Yescarta CAR-T Therapy Leads to Durable Remission of Advanced Lymphoma

Long-term study data show that patients remain cancer-free for up to two years.

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Forty percent of people treated with Yescarta CAR-T therapy for advanced non–Hodgkin lymphoma were still in complete remission 15 months after treatment, exceeding the response rates of available salvage therapies, researchers reported at the American Society of Hematology (ASH) annual meeting this month in Atlanta.

Other studies presented at the conference suggest that using Yescarta with checkpoint inhibitors may give the modified cancer-fighting T cells an extra boost.

Chimeric antigen receptor T-cell, or CAR-T, therapy reprograms immune cells to recognize and attack cancer. The process involves collecting a sample of a patient's T cells and sending them to a manufacturing facility, where they are genetically engineered to create a customized "living drug" for each individual. The supercharged T cells are then multiplied and infused back into the patient.

Yescarta (axicabtagene ciloleucel), developed by Kite Pharma, a Gilead company, modifies T cells to express receptors targeting the CD19 protein on B cells that grow out of control in lymphoma. In October, the Food and Drug Administration (FDA) approved Yescarta for adults with certain types of large B-cell lymphoma that did not respond or relapsed after prior treatment.

Yescarta was approved based on the results of the Phase II ZUMA-1 trial, which enrolled more than 100 adults with three types of refractory (nonresponsive) or relapsed B-cell lymphoma. As reported earlier this year, the overall response rate at 8.7 months was 82 percent, with 54 percent of treated patients achieving a complete response, or no detectable remaining cancer.

At the recent ASH meeting, Sattva Neelapu, MD, of the University of Texas MD Anderson Cancer Center presented long-term results, which were published simultaneously in The New England Journal of Medicine.

After at least a year of follow-up (median 15.4 months) after a single Yescarta infusion, 42 percent

of treated participants continued to respond, including 40 percent with ongoing complete responses. The median response duration was 11.1 months, and a few people who enrolled in the study early were still cancer-free at 24 months. The researchers reported that higher levels of modified T cells in the blood were associated with better response.

The overall survival rate was 52 percent at 18 months and a majority of surviving patients had no evidence of worsening disease. The median survival duration could not be determined because a majority of patients were still alive.

“The durability of response seen with Yescarta in this long-term follow-up reinforces the major advance that CAR-T therapy represents for these patients,” Neelapu said in a Kite press release. In his presentation he noted that people who make it past six months or a year without recurrence are unlikely to relapse later.

CAR-T therapy can cause potentially life-threatening side effects, as unleashing the modified T cells not only kills cancer cells but can also trigger an excessive immune response that harms healthy tissue. Thirteen percent of ZUMA-1 participants experienced severe cytokine release syndrome (CRS), which can cause symptoms ranging from fevers to organ failure, and 28 percent developed severe neurological side effects. In most cases these adverse events were manageable and reversible.

ZUMA-1 response rates were much better than those seen in the SCHOLAR-1 trial of people with aggressive lymphoma treated with available salvage therapies—even though the ZUMA-1 participants were older and had more advanced disease and more prior treatments. In that study, the overall response rate was 26 percent, the complete response rate was 7 percent and the median overall survival duration was 6.3 months. After balancing patient characteristics in the two trials, Neelapu and colleagues concluded that the risk of death was 77 percent lower in ZUMA-1 compared with SCHOLAR-1.

CAR-T therapy sometimes fails to work or stops working as cancer cells evolve to avoid the modified T cells. Combination therapy may be one way to overcome resistance.

Frederick Locke, MD, of Moffitt Cancer Center in Tampa, Florida, and colleagues reported early findings from ZUMA-6, a study in which people were treated with Yescarta followed by the checkpoint inhibitor Tecentriq (atezolizumab).

Checkpoint inhibitors like Opdivo (nivolumab) block the PD-1 receptor on T cells while Tecentriq blocks PD-L1, its ligand, or binding partner, on cancer cells. PD-1 is an immune checkpoint that acts as a brake on T-cell activity. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or PD-L1 release the brakes and restore T-cell activity against cancer cells. A majority of ZUMA-1 participants had PD-L1–positive tumor cells, suggesting that checkpoint inhibitors might improve response.

Locke’s team reported that ZUMA-6 participants treated with the combination had higher levels of modified T cells than people treated with Yescarta alone in ZUMA-1. Early results from a small

number of patients showed promising response rates and the combined side effects were manageable.

In a related presentation, Brian Hill of the Taussig Cancer Institute in Cleveland and colleagues described the case of a ZUMA-1 participant with rapidly progressing lymphoma who did not initially respond to Yescarta. He went on to receive Opdivo, after which his modified T-cell level rose dramatically and he experienced a second episode of cytokine release syndrome, followed by symptom improvement and a 67 percent reduction in tumor size, although he ultimately relapsed again, according to the study abstract.

Based on these findings, the researchers suggested that immune checkpoints may interfere with the activity of CAR-T therapy and checkpoint-blocking drugs could improve response.

Click here to read the ZUMA-1 study ASH abstract.

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

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