TPS7095 **Poster Session**

Sequencing-guided chemotherapy optimization using real-time evaluation in newly diagnosed DLBCL with circulating tumor DNA: SHORTEN-ctDNA (NCT06693830).

Hua-Jay Jeffery Cherng, Stephanie Meek, Cheng-Shiun Leu, Beatriz Corradini, Seda S. Tolu, Jennifer Amengual, Barbara Pro, David M. Kurtz; Columbia University Irving Medical Center, New York, NY; Foresight Diagnostics, Boulder, CO; Columbia University, New York, NY; Columbia University Medical Center, New York, NY; Foresight Diagnostics, Inc., Boulder, CO

Background: Circulating tumor DNA (ctDNA) is a clinically valid tool for detection of measurable residual disease (MRD) in patients with diffuse large B-cell lymphoma (DLBCL). Phased variant enrichment and detection sequencing (PhasED-seq), which uses multiple somatic mutations on individual DNA fragments, improves upon first-generation single nucleotide variant-based MRD tests with improved sensitivity (Kurtz et al. *Nat Biotech* 2021). To utilize ctDNA-MRD testing in a clinical setting to guide treatment decisions, the ability to test and report in a real-time manner is required. However, the feasibility of real-time MRD testing using the PhasED-seq-based Foresight CLARITY platform to inform treatment decisions has yet to be established. Therapy de-escalation after 4 cycles of standard R-CHOP therapy was non-inferior and less toxic than 6 cycles for patients with DLBCL with no baseline risk factors (Poeschel et al. *Lancet* 2019). Identification of patients who are ideal candidates for de-escalation based on treatment response remains a challenge as radiographic imaging has a high false-negative rate (Le Gouill & Casanovas, *Blood* 2017). ctDNA-MRD has a higher sensitivity and may be a better test to guide dose de-escalation decisions in patients with DLBCL. This feasibility study will have two co-primary objectives: (1) to evaluate the feasibility of ctDNA sequencing for real-time guidance of clinical decision making during frontline therapy for DLBCL; and (2) to determine the outcomes of patients with newly diagnosed DLBCL who become undetectable for ctDNA and demonstrate a radiographic complete response (CR) during standard frontline therapy and discontinue chemotherapy early. **Methods:** This single-center investigator-initiated study began enrolling in November 2024 and is enrolling patients (N=32) with newly diagnosed stage II-IV, CD20+ DLBCL with measurable disease. Patients will receive 4 cycles of standard-of-care therapy (R-CHOP or R-pola-CHP). Positron emission tomography/computed tomography (PET/CT) scans will be performed after cycle four (C4) and at the end of therapy. Additionally, whole blood samples will be drawn on C4 day 1 (C4D1) and shipped to Foresight Diagnostics, Inc. (Boulder, CO) for real-time MRD testing. Patients who experience a CR on iPET4 and have undetectable ctDNA on C4D1 will de-escalate therapy and receive rituximab alone for C5-6. Patients not meeting these response criteria or with unsuccessful real-time MRD testing for any reason will continue standard therapy for the remaining cycles. MRD will also be evaluated in a batched manner at the end of the study at other timepoints to evaluate the kinetics of ctDNA as well as correlation with clinical outcomes. The primary efficacy endpoint is the EOT CR rate on PET/CT performed 10-14 weeks after C6D1 in the patients who receive de-escalated treatment. Clinical trial information: NCT06693830. Research Sponsor: Foresight Diagnostics, Inc.; National Cancer Institute; Conquer Cancer, the ASCO Foundation.