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Researchers announce latest results of investigational cellular therapy

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The latest results of clinical trials of more than 125 patients testing an investigational personalized cellular therapy known as CTL019 will be presented by a University of Pennsylvania research team at the 56th American Society of Hematology Annual Meeting and Exposition. Highlights of the new trial results will include a response rate of more than 90 percent among pediatric acute lymphoblastic leukemia patients, and results from the first lymphoma trials testing the approach, including a 100 percent response rate among follicular lymphoma patients and 45 percent response rate among those with diffuse large B-cell lymphoma.

"We have now treated more than 125 patients in our trials of the chimeric antigen receptor (CAR) therapy CTL019, and with each patient, we learn more and more about the potential of this therapy," said the research team's leader, Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine in Penn's Perelman School of Medicine, and director of Translational Research in the Abramson Cancer Center. "We are continuing to refine our approach to ensure the best outcomes for patients who may be eligible for this experimental therapy, and we hope our findings will contribute to the emerging field of cellular therapy as a whole."

This personalized cellular therapy approach begins with patients' own immune cells, collected through a procedure similar to dialysis. The cells are then engineered in a laboratory and infused back into patients' bodies after being trained to hunt and kill their cancer cells. All patients who

enroll in the trials have cancers that have progressed despite multiple conventional therapies.

Updated results of a CTL019 trial for children and young adults with relapsed, treatment-resistant acute lymphocytic leukemia who were treated at the Children's Hospital of Philadelphia (Abstract #380) includes data on 39 patients. The findings, which will be presented by Stephan Grupp, MD, PhD, the Yetta Deitch Novotny Professor of Pediatrics and director of Translational Research in the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia, build on the team's report on 25 pediatric and five adult patients which was published in the *New England Journal of Medicine* in October.

Thirty six of 39 children (92 percent) achieved a complete response (CR) after receiving an infusion of the modified cells. After a median follow-up of six months, more than two-thirds (70 percent) of children who responded remained in remission and 75 percent were alive, including the first patient to receive the therapy, in the spring of 2012. These results were achieved with only 3 of the patients going on to receive stem cell transplant while in remission.

All pediatric patients who responded to the therapy experienced a cytokine release syndrome (CRS) within a few days after receiving their infusions - a key indicator that the engineered cells have begun proliferating and killing tumor cells in the body, but also a known potentially lethal type of toxicity. Patients who experience a CRS typically have varying degrees of flu-like symptoms, with high fevers, nausea, muscle pain, and sometimes, low blood pressure and breathing difficulties. Some patients require treatment with anti-cytokine agents and steroids to manage these symptoms.

The research team will also report the first results of a CTL019 study of patients with relapsed or refractory non-Hodgkin lymphomas (NHL)

(Abstract #3087). In patients with follicular lymphoma (FL) or diffuse large B cell lymphoma (DLBCL) who received infusions of CTL019, assessments at three months after treatment revealed that all five FL patients (100 percent) and five out of 11 DLBCL patients (45 percent) responded to the therapy, including complete responses in four patients (80 percent) with FL and four patients (36 percent) with DLBCL. All patients who received infusions developed varying degrees of CRS. The longest complete response durations are ongoing, at 8.8 months for DLBCL and 7.4 months for FL; all other responses continue, as well. The findings will be presented by Jakub Svoboda, MD, an assistant professor of Medicine in the Abramson Cancer Center, on behalf of the Lymphoma Program under the leadership of the study's principal investigator, Stephen J. Schuster, MD, the Robert and Margarita Louis-Dreyfus Associate Professor of Chronic Lymphocytic Leukemia and Lymphoma.

In updated results of the Penn research team's Phase II dose optimization study of patients with chronic lymphocytic leukemia (CLL) who were treated with CTL019 (Abstract #1982), 10 out of 24 (42 percent) patients responded to the cellular therapy. Of those, five (21 percent) had complete responses, and five (21 percent) had partial responses. After a median follow-up of nine months, overall survival was 68 percent. Eleven patients, including five who responded to the therapy, experienced a cytokine release syndrome (CRS), though the severity of CRS did not correlate with response.

Patients in this trial were randomized to receive two different doses of modified cells. The findings revealed no association between with the amount of cells and greater toxicities, but the researchers say it is still unclear if the amount of cells will affect the response of CLL to CTL019. These results will be presented by David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in Penn's Abramson Cancer Center.

The Penn researchers will also report on three adult ALL patients who died due to refractory CRS within several weeks after receiving infusions of CTL019 (Abstract #2296). These patients were found to have significant concomitant infections: one patient had influenza, a second patient had pseudomonas sepsis and pneumonia, and a third patient had stenotrophomonas sepsis. These significant concomitant infections may have exacerbated the CRS. These findings will be presented by Noelle Frey, MD, MSCE, an assistant professor of Medicine in the Abramson Cancer Center. A companion abstract (Abstract #1983) also presented by Dr. Porter outlines a novel CRS grading system, developed from data on the first 125 patients to receive CTL019, to better identify CRS severity and more accurately guide timing of medication and other therapies to care for patients who develop this side effect. Results from all trials of CTL019 indicate that CRS tends to be most severe among ALL patients with the highest tumor burden.

In July 2014, the U.S. Food and Drug Administration granted CTL019 its Breakthrough Therapy designation for the treatment of relapsed and refractory adult and pediatric ALL, a step which is intended to expedite the development and review of new medicines that treat serious or life-threatening conditions, if a therapy has demonstrated substantial advantages over available treatments. CTL019 is the first personalized cellular therapy to receive the designation.

Provided by University of Pennsylvania School of Medicine