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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL - MOLECULAR AND GENETIC

Lymphovista HL - a Validated Assay for Genotyping and MRD Assessment in Hodgkin Lymphoma

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Introduction

Circulating tumor (ct)DNA sequencing has significantly advanced genotyping and enabled minimal residual disease (MRD) assessment in patients with Hodgkin Lymphoma (HL) (Spina *et al.*, Blood, 2018; Sobesky *et al.*, Med, 2021; Alig *et al.* Nature, 2024; Heger *et al.* JCO, 2024). However, current ctDNA sequencing assays are neither technically validated nor optimized for HL. To overcome this limitation, we designed and validated LymphoVista HL, a ctDNA sequencing assay for ultrasensitive genotyping and MRD assessment in patients with HL.

Methods

LymphoVista HL targets 37 genes covering approx. 83 kbp of the human genome and utilizes multiple methods of sequencing error suppression including duplex barcodes. The incorporation of various non-coding regions affected by highly frequent genetic alterations in HL facilitates ultrasensitive MRD assessment.

We first performed a technical validation study with contrived samples to evaluate sensitivity, specificity, linearity, accuracy, limit of detection (LoD), and precision. Next, we performed a blinded clinical validation study comprising 72 patients with available plasma samples that were treated in the GHSG HD21 trial (Borchmann *et al.*, Lancet, 2024) which established superiority of BrECADD over eBEACOPP in patients with advanced-stage HL. Patients were selected in a case-cohort design including all patients with available plasma samples and a documented progression-free survival (PFS) event as an endpoint at data cut-off. MRD was assessed after two cycles of treatment (MRD-2) to evaluate the prognostic value of MRD-2 concerning PFS. MRD-2 positivity was defined as measurement above LoD. Subgroup analyses were performed for patients with positive vs. negative PET-2 (after two cycles of treatment) as well as for patients treated with BrECADD vs. eBEACOPP. PFS was analyzed using the Kaplan-Meier method and Cox-proportional hazards models were used for survival comparisons. All survival analyses were weighted to correct for event enrichment.

Results

In the technical validation study, LymphoVista HL achieved 91.27% sensitivity and 99.99% specificity for de-novo variant identification of variants ≥ 0.5 % mutated allele frequency (mAF). Linearity analysis confirmed a linear relationship between detected mAF and ground truth mAF (R=0.98, $p<0.0001$). LoD for MRD assessment was determined to be 6.54×10^{-6}. Specificity, sensi-

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tivity, and accuracy were 100% for MRD levels > 1.76×10^{-5}. A precision study assessing the contribution of varying reagent lots, laboratory technicians, and day of assay performance to variation in results revealed robust reproducibility and repeatability even at very low MRD levels.

In the clinical validation study, patients selected with the case-cohort approach were representative of the full HD21 trial population regarding clinical characteristics including age, sex, clinical stage, and IPS. The median follow-up was 50 months. Based on the weighted analysis, the MRD-2 positive rate was 18.5%.

4-year PFS was significantly longer in MRD-2 negative patients as compared to MRD-2 positive patients (95.3% (95%-CI: 88.7-100) vs. 72.2% (95%-CI: 41.5-100), HR 6.9 (95%-CI: 4.5-10.6), $p < 0.0001$).

In subgroup analyses, MRD-2 remained prognostic for patients treated with BrECADD (4-year PFS MRD-2 positive vs. negative: 97.4 vs. 52.0%, HR 25.4 (95%-CI: 12.5 - 51.7), $p < 0.0001$), for patients treated with eBEACOPP (4-year PFS MRD-2 positive vs. negative: 92.4 vs. 80.0%, HR 2.8 (95%-CI: 1.6 - 4.9), $p = 0.0002$), as well as for patients with positive PET-2 (4-year PFS MRD-2 positive vs. negative: 87.7 vs. 63.7%, HR 3.5 (95%-CI: 2.0 - 6.0), $p < 0.0001$), and patients with negative PET-2 (4-year PFS MRD-2 positive vs. negative: 98.4 vs. 81.4%, HR 13.2 (95%-CI: 6.1 - 28.4), $p < 0.0001$).

Conclusion

Here, we present LymphoVista HL, a validated, highly accurate, reproducible ctDNA sequencing assay for ultrasensitive genotyping and MRD assessment in patients with HL. LymphoVista HL is highly predictive of outcomes even if HL patients are treated with highly effective, contemporary regimens.

Disclosures Ferdinandus: *Takeda Oncology:* Honoraria; *Roche Pharma:* Honoraria. **Borchmann:** *Takeda Oncology, BMS, Roche, MSD, Celgene, Miltenyi Biotech, Gilead, Abbvie:* Honoraria; *Takeda Oncology, BMS, Roche, Amgen, Miltenyi Biotech, Gilead, MSD:* Consultancy; *Takeda Oncology, MSD, Incyte:* Research Funding. **Heger:** *Incyte:* Honoraria, Research Funding; *Roche:* Honoraria; *Novartis:* Other: travel support, Research Funding; *Miltenyi Biotec:* Consultancy; *SOBI:* Consultancy, Honoraria, Other: travel support; *SERB Pharmaceuticals:* Consultancy, Honoraria, Other: travel support; *Genmab:* Consultancy. **Borchmann:** *Galapagos:* Consultancy; *Liqomics:* Current equity holder in private company.

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