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ORAL ABSTRACTS

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

NGS-Based Stratification Refines the Risk Stratification in T-ALL and Identifies a Very High-Risk Subgroup of Patients

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Purpose

We previously reported a significantly better outcome in adult and pediatric T-cell acute lymphoblastic leukemia (T-ALL) harboring *NOTCH1* and/or *FBXW7* (*N/F*) mutations without alterations of *K-N-RAS* and *PTEN (R/P)* genes . High-throughput next-generation sequencing strategies (NGS) allowed us to refine the prediction of outcome in T-ALL.

Patients and Methods

198 adult T-ALLs in first remission (CR1) from the GRAALL-2003/2005 protocol were included in the study as the construction cohort, and 242 pediatric T-ALLs from FRALLE2000 were used as a validation cohort. Targeted whole-exome sequencing of 63 T-ALL-related oncogenes was performed. Primary outcome was cumulative incidence of relapse (CIR). To account for the large number of candidates genes, selection was performed using a LASSO penalization in a Fine and Gray model predicting CIR (Fu Z. et al. Lifetime Data Anal., 2017). To construct the final risk-stratification score, we used non-parametric clustering of CIR curves through k-medians algorithm (Villanueva N. et al. Stat. Med., 2019).

Results

We confirm the prognostic classifier *NFRP* in the NGS era and evaluate the impact of 39 new gene alterations in the adult cohort. Alterations affecting *TP53, DNMT3A, IDH1/2, IKZF1*, *PI3K* pathway (*PTEN, PIK3CA* and *PIK3R1*), *EP300*, and *PHF6* were independent prognostic factors in adult T-ALL. This led us to propose the first NGS-based classifier in T-ALL defining low risk patient (LR) as those with *N/F, PHF6* or *EP300* mutations without *N-K-RAS, PI3K* pathway , *TP53, DNMT3A, IDH1/2* and *IKZF1* alterations (234 of 440 patients, 53%). In the adult cohort, the NGS-based classifier separates a high-risk group (HR) (n=90/198, 45%) with a 5-year CIR of 47% (95%CI:36%-57%) and a low-risk group (LR) (n=108/198, 55%) with a 5-year CIR of 21% (95%CI:14%-29%) ($p<0.0001$). Our NGS-classifier was validated in the pediatric cohort, with a 5-year CIR of 35% (95%CI:26%-44%) in HR group (n=116/242, 48%) and 5-year CIR of 17% (95%CI:11%-24%) in the LR group (n=126/242, 52%) (p=0.001) (**Figure A**).

Since the NGS-based classifier is highly prognostic independently of minimal residual disease (MRD) at end of induction (cutoff 10^{-4}) and white blood cells count (WBC) (cutoff 100×10^{9}/L), we then developed and externally validated a global risk stratification model incorporating MRD1, WBC at diagnosis and the NGS-classifier. This model identifies 3 subgroups at CR1: a large favorable Risk (CR1-FAV) group (231/332, 70%) with CIR at 5 years estimated at 19% (95%CI:14%-24%) (**Figure B**), a subgroup of Adverse risk (CR1-ADV) patients (30/332, 9%) with a 5-year CIR of 68% (95%CI:46%-82%) and an Intermediate risk (CR1-INT) group (71/332, 21%) with a 5-year CIR of 37% (95%CI:26%-48%).

Conclusion

T-ALL NGS-based stratification combined with WBC and MRD evaluation sharpens the prognostic classification in T-ALL and identifies a new subgroup of adverse risk patients who should benefit from innovative therapeutic approaches.

Disclosures Cabannes-Hamy: *Gilead Kite, Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Huguet:** *Clinign:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Gilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Incyte Corporation:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Chalandon:** *Astra-Zeneca:* Honoraria, Other: travel support; *Amgen:* Honoraria, Other: travel support; *Gilead:* Honoraria, Other: travel support; *Jazz:* Honoraria, Other: travel support, Speakers Bureau; *Roche:* Honoraria, Other: travel support; *Abbvie:* Honoraria, Other: travel support; *Pfizer:* Honoraria; *BMS:* Honoraria, Other: travel support; *Incyte:* Honoraria, Other: travel support; *Novartis:* Honoraria, Other: travel support; *MSD:* Honoraria, Other: travel support; *Servier:* Honoraria; *Sanofi:* Other: travel support; *Janssen:* Other: travel support. **Dombret:** *Servier:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Research Funding; *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Incyte:* Membership on an entity's Board of Directors or advisory committees; *Astellas:* Research Funding. **Boissel:** *Astellas Pharma:* Honoraria; *Servier:* Consultancy, Honoraria, Other: Advisory role; *ARIAD/Incyte:* Honoraria; *Amgen:* Consultancy, Honoraria, Other: Expert Testimony and advisory role, Research Funding; *Novartis:* Consultancy, Honoraria, Other: Advisory role, Research Funding.

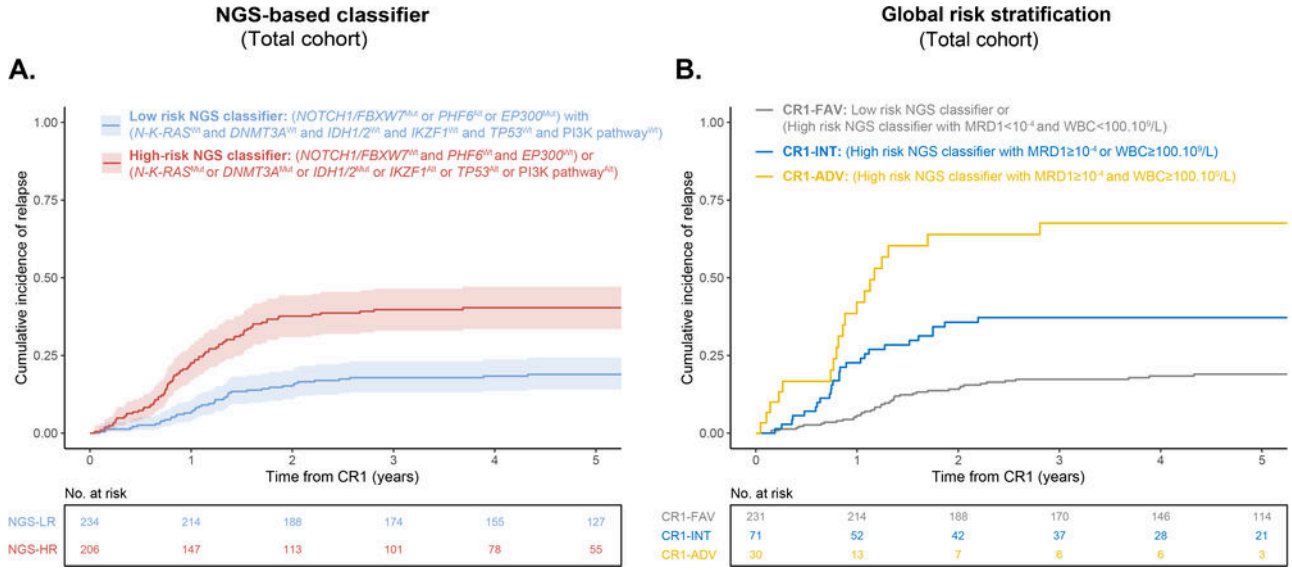

Figure 1

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