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Penn Clinical Briefing™

Advances in Cancer Immunotherapy for Lymphoma

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CLINICAL BRIEFING™

Division of Hematology Oncology • Translational Research Program • Abramson Cancer Center

Advances in Cancer Immunotherapy for Lymphoma

The status of Penn Medicine's Abramson Cancer Center as an international leader in cancer immunotherapy was re-confirmed with the August 2017 landmark Food and Drug Administration (FDA) approval of Kymriah (tisagenlecleucel, formerly CTL-019) for the treatment of refractory/relapsing (r/r) acute lymphoblastic leukemia (ALL) in children and young adults. Kymriah is the first personalized chimeric antigen receptor (CAR) T cell therapy to be FDA approved for any indication, and the first product to emerge from the Center for Advanced Cellular Therapeutics (CACT), the partnership between Penn Medicine and Novartis AG.

In October, Kite Pharmaceutical's Yescarta (axicabtagene ciloleucel) was approved by the FDA for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). While Yescarta was the first to be approved for this indiciation, Penn Medicine is a leading source of CART therapy research in lymphoma. At the Abramson Cancer Center, Stephen J. Schuster, MD, was a lead investigator for both the single-site study treating various types of non-Hodgkin lymphoma with follow-up extending beyond two years (UPCC 13413), the results of which were recently published in the *New England Journal of Medicine*, and the JULIET trial, a global, multi-center trial of tisagenlecleucel in r/r DLBCL.

UPCC 13413, a Phase IIa study using autologous chimeric antigen receptor modified T-cells targeting CD19 (referred to as CART-19) in non-Hodgkins Lymphoma patients, treated 28 patients at the University of Pennsylvania. These patients had relapsed or refractory disease to chemotherapy and immunochemotherapy and had either undergone or were not eligible for curative treatment options (such as autologous or allogeneic stem cell transplant). Of these 28 patients, 14 had CD19+ diffuse large B-cell lymphoma and an equal number had follicular lymphoma. All patients received autologous CTL019 CD19-directed CAR-T cells. In total, 18 had a response (64%). Complete remission occurred in 6/14 patients (43%) with diffuse large B-cell lymphoma and in 10/14 patients (71%) with follicular lymphoma. At a median follow-up of 28.6 months, 57% of all patients remained progression-free. Of patients with diffuse large B-cell lymphoma who had a response and patients with follicular lymphoma who had a response, 86% and 89%, respectively, maintained their response at the median follow-up, 28.6 months.

The JULIET trial (NCT02445248), treated 81 patients who were evaluable for response. In total, 40% of patients had a complete response after treatment with tisagenlecleucel, with 32% of patients continuing to have a complete response at three months and 30% at six months. The results of the JULIET trial, most recently presented at the 59th American Society of Hematology Meeting and Exposition (abstract #577), confirmed the results of the UPCC 13413 DLBCL sub-group in a global clinical trial.

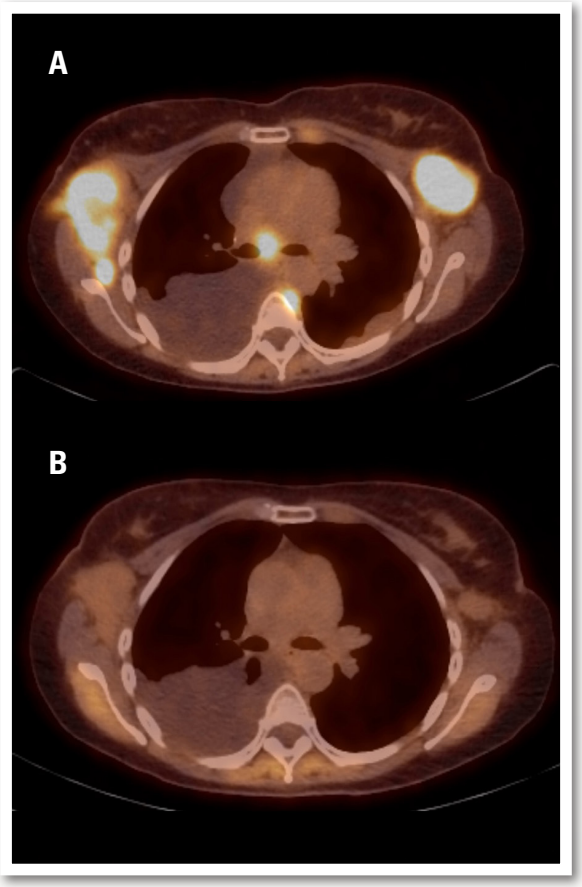

Figure 1: Follicular Lymphoma in a 60-year-old woman 20 days prior to CAR T infusion (A) and 29 days after CAR T infusion (B).

CASE STUDY

Mrs. V, a 60 year old woman, first presented to Penn with a seven year history of follicular lymphoma. She was previously treated with eight lines of therapy, including chemotherapy, radiation, and immunotherapy with the longest remission lasting about 2.5 years. She presented to Penn to be evaluated for the tisagenlecleucel trial (UPCC 13413). At that time, she had chronic neutropenia requiring G-CSF as well as recurrent chylous pleural effusion requiring Pleurex catheter chest tube drainage. Following T-cell collection, she was treated with with low-dose mantle field radiation as lymphodepleting therapy. She continued to have significant pleural effusions.

Following the administration of tisagenlecleucel, she developed a fever, neutropenia, and laryngospasm which required hospitalization for 15 days.

Early response assessment by PET/CT imaging at one month showed no evidence of lymphoma. Mrs. V's pleural effusions resolved at 3 months' post-infusion; at that time, CT imaging and bone marrow examination confirmed complete response to CAR T-19 therapy. She has remained in complete remission for more than 3 years.

Further Innovations in Cancer Immunology at the Abramson Cancer Center

Immune checkpoint inhibitors have shown great promise for the treatment of a variety of cancers, according to reports from the ACC, where researchers have achieved beneficial responses from the combination of two checkpoint inhibitors in patients with triple-negative breast cancer, non-small cell lung cancer, squamous cell cancer of the head and neck, and advanced renal cell cancers, among others.

Cancer vaccines remain an important and growing area of cancer research at the ACC, as well. These agents contain antigens or modified or inactive cancer cells that provoke a response by inducing the immune system to recognize cancer cells as foreign. At this time, vaccines for metastatic breast cancer, primary ovarian cancer, fallopian tube cancer and primary peritoneal cancer are being investigated at the ACC.

About Referring Patients to the Abramson Cancer Center

For information regarding cancer clinical trials at the ACC, please visit the Oncolink Clinical Trial Matching and Referral Service at: **www.oncolink.org/treatment/trials.html**.

A list of currently recruiting adoptive immunotherapy trials in various cancers and HIV can be found at: **https://pathbio.med.upenn.edu/cvpf/site/about/trials**.

ACCESS

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FACULTY TEAM

Investigators with Penn Hematology/Oncology are focused on translating laboratory work into novel therapies and practice-changing discoveries. The scope of Penn's hematology and medical oncology clinical research enterprise is very broad, spanning all phases of clinical research, including pre-clinical work and discovery, phase 1 and 2 studies and leadership of national phase 3 trials intended to change the standard of care.

Conducting Clinical Studies in Cancer Immunotherapy at Penn Medicine

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