

Roswell Park Study Reveals How Venclexta Boosts Response to CAR-T Therapy for CLL

BCL-2 inhibitor venetoclax works synergistically with CAR-T immunotherapy to combat chronic lymphocytic leukemia.

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Highlights:

- New insight into FDA-approved treatment for most common leukemia in the U.S.
- Venetoclax significantly enhances CAR T-cell therapy through immune repair.
- Results set the stage for identifying more effective combination therapies.

Research out of Roswell Park Comprehensive Cancer Center has shed light on how the drug venetoclax (brand name Venclexta) works synergistically with [CAR T-cell immunotherapy](#) to combat chronic lymphocytic leukemia (CLL), the most common type of leukemia in the U.S.

[Matthew Cortese, MD, MPH](#), Assistant Professor of Oncology in Roswell Park's departments of Medicine and Cancer Genetics & Genomics, is first author of the study, which he [presented] during an oral abstract session [December 7] at the 66th annual meeting of the American Society of Hematology (ASH) in San Diego, California.

Chronic lymphocytic leukemia occurs when B cells — infection-fighting white blood cells that are part of the immune system — grow out of control, suppressing the immune system. This can lead to additional cancers, frequent infections and resistance to treatments such as CAR T-cell therapy.

FDA-approved for the treatment of CLL since 2019, venetoclax can cause CLL cells to self-destruct by inhibiting BCL-2, a protein they need to survive. But the Roswell Park study reveals that when it is combined with CAR T-cell therapy, venetoclax works in another way that's less understood — by strengthening cancer-killing T lymphocytes, or T cells, improving their function and fitness.

"This could be an exciting way to repair the immune system in patients with CLL," says Dr. Cortese, who notes that Roswell Park is working to develop a clinical trial that would take the next step in this discovery.

To better understand the drug's effects on the immune system, the research team collected circulating blood from 14 Roswell Park patients whose treatment plan began with standard-of-care venetoclax to treat their CLL.

Using specialized facilities and a multidisciplinary approach at Roswell Park, the team compared those initial blood samples with samples taken after about 30 days of venetoclax treatment, to identify specific changes in patients' immune cells. This "multiomic" analysis included RNA sequencing, flow cytometry, epigenomics and metabolomics. Data from each layer were combined with sophisticated bioinformatic analytical tools. CAR T cells were then made from baseline and treated blood samples and tested against aggressive lymphoma cell lines in the lab.

"By analyzing very large volumes of molecular data in more patients, we hope to develop more effective combination treatments for CLL patients that improve on our best current treatments," says Dr. Cortese. "It's hyper-precision medicine. The goal is to reduce side effects while bringing about ultra-deep responses by combining targeted therapies with immune and cellular therapies, which down the road may ultimately lead to a cure for some patients."

[Francisco Hernandez-Ilizaliturri, MD](#), Professor of Oncology and Director of Lymphoma Research in the Department of Medicine and Associate Professor in the Department of Immunology, is senior author of the study.

Abstract 78, [Multiomic Evaluation of Immunologic Changes in Chronic Lymphocytic Leukemia with Venetoclax Treatment](#)

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