IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

MERCK SHARP & DOHME LLC, Plaintiff, v. THE JOHNS HOPKINS UNIVERSITY, Defendant.	Civil Action No. 22-cv-03059-JRR **JURY TRIAL DEMANDED**

THE JOHNS HOPKINS UNIVERSITY'S FIRST AMENDED ANSWER AND COUNTERCLAIMS TO MERCK'S COMPLAINT FOR DECLARATORY RELIEF

Defendant The Johns Hopkins University ("***Hopkins***"), by and through its undersigned attorneys, hereby answers the Complaint of Plaintiff Merck Sharp & Dohme LLC ("***Merck***"), and counterclaims in response to same.

CASE OVERVIEW

On May 30, 2015, Dr. Dung Le, a professor of oncology at the Johns Hopkins University School of Medicine, presented the results of a groundbreaking clinical trial conducted by Hopkins researchers to a packed house at the 51st annual meeting of the American Society of Clinical Oncology ("***ASCO***") in Chicago, Illinois. Previously, it was the norm in cancer therapy for patients to be treated using specific drugs to treat specific types of cancers arising from specific tissues. Dr. Le, along with a group of her colleagues at Hopkins, discovered that cancers demonstrating certain genetic markers are particularly responsive to treatment with PD-1 checkpoint inhibitors, such as Merck's Keytruda® (pembrolizumab), regardless of the type or the location of cancer. Dr. Le's presentation was viewed in-person or by video feed by more than 10,000 of the world's leading cancer researchers. As Dr. Axel Grothey, then of the Mayo Clinic, noted during his interview of Dr. Le at the ASCO Meeting, "we didn't have a real

biomarker to really figure out who are these patients, and then came along your study and all of a sudden we know so much more." This case is about that remarkable invention, which changed the field of cancer therapy, saved countless lives, and which Merck has used and continues to use to make billions of dollars.

On the same day as Dr. Le's presentation, the New England Journal of Medicine—the world's leading medical journal—published an article entitled "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency" ("***NEJM Article***") that reported the results of the Johns Hopkins' clinical trial.

Dr. Le's presentation and NEJM Article were the culmination of years of work by Dr. Le and her fellow inventors Drs. Luis Diaz, Bert Vogelstein, Kenneth Kinzler, Nickolas Papadopoulos, Drew Pardoll and Suzanne Topalian (collectively, "***the Hopkins Inventors***")—work that began in January of 2012, long *before* there was any agreement between Hopkins and Merck, and led to Hopkins receiving multiple patents on the use of high microsatellite instability ("***MSI-High" or "MSI-H"***) as a biomarker for treatment of cancers with PD-1 inhibitors. The concept for the groundbreaking clinical study developed by Hopkins researchers was, similarly, prepared *before* there was any agreement between Hopkins and Merck, and the contributions Merck alleges to have made to the study protocol were known, trivial and have never been claimed as inventions by the Hopkins Inventors. Quite simply, the patent rights to Hopkins' MSI-High inventions are not subject to any agreement between Hopkins and Merck, and Merck has no rights in or to these Hopkins' patented inventions.

Instead, as explained in greater detail below, the story of those inventions began years before any involvement by Merck, when Hopkins researchers in the field of cancer immunology and immunotherapy, including renowned cancer researchers Drs. Suzanne Topalian and Drew

Pardoll, began to ask important questions regarding patient responses to treatment with PD-1 checkpoint inhibitors. Unable to explain from a cancer immunology perspective why a single patient's cancer went into complete remission when treated with a PD-1 checkpoint inhibitor drug (not pembrolizumab) while over 30 other patients with the same type of cancer had no response, Drs. Topalian and Pardoll raised the issue in January 2012 with renowned cancer geneticists Drs. Bert Vogelstein, Kenneth Kinzler, Nickolas Papadopoulos, and Luiz Diaz. Upon further discussion and contemplation, these researchers hypothesized that the one patient's cancer might have the genetic anomaly known as mismatch repair deficiency ("***dMMR***") and, if so, that might explain that one patient's unusual response. Dr. Topalian subsequently consulted with the patient's physician, who ordered genetic testing of the patient's tumor sample. That testing revealed the patient's cancer did indeed have this deficiency and also MSI-H, a feature unique to dMMR cancers.

Drs. Topalian, Pardoll, Vogelstein, Kinzler, Papadopoulos, and Diaz then decided to take the next step: perform a clinical study (***"MSI Clinical Trial"***) to further explore their hypothesis that MSI-High cancers would indeed respond to anti-PD-l drugs at a rate higher than microsatellite stable ("***MSS***") cancers. Dr. Le, Dr. Diaz, and their teams designed the study. On December 26, 2012, the Hopkins Inventors submitted a Letter of Intent ("***LOI***") to Merck proposing a clinical study titled "Phase 2a Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors." [Ex. 3, Hopkins' Letter of Intent.] The LOI explained Hopkins' primary hypothesis was that "MSI positive tumors, which are deficient in DNA mismatch repair, will be susceptible to immunotherapy," as "[t]his deficiency leads to a high rate of spontaneous mutations and the potential for presentation of immunogenic neo-antigens." [*Id.* at 2.] Indisputably, Merck made no contribution whatsoever to the LOI.

Moreover, when asked to fund the study, Merck declined to provide any financial support. Instead, the Hopkins Inventors funded their clinical study with money obtained from philanthropic sources donated to the University to support such research, with Merck providing only pembrolizumab for use in the study. It was only after the Hopkins-funded research showed impressive results that Merck agreed to provide funding for follow-on work. Merck's funding of Hopkins' follow-on research turned out to be a windfall investment for Merck.

Based on the results of the MSI Clinical Trial and four subsequent clinical trials, including two trials in which Dr. Le and Dr. Diaz were lead investigators, the United States Food and Drug Administration ("***FDA***"), on May 30, 2017, granted accelerated approval of pembrolizumab (by this time branded by Merck as Keytruda®) for adult and pediatric patients with MSI-High or dMMR solid tumors. [*See* Ex. 1, FDA Approval Announcement.] This strikingly rapid approval, less than four years after the first patient was treated in the MSI Clinical Trial, was heralded as FDA's first tissue/site-agnostic approval for treatment with a specific cancer drug. [*Id.*] As the FDA's own Dr. Richard Pazdur said of the approval, "This is an important first for the cancer community. Until now the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancer. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location."

In Merck's press release announcing the "first-of-its kind, tumor-agnostic, indication," Dr. Roger M. Perlmutter, President of Merck Research Laboratories, acknowledged the work of the Hopkins researchers, saying, "This is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and clinicians at Johns Hopkins University for their important scientific work, as well as the patients and their families who helped make

today's approval possible." [Ex. 2, Merck May 25, 2017 Press Release]. Additional FDA approvals for MSI-High related indications followed on June 29, 2020, March 21, 2022 and March 29, 2023.

These MSI-High related approvals directly resulted in billions of dollars in Keytruda® sales for Merck and will result in billions more in future sales. Those sales result from Merck's use of Hopkins' patented inventions. Yet to date, despite knowing of Hopkins' patents, Merck has not paid for the rights from which it is benefitting.

While Merck now complains that Hopkins is seeking a reasonable royalty for Merck's use of Hopkins' patented inventions, Merck fails to explain why that is not fair and just. Hopkins seeks only a small portion of Merck's billions of dollars in sales attributable to the MSI-High indications that resulted from Hopkins' pioneering research. These are sales that Merck would not have made without Hopkins' research, insight, and inventiveness. Hopkins is not asking for any part of Merck's sales generated by the non-MSI indications for Keytruda®. And even with respect to MSI-High indications, Hopkins is seeking only a percentage of the revenue that Merck makes from its use of Hopkins' inventions.

Merck's apparent position is that it is entitled to keep all profits from Keytruda® sales because it allegedly developed the drug. Yet Merck did not even invent pembrolizumab. This drug was developed by Organon Biosciences in the mid-2000's. Organon Biosciences was purchased in 2007 by Schering-Plough Corporation. Merck purchased Schering-Plough in 2009 and thereby inherited pembrolizumab. Merck promptly shelved the pembrolizumab research, only to restart that research when it learned that a competitor's anti-PD-1 drug was showing positive clinical results.

Because of the years of dedicated pioneering research by the Hopkins Inventors that resulted in the Hopkins MSI-High inventions, thousands of patients who would not be alive today are leading full, productive, cancer-free lives. Cancers that were once considered death sentences are now treatable—even curable—as a result of Hopkins' breakthrough invention.

HOPKINS' RESPONSE TO MERCK'S COMPLAINT

Hopkins denies each and every allegation in the Complaint that is not expressly admitted below. Hopkins specifically responds as follows:

1. Hopkins admits this action concerns patents relating to the use of the drug pembrolizumab, which Merck sells under the trade name Keytruda®. Hopkins denies these patents emerged from a joint research collaboration with Merck regarding the use of pembrolizumab. Hopkins denies it partnered with Merck to design and conduct a clinical study administering Keytruda® to cancer patients having tumors that had the genetic biomarker known as microsatellite instability-high ("MSI-H") or were mismatch repair deficient ("dMMR"). Hopkins admits the clinical study it conducted was successful. Hopkins denies Merck made significant contributions to the clinical study, as part of a joint research collaboration or otherwise, apart from supplying pembrolizumab to Hopkins for use in its clinical study and eventually paying for expenses associated with continuing clinical studies. Hopkins otherwise denies the allegations of paragraph 1.

2. Hopkins denies the allegations of paragraph 2.

3. Hopkins admits Merck has brought an action for breach of contract, declaratory judgment of noninfringement and promissory estoppel. Hopkins otherwise denies the allegations of paragraph 3.

4. Hopkins lacks sufficient information to admit the allegations of paragraph 4 and therefore denies them.

5. Hopkins is a Maryland, not-for-profit corporation having its principal place of business at 3400 N. Charles Street, Baltimore, Maryland 21218. Hopkins otherwise denies the allegations of paragraph 5.

6. Hopkins admits this action purports to arise under the Patent Laws of the United States as well as the Declaratory Judgment Act.

7. Hopkins admits the Court has subject matter jurisdiction over this action.

8. Hopkins admits the Court has personal jurisdiction over Hopkins. Hopkins admits the IICT Agreement (defined below) should be construed in accordance with Maryland law. Hopkins otherwise denies the allegations of paragraph 8.

9. Hopkins admits venue is proper in this Court for the purposes of this action.

10. Hopkins admits Keytruda® was the first anti-PD-1 antibody approved by FDA as a cancer drug. Hopkins admits Keytruda® works by aiding the immune system to identify and destroy cancer cells. Hopkins otherwise denies the allegations of paragraph 10.

11. Hopkins lacks sufficient information to admit or deny the allegations of paragraph 11 and therefore denies them.

12. Hopkins lacks sufficient information to admit or deny the allegations of paragraph 12 and therefore denies them.

13. Hopkins admits the document attached to the Complaint as Exhibit A recites the language quoted by paragraph 13. Hopkins otherwise denies the allegations of paragraph 13.

14. Hopkins admits that the document attached to the Complaint as Exhibit A recites the language quoted by paragraph 14. Hopkins otherwise denies the allegations of paragraph 14.

15. Hopkins admits the document attached to the Complaint as Exhibit A refers to clinical studies including the ***MSI Clinical Trial***. Hopkins otherwise denies the allegations of paragraph 15.

16. Hopkins denies the allegations of paragraph 16.

17. Hopkins admits the allegations of paragraph 17.

18. Hopkins admits that on February 25, 2013, Hopkins sent a draft protocol to Merck for a study in which Merck would supply pembrolizumab. Hopkins otherwise denies the allegations of paragraph 18.

19. Hopkins admits employees of Merck suggested edits to the Hopkins-created study protocol. Hopkins otherwise denies the allegations of paragraph 19.

20. Hopkins admits that on April 30, 2013, Merck's Amy Meister suggested what she referred to as "minor protocol edits" to the Hopkins-created study protocol that consisted of a dosing schedule of 10 mg/kg every 2 weeks and performing a first scan at 12 weeks. Hopkins otherwise denies the allegations of paragraph 20.

21. Hopkins admits that on May 1, 2013, Hopkins sent Merck a revised version of the Hopkins-created study protocol incorporating a dosage of 10 mg/kg every 2 weeks and with scans every eight (not 12) weeks. Hopkins otherwise denies the allegations of paragraph 21.

22. Hopkins admits that on June 10, 2013, the Hopkins-created study protocol was published at Clinicaltrials.gov. The Hopkins-created study protocol is the best evidence of what it described. Hopkins otherwise denies the allegations of paragraph 22.

23. Hopkins admits it entered into an Investigator Initiated Clinical Trial Research Agreement ("***IICT Agreement***") with Merck having an effective date of August 14, 2013.

Hopkins admits that a copy of the IICT Agreement, without the later amendments, is attached to the Complaint as Exhibit C. Hopkins otherwise denies the allegations of paragraph 23.

24. Hopkins admits words found in § 12.B of the IICT Agreement are quoted at paragraph 24 of the Complaint. Hopkins otherwise denies the allegations of paragraph 24.

25. Hopkins admits words found in § 12.D of the IICT Agreement are quoted in paragraph 25 of the Complaint. Hopkins otherwise denies the allegations of paragraph 25.

26. Hopkins admits words found in § 9.A of the IICT Agreement are quoted in paragraph 26 of the Complaint. Hopkins otherwise denies the allegations of paragraph 26.

27. Hopkins admits the IICT Agreement specifies that it "shall be construed in accordance with Maryland law." Hopkins otherwise denies the allegations of paragraph 27.

28. Hopkins denies the allegations of paragraph 28.

29. Hopkins denies the allegations of paragraph 29.

30. Hopkins admits the USPTO issued U.S. Patent No. 10,934,356 ("the '356 Patent"), U.S. Patent No. 11,325,974 ("the '974 Patent"), U.S. Patent No. 11,325,975 ("the '975 Patent"), and U.S. Patent No. 11,339,219 ("the '219 Patent") (collectively the "***Hopkins MSI Patents***") in 2021 and 2022. Hopkins admits that copies of the Hopkins MSI Patents are attached to the Complaint as Exhibits D-G. Hopkins otherwise denies the allegations of paragraph 30.

31. Hopkins admits the phrases quoted in paragraph 31 are found in Exhibit D to the Complaint. Hopkins otherwise denies the allegations of paragraph 31.

32. Hopkins admits Merck was not involved in drafting or prosecuting the Hopkins MSI Patents. Hopkins otherwise denies the allegations of paragraph 32.

33. Hopkins admits the file histories of the Hopkins MSI Patents are publicly available. The remainder of paragraph 33 contains attorney argument that requires no response. To the extent a response is required, Hopkins denies Merck's characterization of the file histories of the Hopkins MSI Patents. Hopkins otherwise denies the allegations of paragraph 33.

34. Hopkins admits it submitted two sworn declarations in support of the prosecution of the Hopkins MSI Patent applications, the first of which, the declaration of Dr. Andrew Pardoll, was filed on February 4, 2020. Hopkins admits the phrase quoted in paragraph 34 is found in Dr. Pardoll's declaration. Hopkins otherwise denies the allegations of paragraph 34.

35. Hopkins admits the Patent Office rejected the pending claims of the Hopkins MSI Patent applications on March 9, 2020. Hopkins otherwise denies the allegations of paragraph 35.

36. Hopkins admits it filed a declaration from Dr. Vijay Kuchroo on June 8, 2020. The remainder of paragraph 36 contains attorney argument that requires no response. To the extent a response is required, Hopkins denies Merck's characterization of the file histories of the Hopkins MSI Patents. Hopkins otherwise denies the allegations of paragraph 36.

37. Hopkins admits that on December 14, 2020, the Patent Office issued a notice of allowance for the '356 Patent, which cited to Dr. Kuchroo's declaration. Hopkins otherwise denies the allegations of paragraph 37.

38. Hopkins admits the '356 Patent issued on March 2, 2021, the '974 and '975 Patents issued on May 10, 2022, and the '219 Patent issued on May 24, 2022. Hopkins otherwise denies the allegations of paragraph 38.

39. Hopkins admits Exhibit D at claim 1 recites in part "administering an effective amount of pembrolizumab" and "determining that the patient exhibits an outcome that is improved." Hopkins admits Exhibit D at claim 17 recites in part "wherein the outcome is

assessed in the patient at 20 weeks after administering pembrolizumab." Hopkins admits Exhibit E at claim 1 recites in part "administering an effective amount of pembrolizumab" and "wherein the patient exhibits an outcome that is improved." Hopkins admits Exhibit F at claim 1 recites in part "administering an effective amount of an anti-PD-1 antibody" and "wherein the patient exhibits an outcome that is improved." Hopkins admits Exhibit G at claim 1 recites in part "administering an effective amount of pembrolizumab" and "wherein the patient exhibits an outcome that is improved." Hopkins otherwise denies the allegations of paragraph 39.

40. Hopkins denies the allegations of paragraph 40.

41. Hopkins admits PGDx and QIAGEN issued press releases in October 2016 and June 2017, respectively, that Merck selectively and incompletely purports to quote. The referenced press releases are the best source for what they recite. Hopkins otherwise denies the allegations of paragraph 41.

42. Hopkins lacks sufficient information to admit or deny the allegations of paragraph 42 and therefore denies them.

43. Hopkins admits that on November 28, 2017, representatives of Hopkins including Christy Wyskiel spoke via telephone with representatives from Merck including Kim Folander. Hopkins admits Ms. Wyskiel represented that any future patent rights associated with the then-pending patent applications would not result from the IICT Agreement, and that the Hopkins MSI-High inventions were conceived before the effective date of the IICT Agreement. Hopkins admits that none of the patent applications at issue in this case had matured into patents as of December 5, 2017. Hopkins otherwise denies the allegations of paragraph 43.

44. Hopkins denies the allegations of paragraph 44.

45. Hopkins admits that in March 2021, after Hopkins obtained issuance of the ’356 Patent, Hopkins notified Merck that the ’356 Patent had issued. Hopkins admits it represented that its “inventors are eager for Merck to formally recognize the value of their contributions to the commercial success of Keytruda.” Hopkins otherwise denies the allegations of paragraph 45.

46. Hopkins lacks knowledge or information sufficient to form a belief as to the allegations of paragraph 46 and therefore denies them.

COUNT I

47. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-46 of its Answer.

48. Hopkins admits it did not notify Merck in writing of any inventions that arose from IICT Agreement because there were none. Hopkins otherwise denies the allegations of paragraph 48.

49. Hopkins admits Ms. Wyskiel represented that she spoke with the named inventors. Hopkins admits Ms. Wyskiel represented that any future patent rights associated with the then-pending patent applications would not result from the IICT Agreement, and that the Hopkins MSI-High inventions were conceived before the effective date of the IICT Agreement. Hopkins otherwise denies the allegations of paragraph 49.

50. Hopkins denies the allegations of paragraph 50.

51. Hopkins admits § 12.D of the IICT Agreement states in part that “Institution hereby grants Merck a paid-up non-exclusive royalty-free, sub-licensable, worldwide license to all Institution Inventions for its internal, non-commercial and development purposes, and an exclusive option to obtain an exclusive worldwide license for commercial purposes, including the right to grant sub-licenses; to all Institution Inventions and to Institution’s entire right, title

and interest in and to all Joint Inventions." Hopkins otherwise denies the allegations of paragraph 51.

52. Hopkins denies the allegations of paragraph 52.

53. Hopkins denies the allegations of paragraph 53.

54. Hopkins admits the IICT Agreement is an agreement between Hopkins and Merck. Hopkins otherwise denies the allegations of paragraph 54.

COUNT II

55. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-54 of its Answer.

56. Hopkins denies the allegations of paragraph 56.

57. Hopkins admits Claim 1 of the '356 Patent recites "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status." Hopkins otherwise denies the allegations of paragraph 57.

58. Hopkins admits Claim 11 of the '356 Patent recites "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers." Hopkins admits Claim 19 of the '356 Patent recites "determining that the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not

exhibit a MSI-high or MMR deficiency status." Hopkins otherwise denies the allegations of paragraph 58.

59. Hopkins admits Claim 23 of the '356 Patent recites "observing an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab." Hopkins otherwise denies the allegations of paragraph 59.

60. Hopkins denies the allegations of paragraph 60.

61. Hopkins denies the allegations of paragraph 61.

COUNT III

62. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-61 of its Answer.

63. Hopkins denies the allegations of paragraph 63.

64. Hopkins admits Claim 1 of the '974 Patent recites "wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers." Hopkins otherwise denies the allegations of paragraph 64.

65. Hopkins denies the allegations of paragraph 65.

66. Hopkins denies the allegations of paragraph 66.

COUNT IV

67. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-66 of its Answer.

68. Hopkins denies the allegations of paragraph 68.

69. Hopkins admits Claim 1 of the ’975 Patent recites “wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status.” Hopkins otherwise denies the allegations of paragraph 69.

70. Hopkins admits Claim 9 of the ’975 Patent recites “wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high status or is MMR proficient.” Hopkins otherwise denies the allegations of paragraph 70.

71. Hopkins denies the allegations of paragraph 71.

72. Hopkins denies the allegations of paragraph 72.

COUNT V

73. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-72 of its Answer.

74. Hopkins denies the allegations of paragraph 74.

75. Hopkins admits Claim 1 of the ’219 Patent recites “wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status.” Hopkins otherwise denies the allegations of paragraph 75.

76. Hopkins denies the allegations of paragraph 76.

77. Hopkins denies the allegations of paragraph 77.

COUNT VI

78. Hopkins incorporates its responses to the allegations set forth in paragraphs 1-77 of its Answer.

79. Hopkins denies the allegations in paragraph 79.

REQUEST FOR RELIEF

80. Hopkins denies that Merck is entitled to the relief it seeks or to any other relief.

FACTS RELEVANT TO HOPKINS' AFFIRMATIVE DEFENSES AND COUNTERCLAIMS

81. Hopkins holds a family of patents and pending patent applications on the Hopkins Inventors' MSI-High inventions titled "Checkpoint Blockade and Microsatellite Instability," which includes among others U.S. Patent No. 10,934,356 ("the '356 Patent"), U.S. Patent No. 11,325,974 ("the '974 Patent"), U.S. Patent No. 11,325,975 ("the '975 Patent"), and U.S. Patent No. 11,339,219 ("the '219 Patent"), U.S. Patent No. 11,591,393, U.S. Patent No. 11,643,462 ("the '462 Patent"), U.S. Patent No. 11,629,187 ("the '187 Patent"), U.S. Patent No. 11,649,287 ("the '287 Patent"), and U.S. Patent No. 11,634,491 ("the '491 Patent") (collectively, "the Hopkins MSI Patents").

82. The inventions of the Hopkins MSI Patents grew out of work conducted by Dr. Suzanne Topalian and Dr. Drew Pardoll in the field of cancer immunology and immunotherapy. Between 2006 and 2012, Dr. Topalian and Dr. Pardoll, in collaboration with cancer immunology and immunotherapy colleagues at Hopkins, conducted trials to evaluate the effectiveness of an anti-PD-l antibody on patients with various types of cancer. In one of those anti-PD-1 trials involving a different drug than pembrolizumab ("the Anti-PD-1 Trials"), while the vast majority of patients with colorectal cancer ("CRC") failed to respond, Drs. Topalian and Pardoll noted that one CRC patient, a 71-year old male, exhibited durable antitumor activity. This patient

achieved a complete response in January 2008. The patient was further evaluated in April 2011, having gone over three years without any anti-neoplastic therapy or anti-PD-1 antibody therapy, and had no evidence of disease recurrence.

83. Dr. Topalian, Dr. Pardoll and their cancer immunology colleagues were unable to explain why this one CRC patient had such a remarkable response to anti-PD-1 antibodies when none of the other CRC patients showed any objective response to the drug.

84. On January 18, 2012, Dr. Topalian and Dr. Pardoll had a meeting with renowned cancer geneticists Drs. Bert Vogelstein, Kenneth Kinzler, Nickolas Papadopoulos, and Luiz Diaz, who is also a clinical oncologist. At the meeting, Dr. Topalian and Dr. Pardoll described the results that they had observed and recently reported concerning the CRC patients in the Anti-PD-1 Trials, noting the single CRC responder. They hoped Dr. Vogelstein and his colleagues, widely regarded as the world's premier colon cancer genetic researchers, might have some thoughts about why the one patient had so remarkably responded while the other CRC patients did not.

85. Dr. Vogelstein and his colleagues had the idea that mutational loads in melanoma and lung cancer patients brought about by sun and cigarette exposure, respectively, made them more recognizable by the patient's immune system. While Dr. Vogelstein and his colleagues believed high somatic mutation burdens caused by environmental factors might explain why patients such as those with melanoma and non-small cell lung cancer (NSCLC) were likely to respond to PD-1 inhibitor therapy, their belief as to the CRC patient was different. They instead suggested a genetic explanation—namely, that the patient's tumor might have a mismatch repair deficiency ("dMMR"). Dr. Vogelstein and his colleagues had studied this genetic abnormality in the 1990s.

86. During the meeting, Dr. Diaz asked whether the responding CRC patient's tumor was MSI-High. When Dr. Topalian and Dr. Pardoll explained that they had not evaluated any of these patients' tumors for such a status, the geneticists suggested that they do so.

87. On January 20, 2012, Dr. Topalian asked the responding patient's oncologist whether his tumor had been tested for microsatellite instability ("MSI"). The oncologist responded that it had not been tested and ordered the testing to be done on the patients' original cancer specimen. On January 27, 2012, the results of that testing were reported back to Dr. Topalian. The patient's cancer was indeed MSI-High. The Hopkins researchers now had a hypothesis to explain the otherwise statistically meaningless clinical result (an N of 1 response among 33 colorectal cancers) in the Anti-PD-1 Trials.

88. Drs. Pardoll, Topalian, Vogelstein, Kinzler, Papadopoulos, and Diaz decided to explore further the hypothesis that MSI-High cancers would respond to anti-PD-l antibodies at a rate higher than microsatellite stable ("MSS") cancers. They recruited another colleague and co-inventor, Dr. Dung Le, to design a clinical study for testing the use of anti-PD-1 antibodies to treat MSI-High cancers independent of cancer type.

Hopkins Conducted a Clinical Trial of MSI As Biomarker for PD-1 Blockade

89. Armed with their hypothesis that identifying MSI-High cancers could be used to better predict response to anti-PD-1 antibodies across cancer types, and having crafted a study proposal designed to test that hypothesis, the Hopkins Inventors began reaching out to pharmaceutical suppliers of anti-PD-1 antibodies to sponsor their study.

90. The Hopkins Inventors first approached a pharmaceutical company other than Merck to supply its anti-PD-1 antibody drug product for the study. After that company declined the Hopkins Inventors' request to sponsor their study, Dr. Bert Vogelstein contacted Dr. Robert

Iannone, Merck's Executive Director and Section Head of Clinical Oncology, in late 2012 about using pembrolizumab (also known as MK-3475) in the Hopkins proposed study. At the time, on information and belief, Merck was not pursuing MSI as a biomarker for anti-PD-1 therapy.

91. On December 26, 2012, Dr. Diaz submitted a Letter of Intent ("LOI"), prepared by Hopkins, proposing a clinical study titled "Phase 2a Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors" to Dr. Iannone and Ms. Amy Meister, Associate Clinical Scientist Oncology at Merck. [Ex. 3, Hopkins' Letter of Intent.]

92. In his correspondence accompanying the LOI, Dr. Diaz noted that Hopkins was "in the fortunate position to have some funding available for a study of this size, although [Hopkins] would welcome any support from Merck in addition to a supply of the drug."

93. Hopkins' LOI proposed a study across tumor types "[t]o test the hypothesis that MSI positivity can predict response to MK-3475." [Ex. 3 at 2.] The LOI went on to explain that Hopkins' primary hypothesis was that "MSI positive tumors, which are deficient in DNA mismatch repair, will be susceptible to immunotherapy," as "[t]his deficiency leads to a high rate of spontaneous mutations and the potential for presentation of immunogenic neo-antigens." [*Id.*]

94. On January 2, 2013, Dr. Iannone responded to Dr. Diaz's submission of the LOI, thanking him for the "very interesting LOI" and informing Dr. Diaz that Merck was "very interested in collaborating with your group on this."

95. On January 23, 2013, Dr. Iannone informed Drs. Le, Vogelstein, and Diaz that the Merck Oncology Collaborative Studies Program committee for MK-3475 had found the MSI study proposal meritorious and had approved the concept contingent upon the submission of a full draft protocol and other documentation.

96. Over the ensuing month, Hopkins worked on preparing the full study protocol. Merck's only input, provided via email, related to MK-3475 dosing levels Merck had previously reported for treatment of other cancers.

97. On February 25, 2013, Dr. Diaz submitted the first draft of the protocol for the study of MK-3475 to Merck. [Ex. 4, Draft MSI Clinical Trial Protocol.] The protocol described the study as "a multi-center, open label, two-stage, phase 2 study to evaluate the clinical activity of MK-3475 in MSI positive and MSI negative solid tumors." [*Id.* at 8.] The study would "enroll three cohorts of patients to receive MK-3475: patients with MSI positive colorectal adenocarcinomas (Cohort A); patients with MSI negative colorectal adenocarcinomas (Cohort B); and patients with MSI positive solid tumors but not colorectal adenocarcinoma (Cohort C)." [*Id.*]

98. The dosage of MK-3475 identified in the draft protocol was 10 mg/kg every 21 days. [*Id.*] With respect to assessing disease progression, the draft protocol would determine each patient's progress using immune related response criteria (irRC) at 18 weeks. [*Id.* at 7.] The draft protocol also explained that the immune-mediated responses expected to be triggered by MK-3475 could take weeks to become evident. [*Id.* at 22-23.] It was possible that some patients could even see an increase in tumor volume in the weeks after the start of therapy as the immune system begins infiltrating the original tumor. [*Id.*] To account for this, patients with tumor progression by RECIST imaging or laboratory parameters without clinical deterioration were allowed to continue to be treated with MK-3475 and clinically observed following the assigned imaging schedule for up to six months, to allow detection of a subsequent tumor response. [*Id.* at 23.]

99. On April 30, 2013, Amy Meister sent Hopkins what she described as "minor protocol edits," including the recommendation that the dosing interval for MK-3475 should be decreased to every two weeks and that the first radiological scan be performed at 12 weeks with a confirmation scan at 16 weeks.

100. On May 1, 2013, Dr. Le provided a revised study protocol that initially assessed tumor progression with a radiological scan at 12 weeks with follow up scans at 8-week intervals after that.

101. The MSI Clinical Trial protocol received final approval from Merck on May 7, 2013.

102. Notwithstanding Dr. Diaz's invitation to Merck in his correspondence of December 26, 2012 that Hopkins "would welcome any support from Merck in addition to a supply of the drug," as well as other communications with Merck about Merck potentially funding the MSI Clinical Trial, Merck declined to provide funding for the MSI Clinical Trial. Merck provided only the drug MK-3475.

103. On June 12, 2013, the solicitation for patients was first posted on clinicatrials.gov for study NCT01876511, titled "Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C) ("MSI Clinical Trial"). [Ex. 5, MSI Clinical Trial summary posted at ClinicalTrials.gov.] The first patient was enrolled in September 2013. [*Id.*]

104. In March 2014, Hopkins began sharing preliminary results of the MSI Clinical Trial with Merck, which Merck characterized as "impressive."

105. On May 30, 2015, the Hopkins Inventors and their colleagues published preliminary results of the MSI Clinical Trial in the NEJM Article. [Ex. 6.] They reported an immune-related objective response rate and immune-related progression-free survival rate of

40% and 78%, respectively, for mismatch repair–deficient colorectal cancers and 0% and 11% for mismatch repair–proficient colorectal cancers. [*Id.* at 1.] Consistent with the Hopkins Inventors' hypothesis, these findings were not limited to colorectal cancer patients. The NEJM Article reported that patients with mismatch repair–deficient non-colorectal cancers had responses similar to those of patients with mismatch repair–deficient colorectal cancer, with an immune-related objective response rate of 71% and immune-related progression-free survival rate of 67%. [*Id.*] From these results, the authors concluded "[t]his study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab." [*Id.*]

106. The NEJM Article acknowledged "Merck donated the study drug and reviewed the final drafts of the protocol and of this manuscript before submission; they did not participate in the analysis of the data." [*Id.* at 2.]

Hopkins and Merck Entered into Investigator Initiated Clinical Trial Research Agreement

107. On August 14, 2013, more than two months after patient solicitation had begun for the fully designed and approved MSI Clinical Trial, Hopkins and Merck executed the IICT Agreement, which memorialized the terms of Merck's limited sponsorship of the MSI Clinical Trial. [*See* ECF No. 1-3, Ex. C to the Complaint.] The IICT Agreement does not describe a "joint research collaboration" between Hopkins and Merck. Rather, because it was an Investigator Initiated Clinical Trial, Hopkins was responsible for obtaining (1) an Investigational New Drug Application (IND), (2) Institutional Review Board (IRB) approval, (3) informed consent from each of the participants, and (4) HIPAA authorization to use and disclose the personal health information of the participants. [*Id.* at § 3.A]

108. For its part, Merck agreed to make available sufficient quantities of MK-3475 free of charge to carry out the study. [*Id.*, § 10.A] However, the IICT Agreement specified that "[n]o funding shall be provided by Merck under this Agreement." [*Id.*, § 7.]

109. It was only after the groundbreaking preliminary results of the MSI Clinical Trial were published in the NEJM article on May 30, 2015 that Merck agreed to provide some funding for the ongoing MSI Clinical Trial. On September 25, 2015, Hopkins and Merck executed a second amendment to the IICT Agreement in which Merck agreed to provide "limited funding in support of the [MSI] Study." [Ex. 7, IICT Agreement, Amendment 2] According to the attached Payment Schedule, Merck would pay Hopkins $987,231 based on the achievement by Hopkins of certain identified milestones. [*Id.* at 12.] Merck made its first milestone payment on February 4, 2016. [Ex. 8 (IICT Amendment 3) at Ex. B.] After Hopkins achieved several of those milestones, the parties amended the IICT Agreement again on August 18, 2016 to increase Merck's support to approximately $1.7 million. [*Id.*] After Hopkins achieved still further success, Merck increased its total support to approximately $2.7 million [*See* Ex. 11 (IICT Agreement, Amendment 9).] As Hopkins achieved additional milestones, Merck made milestone payments on August 23, 2016, December 14, 2016, August 2, 2017, August 10, 2017, and October 23, 2019. [Exs. 9 (IICT Agreement, Amendment 4) and 11 at Att. A.] Hopkins received a final milestone payment from Merck on or around November 24, 2020.

Merck Obtains First Tissue-Independent Approval for Cancer Therapy Based on the Hopkins Inventors' Discovery

110. The MSI Clinical Trial found that MSI-High and MMR-deficient cancers have increased responsiveness to anti-PD-1 antibodies, and subsequent clinical trials lead by Dr. Diaz, Dr. Le and others confirmed that finding. Based on the results of those clinical trials, FDA granted accelerated approval of pembrolizumab (Keytruda®) for adult and pediatric patients with

microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors on May 30, 2017. [Ex. 1, FDA Approval Announcement.] This was heralded as "FDA's first tissue/site-agnostic approval" for a cancer therapy. [*Id.*] Two other MSI related indications followed on June 29, 2020 (first line treatment of colorectal cancer) and March 21, 2022 (advanced endometrial cancer). On March 29, 2023, FDA granted full approval of Keytruda® for treatment of adult and pediatric patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, the first full approval for an immunotherapy based on a predictive biomarker, regardless of solid tumor type. [Exhibit 25, Merck 3/29/2023 Press Release.]

111. The clinical success of Keytruda® has translated into commercial success. Merck's sales of Keytruda® have totaled more than $70 billion since 2017, making Keytruda® Merck's top product and the second best-selling drug of any kind worldwide.

AFFIRMATIVE DEFENSES

112. Hopkins asserts the following affirmative defenses in response to Merck's Complaint. Hopkins reserves the right to allege additional and/or different affirmative defenses as they become known throughout the course of discovery.

COUNT I (BREACH OF CONTRACT)

HOPKINS' FIRST AFFIRMATIVE DEFENSE

(Merck Had No Rights to the Hopkins MSI Patents under the IICT Agreement)

113. Hopkins realleges and incorporates by reference paragraphs 1-112 of its Answer.

114. Hopkins has not breached the terms of the IICT Agreement for at least the following reasons. The inventions claimed by the Hopkins MSI Patents ("Hopkins Inventions") did not arise from the performance of the Protocol and Study under that agreement. Hopkins had

no duty to disclose the Hopkins MSI Patents to Merck. Merck has no rights to the Hopkins MSI Patents under §12.B of the IICT Agreement.

115. The Hopkins Inventors of the Hopkins MSI Patents conceived their inventions and designed their study to test their inventions before ever contacting Merck about either their inventions or their study.

116. The Hopkins Inventors of the Hopkins MSI Patents conceived their inventions and designed their study to test their inventions before Hopkins entered into the IICT Agreement.

117. Once the preliminary test data from the study conducted by the Hopkins Inventors confirmed that the Hopkins Inventors' hypothesis was correct, Hopkins pursued patent protection for their invention.

118. The results of the testing performed by the Hopkins Inventors validated the invention that the Hopkins Inventors conceived before the IICT Agreement. The invention of the Hopkins MSI Patents are, therefore, not "Institution Inventions" as defined by §12.B of the IICT Agreement.

119. Nor are the Hopkins MSI Patents "Joint Inventions." Merck's alleged contributions of dosage and scanning frequency are not claimed by the Hopkins MSI Patents. Merck's alleged contributions of dosage and scanning frequency were publicly known before the priority filing date of the Hopkins MSI Patents. Merck's alleged contributions of dosage and scanning frequency were first suggested by Merck after the Hopkins Inventors had conceived of the inventions claimed by the Hopkins MSI Patents.

120. None of the claims of the Hopkins MSI Patents recites the dosing regimen Merck allegedly contributed to the Hopkins Inventions.

121. None of the claims of the Hopkins MSI Patents recites the scanning frequency Merck allegedly contributed to the Hopkins Inventions.

HOPKINS' SECOND AFFIRMATIVE DEFENSE

(The Statute of Limitation Has Expired)

122. Hopkins realleges and incorporates by reference paragraphs 1-121 of its Answer.

123. Merck's breach of contract claim is barred by the Statute of Limitations. In Maryland, the statute of limitations for a civil action is three years from the date the civil action accrues. Maryland Code, Courts and Judicial proceedings §5-101. The statute of limitations begins when a claimant gains knowledge sufficient to put him or her on inquiry notice. From that date forward, a claimant will be charged with knowledge of facts that would have been disclosed by a reasonably diligent investigation.

124. Publicly available information, communications described in Merck's Complaint, and subsequent licensing negotiations between the parties demonstrate that Merck was on inquiry notice of any alleged breach more than three years before it filed the Complaint.

125. No later than June 2017, Merck admits it was aware of the Hopkins license of a MSI-related patent application to PGDx.

126. In September 2017, Kim Folander, Executive Director of Enabling Technologies Business Development & Licensing for Merck Research Laboratories, contacted Hopkins regarding the Hopkins PCT Application.

127. On November 28, 2017, representatives of Hopkins, including Christy Wyskiel, spoke via telephone with representatives from Merck, including Ms. Folander and Shari Wahl, Merck Executive Director of Licensing, Strategy Transaction and Ops. During this call, Merck's representatives informed Hopkins that they were aware of Hopkins' patent application related to

MSI. The Merck representatives further alleged that the intellectual property in this application was generated out of the work of the MSI Clinical Trial, and expressed Merck's interest in exercising an option to negotiate for a license. Ms. Wyskiel responded that, because the invention was Hopkins' alone, no option was created by the IICT Agreement.

128. At least by December 5, 2017, on behalf of Hopkins, Ms. Wyskiel represented to Merck that any future patent rights associated with the then-pending patent applications would not result from IICT Agreement, and that the Hopkins MSI-High inventions were conceived before the effective date of the IICT Agreement.

129. Merck filed its Complaint almost five years later, on November 29, 2022.

130. At least by December 5, 2017, Merck possessed sufficient knowledge of any alleged breach of the IICT Agreement by Hopkins relating to the Hopkins MSI Patents.

131. At least by June 2017, Merck knew that Hopkins had granted licenses to its MSI-related patent application.

132. At least by September 2017, Merck knew that Hopkins was pursuing patents related to the use of anti-PD-1 antibodies to treat cancer in patients who were determined to be dMMR or MSI-High, without involving Merck.

133. At least by September 2017, Merck knew of its alleged inventive contributions to the Hopkins MSI Patents.

134. At least by December 5, 2017, Merck knew that Hopkins' position was that the inventions described and claimed by the Hopkins MSI Patents predated the IICT Agreement and were therefore not subject to the IICT Agreement.

135. Having knowledge of these facts, Merck waited for more than three years to file the Complaint. As a result, Merck's breach of contract claim is barred by the statute of limitations.

HOPKINS' THIRD AFFIRMATIVE DEFENSE

(Any Option Right Merck Claims to Have Had Has Expired)

136. Hopkins realleges and incorporates by reference paragraphs 1-135 of its Answer.

137. Merck did not have an option for an exclusive license to the Hopkins MSI Patents under §12.B of the IICT Agreement.

138. To the extent Merck alleges it did have an option for an exclusive license to the Hopkins MSI Patents under §12.B of the IICT Agreement, that option has expired.

139. While Merck had no option rights, Merck and Hopkins engaged in multiple discussions and negotiations directed to Merck potentially acquiring the rights it desired in and to the Hopkins MSI Patents.

140. Hopkins and Merck engaged in initial rounds of license discussions in late 2017.

141. On January 2019, Roger Perlmutter, Executive Vice President, Merck & Co. and President, Merck Research Laboratories, visited Hopkins. While on campus, he met with Ms. Wyskiel and discussed Hopkins' contribution to Merck's MSI indication for Keytruda®. Mr. Perlmutter identified Mr. Ben Thorner and Ms. Kim Folander as the appropriate people to contact regarding further licensing discussions concerning the Hopkins MSI Patent applications.

142. In April 2019, Ms. Wyskiel connected with Mr. Thorner and Ms. Folander regarding a potential license to the Hopkins MSI patent application. At that time, Merck suggested that the parties put the licensing discussions on hold until a patent had issued.

143. On January 14, 2020, Ms. Folander approached Ms. Wyskiel at a conference in San Francisco and inquired about the status of the pending claims of the Hopkins MSI Patents.

144. The ’356 Patent, the first of the Hopkins MSI Patents to issue, issued on March 2, 2021.

145. On March 2, 2021, Ms. Wyskiel emailed Mr. Thorner and Ms. Folander to inform them of the issuance of the ’356 Patent and “to resume [their] discussion about this important, impactful, and now patented technology.”

146. Even assuming the IICT Agreement is relevant (and it is not), it recites that “[t]he parties agree to use good faith efforts to negotiate commercially reasonable terms for the exclusive license.” [*See* ECF No. 1-3, Ex. C to the Complaint at § 12.D.] However, during negotiations, Merck advised Hopkins that it sought a non-exclusive license to Hopkins MSI Patents.

147. As Merck requested, Hopkins provided Merck with a license proposal on or about March 30, 2021, and the parties engaged in follow-on discussions.

148. Ultimately, on June 4, 2021, Ms. Wyskiel spoke with Mr. Thorner regarding Hopkins’ offer to license the Hopkins MSI Patents. Mr. Thorner represented that Merck was not interested in taking a license to the Hopkins MSI Patents.

149. Hopkins and Merck have not engaged in license discussions since June 4, 2021.

150. Although the parties negotiated in good faith, the parties could not reach agreement on the terms of a license to the Hopkins MSI Patents.

151. Although Hopkins disputes that Merck had an option pursuant to contract to negotiate for a license to the Hopkins MSI Patents, if such an option did exist, it expired when the parties did not reach agreement on the terms of a license. Section 12.D of the IICT

Agreement provides, "In the event that Merck fails to so notify Institution or fails to obtain an exclusive license, then Merck's option shall expire with respect to said invention." [*See* ECF No. 1-3, Ex. C to the Complaint.]

HOPKINS' FOURTH AFFIRMATIVE DEFENSE

(Merck Waived Any Claims of Breach)

152. Hopkins realleges and incorporates by reference paragraphs 1-151 of its Answer.

153. Merck has waived any claim for breach of contract by continuing its own performance under the IICT Agreement and accepting Hopkins' performance under the IICT Agreement after having knowledge of the alleged breach by Hopkins.

154. A party to a contract waives its right to claim breach under that contract if it intentionally continues performance under the contract or accepts further performance from the party who has committed a breach after learning of that breach.

155. In November 2017, Merck and Hopkins discussed a potential license to the Hopkins MSI Patent application.

156. At least by December 5, 2017, Merck knew of Hopkins' MSI Patent application and Hopkins' position that the inventions disclosed by this patent application did not arise from the performance of the IICT Agreement.

157. At no point during the November 2017 discussions, or at any time thereafter, did Merck provide Hopkins with notice that it believed Hopkins was in breach of the IICT as required by § 5 of the IICT Agreement.

158. At no point during the November 2017 discussions, or at any time thereafter, did Merck ask Hopkins to take steps to cure the alleged breach.

159. Merck instead continued to perform under the IICT Agreement. On October 23, 2019, Merck made a seventh milestone payment to Hopkins in recognition of reaching enrollment of 105-117 patients.

160. On November 24, 2020, Hopkins received a final milestone payment from Merck.

161. Merck also continued to accept performance by Hopkins under the IICT Agreement, as indicated by the payments it made up to Hopkins upon reaching specific milestones as described in the Amendments to the IICT Agreement.

162. Merck continued performing its obligations under the IICT and accepting Hopkins' performance, without objection, from November 2017 until filing the Complaint, thereby waiving any right Merck claims to have to pursue a remedy for breach of contract.

COUNT II (MERCK'S DECLARATORY JUDGMENT OF NONINFRINGEMENT OF U.S. PATENT NO. 10,934,356)

HOPKINS' FIRST AFFIRMATIVE DEFENSE

163. Hopkins realleges and incorporates by reference paragraphs 1-162 of its Answer.

164. Merck's claim for declaratory judgment of non-infringement of U.S. Patent No. 10,934,356 fails because Merck induces physicians to infringe the '356 Patent in violation of 35 U.S.C. § 271(b). Hopkins' infringement allegations are detailed below in Counterclaim II.

HOPKINS' SECOND AFFIRMATIVE DEFENSE

165. Hopkins realleges and incorporates by reference paragraphs 1-164 of its Answer.

166. Merck's claim for declaratory judgment of non-infringement of the '356 Patent fails because Merck's infringement of the '356 Patent is not conduct protected by the IICT Agreement. Section 9.A provides that "[t]o the extent permissible by law, [Hopkins] agrees that all Study data and results generated during the course of the Study may be used fully by Merck for any legitimate business purpose with any additional payments being made to [Hopkins] or

Principal Investigator." [*See* ECF No. 1-3, Ex. C to the Complaint.] Infringing the '356 Patent is not use of "Study data" or "results generated during the course of the Study," so Merck's use of the invention claimed in the '356 Patent is not covered by § 9.A. Even if § 9.A did relate to use of the inventions claimed in the '356 Patent, Merck's manufacture, use, sale, offer for sale, and importation of Keytruda® violates 35 U.S.C. § 271(b) and is therefore not a use "permissible by law" allowed by § 9.A. Further, § 12 of the IICT Agreement details the parties' rights with respect inventions and patents, and does not give Merck any rights in or to the '356 Patent.

COUNT III (MERCK'S DECLARATORY JUDGMENT OF NONINFRINGEMENT OF U.S. PATENT NO. 11,325,974)

HOPKINS' FIRST AFFIRMATIVE DEFENSE

167. Hopkins realleges and incorporates by reference Paragraphs 1-166 of its Answer.

168. Merck's claim for declaratory judgment of non-infringement of U.S. Patent No. 11,325,974 fails because Merck induces physicians to infringe the '974 Patent in violation of 35 U.S.C. § 271(b). Hopkins infringement allegations are detailed below in Counterclaim III.

HOPKINS' SECOND AFFIRMATIVE DEFENSE

169. Hopkins realleges and incorporates by reference paragraphs 1-168 of its Answer.

170. Merck's claim for declaratory judgment of non-infringement of the '974 Patent fails because Merck's infringement of the '974 Patent is not conduct protected by the IICT Agreement. Section 9.A provides that "[t]o the extent permissible by law, [Hopkins] agrees that all Study data and results generated during the course of the Study may be used fully by Merck for any legitimate business purpose with any additional payments being made to [Hopkins] or Principal Investigator." [*See* ECF No. 1-3, Ex. C to the Complaint.] Infringing the '974 Patent is not use of "Study data" or "results generated during the course of the Study," so Merck's use of the inventions claimed in the '974 Patent is not covered by § 9.A. Even if § 9.A did relate to

the use of the inventions claimed in the ’974 Patent, Merck’s manufacture, use, sale, offer for sale, and importation of Keytruda® violates 35 U.S.C. § 271(b) and is therefore not a use “permissible by law” allowed by § 9.A. Further, § 12 of the IICT Agreement details the parties’ rights with respect inventions and patents, and does not give Merck any rights to the ’974 Patent.

COUNT IV (MERCK’S DECLARATORY JUDGMENT OF NONINFRINGEMENT OF U.S. PATENT NO. 11,325,975)

HOPKINS’ FIRST AFFIRMATIVE DEFENSE

171. Hopkins realleges and incorporates by reference paragraphs 1-170 of its Answer.

172. Merck’s claim for declaratory judgment of non-infringement of U.S. Patent No. 11,325,975 fails because Merck induces physicians to infringe the ’975 Patent in violation of 35 U.S.C. § 271(b). Hopkins infringement allegations are detailed below in Counterclaim IV.

HOPKINS’ SECOND AFFIRMATIVE DEFENSE

173. Hopkins realleges and incorporates by reference paragraphs 1-172 of its Answer.

174. Merck’s claim for declaratory judgment of non-infringement of the ’975 Patent fails because Merck’s infringement of the ’975 Patent is not conduct protected by the IICT Agreement. Section 9.A provides that “[t]o the extent permissible by law, [Hopkins] agrees that all Study data and results generated during the course of the Study may be used fully by Merck for any legitimate business purpose with any additional payments being made to [Hopkins] or Principal Investigator.” [*See* ECF No. 1-3, Ex. C to the Complaint.] Infringing the ’975 Patent is not use of “Study data” or “results generated during the course of the Study,” so Merck’s use of the inventions claimed in the ’975 Patent is not covered by § 9.A. Even if § 9.A did related to use of the inventions claimed in the ’975 Patent, Merck’s manufacture, use, sale, offer for sale, and importation of Keytruda® violates 35 U.S.C. § 271(b) and is therefore not a use “permissible

by law" allowed by § 9.A. Further, § 12 of the IICT Agreement details the parties' rights with respect inventions and patents, and does not give Merck any rights to the '975 Patent.

COUNT V (MERCK'S DECLARATORY JUDGMENT OF NONINFRINGEMENT OF U.S. PATENT NO. 11,339,219)

HOPKINS' FIRST AFFIRMATIVE DEFENSE

175. Hopkins realleges and incorporates by reference paragraphs 1-174 of its Answer.

176. Merck's claim for declaratory judgment of non-infringement of U.S. Patent No. 11,339,219 fails because Merck induces physicians to infringe the '219 Patent in violation of 35 U.S.C. § 271(b). Hopkins infringement allegations are detailed below in Counterclaim V.

HOPKINS' SECOND AFFIRMATIVE DEFENSE

177. Hopkins realleges and incorporates by reference paragraphs 1-176 of its Answer.

178. Merck's claim for declaratory judgment of non-infringement of the '219 Patent fails because Merck's infringement of the '219 Patent is not conduct protected by the IICT Agreement. Section 9.A provides that "[t]o the extent permissible by law, [Hopkins] agrees that all Study data and results generated during the course of the Study may be used fully by Merck for any legitimate business purpose with any additional payments being made to [Hopkins] or Principal Investigator." [*See* ECF No. 1-3, Ex. C to the Complaint.] Infringing the '219 Patent is not use of "Study data" or "results generated during the course of the Study," so Merck's use of the inventions claimed in the '219 Patent is not covered by § 9.A. Even if § 9.A did relate to use of the invention claimed in the '219 Patent, Merck's manufacture, use, sale, offer for sale, and importation of Keytruda® violates 35 U.S.C. § 271(b) and is therefore not a use "permissible by law" allowed by § 9.A. Further, § 12 of the IICT Agreement details the parties' rights with respect inventions and patents, and does not give Merck any rights to the '219 Patent.

COUNT VI (PROMISSORY ESTOPPEL)

179. Hopkins realleges and incorporates by reference paragraphs 1-178 of its Answer.

180. Merck's claim for promissory estoppel fails because Hopkins made no promise regarding assertion of the Hopkins MSI Patents on which a promissory estoppel claim could be based.

181. Merck's promissory estoppel claim is barred because the IICT Agreement, and its subsequent amendments, concern the same subject matter on which Merck's promissory estoppel claim rests.

182. Promissory estoppel requires (1) a clear and definite promise; (2) where the promisor has a reasonable expectation that the offer will induce action or forbearance on the part of the promisee; (3) which does induce actual and reasonable action or forbearance by the promisee; and (4) causes a detriment which can only be avoided by enforcement of the promise. *Pavel Enterprises, Inc. v. A.S. Johnson Co., Inc.*, 342 Md. 143, 166, 674 A.2d 521, 533 (1996) (citing Restatement (Second) of Contracts § 90(1) (1979)).

183. At no time did Hopkins make a clear and definite promise to Merck with respect to the assertion of the Hopkins MSI Patents or any other issue outside the terms of the IICT Agreement.

184. Merck does not allege that Hopkins made a clear and definite promise regarding assertion of the Hopkins MSI Patents nor does it allege any facts that would constitute such a promise. [*See* ECF No. 1, Complaint, ¶¶ 78-79.]

185. As a matter of law, Merck's promissory estoppel claim cannot be premised on allegations of promises related to the terms of the IICT Agreement. Promissory estoppel is a quasi-contractual claim, and no quasi-contractual claim can arise when a contract exists concerning the same subject matter on which the quasi-contractual claim rests. The allegations

on which Merck's promissory estoppel claim rests all are covered by the terms of the IICT Agreement, and Merck alleges that Agreement concerns the same subject matter as its promissory estoppel claim.

186. Merck acknowledges that the IICT Agreement was a valid and binding agreement. [ECF No. 1, Complaint, ¶ 54.]

187. Merck's allegations regarding the Pardoll and Kuchroo declarations and the issuance of the claims of the Hopkins MSI Patents cannot, as a matter of law, support a claim of promissory estoppel. [ECF No. 1, Complaint, ¶ 79.] Notification of alleged patent rights and offers of a license are expressly addressed by §§ 12.B and 12.D of the IICT Agreement.

188. Merck's allegations regarding the use of study data cannot, as a matter of law, support a claim of promissory estoppel. [ECF No. 1, Complaint, ¶ 79.] Merck's use of data is expressly addressed by §9.A of the IICT Agreement.

189. Merck's allegations regarding expected contributions of a supply of the drug and payments by Merck cannot, as a matter of law, support a claim of promissory estoppel. Contributions of drug and the later payments by Merck are expressly addressed by §10.A of the IICT Agreement and Amendments 2-4 to the IICT Agreement. Merck's failure to plead, and its inability to plead, facts supporting the elements of a promissory estoppel claim preclude such a claim by Merck.

COUNTERCLAIMS

Counterclaim-Plaintiff The Johns Hopkins University ("Hopkins") alleges as follows for its counterclaims against Counterclaim-Defendant Merck Sharp & Dohme LLC ("Merck"). Hopkins incorporates by reference the allegations contained in its Case Overview and in paragraphs 81-111 of its Affirmative Defenses as though reproduced here.

PARTIES

1. Hopkins is a Maryland, not-for-profit corporation having its principal place of business at 3400 N. Charles Street, Baltimore, Maryland 21218.

2. On information and belief, Merck is an LLC organized and existing under the laws of the State of New Jersey with a principal place of business at 126 East Lincoln Avenue, Rahway, New Jersey, 07065.

JURISDICTION AND VENUE

3. These counterclaims arise under the patent laws of the United States, 35 U.S.C. §§ 271 and 281-285.

4. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

5. Merck is subject to the personal jurisdiction of this Court because Merck is the named plaintiff and consented to the jurisdiction of this Court by filing its Complaint here for breach of contract; declaratory judgment of non-infringement; and promissory estoppel, in response to which these counterclaims are asserted.

6. Venue is proper under 28 U.S.C. §§ 1391(b), 1391(c), and 1400(b).

FACTS RELATING TO MERCK'S INFRINGEMENT OF THE HOPKINS MSI PATENTS

7. Merck, including through actions of its subsidiaries, other related entities, or entities acting at Merck's direction or under its control, manufactures Keytruda® (pembrolizumab) for use in approved indications throughout the United States. Merck sells, offers to sell and imports into the United States, Keytruda® for such uses.

8. The FDA-approved labeling for Keytruda® lists three indications relevant to Hopkins' counterclaims. All three indications specify using "an FDA-approved test" to

determine whether the patient has a tumor that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). [ECF No. 1-1, Ex. A, Keytruda® Label at 1.]

9. In Section 2.1 of the Keytruda® Label, titled "Patient Selection," Merck provides a link: "for Information on FDA-approved tests for patient selection is available at: **http://www.fda.gov/CompanionDiagnostics**". The link navigates to a webpage listing the manufacturer and test name for biomarkers for the assessment of MSI-H or dMMR status.

10. All three Keytruda® Label indications relevant to Hopkins' counterclaims are directed to MSI-H or dMMR tumors and are reproduced below:

> **1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer**
>
> KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternate treatment options [*see Dosage and Administration (2.10)*].
>
> **1.15 Endometrial Carcinoma**
>
> KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [*see Dosage and Administration* (2.1)].
>
> **1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colon Cancer**
>
> KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test [*see Dosage and Administration (2.1)*].

11. Merck's label provides a "Recommended Dosage" section that instructs physicians on the dosage, duration, and timing for each of the three relevant indications.

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma or RCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months

[ECF No. 1-1, Ex. A, Keytruda® Label at 8 (highlighting added).]

12. Merck operates the website www.keytrudahcp.com/physician-site/product-info for health care professionals to access. Merck uses the website to further instruct physicians on methods for prescribing and/or treating patients with MSH-H or dMMR tumors using Keytruda®.

FIRST COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,591,393

13. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-12 of these Counterclaims.

14. On February 28, 2023, the United States Patent and Trademark Office ("USPTO") issued U.S. Patent No. 11,591,393 (the "'393 patent").

15. The '393 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

16. A true and correct copy of the '393 patent is attached to this counterclaim as Exhibit 10.

17. Merck has been monitoring Hopkins' MSI patent prosecution since at least 2017. On information and belief, Merck has known of Application No. 17/465,101, which issued as the '393 patent, since on or about December 23, 2021, when Application No. 17/465,101 became publicly available.

18. Representative claim 1 of the '393 patent is reproduced below:

> **1**. A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising:
>
> testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining the patient's colorectal cancer is microsatellite instability high or DNA mismatch repair deficient,
>
> and in response to determining that the colorectal cancer is microsatellite high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.

19. Attached as Exhibit 12 to this counterclaim is a claim chart showing how Merck induces physicians to directly infringe claim 1 of the '393 patent by treating MSI-H or mismatch repair deficient patients with Keytruda®.

20. Merck induces physicians to infringe the '393 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

21. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the methods of at least claim 1 of the '393 patent.

22. Physicians who prescribe Keytruda® within the United States according to the instructions in the product's labeling will directly infringe at least claim 1 of the '393 patent.

23. Merck knows that physicians perform the method covered by claim 1 of the '393 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the '393 patent.

24. Merck specifically intends for physicians to follow the instructions on its FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’393 patent.

25. Merck’s conduct violates Hopkins’ patent rights and has caused and will continue to cause harm to Hopkins.

26. Despite Merck’s knowledge of the ’393 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the ’393 patent. Merck lacks a justifiable belief that its actions do not induce infringement of the ’393 patent.

27. Merck’s acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

28. At least Merck’s willful infringement of the ’393 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys’ fees, in accordance with 35 U.S.C. § 285.

SECOND COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 10,934,356

29. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-28 of these Counterclaims.

30. On March 2, 2021, the USPTO issued U.S. Patent No. 10,934,356 (the “’356 patent”).

31. The ’356 patent is titled “Checkpoint Blockade and Microsatellite Instability” and is assigned to Hopkins.

32. Merck admitted to having actual knowledge of the ’356 patent when it filed its Complaint seeking declaratory judgment of noninfringement of the ’356 patent and attached the ’356 patent as Exhibit D to its Complaint. [*See* ECF No. 1-4.]

33. Representative claim 23 of the ’356 patent is reproduced below:

> **23**. A method of treating cancer in a population of cancer patients in need thereof, comprising:
>
> administering an effective amount of pembrolizumab to patients in the population of cancer patients, which patients have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch (MMR) deficiency status, said tumor having progressed following a prior treatment; and
>
> observing an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab.

34. Attached as Exhibit 13 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 23 of the ’356 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

35. Merck induces physicians to infringe the ’356 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

36. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 23 of the ’356 patent.

37. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 23 of the ’356 patent.

38. Merck knows that physicians perform the method covered by claim 23 of the ’356 patent and thus directly infringe, and intends for them to directly infringe at least claim 23 of the ’356 patent.

39. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 23 of the ’356 patent.

40. Merck's conduct violates Hopkins' patent rights and has caused and will continue to cause harm to Hopkins.

41. Despite Merck's knowledge of the '356 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the '356 patent. Merck lacks a justifiable belief that it does not induce infringement the '356 patent.

42. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

43. At least Merck's willful infringement of the '356 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

THIRD COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,325,974

44. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-43 of these Counterclaims.

45. On May 10, 2022, the USPTO issued U.S. Patent No. 11, 325,974 (the "'974 patent").

46. The '974 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

47. Merck admitted to having actual knowledge of the '974 patent when it filed its complaint seeking declaratory judgment of noninfringement of the '974 patent and attached the '974 patent as Exhibit E to its complaint. [*See* ECF No. 1-5.]

48. Representative claim 1 of the '974 patent is reproduced below:

> **1.** A method for treating cancer in a patient in need thereof,
> wherein a tumor sample obtained from the patient has been determined to exhibit an instability of one or more microsatellite

> markers or a deficiency of one or more mismatch repair markers, the patient having received a prior cancer therapy drug to treat the tumor, the method comprising:
>
> administering an effective amount of pembrolizumab to the patient;
>
> wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibit an instability of the one or more microsatellite markers or a deficiency of the one or more mismatch repair markers.

49. Attached as Exhibit 14 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the ’974 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

50. Merck induces physicians to infringe the ’974 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

51. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the ’974 patent.

52. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 1 of the ’974 patent.

53. Merck knows that physicians perform the method covered by claim 1 of the ’974 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the ’974 patent.

54. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’974 patent.

55. Merck's conduct violates Hopkins patent rights and has caused and will continue to cause harm to Hopkins.

56. Despite Merck's knowledge of the '974 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the '974 patent. Merck lacks a justifiable belief that it does not induce infringement the '974 patent.

57. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

58. At least Merck's willful infringement of the '974 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

FOURTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,325,975

59. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-58 of these Counterclaims.

60. On May 10, 2022, the USPTO issued U.S. Patent No. 11, 325,975 (the "'975 patent").

61. The '975 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

62. Merck admitted to having actual knowledge of the '975 patent when it filed its complaint seeking declaratory judgment of noninfringement of the '975 patent and attached the '975 patent as Exhibit F to its complaint. [*See* ECF No. 1-6.]

63. Representative claim 1 of the '975 patent is reproduced below:

1. A method for treating cancer in a patient in need thereof,

> wherein the patient has been determined to have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, comprising:
>
> administering an effective amount of an anti-PD-1 antibody to the patient;
>
> wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered the anti-PD-1 antibody, wherein the reference patient has a tumor that does not exhibit a MSI-high or a MMR deficiency status; and
>
> wherein the patient has received a prior cancer therapy drug.

64. Attached as Exhibit 15 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the '975 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

65. Merck induces physicians to infringe the '975 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

66. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the '975 patent.

67. Physicians who prescribe Keytruda® within the United States according to the instructions in the product's labeling will directly infringe at least claim 1 of the '975 patent.

68. Merck knows that physicians perform the method covered by claim 1 of the '975 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the '975 patent.

69. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda in a manner that directly infringes at least claim 1 of the '975 patent.

70. Merck's conduct violates Hopkins' patent rights and has caused and will continue to cause harm to Hopkins.

71. Despite Merck's knowledge of the '975 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the '975 patent. Merck lacks a justifiable belief that it does not induce infringement the '975 patent.

72. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

73. At least Merck's willful infringement of the '975 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

FIFTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,339,219

74. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-73 of these Counterclaims.

75. On May 24, 2022, the USPTO issued U.S. Patent No. 11, 339,219 (the "'219 patent").

76. The '219 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

77. Merck admitted to having actual knowledge of the '219 patent when it filed its complaint seeking declaratory judgment of noninfringement of the '219 patent and attached the '219 patent as Exhibit G to its complaint. [*See* ECF No. 1-7.]

78. Representative claim 1 of the '219 patent is reproduced below:

> **1.** A method for treating cancer in a patient in need thereof comprising:

> selecting a patient who has an unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient tumor; and
>
> administering an effective amount of pembrolizumab to the patient;
>
> wherein the patient exhibits an outcome that is improved as compared to a corresponding outcome that would be observed in a reference patient that has been administered pembrolizumab, wherein the reference patient has a tumor that does not exhibits a MSI-high or a MMR deficiency status.

79. Attached as Exhibit 16 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the ’219 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

80. Merck induces physicians to infringe the ’219 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

81. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the ’219 patent.

82. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 1 of the ’219 patent.

83. Merck knows that physicians perform the method covered by claim 1 of the ’219 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the ’219 patent.

84. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’219 patent.

85. Merck's conduct violates Hopkins' patent rights and has caused and will continue to cause harm to Hopkins.

86. Despite Merck's knowledge of the '219 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the '219 patent. Merck lacks a justifiable belief that it does not induce infringement the '219 patent.

87. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

88. At least Merck's willful infringement of the '219 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

SIXTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,643,462

89. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-88 of these Counterclaims.

90. On May 9, 2023, the USPTO issued U.S. Patent No. 11,643,462 (the "'462 patent").

91. The '462 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

92. A true and correct copy of the '462 patent is attached to this counterclaim as Exhibit 17.

93. Merck had actual knowledge of the '462 patent at least since March 14, 2023, when Hopkins provided Merck with an advance copy of its Answer and Counterclaims. The Answer and Counterclaims notified Merck that the USPTO issued a Notice of Allowance of U.S. Application No. 17/354,653, which later issued as the '462 patent, and that Hopkins intended to

amend its counterclaims to assert infringement of one or more claims of the ’462 patent upon issuance. [*See* ECF No. 17, Hopkins’ Counterclaims at ¶¶89-91.]

94. Representative claim 1 of the ’462 patent is reproduced below:

> **1.** A method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, the method comprising:
>
> testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.

95. Attached as Exhibit 18 of this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the ’462 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

96. Merck induces physicians to infringe the ’462 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

97. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the ’462 patent.

98. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 1 of the ’462 patent.

99. Merck knows that physicians perform the method covered by claim 1 of the ’462 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the ’462 patent.

100. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’462 patent.

101. Merck’s conduct violates Hopkins’ patent rights and has caused and will continue to cause harm to Hopkins.

102. Despite Merck’s knowledge of the ’462 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the ’462 patent. Merck lacks a justifiable belief that it does not induce infringement the ’462 patent.

103. Merck’s acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

104. At least Merck’s willful infringement of the ’462 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys’ fees, in accordance with 35 U.S.C. § 285.

SEVENTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,629,187

105. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-104 of these Counterclaims.

106. On April 18, 2023 the USPTO issued U.S. Patent No. 11,629,187 (the ’187 patent).

107. The ’187 patent is titled “Checkpoint Blockade and Microsatellite Instability” and is assigned to Hopkins.

108. A true and correct copy of the ’187 patent is attached to this counterclaim as Exhibit 19.

109. Merck had actual knowledge of the ’187 patent at least since March 14, 2023, when Hopkins provided Merck with an advance copy of its Answer and Counterclaims. The Answer and Counterclaims notified Merck that the USPTO issued a Notice of Allowance of U.S. Application No. 17/354,656, which later issued as the ’187 patent, and that Hopkins intended to amend its counterclaims to assert infringement of one or more claims of the ’187 patent upon issuance. [*See* ECF No. 17, Hopkins’ Counterclaims at ¶¶92-94.]

110. Representative claim 1 of the ’187 patent is reproduced below.

> 1. A method for treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer, the method comprising:
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating a patient having a solid tumor selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer with a therapeutically effective amount of pembrolizumab based on a determination that the solid tumor has progressed following at least one prior cancer treatment, and further based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.

111. Attached as Exhibit 20 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the ’187 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

112. Merck induces physicians to infringe the ’187 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

113. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the ’187 patent.

114. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 1 of the ’187 patent.

115. Merck knows that physicians perform the method covered by claim 1 of the ’187 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the ’187 patent.

116. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’187 patent.

117. Merck’s conduct violates Hopkins’ patent rights and has caused and will continue to cause harm to Hopkins.

118. Despite Merck’s knowledge of the ’187 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the ’187 patent. Merck lacks a justifiable belief that it does not induce infringement the ’187 patent.

119. Merck’s acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

120. At least Merck's willful infringement of the '187 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

EIGHTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,649,287

121. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-120 of these Counterclaims.

122. On May 16, 2023 the USPTO issued U.S. Patent No. 11,649,287 (the '287 patent).

123. The '287 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

124. A true and correct copy of the '287 patent is attached to this counterclaim as Exhibit 21.

125. Merck had actual knowledge of the '287 patent at least since March 14, 2023, when Hopkins sent Merck an advance copy of its Answer and Counterclaims. The Answer and Counterclaims notified Merck that the USPTO issued a Notice of Allowance of U.S. Application No. 17/465,096, which later issued as the '287 patent, and that Hopkins intended to amend its counterclaims to assert infringement of one or more claims of the '287 patent upon issuance. [*See* ECF No. 17, Hopkins' Counterclaims at ¶¶95-97.]

126. Representative claim 1 of the '287 patent is reproduced below:

> 1. A method for treating colorectal cancer in a human patient, the method comprising:
>
> in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab, wherein a biological sample from the patient had previously been tested to

> determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.

127. Attached as Exhibit 22 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the ’287 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

128. Merck induces physicians to infringe the ’287 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

129. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the ’287 patent.

130. Physicians who prescribe Keytruda® within the United States according to the instructions in the product’s labeling will directly infringe at least claim 1 of the ’287 patent.

131. Merck knows that physicians perform the method covered by claim 1 of the ’287 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the ’287 patent.

132. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the ’287 patent.

133. Merck’s conduct violates Hopkins’ patent rights and has caused and will continue to cause harm to Hopkins.

134. Despite Merck’s knowledge of the ’287 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the ’287 patent. Merck lacks a justifiable belief that it does not induce infringement the ’287 patent.

135. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

136. At least Merck's willful infringement of the '287 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

NINTH COUNTERCLAIM FOR INFRINGEMENT OF U.S. PATENT NO. 11,634,491

137. Hopkins realleges and incorporates by reference paragraphs 93-123 of its Answer and paragraphs 1-136 of these Counterclaims.

138. On April 25, 2023 the USPTO issued U.S. Patent No. 11,634,491 (the '491 patent).

139. The '491 patent is titled "Checkpoint Blockade and Microsatellite Instability" and is assigned to Hopkins.

140. A true and correct copy of the '491 patent is attached to this counterclaim as Exhibit 23.

141. Merck had actual knowledge of the '491 patent at least since March 14, 2023, when Hopkins provided Merck with an advance copy of its Answer and Counterclaims. The Answer and Counterclaims notified Merck that the USPTO issued a Notice of Allowance of U.S. Application No. 17/739,278, which later issued as the '491 patent, and that Hopkins intended to amend its counterclaims to assert infringement of one or more claims of the '491 patent upon issuance. [*See* ECF No. 17, Hopkins' Counterclaims at ¶¶98-100.]

142. Representative claim 1 of the '491 patent is reproduced below:

> **1.** A method of treating cancer in a human patient, the method comprising:

> testing or having tested a biological sample obtained from a patient having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer, thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or DNA mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab.

143. Attached as Exhibit 24 to this counterclaim is a claim chart showing how Merck induces physicians to infringe claim 1 of the '491 patent by treating MSI-High or mismatch repair deficient patients with Keytruda®.

144. Merck induces physicians to infringe the '491 patent in violation of 35 U.S.C. § 271(b) by providing materials to physicians that encourage and instruct the physicians to perform the claimed methods of treatment.

145. Merck includes within the packaging of Keytruda®, or otherwise makes available to physicians, labeling that instructs physicians to perform the method of at least claim 1 of the '491 patent.

146. Physicians who prescribe Keytruda® within the United States according to the instructions in the product's labeling will directly infringe at least claim 1 of the '491 patent.

147. Merck knows that physicians perform the method covered by claim 1 of the '491 patent and thus directly infringe, and intends for them to directly infringe at least claim 1 of the '491 patent.

148. Merck specifically intends for physicians to follow the instructions on the FDA-approved labeling to treat patients with Keytruda® in a manner that directly infringes at least claim 1 of the '491 patent.

149. Merck's conduct violates Hopkins' patent rights and has caused and will continue to cause harm to Hopkins.

150. Despite Merck's knowledge of the '491 patent and its ongoing infringement, Merck continues to induce physicians to directly infringe the '491 patent. Merck lacks a justifiable belief that it does not induce infringement the '491 patent.

151. Merck's acts of infringement have been and continue to be willful, deliberate and egregious justifying an increase in the damages to be awarded Hopkins up to three times the amount found or assessed, in accordance with 35 U.S.C. § 284.

152. At least Merck's willful infringement of the '491 patent renders this case an exceptional case, justifying an award to Hopkins of its reasonable attorneys' fees, in accordance with 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Hopkins respectfully requests that the Court enter judgment in Hopkins' favor and against Merck as follows, and provide Hopkins the following relief:

1. A finding that Merck has infringed one or more claims of the '393 patent, the '356 patent, the '274 patent, the '275 patent, the '219 patent, the '462 patent, the '187 patent, the '287 patent, and the '491 patent;

2. A finding that Merck's infringement of the '393 patent, the '356 patent, the '274 patent, the '275 patent, the '219 patent, the '462 patent, the '187 patent, the '287 patent, and the '491 patent has been and is willful;

3. An award to Hopkins of damages adequate to compensate Hopkins for all infringement occurring through the date of judgment, with prejudgment interest, supplemental damages as appropriate, costs and post-judgment interest;

4. An accounting of Merck's infringing activities through trial and judgment;

5. The payment of royalties for Merck's ongoing willful infringement of the '393 patent, the '356 patent, the '274 patent, the '275 patent, the '219 patent, the '462 patent, the '187 patent, the '287 patent, and the '491 patent until such time as Merck halts its infringing activities;

6. An award of enhanced damages under 35 U.S.C. § 284;

7. A finding that this action for infringement is an exceptional case under 35 U.S.C. § 285 and an award to Plaintiff of its reasonable attorneys' fees;

8. An award of any further relief that the Court deems just and proper.

Dated: May 22, 2023 FISH & RICHARDSON P.C.

By: */s/ Ahmed J. Davis*

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