FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

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Release

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

“We’re entering a new frontier in medical innovation with the ability to reprogram a patient’s own cells to attack a deadly cancer,” said FDA Commissioner Scott Gottlieb, M.D. “New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we’re committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving.”

Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient’s own T-cells, a type of white blood cell known as a lymphocyte. The patient’s T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.

ALL is a cancer of the bone marrow and blood, in which the body makes abnormal lymphocytes. The disease progresses quickly and is the most common childhood cancer in the U.S. The National Cancer Institute estimates that approximately 3,100 patients aged 20 and younger are diagnosed with ALL each year. ALL can be of either T-

or B-cell origin, with B-cell the most common. Kymriah is approved for use in pediatric and young adult patients with B-cell ALL and is intended for patients whose cancer has not responded to or has returned after initial treatment, which occurs in an estimated 15-20 percent of patients.

“Kymriah is a first-of-its-kind treatment approach that fills an important unmet need for children and young adults with this serious disease,” said Peter Marks, M.D., Ph.D., director of the FDA’s Center for Biologics Evaluation and Research (CBER). “Not only does Kymriah provide these patients with a new treatment option where very limited options existed, but a treatment option that has shown promising remission and survival rates in clinical trials.”

The safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The overall remission rate within three months of treatment was 83 percent.

Treatment with Kymriah has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms, and for neurological events. Both CRS and neurological events can be life-threatening. Other severe side effects of Kymriah include serious infections, low blood pressure (hypotension), acute kidney injury, fever, and decreased oxygen (hypoxia). Most symptoms appear within one to 22 days following infusion of Kymriah. Since the CD19 antigen is also present on normal B-cells, and Kymriah will also destroy those normal B cells that produce antibodies, there may be an increased risk of infections for a prolonged period of time.

The FDA today also expanded the approval of Actemra (tocilizumab) to treat CAR T-cell-induced severe or life-threatening CRS in patients 2 years of age or older. In clinical trials in patients treated with CAR-T cells, 69 percent of patients had complete resolution of CRS within two weeks following one or two doses of Actemra.

Because of the risk of CRS and neurological events, Kymriah is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). The FDA is requiring that hospitals and their associated clinics that dispense Kymriah be specially certified. As part of that certification, staff involved in the prescribing, dispensing, or administering of Kymriah are required to be trained to recognize and manage CRS and neurological events. Additionally, the certified health care settings are required to have protocols in place to ensure that Kymriah is only given to patients after verifying that tocilizumab is available for immediate administration. The REMS program specifies that patients be informed of the signs and symptoms of CRS and neurological toxicities following infusion – and of the importance of promptly returning to the treatment site if they develop fever or other adverse reactions after receiving treatment with Kymriah.

To further evaluate the long-term safety, Novartis is also required to conduct a post-marketing observational study involving patients treated with Kymriah.

The FDA granted Kymriah **Fast Track (/ForPatients/Approvals/Fast/ucm405399.htm)**, **Priority Review (/ForPatients/Approvals/Fast/ucm405405.htm)** and **Breakthrough Therapy (/ForPatients/Approvals/Fast/ucm405397.htm)** designations. The Kymriah application was reviewed using a coordinated, cross-agency approach. The clinical review was coordinated by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination.

The FDA granted approval of Kymriah to Novartis Pharmaceuticals Corp. The FDA granted the expanded approval of Actemra to Genentech Inc.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines, and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our

nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Inquiries

Media

Andrea Fischer (mailto:andrea.fischer@fda.hhs.gov)
301-796-0393

Angela Stark (mailto:angela.stark@fda.hhs.gov)
301-796-0397

Consumers

888-INFO-FDA, OCOD@fda.hhs.gov (mailto:OCOD@fda.hhs.gov)

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