FDA Approves First CAR-T Therapy for Chronic Lymphocytic Leukemia

Breyanzi, made from a patient's own T cells, controlled relapsed or nonresponsive CLL in 20% of people previously treated with targeted therapies.

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On March 14, the Food and Drug Administration (FDA) granted accelerated approval of Breyanzi (lisocabtagene maraleucel, or liso-cel) as the first CAR-T therapy for previously treated people with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The approval is supported by results from a clinical trial showing that 20% of CLL and SLL patients treated with a one-time infusion of Breyanzi achieved a complete response.

Breyanzi targets the CD19 protein on B cells that grow out of control in several types of leukemia and lymphoma. It was first approved in 2021 to treat large B-cell lymphoma. The new approval is for adults with relapsed or refractory CLL or SLL who have already used at least two prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor, such as Calquence (acalabrutinib) or Imbruvica (ibrutinib), and a B-cell lymphoma 2 (BCL-2) inhibitor, such as Venclexta (venetoclax).

"CLL and SLL are currently considered incurable diseases with few treatment options in the relapsed setting that can confer complete responses, something that has historically been associated with improved long-term outcomes," Tanya Siddiqi, MD, of City of Hope National Medical Center, said in a Bristol Myers Squibb news release. The FDA approval of Breyanzi "is a remarkable breakthrough, shifting the treatment paradigm from continuous therapy with sequential regimens to overcome drug resistance, to a one-time personalized T-cell-based approach that has the potential to offer patients complete and lasting remission."

CLL, one of the most common blood cancers in adults, involves overproduction of abnormal white blood cells, usually antibody-producing B cells. SLL is a related condition classified as a type of non-Hodgkin lymphoma. In CLL, the cancerous cells are mostly in the bloodstream, while in SLL, they are mainly in the lymph nodes. These malignant lymphocytes can crowd out normal blood cells, leading to low blood cell counts, increased susceptibility to infections and other complications. Chemotherapy and targeted therapies can put CLL into remission, but relapse is common, at which point patients have diminishing treatment options.

The Phase I/II TRANSCEND CLL 004 trial (NCT03331198) evaluated Breyanzi for patients with relapsed or refractory CLL or SLL. This "living drug" reprograms a patient's own T cells to fight

cancer. Chimeric antigen receptor T-cell therapy—better known as CAR-T—involves removing a sample of a patient's white blood cells, genetically modifying T cells to recognize and attack their cancer, manufacturing a large number of the modified cells in a laboratory and infusing them back into the body.

TRANSCEND CLL 004 was the first multicenter pivotal trial to evaluate a CAR-T therapy for people with relapsed or refractory CLL or SLL. Siddiqi presented promising early results at the 2018 American Society of Hematology annual meeting. In the latest analysis, which included 65 treated patients, the overall response rate was 45%, and the complete response rate was 20%. The median duration of response was 35.3 months overall but not yet reached among complete responders. Most complete responders had negative minimal residual disease status, meaning no remaining malignant cells were detected in the blood (100%) or bone marrow (92%) using highly sensitive tests.

Breyanzi's safety profile is described as "manageable," but side effects are common. People who undergo CAR-T therapy receive strong chemotherapy to kill off their immune cells and make room for the modified T cells, which can cause adverse effects such as fatigue, nausea, low blood cell counts and infections. Introducing engineered T cells can trigger a strong immune reaction known as cytokine release syndrome (CRS), which can lead to fever and chills, falling blood pressure and organ failure, as well as neurologic toxicity. In this study, 83% developed CRS (9% severe), and 46% experienced neurologic side effects (20% severe).

"For people struggling with relapsed or refractory CLL or SLL, current treatment choices are limited," said Brian Koffman, MD, cofounder and chief medical officer of the CLL Society and a CLL survivor himself. "The approval of Breyanzi as the first CAR T-cell therapy available for relapsed or refractory CLL or SLL brings new hope to these patients with the potential for durable responses after a single CAR T infusion."

Drugs that receive accelerated approval based on overall response rates are expected to undergo further testing to confirm that they offer clinical benefits, such as improved survival, and the FDA can rescind the approval if they fail to measure up. Breyanzi is also being evaluated as a treatment for relapsed or refractory follicular lymphoma and mantle cell lymphoma, with FDA approval decisions expected in May.

Click here for full prescribing information for Breyanzi.
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