Pembrolizumab (Keytruda)

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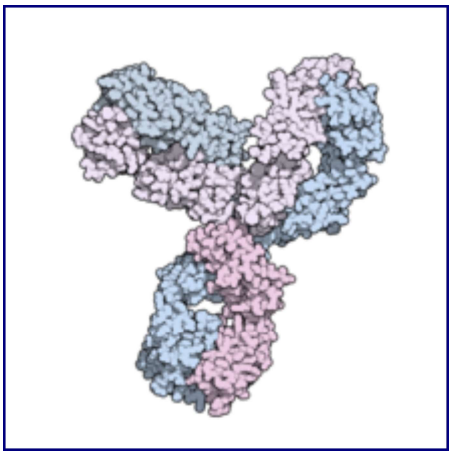
Pembrolizumab (formerly MK-3475 and lambrolizumab, trade name Keytruda)[1] is a humanized antibody used in cancer immunotherapy. It blocks a protective mechanism on cancer cells, and allows the immune system to destroy those cancer cells. It targets the programmed cell death 1 (PD-1) receptor. The drug was initially used to treat metastatic melanoma. In May 2017 it was approved for any unresectable or metastatic solid tumor with certain genetic qualities without regard to the tissue type or site of the tumor, a first for the FDA



Monoclonal antibody

Medical uses

As of 2017, pembrolizumab is used via intravenous infusion to treat inoperable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC) in certain situations, as a second-line treatment for head and neck squamous cell carcinoma (HNSCC), after platinum-based chemotherapy, and for the treatment of adult and pediatric patients with refractory classic Hodgkin's lymphoma (cHL).[2][3][4][5][6]

For NSCLC, pembrolizumab is a first line treatment if the cancer overexpresses PD-L1, a PD-1 receptor ligand, and the cancer has no mutations in EGFR or in ALK; if chemotherapy has already been administered, then pembrolizumab can be used as a second line treatment but if the cancer has EGFR or ALK mutations, agents targeting those mutations should be used first.[2][7] Assessment of PD-L1 must be conducted with a validated and approved companion diagnostic.[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]

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 into breast milk or not.[3]

As of 2017, 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]

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][8]

The common adverse reactions have been fatigue (24%), rash (19%), itchiness (pruritus) (17%), diarrhea (12%), nausea (11%) and joint pain (arthralgia) (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, edema, fever, chills, and flu-like symptoms.[3]

Mechanism of action

Pembrolizumab is a therapeutic antibody that binds to and blocks the PD-1, programmed cell death protein 1 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.[9][10] Many cancers make proteins that bind to PD-1, thus shutting down the ability of the body to kill the cancer on its own.[9] Inhibiting PD-1 on the lymphocytes prevents this, allowing the immune system to target and destroy cancer cells;[11] 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.[10]

Tumors that have mutations that cause DNA mismatch repair, which often results in microsatellite instability, tend to generate many mutated proteins that could serve as tumor antigens; pembrolizumab appears to facilitate clearance of any such tumor by the immune system, by preventing the self-checkpoint system from blocking the clearance.[12]

Pharmacology

Since pembrolizumab is cleared from the circulation through non-specific catabolism, no metabolic drug interactions are expected and no studies were done on routes of elimination.[3] The systemic clearance [rate] is about 0.2 L/day and the terminal half-life is about 25 days.[3]

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.[13]

It is recombinantly manufactured in Chinese hamster ovary (CHO) cells.[14]

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 (now known as LifeArc) starting in 2006 to humanize the antibody; Schering-Plough acquired Organon in 2007 and Merck & Co. acquired Schering-Plough two years later.[15] Carven, van Eenennaam and Dulos were recognized as Inventors of the Year by the Intellectual Property Owners Education Foundation in 2016.[16]

The development program for pembrolizumab was seen as high priority at Organon, but low at Schering, and then at Merck, and in early 2010 Merck terminated development and began preparing to outlicense it.[17] But then later in 2010 scientists from Bristol Myers Squibb published a paper in the New England Journal of Medicine showing that their checkpoint inhibitor, ipilimumab (Yervoy) had shown strong promise in metastatic melanoma and that a second Bristol-Myers Squibb checkpoint inhibitor, nivolumab, (Opdivo) was also promising.[17]

Merck at that time has little commitment and expertise in oncology or immunotherapy, but understood the opportunity and reacted strongly, reactivating the program and filing its IND by the end of 2010.[17] As an example, Martin Huber was one of the few senior people at Merck with strong experience in lung cancer drug development, but had been promoted to senior management and was no longer involved in product development; he ended up stepping down from his role and led clinical development of pembrolizumab for lung cancer.[17]

Scientists at the company argued for developing a companion diagnostic and limiting testing of the drug only to patients with biomarkers showing they were likely to respond; management agreed and some people, including shareholders and analysts, criticized this decision as it limited the potential market size for the drug, but others argued that it increased the chances of proving the drug would work, and made clinical trials faster and needing fewer patients due to the likelihood of greater effect size, and moving quickly and reducing the risk of failure was essential for catching up with Bristol-Myers Squibb, which had an approximately five year lead over Merck.[17]

The phase I study started in early 2011, and Eric Rubin, who was running the melanoma trial, argued for and was able to win expansion of the trial until it reached around 1300 people roughly divided between melanoma and lung cancer, the largest Phase I study ever run in oncology.[17] In 2013 Merck quietly applied for and won a Breakthrough therapy designation for the drug; this regulatory pathway was new at the time and not well understood; one of its advantages is that the FDA holds more frequent meetings with drug developers, which reduces the risk of developers making mistakes or misunderstandings arising between regulator's expectations and what the developers want to do. This was Merck's first use of the designation and the reduction in regulatory risk was one of the reasons why management was willing to put company resources behind the development.[17]

In 2013, the USAN name was changed from lambrolizumab to pembrolizumab.[13] In that year clinical trial results in advanced melanoma were published in the New England Journal of Medicine.[18]

On September 4, 2014, the US Food and Drug Administration (FDA) approved pembrolizumab under the FDA Fast Track Development Program.[19] 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.[20]

As of 2015, the only PD-1/PD-L1 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.[21]

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.[22]

In July 2015, pembrolizumab received marketing approval in Europe.[3][23]

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.[24]

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,[25] and gave an accelerated approval on August 9, 2016.[26]

In August 2016, the FDA granted an accelerated approval to pembrolizumab 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.[26] Full approval depends on the results of the phase III KEYNOTE-040 study (NCT02252042), running until Jan 2017.[26]

In May 2017, pembrolizumab received an accelerated approval from the FDA for use in any unresectable or metastatic solid tumor with DNA mismatch repair deficiencies or a microsatellite instability-high state (or, in the case of colon cancer, tumors that have progressed following chemotherapy). This approval marked the first instance in which the FDA approved marketing of a drug based only on the presence of a genetic mutation, with no limitation on the site of the cancer or the kind of tissue in which it originated.[27][12][28] The approval was based on a clinical trial of 149 patients with microsatellite instability-high or mismatch repair deficient cancers who enrolled on one of five single-arm trials. Ninety patients had colorectal cancer, and 59 patients had one of 14 other cancer types. The objective response rate for all patients was 39.6%. Response rates were similar across all cancer types, including 36% in colorectal cancer and 46% across the other tumor types. Notably, there were 11 complete responses, with the remainder partial responses. Responses lasted for at least six months in 78% of responders.[12] Because the clinical trial was fairly small, Merck was obligated to conduct further post-marketing studies to ensure that the results are valid.[29]

Society and culture

Pembrolizumab was priced at $150,000 per year when it launched (late 2014).[30]

Research

In 2015, Merck reported results in 13 cancer types; much attention was given to early results in head and neck cancer.[31][32]

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).[33] 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.[34]

Results of a Phase II clinical trial in Merkel-cell carcinoma were reported in the New England Journal of Medicine in June 2016.[35]

Results of a clinical trial in people with untreatable metastases arising from various solid tumors were published in *Science* in 2017.[36]

It is in a phase III trial in combination with epacadostat, an Indoleamine 2,3-dioxygenase (IDO1) inhibitor to treat melanoma.[37]