New KIR-CAR T-Cell Therapy Shows Promise in Multiple Solid Cancers

The first-of-its-kind Phase I clinical trial uses a CAR-T therapy modeled after natural killer cells and designed to limit T cell exhaustion.

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An innovative type of CAR T-cell therapy, called KIR-CAR, was shown to be safe, with increasing efficacy corresponding to higher doses of the investigational treatment in nine patients with advanced ovarian cancer, mesothelioma or cholangiocarcinoma (bile duct cancer), according to an early report from an ongoing Phase I dose-escalation clinical trial. The findings represent the first clinical data for this KIR-CAR, which uses natural killer (NK) cell-like receptors to overcome T cell exhaustion and limit side effects.

Janos L. Tanyi, MD, PhD, principal investigator of the multisite STAR-101 Phase I Clinical Trial and an associate professor of Obstetrics and Gynecology in the Perelman School of Medicine at the University of Pennsylvania, shared the findings in a Clinical Trials Plenary Session at the American Association for Cancer Research (AACR) Annual Meeting (Abstract CT104).

“This is exciting because we’re seeing good efficacy signals, even at low doses, and limited toxicity in cancer types that have never had an approved cell therapy,” Tanyi said. “As we continue enrollment and dose escalation, we hope to see more patients’ tumors responding to the therapy and continued persistence and longevity of the T cells, all with less side effects than conventional CAR T cell therapy.”

A CAR T with an ‘on-off’ switch

As Penn CAR T cell therapy pioneer Carl June, MD, the Richard W. Vague Professor in Immunotherapy, noted in the Opening Plenary Session of the AACR Annual Meeting, researchers around the world are working to advance cellular therapies—which transformed the treatment of many blood cancers—into the solid tumor setting.

The KIR-CAR used in this study, SynKIR-110, is the first of its kind to advance into clinical trials. The design, based on NK cell receptors, is a “multi-chain” model, which differs from the “single-chain” approach of traditional CAR T cells. In the new multi-chain model, the antigen binding and stimulatory functions are carried on separate chains. One chain directs the T cell to recognize the target on the surface of the cancer cell, while the other triggers the attack once the target is

found. This allows the T cell to rest when it's not attacking a tumor, rather than constantly being in an active state. When a tumor antigen is found, the two chains come together, activating the T cell to attack the cancer.

"The KIR-CAR design provides a natural 'on-off' mechanism, which helps avoid the problem of T cell exhaustion," Tanyi explained. "The CAR turns on when it finds its target, kills it, and then rests, rather than constantly burning energy. Because it's not continually 'on,' it also limits immune-related adverse events from the CAR T cells engaging with healthy cells."

SynKIR-110 was developed by the clinical trial sponsor, Verismo Therapeutics, a Penn spinout company founded by several current and former faculty members from Penn and Penn's Center for Cellular Immunotherapies.

Positive signals in patients with few options left

SynKIR-110 targets mesothelin, a target chosen because it's widely expressed on several solid tumor cancers and has no or low expression on normal cells. The clinical trial enrolled patients with several mesothelin-expressing cancers, including advanced ovarian cancer, mesothelioma, or cholangiocarcinoma (bile duct cancer). These cancers are typically aggressive and/or rare, with limited effective treatment options, particularly if the cancer comes back after initial treatment. For example, approximately 70% of ovarian cancers recur after standard treatment, which can include surgery, radiation, and chemotherapy.

To be eligible for the study, patients must have already received at least one prior standard of care treatment and experienced a relapse. The nine patients who were part of this report had received an average of four different lines of therapy before they enrolled.

As a Phase I dose-escalation study, the primary objectives were safety and finding maximum tolerated dose, with the dose increasing after three patients were treated on each of the first three cohorts. The treatment was safe, with no dose-limiting toxicities reported. Three patients (33%) experienced low-grade cytokine release syndrome (CRS), a known and manageable side effect of CAR T-cell therapy. There were no cases of immune effector cell-associated neurotoxicity syndrome (ICANS), another known side effect of CAR T-cell therapy.

Up to 44% disease stabilization was seen in four patients, with one patient in the highest dose cohort experiencing a partial response which is still ongoing. Blood samples taken from the patients after treatment also indicated that the peak expansion of CAR T-cell proliferation rose with each dose level.

Clinical trial information

The research team is continuing clinical trial enrollment at Penn's Abramson Cancer Center and three other sites. Eligibility information and enrollment contacts are available here.

A total of 42 patients are expected to enroll in the Phase I study, with plans to continue follow-up

and begin a Phase II study after the maximum dose level is determined.

The study was funded by Verismo Therapeutics.

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