# FDA Approves Kymriah CAR-T Therapy for Lymphoma

The custom immunotherapy is now indicated for adults with relapsed or refractory lymphoma.

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The Food and Drug Administration (FDA) this week approved a new indication for Kymriah, the first-ever CAR-T gene therapy, making it available for adults with large B-cell lymphoma that does not respond to or comes back after other types of treatment.

Chimeric antigen receptor T-cell therapy—better known as CAR-T—involves removing a sample of a patient's white blood cells, genetically reprogramming the T cells to kill cancer cells, multiplying them in a lab and infusing them back into the body. The procedure uses genetic engineering to create a customized "living drug" for each individual that will recognize and attack his or her cancer.

Novartis's Kymriah (tisagenlecleucel; formerly known as CTL019) was first approved last August for children and young adults (up to age 25) with acute lymphoblastic leukemia that is refractory to treatment or has relapsed at least twice. In October, the agency approved Yescarta (axicabtagene ciloleucel), a CAR-T therapy from Kite Pharma, a Gilead company, for adults with refractory or relapsed large B-cell lymphoma. This week's approval puts Kymriah in direct competition with Yescarta for this patient population.

The new approval covers people with diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma who have tried at least two prior systemic therapies; it is not indicated for primary central nervous system lymphoma.

Diffuse large B-cell lymphoma is the most common type of non–Hodgkin lymphoma (NHL). Nearly 75,000 people in the United States will be diagnosed with NHL this year, about a third of whom will have DLBCL, according to the American Cancer Society. Using standard therapy, the median survival for people with relapsed or refractory DLBCL is around four to six months.

"The goal of Kymriah is to provide physicians with a therapy that has demonstrated durable response rates in relapsed or refractory DLBCL patients, a patient population that has endured multiple rounds of chemotherapy with many having experienced unsuccessful stem cell transplants," Stephen J. Schuster, MD, of the University of Pennsylvania Perelman School of Medicine said in a Novartis press release. "With this approval, physicians now have a meaningful

therapeutic option that can achieve and maintain a sustained response without stem cell transplant along with a consistent safety profile."

Kymriah treatment involves a single infusion of modified T cells produced at Novartis's manufacturing facility in New Jersey. The expected turnaround time from cell collection to reinfusion is about 22 days.

Approval of Kymriah for adult lymphoma was based on results from the Phase II JULIET trial, presented at the American Society of Hematology annual meeting last December. About a third of treated participants had complete responses, meaning they had no remaining evidence of cancer. In a smaller study with longer follow-up, the median duration of remission for responders was more than two years.

JULIET enrolled 147 adults with DLBCL in 10 countries in North America, Europe and Asia. The median age was 56 and about three quarters had advanced (Stage III or IV) disease at study entry. They experienced disease progression after receiving at least two types of prior chemotherapy and were either ineligible for or relapsed after an autologous (self-donated) stem cell transplant.

In an analysis of 81 participants who received a single infusion of Kymriah, the overall response rate (meaning complete or partial remission) was 53 percent; 30 percent remained cancer-free at six months. The median duration of response was not reached because a majority of participants were still responding at the time of the analysis. The median overall survival also could not be determined because a majority of participants were still alive, with a 65 percent probability of survival at six months.

CAR-T therapy can potentially cause severe or life-threatening side effects. Unleashing genetically modified T cells not only can kill cancer cells but also can lead to an excessive immune response that harms healthy organs and tissue. This cytokine release syndrome (CRS), or "cytokine storm," can cause symptoms ranging from fever and flu-like symptoms to neurological problems and organ failure. In addition, Kymriah attacks normal antibody-producing B cells along with abnormal leukemia B cells, so treated patients are at increased risk for infections. In the JULIET trial, 23 percent of participants experienced severe CRS, 18 percent had severe neurological side effects and 25 percent developed severe infections.

However, as doctors have become more familiar with this new type of treatment, they are learning to recognize these problems early and successfully manage them with immunosuppressive drugs and supportive care.

Kymriah and Yescarta have not been widely used since their approval last year. In part this is due to their high prices—in the $300,000 to $500,000 range—and payers do not yet have clear policies about when and how to cover them. In addition, manufacturing and administering modified T cells presents logistical challenges, and the FDA requires that hospitals offering CAR-T therapy must be certified and staff must be trained to recognize and manage CRS and other side effects.

Novartis said it will offer patient assistance programs and the company is working with the Centers

for Medicare and Medicaid Services to develop value-based pricing approaches, such as requiring payment only if a patient responds. Novartis indicated that it would match Gilead’s price for the new lymphoma indication.

Click here to read a Novartis press release about the new Kymriah approval.

Click here to see full prescribing information for Kymriah.

Click here to read an overview of CAR-T therapy in the premier issue of Cancer Health.

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