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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Distinct Circulating Genomic Features of Classical Hodgkin Lymphoma of Older Adults

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Introduction: Despite significant progress in curing younger patients with classical Hodgkin lymphoma (cHL), older patients continue to have substantially inferior outcomes. The bimodal distribution of age at cHL diagnosis has suggested distinct underlying pathogenesis in older adults. For example, among older patients where EBV+ disease is more prevalent, EBV+ status is associated with worse outcomes, unlike younger patients where it confers more favorable prognosis (Keegan, JCO 2005). The reasons for this disparity remain enigmatic. To address these challenges, we used circulating tumor DNA (ctDNA) profiling, enabling noninvasive genotyping, risk stratification, and classification into distinct molecular subtypes (Spina, Blood 2018; Alig, ASH 2022). We leveraged several non-invasive techniques to systematically characterize the genomic peculiarities of elderly cHL patients distinguishing them from younger counterparts, with special attention to EBV status.
Methods: We comprehensively profiled newly diagnosed cHL patients from 3 prospective clinical trials: LYSA-PVAB (NCT02414568) for subjects ≥60 years (Ghesquières, ASH 2019), AHL2011 (NCT01358747) for patients aged 16-59 years with advanced cHL, and BIO-LYMPH (NCT04417803) for patients ≥18 years. We used age ≥60 as a threshold for stratification of older versus younger patients, a common cutoff in clinical trials. We identified somatic single nucleotide variants using CAPP-Seq (Newman et al, Nature Biotech 2016); and analyzed copy number alterations with CANARy (Chabon, Nature 2020). Patients were categorized into high vs low pretreatment ctDNA levels using a predefined threshold (2.5 log hGE/mL; Kurtz, JCO 2018). We determined EBV status using EBER and/or LMP1 staining of FFPE tumor tissue or plasma EBV levels (>32 copies/mL) by VirCAPP-Seq (Garofalo, ASH 2022).
Results: A total of 215 newly diagnosed cHL patients were evaluable, with a median age of 51 years, and 35% being older (≥60 years). In this cohort, 82% had advanced stage disease, 68% had high IPS (≥3), and 57% had extra nodal involvement. At 4-year follow-up, OS and PFS were 84% and 74%, respectively.
At presentation, older patients (≥60y) had more advanced stage (93% vs 73%, p<0.001), higher IPS (78% vs 61%, p<0.001), and greater EBV+ prevalence (63% vs 36%, p<0.001). Older patients also experienced significantly more relapses (39% vs 17%, p<0.001). and mortality (29% vs 6%, p<0.001). The median pre-treatment ctDNA level was 982 hGE/mL, but not significantly different in older vs younger patients (p=0.28). Higher ctDNA levels were positively associated with risk-associated features including B symptoms (p=0.01), IPS (p<0.001), bulky disease (p=0.04), extra nodal disease (p=0.02) and correlated with TMTV (R=0.47, p<.001).
Older patients had significantly fewer somatic mutations than younger counterparts (Median 107 vs 192 SNVs within targeted genomic regions, p<0.001; **Fig. 1A top**); among older patients, EBV+ cases had even fewer mutations than EBV- counterparts

(Median 83 vs 142 SNVs, p=0.05). Older cHL cases harbored significantly more *BCL2* mutations and recurrent copy number anomalies, but had significantly fewer mutations in *STAT6, ITPKB, B2M, GNA13, PAX5* and *XPO1* among others(all p<0.05 **Fig. 1A bottom**).

The H2 genomic subtype prevalence, characterized by genomic instability as well as mutations in *TP53, KMT2D*, and *BCL2* (Alig et al, ICML 2023), was higher among older patients (56%) than younger patients (21%) (p=0.01). Older H2 cHL showed no significant difference in EBV+ status compared to H1 counterparts (p=0.9). In older patients, multivariate Cox regression (including EBV status, ctDNA, and IPS) identified EBV+ status (HR=2.2, p=0.02) as an independent predictor of worse PFS and DFS outcomes (HR=2.5, p=0.02 and HR=2.7, p=0.04). When older cHL patients were stratified by baseline ctDNA level and EBV status, high-risk cases (EBV+ and ctDNA High) had particularly poor outcomes in terms of both PFS and DFS (**Fig. 1B**).

Conclusion: Older cHL patients exhibit unique genomic characteristics compared to younger counterparts, including more prevalent H2 tumor genetic subtype and EBV positivity. Identifying of a high-risk subgroup of older cHL underscores the importance of ctDNA levels and EBV status. We envision future trials of personalized biomarker driven treatment strategies could therapeutically target this risk, including by PD1 blockade.

Disclosures Alig: *Takeda:* Honoraria. **Shahrokh Esfahani:** *Foresight Diagnostics:* Consultancy. **Kurtz:** *Foresight Diagnostics:* Consultancy, Current equity holder in private company, Current holder of *stock options* in a privately-held company, Patents & Royalties: Patents Pertaining to circulating tumor DNA licensed to Foresight Diagnostics. **Hamilton:** *Kite Pharma:* Other: Advisory Board. **Casasnovas:** *Abbvie:* Consultancy, Honoraria; *ADC Therapeutics:* Consultancy, Honoraria; *AMGEN:* Consultancy, Honoraria; *Astra Zeneca:* Consultancy, Honoraria; *BEIGENE:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GILEAD/KITE:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *MSD:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *ROCHE:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *TAKEDA:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Diehn:** *Gritstone Bio:* Consultancy; *BioNTech:* Consultancy; *CiberMed:* Current holder of *stock options* in a privately-held company; *Roche:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *Illumina:* Consultancy, Research Funding; *Stanford University:* Patents & Royalties: ctDNA detection, tumor treatment resistance Mechanisms; *Novartis:* Consultancy; *Boehringer Ingelheim:* Consultancy; *Varian Medical Systems:* Research Funding; *Genentech:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *Boehringer Ingelheim:* Consultancy; *Varian Medical Systems:* Research Funding; *Foresight Diagnostics:* Current Employment, Current holder of *stock options* in a privately-held company; *Stanford University:* Patents & Royalties: ctDNA detection, tumor treatment resistance Mechanisms. **Ghesquieres:** *Gilead, Roche, Bristol Myers Squibb, AbbVie, Novartis:* Honoraria; *Gilead, Roche:* Consultancy. **Alizadeh:** *Celgene:* Consultancy, Research Funding; *Janssen Oncology:* Honoraria; *Gilead Sciences:* Consultancy, Other: Travel, accommodations and expenses; *Roche:* Consultancy, Honoraria, Other: Travel, accommodations and expenses; *Foresight Diagnostics:* Consultancy, Current holder of *stock options* in a privately-held company; *Syncopation Life Sciences:* Current holder of *stock options* in a privately-held company; *Forty Seven:* Current holder of *stock options* in a privately-held company; *CiberMed:* Consultancy, Current holder of *stock options* in a privately-held company; *CAPP Medical:* Current holder of *stock options* in a privately-held company; *Lymphoma Research Foundation:* Consultancy; *Stanford University:* Patents & Royalties: ctDNA detection.

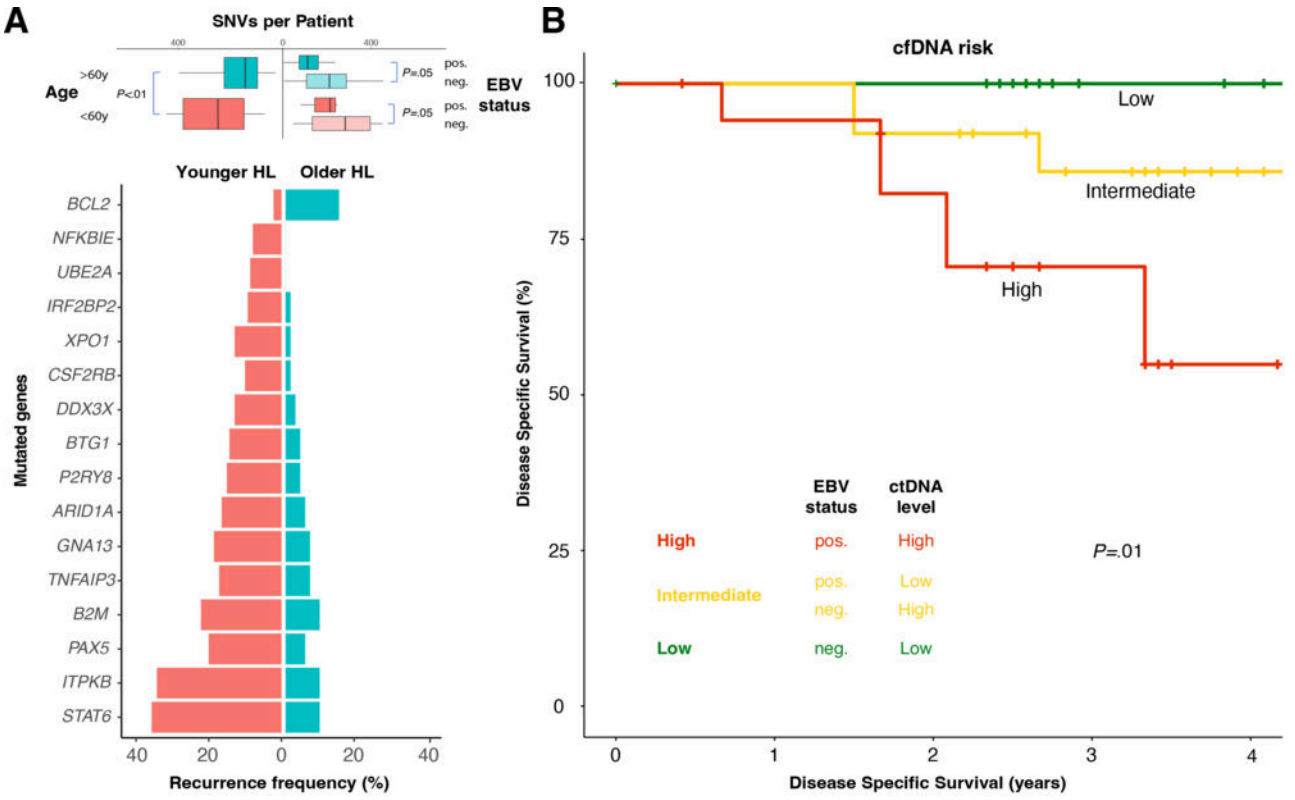

Figure: (A) Older (≥60; turquoise) cHL patients have significantly fewer mutations in cfDNA than younger (orange) patients (top left panel), regardless of EBV status (top right panel). EBV+ tumors harbor significantly fewer mutations than EBV- tumors (top right panel), regardless of age. Recurrently mutated genes differ significantly in frequency (all Fisher p<0.05) between older and younger patients (bottom). (B) Kaplan Meier plot illustrates significant stratification of Disease Specific Survival in older (≥60) patients, when using baseline cfDNA features including pre-treatment ctDNA level (high vs low using a predefined threshold), and EBV status, to define 3 risk groups.

Figure 1

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