Toward a Paradigm Shift in Personalized Therapies for DLBCL Using Liquid Biopsies

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As our most common lymphoma subtype, diffuse large B-cell lymphoma (DLBCL) is highly curable for many patients with first-line chemoimmunotherapy, yet relapse remains the main driver of mortality. For most haematologists and oncologists who manage this disease, the uncomfortable reality is that we still make most decisions from a single diagnostic biopsy and intermittent PET/CT snapshots, then default to observation after an apparent complete response—even though most clinically meaningful residual disease can persist below radiographic thresholds and outside the spatial reach of invisibly accessible tumor tissue. Conversely, for patients with apparent radiographic evidence of residual burden at end-of-therapy after frontline induction, current PET/CT evaluations have soberingly low positive predictive value, requiring invasive tissue diagnosis to confirm frank residual or recurrent tumors.

Auspiciously, circulating tumor DNA (ctDNA) provides a quantitative, repeatable, noninvasive window into both tumor genetics and tumor burden. Various methods to interrogate ctDNA such as first-generation techniques such as CAPP-Seq and Ig-HTS relying on capture-based sequencing such as CAPP-Seq enable biopsy-free genotyping and molecular subtype inference from plasma while simultaneously yielding an absolute disease-burden measurement. When sampled serially during treatment, ctDNA kinetics behave like a real-time pharmacodynamic readout of chemosensitivity. In large cohorts, baseline ctDNA is detectable in nearly all DLBCL patients. Early molecular response (EMR), defined as a ≥2-log decline in ctDNA after one cycle of therapy, and major molecular response (MMR), defined as a ≥2.5-log decline after two cycles, stratify event-free and progression-free survival independent of IPI and interim PET, creating a rational window for response-adaptive escalation or de-escalation, as being tested in ongoing trials.

A key next inflection point is end-of-therapy minimal residual disease (MRD), where first-generation assays often plateau. Phased-variant approaches such as PhasED-Seq suppress technical error by requiring concordant non-reference events on the same DNA molecule, enabling parts-per-million sensitivity and making MRD a trigger for action. This concept is now being tested prospectively in the randomized pivotal ALPHA3 trial, which applies an investigational ctDNA-MRD assay at completion of standard first-line therapy to identify MRD-positive patients and randomize them to observation versus a single infusion of the off-the-shelf allogeneic anti-CD19 CAR-T product cemacabtagene ansegedleucel (cema-cel), aiming to prevent clinical relapse while disease burden is lowest.

In this talk, I will synthesize the existing evidence base and propose a noninvasive biomarker-driven framework—baseline plasma genotyping, on-treatment molecular response, and MRD-guided consolidation—while addressing practical hurdles (turnaround time, clonal hematopoiesis, and assay harmonization) required to move DLBCL management from reactive salvage to proactive prevention.