Pembrolizumab

Pembrolizumab (formerly **MK-3475** and **lambrolizumab**, trade name **Keytruda**)[1] is a humanized antibody used in cancer immunotherapy. It destroys a protective mechanism on cancer cells, and allows the immune system to destroy those cancer cells. It targets the programmed cell death 1 (PD-1) receptor. The drug was initially used in treating metastatic melanoma.

1 Medical uses

As of 2016, pembrolizumab is used via intravenous infusion to treat inoperable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC) in certain situations, and as a second-line treatment for head and neck squamous cell carcinoma (HNSCC), after platinum-based chemotherapy.[2][3][4][5]

For NSCLC, pembrolizumab is a first line treatment if the cancer overexpresses PDL1 and the cancer has no mutations in EGFR or in ALK; if chemotherapy has already been administered, then pembrolizumab can be used a second line treatment but if the cancer has EGFR or ALK mutations, agents targeting those mutations should be used first.[2][6] Assessment of PDL1 must be conducted with a validated and approved companion diagnostic.[2]

Women of child-bearing age should use contraception when taking pembrolizumab; it should not be administered to pregnant women because animal studies have shown that it can reduce tolerance to the fetus and increases the risk of miscarriage. It is not known if pembrolizumab is secreted in breast milk or not.[3]

As of 2016, the drug had not been tested in people with active infections including any HIV, hepatitis B or hepatitis C infection, kidney or liver disease, active CNS metastases, active systemic autoimmune disease, interstitial lung disease; prior pneumonia, and people with a history of severe reaction to another monoclonal antibody.[3]

2 Contraindications

If a person is taking corticosteroids or immunosuppressants those drugs should be stopped before starting pembrolizumab because they may interfere with pembrolizumab; they can be used after pembrolizumab is started to deal with immune-related adverse effects.[3]

3 Adverse effects

People have had severe infusion-related reactions to pembrolizumab. There have also been severe immune-related adverse effects including lung inflammation (including fatal cases) and inflammation of endocrine organs that caused inflammation of the pituitary gland, of the thyroid (causing both hypothyroidism and hyperthyroidism in different people), and pancreatitis that caused Type 1 diabetes and diabetic ketoacidosis; some people have had to go on lifelong hormone therapy as a result (e.g. insulin therapy or thyroid hormones). People have also had colon inflammation, liver inflammation, kidney inflammation due to the drug.[3][7]

The common adverse reactions have been fatigue (24%), rash (19%), itchiness (18%), diarrhea (12%), nausea (11%) and joint pain (10%).[3]

Other adverse effects occurring in between 1% and 10% of people taking pembrolizumab have included anemia, decreased appetite, headache, dizziness, distortion of the sense of taste, dry eye, high blood pressure, abdominal pain, constipation, dry mouth, severe skin reactions, vitiligo, various kinds of acne, dry skin, eczema, muscle pain, pain in a limb, arthritis, weakness, edemoa, fever, chills, and flu-like symptoms.[3]

4 Mechanism of action

Pembrolizumab is a therapeutic antibody that binds to and blocks the programmed cell death 1 receptor located on lymphocytes. This receptor is generally responsible for preventing the immune system from attacking the body's own tissues; it is a so-called immune checkpoint.[8][9] Many cancers make proteins that bind to PD-1, thus shutting down the ability of the body to kill the cancer on its own.[8] Inhibiting PD-1 on the lymphocytes prevents this, allowing the immune system to target and destroy cancer cells;[10] this same mechanism also allows the immune system to attack the body itself, and checkpoint inhibitors like pembrolizumab have immune-dysfunction side effects as a result.[9]

5 Pharmacology

Since pembrolizumab is cleared from the circulation through non-specific catabolism, no metabolic drug-drug

interactions are expected and no studies were done on routes of elimination.[3] The systemic clearance [rate] is ~0.2 L/day and the terminal half-life is ~27 days.[3]

6 Chemistry and manufacturing

Pembrolizumab is an Immunoglobulin G4, with a variable region against the human programmed cell death 1 receptor, a humanized mouse monoclonal [228-L-proline(H10-S>P)]γ4 heavy chain (134-218') disulfide and a humanized mouse monoclonal κ light chain dimer (226-226:*229-229*)-bisdisulfide.[11]

It is recombinantly manufactured in Chinese hamster ovary (CHO) cells.[12]

7 History

Pembrolizumab was invented by scientists Gregory Carven, Hans van Eenennaam and John Dulos at Organon after which they worked with Medical Research Council Technology starting in 2006 to humanize the antibody; Schering-Plough acquired Organon in 2007 and Merck & Co. acquired Schering-Plough two years later.[13]

In 2013, the USAN name was changed from lambrolizumab to pembrolizumab.[11] In that year clinical trial results in advanced melanoma were published in the New England Journal of Medicine.[14]

On September 4, 2014, the US Food and Drug Administration (FDA) approved pembrolizumab under the FDA Fast Track Development Program.[15] It is approved for use following treatment with ipilimumab, or after treatment with Ipilimumab and a BRAF inhibitor in advanced melanoma patients who carry a BRAF mutation.[16]

As of 2015, the only PDL-1 targeting drugs on the market were pembrolizumab and Bristol-Myers Squibb's Yervoy and Opdivo, and clinical developments in the class of drugs received coverage in the New York Times.[17]

By April 2016, Merck had applied for approval to market the drug in Japan and had signed an agreement with Taiho Pharmaceutical to co-promote it there.[18]

In July 2015, pembrolizumab received marketing approval in Europe.[3][19]

On October 2, 2015, the FDA approved pembrolizumab for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients whose tumors express PD-L1 and who have failed treatment with other chemotherapeutic agents.[20]

In July 2016, the US FDA accepted for priority review an application for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after a platinum-based chemotherapy,[21] and gave an accelerated approval on August 9, 2016.[22]

In August 2016, the FDA granted an accelerated approval to pembrolizumab (Keytruda) as a treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) ("regardless of PD-L1 staining") following progression on a platinum-based chemotherapy, based on objective response rates (ORR) in the phase Ib KEYNOTE-012 study.[22] Full approval depends on the results from the phase III KEYNOTE-040 study (NCT02252042), running until Jan 2017.[22]

8 Society and culture

Pembrolizumab was priced at $150,000 per year when it launched (late 2014).[23]

9 Research

In 2015, Merck reported results in 13 cancer types; much attention was given to early results in head and neck cancer.[24][25]

As of May 2016, pembrolizumab was in Phase IB clinical trials for triple-negative breast cancer (TNBC), gastric cancer, urothelial cancer, and head and neck cancer (all under the "Keynote-012" trial) and in Phase II trial for TNBC (the "Keynote-086" trial).[26] At ASCO in June 2016, Merck reported that the clinical development program was directed to around 30 cancers and that it was running over 270 clinical trials (around 100 in combination with other treatments) and had four registration-enabling studies in process.[27]

Results of a Phase II clinical trial in Merkel-cell carcinoma were reported in the New England Journal of Medicine in June 2016.[28]

As of 2016, the role of biomarkers in guiding pembrolizumab use was still uncertain.[29][30]

10 See also

- Checkpoint therapy

11 References

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