Abstract: P1261

Title: SERIAL MONITORING OF CIRCULATING TUMOR DNA WITH AN ULTRASENSITIVE ASSAY FACILITATES OUTCOME PREDICTION IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA TREATED WITH MODERN AGENTS

Abstract Type: Poster Presentation

Topic: Lymphoma biology & translational research

Background:

Various novel agents have become available for patients with relapsed/refractory (rr) diffuse large B-cell lymphoma (DLBCL). However, identifying which patient will ultimately respond to a certain agent remains a challenge to be addressed. Circulating tumor (ct)DNA has been shown to be a promising biomarker for risk stratification and response assessment in previously untreated DLBCL as well as rrDLBCL following chimeric antigen receptor (CAR) T-cell therapy (Sworder et al, 2023).

Aims:

1. Is ctDNA-based Minimal Residual Disease (MRD) detection applicable to modern agents of DLBCL beyond CAR-T cells?
2. Is it applicable in a real-world, multicentric setting in heavily pretreated patients?
3. How do we define ctDNA-based MRD response when using an ultrasensitive assay?

Methods:

We applied our ultrasensitive ctDNA sequencing approach (Sobesky et al, 2021; Heger et al, 2023) to 326 blood samples from 88 patients with rrDLBCL with a total number of 131 treatment lines at two academic centers in Germany. Samples were collected pre-treatment and at six pre-determined timepoints after treatment.

Results:

Treatments included CAR-T cell therapy (68, 52%), immunochemotherapy and antibody-drug conjugate combinations (36, 27%), high-dose chemotherapy with autologous stem cell transplant (12, 9%), allogenic transplant (5, 4%), radiotherapy (4, 3%) and bispecific antibodies (3, 2%). 3 patients (2%) died before treatment initiation. Pre-treatment ctDNA in log haploid genome equivalents (hGE)/mL significantly correlated with LDH ($R = 0.61$, $p<0.0001$) and IPI risk scores ($p=0.00062$). First, we defined 3 groups based on pre-treatment ctDNA log hGE/mL levels: low- (0-1.65), intermediate- (1.65-2.59) and high-risk (>2.59) with respective 12-months overall survival (OS) of 68%, 51% and 30% ($p=0.0005$). Second, assessing early ctDNA response 14-21 days after treatment initiation, we identified 3 groups based on ctDNA log-fold reduction: strong- (>1.5), partial- (1.5-0.23) and insufficient response (<0.23 or >0) with respective 12-months OS of 73%, 60% and 23% ($p<0.0001$). In multivariate analysis, both pre-treatment ctDNA (HR 1.89 per log hGE/mL, 95% CI 1.24-2.88, $p=0.0029$) and ctDNA response after 14-21 days (HR 2.14 per log-fold reduction, 95% CI 1.37-3.35, $p=0.0008$) were independent outcome predictors for OS. We determined the limit of detection (LOD) of our validated assay to be an absolute MRD level of 5.93 x10-6. Patients with MRD below LOD were classified as MRD negative. Patients that reached MRD-negativity at any timepoint had significantly longer 18-months OS of 77% compared to 33% for never MRD negative patients (HR 4.61, 95% CI 2.38-8.92, $p<0.0001$). 18-months progression-free survival (PFS) was 51% for MRD-negative versus 5% for MRD-positive cases (HR 4.32, 95% CI 2.46-7.61, $p<0.0001$). (**Fig. 1**). Never reaching MRD-negativity was an independent outcome predictor for poor OS and PFS in multivariate analysis including IPI and pre-treatment ctDNA (OS: HR 4.79, 95% CI 2.39-9.59, $p<0.0001$; PFS: 4.45, 95% CI 2.39-8.30, $p<0.0001$). Results were comparable to a subgroup analysis of patients receiving CAR-T treatment. We observed similar trends regarding 12-months OS (MRD negative 3/4, 75% vs. MRD positive 1/6, 18%) and 12-months PFS (MRD negative 2/4, 50% vs. MRD positive

1/6, 18%) for high-dose chemotherapy with autologous stem cell transplant, yet due to small sample size, analysis was limited.

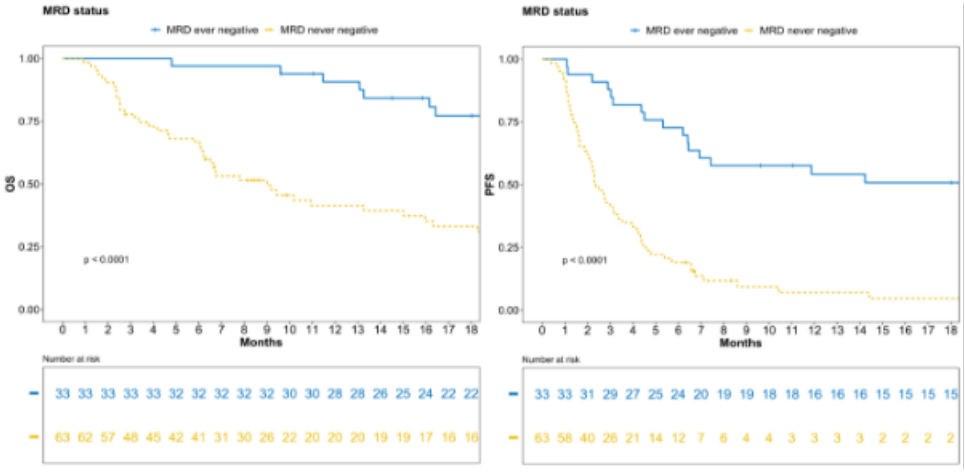

Figure 1: Kaplan-Meier curve showing OS and PFS stratified by MRD status.

Summary/Conclusion

Our findings underscore the potential of ctDNA-based MRD monitoring to guide early treatment decisions to improve outcome in real-world rrDLBCL patients across modern agents. Employing our validated ultrasensitive ctDNA sequencing approach, we identify both pre-treatment ctDNA levels and early response kinetics as prognostic for outcome prediction. Tackling the unanswered question of how to use ctDNA as a biomarker in DLBCL with ultrasensitive assays, we propose developing prognostic models taking both pre-treatment ctDNA and early-response into account. In addition, reaching MRD negativity with ultrasensitive assays is associated with an excellent outcome when rrDLBCL is treated with modern agents (**Fig. 1**).

Keywords: ctDNA, Diffuse large B cell lymphoma, Minimal residual disease (MRD), liquid biopsy