UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO. and E. R. SQUIBB & SONS, L.L.C.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	**JURY TRIAL DEMANDED**
ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA AB.,	)	
Defendants.	)	

COMPLAINT

Plaintiffs Bristol-Myers Squibb Co. and E. R. Squibb & Sons, L.L.C. (collectively, "BMS") for their complaint for patent infringement against Defendants AstraZeneca Pharmaceuticals LP and AstraZeneca AB (collectively, "Defendants" or "AstraZeneca"), hereby allege as follows:

INTRODUCTION

1. According to the United States Centers for Disease Control and Prevention, more than 1.7 million people in the United States are diagnosed with cancer each year (https://www.cdc.gov/chronicdisease/resources/publications/factsheets/cancer.htm). 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.

2. This lawsuit relates to BMS's groundbreaking treatments for cancer that fall within a field known as "cancer immunotherapy." The treatment of cancer using immunotherapy represents a scientific breakthrough that has revolutionized 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 cancer cells, and to do that the T cell must distinguish healthy cells from infected or cancerous cells through the activation or deactivation of various receptors on the T cell surface, which are known as immune checkpoint receptors. Such receptors can be activated or deactivated by binding to other proteins known as ligands.

4. One such immune checkpoint receptor that regulates the body's immune response is the T cell receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). The CTLA-4 receptor can bind two ligands, B7-1 (CD80) and B7-2 (CD86), which can be found on another type of immune system cell, called an antigen-presenting cell. When a T cell's CTLA-4 receptor binds its ligands, the T cell is deactivated and rendered unable to destroy cancer cells. When the interaction between a T cell's CTLA-4 receptor and its ligands B7-1 and B7-2 is blocked, however, the B7 ligands are then free to bind another signaling protein located on the T cell, called CD28, that has the opposite effect on the T cell—it induces T cell activation so that the T-cell can target and kill cancer cells.

5. BMS has been at the forefront of the cancer immunotherapy field, and has developed biopharmaceuticals known as checkpoint inhibitors that improve the abilities of patients' immune systems to target and kill cancers cells. Indeed, BMS's extensive research

efforts have led to it having developed three FDA-approved checkpoint inhibitors to date. BMS, in fact, developed the first checkpoint inhibitor to be approved anywhere in the world, ipilimumab (YERVOY®). In March 2011, the FDA awarded BMS's YERVOY® approval for the treatment of melanoma. With this approval, YERVOY® also became the first new treatment approved for metastatic melanoma in more than a decade. YERVOY® is a human monoclonal IgG1 anti-CTLA-4 antibody. It is a blocking antibody, meaning it prevents the interaction between CTLA-4 and the B7 ligands, thereby allowing for tumor-specific T-cell activation.

6. Following YERVOY®'s approval for metastatic melanoma, BMS continued to conduct extensive research and development in the field of cancer immunotherapy, leading to the FDA awarding BMS approvals for the use of YERVOY® to treat several additional cancer indications. For example, on October 1, 2015, the FDA approved YERVOY® in combination with nivolumab (OPDIVO®), BMS's anti-PD-1 antibody, for the treatment of metastatic melanoma, making it the first-ever combination immunotherapy treatment to be approved by the FDA. Currently, YERVOY® has been approved by the FDA to treat melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer (NSCLC), malignant pleural mesothelioma, and esophageal cancer, either alone or in combination with OPDIVO®.

7. In addition, BMS continues worldwide development of YERVOY® for the treatment of a broad spectrum of cancers and is engaged in clinical testing with a variety of combination therapies. On May 26, 2020, the FDA approved the combination of YERVOY® plus OPDIVO® and platinum-based chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC. The treatment was the first combination of multiple immunotherapies and chemotherapy to gain approval by the FDA.

8. Defendants are exploiting BMS's inventions and willfully infringing BMS's intellectual property rights by marketing an infringing anti-CTLA-4 antibody product, IMJUDO® (tremelimumab-actl), for use in methods for treating cancer, without having first obtained permission from BMS or a license to BMS's intellectual property rights.

9. Since BMS and Defendants are direct competitors in the field of immunotherapy, BMS has suffered, and continues to suffer, substantial damages, including lost profits, as a result of Defendants' willful infringement.

PARTIES

10. Bristol-Myers Squibb Co. is a corporation organized under the laws of the state of Delaware, with a principal place of business in New Jersey. E. R. Squibb & Sons, L.L.C., is a limited liability company organized and existing under the laws of the state of Delaware, with a principal place of business in New Jersey.

11. On information and belief, AstraZeneca Pharmaceuticals LP is a limited partnership organized under the laws of the state of Delaware, with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803.

12. On information and belief, AstraZeneca AB is a private limited company organized under the laws of Sweden, with its registered office at Södertälje, Sweden SE-15185.

13. AstraZeneca Pharmaceuticals LP and AstraZeneca AB are in the business of manufacturing, marketing, distributing, offering for sale, and selling drug products that are distributed and sold throughout the United States, including in Delaware.

14. AstraZeneca Pharmaceuticals LP and AstraZeneca AB are sophisticated pharmaceutical companies. On information and belief, Defendants rely on and actively seek patent protection for their products. On information and belief, Defendants regularly enforce

their patents and other intellectual property rights. This lawsuit seeks to have Defendants respect BMS's patent rights just as Defendants expect third parties to respect their patent rights.

JURISDICTION AND VENUE

15. 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.

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

17. This Court has personal jurisdiction over AstraZeneca Pharmaceuticals LP because it is a Delaware entity located in Delaware.

18. This Court has jurisdiction over AstraZeneca AB, *inter alia*, because its subsidiary and agent, AstraZeneca Pharmaceuticals LP, is incorporated in Delaware and, upon information and belief, markets and sells IMJUDO® in Delaware as AstraZeneca AB's authorized agent and under AstraZeneca AB's direction and control.

19. On information and belief, AstraZeneca Pharmaceuticals LP and AstraZeneca AB are engaged in a single business activity of biopharmaceuticals and are not separated into multiple operating segments. On information and belief, AstraZeneca's business activities take place (and are managed) globally on a highly integrated basis and are not managed separately.

20. On information and belief, AstraZeneca Pharmaceuticals LP and AstraZeneca AB have consented to jurisdiction in Delaware in one or more prior cases arising out of the manufacture, use, offer for sale, sale and/or importation of pharmaceutical products, including cases Defendants initiated as the plaintiffs.

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

THE PATENTS-IN-SUIT

22. On April 26, 2016, the USPTO duly and legally issued U.S. Patent No. 9,320,811 ("the '811 patent") titled "Combination of Anti-CTLA4 Antibody with Diverse Therapeutic Regimens for the Synergistic Treatment of Proliferative Diseases." A true and correct copy of the '811 patent is attached hereto as Exhibit 1. The '811 patent is assigned to Bristol-Myers Squibb Co.

23. The '811 patent issued from U.S. Application No. 14/168,465, filed January 30, 2014, which is a divisional of U.S. Application No. 13/384,900, filed January 19, 2012 (now U.S. Patent No. 8,685,394), which is a national stage entry of PCT Application No. PCT/US2009/062519, filed October 29, 2009, which claims the benefit of U.S. Provisional Patent Application No. 61/085,466, filed August 1, 2008 and U.S. Provisional Patent Application No. 61/226,910, filed July 20, 2009.

24. The claims of the '811 patent are generally directed to methods for the treatment of cancer by administering an anti-CTLA-4 antibody in combination with chemotherapy drug gemcitabine. By way of example, claim 1 of the '811 patent is:

> A method for the treatment of cancer, comprising the concurrent administration to a mammal in need thereof a synergistic, therapeutically effective amount of an anti-CTLA-4 antibody with 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer), or a pharmaceutically acceptable salt, solvate, or hydrate thereof.[1]

25. On March 1, 2016, the USPTO duly and legally issued U.S. Patent No. 9,273,135 ("the '135 patent") titled "Human Monoclonal Antibodies to Programmed Death Ligand 1 (PD-

[1] 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer) is the chemical name of gemcitabine hydrochloride.

L1)." A true and correct copy of the '135 patent is attached hereto as Exhibit 2. The '135 patent is assigned to E. R. Squibb & Sons, L.L.C.

26. The '135 patent issued from U.S. Application No. 14/796,956, filed July 10, 2015, which is a divisional of U.S. Application No. 13/746,773, filed January 22, 2013 (now U.S. Pat. No. 9,102,725), which is a divisional application of U.S. Application No. 13/091,936, filed April 21, 2011 (now U.S. Pat. No. 8,383,796), which is a divisional application of U.S. Application No. 11/917,727, filed June 9, 2008 (now U.S. Pat. No. 7,943,743), which is a national stage entry of PCT Application No. PCT/US2006/026046, filed June 30, 2006, which claims the benefit of U.S. Provisional Patent Application No. 60/696,426, filed July 1, 2005.

27. The claims of the '135 patent are generally directed to methods for enhancing an immune response in a subject by administering an anti-PD-L1 monoclonal antibody in combination with an anti-CTLA-4 antibody, where the anti-PD-L1 antibody cross-competes for binding to PD-L1 with a reference antibody. By way of example, claim 1 of the '135 patent is:

> A method for enhancing an immune response in a subject comprising administering to the subject a combination of an anti-PD-L1 monoclonal antibody or an antigen-binding portion thereof and an anti-CTLA-4 monoclonal antibody or an antigen-binding portion thereof, wherein the anti-PD-L1 monoclonal antibody or antigen-binding portion thereof cross-competes for binding to PD-L1 with a reference antibody comprising:
>
> (a) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:1 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:11;
> (b) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:2 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:12;
> (c) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:3 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:13;
> (d) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:4 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:14;

(e) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:5 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:15;
(f) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:6 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:16;
(g) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:7 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:17;
(h) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:8 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:18;
(i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:9 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:19; or
(j) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:10 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:20, and
wherein enhancing the immune response results in inhibition of growth of tumor cells in the subject.

ASTRAZENECA'S IMJUDO® PRODUCT

28. AstraZeneca AB is the holder of Biologics License Application ("BLA") No. 761289 for IMJUDO® (tremelimumab-actl). According to its prescribing information, IMJUDO® contains an anti-CTLA-4 blocking antibody named tremelimumab-actl that is indicated for treating patients with specific types of cancer. The FDA-approved label for IMJUDO® indicates that IMJUDO® is manufactured for AstraZeneca Pharmaceuticals LP by AstraZeneca AB. On information and belief, AstraZeneca Pharmaceuticals LP is marketing, using, distributing, offering for sale, selling, and importing IMJUDO® in the United States as AstraZeneca AB's authorized agent.

29. On October 21, 2022, the FDA approved IMJUDO® in combination with durvalumab (IMFINZI®) as a treatment for adult patients with unresectable hepatocellular

carcinoma (uHCC).[2] The prescribing information that Defendants provided and that the FDA approved in October 2022 instructed that for patients weighing 30 kg and more, IMJUDO® is to be administered as an intravenous infusion over 60 minutes as a single dose of 300 mg in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. For patients weighing less than 30 kg, 4mg/kg of IMJUDO® is to be administered as an intravenous infusion over 60 minutes as a single dose in combination with durvalumab 20 mg/kg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks for the treatment of uHCC.[3]

30. On information and belief Defendants began marketing IMJUDO® for the treatment of uHCC according to the prescribing information in the United States on October 21, 2022.[4]

31. On November 10, 2022, the FDA approved IMJUDO® in combination with durvalumab and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.[5] The prescribing information that Defendants provided and the FDA approved for the use of IMJUDO® to treat NSCLC indicates that IMJUDO® is to be administered as an intravenous infusion over 60 minutes as a single dose of 75 mg every 3 weeks

[2] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma#:~:text=FDA%20approves%20tremelimumab%20in%20combination%20with%20durvalumab%20for%20unresectable%20hepatocellular%20carcinoma,-Share&text=On%20October%2021%2C%202022%2C%20the,unresectable%20hepatocellular%20carcinoma%20(uHCC).

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf.

[4] https://www.imfinzihcp.com/hepatocellular-carcinoma.html

[5] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-and-platinum-based-chemotherapy-metastatic-non

in combination with durvalumab 1,500 mg and platinum-based therapy for 4 cycles, followed by durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks and a then a fifth dose of IMJUDO® 75 mg in combination with durvalumab. Alternatively, IMJUDO® is to be administered as an intravenous infusion over 60 minutes at 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks and then a fifth dose of IMJUDO® 1 mg/kg in combination with durvalumab for the treatment of NSCLC.[6]

32. On information and belief, Defendants began marketing IMJUDO® for the treatment of NSCLC in the United States on November 10, 2022.[7]

33. The active ingredient in AstraZeneca's IMJUDO® product is the anti-CTLA-4 antibody tremelimumab-actl. Tremelimumab is a human IgG2 monoclonal antibody that binds to human CTLA-4.

The Use of IMJUDO® Infringes the '811 Patent

34. On information and belief, Defendants have manufactured, distributed, used, offered for sale, sold, and/or imported in the United States the IMJUDO® antibody product to be prescribed and used for the treatment cancer, including NSCLC.

35. As described above, and according to IMJUDO®'s prescribing information, IMJUDO® is an anti-CTLA-4 antibody used for treating cancer in patients in need of such treatment. IMJUDO® is specifically indicated for the treatment of NSCLC. IMJUDO® is specifically indicated for use in combination with durvalumab and platinum-based chemotherapy

[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf

[7] https://www.imfinzihcp.com/?source=imz_n_h_4799&umedium=cpc&uadpub=google&ucampaign=2022imfinzihcpbtcbranded_alone_hcp&ucreative=branded_alone_ex&uplace=imfinzi&outcome=hcp&cmpid=1&gclid=EAIaIQobChMIgIPck5zk-wIVlsDICh1SRAdHEAAYASAAEgLXYvD_BwE&gclsrc=aw.ds

in patients with NSCLC. According to IMJUDO®'s prescribing information, it is indicated for use in combination with durvalumab and platinum-based chemotherapy in patients with NSCLC, where platinum-based chemotherapy regimen for patients with squamous NSCLC includes carboplatin and gemcitabine or cisplatin and gemcitabine.

36. As described above, and according to its prescribing information, IMJUDO® is administered as an intravenous infusion over 60 minutes as a single dose of 75 mg every 3 weeks in combination with durvalumab 1,500 mg and platinum-based therapy for 4 cycles, followed by durvalumab 1,500 mg every 4 weeks as a single agent and then a fifth dose of IMJUDO® 75 mg in combination with durvalumab. Alternatively, IMJUDO® is administered as an intravenous infusion over 60 minutes at 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then durvalumab 20 mg/kg every 4 weeks as a single agent and then a fifth dose of IMJUDO® 1 mg/kg in combination with durvalumab for the treatment of squamous NSCLC, where platinum-based chemotherapy regimen includes carboplatin and gemcitabine or cisplatin and gemcitabine.

37. According to its prescribing information, IMJUDO® was administered in combination with durvalumab plus platinum and gemcitabine chemotherapy to patients with squamous NSCLC on the same day. In the POSEIDON study, patients received IMJUDO® 75 mg (or 10 mg/kg for patients < 30 kg) in combination with durvalumab 1,500 mg and histology-based platinum chemotherapy every 3 weeks for 4 cycles, followed by durvalumab 1,500 mg every 4 weeks as a single agent. A fifth does of IMJUDO® 75 mg (or 10 mg/kg for patients < 30 kg) was given at week 16 in combination with durvalumab dose 6. An addition to IMJUDO® and durvalumab, patients with squamous NSCLC received gemcitabine 1,000 or 1,250 mg/m^2 on

Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.

38. According to IMJUDO®'s prescribing information, patients are administered durvalumab followed by platinum-containing chemotherapy on the same day they receive IMJUDO® for the treatment of NSCLC.

39. On information and belief, IMJUDO® has been used according to the instructions in its prescribing information. The use of IMJUDO® according to the instructions in its prescribing information infringes at least claims 1-2, 4-5, 7-9, and 13-16 of the '811 patent.

40. On information and belief, Defendants have had knowledge of the '811 patent since the '811 patent issued because U.S. Publication 2010/0098701, the publication of U.S. Patent Application No. 12/462,168 ("the '168 Application"), which claims priority to the same provisional applications as the '811 patent and lists the same named inventor was identified during prosecution of Defendants' own patent application. U.S. 2010/0098701 includes a specification and claims that are very similar to those of the '811 patent. Examples included in the U.S. 2010/0098701 specification disclose a synergistic benefit of combining gemcitabine with an anti-CTLA-4 antibody for the treatment of lung carcinoma. On February 12, 2019, U.S. 2010/0098701 was identified by the examiner as relevant to all claims in AstraZeneca's subsidiary MedImmune's U.S. Application No. 15/525,804. On information and belief, Defendants were aware of the MedImmune patent applications, and the citations to the BMS patents, because, for example, they related to Defendants' product IMJUDO®.

41. On information and belief, Defendants have known about the '811 patent since at least as early as December 2021 when Defendants approached BMS about licensing BMS's CTLA-4 patent estate, but in any event, no later than the date they received a copy of this

complaint. Defendants and BMS are direct competitors in the immunotherapy field, and more specifically, in the CTLA-4 antibody field. Defendants market their anti-CTLA-4 antibody tremelimumab under the name IMJUDO® for the treatment of uHCC and NSCLC. BMS markets the anti-CTLA-4 antibody ipilumumab under the name YERVOY® for the treatment of hepatocellular cancer and NSCLC. On information and belief, Defendants began marketing IMJUDO® on October 21, 2022. On information and belief, Defendants actively monitor their competitors' patent portfolios that could cover the IMJUDO® product.

42. Defendants have had knowledge of the '811 patent since the '811 patent issued because AstraZeneca is a large company that monitors its competitors' patent portfolios for patents that cover IMJUDO®. On information and belief, Defendants monitored BMS's patent portfolio because in or around December 2021, Defendants approached BMS about licensing one or more patents in BMS's CTLA-4 patent portfolio. On information and belief, at least in connection with that approach by Defendants to BMS to license BMS's CTLA-4 patent portfolio, Defendants investigated BMS's portfolio of CTLA-4-related patents and patent applications, which included the '811 patent at that point. Therefore, Defendants would have had knowledge of the '811 patent since at least that time. At various points in 2022, BMS and Defendants again discussed licensing BMS's CTLA-4 patent estate.

43. In the absence of actual knowledge, Defendants have at least been willfully blind to the existence of the '811 patent since the '811 patent issued. Defendants own or control numerous patents covering IMJUDO®. Defendants knew that BMS owned or licensed patents covering anti-CTLA-4 antibodies, and their use, since at least December 2021 based on previous licensing discussions between the parties. Defendants subjectively believed there was a high probability that the '811 patent existed. Additionally, BMS and Defendants are actively involved

in patent litigation over Defendants' anti-PD-L1 antibody, IMFINZI®. IMJUDO® and IMFINZI® are both immunotherapy products used to treat cancer. IMJUDO® has only been approved for use in combination with IMFINZI® (durvalumab). At least one of the patents asserted in the IMFINZI® litigation includes claims that describe administering anti-CTLA-4 antibodies in combination with anti-PD-L1 antibodies. Thus, as a result of the IMFINZI® litigation, Defendants were on notice that BMS owns patents that cover methods of treatment using anti-CTLA-4 antibodies in combination with anti-PD-L1 antibodies, i.e., the combination for which IMJUDO® is approved. To the extent Defendants have not investigated the full scope of BMS's anti-CTLA-4 patent portfolio, including whether BMS owns patents that may cover IMJUDO® or its use in methods of treating cancer, they have been willfully blind to these patents.

44. Defendants also had knowledge of other patents owned/licensed by BMS that related to the use of an anti-CTLA-4 antibody. AstraZeneca is a sophisticated company and, on information and belief, monitors the patent estates of its competitors for patents that could cover the use of IMJUDO®, particularly competitors, like BMS, whom Defendants have approached about licensing patents that cover IMJUDO®. If Defendants did not have actual knowledge of the '811 patent, it is because Defendants took deliberate actions to avoid learning specifically about the '811 patent. If Defendants did not have actual knowledge of the existence of the '811 patent, it is because Defendants were willfully blind to the existence of the '811 patent.

45. Defendants have known that the use of IMJUDO® in patients to treat cancer will infringe and does infringe at least claims 1-2, 4-5, 7-9, and 13-16 of the '811 patent since at least as early as 2021, but in any event, no later than the date they received a copy of this complaint. IMJUDO® is sold in a highly regulated market and Defendants provided detailed prescribing information to users about how to administer and use IMJUDO®. As detailed above, limitations

of the claims of the '811 patent are found directly in IMJUDO®'s prescribing information. Accordingly, once Defendants knew of the '811 patent, Defendants knew that the use of IMJUDO® according to its prescribing information would infringe the '811 patent.

46. If Defendants did not have actual knowledge that the use of IMJUDO® in patients to treat cancer infringes at least claims 1-2, 4-5, 7-9, and 13-16 of the '811 patent, then Defendants were willfully blind to that fact. Defendants had actual knowledge of the '811 patent or were willfully blind to the existence of the '811 patent. AstraZeneca is a sophisticated company and upon learning of a patent that covers the use of an anti-CTLA-4 antibody according to the treatment regimen in IMJUDO®'s prescribing information, Defendants subjectively believed that there was a high probability the use of IMJUDO® would infringe the '811 patent. Based on the similarity between the '811 patent's claims and IMJUDO®'s prescribing information, the only way that Defendants would not know that the use of IMJUDO® infringed the '811 patent would be because Defendants took deliberate action to avoid learning that the use of IMJUDO® infringed the '811 patent.

47. Defendants have contributed, and continue to contribute, to the infringement of at least claims 1-2, 4-5, 7-9, and 13-16 of the '811 patent. IMJUDO® is, and has been, especially made to bind to human CTLA-4. Thus, IMJUDO® is especially made, and has been made, for use to infringe the claims of the '811 patent. Further, IMJUDO® is only available, and has only been available, to purchase for use as a product with the claimed features and is not a staple article of commerce or suited for any substantial non-infringing use. For all of the reasons above, Defendants know, and have known since at least as early as December 2021, that IMJUDO® is and has been especially made and/or especially adapted for use in infringing the '811 patent.

48. Through their prescribing information, Defendants have and continue to recommend and encourage healthcare providers to infringe the claims of the '811 patent. Defendants have had and continue to have the specific intent to infringe and actively induce others to infringe the '811 patent.

The Use of IMJUDO® Infringes the '135 Patent

49. On information and belief, Defendants have manufactured, distributed, used, offered for sale, sold, and/or imported in the United States the IMJUDO® antibody product to be prescribed and used for the treatment of cancer.

50. As described above, and according to prescribing information for IMJUDO®, IMJUDO® is an anti-CTLA-4 antibody used for treating cancer in patients in need of such treatment. IMJUDO® is specifically indicated for the treatment of uHCC and NSCLC. IMJUDO® is specifically indicated for use in combination with durvalumab in patients with uHCC and in combination with durvalumab and platinum-based chemotherapy in patients with NSCLC. Based on public information, administering IMJUDO® to a human patient enhances an immune response and inhibits growth of tumor cells in the patient.

51. As described above, and according to its prescribing information, IMJUDO® is administered as an intravenous infusion over 60 minutes as a single dose of 300 mg in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks or 4 mg/kg of IMJUDO® is administered as an intravenous infusion over 60 minutes as a single dose in combination with durvalumab 20 mg/kg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks for the treatment of uHCC.

52. As described above, and according to its prescribing information, IMJUDO® is administered as an intravenous infusion over 60 minutes as a single dose of 75 mg every 3 weeks

in combination with durvalumab 1,500 mg and platinum-based therapy for 4 cycles, followed by durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks and then a fifth dose of IMJUDO® 75 mg in combination with durvalumab. Alternatively, IMJUDO® is to be administered as an intravenous infusion over 60 minutes at 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks and then a fifth dose of IMJUDO® 1 mg/kg in combination with durvalumab for the treatment of NSCLC.[8]

53. Durvalumab is a human, monoclonal anti-PD-L1 antibody with a VH of IgG1 isotype that cross-competes for binding to human PD-L1 with at least the reference antibody or antigen-binding portion thereof which comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:2 and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:12. Based on public information, the sequence of durvalumab includes sequences recited in each of claims 1-3, 6-9, 11, 13-14, 17, 24, and 27 of the ’135 patent. Therefore, the use of IMJUDO® according to the instructions in its prescribing information infringes at least claims 1-3, 6-9, 11, 13-14, 17, 24, and 27 of the ’135 patent.

54. As described above, and according to IMJUDO®’s prescribing information, IMJUDO® is a human IgG2 anti-CTLA-4 monoclonal antibody. The use of IMJUDO® according to the instructions in its prescribing information infringes at least claim 20 of the ’135 patent.

55. As described above, and according to IMJUDO®’s prescribing information, IMJUDO® is an anti-CTLA-4 antibody used for treating a cancer in a subject. According to its

[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf

prescribing information, IMJUDO® is administered for uHCC and NSCLC. Therefore, the use of IMJUDO® according to the instructions in its prescribing information infringes at least claims 15-16, and 30 of the '135 patent.

56. As described above, and according to IMJUDO®'s prescribing information, IMJUDO® is administered in combination with durvalumab to patients on the same day. Therefore, the use of IMJUDO® according to the instructions in its prescribing information infringes at least claim 26.

57. On information and belief, Defendants have known about the '135 patent since as early as March 1, 2016, when the '135 patent issued, but in any event, at least before receiving a copy of this complaint.

58. Defendants have had knowledge of the '135 patent since the '135 patent issued because AstraZeneca's subsidiary MedImmune, cited the related International Publication No. WO2007/005874 (International Application No. PCT/US2006/026046), which claims priority to the same provisional application as the '135 patent, in its own International Publication No. WO2019/219658 (International Application No. PCT/EP2019/062305). On information and belief, Defendants were aware of the MedImmune patent applications, and the citations to the BMS patents, because, for example, they related to Defendants' product IMFINZI®.

59. Moreover, Defendants have had knowledge of the '135 patent since the '135 patent issued because Defendants and BMS are direct competitors in the immunotherapy field, and more specifically, in the PD-L1 and CTLA-4 antibody fields. Defendants market their anti-PD-L1 antibody durvalumab under the name IMFINZI® for the treatment of urothelial carcinoma and NSCLC. BMS markets the anti-PD-1 antibody nivolumab under the name OPDIVO® for treating those same types of cancer. On information and belief, Defendants began marketing

IMFINZI® on May 1, 2017. Defendants market their anti-CTLA-4 antibody tremelimumab under the name IMJUDO® for the treatment of uHCC and NSCLC. BMS markets the anti-CTLA-4 antibody ipilumumab under the name YERVOY® for the treatment of hepatocellular cancer and NSCLC. On information and belief, Defendants began marketing IMJUDO® on October 21, 2022. On information and belief, Defendants actively monitor their competitors' patent portfolios that could cover the IMJUDO® product.

60. AstraZeneca has had knowledge of the '135 patent since the '135 patent issued because it is a large company that monitors its competitors' patent portfolios for patents that cover IMFINZI® and IMJUDO®.

61. In the absence of actual knowledge, Defendants have at least been willfully blind to the existence of the '135 patent since the '135 patent issued. Defendants own or control numerous patents covering IMFINZI® and IMJUDO ®. Additionally, BMS and Defendants are actively involved in patent litigation over IMFINZI®. IMJUDO® and IMFINZI® are related products—both are immunotherapy products used to treat cancer. IMJUDO® has only been approved for use in combination with IMFINZI® (durvalumab). At least one of the patents asserted in the IMFINZI® litigation includes claims that describe administering anti-CTLA-4 antibodies in combination with anti-PD-L1 antibodies. Moreover, the '135 patent belongs to the same family of patents as two of the patents asserted in the IMFINZI® litigation and covers anti-PD-L1 antibodies with the same structural features as those asserted in the IMFINZI® litigation. Thus, as a result of the IMFINZI® litigation, which commenced on March 17, 2022, Defendants were on notice that BMS owns patents that cover methods of treatment using anti-CTLA-4 antibodies in combination with anti-PD-L1 antibodies, i.e., the combination for which IMJUDO® is approved. To the extent Defendants have not investigated the full scope of BMS's anti-CTLA-

4 patent portfolio, including whether BMS owns patents that may cover IMJUDO® or its use in methods of treating cancer, they have been willfully blind to these patents.

62. Defendants also had knowledge of other patents owned/licensed by BMS that related to the use of an anti-CTLA-4 antibody. AstraZeneca is a sophisticated company and, on information and belief, monitors the patent estates of its competitors for patents that could cover the use of IMJUDO®. If Defendants did not have actual knowledge of the '135 patent, it is because Defendants took deliberate actions to avoid learning specifically about the '135 patent. If Defendants did not have actual knowledge of the existence of the '135 patent, it is because Defendants were willfully blind to the existence of the '135 patent.

63. Defendants have known that the use of IMJUDO® in patients to treat cancer will infringe and does infringe at least claims 1-3, 6-9, 11, 13-16, 17, 20, 24, 26-27 and 30 of the '135 patent since at least as early as March 2022, but in any event, no later than the date they received a copy of this complaint. IMJUDO® is sold in a highly regulated market and Defendants provided detailed prescribing information to users about how to administer and use IMJUDO®.

64. If Defendants did not have actual knowledge that the use of IMJUDO® in patients to treat cancer infringes at least claims 1-3, 6-9, 11, 13-16, 17, 20, 24, 26-27 and 30 of the '135 patent, then Defendants were willfully blind to that fact. Defendants had actual knowledge of the '135 patent or were willfully blind to the existence of the '135 patent. AstraZeneca is a sophisticated company and upon learning of a patent that covers the use of an anti-CTLA-4 antibody according to the treatment regimen in IMJUDO®'s prescribing information, Defendants subjectively believed that there was a high probability the use of IMJUDO® would infringe the '135 patent. Based on the similarity between the '135 patent's claims, IMFINIZI®'s amino acid sequence, and IMJUDO®'s prescribing information, the only way that Defendants would not

know that the use of IMJUDO® infringed the '135 patent would be because Defendants took deliberate action to avoid learning that the use of IMJUDO® infringed the '135 patent.

65. Defendants have contributed, and continue to contribute, to the infringement of at least claims 1-3, 6-9, 11, 13-16, 17, 20, 24, 26-27 and 30 of the '135 patent. IMJUDO® is, and has been, especially made to bind to human CTLA-4. IMJUDO® is only approved for use in combination with IMFINZI®. Durvalumab, the active ingredient in IMFINZI®, has the features of the anti-PD-L1 antibody described in the claims. Thus, IMJUDO® is especially made, and has been made, for use to infringe the claims of the '135 patent. Further, IMJUDO® is only available, and has only been available, to purchase for use as a product with the claimed features and is not a staple article of commerce or suited for any substantial non-infringing use. For all of the reasons above, Defendants know, and have known since at least as early as March 2022 that IMJUDO® is and has been especially made and/or especially adapted for use in infringing the '135 patent.

66. Through its prescribing information, Defendants have and continue to recommend and encourage healthcare providers to infringe the claims of the '135 patent. Defendants have had and continue to have the specific intent to infringe and actively induce others to infringe the '135 patent.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 9,320,811

67. BMS incorporates by reference paragraphs 1-66 as if fully set forth herein.

68. On information and belief, Defendants have marketed, made, used, sold, offered for sale, and/or imported IMJUDO® in the United States for the treatment of cancer, and continue to do so. On information and belief, IMJUDO® was and continues to be used for the treatment of cancer in the United States. As set forth above, Defendants are thereby infringing at least claims

1-2, 4-5, 7-9, and 13-16 of the '811 patent, including by actively inducing infringement under 35 U.S.C. § 271(b) and as contributory infringers under 35 U.S.C. § 271(c).

69. On information and belief, Defendants have been aware of the '811 patent since at least as early as December 2021 and Defendants' infringement is deliberate, egregious, willful, and in reckless disregard of valid patent claims of the '811 patent.

70. BMS has been and will continue to be injured by, and has suffered, and will continue to suffer, substantial damages, including lost profits, as a result of Defendants' infringement.

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

COUNT II: INFRINGEMENT OF U.S. PATENT NO. 9,273,135

72. BMS incorporates by reference paragraphs 1-71 as if fully set forth herein.

73. On information and belief, Defendants have marketed, made, used, sold, offered for sale, and/or imported IMJUDO® in the United States for the treatment of cancer, and continue to do so. On information and belief, IMJUDO® was and continues to be used for the treatment of cancer in the United States. As set forth above, Defendants are thereby infringing at least claims 1-3, 6-9, 11, 13-16, 17, 20, 24, 26-27 and 30 of the '135 patent, including by actively inducing infringement under 35 U.S.C. § 271(b) and as contributory infringers under 35 U.S.C. § 271(c).

74. On information and belief, Defendants have been aware of the '135 patent since at least as early as March 2022 and Defendants' infringement is deliberate, egregious, willful, and in reckless disregard of valid patent claims of the '135 patent.

75. BMS has been and will continue to be injured by, and has suffered, and will continue to suffer, substantial damages, including lost profits, as a result of Defendants' infringement.

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

JURY DEMAND

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

PRAYER FOR RELIEF

Wherefore, BMS respectfully requests the following relief:

(a) entry of a judgment that Defendants infringe and will infringe the '811 patent;

(b) entry of a judgment that Defendants infringe and will infringe the '135 patent;

(c) an award of damages sufficient to compensate BMS for infringement of the '811 and '135 patents, together with pre- and post-judgment interest and costs as fixed by the Court as provided by 35 U.S.C. § 284;

(d) entry of an order compelling Defendants to compensate BMS for any ongoing or future infringement of the '811 and '135 patents, in an amount and under terms appropriate for the circumstances;

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

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

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

Dated: January 23, 2023

Respectfully submitted,

/s/ Michael J. Farnan

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