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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

DNMT3A Mutants Are Enriched in NPMc+ AML and Associated with Adverse Outcome in Childhood AML

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Background: Somatic mutations in the DNA methyltransferase 3 alphagene (DNMT3A) are common in adult acute myeloid leukemia (AML), but are rare events in childhood AML (Ho, Ped Blood Cancer, 2011). Missense mutations occur most frequently in the catalytic domain at R882, resulting in loss of enzyme methylation activity and the ability of the enzyme to bind DNA. DNMT3Amutations are associated with adverse outcome in adults, while their impact is understudied in childhood AML. Our objective was to identify the prevalence of DNMT3A -mutated AML across the childhood age spectrum utilizing a large cohort of patients enrolled on pediatric trials and compare findings with adult cohorts.
Methods: Pediatric patients treated on two consecutive COG trials with publicly available data were included (n=1607). Mutational profiling was performed by whole genome and transcriptome sequencing methods. Prevalence of DNMT3Amutations, co-occurring mutations, and outcomes (5-year event-free [EFS] and 5-year overall survival [OS]) were analyzed.
Results: The prevalence of DNMT3Amutations amongst the entire childhood cohort was 1.2% (n=20/1607). DNMT3A mutations were absent in children <10 years with increased incidence up to 2.6% in patients >10yrs of age. All variants were missense, with the exception of one nonsense mutation and alterations at the 882 residue were the most common (70%). Most importantly, all but 4 DNMT3A mutations occurred in patients with NPM1 mutations (NPMc+; 80%). Conversely, DNMT3A mutations were seen in 9% of all NPM positive patients, demonstrating unique enrichment of this mutation within the NPM1 mutant cohort. Further, R882 mutations were seen in all but a single patient with the dual NPM/DNMT3A variant. It is notable that 11 patients harbored additional FLT3-ITD mutations (triple positive), which we have previously reported to be associated with adverse outcome in adults. In addition to mutations in NPM1 and FLT3, co-occurring variants with DNMT3A were also found in PTPN11 (35%), and WT1, IDH1/2 and MYC each at 10% frequency (Fig.A). Given the recent report of association of NPM1 mutation genotype and association of Type D mutation with adverse outcome (Pigazzi, ASH 2023), we evaluated NPM1 mutation genotype in those with cooperating DNMT3A mutation which demonstrated lack of association of DNMT3A mutations and Type D NPM1 mutations.
Current risk classification in COG pediatric AML trials treat NPMc+ patients as favorable risk. Given the prevalence of DNMT3A mutations in NPMc+ patients we inquired whether DNMT3A mutations might modify outcome in this population. The 5 yr EFS estimates for NPMc+; patients with and without DNMT3A was 26.8% vs. 74.8% (p<0.0001; Fig.B) with a corresponding OS estimate at 5yrs of 60.3% vs. 82.2% (p=0.0169). We further concluded that presence or absence of FLT3-ITD does not impact

the adverse outcome with similar 5 yr EFS for those with dual NPM1/DNMT3A or triple NPM1/DNMT3A/FLT3-ITD positive AML(20.0% vs. 30.3%respectively).
These data are consistent with the adult DNMT3A data previously presented last year (Torabi; ASH 2022; abstract #306) regarding clinical implications of DNMT3A mutation in the setting of cooperating NPM1 mutation.
Conclusion: Mutational profiling of children with AML identified DNMT3A mutations in adolescents and young adults and is enriched in those with NPMc+ mutations. As NPMc+ patients are considered to be favorable risk, knowledge of DNMT3A mutations would provide additional information for more precise risk stratification in childhood AML. Children with *de novo* AML and dual DNMT3A/NPM1 mutations remain at high risk of relapse and adverse outcome regardless of FLT3-ITD status.

Disclosures No relevant conflicts of interest to declare.

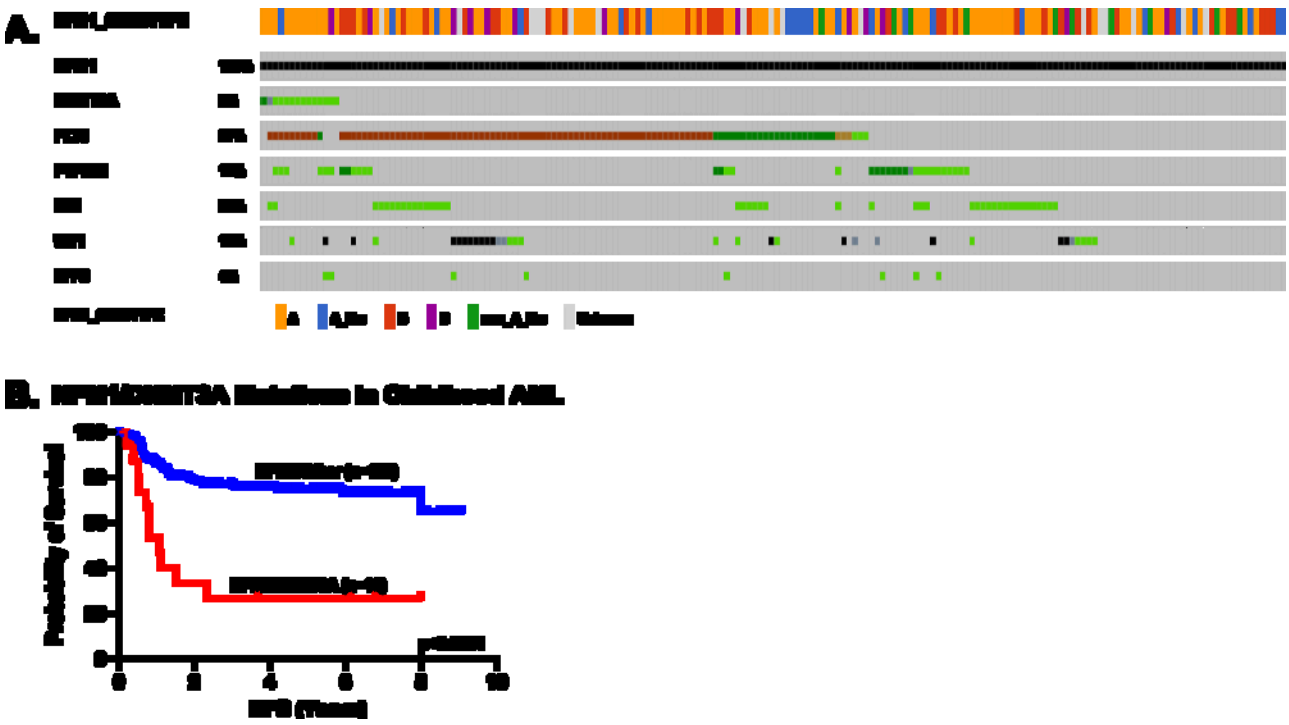

Figure 1

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