Sequencing-guided cHemotherapy Optimization Using Real-Time Evaluation in Newly Diagnosed DLBCL With Circulating Tumor DNA: SHORTEN-ctDNA (NCT06693830)

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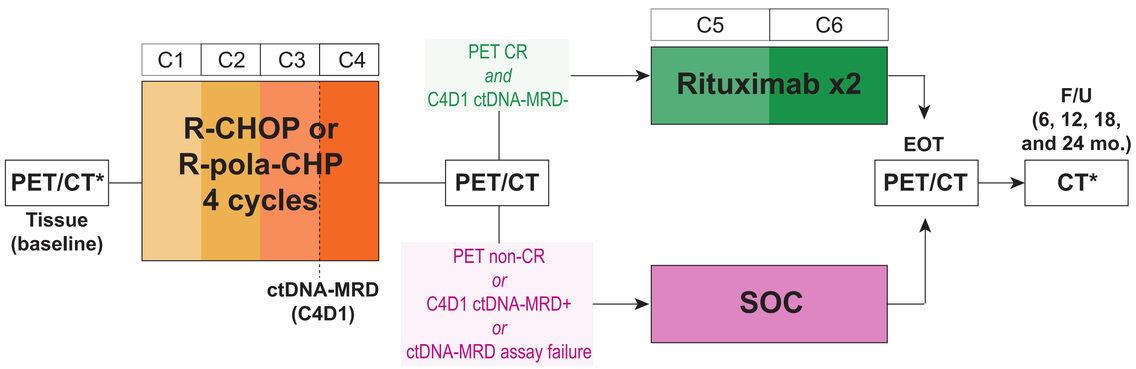
Background

- 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).[1]
- 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.[2]
- Therapy de-escalation after 4 cycles of standard R-CHOP was non-inferior and less toxic than 6 cycles for patients with DLBCL with no baseline international prognostic index (IPI) risk factors.[3]
- ctDNA-MRD has a higher sensitivity than PET/CT and could potentially be used to guide dose de-escalation in patients with DLBCL based on interim treatment response.[2,4-5]
  - A previous study showed that achieving undetectable ctDNA-MRD after the first 3 cycles of frontline therapy was highly prognostic for progression-free survival,[6] indicating that some patients may be currently over-treated and de-escalation could be warranted.
- This feasibility study has 2 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 (CUIMC) investigator-initiated study began enrolling in December 2024 and is enrolling patients (N=32) meeting the following inclusion criteria:
  - Newly diagnosed, histologically-confirmed stage II-IV CD20+ DLBCL with any IPI score
  - Planned for 6 cycles anthracycline-based therapy with standard dosed R-CHOP or R-pola-CHP without consolidative radiation
  - Measurable disease on cross section imaging ≥1.5 cm in longest diameter
- Patients can be enrolled after pre-phase therapy and/or a single cycle of rituximab-chemotherapy.
- Patients with transformed indolent lymphoma, double-hit lymphoma, primary mediastinal BCL, and secondary CNS lymphoma are excluded from the study.
- The study schema is presented in Figure 1.

Figure 1. Treatment and Response Assessment with ctDNA-Guided Treatment De-Escalation During Frontline DLBCL Therapy



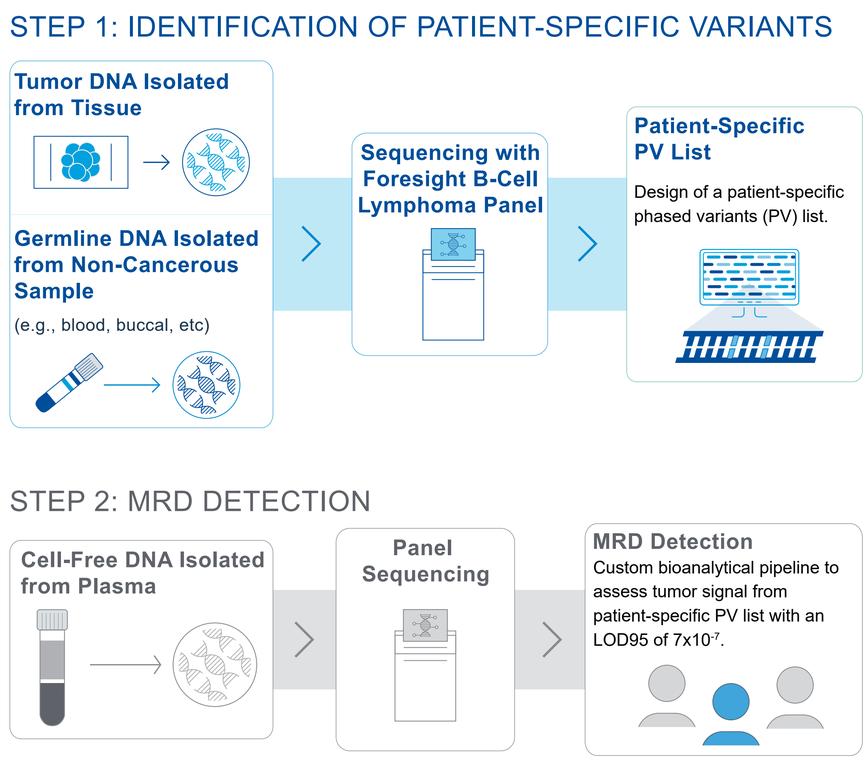
*PET/CT and CT scans can be performed interchangeably per clinician discretion for the screening assessment and during follow up. CR: complete response on iPET4 by Lugano criteria; EOT: end of therapy; F/U: follow-up; PET/CT: positron emission tomography/computed tomography; SOC: standard of care.

- Whole blood samples will be drawn on cycle 4 day 1 (C4D1) and shipped to Foresight Diagnostics, Inc. (Boulder, CO) for real-time MRD testing (Figure 2).
- Patients who experience a CR on iPET4 and have undetectable ctDNA on C4D1 will de-escalate therapy and receive rituximab alone for C5-6.

Figure 2. Overview of ctDNA-MRD Testing

Real-time MRD testing will be performed using Foresight CLARITY. MRD testing consists of 2 steps: (1) development of a patient-specific phased variant (PV) list and (2) MRD detection using that list. PV list generation is performed using a tumor tissue sample and a germline sample to identify PVs present only in the tumor and not the germline.

PVs are 2 or more mutations occur in *cis* (i.e. on the same strand of DNA).[2]



- Patients not meeting these response criteria or with unsuccessful real-time MRD testing will continue standard therapy.
- 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 feasibility endpoint is the success rate of real-time ctDNA-MRD testing.
  - Success is defined as C4D1 sample collected and MRD result available within 28 days of C4D1.
- 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 (estimated n=13); the expected EOT CR rate is at least 94%.

Conclusions

- Enrollment began in December 2024, with 5 patients being enrolled and 2 of those patients completing C4D1 ctDNA-MRD testing so far.
  - Based on projected enrollment, the study is expected to complete enrolling in early 2027.
- This study will provide critical information on the feasibility of utilizing real-time ctDNA-MRD testing in clinical treatment of patients with DLBCL, specifically to inform treatment de-escalation strategies.

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CONQUER CANCER® THE ASCO FOUNDATION

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