



Blood 142 (2023) 844–846



The 65th ASH Annual Meeting Abstracts

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 candidate 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 $100 \times 10^9/L$), 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.

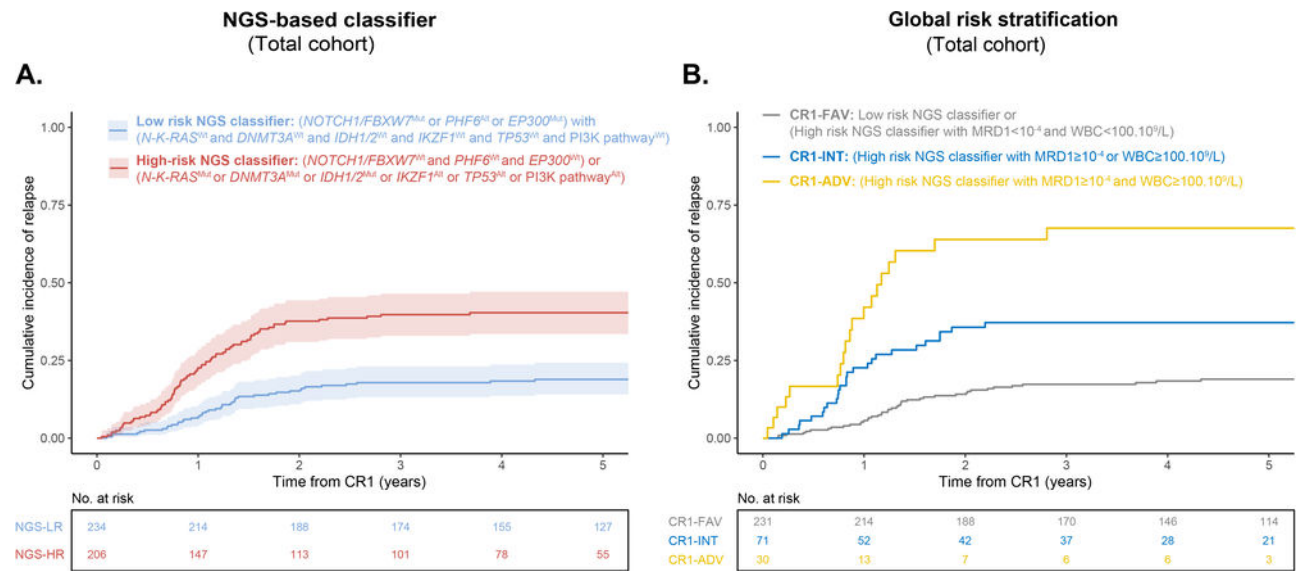


Figure 1

<https://doi.org/10.1182/blood-2023-179298>