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ORAL ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

STAG2/LMO2 Gamma-Delta ($\gamma\delta$) T-ALL: Identification and Characterization of an Extremely High Risk Group of T-ALL in the Very Young

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Background
The prognosis of pediatric T-cell acute lymphoblastic leukemia (T-ALL) has improved with minimal residual disease (MRD)-stratified therapy, however, gamma delta T cell receptor positive ($\gamma\delta$) T-ALL remains a high-risk (HR) group. Limited studies have explored the clinical and genomic characteristics of $\gamma\delta$ T-ALL, prompting us to conduct a comprehensive analysis of this entity and to identify determinants of outcome.
Methods
Through a consortium of 13 groups, we assembled a cohort of 200 patients up to 25 years of age with $\gamma\delta$ T-ALL enrolled in clinical trials between 2000 and 2018. Clinical data of patients with non-$\gamma\delta$ T-ALL enrolled on the same clinical trials were collected (n = 1,067). Complete remission (CR) was defined when bone marrow (BM) showed M1 cytomorphology and/or MRD <1% without evidence of extramedullary disease at end of induction/consolidation (EOI/EOC) and failure to achieve CR was considered treatment failure. A total of 76 $\gamma\delta$ T-ALL samples were analyzed by whole genome (WGS) and/or transcriptome (RNAseq) sequencing.
Results
The frequency of $\gamma\delta$ T-ALL was 8.0% of T-ALL cases. Patients with $\gamma\delta$ T-ALL exhibited a higher rate of poor prednisone response (P<0.01), MRD >1% at day 15 (P<0.01), at EOI (P<0.01) and EOC (P<0.01), compared to non-$\gamma\delta$ T-ALL cases. Furthermore, patients with $\gamma\delta$ T-ALL showed significantly worse 5-year event free survival (EFS, 65% v. 78%, P<0.01) and overall survival (OS,

77% vs 83%, *P*=0.048). Almost all relapses of $\gamma\delta$ T-ALL were isolated BM, while the central nervous system was the main site of relapse in non-$\gamma\delta$ T-ALL, suggesting slow treatment response and chemo-resistance to the current treatment in $\gamma\delta$ T-ALL. However, $\gamma\delta$ T-ALL showed a higher rate of toxic death during treatment (7.6% vs 4.0%, *P*<0.01), suggesting the need for different therapeutic strategies and risk-classification, rather than treatment intensification.

Strikingly, patients less than 3 years of age with $\gamma\delta$ T-ALL exhibited significantly poor EFS (33% v. 70% [3-10 years] and 73% [>10], *P*<0.01) and OS (49% v. 78% [3-10] and 82% [>10], *P*< 0.01) (**Fig. A**), a difference not observed in non-$\gamma\delta$ T-ALL. MRD >1% at EOI showed poor EFS (51% v. 96% [MRD<0.01%] and 91% [1%>MRD>0.01%], *P*<0.01) and OS (66%).

Integrated analysis of WGS and RNAseq identified enrichment of several genomic subtypes in $\gamma\delta$ T-ALL, including *STAG2/LMO2*, hyperdiploidy with recurrent gains of chromosomes 8, 10, 11, 13q and 19, a recently identified "*LMO2* $\gamma\delta$-like" subtype with distinct gene expression and *LMO2/MYC/MYCN* alterations, *TLX3*-rearranged (-R), and *PICALM::MLLT10*. No *TAL1* nor *TLX1*-R were detected. *STAG2/LMO2* was associated with age at diagnosis before 3 years, and extremely poor outcome, with 4 out of 5 cases dying within three years of diagnosis (**Fig. B**).

Of 24 *STAG2/LMO2* T-ALL (additional 5 non-$\gamma\delta$, 13 TCR unknown cases), 22 of which were diagnosed by age three. All *STAG2/LMO2* cases had alterations resulting in *LMO2* activation and *STAG2* inactivation, most commonly a single rearrangement between these two genes, and upregulation of *HBE1*, the LIN28-let7 pathway and stem cell proliferation pathways, suggesting a fetal hematopoietic origin.

STAG2 has a critical role in the maintenance of enhancer-promoter looping mediated by the cohesin complex. To examine the consequences of *STAG2* alterations, we performed integrated genomic/epigenomic analysis of the *STAG2/LMO2* (MOLT-14 and PER-117) and *STAG2* knockout (KO)/addback T-ALL lines. Chromatin loop sizes defined by H3K27ac HiChIP was highest in *STAG2/LMO2* lines compared to other T-ALL. Following restoration of *STAG2* expression in MOLT-14, *CD34* and *ID1/2* were down-regulated and H3K27ac was enriched in pathways related to T-cell differentiation. *STAG2* KO in the non- *STAG2/LMO2*, *LMO2*-activated line PF382 identified genes also upregulated in *STAG2/LMO2* primary samples, including *CDK4* and *STAG1*. *STAG2* KO lines exhibited partial compensation of STAG2 binding sites by STAG1 and upregulation of $\gamma\delta$-related genes, *RORC* and *ID1/3*. High throughput screening of 2,050 small molecules identified efficacy of HDAC, CDK and PARP inhibitors in *STAG2/LMO2* lines.

Conclusion

Very young onset $\gamma\delta$ T-ALL, but not non-$\gamma\delta$ T-ALL, is enriched for the *STAG2/LMO2* subtype and is a very high risk form of T-ALL. STAG2 loss perturbs chromatin organization and hematopoietic differentiation. Moreover, we demonstrate efficacy of novel therapeutic approaches that are needed to cure this form of leukemia.

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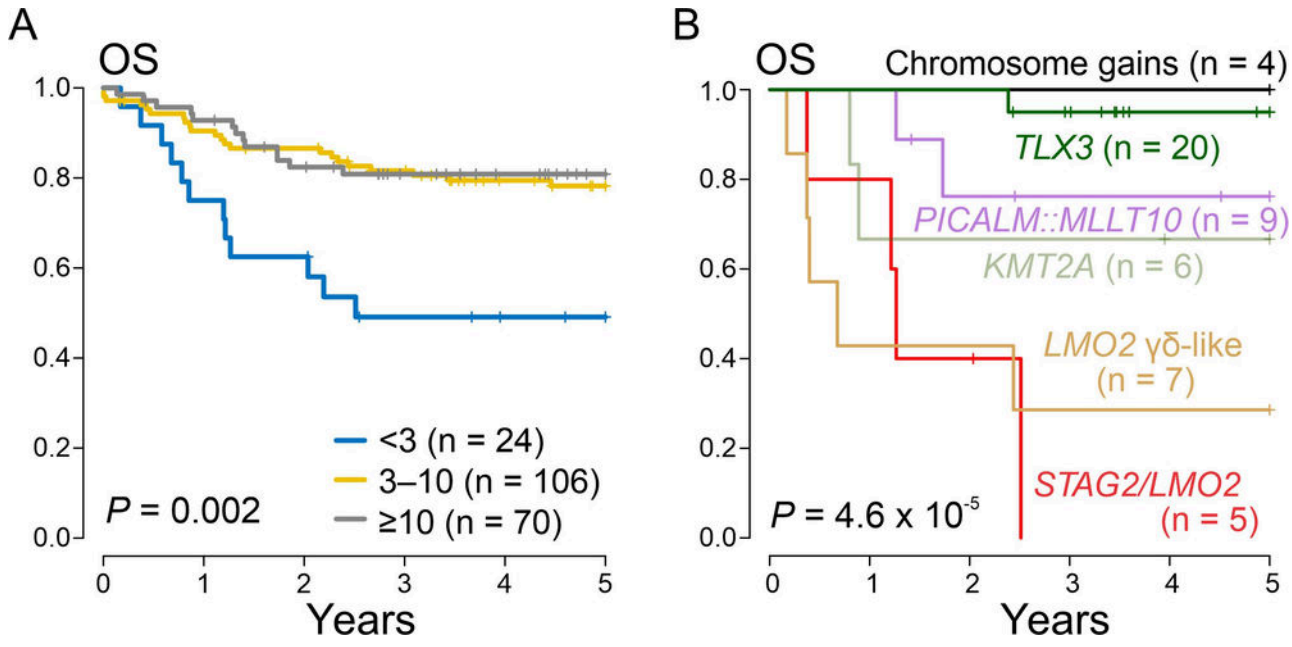

Figure 1

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