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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Prognostic Impact of Clonality of Myelodysplasia-Related Gene Mutations in AML

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Introduction: The 2022 International Consensus Classification (ICC) stresses the importance of molecular- and cytogenetic aberrations over previous medical history. Nine mutations are used to define a subgroup of AML with myelodysplasia related gene mutations (AML-MRGM). On a lower hierarchical level specific cytogenetic changes are used to define a subgroup of AML with myelodysplasia related cytogenetic abnormalities (AML-MRCA). Both groups together with *TP53* mutations are categorized within the adverse risk group of the 2022 ELN classification. We evaluated the prognostic implications of clonality of MRGM mutations.

Methods: 552 newly-diagnosed adult AML patients (pts.) with a median age of 55 years who received intensive induction chemotherapy followed by consolidation chemotherapy or allogeneic stem cell transplantation and with available genetic and follow-up data were included. Mutations present at diagnosis were identified by Illumina myeloid panel sequencing covering 48 AML-associated genes. Variant allele frequency (VAF) was adjusted for sex for mutations located on the X chromosome *(BCOR, STAG2, ZRSR2)*. The prognostic VAF cutoff was identified by maximally selected rank statistics. We defined AML-MRGM as having at least one MRG mutation, AML-MRCA as having at least one MRCA without MRGM, *TP53* mutated patients as having *TP53* mutations regardless of the presence of MRGM or MRCA and for the remaining pts. de novo AML and secondary/therapy-related AML according to medical history of the patient. For multivariate analysis value imputation was used for missing values.

Results:40 (7.2%) of 552 pts. were *TP53* mutated,196 (35.5%) had at least one MRGM, and 47 pts. (8.5%) had MRCA. Among the clinically defined cases 215 pts. (38.9%) had genuine de novo AML and 54 (9.8%) had a previous history of a hematologic malignancy or cytotoxic treatment. The median follow-up was 5.8 years. Overall survival (OS) and relapse free survival (RFS) for de novo AML and secondary AML based on medical history were not significantly different and were therefore grouped together as clinically-defined AML (cdAML). AML-MRGM pts. had a significantly lower complete remission (CR) rate (OR=0.32, 95%CI 0.18-0.56, p<0.001) and shorter OS, but not RFS, compared to cdAML pts. (OS, HR 1.38, 95%CI 1.04-1.83, p=0.02; RFS, HR 1.12, 95%CI 0.84-1.48, p=0.44). AML-MRCA had similar OS and RFS compared to both cdAML and AML-MRGM pts., but a significantly better CR rate than AML-MRGM pts. (OR 5.68, 95%CI 1.64-38.65, p=0.01). Pts. with *TP53* mutations had a worse OS and RFS than all other subgroups.

A VAF of 45% was identified as a prognostic cutoff by maximally selected rank statistics. Patients with MRGM and VAF $\geq$ 45% were associated with higher age (p=0.04) and a lower platelet count at diagnosis (p=0.04). A VAF $\geq$ 45% was identified in 81 pts. (41.3%) and was associated with a significantly worse OS and RFS compared to the 115 pts. (58.7%) with a VAF below 45% (OS, HR 1.70, 95%CI 1.12-2.57, p=0.01; RFS, HR 1.65, 95%CI 1.05-2.57, p=0.03) (Figure 1). Patients with VAF $\geq$ 45% had an OS and RFS similar to AML-MRCA pts., but significantly shorter OS and RFS than cdAML pts. (OS, HR 1.89, 95%CI 1.32-2.69, p<0.001; RFS, HR 1.52, 95%CI 1.04-2.21, p=0.03). In multivariate analysis the presence of MRGM with a VAF $\geq$45% was an independent adverse prognostic factor for OS.

Conclusion: In the present study, we confirm myelodysplasia-related gene mutations and *TP53* mutations as negative prognostic markers in line with the hierarchical significance proposed by ELN. Our study suggests that the presence of MRGM is

associated with worse OS especially if it is present at a VAF ≥ 45%, likely representing patients with at least one MRG mutation in the major AML clone.

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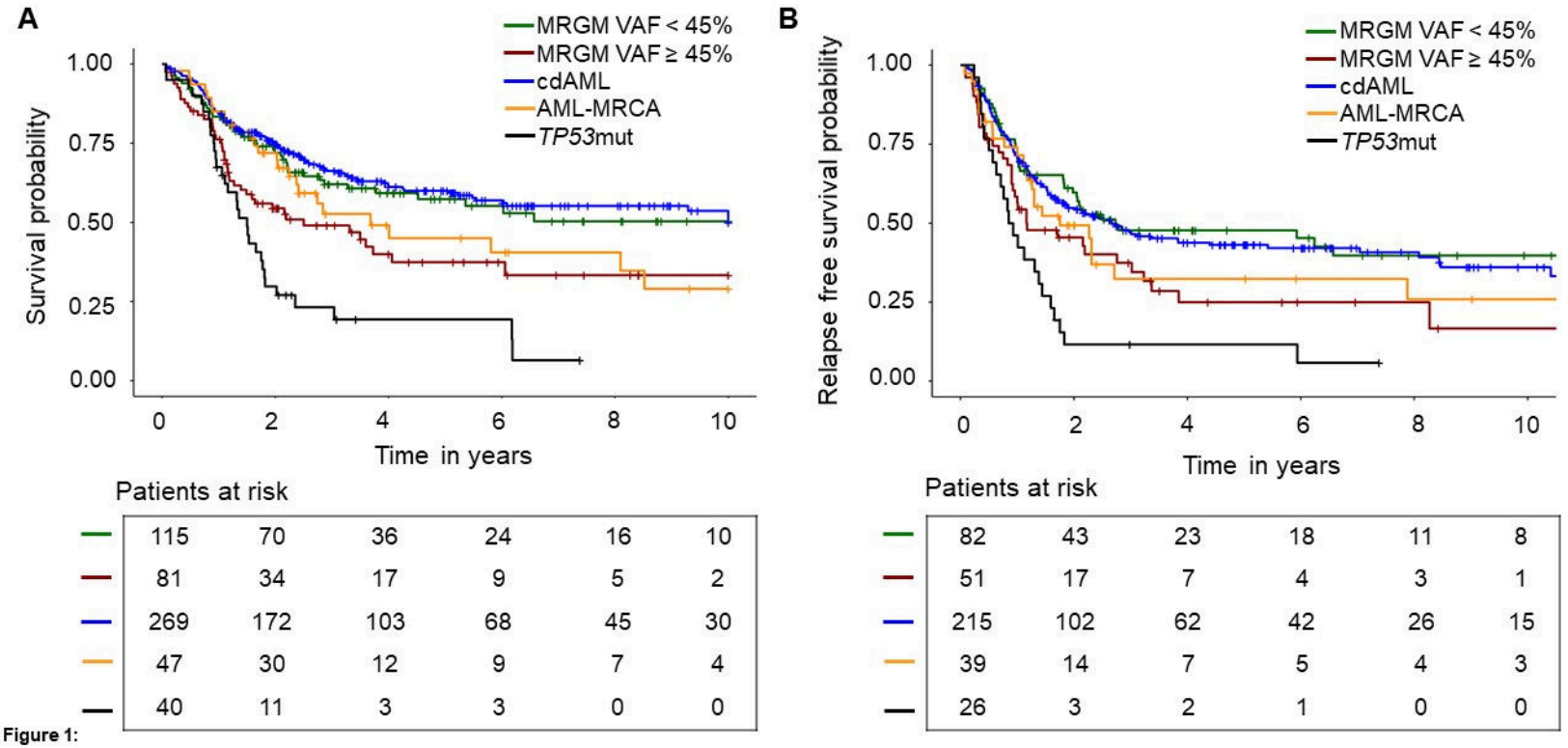

Figure 1:

(A) OS of patients with AML-MRGM, where all MRG mutations have a VAF <45%, with AML-MRGM, where at least one MRG mutation has a VAF ≥ 45%, clinically-defined AML (cdAML) including de novo AML and clinically defined secondary AML or therapy-related AML, AML-MRCA, and patients with *TP53* mutations.

(B) RFS of patients with AML-MRGM, where all MRG mutations have a VAF <45%, with AML-MRGM, where at least one MRG mutation has a VAF ≥ 45%, clinically-defined AML (cdAML) including de novo AML and clinically defined secondary AML or therapy-related AML, AML-MRCA, and patients with *TP53* mutations.

Figure 1