, we used immunohistochemistry (IHC) with a specific mAb to human B7-H1 [PD-L1] to examine patterns of membranous B7-H1 expression by both melanocytes/melanoma cells and TILs in 150 melanocytic lesions...”). I discuss IHC further below. *See* Paragraphs 97-99.

93. *Taube 2012* taught the quantification of PD-L1 expression in tumor cells, stating that “[p]ercentages of tumor cells exhibiting a membranous staining pattern for B7-H1 [PD-L1] were independently quantified as <5%, 5 to 9%, and

then in 10% increments.” EX1013, 8. *Taube 2012* categorized lesions in which at least 5% of tumor cells exhibited PD-L1 expression in IHC as PD-L1⁺. EX1013, 3 (“the degree of B7-H1 cell surface (membranous) expression based on IHC... positive $\geq 5\%$.”).

94. *Taube 2012* also taught quantifying PD-L1 expression in tumor immune cell infiltrates, including MICs such as lymphocytes and macrophages. EX1013, 3. *Taube 2012* employed an adjusted inflammation score (AIS) defined as the intensity of intratumoral inflammation multiplied by the percent of inflammatory cells expressing B7-H1 (PD-L1). EX1013, 8 (“The intensity of the infiltrate was graded as none (0), mild (score of 1, rare lymphocytes), moderate (2, focal infiltration of tumor by lymphohistiocytic aggregates), or severe (3, diffuse infiltration”); *see also id.*, 3-4.

C. By 2016, Companion Diagnostics Using PD-L1 Expression To Identify Candidates for Anti-PD Therapy Were Routinely Used

95. The knowledge that binding of PD-L1 to PD-1 could negatively regulate T-cell activation led to the hypothesis that “[b]locking PD-L1 should... enhance anti-cancer immunity” and prompted investigation into whether PD-L1 expression could predict which patients may benefit anti- PD-1 therapy. EX1017, 563.

96. As summarized in Table 3 of *González-Cao*, by 2015 there was extensive investigation of the correlation between PD-L1 expression by IHC

analysis and antitumoral activity. Those studies included the anti-PD therapies pembrolizumab, nivolumab, and MPDL3280 (all discussed below), a variety of IHC antibodies, and PD-L1 positivity thresholds of 1%, 5%, and 50%. EX1062, 63 (Table 3); *see also* EX1031, Table 1.

1. IHC and Biomarker Assays for Cancer Diagnosis and Treatment Predictions Were Routinely Used

97. By 2016, IHC had been used for decades to assay for biological markers (“biomarkers”) with the results used to diagnose and predict treatment response. EX1012, 15. Use of flow cytometry and single cell sequencing was also well known and conventional. EX1012, 87, 119; EX1060, 229, Box 1.

98. The first IHC techniques were developed in the 1940s, when scientists bound labeled antibodies to specific biomarkers in actual slices of tissue. EX1012, 13. The development of monoclonal antibodies facilitated the more routine use of IHC to analyze blocks of tissue, not just urine or blood samples, for biomarkers for the research and diagnosis of cancer. *Id.* After that, while standardization of IHC improved, the advances were considered incremental, “with little impact on the basics of the method.” *Id.*, 14. By 2016, IHC had “widespread use as an important method in routine cancer diagnosis.” *Id.*, 13. As an example, in 1998, an FDA approved IHC based companion diagnostic for HER2 was launched. *Id.*

99. In IHC, tissue specimens obtained surgically are routinely preserved and fixed with a chemical, usually formalin, and embedded in another material,

such as paraffin wax. *Id.*, 11-12, 31. The embedded tissue specimens can be sliced in ultrathin sections (*i.e.*, “sectioned”), and the slices are placed on glass microscope slides. *Id.*, 11. Hematoxylin, which stains cell nuclei blue, produces a high level of contrast to the typical brown staining from enzyme-labeled antibodies used in IHC, and is frequently used as a counterstain to assist with cell counting. *Id.*, 69. Both hematoxylin and eosin, which stains the cytoplasm pink, were first introduced in the 1850s and were in common use by 2016 to confirm cellular morphology for cancer diagnoses. *Id.*, 95. Hematoxylin and eosin were particularly used for a long time for formalin-fixed, paraffin-embedded (FFPE) tissue sections. *Id.*, 31. An example of IHC staining for PD-L1 expression with hematoxylin and eosin (H&E) is presented below.

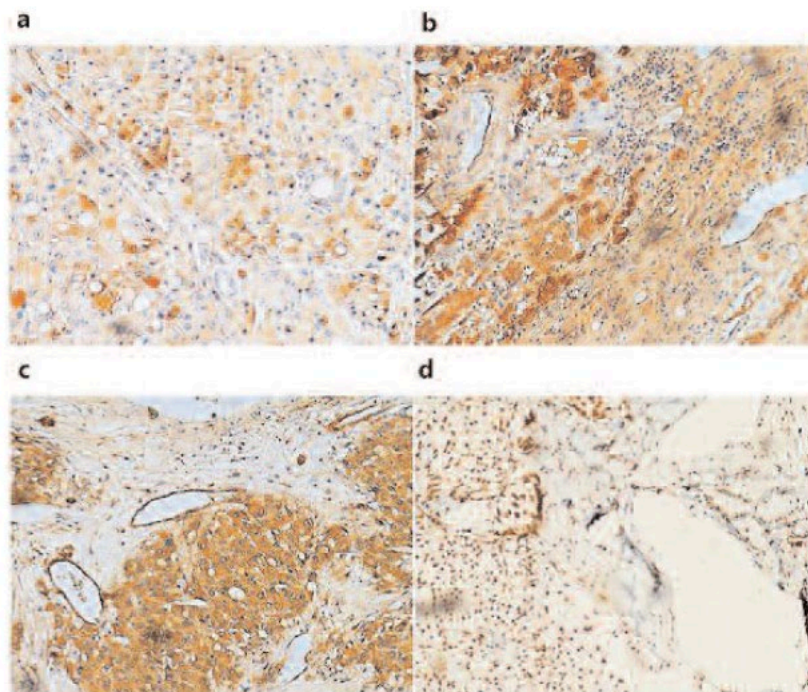


Figure 1. The positive expression of PD-L1 in hepatocellular carcinoma tissues, para carcinoma, portal area and adipose tissue. *A*, Hepatocellular carcinoma; *B*, Cancer adjacent connective tissue; *C*, Department of irrigation area; *D*, Adipose tissue. H&E, 200x.

EX1036, 3066, Fig. 1.

2. By 2016, Companion Diagnostics Routinely Enhanced the Use of Therapeutic Products and Were Essential for the Safe and Effective Use of Some Products

100. FDA published a draft guidance on “In Vitro Companion Diagnostic Devices” in 2011, later made final in 2014, to specifically address the development of such companion diagnostics. *See* EX1038. The FDA noted that “[d]iagnostic tests have been used for many years to enhance the use of therapeutic products,” but that “[r]ecently, the development of therapeutic products for which the use of a diagnostic test is essential for the products to meet their labeled safety and effectiveness claims has become more common.” *Id.*, 5. The FDA Guidance specified several areas where a companion diagnostic device could be “*essential*

for the safe and effective use of a corresponding therapeutic product” (emphasis added), including:

- To identify patients who are most likely to benefit from the therapeutic product
- To identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- To monitor response to treatment with the therapeutic product for the purpose of adjusting treatment

Id., 7.

101. For cancer immunotherapy in particular, which targets anti-tumor immune cells, it was important to identify factors predicting a positive response so that one could pre-select patients likely to benefit and avoid unnecessary adverse side effects in those unlikely to benefit. EX1013, 1-2. By 2016, companion diagnostic assays had been approved for many different biomarkers. *See, e.g.*, EX1012, 135, Table 11.1.

3. Measurement of PD-L1 Expression To Predict Outcomes and/or Determine Eligibility for Anti-PD Therapy Was Being Extensively Studied

102. *Taube 2012* hypothesized that cell surface PD-L1 expression was particularly relevant as a biomarker for predicting patients’ response to treatment with therapeutic agents blocking the PD-1/PD-L1 pathway. EX1013, 7 (“We hypothesize that cell surface expression of B7-H1 [PD-L1] is the most immediately biologically relevant as a potential biomarker predicting clinical response to PD-1

blockade... These findings highlight a therapeutic opportunity in administering agents blocking the PD-1/B7-H1 pathway to patients with metastatic melanoma.”).

103. Similarly, *Muenst 2013* taught that PD-L1 expression was known to be a clinically relevant feature of the breast cancer microenvironment. EX1015, 668 (“... upregulation of... PD-L1 on breast cancer cells... In a similar study, the same authors also found expression of PD-L1 on breast cancers cells as well as on TIL in 50 % of cases...”).

104. *Muenst 2013* discussed clinical studies of the PD-1/PD-L1 pathway and noted that results suggested that PD-L1 expression by cancer cells was associated with improved outcome following anti-PD-1 antibody therapy, identifying PD-L1 as a candidate biomarker for anti-PD-1 immunotherapy. EX1015, 673-74 (“Of note, Topalian et al. were able to assess PD-L1 expression in a subset of cancers, and preliminary results suggest that PD-L1 expression by the cancer is associated with improved outcome following anti-PD-1 antibody therapy, suggesting that PD-L1 is a candidate biomarker for anti-PD-1 immunotherapy. The data from this study, particularly the association between the presence of PD-1⁺ TIL and higher stage, grade and worse survival, suggest that PD-1 may also be a candidate biomarker for predicting response to therapy.”).

105. *Muenst 2013* also discussed PD-L1 expression in tumor-infiltrating lymphocytes. *Muenst 2013* referred to prior breast cancer studies finding PD-L1

expression on both cancer cells and TILs and concluded that the results of the studies “suggest that activation of the PD-1/PD-L1 signaling pathway in the breast cancer microenvironment may modulate antitumor immunity, permitting cancer progression.” EX1015, 668; *id.*, 674 (“PD-1 plays a functional inhibitory role in human breast cancer immunosurveillance, a fact that should encourage immunotherapeutic approaches targeting the PD-1/PD-L1 signaling pathway in breast cancer”).

106. *Muenst 2014* described a study demonstrating that “PD-L1 expression is an independent negative prognostic factor in human breast cancer” and stated that this finding “has important implications for the application of antibody therapies targeting the PD-1/PD-L1 signaling pathway in this [breast cancer].” EX1016, 15; *see also id.*, 22 (“Our finding is also consistent with the hypothesis that therapeutic blockade of the PD-1/PD-L1 pathway might be a valid treatment approach in breast cancer.”).

107. *Ali* taught that PD-L1 expression in solid tumors “has been shown to predict whether patients are likely to respond to anti-PD-L1 therapies.” EX1022, Abstract. *Ali* further taught that “[e]xpression of PD-L1 by either tumour cells or infiltrating immune cells was positively correlated with infiltration by both cytotoxic and regulatory T cells ($P < 0.001$).” *Id.*

108. With respect to PD-L1 expression in immune cells, *Ali* reported that in ER-negative breast cancers, PD-L1 expression in >10% of the immune cells was associated (nominally statistically significant, $P = 0.08$) with reduced disease-specific mortality. *Id.*, 1491.

109. *Ali* concluded that its “observations suggest that PD-L1 inhibitors may benefit a small subset of women with breast cancer with tumours that express PD-L1, most of which will prove to be basal-like,” such as triple negative tumors. EX1022, 1492.

110. By 2015, as summarized in Table 1 in EX1056, it was known that various tumors in human cancers expressed PD-L1. EX1056, 848-49 (“Multiple solid tumor types including melanoma, RCC, NSCLC, thymoma, ovarian, and colorectal cancer co-opt this immune shield by expressing PD-L1 to generate an immunosuppressive tumor microenvironment and avoid T cell cytolysis”). “[S]ubstantial effort ha[d] been expended on ... immunohistochemical approaches to screen tumors for PD-L1 expression in order to select for patients who may benefit from anti-PD-1/PD-L1 directed therapies.” *Id.*, 848. It was also known that “[t]umor PD-L1 overexpression confers a poorer prognosis across multiple tumor histologies, making therapeutic intervention on this immunomodulatory axis [the PD-1/PD-L1 axis] enticing” (*id.*) and that “[p]atients who have PD-L1 overexpression, based on different assays with varying cutoffs, tend to have more

robust responses to anti-PD-L1-directed therapy” (*id.*, 853). It was also well understood that to capitalize on anti-PD therapies, “biomarkers predictive of response to therapy are central to treatment decision making.” EX1031, 985.

4. Methods for Using PD-L1 as a Biomarker in a Companion Diagnostic Were Conventional

111. The methods employed for measuring PD-L1 expression to predict outcomes and/or assess eligibility for anti-PD therapy were conventional.

112. For example, by 2016, it was known that tumor cells expressing PD-L1 could evade a natural anti-cancer immune response. EX1013, 2. In addition, by 2016, many companies had developed or were developing cancer treatments to interrupt the PD-1/PD-L1 axis, and had developed companion diagnostics to use with those treatments, with IHC was identified as “the favored biomarker” to predict response to such therapy. *See, e.g.*, EX1031, 985 (describing four therapeutic agents targeting either PD-L1 or PD-1). Indeed, since as early as 2004, researchers had been using IHC to observe PD-L1 staining for predicting a patient’s cancer prognosis or to simply understand the role of PD-L1 positivity in cancer. EX1032; EX1058, 1330, 1335-336; EX1059, 463, 467-68.

113. It was also known that in addition to the tumor itself, the local tumor microenvironment, including both tumor cells and tumor infiltrating immune cells and the surrounding stroma, were key sites for biomarkers to predict clinical response to PD-1 pathway blockade. EX1013, 2. It was therefore conventional to

test for PD-L1 expression in tumor cells and tumor infiltrating immune cells, rather than only one or the other. EX1031, 985, 987.

114. Moreover, while different antibodies and formulae were used for each of the therapeutic agents targeting the PD-1/PD-L1 pathway, the IHC methodology remained conventional. *See, e.g.*, EX1062, Table 3 (identifying four drugs and five IHC antibodies, but not identifying any novel IHC techniques).

D. By 2016, Various Formulas for Calculating PD-L1 Expression Scores Had Been Developed, Including Formulas Accounting For PD-L1 Expression in Tumor Cells and MICs

115. IHC staining for PD-L1⁺ tumor cells and infiltrating leukocytes had been used for more than a decade before the earliest possible effective filing date of *US702*. For example, *Thompson* describes a study that quantified the percentages of tumor cells and lymphocytes that stained positive for B7-H1 (PD-L1). EX1032, 17175.

116. Counting the number of PD-L1⁺ tumor cells was also well known. For example, *Nomi* described using IHC staining to identify and count the number of PD-L1⁺ tumor cells:

All of the immunostained sections were examined under low power (4x objective) to identify regions containing low-staining tumor cells. In case of multiple areas with low intensity, five randomly selected areas were scored, and in sections where all of the staining appeared intense, one field was selected at random. The proportion of tumor cells showing high and low staining in each selected field was determined by counting individual tumor cells at high magnification. At least 200 tumor cells were scored

per x400 field. Because most prognostic factors are usually considered as dichotomized, discontinuous variables, a cutoff point was selected to give the optimal separation between low risk and high risk of the overall survival as previously described by others and us (17, 22, 23). Then, we selected 10% as cutoff point based on preliminary analysis and recent report on PD-L1 expression in human cancer (16). Specimens with a $\geq 10\%$ PD-L₁-positive tumor cells were classified as positive.

EX1040, 2153.

117. Similarly, *Tumeh* and *WO422* described staining tumor and infiltrating cells to quantify PD-L1⁺ cells. EX1033, 5 (methods); *id.*, 15 (Ext. Data Table 3); EX1010, [0025]-[0029].

118. Before the filing of *US702*, several methods had been proposed for calculating PD-L1 expression scores in cancer cells and MICs. For example, *Hamanishi* described assessing overall PD-L1⁺ staining without counting or estimating PD-L1⁺ cells. EX1048, 3364. *Herbst* and *Hou* described separately scoring the percentage of PD-L1⁺ tumor cells and the density of PD-L1⁺ tumor infiltrating lymphocytes (TILs). EX1017, 6 (methods); EX1080, 285.

WO 2014/165422 (“*WO422*”), a published Merck application, described various methods for calculating PD-L1 expression scores and proposed and claimed a modified scoring method that could be used to identifying “PD-L1 expression levels that correlate with response of cancer patients to therapy with antagonists of Programmed Death 1 (PD-1).” EX1010, [0001].

119. *WO422* described use of a modified proportion score (MPS) for PD-L1 expression calculated using both PD-L1⁺ tumor cells and MICs: “assigning the MPS comprises estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity. EX1010, Exemplary Specific Embodiments 1, 12, and 23, and claims 1, 10, and 18.

120. In addition, U.S. Patent Application Publication No. 2013/0309250 (*Pub250*), filed by Bristol-Meyers Squibb, the developer of anti-PD-1 agent nivolumab, described methods of treating cancer by disrupting the PD-1/PD-L1 axis. *See, e.g.*, EX1061, claim 1. *Pub250* noted that PD-L1 expression is not only relevant on tumor cells, but also tumor-infiltrating immune cells, saying that “cell surface expression of PD-L1 in tumors and/or tumor-infiltrating inflammatory cells is a marker not just for selecting cancer patients who would benefit from treatment with an anti-PD-1 Ab, but also for treatment with an anti-PD-L1 Ab as well as treatments targeting inhibitory immunoregulatory pathways other than the PD-1/PD-L1 pathway.” *Id.*, [0175].

121. *Pub250* further disclosed methods for selecting patients for treatment with anti-PD-1 or anti-PD-L1 agents that account for PD-L1 expression on both tumor cells and tumor-infiltrating immune cells. Specifically, *Pub250* disclosed a selection method comprising three steps: “(i) optionally providing a test tissue

sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells, (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface, and (iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and (b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the selected subject.” *Id.*, [0007].

122. While *Pub250* did not disclose particular thresholds applicable to specific agents or tumors, it disclosed that “the predetermined threshold is based on a proportion of (a) tumor cells, (b) tumor-infiltrating inflammatory cells, (c) particular tumor-infiltrating inflammatory cells, e.g., TILs or macrophages, or (d) a combination of tumor cells and tumor-infiltrating inflammatory cells, in a test tissue sample that expresses PD-L1 on the cell surface” and that the proportions of PD-L1 expressing cells would be compared to a denominator of tumor cells or tumor-infiltrating cells. *Id.*, [0193]; *see also id.*, claim 9.

123. *Pub250* considered both immune cells inside the tumor as well as those outside the tumor that were found in the periphery associated with connective or adjacent tissue (*i.e.*, the stroma). Specifically, *Pub250* taught assessing staining in tumor-infiltrating inflammatory cells such as macrophages

and lymphocytes inside or outside the tumor. *See, e.g., id.*, [0169] (“Staining is also characterized according to an outside/inside tumor immune cell designation. ‘Inside’ means the immune cell is within the tumor tissue and/or on the boundaries of the tumor region without being physically intercalated among the tumor cells. ‘Outside’ means that there is no physical association with the tumor, the immune cells being found in the periphery associated with connective or any associated adjacent tissue.”))

E. There Were Established Methods for Using PD-L1 Expression and Patient Response Data To Determine a Threshold

124. Once a score is calculated for a cohort of subjects, it can be analyzed together with clinical data to identify a score that best distinguishes responders from non-responders. A Receiver Operating Characteristic (ROC) curve can be used for this purpose. EX1072, 861.

125. A ROC curve plots the true positive rate (sensitivity) against the false positive rate (1-specificity). The following equations are used to calculate these values at different thresholds, which together generate the ROC curve.

True Positive Rate = True Positives / (True Positives + False Negatives)

False Positive Rate = False Positives / (False Positives + True Negatives)

Id., 862.

126. By calculating the true positive and false positive rates at different cutoff thresholds, an ROC curve can be generated and its area under the curve (AUC) calculated. An AUC of 0.5 indicates that the score performs no better than random chance. The closer the AUC is to 1.0, the more predictive the score is at distinguishing responders from non-responders. *Id.*, 867.

V. OVERVIEW OF *US702*

A. The Specification of *US702*

127. *US702*, titled “Scoring Methods for Anti-PD Therapy Eligibility and Compositions for Performing Same,” issued on January 20, 2026. EX1001, 1. I have been informed that the earliest possible effective filing date is April 1, 2016.

128. The background of *US702* notes that it was known that “Programmed cell death 1 ligand (PD-L1) expression is implicated in evasion of immune responses involved in many contexts, including suppression of anti-tumor immune activity.” EX1001, 1:17-20. *US702* notes further that “PD-L1 expression has been shown in situ on a wide variety of solid tumors including breast, lung, colon, ovarian, melanoma, bladder, liver, salivary, stomach, gliomas, thyroid, thymic epithelial, and head and neck cancers,” and also is associated with unfavorable prognosis in “kidney, ovarian, bladder, breast, gastric, and pancreatic cancer.” EX1001, 1:20-23, 1:45-48 (citations omitted).

129. *US702* also states in its background section that the known role of PD-1/PD-L1 in tumor biology generated significant interest in therapeutic agents that target PD-1: “[g]iven the role PD-1/PD-L1 plays in tumor biology, therapeutic agents that target this molecule have been of significant interest.” EX1001, 2:5-7.

130. The background of *US702* states that anti-PD therapy has been shown to have an acceptable safety profile and induce rapid and significant improvement in subjects with a broad spectrum of cancers:

Indeed, anti-PD-1/PD-L1 therapy (or anti-PD therapy) has generated significant clinical benefits by inducing regression of advanced and metastatic tumors and improving survival. Anti-PD therapy can have durable effects, tolerable toxicity, and is applicable to a broad spectrum of cancer types, especially in solid tumors.

EX1001, 2:7-12.

131. According to *US702*, examples of said effective and safe treatments include the approved products nivolumab (Opdivo) and pembrolizumab (Keytruda), and molecules under development, including BMS-936559, MPDL3280A, Pidilizumab (Medivation/CureTech), MEDI4736 (AstraZeneca), and Avelumab (Merck-Sorono). EX1001, 2:13-56.

132. *US702* defines the term “antibody” as “a protein consisting of one or more polypeptides that specifically binds an antigen. EX1001, 7:1-5. The specification further explains that antibodies include “fragments of antibodies which retain specific binding to antigen or target, including, but not limited to, Fab,

Fv, scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, bi-specific hybrid anti-bodies, and fusion proteins comprising an antigen-binding portion of an antibody and a non-antibody protein.” EX1001, 7:11-17.

133. *US702* defines the term “subject” as including humans and non-human animals: “A ‘subject’ of diagnosis or treatment is a plant or animal, including a human. Non-human animals subject to diagnosis or treatment include, for example, livestock and pets.” EX1001, 5:44-46. Consistent with this, Example embodiment 28 specifically limits prior embodiments to humans, indicating that the prior embodiments encompassed more than humans: “The method of any preceding embodiment, wherein the subject is a human.” EX1001, 22:53-54.

134. Likewise, *US702* does not limit the source of tissue sections or samples to humans, instead referring to humans as an example (“e.g.”): “As used herein, the term ‘tissue section’ refers to a piece of tissue that has been obtained from a subject and mounted on a planar surface, e.g., a microscope slide. The sample may be fixed and/or sectioned as desired. A ‘tumor tissue sample’ or ‘tumor tissue biopsy sample’ includes cells derived from a tumor in a subject, e.g., a human subject having a malignancy. Such tissue samples are sometimes referred to simply as a ‘biopsy’.” EX1001, 5:47-54.

135. *US702* states that there are published methods of using IHC to score the extent of PD-L1 expression on tumor cells and/or tumor-associated immune cells:

[W]ork in this area has included performing more detailed analysis of not only the malignant cells in tumor biopsies, but also non-malignant cells to identify patients who may respond to these therapies. For example, some published scoring methods for PD-L1 immunohistochemistry (IHC) staining are either capturing percentage of staining and or staining intensity on tumor cells or the PD-L1 staining and staining intensity on tumor-associated immune cells..... More and more clinical trials indicated that in some tumor indications PD-L1 staining on both tumor and tumor-associated immune cells is associated with clinical outcome.”

EX1001, 2:58-3:5 (citations omitted).

136. *US702* reports that then-current scores required capturing two thresholds, “one for tumor cells and one for non-tumor cells.” EX1001, 3:8-14.

137. *US702* discloses the CPS and contends that the CPS addresses the “need to improve tumor tissue scoring methods for identifying patients that will respond effectively to anti-PD therapy.” EX1001, 3:14-16.

138. *US702* states that the CPS requires “determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy; and calculating a combined positive score (CPS) for the tumor tissue sample using the formula:

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

wherein the subject is eligible for treatment with an anti-PD therapeutic agent when the CPS is above a threshold.” EX1001, 3:24-40.

139. *US702* further describes commonly known techniques for counting PD-L1 positive and negative cells, *i.e.*, flow cytometry and single cell sequencing. EX1001, 9:37-44, 9:50-55, 21:58-62, 22:18-22. *US702* also states that staining techniques and methods for obtaining cell suspensions are known in the art. *Id.*, 5:55-63, 9:67-10:9.

140. *US702* states that when calculating the CPS, “the tissue sample (or specimen) must contain a minimum number of viable cells for evaluation, *e.g.*, at least 50 viable tumor cells, at least 100 viable tumor cells, at least 150 viable tumor cells, at least 250 viable tumor cells, etc.” EX1001, 8:60-63. *US702* also states that in some embodiments, “the percentage of viable PD-L1 positive and negative tumor cells and PD-L1 positive mononuclear inflammatory cells (MIC) is determined within the tumor nests and the adjacent supporting stroma.” *See, e.g.*, 9:15-19. *US702* does not identify any benefit related to determining the percentage of PD-L1⁺ MICs in the stroma.

141. *US702* provides examples for calculating the CPS. One of those examples describes estimating the number of PD-L1 positive and negative tumor cells and PD-L1 positive MICs: “To calculate the CPS, the stained area is evaluated at a higher magnification (right) *to estimate the number* of PD-L1 positive and negative tumor cells and mononuclear inflammatory cells that are PD-L1 positive.” EX1001, 17:41-44. In addition, the specification describes estimations based on staining of only 10% of a sample: “Because only 10% of the sample was stained, the CPS score is adjusted by multiplying the CPS of the stained area with the percentage of the tissue that was stained (in this case, 10%).” *Id.*, 17:39-41, 53-56.

142. Example 1 is the only example in *US702*. It describes a hypothetical study in which specimens from subjects having gastric carcinoma are analyzed. EX1001, 19:58-61. Example 1 does not identify the anti-PD therapy that was hypothetically administered, and neither does the remainder of the specification.

143. Example 1 states that H&E staining is used to confirm diagnosis and situate the tumor, and that “[h]ematoxylin counterstain on the PD-L1 slide is used to estimate the number of cells.” EX1001, 20:29-32.

144. In Example 1, PD-L1 expression was determined and interpreted to generate three PD-L1 expression scores, the Tumor Proportion Score (TPS), the Mononuclear Inflammatory Density Score (MIDS), and the CPS.

145. Example 1 describes the TPS, MIDS, and CPS as follows:

- The TPS measures “the percentage of tumor cells expressing PD-L1 on the cell membrane.”
- The MIDS measures “the ratio of the number of PD-L1 expressing mononuclear inflammatory cells infiltrating or adjacent to the tumor compared to the total number of tumor cells.”
- The CPS measures “the ratio of the number of PD-L1 positive tumor cells and PD-L1 positive mononuclear inflammatory cells (MIC) within the tumor nests and the adjacent supporting stroma (numerator) compared to the total number tumor cells (denominator; i.e., the number of PD-L1 positive and PD-L1 negative tumor cells).”

EX1001, 20:35-59.

146. Example 1 states:

A cut-off is the score that differentiates diagnostically positive from diagnostically negative. The cut-off can be set to achieve the following goals:

1. Identify all responders (i.e., no false negatives); and
2. Minimize the number of non-responders (i.e., false positives).

It is expected that setting the cut-off at $\geq 1\%$ for a positive result for the scores above, CPS will identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses described above.”

EX1001, 20:60-21:2.

147. Neither Example 1 nor the remainder of the specification of *US702* provide data supporting the statement that, with respect to the gastric carcinoma of Example 1, “setting the cut-off at $\geq 1\%$ for a positive result for the scores above,

CPS will identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses described above.” Example 1 and the specification of *US702* also do not provide data that supports setting the CPS threshold at $\geq 1\%$ for gastric carcinoma when using the unidentified anti-PD therapy used in Example 1, or when using any other anti-PD therapy.

148. In addition, neither Example 1 nor the remainder of the specification of *US702* provide data or principles from which a POSA could extrapolate the hypothetical information in Example 1 to any other malignancy or any particular anti-PD therapy/malignancy combination.

149. *US702* also states, without support, that “[t]he CPS approach is generally applicable to any cancers expressing PD-L1 in either tumor and/or immune cells” and that “CPS can be used to analyze triple negative breast carcinoma using a similar cut-off value as described above.” EX1001, 21:7-10.

B. The Claims of *US702*

150. *US702* issued with independent claims 1, and dependent claims 2 through 21. Claims 1-21 are reproduced below:

1. A method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent, the method comprising: determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy; calculating a combined positive score (CPS) for the tumor tissue sample using the formula:

$CPS =$

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold, wherein said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.

2. The method of claim 1, wherein the threshold is from 10% to 1%.
3. The method of claim 1, wherein the threshold is 1 %.
4. The method of claim 1, wherein the tumor tissue sample is a tissue section of a tumor biopsy.
5. The method of claim 4, wherein PD-L1 is detected by immunohistochemistry (IHC) staining.
6. The method of claim 4, wherein the tumor tissue section is a formalin fixed and embedded in paraffin wax (FFPE) tumor tissue section.
7. The method of claim 4, wherein the tissue section is stained.
8. The method of claim 7, wherein the stain is a hematoxylin and eosin (H&E) stain.
9. The method of claim 4, wherein the viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC are counted in the tumor nests and the adjacent supporting stroma of the tumor tissue sample
10. The method of claim 1, wherein the tumor tissue sample is a cell suspension.
11. The method of claim 10, wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor

cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determining [sic] by flow cytometry.

12. The method of claim 1, wherein one or more additional marker is detected in the tumor tissue sample.

13. The method of claim 12, wherein the marker is specific for MIC or is selected from the group consisting of: CD3, CD5, CD4, CD7, CD8, and CD20.

14. The method of claim 1, wherein the method further comprises, prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof.

15. The method of claim 1, wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determined by single cell sequencing.

16. The method of claim 1, wherein the malignancy is selected from the group consisting of: gastric cancer, head and neck cancer, renal cell carcinoma, urothelial/bladder carcinoma, ovarian carcinoma, myeloma, melanoma, lung cancer, squamous cell carcinoma, classical Hodgkin's lymphoma, breast cancer, small cell lung cancer, salivary gland carcinoma, vulvar carcinoma, thyroid carcinoma, anal canal carcinoma, biliary carcinoma, mesothelioma, cervical carcinoma, and neuroendocrine carcinoma.

17. The method of claim 1, wherein the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1.

18. The method of claim 1, wherein the anti-PD therapeutic agent is selected from the group consisting of: Avelumab (MSB0010178C), Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736.

19. The method of claim 16, wherein the breast cancer is triple negative breast cancer, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer.

20. The method of claim 1, further comprising administering said anti-PD therapeutic agent to the subject when the CPS is above the threshold.

21. The method of claim 20, wherein the threshold is greater than or equal to 1 %.

VI. OVERVIEW OF THE PRIOR ART

A. WO422 (EX1010)

151. International publication number WO 2014/165422 (“*WO422*”), titled “Immunohistochemical Assay for Detecting Expression of Programmed Death Ligand 1 (PD-L1) in Tumor Tissue,” published October 9, 2014 (EX1010, cover page), and therefore was a printed publication available more than one year before the earliest possible effective filing date of *US702*. Merck is the applicant of *WO422*.

152. *WO422* is directed to using IHC to quantify PD-L1 expression on tumor cells and MICs in tumor sections and identifying PD-L1 expression levels that correlate with cancer patient response to anti-PD therapy. EX1010, [0001] (“The present invention relates to the quantitation of PD-L1 expression in animal tissue samples by immunohistochemical (IHC) assay... [and] the identification of PD-L1 expression levels that correlate with response of cancer patients to therapy with antagonists of Programmed Death 1 (PD-1)”; *see id.*, [0009].

153. *WO422* taught that PD-L1 expression has been observed in a variety of cancers, that it can induce inhibition or apoptosis of tumor-specific T-cells, and

that it correlated with poor prognosis and reduced overall survival in “ovarian, renal, colorectal, pancreatic, liver cancers and melanoma.” EX1010, [0003].

154. *WO422* disclosed various anti-PD-1 monoclonal antibodies and taught that patients whose tumors express PD-L1 are more likely to respond to them. EX1010, [0003] (“Anti-PD-1 monoclonal antibodies (mAbs) that block binding of PD-L1 to PD-1 have been shown to have anti-tumor activity against a variety of tumor types, with early human clinical data suggesting that patients whose tumors express PD-L1 are more likely to respond to anti-PD-1 therapy.”)

155. *WO422* referred to prior art approaches for determining patient eligibility for treatment based on IHC: “One approach employed a simple binary end-point of positive or negative for PD-L1 expression, with a positive result defined in terms of the percentage of tumor cells that exhibited histologic evidence of cell-surface membrane staining.” EX1010, [0005]. This score, which is now known as the Tumor Proportion Score (TPS), can be expressed as/determined using the following calculation:

$$\frac{\text{PD-L1-stained viable tumor cells}}{\text{Total viable tumor cells}} \times 100\%$$

EX1010, [0005].

156. *WO422* also disclosed that in other approaches, like the methods in *WO422* and in *US702*, “PD-L1 expression in the tumor tissue section was quantified in the tumor cells as well as in infiltrating immune cells, which

predominantly comprise lymphocytes.” EX1010, [0006] (citing *Taube 2012* (EX1013) and *Thompson* (EX1032)).

157. *WO422* also disclosed determining the percentage of MICs stained in studies measuring PD-L1 expression in tumor tissue sections. EX1010, [0011]-[0012].

158. *WO422* taught that quantifying PD-L1 expression using IHC, “beyond a simple binary positive/negative characterization, can provide valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.” EX1010, [0009]. *WO422* further taught a scoring process “intended to facilitate standardizing the quantitation of PD-L1 expression across multiple stained tissue section and pathology laboratories” and indicates that the resulting score “may be useful in selecting patients to receive anti-PD-1 therapy.” *Id.*

159. The *WO422* scoring process entails obtaining a tissue section from a tumor stained with an antibody that binds to PD-L1 and assigning one or both of a modified H score (MHS) and a modified proportion score (MPS). EX1010, [0010].

160. *WO422* states that the MPS is assigned as follows:

[A]ssigning the MPS comprises estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least

partial membrane staining of any intensity, and assigning the resulting percentage as the MPS.

EX1010, Exemplary Specific Embodiments 1, 12, and 23, and claims 1, 10, and 18. A POSA therefore would have understood that the formula for the MPS is the following, wherein the numerator includes PD-L1 positive tumor cells and MICs, and the denominator includes the total number of viable tumor cells plus the total number of mononuclear inflammatory cells (MIC):

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

161. *WO422* further described examining the stroma surrounding each tumor nest for the presence or absence of a band of anti-membrane-stained stained cells, and assigning a stroma score (SS). An SS of “positive” is assigned if a band is detected in the stroma surrounding at least one tumor nest, and an SS of negative is assigned to the tissue section if a band is not detected. EX1010, [0013]; *see id.*, Exemplary Specific Embodiments 5, 6, 8, Claims 3, 4, 6, and 23.

162. A tumor is considered PD-L1⁺ if, for example, the MPS is greater than zero. *Id.*, [0016].

163. *WO422* also taught a method of treating a human patient diagnosed with NSCLC, wherein the patient is treated with a PD-1 antagonist if “the MPS is at or above a specified threshold.” EX1010, [0019]. *WO422* further stated that “the specified threshold for MPS is greater than zero,” and that in one preferred

embodiment, the specified MPS threshold is 90. *Id.* WO422 also discloses the use of NSCLC MPS thresholds between 80 and 100. EX1010, [0116], Exemplary Specific Embodiment 24, Claim 19.

164. WO422 taught use of the following anti-PD therapeutic agents, all of which are PD-1 antagonists and therefore inhibit the anti-cell death activity of PD-1/PD-L1: Nivolumab, BMS-936559, MPDL3280A, and MEDI4736. EX1010, [0072], claim 20. It also refers, as a preferred PD-1 antagonist, to a molecule with a heavy chain and a light chain where the heavy chain comprises SEQ ID NO:32 and the light chain comprises SEQ ID NO:33. EX1010, [0072], Figs. 9A, 9B, 10, Exemplary Specific Embodiments 26-27, claim 21; *see also id.* at [0032], [0033]. A POSA would have known that this molecule corresponded to pembrolizumab. For example, Figure 6 of WO2015026634 (EX1052) discloses the same heavy and light chains and states that those sequences correspond with MK-3475. EX1052, [0023]. Based on a May 30, 2014 Merck press release, a POSA would have known that MK-3475 was a name for a Merck investigational anti-PD-1 antibody, and that pembrolizumab was the nonproprietary name for MK-3475. EX1063; *see also* EX1018, 1 (“Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma.”); EX1024 (same).

165. *WO422* stated that the tumor sample is selected from the following group:

[G]astric cancer, bladder cancer, melanoma, NSCLC, head and neck cancer, colon or rectal adenocarcinoma, Hodgkins lymphoma, non-Hodgkins lymphoma, multiple myeloma, Myelodysplastic syndrome (MDS), anal canal squamous cell carcinoma, pancreas adenocarcinoma, esophageal squamous cell carcinoma or adenocarcinoma, biliary tract adenocarcinoma (gallbladder and biliary tree but excluding ampulla of vater cancers), carcinoid tumors, neuroendocrine carcinomas, well or moderately differentiated pancreatic neuroendocrine tumor, estrogen receptor (ER) positive HER2 negative breast cancer, HER2 positive breast cancer, triple negative breast cancer, ovarian epithelial, fallopian tube or primary peritoneal carcinoma, endometrial carcinoma, cervical squamous cell cancer, vulvar squamous cell carcinoma, small cell lung cancer, mesothelioma (malignant pleural [m]esothelioma [sic]), thyroid cancer, including of papillary or follicular subtype, salivary gland carcinoma, nasopharyngeal carcinoma, glioblastoma multiforme, leiomyosarcoma, prostate adenocarcinoma.

EX1010, [0017].

166. *WO422* describes prior art in which the threshold for positive PD-L1 expression is 1% or 5% of total tumor cells. EX1010, [0005] (citing EX1014 and EX1042).

167. *WO422* disclosed conventional techniques for measuring PD-L1 expression in tumor tissue samples, for example:

- The tumor tissue sample can be obtained by a variety of procedures, including biopsy. EX1010, [0081] (“The tumor sample can be obtained by a variety of procedures including, but not limited to, surgical excision, aspiration or biopsy. The tissue sample may be sectioned and examined for PD-LI as a

fresh specimen”; *id.*, [00113] (“For example, a surgeon may obtain by biopsy a tissue sample from a cancer patient's tumor and then send the tissue sample to a pathology lab, which may fix the tissue sample and then prepare one or more slides, each with a single tissue section, for IHC assay.”)

- The tumor tissue is fixed on a slide, such as by FFPE. EX1010, [0082] (“The tissue sample may be fixed by conventional methodology, with the length of fixation depending on the size of the tissue sample and the fixative used.... In preferred embodiments, the tissue sample is fixed with formalin. In some embodiments, the fixed tissue sample is also embedded in paraffin to prepare a formalin-fixed and paraffin-embedded (FFPE) tissue sample.”); *see id.*, [0021] (“In any of the aspects and embodiments of the invention described above or elsewhere herein, the tissue section is preferably a formalin-fixed, paraffin-embedded tissue section), Exemplary Specific Embodiment 17, claim 13.
- Tissues are stained, including IHC staining to identify PD-L1. EX1010, ([0010], [0017], [0024]-[0029], [0066], [0080], [00122], [00129], Exemplary Specific Embodiments 1, 12, Claims 1, 10, 23), [00113] (“For example, a surgeon may obtain by biopsy a tissue sample from a cancer patient's tumor and then send the tissue sample to a pathology lab, which may fix the tissue sample and then prepare one or more slides, each with a single tissue section, for IHC assay.”).
- IHC could be conducted using conventional techniques: “IHC assay may be performed using an automated pathology system, which may include automated staining (conventional stains, histochemical techniques, immunostainers.” EX1010, [0097].
- Techniques including staining (or contacting) tissue samples with anti-PD-L1 antibodies like antibody 22C3 for detecting PD-L1⁺ cells, EX1010, [0022], [0025]-[0029], [00101], Figs. 2-6. Routine conditions could be used to expose a tissue section to an anti-PD-L1 antibody such that the antibody binds to PD-L1 in the tissue section: “[T]he tissue section is exposed to an anti-PD-L1 antibody as the primary antibody for a sufficient period of time and under suitable conditions to allow

the primary antibody to bind to the PD-L1 protein in the tissue section. Appropriate conditions for achieving this can be determined by routine experimentation.” EX1010, [00093].

168. *WO422* also incorporated by reference *Taube 2012*, which disclosed using an IHC marker for PD-L1 expression by tumor cells and tumor infiltrating immune cells along with CD3 and CD68 immunostains to interpret which cell type demonstrated expression of a given ligand. EX1010, [0004] (citing EX1013, 8), [00131] (incorporation by reference).

B. *Bellmunt* (EX1023)

169. Bellmunt, J., et al., Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma, *Annals of Oncology* 26: 812-17, 2015 (“Bellmunt”), was published online in January 2015 (EX1023), and therefore was a printed publication available more than one year before the earliest possible effective filing date of *US702*.

170. *Bellmunt* described an evaluation of PD-L1 expression in tumor cells and MICs in urothelial carcinoma (UC). One goal was to see whether PD-L1 expression was predictive of overall survival or longer survival. EX1023, 812.

171. *Bellmunt* used H&E staining to examine PD-L1 positivity in tumor cells and infiltrating immune cells. *Bellmunt* defined PD-L1 positivity on tumor cell membranes as $\geq 5\%$ of tumor cell membrane staining. EX1023, 812. Thus, positivity in *Bellmunt* was calculated as follows:

$$\frac{\text{PD-L1-stained viable tumor cells}}{\text{Total viable tumor cells}} \times 100\%$$

172. *Bellmunt* reported that “the extent of tumor infiltrating mononuclear cells (TIMCs) as well as PD-L1 expression on TIMCs was scored from 0 to 4” wherein “[a] score of 2, 3, or 4 was considered PD-L1 positive.” EX1023, 812. In this scoring scale, the extent of staining for each score was as follows:

- (0) = “absent”
- (1) = “focal”
- (2) = “mild”
- (3) = “moderate”
- (4) = “severe”

Id. 813. A score of 2-4 was considered positive. *Id.* A POSA would have understood that the investigators did not score PD-L1⁺ MICs by comparing them to total MICs in the tumor sample. First, the authors explicitly compared PD-L1⁺ tumor cells to total tumor cells, but indicated no such comparison for MICs, *i.e.*, the authors did not indicate that PD-L1⁺ MICs were compared to total MICs (PD-L1⁺ and PD-L1⁻). Second, *Bellmunt* refers to “the extent of tumor-infiltrating mononuclear cells (TIMCs) as well as PD-L1 expression on TIMCs was scored from 0 to 4.” *Id.*, 812. A POSA would have understood that for both of these analyses, “the extent of” is in reference to the tumor overall.

173. *Bellmunt* concluded that “PD-L1 is widely expressed in tumor cell membrane and TIMCs in UC [urothelial cancer]” and that while “PD-L1 in tumor cells was not predictive of OS,” “positive PD-L1 expression in TIMCs was significantly associated with longer survival in those patient who developed metastases.” *Id.*

C. *Savas* (EX1060)

174. Savas, P., et al., *Clinical relevance of host immunity in breast cancer: from TILs to the clinic*, 13 NATURE REVIEWS CLINICAL ONCOLOGY 4, 228-41 (Epub Dec. 15, 2015) (*Savas*) published online on December 15, 2015, before *US702*’s earliest possible effective filing date.

175. Although 2016 is the year in the citation for *Savas*, the face of the publication makes clear that it was available online in December 2015. Additionally, a later referenced published on April 5, 2016, cites *Savas*, noting that it was available in December 2015. EX1071, reference number 18. POSAs knew that many journals, including Nature Reviews Clinical Oncology, provided online, pre-print versions before disseminating hard-copies, and that such online versions would be the same as the hard-copy versions. When such journals would publish online, POSAs would often obtain material online soon after it became available so as to stay at the forefront of the science. Thus, a POSA would have had access to *Savas* on December 15, 2015.

176. *Savas* discussed the clinical relevance of a patient's immune system, as represented by tumor-infiltrating lymphocytes (TILs), which *Savas* described as "mononuclear immune cells that infiltrate tumour tissue," *i.e.*, MICs. EX1060, 228. *Savas* specifically focused on the relevance of the host immune system in breast cancer. *Id.*

177. *Savas* taught that TILs "seem to reflect favourable host antitumour immune responses, suggesting that immune activation is important for improving survival outcomes" (*id.*, 228) and that in certain solid tumors, "the expression of PD-L1 on the intratumoural TILs seems to predict better responses to the anti-PD-L1 agent" (*id.*, 238).

178. *Savas* distinguished between intratumoral TILs and stromal TILs, but stated that both "comprise a complex mixture of different lymphocyte subtypes, dominated by T cells, with lesser proportions of B cells, NK cells, and macrophages." EX1060, 229. *Savas* stated that "[a]t any given point in time, the majority of TILs in breast cancers are typically located in the tumour stroma." *Id.* Based on this, a POSA considering the impact of TILs on breast cancer would have been interested in studying TILs in the stroma, not just intratumoral TILs.

179. *Savas* taught a correlation in TNBC (triple negative breast carcinoma) and in HER-2 positive patients between an increase in TILs over time (without

regard to PD-L1 expression status) and improved recurrence-free survival. *Id.*, 231.

180. *Savas* also described the use of anti-PD therapy in patients whose tumor cells and TILs expressed PD-L1. In particular, it described a study in which promising results were seen when the anti-PD-L1 antibody MPDL3280A was administered to patients with PD-L1-positive TNBC. EX1060, 237. In the study, patients were considered PD-L1 positive if they had at least 5% PD-L1⁺ TILs. *Id.*

D. *Dako* (EX1012)

181. *Dako*, an IHC Guidebook titled “Immunohistochemical Staining Methods,” published in 2013 (EX1012, 2), and therefore was a printed publication available more than one year before the earliest possible effective filing date of *US702*. *Dako* was copyrighted in 2013 to Dako Denmark A/S, an Agilent Technologies Company. Agilent Technologies Inc. is one of the assignees of *US702*.

182. *Dako* aimed to “provide a comprehensive immunohistochemistry (IHC) resource for lab managers, lab technicians, learning pathologists, and students.” EX1012, 9.

183. *Dako* described the long/conventional use of FFPE and hematoxylin/eosin stains. EX1012, 31 (“In the majority of cases, tissue specimens for immunohistochemical (IHC) staining are routinely fixed in formalin and

subsequently embedded in paraffin. Because of the long history of the use of formalin-fixed, paraffin-embedded (FFPE) tissue sections in histopathology, most of the criteria for pathological diagnosis have been established by the observation of FFPE tissue sections stained by hematoxylin and eosin.”).

184. *Dako* taught that a tumor tissue sample can be a cell suspension, and that when using a cell suspension, flow cytometry can be used to count positive versus negative cells. EX1012, 87 (Immunofluorescence (IF) can be used for “evaluation of cells in suspension... The degree of fluorescence can then be quantified using a flow cytometer... IF techniques can be used on both fresh and fixed tissue samples, though the latter present problems of autofluorescence.”) *Dako* further taught the use of a flow cytometer to evaluate and quantify what is seen in cells in suspension: “Immunofluorescence (IF) is a common laboratory technique.... Applications include the evaluation of cells in suspension.... The degree of fluorescence can then be quantified using a flow cytometer.” *Id.*

185. *Dako* taught that next generation sequencing, which includes single cell sequencing, can be used to count the number of positive and negative cells. EX1012, 119 (“New, non-slide-based tests, e.g. next generation sequencing, are in the process of entering routine diagnostic application providing new important information for cancer diagnostics, but at the cost of morphological information.”)

E. *Herbst* (EX1017)

186. Herbst, R.S., *et al.*, *Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients*, *Nature* 515(7528):563-7 (2014) (“*Herbst*”), was published in November 2014 (EX1017), and therefore was a printed publication available more than one year before the earliest possible effective filing date of *US702*.

187. *Herbst* discusses that tumors can evade immune-mediated rejection through an immunosuppressive microenvironment and identified PD-L1, expressed on both cancer and immune cells, because its interaction with PD-1 and B7.1 suppresses T-cell activity and tumor cell killing. EX1017, 563.

188. To investigate PD-L1 in human cancers, the researchers used an anti-PD-L1 IHC antibody with formalin fixed paraffin embedded specimens and evaluated PD-L1 expression separately on tumor cells and tumor infiltrating immune cells. PD-L1 staining was observed on both populations, with PD-L1⁺ tumor infiltrating immune cells occurring more frequently than PD-L1⁺ tumor cells and immunofluorescence showed that the PD-L1⁺ immune cell population included macrophages, dendritic cells, and T-cells. *Id.*

189. *Herbst* reported that “[f]or tumour cells the proportion of PD-L1-positive cells was estimated as the percentage of total tumour cells.” EX1017 (Methods). This is the same as the tumor proportion score/TPS, *i.e.*:

$$\frac{\text{PD-L1 positive viable tumor cells}}{\text{Total viable tumor cells}} \times 100\%$$

190. *Herbst* further reported that “[f]or tumour-infiltrating immune cells, the percentage of PD-L1-positive tumour-infiltrating immune cells occupying the tumour was recorded.” *Id.* A single score for PD-L1 positivity in MICs was calculated that included MICs in both the intra-nest and adjacent stromal areas. *Id.*

191. *Herbst* evaluated whether PD-L1 expression predicted response to the anti-PD-L1 antibody MPDL3280A in a phase I study involving patients with multiple cancer types. EX1017, 563. The researchers found that the association between response and PD-L1 expression on tumor infiltrating immune cells was statistically significant in NSCLC and across all tumor types, whereas the corresponding association with PD-L1 expression on tumor cells was not significant in NSCLC or across all tumor types. EX1017, 566, Ext. Fig. 4. *Herbst* stated that this result was unexpected: “It was unexpected that the association of tumour-infiltrating immune cell PD-L1 expression with treatment response appeared stronger than that with tumour cell PD-L1 expression.” *Id.*

192. *Herbst* explained that the presence of CD8⁺ T-cells alone did not predict response to MPDL3280A. *Id.*, 566. Instead, responding tumors were characterized by PD-L1⁺ immune infiltrates and nonresponding tumors included tumors with immune infiltrates exhibiting little or no PD-L1 expression. *Id.*

193. *Herbst* reported the association of PD-L1 expression with clinical response to MPDL3280A as its “most important finding.” *Id.*

194. A POSA would have understood that *Herbst*’s findings support the conclusion that PD-L1 expression by tumor infiltrating immune cells provided information concerning the immune suppressive state of the tumor microenvironment and the likelihood of response to anti-PD-L1 therapy.

VII. DETAILED OPINIONS REGARDING *US702*

A. The Claims of *US702* and Their Construction

195. *US702* issued with 21 claims. Claim 1 is an independent claim and claims 2-21 are dependent claims. EX1001, 23:36-24:63.

196. In conducting my analysis, I applied the following claim constructions. My opinions would not change if a different construction were to be adopted.

1. The Term “Subject” in Claim 1 Encompasses a Single Subject

197. Independent claim 1 recites “[a] method for determining eligibility of a subject.” A POSA would have understood that administering to “a subject” encompasses administering to a single subject.

2. The Terms “Determining the Number” (Claim 1) and “Counted” (Claim 9) Include Estimating

198. Claim 1 recites “determining the number of...” and claim 9 recites “wherein the viable PD-L1 positive tumor cells, the number of viable PD-L1

negative tumor cells, and the number of viable PD-L1 positive MIC are counted...”. For the following reasons, a POSA would have understood that the term “determining the number” in claim 1 and the term “counted” in claim 9 encompass an estimate or approximate numerical assessment by a POSA and are not limited to exact enumeration of every cell.

199. First, a POSA would have understood from the specification of *US702* that “determining the number” (claim 1) and “counted” (claim 9) encompassed estimating because the specification describes using such estimations when calculating the CPS. For example, in an example of how to calculate the CPS, the number of PD-L1 positive and negative cells and MICs are estimated: “To calculate the CPS, the stained area is evaluated at a higher magnification (right) *to estimate the number* of PD-L1 positive and negative tumor cells and mononuclear inflammatory cells that are PD-L1 positive.” EX1001, 17:41-44. In addition, the specification describes estimations based on staining of only 10% of a sample: “Because only 10% of the sample was stained, the CPS score is adjusted by multiplying the CPS of the stained area with the percentage of the tissue that was stained (in this case, 10%).” *Id.*, 17:53-6; *see also id.*, 17:39-40. There is no teaching in this example calculation to exactly enumerate every PD-L1⁺ tumor cell, every PD-L1⁻ tumor cell, or every PD-L1⁺ MIC.

200. Second, I have been informed that during prosecution of U.S. Patent No. 10,613,092 (“US902”, EX1008), to which US702 claims priority, Patent Owner argued that the presently claimed method is a *semi-quantitative method* which calculates the number of PD-LI positive cells in relation to the total number of tumor cells rather than the qualitative method of Kowanetz et al. which is based on the number of tumor-infiltrating immune cells within a given area, and made the same argument regarding Chen. A POSA would have understood that Patent Owner was characterizing the claimed method as “semi-quantitative,” as opposed to “quantitative.” A POSA would have understood that a semi-quantitative measurement is consistent with an approximation, not an exact enumeration. For example, prior art such as *Walker* and its related/follow-on article, *Taylor*, distinguishes between semiquantitative and quantitative assessments. *Taylor* defines quantitative as “of, concerned with, or measured by, quantity” and states that “[t]he term ‘semiquantitative’ lacks clear definition, but would imply having some features of ‘quantitative’, as in ‘semiprecious’, or not quite precious.” EX1065, 411; *see also* EX1064, 408.

201. Third, the prior art is consistent with the intrinsic evidence. For example, *Taylor* explains that IHC is “difficult to run in a manner that lends itself to quantitative analysis” due to, among other things, lack of standardization in pre-analytical steps (transportation, fixation, and sectioning) and analytical steps

(antigen retrieval, protocols, reagents, and controls). EX1065, 412-14. As another example, *Walker* provides the following examples of counting: “counting up to 1000 cells for reactivity to give a percentage or counting number of positive cells in 10 high-power fields (HPF).” EX1064, 407. The latter scenario in *Walker*, where an estimate is made based on counting only a portion of the cells, is the same as the method described above that was used in the *US702* specification.

3. The Term “Eligible for Treatment” Does Not Require Treatment

202. Claim 1 recites a “method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent... wherein the subject is eligible for treatment with said... agent when the CPS is above a threshold.” *US702* does not specifically define the term “eligible” or the term “eligibility.” A POSA would have understood that that the terms “eligible” for treatment and “eligibility” for treatment have their common meaning, which is that a subject is qualified to participate in treatment or permitted to be chosen for treatment, not that treatment must be administered. *See* EX1078, 404. The decision whether to treat the subject remains with the physician, who considers many other factors related to the subject, such as the subject’s condition, whether there is any pre-existing autoimmune disease, a history of organ or bone marrow transplantation, prior drugs administered, current drugs being administered,

including, for example, corticosteroid use, etc. Thus, the claims do not require treatment with an anti-PD therapeutic agent even if the CPS threshold is met.

B. Claims 1-21 Do Not Contain Patent Eligible Subject Matter

203. As explained below, claims 1-21 are directed to a natural law, an abstract idea, and a mental step, which I understand are not patent eligible subject matter. Other than the natural law, abstract idea, and mental step, the claims include only routine and conventional steps that do not make the claimed methods patentable. Therefore, claims 1-21 of *US702* are directed to patent-ineligible concepts.

204. As discussed further below, claim 1 is directed to what I understand to be considered a natural law: the correlation between the effectiveness of anti-PD therapeutic agents and the extent of PD-L1 expression in cancer cells and MICs. It is also directed to an abstract idea: the mathematical formula for calculating the CPS. It is also directed to a mental step: determining eligibility for anti-PD therapy based on whether the calculated CPS exceeds a threshold, a step that takes place in the mind of a doctor. The remaining elements in claim 1, such as determining the number of PD-L1⁺ tumor cells and MICs, are routine, conventional activities. Whether the steps of claim 1 are considered individually or in an ordered combination, claim 1 is still directed to only the natural law, abstract idea, and mental steps identified above.

205. Claims 2-21 each depend directly or indirectly on claim 1, and therefore incorporate and are directed to the same natural law, abstract idea, and mental step as claim 1. Like claim 1, the remaining elements in claims 2-21, including the elements added by each specific claim, are routine, conventional activities, and whether the steps of the claims are considered individually or in an ordered combination, claims 2-21 are still directed to only the natural law, abstract idea, and mental steps identified above.

1. Claim 1 Is Directed to a Natural Law, Abstract Idea, and Mental Step and Does Not Add Specific Limitations That Transform the Nature of the Claim

206. Claim 1 is reproduced below with its various elements split out for ease of reference.

[Preamble] A method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent, the method comprising:

[A] determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy;

[B] calculating a combined positive score (CPS) for the tumor tissue sample using the formula:

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive } MIC}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

[C] wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold,

[D] wherein said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.

207. Thus, claim 1 recites a “method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent,” with the following steps:

- **The Determining Step:** “determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC cells in a tumor tissue sample from a subject having a malignancy.”
- **The Calculating Step:** “calculating a [CPS] for the tumor tissue sample using the [CPS] formula”
- **The Eligibility Step:** “wherein the subject is eligible for treatment with said ant-PD therapeutic agent when the CPS is above a threshold.”

208. In other words, a POSA would have understood that claim 1 recites a method for determining whether a subject with a cancer malignancy is eligible for treatment with an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof based on whether the CPS for the tumor exceeds a threshold. The CPS is calculated using the following formula:

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

209. A POSA would have understood that claim 1 does not specify the subject (human or non-human animal), type of cancer, the claimed threshold, the identity of the anti-PD or anti-PD-L1 specific antibody or binding fragment, or the dose of dosing regimen for the anti-PD or anti-PD-L1 specific antibody or binding fragment. In addition, a POSA would have understood that claim 1 does not require any specific action after determining whether a subject is eligible for anti-PD therapy.

a. Claim 1 Is Directed to a Natural Law, Abstract Idea, and Mental Step

210. It is my opinion that claim 1 is directed to three categories of subject matter that are not patent eligible.

211. First, it is directed to the following **natural law**: the correlation between (a) the extent of PD-L1 expression in cancer cells and MICs and (b) the likely effectiveness of anti-PD therapeutic agents.

212. Claim 1 recites this natural law by reciting the following: (a) a CPS is calculated, and (b) a subject is “eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold.”

213. The calculated CPS, which is based on the extent of PD-L1 expression in cancer cells and MICs, represents element (a) of the natural law: the extent of PD-L1 expression in cancer cells and MICs.

214. The claim language reciting that a subject is “eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold” directly correlates the calculated CPS to the likelihood that an anti-PD therapy would be effective.

215. Based on the legal standards provided to me, this correlation is a natural law, and not the product of any human action, because the correlation between PD-L1 expression and response to anti-PD therapy exists apart from human action. It exists regardless of whether PD-L1 expression is measured, regardless of whether a CPS is calculated, and regardless of whether an anti-PD therapy is administered.

216. Second, claim 1 is directed to the use of a **mathematical formula/algorithm** to calculate the CPS, which, based on the legal standards as explained to me, is an abstract idea.

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

217. I understand that Patent Owner relied on the CPS for its alleged novelty. For example, the specification of *US702* states: “[I]t is clear that using current [non-CPS] scoring methods to capture PD-L1 expression on tumor as well as non-tumor cells (e.g., immune cells) is not practical from an assay development

standpoint, as it can double the pathologist's workload and/or lead to confusion with respect to having 2 different cutoffs (one for tumor cells and one for non-tumor cells)." EX1001, 3:8-14. US702 then states that a need exists for a better scoring method: "There is thus still a need to improve tumor scoring methods for identifying patients that will respond effectively to anti-PD therapy." EX1001, 3:14-16. US702 then introduces the CPS as the alleged solution to this problem. EX1001, 3:17-42.

218. Third, claim 1 is directed to the **mental step** of determining eligibility for anti-PD therapy based on whether the calculated CPS exceeds a threshold. Once the CPS is calculated, it is up to a doctor to decide whether to treat a patient with an anti-PD therapy. That decision, which may entail comparing a subject's CPS against a threshold, is conducted in the human mind, making it a mental step.

219. As explained below, the remaining elements in claim 1 were well known and conventional activities that do not integrate the natural law, abstract idea, and mental step into a practical application.

b. Claim 1 as a Whole Does Not Integrate the Natural Law, Abstract Idea, and Mental Step Into a Practical Application

220. I have been asked whether claim 1 as a whole integrates the natural law, abstract idea, and mental step mentioned above into a practical application. It does not. The Calculating and Eligibility Steps merely recite the natural law,

abstract idea, and mental step, and the Determining Step is simply a data gathering step. It is a step that has to be conducted to gather data to calculate the CPS using the CPS formula, which is an abstract idea.

221. In addition, claim 1 is very general and non-specific and does not place any meaningful limits on the claimed natural law, abstract idea, and mental step. For example, it does not specify any of the following:

- the subject (human vs. non-human animal);
- the malignancy;
- the CPS threshold; or
- the anti-PD therapy, dose, or dosing regimen.

And, as explained above, claim 1 does not require taking any action after assessing eligibility. Claim 1 therefore does not provide enough information to integrate the natural law, abstract idea, and mental step into a practical application, convert them into an improved method of treatment, or to practice a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome.

c. The Steps in Claim 1, Whether Considered Individually or as an Ordered Combination, Do Not Transform the Nature of the Claim

222. The natural law, abstract idea, and mental step in claim 1, and any additional steps in claim 1, do not transform the nature of the claim and simply encompass well-known, routine, conventional activities.

223. As explained below, the Determining, Calculating, and Eligibility steps, whether considered individually, or as an ordered combination, do not transform the nature of the claim into patent-eligible subject matter or add anything other than well-understood, routine, and conventional activities previously known in the industry and specified at a high level of generality.

224. **The Determining Step:** the Determining Step merely calls for counting the number of viable PD-L1⁺ tumor and MICs and counting the number of viable PD-L1⁻ tumor cells. As of the earliest possible effective filing date of *US702*, such counting was a conventional activity. For example, *Tumeh* discloses using quantitative IHC, in which PD-L1⁺ tumor cells and MICs were counted. EX1033, 568, Ext. Table 3; Paragraphs 116-17, 268.

225. In addition, the Determining Step of claim 1 is very general. It requires determining the number of PD-L1⁺ and PD-L1⁻ tumor cells and PD-L1⁺ MICs in a tumor tissue sample, but does not indicate how to count the cells or limit the methodology or technique for counting PD-L1⁺ and PD-L1⁻ cells. Indeed, the specification expressly states that any convenient method can be used to detect PD-L1⁺ cells, and says nothing about how to count the cells: “Detecting PD-L1 positive cells in a tumor sample can be done in any convenient manner.” EX1001, 9:6-7.

226. The specification of *US702* discloses the use of flow cytometry or single cell sequencing for counting the number of PD-L1⁺ tumor and MIC cells. EX1001, 9:37-44, 9:50-55, 21:51-55, 22:11-15. As explained below, both of those techniques were known and conventional before the earliest potential effective filing date of *US702*. Regardless, claim 1 is not limited to the using flow cytometry or single cell sequencing. *See* Paragraphs 97, 139, 184-85.

227. Moreover, the Determining Step requires that the PD-L1 expression is determined in a tumor tissue from a subject with a malignancy, but does not indicate whether the subject is human or a non-human animal, and does not limit the type of malignancy. *See* Paragraphs 133, 209, 221.

228. For all of the above reasons, the Determining Step fails to transform claim 1, which remains directed to a natural law, abstract idea, or mental step.

229. **The Calculating Step:** the Calculating Step merely performs the abstract act of calculating the CPS. As explained above, the concept of calculating a score to represent the extent of PD-L1 expression in tumor and MIC cells was conventional. While the scores used in the prior art were different than the score calculated in claim 1, the concept of calculating such a score that considers PD-L1 expression in tumor cells and immune cells was well known. EX1010, claim 1; EX1033, Ext. Data Table 3; EX1013, 5066; EX1059, 463; EX1017, 568; Paragraphs 117-19, 159-60, 224, above. Furthermore, I have been informed that

including an abstract step does not transform a claim, even if the result of the calculation has alleged advantages. As a result, the Calculating Step fails to transform claim 1, which remains directed to a natural law, abstract idea, or mental step.

230. **The Eligibility Step:** the Eligibility Step is a mental step, conducted in the mind of a doctor, that assesses eligibility for anti-PD therapy based on a comparison of the calculated CPS (an abstract idea) to an unspecified threshold. The Eligibility Step (a mental step), when combined with the Calculating Step (an abstract idea), merely restates the natural law that is the focus of claim 1. Moreover, the use of a threshold to assess eligibility for treatment was known and conventional as of the earliest potential effective filing date of *US702* (April 1, 2016). For example, Merck's *WO422* taught the use of a PD-L1 expression score threshold to assess eligibility for treatment with an anti-PD therapeutic. EX1010, [0019]; Paragraph 163.

231. In addition, the Eligibility Step in claim 1 is very general. The eligibility step refers to eligibility for treatment with an anti-PD therapeutic agent when the CPS is above a threshold, but does not specify a threshold. In addition, the claim indicates that the anti-PD therapeutic "comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof," which may include thousands of potential therapeutic agents and therefore does not meaningfully limit the claim.

232. For all of the above reasons, the Eligibility Step fails to transform claim 1, which remains directed to a natural law or abstract idea.

233. For the reasons set forth above, the steps of claim 1, when considered individually, do not transform the nature of claim 1. As explained below, the steps of claim 1, when considered as an ordered combination, do not transform the nature of claim 1.

234. **Ordered Combination:** The Determining, Calculating, and Eligibility Steps of claim 1, when considered as an ordered combination, merely recite (a) an abstract idea, *i.e.*, the CPS calculation, (b) a natural law, *i.e.*, the correlation between the extent of PD-L1 expression as represented by the CPS score and the effectiveness of anti-PD therapy, and (c) a mental step, *i.e.*, assessing eligibility for treatment with an anti-PD therapy.

235. Thus, the Determining Step merely generates inputs for the abstract idea represented by the CPS formula in the Calculating Step. And, as explained above, the Eligibility step is a mental step, and the Calculating and Eligibility Step together represent the natural law that is the focus of claim 1.

236. For the above reasons, the Determining, Calculating, and Eligibility Steps of claim 1, considered individually or as an ordered combination, do not transform the nature of claim 1, which remains directed to a natural law, abstract idea, and mental step.

d. Claim 1 Has a Fact Pattern that is Very Similar to that of USPTO Example 49

237. I understand that in July 2024, the USPTO published a series of Examples to illustrate how to assess subject matter eligibility. EX1081. I reviewed Example 49 and found that claim 1 of Example 49 presents a fact pattern that is very similar to claim 1 of Example 49.

238. Example 49 concerned a claim to a method of treating post-surgical fibrosis in which:

- (a) a sample collected from a glaucoma patient is genotyped;
- (b) the genotype is used to calculate a “weighted polygenic risk score” that is then used to identify whether the patient is at high risk for post-implantation inflammation (“PI”); and
- (c) administering an appropriate treatment to the patient at high risk of PI after microstent implantation surgery.

EX1081, 30.

239. The USPTO explained that Example 49 recites a natural law (a correlation between patient genotype PI risk), a mathematical calculation (a weighted polygenic risk score formula), and a mental step (identifying whether the patient is at high risk of PI based on the weighted polygenic risk score).

240. Claim 1 of *US702* likewise claims a natural law (a correlation between a subject’s tumor cell and MIC phenotype (whether those cells express PD-L1) and whether those cells will respond to anti-PD therapy), a mathematical

calculation (the CPS formula), and a mental step (identifying whether a patient is eligible for anti-PD therapy based on the CPS).

241. Unlike claim 1 of Example 49, claim 1 of *US702* does not recite an administration step.

* * *

242. For all of the above reasons, claim 1 of *US702* does not claim patent eligible subject matter.

2. Dependent Claims 2-21 Are Directed to the Same Natural Law, Abstract Idea, and Mental Step of Claim 1 and Do Not Add Specific Limitations That Transform the Nature of the Claim

243. I understand that because claims 2-21 depend directly or indirectly on claim 1, claims 2-21 incorporate the limitations of claim 1. Therefore, claims 2-21 claim the same natural law, abstract idea, and mental step that are the focus of claim 1.

244. As explained below (Paragraphs 245-309), the additional limitations added by each of claims 2-21 do not transform the nature of the claims and do not change that the claims are directed to a natural law, an abstract idea, and a mental step.

a. Dependent Claims 2 and 3 Do Not Add Specific Limitations That Transform the Nature of the Claims

245. Claims 2 and 3 depend on claim 1 and recite that the claimed “threshold” for determining eligibility is from 10% to 1% (claim 2) or is 1% (claim 3).

246. Through their dependence on claim 1, claims 2 and 3 incorporate the following:

- The natural law that is the focus of claim 1, *i.e.*, the correlation between the extent of PD-L1 expression in cancer cells and MICs and the likely effectiveness of anti-PD therapeutic agents.
- The abstract idea that is the focus of claim 1, *i.e.*, the mathematical CPS formula.
- The mental step that is the focus of claim 1, *i.e.*, assessing eligibility for anti-PD-L1 therapy.

247. The added threshold limitations in claims 2 and 3 do not add a new step or nonconventional concept to claim 1. As explained above, the concept of a PD-L1 positivity threshold for eligibility for anti-PD therapy is conventional. *See* EX1010, [0003] (citing EX1045, EX1046, EX1047, EX1048, EX1049, EX1050, EX1051 in support thereof). *WO422* further teaches that thresholds of 1% or 10% to 1% are conventional, disclosing “cut-offs” or thresholds for positive PD-L1

expression of 1% or 5% of total tumor cells. EX1010, [0005]-[0006]; *see also* EX1052, [0085].

248. Moreover, like claim 1, claims 2 and 3 are very general in that they do not require a specific action after determining a subject's eligibility for anti-PD therapy, let alone an action that transforms the claims. While claims 2 and 3 add some specificity regarding the threshold limitation, neither specifies how to determine the threshold. In addition, neither claim identifies the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen associated with the threshold. Claims 2 and 3 therefore remain very general and the nature of the claims remain the claimed natural law, abstract idea, and mental step.

249. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claims 2 and 3, whether considered individually or as an ordered combination, do not change the nature of claims 2 or 3 or convert the method of claims 2 or 3 into an improved method of treatment.

b. Dependent Claim 4 Does Not Add Specific Limitations That Transform the Nature of the Claim

250. Claim 4 depends on claim 1 and further requires that the tumor tissue sample used in the method is a tissue section of a tumor biopsy.

251. Through its dependence on claim 1, claim 4 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

252. The added “biopsy” limitation in claim 4 does not add a new step or nonconventional concept to claim 1. It relates to the conventional use of a tumor biopsy as a tumor tissue sample. For example, Merck’s prior art *WO422* teaches that a “tumor sample can be obtained by a variety of procedures including, but not limited to... biopsy.” EX1010, [0081]. Other prior art also teaches the use of biopsies for IHC staining. *See* EX1012, 11, 26 (“There is a trend away from invasive surgical procedures towards less invasive biopsy techniques for pathological diagnosis.”); Paragraphs 98, 167.

253. Moreover, like claim 1, claim 4 is very general in that it does not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claims. It also does not provide a threshold limitation, identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. The nature of the claim remains the claimed natural law, abstract idea, and mental step.

254. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claim 4, whether considered individually or as an ordered combination, do not change the nature of claim 4 or convert the method of claim 4 into an improved method of treatment.

c. Dependent Claim 5 Does Not Add Specific Limitations That Transform the Nature of the Claim

255. Claim 5 depends on claim 4 and specifies that the PD-L1 is detected by IHC staining.

256. Through its dependence on claim 4, and indirect dependence on claim 1, claim 5 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

257. The added “IHC staining” limitation in claim 5 does not add any new action to take after assessing eligibility for anti-PD therapy and does not add any non-conventional concepts to claim 1 or claim 4. Instead, the added limitation relates to the conventional step of using IHC staining to detect PD-L1. For example, Merck’s prior art *WO422* teaches the conventional nature of using IHC staining to detect PD-L1, specifically teaching the use of IHC staining by the antibody 22C3 in FFPE tissue samples to detect PD-L1. EX1010, [0025]-[0029], Figs. 2-6. Moreover, nothing in *US702* advances the field of IHC beyond what is taught in prior art like *Dako*. EX1012.

258. Moreover, like claim 1, claim 5 is very general in that it does not require a specific action, after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claim. In addition, claim 5 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold

applies. Claim 5 therefore remains very general and the nature of the claim remains the claimed natural law, abstract idea, and natural step.

259. For the above reasons, and the reasons set forth above with respect to claims 1 and 4 (Paragraphs 206-44, 250-54), the elements in claim 5, whether considered individually or as an ordered combination, do not change the nature of claim 5 or convert the method of claim 5 into an improved method of treatment.

d. Dependent Claims 6-8 Do Not Add Specific Limitations That Transform the Nature of the Claims

260. Claims 6-8 depend on claim 4 and provide further limitations relating to the tumor tissue section and its staining. More specifically, claim 6 depends on claim 4 and specifies that the tumor tissue section is an FFPE tumor tissue section. Claim 7 depends on claim 4 and requires that the tumor tissue section is stained, and claim 8 depends on claim 7 and requires that the stain is H&E.

261. Through their dependence on claim 4, and indirect dependence on claim 1, claims 6-8 incorporate the natural law, abstract idea, and mental step that are the focus of claim 1.

262. The added tumor section and staining limitations in claims 6-8 do not add any new action to take after assessing eligibility for anti-PD therapy and do not add any non-conventional concepts to claim 1 or claim 4. Instead, the added limitations in claims 6-8 relate to the conventional use of FFPE tumor tissue sections and stained/H&E stained tumor tissue sections. For example, *Dako*

teaches that the use of FFPE tissue sections has a “long history” and that staining tissue sections is conventional: “In the majority of cases, tissue specimens for *immunohistochemical (IHC) staining* are routinely fixed in formalin and subsequently embedded in paraffin. Because of the *long history* of the use of formalin-fixed, paraffin-embedded (*FFPE*) tissue sections in histopathology, *most of the criteria for pathological diagnosis have been established by the observation of FFPE tissue sections stained by hematoxylin and eosin [H&E].*” EX1012, 31 (emphasis added). Likewise, Merck’s *WO422* teaches the use of FFPE and stained tumor tissue sections. EX1010, [0082] (FFPE), [00113] (stained tissue samples).

263. In addition, *US702* acknowledges the conventional nature of staining tumor tissue sections, stating that H&E stain “is the most commonly used light microscopy stain in histology and histopathology” and that “there are many other staining techniques known in [sic] to those of skill in the art that can be used to selectively stain cells and cellular components that find use in the present disclosure, and as such no limitation in this regard is intended.” EX1001, 10:2-19.

264. Moreover, like claim 1, claims 6-8 are very general in that they do not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claims. They also do not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD

therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claims 6-8 therefore remain very general and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

265. For the above reasons, and the reasons set forth above with respect to claims 1 and 4 (Paragraphs 206-44, 250-54), the elements in claims 6-8, whether considered individually or as an ordered combination, do not change the nature of claims 6-8 or convert the method of claim 6, 7, or 8 into an improved method of treatment.

e. Dependent Claim 9 Does Not Add Specific Limitations That Transform the Nature of the Claim

266. Claim 9 depends on claim 4 and specifies counting PD-L1⁺ and PD-L1⁻ cells in tumor nests and adjacent supporting stroma.

267. Through its dependence on claim 4, and indirect dependence on claim 1, claim 9 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

268. The added limitation in claim 9 regarding where to count tumor cells and MICs does not add any new action to take after assessing eligibility for anti-PD therapy and does not add any non-conventional concepts to claim 1 or claim 4. Instead, the added limitation in claim 9 relates to the conventional step of assessing PD-L1 expression in tumor nests and the adjacent supporting stroma. For example, Merck's prior art *WO422* teaches the conventional nature of determining

the extent of staining in tumor nests (claim 1) and the stroma surrounding each tumor nest. EX1010, claim 3. In addition, *Tumeh* discloses counting the number of PD-L1⁺ cells in the tumor parenchyma (intratumoral) and in the invasive margin (stroma). EX1033, 5 (“Slides were examined for the presence of CD8, CD4, Ki67, PD-1, and PD-L1 within the tumour parenchyma (tumour) and the connective tissue surrounding the tumour (invasive margin)”; Paragraphs 81, 84, 113, 123, 161.

269. Moreover, like claim 1, claim 9 is very general in that it does not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claim. In addition, claim 9 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claim 9 therefore remains very general and the nature of the claim remains the claimed natural law, abstract idea, and mental step.

270. For the above reasons, and the reasons set forth above with respect to claims 1 and 4 (Paragraphs 206-44, 250-54), the elements in claim 9, whether considered individually or as an ordered combination, do not change the nature of claim 9 or convert the method of claim 9 into an improved method of treatment.

**f. Dependent Claim 10 Does Not Add Specific
Limitations That Transform the Nature of the Claim**

271. Claim 10 depends on claim 1 and requires that the tumor tissue sample is a cell suspension.

272. Through its dependence on claim 1, claim 10 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

273. The added “cell suspension” limitation in claim 10 does not add any new step or non-conventional concept to claims 1 or 10. Instead, it relates to the conventional step of using a cell suspension as a tumor tissue sample. For example, *Dako* taught that immunofluorescence is a common laboratory technique used to evaluate cells in suspension. EX1012, 87. Accordingly, cells in suspension are also conventional. In addition, *US702* acknowledges that methods for obtaining cell suspensions “are known in the art.” EX1001, 5:56-63.

274. Moreover, like claim 1, claim 10 is very general in that it does not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claim. In addition, claim 10 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claim 10 therefore remains very general and the nature of the claim remains the claimed natural law, abstract idea, and mental step.

275. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claim 10, whether considered individually or as an ordered combination, do not change the nature of claim 10 or convert the method of claim 10 into an improved method of treatment.

g. Dependent Claim 11 Does Not Add Specific Limitations That Transform the Nature of the Claim

276. Claim 11 depends on claim 10 and further requires that flow cytometry is used to count the number of PD-L1 and MIC cells.

277. Through its dependence on claim 10 and indirect dependence on claim 1, claim 11 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

278. The added “flow cytometry” limitation in claim 11 does not add any new action to take after assessing eligibility for anti-PD therapy and does not add any non-conventional concepts to claims 1, 10, or 11. Instead, the added limitation in claim 11 relates to the conventional step of using flow cytometry to count PD-L1⁺ and PD-L1⁻ cells. For example, *Dako* taught the use of a flow cytometer to evaluate and quantify what is seen in cells in suspension: “Immunofluorescence (IF) is a common laboratory technique.... Applications include the evaluation of cells in suspension.... The degree of fluorescence can then be quantified using a flow cytometer.” EX1012, 87. *Savas* also taught the use of flow cytometry. EX1060, 229 Box 1, 230; Paragraphs 97, 184, 456.

279. Moreover, like claim 1, claim 11 is very general in that it does not require a specific action after determining a subject's eligibility for anti-PD therapy, let alone an action that transforms the claim. In addition, claim 11 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claim 11 therefore remains very general, and the nature of the claim remains the claimed natural law and abstract idea.

280. For the above reasons, and the reasons set forth above with respect to claims 1 and 10 (Paragraphs 206-44, 271-75), the elements in claim 11, whether considered individually or as an ordered combination, do not change the nature of claim 11 or convert the method of claim 11 into an improved method of treatment.

h. Dependent Claims 12 and 13 Do Not Add Specific Limitations That Transform the Nature of the Claim

281. Claim 12 depends on claim 1 and requires detecting one or more additional marker in the tumor tissue sample, *i.e.*, in addition to PD-L1. Claim 13 depends on claim 12 and specifies that “the marker is specific for MIC or is selected from the group consisting of CD3, CD5, CD4, CD7, CD8, and CD20.

282. Through direct or indirect dependence on claim 1, claims 12 and 13 incorporate the natural law, abstract idea, and mental step that are the focus of claim 1.

283. The added marker limitations in claims 12 and 13 do not add any new action to take after assessing eligibility for anti-PD therapy and do not add any non-conventional concepts to claims 1, 12, or 13. Instead, the added limitations in claims 12 and 13 relate to the conventional step of detecting a second marker that can be specific for MIC or other protein complexes. For example, *Dako* taught the use of multi-staining IHC, wherein multiple targets are detected in a tumor sample, for example, when using sequential staining. EX1012, 83 (Chapter 6.7). Other prior art references also disclosed the use of IHC for detecting PD-L1 and one or more additional markers recited in claim 13. For example, *Taube 2012* disclosed use of IHC markers for PD-L1 expression by tumor cells and tumor infiltrating immune cells and detection of CD3 and CD68 immunostains to interpret which cell type demonstrated expression of a given ligand. EX1013, 8 (“IHC for select cell lineage markers including CD3, D100, and CD68 for T cells, melanocytes, and macrophages, respectively was performed...”). See Paragraphs 111-13.

284. Moreover, like claim 1, claims 12 and 13 are very general in that they do not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claims. In addition, claims 12 and 13 do not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claims 12 and 13 therefore remain very general

and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

285. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claims 12 and 13, whether considered individually or as an ordered combination, do not change the nature of claims 12 or 13 or convert the method of claim 12 or 13 into an improved method of treatment.

i. Dependent Claim 14 Does Not Add Specific Limitations That Transform the Nature of the Claim

286. Claim 14 depends on claim 1 and requires, “prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof.” Through dependence on claim 1, claim 14 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

287. The added “contacting” limitation in claim 14 does not add any new action to take after assessing eligibility for anti-PD therapy and does not add any non-conventional concepts to claims 1 or 14. Instead, the added “contacting” step is a conventional step when using IHC staining to detect PD-L1. First, a POSA would have known that when staining cells in a tumor tissue sample, the cells in the sample are generally contacted with a detectible target-specific binding agent. Second, with respect to detecting PD-L1, *WO422* taught using that the preferred anti-PD-L1 antibody used for IHC staining was antibody 22C3 (EX1010, [0022]) and disclosed examples in which tumor tissue samples were stained by IHC with

antibody 22C3 (EX1010, [0025]-[0029], Figs. 2-6). A POSA would have understood that as part of the IHC staining process in *WO422*, the tumor tissue sample would have been contacted with antibody 22C3. *See* Paragraphs 97-9, 167, 257.

288. Moreover, like claim 1, claim 14 is very general in that it does not require a specific action after determining a subject's eligibility for anti-PD therapy, let alone an action that transforms the claim. Indeed, claim 14 recites an action that must be taken before assessing whether the CPS threshold is met. In addition, claim 14 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claim 14 therefore remains very general and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

289. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claim 14, whether considered individually or as an ordered combination, do not change the nature of claim 14 or convert the method of claim 14 into an improved method of treatment.

j. Dependent Claim 15 Does Not Add Specific Limitations That Transform the Nature of the Claim

290. Claim 15 depends on claim 1 and requires that single cell sequencing is used to count the number of PD-L1 and MIC cells. EX1001, 9:50-55.

291. Through dependence on claim 1, claim 14 incorporates the natural law, abstract idea, and mental step that are the focus of claim 1.

292. The added “single cell sequencing” limitation in claim 15 does not add any new action to take after assessing eligibility for anti-PD therapy and does not add any non-conventional concepts to claims 1 or 15. Instead, the added limitation in claim 15 relates to the conventional step of using single cell sequencing to count PD-L1⁺ and PD-L1⁻ cells. For example, *Dako* taught that next generation sequencing, which encompasses single cell sequencing, was entering routine diagnostic application. EX1012, 119; EX1001, 9:50-55. *Savas* also taught single cell sequencing. EX1060, 230. In addition, *US702* does not purport to claim a new or different type of single cell sequencing or provide any guidance on how to use single cell sequencing for practicing the claimed method.

293. Moreover, like claim 1, claim 15 is very general in that it does not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claim. In addition, claim 15 does not provide a threshold limitation, or identify the subject, cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Claim 15 therefore remains very general and the nature of the claim remains the claimed natural law, abstract idea, and mental step.

294. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claim 15, whether considered individually or as an ordered combination, do not change the nature of claim 15 or convert the method of claim 15 into an improved method of treatment.

k. Dependent Claims 16 and 19 Do Not Add Specific Limitations That Transform the Nature of the Claims

295. Claim 16 depends on claim 1 and further requires that the malignancy is selected from a group of identified cancers, including breast cancer. Claim 19 depends on claim 16 and specifies that the breast cancer is TNBC, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer.

296. Through direct or indirect dependence on claim 1, claims 16 and 19 incorporate the natural law, abstract idea, and mental step that are the focus of claim 1.

297. The added “malignancy” limitations in claims 16 and 19 do not add any new action to take after assessing eligibility for anti-PD therapy and do not add any non-conventional concepts to claims 1, 16, or 19. Instead, the added malignancy limitations in claims 16 and 19 merely identify conventional malignancies of subjects who are tested for eligibility for anti-PD therapy. For example, *WO422* teaches assessing PD-L1 positivity in most of the cancer types listed in claim 16, including the estrogen receptor positive breast cancer, HER2

positive breast cancer, and TNBC recited in claim 19. EX1010, [0017];

Paragraphs 165, 405, 434.

298. Moreover, like claim 1, claims 16 and 19 are very general in that they do not require a specific action after determining a subject's eligibility for anti-PD therapy, let alone an action that transforms the claims. In addition, they do not provide a threshold limitation, or identify a subject, a specific cancer to be treated, or the anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Indeed, claim 16 identifies 20 categories of cancer, many of which include subcategories of cancer, and even claim 19 includes at least 5 types of breast cancer. Claims 16 and 19 therefore remain very general and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

299. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claims 16 and 19, whether considered individually or as an ordered combination, do not change the nature of claims 16 or 19 or convert the method of claim 16 or 19 into an improved method of treatment.

I. Dependent Claims 17 and 18 Do Not Add Specific Limitations That Transform the Nature of the Claims

300. Claim 17 depends on claim 1 and requires that the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1. Claim 18 depends on claim 1 and requires that the anti-PD therapeutic agent is selected from the group

consisting of: Avelumab, Nivolumab, Pembrolizumab, BMS-936559, MPDL3280, Pidilizumab, and MEDI4736.

301. Through dependence on claim 1, claims 17 and 18 incorporate the natural law, abstract idea, and mental step that are the focus of claim 1.

302. The added “anti-PD therapeutic agent” limitations in claims 17 and 18 do not add any new action to take after assessing eligibility for anti-PD therapy and do not add any non-conventional concepts to claims 1, 17, or 18. Instead, the anti-PD therapeutic agents identified in claims 17 and 18 were conventional anti-PD therapeutic agents that were known in the prior art. For example, *WO422* discloses the use of nivolumab, pidilizumab, MPDL 3280, MEDI4736, and pembrolizumab. EX1010, Exemplary Specific Embodiments 25-27; *see* Paragraph 164; *see also* EX1019, 1; Paragraphs 68-78.

303. Moreover, like claim 1, claims 17 and 18 are very general in that they do not require a specific action after determining a subject’s eligibility for anti-PD therapy, let alone an action that transforms the claims. In addition, they do not provide a threshold limitation, or identify a subject, cancer to be treated, or a specific anti-PD therapy/effective dose/dosing regimen to which the unidentified threshold applies. Indeed, claim 17 identifies a broad category of anti-PD therapeutics, and claim 18 identifies 7 different anti-PD therapeutics. Claims 17

and 18 therefore remain very general and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

304. For the above reasons, and the reasons set forth above with respect to claim 1 (Paragraphs 206-44), the elements in claims 17 and 18, whether considered individually or as an ordered combination, do not change the nature of claims 17 or 18 or convert the method of claim 17 or 18 into an improved method of treatment.

m. Dependent Claims 20 and 21 Do Not Add Specific Limitations That Transform the Nature of the Claims

305. Claim 20 depends on claim 1 and further requires administering the anti-PD therapeutic agent to the subject when the CPS is above the threshold. Claim 21 depends on claim 20 and further requires that the threshold is greater than or equal to 1%.

306. Through direct or indirect dependence on claim 1, claims 20 and 21 incorporate the natural law, abstract idea, and mental step that are the focus of claim 1.

307. The added “administration” limitation (claims 20 and 21) and “threshold” limitation (claim 21) do not add any non-conventional concepts to claims 1, 20, or 21. Instead, they recite administering an anti-PD therapy to a subject with a malignancy, which was conventional. For example, administering an anti-PD therapy after assessing PD-L1 expression and comparing it to an expression score was well-known and routine, as evidenced by the disclosure of

such steps in, for example, *WO422*. EX1010, [00118]. In addition, as explained above (Paragraphs 68-78), by 2016, pembrolizumab and nivolumab were approved for treating malignancies, and many other anti-PD therapies were being studied. To the extent that a subject was already receiving an anti-PD therapy, claims 20 and 21 do not recite any change in dosing regimen based on whether a CPS threshold is exceeded, meaning the treatment for such subjects would not change. At best, claims 20 and 21 might identify anti-PD therapy naïve patients with CPS scores below the claimed threshold who a doctor could choose not to treat with an anti-PD therapy, although nothing in the claim precludes such treatment.

308. Moreover, like claim 1, claims 20 and 21 are very general because claim 20 does not provide a threshold limitation, and neither claim 20 nor 21 identifies a subject, specific cancer to be treated, a specific anti-PD therapy to administer, or a specific anti-PD therapy/effective dose/dosing regimen to which the threshold applies. The administration step in claims 20 and 21 is therefore factually similar to the administration step in claim 1 of USPTO example 49 (EX1081), *i.e.*, the administration step in claims 20 and 21 does not provide any information as to how the patient is to be treated or what the treatment is, and instead covers any possible treatment that a medical professional decides to administer to the patient. Like the administration step in hypothetical claim 1 of USPTO example 49, the added limitations in claims 20 and 21 therefore do not

meaningfully limit the claims. *See* EX1081, 33. And unlike hypothetical claim 2, which recites administering a specific novel therapeutic agent (compound X) to address a specific ailment (risk of PI in a glaucoma patient), claims 20 and 21 of *US702* do not identify a specific compound for administration or a specific malignancy to treat. Put another way, neither claim 20 nor 21 provides a specific method of treatment for specific patients using a specific compound at a specific dose to achieve a specific outcome. Claims 20 and 21 therefore remain very general and the nature of the claims remains the claimed natural law, abstract idea, and mental step.

309. For the above reasons, and the reasons set forth above with respect to claims 1-3 (Paragraphs 206-49), the elements in claims 20 and 21, whether considered individually or as an ordered combination, do not change the nature of claims 20 or 21 or convert the method of claim 20 or 21 into an improved method of treatment.

C. A POSA Would Have Required Undue Experimentation to Practice the Methods of Claims 1-21 of *US702*

310. As explained above (Paragraphs 40-5), I have been informed that a patent specification must enable the full scope of a claimed method so that it can be practiced by a POSA without undue experimentation. I have also been informed that the following factors, known as the *Wands* factors, are considered

when assessing whether a POSA would have required undue experimentation when practicing the full scope of a claimed method:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented in the disclosure;
- (3) The presence or absence of working examples in the disclosure;
- (4) The nature of the invention;
- (5) The predictability or unpredictability of the art;
- (6) The state of the prior art;
- (7) The relative skill of those in the art; and
- (8) The quantity of experimentation necessary.

311. Claims 1-21 are very broad, and the teaching in the specification of *US702* provides very little guidance. For example, claim 1 recites assessing eligibility for an unspecified anti-PD therapy (there are at least dozens) based on whether a tumor tissue sample from a subject (any human or non-human animal) with an unspecified malignancy (there are potentially hundreds) has a CPS that exceeds an unspecified threshold. Yet that claimed CPS threshold, the criterion for determining eligibility, itself depends on the subject, malignancy, the anti-PD therapy and line of anti-PD therapy, and the combination of these factors. *See* Paragraphs 96, 166. The only method the specification provides for determining

the CPS threshold is to generate an ROC curve. ROC analysis requires either conducting, for each subject/anti-PD therapy/malignancy combination, a carefully designed clinical trial or access to retrospective clinical-trial data sufficient to determine the true positive and negative rates. *See* Paragraphs 125-26. Such retrospective data would also have to be tabulated at the individual subject level. However, obtaining such subject level data is complex and burdensome and availability is uncertain. Such data is generally available only after a requester prepares and submits a scientifically complete petition and obtains approval from both the clinical trial investigators and their IRB. Approval of the petition by those two groups depends on assessment of scientific merit, the specific clinical trial and applicable IRB rules for subject privacy, and the specific clinical trial rules that govern academic priority and competition resulting from third-party analysis. In addition, even if access is secured, a valid retrospective analysis requires study design and statistical analysis that may be beyond the areas of scientific expertise of medical practitioners, and hence often entails the full burden of a new research project. Thus, the specification's reference to ROC analysis leaves the POSA to undertake, for each subject/anti-PD therapy/malignancy combination, the research needed to establish the threshold on which the claimed eligibility determination depends.

312. Moreover, a separate ROC curve would have to be generated for each subject/anti-PD therapy/malignancy combination. The specification of *US702* provides only a hypothetical threshold for one malignancy (gastric carcinoma), without specifying the anti-PD therapy, and provides no guidance or principles that would permit a POSA to extrapolate from that teaching to other malignancies, anti-PD therapies, or combinations thereof.

313. As an example of the breadth of the claims with respect to the malignancy, there are many different kinds of cancers, including carcinomas, sarcomas, lymphomas, leukemias, and germ cell tumors. The most common cancers are carcinomas, which are cancers derived from the epithelium—skin, glands, or other lining elements and organs in our bodies. EX1079, 295-97. Breast cancer, lung cancer, and prostate cancer are categorized as epithelial tumors (carcinoma), but they are very different diseases. Even within each tissue type, many different subtypes can occur, each displaying a different morphology, subtype treatment plans, and prognosis. In addition, there are inter- and intraindividual heterogeneity of particular cancer subtypes, with distinct combinations of driver and modifier gene mutants and signaling pathways, and concordant treatments targeting those genes and pathways. EX1039, 338. The granularity of cancer typing is evidence of the diverse nature of cancer. Because

the types of cancers and ways in which they develop are so varied, each cancer type may require a different treatment approach.

314. Moreover, the CPS threshold depends on clinical responses that vary based on the subject's malignancy, anti-PD therapy, and line of therapy. The unpredictability of such clinical responses renders the CPS threshold unpredictable for any given combination. *US702* does not provide any teachings that reduce this unpredictability, because *US702* does not provide a single example of a threshold for a specified malignancy/anti-PD therapy combination, and does not disclose any general principles that would permit a POSA to determine such a threshold without undue experimentation. Essentially, the claims of *US702* leave scientists with the following research assignment to practice the full scope of the claims: engage in painstaking experimentation to identify thresholds that distinguish responders from nonresponders across at least thousands of combinations of subject, malignancy, anti-PD therapy, and threshold, ideally identifying all responders (no false negatives) while minimizing the number of non-responders incorrectly classified as responders (*i.e.*, false positives). *See* EX1001, 20:60-65.

315. In addition, researchers have encountered various issues when using PD-L1 as a predictive biomarker. As an initial matter, there was "wide variability" in the percent tumor samples overexpressing PD-L1 for tumors that responded to anti-PD-1 therapy, *i.e.*, 14% to 100%. EX1056, 848-49, Table 1. Moreover, even

tumors that generally did not respond to such therapy had 12%-53% positivity for PD-L1, meaning that PD-L1 positivity is not the sole determinant of which tumors will respond to anti-PD therapy. *Id.*; EX1031, 986 (positivity rates for PD-L1 ranging from 13-70%, correlation between biomarker positivity and treatment response rates from 13-83%, and response rates of 3-20% in PD-L1 negative cases).

316. Moreover, the role that immune checkpoints play may differ depending on the tumor molecule phenotype. EX1056, 848-850. For instance, “[e]xpression of PD-L1 [determined] by IHC appears to be increased in TNBC [triple negative breast cancer] relative to that in hormone-driven tumors, and the prognostic importance of TILs in TNBC make the PD-1/PD-L1 axis appealing as a therapeutic target.” *Id.* at 850. Moreover, in colorectal cancer, patients with microsatellite unstable (MSI-H) primary tumors have an increased superior prognosis, associated with increased TILs within the tumor. *Id.*

317. As reported in *Patel*, use of PD-L1 IHC as a predictive biomarker “is confounded by multiple unresolved issues: variable detection antibodies, differing IHC cutoffs, tissue preparation, processing variability, primary versus metastatic biopsies, oncogenic versus induced PD-L1 expression, and staining of tumor versus immune cells.” EX1056, 847. In addition, “the prognostic and predictive impact of PD-L1 IHC is temporally dependent on the time of biopsy in relation to

the development of the lesion as well as in relation to antecedent therapies.” *Id.*, 852. In addition, *Kerr* reported that predicting response to therapy may “depend on which line of therapy for which the immune checkpoint inhibitory agent is given (Table 1).” EX1031, 986.

318. *Kerr* identified the following regarding the difficulties in determining a positive, predictive biomarker threshold:

Determining the threshold that defines a positive, predictive test is a difficult issue. Thresholds may be predetermined, before outcome data are known, or as a more useful approach, the response data may be used to indicate the threshold that gives best discrimination between responders and nonresponders, or between patients who do or do not derive significant survival benefit from the therapy. It has, however, been noted that traditional response evaluation criteria in solid tumors for assessing tumor response may not be best suited to assessing clinically significant responses to immune checkpoint inhibitor therapy, at least in a small proportion of the cases. There is then a potential trade-off between improving upon the response rates seen in an unselected treated population, the acceptability of this response rate in an unselected population versus that seen with standard of care treatment, and any considerations to maximize the population eligible for treatment. In addition, to date, response (overall response rate) alone does not seem to be the best way to evaluate the benefit of immunotherapy; this is probably better captured by progression-free or overall survival data. Finally, if very low staining thresholds such as 1% or even 5% of cells are chosen, there is a greater risk that scoring will be inconsistent and is more likely to reflect inaccurately the patient’s tumor burden overall, because of heterogeneity.

Id., 986. *Kerr* also noted a particular concern with biomarker tests predicated on biomarker expression in tumor infiltrating immune cells due to difficulties in

identifying the infiltrating cells, and in determining whether such cells are reacting to the tumor or are bystander cells native to the tissue where the tumor developed (such as in a lymph node). *Id.*, 987.

319. *Kerr* identified several differences in diagnostic approaches, including the use of different antibodies, different technical staining platforms, and critically, different definitions of a “positive” predictive score. EX1031, 986-87; *see also id.*, 987, Table 1. Use of different definitions of a “positive” score resulted in a wide range of positivity for PD-L1 from 13% to 70%, and treatment response rates varied from 13% to 83%, depending on the biomarker-defined cohort and therapy used. *Id.*, 986. Given the wide range of response rates, it was recognized that determining the threshold for a positive, predictive test was difficult. *Id.* In particular, “very low staining thresholds such as 1% or even 5% of cells” were recognized to lead to “a greater risk that scoring will be inconsistent.” *Id.*, 986.

320. Notably, significant responses were also reported for cases identified as “negative.” EX1031, 986. The presence of patients who responded to therapy and yet scored as “negative” according to these biomarker tests called into question the value of PD-L1 IHC as a predictive biomarker to select patients for treatment with agents targeting the PD-1/PD-L1 pathway. *Id.*, 986-87.

321. For the above reasons, and as I explain more fully below, a POSA would have required undue experimentation to practice the methods of claims 1-21 of *US702*, and it is my opinion that those claims are therefore not enabled.

1. Claim 1

322. As explained above, claim 1, the only independent claim, recites a method for assessing whether a subject with a malignancy has a CPS above a threshold and is therefore eligible for treatment with an anti-PD therapy.

323. Claim 1 does not identify whether the subject is a human or non-human animal, does not identify a malignancy or anti-PD therapy, and does not limit the malignancy, anti-PD therapy, or CPS threshold in any way. As explained below (Paragraphs 327-34), claim 1 is very broad in scope because it lacks these limitations.

324. In addition, the CPS threshold depends on the malignancy, the anti-PD therapy (and line of therapy), and the combination thereof, and the threshold for any malignancy/anti-PD therapy is unpredictable.

325. Despite the breadth of the claim, which encompasses all malignancy/anti-PD therapies and associated CPS thresholds, and the unpredictability of the CPS threshold associated with any given malignancy/anti-PD therapy combination, *US702* neither provides a threshold for a specific

malignancy/anti-PD therapy combination nor any principles that a POSA could use to predict such a threshold.

326. As explained above (Paragraph 45), I have been informed that the *Wands* factors can be used to assess whether a POSA would require undue experimentation to practice the full scope of claim 1. As explained below, and as supported by my assessment of the *Wands* factors, in view of the breadth of claim 1, the unpredictability of CPS thresholds for any malignancy/anti-PD therapy combination, and the lack of teaching in the specification, a POSA would have required extensive/undue experimentation to practice the full scope of claim 1.

a. The Breadth of the Claims (Factor 1): The Claims Are Very Broad

327. As explained above, claim 1 of *US702* is directed to determining whether an unspecified subject with an unspecified malignancy is eligible for treatment with an unspecified anti-PD therapy based on whether a calculated CPS exceeds an unspecified threshold. As explained below, each of these unspecified elements is broad, and the combination makes claim 1 exceptionally broad. That breadth is compounded by the interdependence of those elements, for which the specification provides no generalizable teachings.

328. **The Subject:** Claim 1 encompasses “determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent...wherein the subject is eligible for treatment with said anti-PD therapeutic

agent when...” EX1001, claim 1. The specification defines the subject as encompassing at least humans and non-human animals. *See* Paragraph 133; EX1001, 5:44-54; 22:53-54.

329. **The Malignancy:** It has been reported that there are over 200 cancer malignancies. EX1025. Claim 1 does not specify a malignancy, and therefore encompasses all known malignancies. A POSA would have expected the CPS threshold to depend on the malignancy because both PD-L1 expression and responses to anti-PD therapy regardless of PD-L1 expression varied across different malignancies. EX1060, 229, 231-32; EX1017, 565, Table 2; EX1013, 5067; EX1068, 1-2. Accordingly, leaving the malignancy unspecified makes claim 1 very broad and, as explained below, makes practicing claim 1 unpredictable.

330. **The Anti-PD Therapy:** Claim 1 states that “said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.” *US702* defines fragments as including the following: “fragments of antibodies which retain specific binding to antigen or target, including, but not limited to, Fab, Fv, scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, bi-specific hybrid anti-bodies, and fusion proteins comprising an antigen-binding portion of an antibody and a non-antibody protein.” EX1001, 7:11-17. It has been reported that 8 anti-PD antibodies have

been approved in the U.S. and 18 have been approved worldwide (EX1075, 1; EX1073, 1), with some reports indicating that about 30 anti-PD antibodies have been approved worldwide (EX1074, 1, 5). All of these fall within the claimed anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.

331. In addition, *Kerr* indicates that whether the anti-PD therapy is used as a first-line or second or later-line therapy can impact the CPS threshold. EX1031, 986, 987 (Table 1).

332. Finally, *US702* acknowledges that the CPS threshold “is specific to the drug used.” EX1001, 8:49-51.

333. For these reasons, leaving the anti-PD therapy unspecified makes claim 1 very broad and, as explained below, makes practicing claim 1 unpredictable.

334. **The Threshold:** The only method the specification provides for determining the CPS threshold is to generate an ROC curve. The specification of *US702* provides only a hypothetical threshold for one malignancy (gastric carcinoma), without specifying the anti-PD therapy, and provides no guidance or principles that would permit a POSA to extrapolate from that teaching to other subjects, malignancies, anti-PD therapies, or combinations thereof. As explained in Paragraphs 311-12, ROC analysis would therefore require, for each subject/malignancy/anti-PD therapy combination, either conducting a carefully

designed clinical trial or access to retrospective clinical-trial data sufficient to determine the true positive and negative rates, activities that are complex and burdensome. *See* Paragraphs 125-26. Thus, the specification's reference to ROC analysis leaves the POSA to undertake, for each subject/malignancy/anti-PD therapy combination, the research needed to establish the threshold on which the claimed eligibility determination depends. Finally, a POSA also would have understood that because claim 1 does not recite a threshold, the threshold could be any value between 0 and 100%.

**b. The Amount of Direction or Guidance Presented
(Factor 2): The Specification Provides Little
Guidance**

335. *US702* states that the threshold can be any applicable CPS value, and that in some embodiments the threshold is 1% (EX1001, 8:49-52), but does not provide a threshold applicable to any malignancy/anti-PD therapy combination.

336. *US702* states that the threshold is “specific to the drug used” (EX1001, 8:51), but does not provide the threshold applicable for any specific anti-PD therapy.

337. *US702* includes only a single hypothetical example, Example 1. EX1001, 20:66-21:2. In Example 1, the tumor tissue sample is obtained from a subject with gastric carcinoma. But Example 1 does not indicate whether the subject is human or a non-human animal.

338. Example 1 does not identify the hypothetical treatment, but speculates that a CPS cut-off/threshold of $\geq 1\%$ is expected to “identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses.” EX1001, 20:66-21:2.

339. The specification also states that “CPS can be used to analyze triple negative breast carcinoma [TNBC] using a similar cut-off value as described above.” EX1001, 21:9-10. Again, this identifies a malignancy, but does not identify the anti-PD therapy, which impacts the threshold, and also does not identify the subject.

340. Other than the above “disclosures,” the specification does not teach any CPS threshold that is therapeutically meaningful for any subject, malignancy, anti-PD therapy, or combination thereof.

341. With respect to determining a CPS cut-off/threshold, as explained above, the specification provides only one method for doing so, generating an ROC curve. EX1001, 8:47-48. The specification also states that a cut-off/threshold is “the score that differentiates diagnostically positive from diagnostically negative” (EX1001, 20:60-61), but this fails to provide any teaching about how to determine a threshold.

342. As to generating an ROC curve, a POSA would have known that doing so requires responder/non-responder data obtained from a clinical trial. A

POSA also would have known that the correlation between tumor cell PD-L1 expression, immune cell PD-L1 expression, and cancer treatment may differ for different malignancies and anti-PD therapies, and that therefore a separate clinical trial would be required to generate the ROC curve for each drug/dosage regimen/malignancy combination. This also leads to a great deal of unpredictability when attempting to practice the method of claim 1. *See* Paragraphs 124-26.

343. The specification provides no principles or relationships between subject, drug, malignancy, or combinations thereof from which a POSA could extrapolate a CPS threshold from hypothetical Example 1 or the information on TNBC to any other subject/drug therapy/malignancy combination. The specification's teachings regarding how to perform IHC and calculate CPS do not fill this gap, because those steps merely tell the POSA how to collect data, they do not provide guidance on the CPS threshold for any particular subject/drug therapy/malignancy combination.

**c. The Presence or Absence of Working Examples
(Factor 3): The Single Example Is Not a Working
Example; It Is Prophetic, Narrow, and Incomplete**

344. Example 1 is the only example in *US702* that identifies a malignancy and a threshold, albeit a prophetic/"expected" threshold. I have been informed that an example is a "working" example if it reports actual experimental results, and

that the past tense is used to do so. I have also been informed that an example is a “prophetic” example if it describes predicted experimental results, and that the present or future tense is used to do so.

345. Example 1 uses the present tense and provides only predicted results.

As representative examples, Example 1 states the following:

- “Specimens from subjects having gastric carcinoma patients [sic] **are** analyzed” (present tense). EX1001, 19:60-61 (emphasis added).
- “Specimens for analysis **are** formalin-fixed and paraffin-embedded (FFPE) tissue sections. Sections **are** cut to a desired thickness (e.g., 4 um thickness)” (present tense). EX1001, 19:65-67 (emphasis added).
- “The IHC staining for PD-L1 expression **is** performed using the Dako Autostainer Link 48 platform (Dako AS480) and an automated staining protocol validated for the PD-L1 IHC 22C3 pharmDx assay” (present tense). EX1001, 20:5-8 (emphasis added).
- “**It is expected** that setting the cut-off at $\geq 1\%$ for a positive result for the scores above, CPS will identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses described above” (present tense/predicted result). EX1001, 20:66-21:2 (emphasis added).

Accordingly, Example 1 is a prophetic example, not a working example.

346. In addition, prophetic Example 1 is narrow and incomplete. It is narrow because it relates to only one malignancy: gastric carcinoma. It is incomplete because it does not identify whether the subject is a human or non-human animal (and if so, which species of non-human animal), and does not

identify the anti-PD therapy that is hypothetically used. *See* Paragraphs 337-40, 344-45. In addition, while the example includes prophetic steps up to estimating the number of PD-L1^{+/+} cells, no results are provided. For example, the estimated number of PD-L1^{+/+} cells is not provided, no TPS (tumor proportion score), MIDS (mononuclear inflammatory density score), or CPS is calculated, and no population of subjects was analyzed to assess responsiveness, generate an ROC curve, or identify a threshold. EX1001, 19:42-21:5.

347. For all of the above reasons, the prophetic example in *US702* does not convey any information that would let a POSA determine the CPS eligibility threshold for any subject/drug/malignancy combination without extensive/undue experimentation. At best, it invites scientists to engage in painstaking experimentation to determine combinations of subject, malignancy, anti-PD therapy, and threshold that work.

d. The Nature of the Invention (Factor 4), the Predictability or Unpredictability of the Art (Factor 5), and the State of the Prior Art (Factor 6): The Claimed Methods Require Determining Clinically Meaningful Correlations Between Biomarker Expression and Therapeutic Response

348. The claimed methods assess whether a subject with a malignancy has a CPS that exceeds a threshold and is therefore eligible for anti-PD therapy. The CPS threshold, which must be determined, is a correlation between biomarker (PD-L1) expression and clinical response. While POSAs understood that in some

drug/malignancy combinations there was an association between PD-L1 expression and response to anti-PD therapy, a POSA could not have known, without significant experimentation, the CPS threshold for any given scoring methodology that would differentiate between diagnostically positive and diagnostically negative. *See* EX1001, 20:60-62; EX1060, 229, 231-32; EX1017, 565, Table 2; EX1013, 5067; EX1068, 1-2.

349. Moreover, responsiveness to PD-L1 therapy was not always predictable based on PD-L1 expression. For example, *Ali* found that basal-like breast cancer tumors, such as TNBC, were characteristically enriched in PD-L1 expression and therefore more likely to respond to anti-PD therapy than other breast cancers. EX1022, 1491. But other researchers found that PD-L1 expression did not correlate with response to anti-PD therapy in some cancers. EX1060, 229, 231-32; EX1017, 565, Table 2; EX1013, 5067; EX1068, 1-2. *US702* leaves a POSA to figure out for themselves whether for any given tumor there was such a correlation, unless such information was already taught in the art.

350. In addition, as explained above in, *e.g.*, Paragraphs 96, 166, and 329-34, the CPS threshold varies depending on the malignancy and, as *US702* acknowledges, the anti-PD therapy. EX1001, 8:49-51.

351. The above considerations make it necessary to conduct a non-trivial clinical study designed to determine the number of responders and false responders

to determine the CPS threshold for any subject/drug/malignancy combination. Such a clinical study would be required for each drug/malignancy combination, and the data from such clinical trials is necessary to support the claimed eligibility decisions, with more work required for other combinations depending on what the art already taught about the tumor-type being evaluated.

e. The Relative Skill of Those in the Art (Factor 7): The Level of Skill of the POSA Does Not Change the Amount of Experimentation Required

352. As explained above (*see* Paragraph 342), the claimed method requires determining a CPS threshold through a clinical trial for each subject/drug/malignancy combination. Moreover, neither the specification of *US702* nor the prior art provides a CPS threshold for any specific subject/drug/malignancy combination or general principles for predicting such a threshold.

353. For the above reasons, and in view of the wide breadth of claim 1, the nature of the claimed method/CPS threshold, and the need to empirically determine a CPS threshold through a clinical trial for each subject/drug/malignancy combination, the level of skill of a POSA, even if high, would not impact the extensive/undue experimentation required to practice the full scope of the claimed methods.

f. The Quantity of Experimentation Necessary (Factor 8): Extensive/Undue Experimentation Would Have Been Required To Practice the Full Scope of Claim 1

354. For all of the reasons in Paragraphs 327-53, above, a POSA would have required extensive/undue experimentation to practice the full scope of the claimed method. More specifically, to practice the full scope of the claimed methods, a POSA would have been required to empirically determine a CPS threshold for at least thousands of subject/drug/malignancy combinations, a determination that would require specially designed clinical experimentation for each combination, not routine laboratory optimization. Claim 1 thus presents a research assignment that would have required scientists to design and conduct clinical studies to determine combinations of subject, malignancy, anti-PD therapy, and threshold that differentiate diagnostically positive from diagnostically negative subjects.

* * *

355. For all of the above reasons, a POSA would have required undue experimentation to practice the full scope of the claimed methods. Accordingly, claim 1 is not enabled. And for the reasons discussed below in Paragraphs 356-70, the remaining claims are also not enabled because they do not cure the deficiencies with claim 1.

2. Claims 2 and 3

356. Claims 2 and 3 depend on claim 1 and add threshold limitations:

Claim 2 recites a CPS threshold of “from 10% to 1%” and claim 3 recites a threshold of “1%.” These recited thresholds do not narrow claim 1 in a way that would reduce the extensive/undue experimentation needed to practice claims 2 and 3. This is because neither claim 2 nor claim 3 identifies a subject (human or non-human animal), a cancer (there are potentially over 200), an anti-PD therapy or line of therapy (there are at least dozens), or a dose/dosing regimen, all of which can impact the CPS threshold. Without conducting a clinical trial for each subject/anti-PD therapy/malignancy combination and generating an ROC curve, a POSA would not know which combinations would work with a CPS threshold of “from 10% to 1%” (claim 2) or of “1%” (claim 3). *See* Paragraphs 231, 329-30.

357. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 2 and 3 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

3. Claims 4 and 10

358. Claims 4 and 10 depend on claim 1 and add limitations regarding the type of tumor tissue sample: claim 4 recites that the tumor tissue sample is a tissue section of a tumor biopsy, and claim 10 says that the tumor tissue sample is a cell suspension.

359. The added limitations in claims 4 and 10 do not materially narrow the subject, anti-PD therapy, or threshold limitations in claim 1. Limiting the tumor tissue sample to a tissue section of a biopsy merely limits the potential malignancies to solid tumors, and cell suspensions can potentially be prepared from any solid or liquid tumor.

360. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 4 and 10 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

4. Claims 5-8

361. Claims 5-7 depend on claim 4 and recite limitations regarding the processing of the tissue sample: claim 5 recites that the PD-L1 is detected by IHC staining, claim 6 recites that the tumor tissue sample is a FFPE tumor tissue sample, and claim 7 recites that tissue section is stained. Claim 8 depends on claim 7 and recites that the stain is an H&E stain. These steps relate to the processing of the tissue sample and do not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 5-8 for the same reasons as set forth above with respect to claims 1 and 4. *See* Paragraphs 310-55, 358-60.

5. Claim 9

362. Claim 9 depends on claim 4 and recites that “the viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC are counted in the tumor nests and the adjacent supporting stroma of the tumor tissue sample.” This limitation relates to where cells are analyzed. It does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 9 for the same reasons as set forth above with respect to claims 1 and 4. *See* Paragraphs 310-55, 358-60.

6. Claim 11

363. Claim 11 depends on claim 10 and recites that “the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determined by flow cytometry.” This limitation relates how the number of PD-L1 positive and negative cells are determined. It does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 11 for the same reasons as set forth above with respect to claims 1 and 10. *See* Paragraphs 310-55, 358-60.

7. Claims 12 and 13

364. Claim 12 depends on claim 1 and recites that one or more additional markers are detected in the tumor tissue sample. Claim 13 depends on claim 12 and recites that the “marker is specific for MIC or is selected from the group consisting of CD3, CD5, CD4, CD7, CD8, and CD20.” Detecting additional markers does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 12 and 13 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

8. Claim 14

365. Claim 14 depends on claim 1 and recites that the method further comprises, prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof. This added step is part of IHC analysis. As claim 14 indicates, this added step occurs before the determining step. This added step does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 14 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

9. Claim 15

366. Claim 15 depends on claim 1 and recites that “the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determined by single cell sequencing.” This limitation relates how the number of PD-L1 positive and negative cells are determined. It does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 15 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

10. Claims 16 and 19

367. Claim 16 depends on claim 1 and recites that the malignancy is selected from a group consisting of 20 different types of cancers, some of which are categories of cancers. Claim 19 depends on claim 16 and recites that “the breast cancer is triple negative breast cancer, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer.” Thus, even when considering the added limitation in claims 16 and 19, those claims still cover at least 24 malignancies, and actually cover many more than that, because many of the malignancies recited in claim 16 are, like “breast cancer,” categories of

malignancies. For example, the three most common histological subtypes of renal cell carcinoma are clear cell, papillary, and chromophobe. EX1070, 166. The malignancy limitations in claims 16 and 19 do not narrow claim 1 in a way that would reduce the extensive/undue experimentation needed to practice claims 16 and 19. This is because neither claim 16 nor claim 19 identifies a subject or an anti-PD therapy or line of therapy (there are at least dozens), a dose/dosing regimen, or a threshold, and even the malignancy limitations narrow the claim to, at minimum, 24 malignancies (the 19 non-breast cancer malignancies in claim 16 plus the 5 breast cancer malignancies in claim 19). Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 16 and 19 for these reasons and the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

11. Claims 17 and 18

368. Claim 17 depends on claim 1 and recites that the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1. Claim 18 depends on claim 1 and limits the anti-PD therapeutic agent to an agent selected from the following group of 7 agents: avelumab, nivolumab, pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736. While claim 18 narrows the potential anti-PD therapy to one of seven identified therapies, neither claim 17 nor 18 limits the subject or malignancy, and neither claim includes a CPS threshold. As

explained above, a clinical trial would be required to determine the CPS threshold for every combination of those seven anti-PD therapies, potential subjects, and the hundreds of potential malignancies. *See* Paragraph 329. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the methods of claims 17 and 18 for these reasons and the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

12. Claim 20

369. Claim 20 depends on claim 1 and adds “administering said anti-PD therapeutic agent to the subject when the CPS is above the threshold.” This administration step comes after all of the other steps in claim 1. It does not narrow the subject, malignancy, anti-PD therapy (or line of therapy), or CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 20 for the same reasons as set forth above with respect to claim 1. *See* Paragraphs 310-55.

13. Claim 21

370. Claim 21 depends on claim 20 and adds that the threshold “is greater than or equal to 1%.” This limitation does not narrow claim 20 in a way that would reduce the extensive/undue experimentation needed to practice claim 21. This is because claim 21 does not identify a subject, a cancer (there are potentially over 200), an anti-PD therapy or line of therapy (there are at least dozens), or a

dose/dosing regimen, all of which can impact the CPS threshold. Accordingly, a POSA would have required extensive/undue experimentation to practice the full scope of the method of claim 21 for the same reasons as set forth above with respect to claims 1 and 20. *See* Paragraphs 310-55, 369.

D. The Claims of *US702* Are Obvious

1. Claims 1-8, 12-14, and 16-21 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas*

a. Claim 1 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas*

371. Claim 1 is directed to a method for determining whether a cancer subject is eligible for treatment with an anti-PD therapeutic agent.

372. As explained below, *WO422* taught all of the elements of claim 1 other than the specific CPS formula.

373. As explained above (Paragraph 152), *WO422* stated it relates to “the quantitation of PD-L1 expression in animal tissue samples by immunohistochemical (IHC) assay” and “the identification of PD-L1 expression levels that correlate with response of cancer patients to therapy with antagonists of [PD-1].” EX1010, [0001]. *WO422* further teaches that the disclosed methods are for identifying patients that may benefit from anti-PD-1 therapy. *Id.*, [0009]. In those studies, frozen or FFPE tumor samples are stained with a primary antibody that binds to PD-L1. *Id.*, [0010].

374. *WO422* reflected the knowledge in the art regarding the correlation of (a) PD-L1 expression in a large set of tumors, including ovarian, renal, colorectal, pancreatic, liver cancers, and melanoma, and (b) poor prognosis and reduced overall survival. *Id.*, [0003]; *see also* Paragraph 153. *WO422* further taught that antibodies that block the binding of PD-L1 to PD-1, *i.e.*, anti-PD antibodies, have been shown to have anti-tumor activity against a variety of tumor types, with early clinical data suggesting that patients with tumors expressing PD-L1 are most likely to respond. EX1010, [0003]; *see also* Paragraph 154.

375. *WO422* described several prior art approaches for scoring PD-L1 expression. One approach was to determine the percentage of tumor cells that exhibit staining with anti-PD-L1 antibody compared to the total number of tumor cells. EX1010, [0005]. That score can be expressed as:

$$\frac{\text{PD-L1-stained viable tumor cells}}{\text{Total viable tumor cells}} \times 100\%$$

WO422 taught that different studies set different cut-offs/thresholds for designating the tumor as PD-L1 positive, citing a threshold of 1% in *Gadiot* (EX1014), and a threshold of 5% in *Topalian* (EX1042). EX1010, [0005]; *see also* Paragraph 166.

376. *WO422* taught another approach, in which PD-L1 expression was quantified separately in tumor cells and in infiltrating immune cells, which *WO422* stated predominantly comprise lymphocytes. EX1010, [0006] (citing *Taube 2012* (EX1013) and *Thompson* (EX1032)). *WO422* stated that the threshold of PD-L1

expression for designating a tumor as positive was $\geq 5\%$. *WO422* explained that PD-L1 expression in infiltrating immune cells was reported as the AIS, described above. *See* Paragraphs 94, 156, 166; EX1010, [0006].

377. As explained above (Paragraph 158), *WO422* taught that quantifying PD-L1 expression using IHC analysis, “beyond a simple binary positive/negative characterization, can provide valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.” EX1010, [0009]. As an example of such an approach, in Exemplary Specific Embodiment 1, *WO422* taught staining a tumor tissue section with an anti-PD-L1 antibody, examining the tissue section for staining, and determining an MPS. *Id.*, Exemplary Specific Embodiment 1.

378. As explained above, *WO422* taught assigning an MPS by estimating the percentage of PD-L1⁺ tumor cells and MICs in the examined tumor nests:

[w]herein assigning the MPS comprises estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity, and assigning the resulting percentage to the tissue section as the MPS.

EX1010, Exemplary Specific Embodiment 1; *see also* Exemplary Specific Embodiments 12 and 23, claims 1, 10, and 18.

379. The MPS thus incorporated the number of PD-L1⁺ tumor cells *and* the number of PD-L1⁺ MICs. The MPS can therefore be determined using the following calculation:

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

380. The MPS calculation and the claimed CPS calculation therefore differ in one way, *i.e.*, the CPS does not include the total number of MICs in the denominator, while the MPS does. This can be seen when comparing the two formulas:

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

$$\text{CPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{PD-L1 positive tumor cells} + \text{PD-L1 negative tumor cells}} \times 100\%$$

381. *WO422* and *US702* are therefore conceptually directed to the same thing, *i.e.*, an anti-PD therapy eligibility score that requires the counting of **both** PD-L1⁺ tumor cells and PD-L1⁺ MICs.

382. As explained below, a POSA would have been motivated to remove the total number of MICs from the denominator of the MPS to arrive at the CPS, and would have had a reasonable expectation of success when using such a score to determine whether a patient is eligible for anti-PD therapy.

- i. **“A method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent, the method comprising:”**

383. As discussed above, *WO422* relates to “quantitation of PD-L1 expression in animal tissue samples by immunohistochemical (IHC) assay” for identifying patients that may benefit from anti-PD therapy. EX1010, [0001], [0009]. *WO422* therefore teaches the subject matter of this element of claim 1.

- ii. **“determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy:”**

384. As explained above, *WO422* taught a method in which a tumor tissue section is stained with an anti-PD-L1 antibody and an MPS is determined by “estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity, and assigning the resulting percentage to the tissue section.” EX1010, *e.g.*, Exemplary Specific Embodiment 1, claim 1.

385. *WO422* also taught methods for estimating the number and intensity of viable tumor cells and MICs: “Medium and high power is typically used to examine individual tumor nests to estimate the number and intensity of viable

tumor and mononuclear inflammatory cells that exhibit at least partial membrane staining.” EX1010, [0112].

386. As explained above, a POSA would have understood that the Determining Step in claim 1 encompasses approximate numerical assessment or estimating of cells as taught in *WO422*. See Paragraphs 198-201.

387. For the above reasons, *WO422* discloses this step of claim 1.

**iii. “calculating a combined positive score (CPS)
for the tumor tissue sample using the [CPS]
formula:”**

388. As explained above, the following formula can be used to calculate the MPS:

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

Thus, the MPS differs from the CPS only in that the formula for the MPS includes the total number of MICs in the denominator while the formula for the CPS does not.

389. As explained below, at least for assessing eligibility for anti-PD therapy for certain tumors, a POSA would have been motivated to modify the MPS to remove the total number of MICs from the denominator for at least the following reasons: (a) to reduce the risk of false negatives; (b) because other investigators had focused on PD-L1⁺ MICs and excluded PD-L1⁻ MICs from

scores; and (c) PD-L1⁺ MICs reflect favorable antitumor response in some types of cancer.

390. A POSA would have understood that for an eligibility score that is calculated based on a numerator and a denominator, the numerator is intended to include the elements of the score that are expected to have predictive value for the desired effect. With respect to the MPS, the desired effect is to determine therapeutically beneficial eligibility for anti-PD therapy. Therefore, a POSA would want the numerator of the formula for the “score” to include in the numerator those elements that are expected to be predictive for eligibility for anti-PD therapy/response to anti-PD therapy. *WO422* itself emphasizes the importance of accuracy and reliability, stating that “new scoring rules are needed to accurately and reliably quantify the level of PD-L1 expression across multiple tissue samples and pathologists doing the scoring.” EX1010, [0008].

391. As explained above, *WO422* (and other prior art) taught that anti-PD antibodies have been shown to have anti-tumor activity against a variety of tumor types, with early clinical data suggesting that patients with tumors expressing PD-L1 are most likely to respond. A POSA would have understood that the MPS includes the number of PD-L1⁺ cells in the numerator, and that an eligibility score should have the number of PD-L1⁺ cells in the numerator, because early clinical

data suggested that tumors with such PD-L1 expression are most likely to respond to anti-PD therapy. EX1010, [0003].

392. Likewise, as discussed above (Paragraph 81), a POSA would have understood the biologic basis for including PD-L1⁺ MICs in the numerator when assessing the likelihood of response to anti-PD therapy, *i.e.*, that PD-L1 expression by MICs disrupts the body's immune response against the tumor by binding to PD-1 on T-cells and thereby inhibiting T-cell function. *E.g.*, EX1016, 8. Moreover, a POSA would have known that, at least in certain tumors, "the expression of PD-L1 on the intratumoural TILs seems to predict better responses to the anti-PD-L1 agent." EX1060, 238. A POSA would have therefore understood that the MPS includes the number of PD-L1⁺ cells in the numerator, and that an eligibility score should have the number of PD-L1⁺ cells in the numerator, because the presence of PD-L1⁺ intratumoral TILs seems to predict better responses to anti-PD therapy.

393. A POSA also would have understood that while anti-PD therapy will block the interaction of PD-1 and PD-L1 on PD-L1⁺ MICs, such therapy does not block anything on PD-L1⁻ MICs. A POSA therefore would not have expected that including PD-L1⁻ MICs in the formula would provide any predictive value for two reasons: (a) false negative effect; and (b) effector cell paradox. That would have motivated a POSA to remove such PD-L1⁻ MICs from the denominator of the MPS.

394. The impact of PD-L1⁻ MICs on the MPS, and their potential for resulting in false negatives, is best demonstrated through an example.

395. This example assumes the following:

- 100 viable tumor cells
- 10 of the viable tumor cells are PD-L1⁺
- 50 MICs
- 3 PD-L1⁺ MICs
- 10% Threshold for PD-L1 positivity (and eligibility for anti-PD therapy)

In the table below, I calculate a score using the MPS, which includes all MICs in the denominator, and a second score which does not include any MICs in the denominator, and indicate whether the tumor exceeds the 10% threshold and would therefore be considered PD-L1 positive, making the subject eligible for PD-L1 therapy.

		No MICs in Denom.	MPS (MICs in Denom.)
Numerator	PD-L1 ⁺ Tumor	10	10
	PD-L1 ⁺ MIC	3	3
	Total	13	13
Denominator	All Tumor	100	100
	All MIC	N/A	50
	Total	100	150
Score		13/100 = 13%	13/150 = 8.67%
Eligible For PD-L1 Therapy?		YES [ELIGIBLE]	NO [FALSE NEGATIVE]

396. As demonstrated in the table above, if, as in the MPS, total MICs are included in the denominator even though they have no prognostic value, the inclusion of total MICs in the denominator lowers the score and results in a potential false negative.

397. As another example, just changing the number of total MICs while holding all else constant, and more importantly, while holding the number of PD-L1⁺ tumor cells and MICs constant, can impact whether a tumor is considered positive or negative for PD-L1 expression. In this example, the assumptions are the same as above, except that the total number of MICs is varied between 20 and 50.

		MPS	
		(20 MICs in Denom.)	(50 MICs in Denom.)
Numerator	PD-L1 ⁺ Tumor	10	10
	PD-L1 ⁺ MIC	3	3
	Total	13	13
Denominator	All Tumor	100	100
	All MIC	20	50
	Total	120	150
Score		13/120 = 10.8%	13/150 = 8.67%
Eligible For PD-L1 Therapy?		YES [ELIGIBLE]	NO [FALSE NEGATIVE]

398. The above example shows how an increase in the number of PD-L1⁺ MICs, when holding all else constant, can lead to a false negative. Merely adjusting the threshold to a lower value would not resolve this issue because it might instead lead to a higher rate of false positives.

399. A POSA would have been motivated to remove the total MICs from the denominator of the score to reduce the risk of a false negative. WO422 emphasizes the importance of generating “valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.” EX1010, [0009].

400. In addition, a POSA would have been aware of other circumstances in which investigators evaluated the predictive value of MICs by evaluating the extent of PD-L1⁺ MICs in the tumor, without looking at the total number of MICs or considering the number of PD-L1⁺ MICs. For example, *Bellmunt*, which

evaluated the predictive value of PD-L1⁺ MICs, scored PD-L1 expression by evaluating “[t]he extent of PD-L1-positive [MICs]” in the tumor. EX1023, 812-13. A POSA would have understood from *Bellmunt* that the total number of MICs, and more specifically the number of PD-L1⁻ MICs, do not carry any weight when assessing the value of PD-L1⁺ MICs for predicting whether anti-PD therapy will benefit a patient. This also would have motivated a POSA to focus an “eligibility” score on the presence of PD-L1⁺ MICs and to exclude total MICs from the denominator.

401. Effector cell paradox is another reason that a POSA would have been motivated to exclude total MICs from the denominator, whether PD-L1 positive or PD-L1 negative.

402. A POSA would have known that MICs produce tumor growth arrest or death through their effector cell roles. These roles include the local release of anti-tumor molecules (for example, cytokines) by both PD-L1⁻ and PD-L1⁺ MICs, and the predominant role of cytotoxic contact mechanisms, in particular, cytolysis by CD8⁺ T-lymphocytes. Notably, CD8⁺ T-lymphocytes are the predominant MIC cell type, and they are typically PD-L1 negative. EX1033, 570, Fig. 3a; EX1017, 564, 565, Fig. 1c and 4b; EX1060, 228, Fig. 1.

403. Accordingly, a POSA would have understood that anti-tumor effector cell numbers correlate with favorable anti-tumor immune responses. For example,

Savas, like *WO422*, discusses the use of PD-L1 staining of tumor cells and MICs for predicting whether patients with breast cancer, including TNBC, will benefit from anti-PD therapy. *Savas* explains that generally, “[t]hese infiltrates [MICs] seem to reflect favourable host antitumour immune responses, suggesting that immune activation is important for improving survival outcomes.” EX1060, 228.

404. A POSA would have understood that to the extent that both PD-L1 positive and negative MICs reflect favorable antitumor response, such MICs do not belong in the denominator of the score where they would reduce the score, erroneously being treated as harmful and/or undesirable. In this regard, including MICs in the MPS denominator undermines *WO422*’s stated use of the score, in which a below threshold score “indicates that the patient has a PD-L1 expression score that is correlated with no response or poor response to treatment with a PD-1 antagonist,” given that MICs associated with a greater response to treatment with a PD-1 antagonist can themselves cause the MPS to fall below that threshold. *See, e.g.,* EX1010, [0116]. Accordingly, the fact that even PD-L1⁺ MICs may benefit cancer patients provides a POSA with further motivation to remove the total number of MICs from the MPS denominator for tumors, like breast cancer, that are susceptible to anti-PD therapy.

405. A POSA would have been motivated to combine the teachings of *WO422*, *Bellmunt*, and *Savas* for the following reasons. First, all three references

relate to the treatment of cancer with anti-PD therapy and how PD-L1 expression relates thereto. Second, *WO422* teaches that the tumor sample for use in its method can be selected from a group that includes bladder cancer and several forms of breast cancer (estrogen receptor positive HER2 negative breast cancer, HER2 positive breast cancer, and TNBC). EX1010, [0017]. *Bellmont* focuses on urothelial cancer, which is the most common form of bladder cancer, and *Savas* focuses on breast cancer, including HER2-positive breast cancer, HER2-negative breast cancer, and TNBC. EX1023, 812; EX1060, 229. Third, *WO422* describes a score, the MPS, that includes PD-L1⁺ tumor cells and MICs. Both *Bellmont* and *Savas* focus on the importance of MICs and their relation to cancer outcomes. Together, these teachings would have motivated a POSA to exclude MICs from the MPS denominator both to reduce false negatives without an associated tradeoff of increased false positives, and to avoid the counterintuitive result of lowering a patient's eligibility score because of immune cell infiltration associated with a greater likelihood of responding to therapy, as explained in further detail in Paragraphs 371-404. For all of these reasons, a POSA would have been motivated to combine the teachings of *WO422*, *Bellmont*, and *Savas*.

406. For all of the above reasons, a POSA would have been motivated to remove total MICs from the denominator of the MPS. Doing so would have resulted in claim 1.

407. For the following reasons, a POSA would have had a reasonable expectation that the score resulting from removing the total MICs from the denominator of the MPS would continue to facilitate identification of patients eligible for anti-PD therapy.

408. First, *WO422* states that the MPS “provide[s] valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.... A PD-L1 expression score produced by performing this scoring process may be useful in selecting patients to receive anti-PD-1 therapy.” EX1010, [0009].

409. *WO422* states that a tumor sample may be designated as PD-L1 positive if it has an MPS greater than 0. Accordingly, an MPS greater than zero, and designation as PD-L1 positive, could result from having as few as one positive tumor cell or one positive MIC. While removing MICs from the denominator would increase the calculated score, it would not change the fact that a PD-L1⁺ designation could result from having as few as one positive tumor cell or one positive MIC. For this reason alone, a POSA would have had a reasonable expectation of success of identifying subjects eligible for anti-PD therapy when using a score like the MPS in which MICs were removed from the denominator.

410. Second, as explained above, a POSA would have expected that removing total MICs from the denominator would result in a score that would

likely reduce the risk of false negatives, *i.e.*, the score would still be useful for selecting patients to receive anti-PD therapy.

411. Third, a POSA would have known of data in the literature confirming the one could use an assessment of PD-L1⁺ tumor cells and MICs as biomarkers for predicting treatment success with anti-PD therapy in tumors like TNBC.

EX1022, 1491-92; EX1010; *see* Paragraphs 107-09, 165, 179-80.

412. Fourth, a POSA would have understood that the known ROC method could be used to determine an appropriate eligibility threshold and thereby facilitate identifying patients with a malignancy that are eligible for anti-PD therapy. *See* Paragraphs 124-26.

413. Finally, as explained above (Paragraph 202), claim 1 only requires assessing eligibility for anti-PD therapy by comparing a score to an unspecified threshold. Claim 1 does not require actual therapy.

414. Based on all of the above, a POSA would have reasonably expected that removing MICs from the denominator of the MPS would result in a useful, predictive score that would facilitate assessing a subject's eligibility for anti-PD therapy.

- iv. **“wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold, wherein said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.”**

415. *WO422* teaches treating a subject with a PD-1 antagonist if the MPS exceeds a threshold. EX1010, [0019], [00118], Embodiments 23-24, Claims 18-19. Accordingly, *WO422* teaches this element.

* * *

416. For all of the above reasons (Paragraphs 371-415), a POSA would have been motivated to modify *WO422*'s MPS by removing total MICs from the denominator, which would result in the CPS, and would have had a reasonable expectation of success in using such a score to determine patients eligible for anti-PD therapy. For these reasons, a POSA would have found the method of claim 1 obvious over the combination of *WO422*, *Bellmunt*, and *Savas*.

- b. **Claims 2 and 3 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas***

Claim 2: “wherein the threshold is from 10% to 1%”

Claim 3: “wherein the threshold is 1%”

417. As explained above, claims 2 and 3 each depend on claim 1 and add threshold limitations: claim 2 recites a CPS threshold of “from 10% to 1%” and claim 3 recites a threshold of “1%.”

418. *WO422* teaches a method to predict if a patient has a PD-L1⁺ tumor and is thus likely to respond to treatment with a PD-1 antagonist. EX1010, [0010]. It further teaches that a tumor like breast cancer could be considered PD-L1⁺ if it has an MPS score greater than zero. *Id.*, [0016]. This would essentially equate to an MPS threshold of 1.

419. A POSA would have understood that an MPS threshold of 1 (1%) indicates that PD-L1⁺ tumor cells and/or MICs exist. As explained above (*see* Paragraph 409), as few as one PD-L1⁺ tumor cell or MIC would result in an MPS of greater than zero, which would not be impacted by removing MICs from the denominator. For these reasons, a POSA would have been motivated to set the threshold for the MPS, or for the MPS as modified above to remove total MICs from the denominator (Paragraphs 388-414), as 1%, which is within the “10% to 1%” range of thresholds in claim 2, and is the same as the “1%” threshold in claim 3.

420. For the above reasons, and the reasons given with regard to claim 1 (*see* Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, and *Savas* would have motivated a POSA to practice the methods of claims 2 and 3 with a reasonable expectation of success. Therefore, claims 2 and 3 would have been obvious to a POSA.

c. Claims 4-7 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, and *Savas*

Claim 4: “wherein the tumor tissue sample is a tissue section of a tumor biopsy”

Claim 5: “wherein PD-L1 is detected by immunohistochemistry (IHC) staining”

Claim 6: “wherein the tumor tissue section is a formalin fixed and embedded in paraffin wax (FFPE) tumor tissue section”

Claim 7: “wherein the tissue section is stained”

421. Claim 4 depends on claim 1 and further requires that the tumor tissue sample used in the method is a tissue section of a tumor biopsy. It would have been obvious to a POSA to use a tumor biopsy to assess PD-L1 expression levels because, as of the earliest possible effective filing date, doing so was routine and conventional. For example, *WO422* taught obtaining a tumor tissue sample from a biopsy. EX1010, [0081], [00113].

422. Claim 5 depends on claim 4 and specifies that the PD-L1 is detected by IHC. It would have been obvious to a POSA to use IHC to detect PD-L1 because, as of the earliest possible effective filing date, doing so was routine and conventional. For example, *WO422* taught the use of IHC staining to detect PD-L1. EX1010, [0025]-[0029], [00113].

423. Claim 6 depends on claim 4 and specifies that the tumor tissue section is an FFPE tumor tissue section. Claim 7 depends on claim 4 and requires that the

tumor tissue section is stained. It would have been obvious to a POSA to use an FFPE tumor tissue section and staining when conducting IHC staining because, as of the earliest possible effective filing date, doing so was routine and conventional. For example, *WO422* taught the use of an FFPE tumor tissue section ([0021], [0082], Exemplary Specific Embodiment 17, Claim 13), and staining a tissue section ([0010], [0017], [0024]-[0029], [0066], [0080], [00113], [00122], [00129], Exemplary Specific Embodiments 1, 12, Claims 1, 10, 23).

424. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 371-415), the combined teachings of *WO422*, *Bellmont*, and *Savas* would have motivated a POSA to practice the methods of claims 4-7 with a reasonable expectation of success. Therefore, claims 4-7 would have been obvious to a POSA.

d. Claim 8 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, and *Savas*

Claim 8: “wherein the stain is a hematoxylin and eosin (H&E) stain”

425. Claim 8 depends on claim 7, and adds that the stain is an H&E stain. It would have been obvious to a POSA to use H&E stain because, as of the earliest possible effective filing date, its use was routine and conventional. For example, *WO422* teaches that the “IHC assay may be performed using an automated pathology system, which may include automated staining (conventional stains,

histochemical techniques, immunostainers)” EX1010, [0097]. As explained by *Dako*, H&E is a conventional stain: “Because of the long history of the use of formalin-fixed, paraffin-embedded (FFPE) tissue sections in histopathology, most of the criteria for pathological diagnosis have been established by the observation of FFPE tissue sections stained by hematoxylin and eosin.” EX1012, 31.

Moreover, *Bellmunt* and *Savas* taught the use of H&E staining for scoring PD-L1 expression. EX1023, 813; *see also* EX1060, 229 (“TILs are commonly detected in haematoxylin and eosin (H&E) stained histological slides via light microscopy”).

426. For the above reasons, and the reasons given with regard to claim 1, 4, and 7 (*see* Paragraphs 371-415, 421, 423-24), the combined teachings of *WO422*, *Bellmunt*, and *Savas* would have motivated a POSA to practice the method of claim 8 with a reasonable expectation of success. Therefore, claim 8 would have been obvious to a POSA.

e. **Claims 12 and 13 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas***

Claim 12: “wherein one or more additional marker is detected in the tumor tissue sample”

Claim 13: “wherein the marker is specific for MIC or is selected from the group consisting of: CD3, CD5, CD4, CD7, CD8, and CD20”

427. Claim 12 depends on claim 1 and recites that an additional marker is detected. Claim 13 depends on claim 12 and limits the marker to one of CD3, CD5, CD4, CD7, CD8, and CD20.

428. It would have been obvious to a POSA to test for additional markers, including one of CD3, CD5, CD4, CD7, CD8, and CD20, because the prior art, like *Savas*, taught doing so. For example, *Savas* taught that the immune microenvironment of the tumor is shaped by competing co-stimulatory and co-inhibitory signals. EX1060, 236. For example, *Savas* notes that “the presence of activated CD8⁺ T-cells in the tumour microenvironment is associated with favourable outcomes,” although they may also induce counter-immune mechanisms. *Id.* *Savas*’s teaching that CD8 may be associated with favorable outcomes would have motivated a POSA to test for the presence of CD8⁺ T-cells and to determine whether those T-cells are expressing PD-L1.

429. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, and *Savas*

would have motivated a POSA to practice the methods of claim 12 and 13 with a reasonable expectation of success. Therefore, claims 12 and 13 would have been obvious to a POSA.

f. Claim 14 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas*

Claim 14: “wherein the method further comprises, prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof”

430. Claim 14 depends on claim 1 and requires contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof and doing so prior to the Determining Step. It would have been obvious to a POSA to contact a tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof prior to the Determining Step because, as of the earliest possible effective filing date, doing so was routine and conventional. *See* Paragraph 287.

431. For example, *WO422* taught the use of anti-PD-L1 antibodies for detecting PD-L1⁺ cells. EX1010, [00101]. A POSA would have understood that using anti-PD-L1 antibodies to detect PD-L1⁺ cells would entail contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof prior to the Determining Step.

432. For the above reasons, and the reasons given with regard to claim 1 (*see* Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, and *Savas*

would have motivated a POSA to practice the method of claim 14 with a reasonable expectation of success. Therefore, claim 14 would have been obvious to a POSA.

g. Claims 16 and 19 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, and *Savas*

Claim 16: “wherein the malignancy is selected from the group consisting of: [listing of 20 cancer-type categories]”

Claim 19: “wherein the breast cancer is triple negative breast cancer, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer”

433. Claim 16 depends on claim 1 and adds that the malignancy is selected from the following list of categories of cancer: gastric cancer, head and neck cancer, renal cell carcinoma, urothelial/bladder carcinoma, ovarian carcinoma, myeloma, melanoma, lung cancer, squamous cell carcinoma, classical Hodgkin’s lymphoma, breast cancer, small cell lung cancer, salivary gland carcinoma, vulvar carcinoma, thyroid carcinoma, anal canal carcinoma, biliary carcinoma, mesothelioma, cervical carcinoma, and neuroendocrine carcinoma. Claim 19 depends on claim 16 and adds that the breast cancer identified in claim 16 is TNBC, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer.

434. As explained above (Paragraphs 371-415), it would have been obvious to a POSA to practice the method of claim 1. Moreover, it would have been obvious to a POSA to practice that method with respect to one of the malignancies identified in claims 16 or 19 because *WO422* taught selecting the tumor from a group of 20 categories of cancers that overlap significantly with the claimed categories, and include TNBC, estrogen receptor positive Her2 negative breast cancer, and Her2 positive breast cancer. EX1010, [0017]. *Savas* also discloses that the “presence of high levels of lymphocytic infiltration has been consistently associated with a more-favourable prognosis in patients with early stage triple-negative and HER2-positive breast cancer.” EX1060, 228. This would have provided further motivation for a POSA to practice the method of claim 1 wherein the malignancy is TNBC or HER-2 positive breast cancer as required by claims 16 and 19.

435. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, and *Savas* would have motivated a POSA to practice the methods of claims 16 and 19 with a reasonable expectation of success. Therefore, claims 16 and 19 would have been obvious to a POSA.

h. Claims 17 and 18 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas*

Claim 17: “wherein the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1”

Claim 18: “wherein the anti-PD therapeutic agent is selected from the group consisting of: Avelumab (MSB0010178C), Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736”

436. Claim 17 depends on claim 1 and adds that the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1. Claim 18 depends on claim 1 and specifies that the anti-PD therapy is selected from the group consisting of: Avelumab (MSB0010178C), Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736.

437. As explained above (Paragraphs 371-415), it would have been obvious to a POSA to practice the method of claim 1. For the following reasons, it also would have been obvious to a POSA to practice that method with an anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1 or with an anti-PD therapy selected from the group consisting of: Avelumab (MSB0010178C), Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736.

438. First, *WO422* taught the use of PD-1 antagonists and defines a “PD-1 antagonist” as “any chemical compound or biological molecule that blocks binding of PD-L1 to PD-1, and includes antibodies and fusion proteins that bind to PD-1 or

PD-L1.” EX1010, [0072], [0080]. A POSA would have understood that by blocking the binding of PD-L1 to PD-1, such PD-1 antagonists would “inhibit[] the anti-cell death activity of PD-1/PD-L1,” as recited in claim 17. The added limitation in claim 17 would therefore have been obvious to a POSA.

439. *WO422* also identifies specific examples of PD-1 antagonists, including nivolumab, MPDL3280A, BMS-936559, MEDI4736, and pembrolizumab, all of which are included in claim 18. EX1010, [0072], Exemplary Specific Embodiments 25-27, Claims 20-21. The added limitation in claim 18 would have been obvious to a POSA.

440. For the above reasons, and the reasons given with regard to claim 1 (*see* Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, and *Savas* would have motivated a POSA to practice the methods of claims 17 and 18 with a reasonable expectation of success. Therefore, claims 17 and 18 would have been obvious to a POSA.

i. Claims 20 and 21 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, and *Savas*

Claim 20: “further comprising administering said anti-PD therapeutic agent to the subject when the CPS is above the threshold”

Claim 21: “wherein the threshold is greater than or equal to 1%”

441. Claim 20 depends on claim 1 and further adds a step of administering an anti-PD therapeutic agent when the CPS is above the threshold (but no threshold is provided in claim 20 or claim 1). Claim 21 depends on claim 20 and adds that the threshold is “greater than or equal to 1%.”

442. The added limitation in claim 20 would have been obvious to a POSA because *WO422* taught treating a patient with a PD-1 antagonist when the score is above a threshold. EX1010, [0019], [00118], Embodiment 23, Claim 18.

443. The added limitation in claim 21 would have been obvious to a POSA because, as discussed above with respect to claims 2-3, *WO422* teaches thresholds from above zero to 90%, which would include thresholds of greater than or equal to 1%. See Paragraphs 417-20, above.

444. For the above reasons, and the reasons given with regard to claims 1-3 (see Paragraphs 371-420), the combined teachings of *WO422*, *Bellmunt*, and *Savas* would have motivated a POSA to practice the methods of claims 20 and 21 with a

reasonable expectation of success. Therefore, claims 20 and 21 would have been obvious to a POSA.

2. Claim 9 Would Have Been Obvious to a POSA over the Combination of WO422, Bellmunt, Savas, and Herbst

Claim 9: “wherein the viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC are counted in the tumor nests and the adjacent supporting stroma of the tumor tissue sample”

445. Claim 9 depends on claim 4, which depends on claim 1. Claim 9 adds the limitation that the PD-L1 positive MICs are also counted in the stroma. As explained below, it would have been obvious to a POSA to count PD-L1⁺ cells in tumor nests and adjacent supporting stroma and to consider the overall abundance of PD-L1⁺ MICs in those locations.

446. *Savas* disclosed that stromal TILs (tumor infiltrating lymphocytes) are associated with a better prognosis. EX1060, 229. *Savas* also taught that because the fibrous stroma is considered part of the malignant tumor, stromal immune cells are considered to be true tumor-infiltrating cells, and that stromal compartment TILs should therefore be considered when looking at the relationship between TILs and cancer response. EX1060, 229.

447. In addition, *WO422* recognized the need to assess MIC PD-L1 positivity in both tumor nests and stroma for purposes of predicting whether a patient will benefit from anti-PD therapy. EX1010, [0012]–[0017]. Indeed,

WO422 taught that a tumor with PD-L1⁺ MICs in its stroma could be scored as PD-L1⁺ even if there were no PD-L1⁺ tumor cells. *Id.*, [0017].

448. A POSA also would have known that pooling the PD-L1⁺ MICs from within the tumor and stroma would simplify the assessment of PD-L1 positivity and its predictive value, as reflected in the prior art. For example, in clinical trials of Roche's anti-PD therapy, MPDL3280A, a single score for PD-L1 positivity in MICs was calculated, as opposed to separate scores for the intra-nest and adjacent stromal areas. EX1017, 9-10; *see also* Paragraph 190. *Bellmunt* also provides a single score for MICs in the tumor nest and stroma. EX1023, 813.

449. I explained above, in Paragraphs 371-406, why a POSA would have been motivated to combine the teachings of *WO422*, *Bellmunt*, and *Savas*. A POSA would have been motivated to combine the teachings of *Herbst* with the teachings of *WO422*, *Bellmunt*, and *Savas* because, like those references, *Herbst* relates to the treatment of cancer, including patients with breast cancer, with anti-PD therapy.

450. A POSA would have had a reasonable expectation of success for the same reasons as set forth above in Paragraphs 407-14.

451. For the above reasons, and the reasons given with regard to claims 1 and 4 (*see* Paragraphs 371-415, 421, 424), the combined teachings of *WO422*, *Bellmunt*, *Savas*, and *Herbst*, would have motivated a POSA to count the PD-L1⁺

MICs in the tumor nests and the adjacent supporting stroma of the tumor tissue sample and thereby practice the methods of claim 9 with a reasonable expectation of success. Therefore, claim 9 would have been obvious to a POSA.

3. Claims 10, 11, and 15 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, *Savas*, and *Dako*

a. Claim 10 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, *Savas*, and *Dako*

Claim 10: “wherein the tumor tissue sample is a cell suspension”

452. Claim 10 depends on claim 1 and adds that the tumor tissue sample is a cell suspension. It would have been obvious to a POSA to use a tumor tissue sample that is a cell suspension because, as of the earliest possible effective filing date, doing so was routine and conventional. For example, *Dako* taught that immunofluorescence (IF) is a common laboratory technique, and that applications include evaluating cells in suspension. EX1012, 87 (“Immunofluorescence (IF) is a common laboratory technique used in almost all aspects of biology.... Applications include the evaluation of cells in suspension, cultured cells, frozen tissue, FFPE tissue, beads, and microarrays for the detection of specific proteins.”) In addition, *Savas* described the use of flow cytometry, which a POSA would have understood entailed analyzing a cell suspension. EX1060, 230.

453. I explained above, in Paragraphs 371-406, why a POSA would have been motivated to combine the teachings of *WO422*, *Bellmont*, and *Savas*. A POSA would have been motivated to combine the teachings of *Dako* with the teachings of *WO422*, *Bellmont*, and *Savas* because *Dako* relates to methods for analyzing tumor tissue samples, which is a major aspect of those references.

454. A POSA would have had a reasonable expectation of success for the same reasons as set forth above in Paragraphs 407-14.

455. For the above reasons, and the reasons given with regard to claim 1 (*see* Paragraphs 371-415), the combined teachings of *WO422*, *Bellmont*, *Savas*, and *Dako* would have motivated a POSA to practice the method of claim 10 with a reasonable expectation of success. Therefore, claim 10 would have been obvious to a POSA.

b. Claim 11 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmont*, *Savas*, and *Dako*

Claim 11: “wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determining [sic] by flow cytometry”

456. Claim 11 depends on claim 10, and adds the limitation that the number of PD-L1 positive and negative tumor cells and PD-L1 positive MICs are determined by flow cytometry. It would have been obvious to assess PD-L1

expression using flow cytometry because, as of the earliest possible effective filing date, doing so was routine and conventional. For example, *Savas* describes flow cytometry as the “analysis of single cells using a variety of cell surface and intracellular fluorescent markers.” EX1060, 229 (Box 1). *Savas* further notes that flow cytometry may be used to assess markers on a cell, and that flow cytometry is a more comprehensive technique than IHC. *Id.*, 230.

457. For the above reasons, and the reasons given with regard to claim 1 and 10 (*see* Paragraphs 371-415, 452-55), the combined teachings of *WO422*, *Bellmunt*, *Savas*, and *Dako* would have motivated a POSA to practice the method of claim 11 with a reasonable expectation of success. Therefore, claim 11 would have been obvious to a POSA.

c. Claim 15 Would Have Been Obvious to a POSA over the Combination of *WO422*, *Bellmunt*, *Savas*, and *Dako*

Claim 15: “wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determined by single cell sequencing”

458. Claim 15 depends on claim 1 and adds the limitation that the number of PD-L1 positive and negative tumor cells and PD-L1 positive MICs are determined by single cell sequencing. It would have been obvious to assess PD-L1 expression using single cell sequencing because, as of the earliest possible

effective filing date, doing so was routine and conventional. For example, *Savas* teaches that gene expression analysis/single cell sequencing may be used to provide information about relevant lymphocyte subpopulations. EX1060, 230. In addition, as discussed above (*see* Paragraph 185), as of the earliest possible effective filing date, *Dako* taught that it was routine and conventional to count cells using single cell sequencing (which *Dako* calls next generation sequencing). *See* EX1012, 119 (“New, non-slide-based tests, e.g. next generation sequencing, are in the process of entering routine diagnostic application providing new important information for cancer diagnostics, but at the cost of morphological information.”).

459. For the above reasons, and the reasons given with regard to claim 1 (*see* Paragraphs 371-415), the combined teachings of *WO422*, *Bellmunt*, *Savas*, and *Dako* would have motivated a POSA to practice the method of claim 15 with a reasonable expectation of success. Therefore, claim 15 would have been obvious to a POSA.

4. Objective Indicia of Non-Obviousness

460. I am not aware of any relevant objective indicia of non-obviousness that have a nexus to, or are commensurate in scope with, any of the challenged claims.

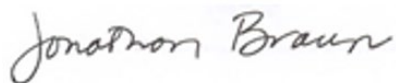
461. I reserve the right to respond to any allegations that objective indicia support the validity of the challenged claims.

VIII. CONCLUSION

462. For the foregoing reasons, claims 1-21 of *US702* are invalid under 35 U.S.C. §101 and 35 U.S.C. §112 and would have been obvious under 35 U.S.C. §103.

463. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully Submitted,



Dated: October 20, 2026

APPENDIX 1: LIST OF EXHIBITS RELIED UPON

In preparing my declaration, I relied upon the exhibits cited below, and any other document cited in my declaration.

Exhibit No.	Description
1001	U.S. Patent No. 12,529,702 to Kulangara et al. (Jan. 20, 2026) (“ <i>US702</i> ”)
1003	Jonathan Braun, M.D., Ph.D. <i>curriculum vitae</i>
1008	U.S. Patent No. 10,613,092 to Kulangara et al. (Apr. 7, 2020) (“ <i>US092</i> ”)
1010	International Publication WO 2014/165422 A1 to Dolled-Filhart et al. (Oct. 9, 2014) (“ <i>WO422</i> ”)
1012	Taylor, C.R. & Rudbeck, L. (eds.), <i>IHC Guidebook, Immunohistochemical Staining Methods</i> , 6th ed., Dako Denmark A/S (Nov. 7, 2013) (“ <i>Dako</i> ”)
1013	Taube, J.M., et al., <i>Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape</i> , 4 SCIENCE TRANSLATIONAL MEDICINE 127:127RA37, 1-10 & Supplementary Materials (Mar. 28, 2012) (“ <i>Taube 2012</i> ”)
1014	Gadiot, J., et al., <i>Overall survival and PD-L1 expression in metastasized malignant melanoma</i> , 117 CANCER 10, 2192-201 (Epub Nov. 29, 2010) (“ <i>Gadiot</i> ”)
1015	Muenst, S., et al., <i>The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer</i> , 139 BREAST CANCER RESEARCH AND TREATMENT 3, 667-76 (Epub June 12, 2013) (“ <i>Muenst 2013</i> ”)
1016	Muenst, S., et al., <i>Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer</i> , 146 BREAST CANCER RESEARCH AND TREATMENT 1, 15-24 (Epub May 20, 2014) (“ <i>Muenst 2014</i> ”)
1017	Herbst, R.S., et al. <i>Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients</i> , 515 NATURE 7528, 563-67 & Extended Data (Nov. 27, 2014) (“ <i>Herbst</i> ”)

Exhibit No.	Description
1018	U.S. National Library of Medicine, ClinicalTrials.gov, NCT01295827, <i>Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/ MK-3475-001/ KEYNOTE-001) (KEYNOTE-001)</i> , (Version 56, Jan. 30, 2015), available at https://clinicaltrials.gov/study/NCT01295827 (“NCT827-V56”)
1019	<i>KEYTRUDA® (pembrolizumab) for injection, for intravenous use</i> , FOOD AND DRUG ADMINISTRATION (Sept. 2014) available at https://www.accessdata.fda.gov/Drugsatfda_docs/Label/2014/1255141bl.Pdf (“Keytruda 2014PF”)
1020	<i>OPDIVO® (nivolumab) injection, for intravenous use</i> , FOOD AND DRUG ADMINISTRATION (Dec. 2014) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000LBL.pdf (“Opdivo 2014PF”)
1021	Bristol-Myers Squibb, <i>Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration</i> (Dec. 22, 2014), available at https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx (“BMS-PR2014”)
1022	Ali, H.R., et al., <i>PD-L1 protein expression in breast cancer is rare, enriched in basal-like tumours and associated with infiltrating lymphocytes</i> , 26 ANNALS OF ONCOLOGY 7, 1488-93 & Supplemental Data (Epub Apr. 20, 2015) (“Ali”)
1023	Bellmunt, J., et al., <i>Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma</i> , 26 ANNALS OF ONCOLOGY 4, 812-17 & Supplementary Data (excluding unavailable Supplementary Fig. S3, Table S4, and Table S5) (Epub Jan. 18, 2015) (“Bellmunt”)
1024	U.S. National Library of Medicine, ClinicalTrials.gov, NCT01295827, <i>Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/ MK-3475-001/ KEYNOTE-001) (KEYNOTE-001)</i> , (Version 1, Feb. 14, 2011), available at https://clinicaltrials.gov/study/NCT01295827 (“NCT827-VI”)

Exhibit No.	Description
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1026	Irwin, K. & McConnel, K., University of California, Los Angeles (UCLA), <i>FDA Approves New Breast Cancer Drug Herceptin</i> , (Sept. 29, 1998) available at https://www.newswise.com/articles/fda-approves-new-breast-cancer-drug-herceptin (“ <i>UCLA-PR1998</i> ”)
1027	Taube, J.M., et al., <i>Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy</i> , 20 CLINICAL CANCER RESEARCH 19, 5064-74 & Supplementary Materials (Apr. 8, 2014) (“ <i>Taube 2014</i> ”)
1028	Detjen, K.M., et al, <i>Molecular mechanism of interferon alfa-mediated growth inhibition in human neuroendocrine tumor cells</i> , 118 GASTROENTEROLOGY 4, 735-48 (Apr. 2000) (“ <i>Detjen</i> ”)
1030	Raedler, L.A., <i>Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable or Metastatic Melanoma</i> , 8 AMERICAN HEALTH & DRUG BENEFITS (SPEC FEATURE), 96-100 (Mar. 2015) (“ <i>Raedler</i> ”)
1031	Kerr, K.M., et al., <i>Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art?</i> 10 JOURNAL OF THORACIC ONCOLOGY: OFFICIAL PUBLICATION OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER 7, 985-89 (Jul. 2015) (“ <i>Kerr</i> ”)
1032	Thompson, R.H., et al., <i>Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target</i> , 101 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 49, 17174-179 (Epub Nov. 29, 2004) (“ <i>Thompson</i> ”)
1033	Tumeh, P.C., et al., <i>PD-1 blockade induces responses by inhibiting adaptive immune resistance</i> , 515 NATURE 7528, 568-71 & Extended Data (Nov. 27, 2014) (“ <i>Tumeh</i> ”)
1034	Lu, B., et al., <i>T-cell-mediated tumor immune surveillance and expression of B7 co-inhibitory molecules in cancers of the upper gastrointestinal tract</i> , 50 IMMUNOLOGIC RESEARCH, 269-75 (Jun. 30, 2011) (“ <i>Lu</i> ”)

Exhibit No.	Description
1035	Santoiemma, P.P., et al., <i>Tumor infiltrating lymphocytes in ovarian cancer</i> , 16 CANCER BIOLOGY & THERAPY 6, 807-20 (Epub Apr. 20, 2015) (“Santoiemma”)
1036	Kan, G. & Dong, W., <i>The expression of PD-L1 APE1 and P53 in hepatocellular carcinoma and its relationship to clinical pathology</i> , 19 EUROPEAN REVIEW FOR MEDICAL AND PHARMACOLOGICAL SCIENCES 16, 3063-71 (Aug. 4, 2015) (“Kan”)
1038	U.S. Food & Drug Admin., <i>In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff</i> (Aug. 6, 2014) (“FDA Companion Diagnostic Guidance”)
1039	Kandoth, C., et al., <i>Mutational landscape and significance across 12 major cancer types</i> , 502 NATURE, 333-39 (excluding Supplementary Data) (Oct. 17, 2013) (“Kandoth”)
1040	Nomi, T., et al., <i>Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer</i> , 13 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 7, 2151-157 (Apr. 1, 2007) (“Nomi”)
1042	Topalian, S.L., et al., <i>Safety, activity, and immune correlates of anti-PD-1 antibody in cancer</i> , 366 THE NEW ENGLAND JOURNAL OF MEDICINE 26, 2443-54 & Appendix (excluding trial protocol and disclosure forms) (Jun. 28, 2012) (“Topalian”)
1045	Iwai, Y., et al., <i>Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade</i> , 99 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 19, 12293-297 (Epub Sep. 6, 2002) (“Iwai”)
1046	Ohigashi, Y., et al., <i>Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer</i> , 11 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 8, 2947-53 (Apr. 15, 2005) (“Ohigashi”)
1047	Ghebeh, H., et al., <i>The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors</i> , 8 NEOPLASIA 3, 190-98 (Mar. 2006) (“Ghebeh”)

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1048	Hamanishi, J., et al., <i>Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer</i> , 104 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 9, 3360-65 & Supplementary Material (Epub Feb. 21, 2007) (“Hamanishi”)
1049	Yang, W., et al., <i>PD-L1: PD-1 interaction contributes to the functional suppression of T-cell responses to human uveal melanoma cells in vitro</i> , 49 INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 6, 2518-25 (Epub Feb. 22, 2008) (“Yang”)
1050	Gao, Q., et al., <i>Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma</i> , 15 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 3, 971-79 & Supplementary Data (Feb. 1, 2009) (“Gao”)
1051	Brahmer, J.R., et al., <i>Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates</i> 28 JOURNAL OF CLINICAL ONCOLOGY: OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY 19, 3167-75 & Appendix (Epub Jun. 1, 2010) (“Brahmer”)
1052	International Publication WO 2015/026634 A1 to Strack et al. (Feb. 26, 2015) (“WO634”)
1056	Patel, S.P. & Kurzrock, R., <i>PD-L1 expression as a predictive biomarker in cancer immunotherapy</i> , 14 MOLECULAR CANCER THERAPEUTICS 4, 847-56 (Apr. 2015) (“Patel”)
1058	Kuang, D., et al., <i>Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1</i> , 206 JOURNAL OF EXPERIMENTAL MEDICINE 6, 1327-37 & Supplementary Material (Epub May 18, 2009) (“Kuang”)
1059	Lipson, E.J., et al., <i>Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody</i> , 19 CLINICAL CANCER RESEARCH 2, 462-68 (Epub Nov. 20, 2012) (“Lipson”)
1060	Savas, P., et al., <i>Clinical relevance of host immunity in breast cancer: from TILs to the clinic</i> , 13 NATURE REVIEWS CLINICAL ONCOLOGY 4, 228-41 (Epub Dec. 15, 2015) (“Savas”)

Exhibit No.	Description
1061	U.S. Patent Application Publication 2013/0309250 A1 to Cogswell et al. (Nov. 21, 2013) (“ <i>Pub250</i> ”)
1062	González-Cao, M., et al., <i>Targeting PD-1/PD-L1 in lung cancer: current perspectives</i> , 2015 LUNG CANCER: TARGETS AND THERAPY 6, 55-70 (July 31, 2015) (“ <i>González-Cao</i> ”)
1063	Merck & Co., Inc., <i>Merck Announces Generic Name for MK-3475, Merck’s Investigational anti-PD-1 Antibody: Pembrolizumab</i> , (May 30, 2014) available at https://www.merck.com/news/merck-announces-generic-name-for-mk-3475-mercks-investigational-anti-pd-1-antibody-pembrolizumab/ (“ <i>Merck-PR2014</i> ”)
1064	Walker, R.A., <i>Quantification of immunohistochemistry—issues concerning methods, utility and semiquantitative assessment I</i> , 2006 HISTOPATHOLOGY 49, 406-10 (“ <i>Walker</i> ”)
1065	Taylor, C.R. & Levenson, R.M., <i>Quantification of immunohistochemistry—issues concerning methods, utility and semiquantitative assessment II</i> , 2006 HISTOPATHOLOGY 49, 411-24 (“ <i>Taylor</i> ”)
1066	Denkert, C., et al., <i>Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers</i> , 33 JOURNAL OF CLINICAL ONCOLOGY 9, 983-91 & Appendix (Mar. 20, 2015) (“ <i>Denkert</i> ”)
1067	Schalper, K.A., <i>PD-L1 expression and tumor-infiltrating lymphocytes: Revisiting the antitumor immune response potential in breast cancer</i> , 2014 ONCOIMMUNOLOGY 3, e29288-1-e29288-2 (June 25, 2014) (“ <i>Schalper</i> ”)
1068	Carbognin, L., et al., <i>Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers</i> , 10 PLOS ONE 6 (June 18, 2015) (“ <i>Carbognin</i> ”)
1069	Geissmann, F., et al., <i>Development of monocytes, macrophages, and dendritic cells</i> , 327 SCIENCE 5966, 656-61 (Feb. 5, 2010) (“ <i>Geissmann</i> ”)
1070	Muglia, V.F. & Prando, A., <i>Renal cell carcinoma: histological classification and correlation with imaging findings</i> , 48 RADIOLOGIA BRASILEIRA 3, 166-74 (May-June 2015) (“ <i>Muglia</i> ”)

Exhibit No.	Description
1071	García-Tejido, P., et al., <i>Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cancer: The Future of Immune Targeting</i> , 10 CLINICAL MEDICINE INSIGHTS: ONCOLOGY SUPPL 1, 31-9 (Epub April 5, 2016) (“ <i>García-Tejido</i> ”)
1072	Fawcett, T., <i>An Introduction to ROC Analysis</i> , 27 PATTERN RECOGNITION LETTERS 8, 861-74 (Epub Dec. 19, 2005) (“ <i>Fawcett</i> ”)
1073	Almagro, J.C., et al., <i>Engineering strategies and binding mechanisms of therapeutic anti-PD-1 antibodies approved by regulatory agencies globally</i> , 17 FRONTIERS IN IMMUNOLOGY (May 21, 2026) (“ <i>Almagro</i> ”)
1074	Li, L., et al., <i>Overcoming resistance to anti-PD-1/PD-L1 therapy in cancer</i> , 9 CANCER DRUG RESISTANCE 18 & Supplementary Materials (May 15, 2026) (“ <i>Li</i> ”)
1075	Cancer Research Institute, <i>Regulatory Approval Timeline of Active Immunotherapies</i> , available at https://www.cancerresearch.org/regulatory-approval-timeline-of-active-immunotherapies (accessed on Oct. 11, 2026) (“ <i>Cancer Research Institute</i> ”)
1077	Pardoll, D.M., <i>The blockade of immune checkpoints in cancer immunotherapy</i> , 12 NATURE REVIEWS CANCER 4, 252-64 (Mar. 22, 2012) (“ <i>Pardoll</i> ”)
1078	Merriam-Webster’s Collegiate Dictionary (11th ed. 2003) (excerpt p. 404) (“ <i>Merriam-Webster</i> ”)
1079	Dorland’s Illustrated Medical Dictionary (Saunders Elsevier, 31st ed. 2007) (excerpt pp. 284, 295-98) (“ <i>Dorland’s</i> ”)
1080	Hou, J., et al, <i>Correlation between infiltration of FOXP3+ regulatory T cells and expression of B7-H1 in the tumor tissues of gastric cancer</i> , 96 EXPERIMENTAL AND MOLECULAR PATHOLOGY 3, 284-91 (Epub Mar. 20, 2014) (“ <i>Hou</i> ”)
1081	USPTO, <i>July 2024 Subject Matter Eligibility Examples</i> (July 2024), available at https://www.uspto.gov/sites/default/files/documents/2024-AI-SMEUpdateExamples47-49.pdf (“ <i>USPTO Examples</i> ”)