IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO,	)	C.A. No. _____
Plaintiffs,	)	**JURY TRIAL DEMANDED**
v.	)	
EMD SERONO, INC., MERCK KGaA, and PFIZER INC.,	)	
Defendants.	)	

COMPLAINT

Plaintiffs Bristol-Myers Squibb Co. ("BMS"), E. R. Squibb & Sons L.L.C. ("Squibb"), Ono Pharmaceutical Co., Ltd. ("Ono"), and Tasuku Honjo (collectively "Plaintiffs"), for their complaint for patent infringement against Defendants EMD Serono, Inc. ("Serono"), Merck KGaA ("Merck"), and Pfizer Inc. ("Pfizer") (collectively, "Defendants"), hereby allege as follows:

INTRODUCTION

1. According to the American Cancer Society, more than one million people in the United States are diagnosed with cancer each year (http://www.cancer.org/cancer/index). Cancer is a disease that results from the uncontrolled proliferation of cells that were once normal but have transformed into cancerous cells. Although the human immune system sometimes has the potential to eliminate cancerous cells, cancer cells have the ability to "turn off" or evade the immune system, allowing the cancer cells to grow unchecked. Tumor growth and tumor metastasis can lead to devastating disease, and possibly death. Cancer treatments are therefore developed to decrease tumor growth and metastasis.

2. This case relates to groundbreaking treatments for cancer that fall within a field known as "immunotherapy." The treatment of cancer using immunotherapy represents a scientific breakthrough that is revolutionizing cancer treatment by manipulating a patient's immune system to eliminate cancer cells.

3. The human immune system is formed of organs, specialized cells, and substances that protect individuals from infections and disease. T cells are one class of specialized cells that play an important role in the human immune system. One major function of T cells is to destroy pathogens or malignant cells, and to do that the T cell must distinguish healthy cells from pathogens or malignant cells through the activation or deactivation of various receptors on the T cell surface. One of the receptors that T cells carry on their surface is a protein called programmed death-1 receptor ("PD-1"). PD-1 functions as a checkpoint on the immune system that can downregulate T cell activity to prevent an overactive immune response. To activate its inhibitory function, PD-1 must bind to one of its ligands. Programmed death-ligand 1 ("PD-L1") is one of these ligands.

4. Numerous forms of cancers express PD-L1 on their cell surface, and can therefore exploit PD-1's ability to downregulate the immune response. When PD-L1, such as that expressed on a cancer cell, binds to PD-1 on immune cells, such as a T cell, it can result in the suppression of T cell migration, proliferation and secretion of cytotoxic mediators, which in turn will eliminate or decrease an anticancer immune response. In other words, cancer cells expressing PD-L1 can activate the PD-1 checkpoint to prevent a patient's immune system from destroying cancer cells.

5. The inventions at issue here generally relate to treatments for cancer and enhancing immune responses by administering antibodies that bind to PD-L1 ("anti-PD-L1

antibodies"). Types of anti-PD-L1 antibodies are shown by the inventions to inhibit the interaction between PD-1 and PD-L1. By binding to PD-L1 and blocking its interaction with PD-1, the anti-PD-L1 antibodies act as checkpoint inhibitors that release the brakes on the immune system, freeing the immune cells to recognize, attack and destroy cancer cells.

6. The Plaintiffs also invented antibodies that bind to PD-1 ("anti-PD-1 antibodies"), and put this scientific breakthrough into practice by developing an anti-PD-1 antibody called OPDIVO® (nivolumab), the first anti-PD-1 antibody approved anywhere in the world for cancer treatment, and the first anti-PD-1 antibody approved in the United States for the treatment of lung cancer.

7. Nivolumab is a monoclonal antibody that recognizes and binds to PD-1. When nivolumab binds to PD-1, it prevents PD-1 from binding its ligands. Using nivolumab to block the interaction between PD-1 and its ligands enhances the T cell response generated by the patient's immune system.

8. Clinical testing of nivolumab confirmed the remarkable promise of checkpoint inhibitors as targets for immunotherapy. After rigorous worldwide testing, on July 4, 2014, nivolumab became the first anti-PD-1 antibody approved anywhere in the world for treating cancer, when Japanese regulatory authorities approved nivolumab for the treatment of melanoma, a deadly form of skin cancer (http://www.ono.co.jp/eng/news/pdf/sm_cn140704.pdf). On December 22, 2014, the FDA approved nivolumab for treatment of advanced melanoma in the United States.

9. Plaintiffs have continued worldwide development of nivolumab for treatment of a broad range of cancers, including non-small cell lung cancer, renal cell carcinoma, head and neck cancer, glioblastoma, and non-Hodgkin lymphoma. In Phase III clinical testing for lung cancer,

patients with advanced lung cancer who received nivolumab showed superior overall survival (41% reduction in the risk of death) compared to those who received the standard of care chemotherapy agent docetaxol (http://news.bms.com/press-release/fda-approves-opdivo-nivolumab-treatment-patients-previously-treated-metastatic-squamou). Based, at least in part, on these clinical results, on February 27, 2015, the FDA accepted Plaintiffs' Biologics License Application ("BLA") for use of nivolumab to treat lung cancer. Just days later, on March 4, 2015, the FDA approved nivolumab for treatment of advanced non-small cell lung cancer in the United States. On November, 23, 2015, the FDA approved nivolumab for the treatment of patients with advanced renal cell carcinoma, a form of kidney cancer. These clinical results and the FDA's recent approval of nivolumab for the treatment of various additional forms of cancer confirm that the cancer treatments developed by the Plaintiffs can be used to save the lives of patients suffering from cancer.

10. Plaintiffs and Defendants are competitors in the field of immunotherapy.

11. Defendants are exploiting Plaintiffs' inventions with their later-developed antibody product BAVENCIO® (avelumab), an anti-PD-L1 antibody used in methods for treating cancer.

PARTIES

12. BMS is a corporation organized under the laws of the state of Delaware, with a principal place of business at 345 Park Ave., New York, New York 10154. E. R. Squibb & Sons L.L.C., is a limited liability company organized and existing under the laws of the state of Delaware, with its principal place of business at Route 206 & Province Line Road, Princeton, New Jersey 08543. Ono is a corporation organized under the laws of Japan, with a place of business at 8-2 Kyutaromachi 1-chome, Chuo-ku, Osaka 541-8564, Japan. Tasuku Honjo is an

individual with a place of business at Kyoto University, Graduate School of Medicine, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan.

13. On information and belief, Defendant Serono is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at One Technology Place, Rockland, Massachusetts 02370. Serono is a U.S. subsidiary and the biopharmaceutical division of Defendant Merck.

14. On information and belief, Defendant Merck is a German corporation having a principal place at Frankfurter Str. 250, 64293 Darmstadt Hessen, Germany.

15. On information and belief, Defendant Pfizer is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 235 East 42nd Street, New York, New York 10017.

16. Defendants are in the business of developing, manufacturing, marketing, distributing, offering for sale, and/or selling biologic drug products that are distributed and sold throughout the United States, including in Delaware.

JURISDICTION AND VENUE

17. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. §§ 271 *et seq*., including an action seeking a declaratory judgment pursuant to 28 U.S.C. §§ 2201-2202.

18. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

19. This Court has personal jurisdiction over Serono because it is a corporation organized and existing under the law of Delaware and, upon information and belief, Serono has systematic and continuous contacts in Delaware, regularly transacts business in Delaware, has

derived substantial revenue from sales of pharmaceutical products in Delaware, and markets Defendants' anti-PD-L1 antibody avelumab in Delaware.

20. This Court has jurisdiction over Merck because, *inter alia*, its subsidiary and agent, Serono, is incorporated in Delaware and, upon information and belief, markets and sells avelumab in Delaware as the biopharmaceutical division of Merck and as Merck's authorized agent and under Merck's direction and control. Furthermore, on information and belief, Merck and Serono operate and act in concert as an integrated, unitary business. For example, Serono operates in the United States as Merck's agent, including with respect to the regulatory approval, marketing and sale of Defendants' anti-PD-L1 antibody avelumab.

21. Moreover, Merck has consented to jurisdiction in Delaware and/or has purposefully availed itself of the privileges and benefits of the laws of Delaware in one or more prior cases arising out of the manufacture, use, offer for sale, sale and/or importation of Merck's pharmaceutical products, including patent infringement lawsuits that Merck has initiated as plaintiff and which are pending in this Court.

22. This Court has personal jurisdiction over Pfizer because it is a corporation organized and existing under the law of Delaware and, upon information and belief, Pfizer has systematic and continuous contacts in Delaware, regularly transacts business in Delaware, has derived substantial revenue from sales of pharmaceutical products in Delaware, and markets Defendants' anti-PD-L1 antibody avelumab in Delaware.

23. On information and belief, Merck and Pfizer formed an alliance to develop Defendants' anti-PD-L1 antibody avelumab, with both companies jointly funding development and marketing costs and sharing revenues equally. On information and belief, pursuant to this

alliance, Serono (as Merck's authorized agent) and Pfizer are responsible for the commercialization of Defendants' anti-PD-L1 antibody avelumab in the United States.

24. On information and belief, and further pursuant to this alliance, Merck has acted directly in the United States, or indirectly in the United States through its authorized agent Serono, and in Delaware in particular, to commercialize, market and sell avelumab in the United States, including in Delaware.

25. On information and belief, Merck is the owner in the United States of the mark "Bavencio," the trademark used to market Defendants' anti-PD-L1 antibody avelumab.

26. In the alternative, this Court may exercise personal jurisdiction over Merck pursuant to Fed. R. Civ. P. 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Merck is a foreign company not subject to personal jurisdiction in the courts of any state; and (c) Merck has sufficient contacts with the United States as a whole, including but not limited to the marketing and selling of pharmaceutical products, including avelumab, that are distributed and sold throughout the United States, such that this Court's exercise of jurisdiction over Merck satisfies due process.

27. Venue is proper in this district under 28 U.S.C. §§ 1391(c) and 1400(b).

THE PATENT-IN-SUIT

28. On August 2, 2016, the United States Patent & Trademark Office ("USPTO") duly and legally issued U.S. Patent No. 9,402,899 ("the '899 patent") titled "Immunopotentiative Composition." A true and correct copy of the '899 patent is attached hereto as Exhibit 1. The inventors of the '899 patent showed for the first time that anti-PD-L1 antibodies were useful in methods to treat cancer. Dr. Tasuku Honjo is a co-inventor and original co-assignee of the '899 patent. Ono is an original co-assignee and exclusive licensor of BMS under the '899 patent.

BMS and Squibb are each exclusive licensees of one or more exclusionary rights under the '899 patent.

29. The '899 patent issued from a divisional application of U.S. Application No. 12/959,307, filed on December 2, 2010 (now U.S. Pat. No. 8,728,474), which is a divisional application of U.S. Application No. 12/538,698, filed on August 10, 2009 (now U.S. Pat. No. 8,168,179), which is a divisional application of U.S. Application No. 10/519,925, filed on January 3, 2005 (now U.S. Pat. No. 7,595,048), which is a National Stage Entry of PCT/JP03/08420 filed on July 2, 2003, which claims priority based on Japanese Patent Application Nos. 2002-194491 and 2003-029846 filed on July 3, 2002 and February 6, 2003, respectively.

30. The claims of the '899 patent are generally directed to methods of treating cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1. By way of example, claim 1 of the '899 patent is:

> A method of treating a tumor in a human patient in need thereof comprising administering to the human an effective amount of an anti-PD-L1 monoclonal antibody that inhibits an interaction between PD-1 and PD-L1, wherein the anti-PD-L1 monoclonal antibody treats the tumor in the patient.

DEFENDANTS' BAVENCIO PRODUCT

31. Serono is the holder of Biologics License Application ("BLA") No. 761049 for BAVENCIO (avelumab). According to its prescribing information, BAVENCIO is a PD-L1 blocking antibody that is indicated for treating patients with metastatic Merkel cell carcinoma (MCC) and/or locally advanced or metastatic urothelial carcinoma (UC). On information and belief, Serono (as Merck's authorized agent) and Pfizer are marketing, using, distributing, offering for sale, selling, and/or importing BAVENCIO in the United States.

32. As shown by the prescribing information for BAVENCIO, Serono received approval from the FDA on March 23, 2017 to market and sell BAVENCIO as a treatment for adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC) and on May 9, 2017, to market BAVENCIO as a treatment for patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

33. BAVENCIO is administered in a 10 mg/kg dose as an intravenous infusion over 60 minutes every 2 weeks.

34. The active ingredient in BAVENCIO is the anti-PD-L1 antibody avelumab. As stated in the BAVENCIO prescribing information, avelumab is a human IgG1 monoclonal antibody that binds to human PD-L1, thereby inhibiting the interaction of PD-L1 with PD-1. Avelumab releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response.

The Use of BAVENCIO Infringes the '899 Patent

35. On information and belief Defendants are currently manufacturing, distributing, using, offering for sale, selling, and/or importing in the United States their BAVENCIO antibody product to be prescribed and used for the treatment of cancer according to the BAVENCIO prescribing information.

36. As described above, BAVENCIO is used for treating a tumor in a human patient. BAVENCIO is administered in an effective amount. The BAVENCIO antibody (avelumab) is an anti-PD-L1 monoclonal antibody that inhibits an interaction between PD-1 and PD-L1. When

administered to a human patient with a tumor, the BAVENCIO antibody treats the tumor in the patient.

37. On information and belief, BAVENCIO has been and is currently being used according to the prescribing information. The use of BAVENCIO according to the prescribing information infringes at least claim 1 of the '899 patent.

38. As described above, the prescribing information for BAVENCIO describes avelumab as a human antibody. The use of BAVENCIO according to the prescribing information therefore infringes at least claims 2, 20, and 43 of the '899 patent.

39. BAVENCIO has been approved to treat Merkel cell carcinoma (MCC) and urothelial carcinoma (UC), as described above, including solid tumors. The use of BAVENCIO according to the prescribing information therefore infringes at least claims 3, 21, and 37 of the '899 patent.

40. On information and belief, the administration of BAVENCIO to patients results in a decrease in tumor growth. The use of BAVENCIO according to the prescribing information therefore infringes at least claims 4 and 19 of the '899 patent.

41. On information and belief, the administration of BAVENCIO to patients results in a suppression of tumor metastasis. The use of BAVENCIO according to the prescribing information therefore infringes at least claims 5, 22, and 36 of the '899 patent.

42. As described above, BAVENCIO has been approved to treat Merkel cell carcinoma (MCC) and urothelial carcinoma (UC). The use of BAVENCIO according to the prescribing information therefore infringes at least claims 6, 23, 38, 44, and 45 of the '899 patent.

43. BAVENCIO has been approved for administration by intravenous infusion. The use of BAVENCIO according to the prescribing information therefore infringes at lease claims 16, 17, 33, and 34 of the '899 patent.

44. As described above, the prescribing information for BAVENCIO describes avelumab as an IgG1 antibody. The use of BAVENCIO according to the prescribing information therefore infringes at least claims 46-51 of the '899 patent.

45. When medical professionals or others administer BAVENCIO according to the prescribing information, they directly infringe the '899 patent.

46. On information and belief, Defendants know that BAVENCIO has been and is currently being used according to the prescribing information.

47. On information and belief, Merck Patent GmbH is a subsidiary of Merck KGaA, or is otherwise related to Merck KGaA such that Merck KGaA directs, supervises and controls the actions of Merck Patent GmbH. Merck Patent GmbH, *inter alia*, holds and enforces patents obtained on subject matter made by or on behalf of Merck KGaA.

48. On information and belief, Defendants' antibody avelumab is described in PCT publication WO 2013/079174 ("the '174 publication") of which Merck Patent GmbH is the applicant and which is titled "Anti-PD-L1 Antibodies and Uses Thereof."

49. On information and belief, antibody A09-246-2 corresponding to SEQ ID NO:32 (heavy chain) and SEQ ID NO:33 (light chain) disclosed in the '174 publication is avelumab, the active ingredient in BAVENCIO.

50. On information and belief, Defendants' antibody avelumab is also disclosed in PCT publication WO 2016/137895 ("the '895 publication") of which Merck Patent GmbH and Pfizer are applicants and which is titled "PD-1/PD-L1 Inhibitors For the Treatment of Cancer."

51. On information and belief, at least Figure 1 (SEQ ID NO:7) and Figure 2 (SEQ ID NO:9) of the '895 publication show the heavy chain and light chain, respectively, of avelumab, the active ingredient in BAVENCIO.

52. On information and belief, Defendants have known about the '899 patent and have known that the use of BAVENCIO to treat cancer infringes at least claims 1-6, 16, 17, 19-23, 33, 34, 36-38, 43-51 of the '899 patent since at least approximately August 2, 2016 when the '899 patent issued and, in any event, no later than upon receiving a copy of this complaint.

53. In an International Search Report issued on June 6, 2013, during the International Phase of the '174 publication, the International Search Authority cited to EP1537878 A1 ("EP 878 publication") as an "X" category document of particular relevance, *i.e.*, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone. The EP 878 publication is a European counterpart to the '899 patent and discloses methods of treating tumors with anti-PD-L1 antibodies. On information and belief, by at least as early as June 6, 2013, Defendants, or at least Merck, were aware of the '899 patent family and were aware that the '899 patent family included a patent application containing claims that are substantially the same as the claims issued in the '899 patent, *i.e.*, claims to methods of using anti-PD-L1 antibodies to treat tumors. On information and belief, Defendants, or at least Merck, knew or should have known that the use of an anti-PD-L1 antibody, such BAVENCIO, in methods of treating a tumor was disclosed in the '899 patent family at least as early as June 6, 2013.

54. Defendants' BAVENCIO is especially made for use in infringing the '899 patent, and has no substantial non-infringing uses. By virtue of obtaining approval to market and sell BAVENCIO as a treatment for certain patients with Merkel cell carcinoma and/or urothelial

carcinoma, Defendants have the specific intent to cause infringement of the '899 patent or, at a minimum, Defendants have been willfully blind to the infringement of the '899 patent that will inevitably result.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 9,402,899

55. Plaintiffs incorporate by reference paragraphs 1-54 as if fully set forth herein.

56. On information and belief, Defendants are marketing, making, using, selling, offering for sale, and/or importing avelumab in the United States for the treatment of cancer. On information and belief, avelumab is being used for the treatment of cancer in the United States. As set forth above, Defendants thereby infringe at least claims 1-6, 16, 17, 19-23, 33, 34, 36-38, 43-51 of the '899 patent, including by actively inducing infringement under 35 U.S.C. § 271(b) and as a contributory infringer under 35 U.S.C. § 271(c).

57. On information and belief, Defendants have been aware of the '899 patent since at least approximately August 2, 2016, when the USPTO issued the '899 patent and Defendants' infringement is deliberate, egregious, willful, and in reckless disregard of valid patent claims of the '899 patent.

58. Plaintiffs have been and will continue to be injured by and have been and will continue to suffer substantial damages as a result of Defendants' infringement.

59. This case is exceptional and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

JURY DEMAND

Under Federal Rule of Civil Procedure 38, Plaintiffs demand trial by jury of all issues so triable.

PRAYER FOR RELIEF

Wherefore, Plaintiffs respectfully request the following relief:

(a) entry of a judgment that Defendants infringe and will infringe the '899 patent;

(b) an award of damages sufficient to compensate Plaintiffs for infringement of the '899 patent, together with pre- and post-judgment interest and costs as fixed by the Court as provided by 35 U.S.C. § 284;

(c) entry of an order compelling Defendants to compensate Plaintiffs for any ongoing or future infringement of the '899 patent, in an amount and under terms appropriate for the circumstances;

(d) entry of an order that Defendants' infringement has been willful, and increased damages pursuant to 35 U.S.C. § 284;

(e) judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and an award to Plaintiffs of their reasonable attorney fees, costs, and expenses in this action pursuant to 35 U.S.C. § 285; and

(f) such other relief as the Court may deem just and proper.

/s/ Kelly E. Farnan

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