Kymriah CAR-T Therapy Leads to Long-Term Remission in Adults With Lymphoma

Findings from the JULIET trial support expanded Food and Drug Administration approval of customized T cells.

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Kymriah, the first approved CAR-T therapy, has shown good results in adults with hard-to-treat non–Hodgkin lymphoma, researchers reported at the American Society of Hematology annual meeting this week in Atlanta.

About a third of treated patients with diffuse large B-cell lymphoma (DLBCL) in the JULIET study saw complete responses within three months after a single dose of custom-engineered T cells. In a smaller study with longer follow-up, the median duration of remission was more than two years.

Kymriah (tisagenlecleucel; formerly CTL019), a groundbreaking type of immunotherapy, was approved by the Food and Drug Administration (FDA) in August for the treatment of children and young adults with acute lymphoblastic leukemia.

Chimeric antigen receptor T-cell (CAR-T) therapy reprograms immune cells to recognize and attack cancer. The process involves collecting a sample of a patient's normal T cells and sending them to a manufacturing facility, where they are genetically engineered to create a customized "living drug" for each individual. Using an inactivated virus, scientists insert receptors that target the CD19 protein on B cells that grow out of control in lymphoma and leukemia. The supercharged cells are then multiplied and infused back into the patient.

Stephen Schuster, MD, of the University of Pennsylvania Abramson Cancer Center presented primary findings from JULIET, a Phase II study of Kymriah for people with relapsed or refractory (nonresponsive) DLBCL.

The study enrolled 147 adults with DLBCL at 27 centers in 10 countries in North America, Europe and Asia, as well as Australia. 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. Using standard therapy, median survival for people

with relapsed or refractory DLBCL is only about four months, Schuster told reporters at a press briefing.

Kymriah for each patient was manufactured at facilities in the United States or Germany. Each participant received a single infusion of their custom-engineered T cells. More than a quarter were given Kymriah in an outpatient setting. Before reinfusion, most received strong chemotherapy to kill off cancerous immune cells and make room for the new ones. This open-label study had no placebo or comparison drug control group.

The primary analysis included 81 participants who received infusions of CAR-T cells manufactured at the U.S. facility. The overall response rate, meaning complete or partial remission, was 53 percent. The complete response rate was 32 percent at three months and 30 percent at six months—that is, most people who were in full remission at three months were still cancer-free at six months. Partial response rates were 6 percent and 7 percent, respectively. Modified T cells were detected in the blood of responders for up to a year so far. Follow-up is ongoing.

The median duration of response was not reached because a majority of participants were still responding. The probability of being relapse-free at six months was 74 percent, Schuster reported. Likewise, median overall survival could not be determined because a majority of participants were still alive. The probability of survival at six months was 65 percent.

A previous pilot study of Kymriah by the same research team has accrued longer follow-up. As reported in The New England Journal of Medicine, 6 of 14 patients with DLBCL (43 percent) and 10 of 14 people with follicular lymphoma (71 percent) had complete responses at six months. All those in full remission at six months were still cancer-free after a median of 29 months and a maximum of 38 months.

“Taken together, our data from both trials show that most patients who are in remission at three months stay in remission,” Schuster said in a University of Pennsylvania press release. “About a third of patients who fail all current therapies, even transplant, could now have a form of therapy that may offer them durable remissions.”

Kymriah side effects were common and in some cases severe. Unleashing genetically modified T cells can trigger a flood of immune system chemicals, known as cytokine release syndrome (CRS), or a cytokine storm, leading to side effects such as high fever, low blood pressure, brain swelling and organ failure. CAR-T therapy can also kill off healthy antibody-producing B cells, making patients more susceptible to infections.

A majority of participants in the JULIET study experienced adverse events. Fifty-eight percent developed cytokine release syndrome, which was severe (grade 3) in 15 percent and life-threatening (grade 4) in 8 percent. Patients with CRS were managed according to a specified algorithm, which included use of the immunosuppressant drug Actemra (tocilizumab) or corticosteroids; all patients recovered.

In addition, 36 percent of patients developed blood cell deficiencies lasting more than a month, 34

percent developed infections, 21 percent had neurological adverse events and 13 percent had low white blood cell counts with fever, all of which resolved. No cases of brain swelling were reported. Three people died after treatment due to lymphoma progression, but no deaths were attributed to CAR-T treatment.

“CRS and other adverse events could be effectively and reproducibly managed by appropriately trained investigators without treatment-related mortality,” the researchers concluded.

These findings support Novartis’s recent application to expand FDA approval of Kymriah to include adults with DLBCL. If that happens, it will compete with Yescarta (axicabtagene ciloleucel) from Kite Pharma, a Gilead company, which was approved in October for adults with certain types of relapsed or refractory B-cell lymphoma.

Click here to read the JULIET study abstract.

Click here to read the New England Journal of Medicine article.

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http://beta.docker.cancerhealth.com/article/kymriah-cart-therapy-leads-longterm-remission-adults-bcell-lymphoma