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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Secondary-Type Mutations Do Not Impact the Favorable Outcome of *NPM1*-Mutated Acute Myeloid Leukemia Patients - Results from a Large Cohort of Intensively Treated Patients

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Introduction: In 2022, the ELN risk classification for AML was updated for the second time. One of the major novelties of the ELN2022 is that all secondary-type mutations (STMs, *i.e.*, mutations in the genes *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, and *STAG2*) were now added to the adverse risk characteristics. However, a pertinent question also raised by the ELN expert panel is whether STMs abrogate the positive prognostic value of co-occurring, favorable *NPM1* mutations.
Aim: The aim of this study was to analyze the prognostic value of STMs in AML patients (pts) who also harbor an *NPM1* mutation.
Methods: We investigated a pooled cohort of 936 *NPM1*-mutated AML pts who were treated in previously reported multicenter trials of the Study Alliance Leukemia or the AML Cooperative Group. Eligibility was determined based on diagnosis of non-APL, age ≥ 18 years, *NPM1* mutation detected in targeted sequencing, curative treatment intent, and available biomaterial at diagnosis. Standard techniques for chromosome banding and fluorescence-in-situ-hybridization (FISH) were used for karyotyping. Next-generation panel sequencing was performed to detect genetic alterations that are recurrently found in myeloid neoplasms.
Results: In our multicenter cohort of 936 *NPM1*-mutated AML pts, median follow-up for the entire cohort was 8.0 years. We found 125 patients (13.4%) harboring at least one STM (*SRSF2* [n=48; 5.1%], *STAG2* [n=32; 3.2%], *EZH2* [n=22, 2.4%], *BCOR* [n=16; 1.7%], *SF3B1* [n=13; 1.4%], *ASXL1* [n=12; 1.3%], *ZRSR2* [n=5; 0.5%], and *U2AF1* [n=4; 0,4%]). A comparison of pretreatment clinical and genetic features revealed that pts with a STM were significantly older (p=.003, median 59 vs. 55 years), had lower white blood cell counts (p<.001, 22.2*10 ^{9}/L vs. 39.7*10 ^{9}/L,) and platelet counts (p<.001, 46.5*10 ^{9}/L vs. 65.0 10 ^{9}/L). The strongest pair-wise associations between gene mutations were observed between *U2AF1* and *RUNX1* (p<.001) as well as *SRSF2* and *IDH2* (p<.001).
With respect to outcome, complete remission (CR) rate did not differ significantly between *NPM1*-mutated patients with or without additional STMs (p=.41, 74.4% vs. 77.7%, OR 0.83 [95%-CI 0.54-1.29]). Median RFS for *NPM1*-mutated pts with STMs was 32.9 months (95%-CI: 13.0-46.0) while patients without STMs had a median RFS of 24.3 months (95%-CI: 18.7-33.3) corresponding to a HR of 1.04 (p=0.80, 95%-CI 0.79-1.37; Figure A). Median OS for *NPM1*-mutated pts with or without STMs was 27.2 months (95%-CI: 14.2-49.0) and 29.1 months (95%-CI: 23.5-41.4), respectively, corresponding to a HR of 1.11 (p=.37, 95%-CI 0.88-1.41; Figure B).
To focus solely on the impact of STMs, we subsequently excluded patients with co-occurring mutations in *TP53* or myelodysplasia-related cytogenetics, which all define an ELN adverse risk. Again, we observed no differences in CR rate (p=.54, 78% vs. 75.4%), RFS (p=.59, median 33.2 months vs. 26.6 months), or OS (p=.33, median 27.4 month vs. 32.6 month) between *NPM1*-mutated patients with or without STMs. Next, we restricted our analysis to pts who are classified favorable risk according to ELN2022. Again, we found no significant outcome differences based on the STM status (unmutated vs. mutated: CR rate, 80% vs. 70.7% [p=.072]; RFS, median 49.7 months vs. 46.0 months [p=.702]; OS, median 45.3 months vs. 59.8 months [p=.092]).
Conclusion: *NPM1* mutations rank as the second most frequent mutations in AMLand the most common in patients with a normal karyotype and serve as an established favorable prognostic marker. Our data from a large cohort demonstrate that additional STMs have no adverse effect on the clinical outcome of *NPM1*-mutated patients. As a result, these patients should still be considered ELN favorable risk.

Disclosures Sauer: *Novartis:* Consultancy; *BMS:* Consultancy; *Ridgeline Discovery:* Consultancy; *Takeda:* Consultancy; *Pfizer:* Honoraria; *Gilead:* Honoraria; *Stemline:* Consultancy; *AbbVie:* Consultancy, Other: Travel, Accommodation, Expenses; *Amgen:* Consultancy; *Astellas:* Consultancy; *Jazz:* Honoraria, Other: Travel, Accommodation, Expenses. **Hochhaus:** *Bristol Myers Squibb:* Consultancy, Research Funding; *Pfizer:* Research Funding; *Incyte:* Research Funding; *Takeda:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding. **Crysandt:** *Pfizer:* Other: Travel grant. **Brümmendorf:** *Pfizer:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Patents & Royalties, Research Funding, Speakers Bureau; *Gilead:* Consultancy, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Merck:* Consultancy, Honoraria, Speakers Bureau. **Krug:** *AbbVie:* Honoraria; *Sanofi:* Honoraria; *Leo Pharma:* Honoraria; *BMS:* Honoraria. **Einsele:** *Novartis:* Honoraria, Other: Consulting or advisory role, Travel support; *Takeda:* Honoraria, Other: Consulting or advisory role, Travel support; *Amgen:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Sanofi:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Janssen:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *GlaxoSmithKline:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding; *Bristol Myers Squibb/Celgene:* Honoraria, Other: Consulting or advisory role, Travel support, Research Funding. **Burchert:** *Novartis:* Honoraria, Research Funding; *MSD:* Research Funding; *Incyte:* Honoraria. **Schliemann:** *Bristol Myers Squibb:* Honoraria, Other; *Jazz Pharmaceuticals:* Honoraria, Other, Research Funding; *Novartis AG:* Honoraria; *Roche:* Honoraria; *Pfizer:* Honoraria, Other; *AngioBiomed:* Research Funding; *Boehringer Ingelheim:* Research Funding; *Laboratoires*

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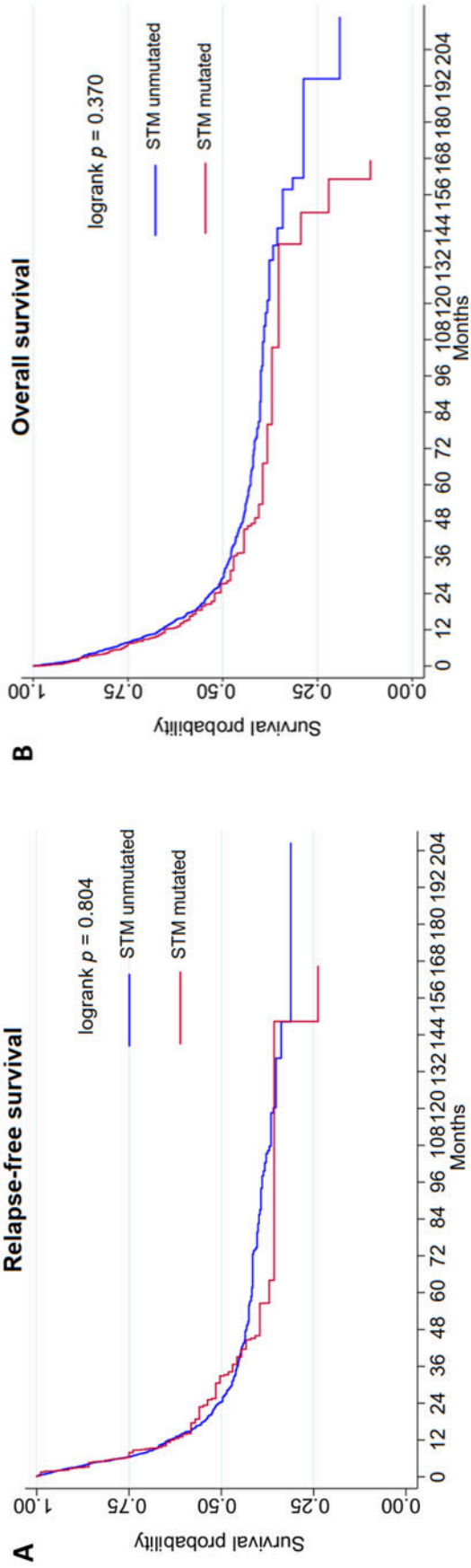

Figure 1. Outcome in NPM1-mutated AML according to STM co-mutational status.