Keytruda (Pembrolizumab)

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Keytruda (pembrolizumab) is a drug developed by Merck (or MSD outside of the U.S. and Canada). It has been approved by the U.S. Food and Drug Administration (FDA) and the European Commission for the treatment of a range of advanced cancers.

How Keytruda works

Keytruda works by aiding the body's own immune system to fight and kill cancer cells.Normally, the immune system can detect and target an abnormal cell for destruction using lymphocytes (white blood cells involved in the immune response) called T-cells. However, to prevent the T-cells from attacking the body's own cells, the immune system has a series of checkpoints. One of these checkpoints is the PD-1 pathway. Some tumor cells "hijack" the pathway to hide from T-cells and escape being targeted. T-cells normally produce a receptor protein called programmed cell death 1 (PD-1), which blocks killing a cell when it interacts with ligands (small molecules that, in this case, are attached to other cells) called PD-L1. Some tumor cells produce these ligands to evade T-cells.

Keytruda is a monoclonal antibody designed to identify and block the PD-1 receptor. By blocking PD-1, the T-cells can "find" and destroy the cancer cells. However, as Keytruda acts to remove an immune system checkpoint, it may also cause T-cells to attack healthy cells.

History of Keytruda

Keytruda has been tested and continues to be tested in a wide range of clinical trials worldwide. These have been termed Keynote trials, and have been instrumental in gaining approval from the FDA and the European Commission.

Keytruda received its first FDA approval — as a therapy for advanced or unresectable melanoma (a type of skin cancer) — on Sept. 4, 2014, after key clinical trials demonstrated increased survival, tumor reduction, and reduced risk of disease progression in patients treated with Keytruda compared to those treated with a similar immunotherapy (Yervoy, ipilimumab).

Originally, Keytruda was to be prescribed following treatment with ipilimumab. Then, on Dec. 18, 2015, Keytruda was approved as a first-line treatment of melanoma on based on results of the Phase 3 KEYNOTE-006 (NCT01866319) trial, published in the *New England Journal of Medicine*. This drug had previously been approved to treat advanced melanoma by the European Commission on July 22, 2015.

The FDA approved Keytruda for the treatment of advanced non-small cell lung cancer (NSCLC) with high PD-L1 expression on Oct. 24, 2016, expanding upon its previous approval in 2015, which required these patients to have failed to respond to other treatments first. Keytruda was likewise approved for first-line use on NSCLC with high PD-L1 expression by the European Commission on Jan. 31, 2017.

On May 10, 2017, Keytruda was granted accelerated approval by the FDA as a first-line combination therapy for metastatic non-squamous NSCLC regardless of PD-L1 status, based on the results of the KEYNOTE-021 Phase 1/2 clinical trial (NCT02039674), published in *The Lancet Oncology*.

Keytruda more recently received FDA approval for the treatment of several other cancers. These include: recurrent or metastatic head and neck squamous cell carcinoma (approved on Aug. 5 2016, and on Jan. 31, 2017, by the European Commission); refractory classical Hodgkin lymphoma (cHL) (approved on March 15, 2017, and on May 5, 2017, by the European Commission) and locally advanced metastatic urothelial carcinoma, or bladder cancer (approved on May 18, 2017).

Keytruda is under priority review for FDA approval to treat recurrent or advanced gastric or gastroesophageal junction adenocarcinoma.

On May 23, 2017, the FDA granted Keytruda accelerated approval for the treatment of unresectable or metastatic solid tumors with a specific biomarker — microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR). Accelerated approval status means the FDA has approved the treatment for marketing, but continued approval is contingent on the results of ongoing clinical trials. The FDA aims to have made a final decision within the next six months, as part of Keytruda's priority review for this indication. This decision makes Keytruda the first cancer treatment to be approved based on a genetic marker as opposed to the location in the body where a tumor originated.

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