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 UK LTD.,	)	
Defendants.	)	

COMPLAINT

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

INTRODUCTION

1. According to the United States Centers for Disease Control and Prevention, more than 1.6 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. 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 infected or malignant cells through the activation or deactivation of various receptors on the T cell surface. One of the receptors that T cells express 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 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. When cancer cells are present, this pathway can prevent the immune system from eliminating those cancer cells. 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. Plaintiffs invented methods for treating cancer and methods for enhancing immune responses by administering antibodies that bind to PD-L1 ("anti-PD-L1 antibodies").

The inventions also cover using specific types of anti-PD-L1 antibodies 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. Plaintiffs also invented anti-PD-L1 antibodies with specific properties for use in methods of treatment and methods for enhancing immune responses.

6. 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 to its ligands, e.g., PD-L1. 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 (OPDIVO) for the treatment of melanoma, a deadly form of skin cancer (https://www.cancerresearch.org/en-us/immunotherapy/timeline-of-progress). On December 22, 2014, the U.S. Food and Drug Administration ("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, urothelial carcinoma, renal cell carcinoma, head and neck cancer, malignant pleural mesothelioma, lymphoma, colorectal cancer, hepatocellular carcinomas, esophageal cancer, and gastric cancers. 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 (https://news.bms.com/news/details/2015/FDA-Approves-Opdivo-nivolumab-for-the-Treatment-of-Patients-with-Previously-Treated-Metastatic-Squamous-Non-Small-Cell-Lung-Cancer/default.aspx). 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. In Phase III clinical testing for urothelial carcinoma, median disease-free survival was nearly twice as long in patients who received nivolumab as compared to placebo (https://news.bms.com/news/details/2021/U.S.-Food-and-Drug-Administration-Approves-Opdivo-nivolumab-for-the-Adjuvant-Treatment-of-Patients-with-High-Risk-Urothelial-Carcinoma/default.aspx). On August 29, 2021, based at least in part on those clinical results, the FDA approved nivolumab to treat certain types of urothelial carcinoma. The clinical results and the FDA's 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. AstraZeneca is exploiting Plaintiffs' inventions and infringing Plaintiffs' intellectual property rights by marketing a later-developed anti-PD-L1 antibody product,

IMFINZI (durvalumab), which is used in methods for treating cancer and for enhancing the immune response.

11. Since Plaintiffs and AstraZeneca are direct competitors in the field of immunotherapy, Plaintiffs have suffered, and continue to suffer, substantial damages, including lost profits, as a result of AstraZeneca's infringement. Marking pursuant to 35 U.S.C. § 287 was not required because Plaintiffs' product OPDIVO is an anti-PD-1 antibody and is not a patented article under the asserted patents.

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.

13. 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.

14. On information and belief, AstraZeneca UK Limited is a private limited company organized under the laws of England and Wales, with its registered office at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, United Kingdom, CB2 0AA.

15. AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited 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.

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