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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Influence of Bone Marrow Blast Enumeration and Co-Occurring Myelodysplasia Related Gene Mutations in *NPM1*-Mutated Myeloid Malignancies

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Introduction

Both World Health Organization (WHO 5th) and International Consensus Classification (ICC) guidelines recognize mutations in nucleophosmin 1 (*NPM1* ^{mut}) as a class defining molecular event in acute myeloid leukemia (AML). WHO 5th omitted the blast percentage requirement and ICC lowered the blast threshold to 10%. *NPM1* ^{mut} AML without *FLT3* ITD or adverse risk cytogenetics is considered favorable risk in European LeukemiaNet (ELN) 2022, however co-occurring adverse-risk myelodysplasia related mutations (MR ^{mut}) do not influence ELN 2022 risk stratification. This analysis addresses the prognostic impact of blast enumeration in *NPM1* ^{mut} myeloid neoplasms (MN) with <10% blasts and influence of co-occurring mutations in *NPM1* ^{mut} AML.

Methods

We interrogated publicly available data from adult (≥18 years) patients (pts) with chronic myeloid neoplasms included in the International Working Group for Prognosis in MDS (N= 3,323; Bernard et al. *NEJM Evid* 2022) and two independent AML cohorts (AMLSG [N=1540] Papaemmanuil et al. *NEJM* 2016; UKNCRI [N=2,113] Tazi et al. *Nat. Commun.* 2022). Between group differences were assessed using the Wilcoxon rank-sum test or Fisher's exact test as appropriate. Time to event endpoints were analyzed using the log-rank method. Multivariate analysis (MVA) used cox proportional hazards regression.

Results

NPM1 ^{mut} was identified in 17% (N=1148) of pts (AML: 30% [1109/3653], MN with <20% blasts: 1.2% [39/3,323]). Compared to pts with *NPM1* ^{mut} AML, pts with *NPM1* ^{mut} MN (MDS, CMML, aCML) with blast < 20% were older (median age 65 vs. 55 years, $p < 0.001$), had a lower median total WBC count (5 vs. 32 x10 ^{9} /L, $p < 0.001$) and bone marrow (BM) blast percentage (8% vs. 76%, $p < 0.001$). No significant difference was observed between *NPM1* ^{mut} AML and MN with <20% blasts in median hemoglobin (9.1 vs. 9 x10 ^{9}, p: 0.44), platelets (62 vs. 66 x10 ^{9} /L, p: 0.55), or *NPM1* ^{mut} variant allele frequency (VAF; 35% vs. 37%, p: 0.64).

After a median follow up of 4.7 years (range: 0-12), no difference in overall survival (OS) was observed between pts with low blast (LB; <10%) *NPM1* ^{mut} MN (N=19) vs. ≥10% blasts (N=18) (median OS: 0.64 years [95% CI: 0.31-3.0] vs. 1.1 years [95% CI:

0.95-NR], p=0.32). Median leukemia free survival (LFS) was 0.81 years (95% CI: 0.67-1.5) and not significantly different between *NPM1* ^{mut} MN pts with <10 vs. ≥10% blasts (median LFS: 0.55 vs. 0.91 years, p=0.27).
In pts with *NPM1* ^{mut} AML (N=1109), 52% (N=581) were ELN 2022 favorable-risk; 15% (N=92) had MR ^{mut} including *SRSF2* (51%, N=47), *STAG2* (21%, N=19), *ASXL1* (9%, N=8), *BCOR* (9%, N=8), *RUNX1* (8%, N=7), *EZH2* (5%, N=5), *SF3B1* (5%, N=5), *U2AF1* (1%, N=1), and *ZRSR2* (1%, N=1). Pts with MR ^{mut} were older (median age 62 vs. 53 years, p < 0.001), had higher BM blasts (80% vs. 72% p=0.019), and lower platelets (45 vs. 77 x10 ^{9}/L p < 0.001) compared to pts with *NPM1* ^{mut} AML without MR ^{mut}. No significant difference in *NPM1* ^{mut} VAF was observed (34% in both groups).
After a median follow up of 3.5 years (range: 0-15), median OS was 6.2 years in pts with *NPM1* ^{mut} AML (95% CI: 4.2-9.7). Inferior OS was observed in ELN favorable risk *NPM1* ^{mut} pts with vs. without MR ^{mut}, respectively (2 vs. 8.4 years, p=0.0001). When stratified by age < 60 vs. ≥ 60 years, younger pts with MR ^{mut} had an increased risk of death (HR 1.7 95% CI: 1.1-2.8, p: 0.02). No OS difference was observed in older pts with or without MR ^{mut} (HR: 1.2, 95% CI: 0.80-1.68, p=0.44), however OS was significantly shorter in older pts with *NPM1* ^{mut} compared to younger pts (median 1.7 years vs. NR, p < 0.001). Patients with *NPM1* ^{mut} /MR ^{mut} AML had survival comparable to patients with ELN 2022 intermediate risk AML (2.0 vs. 2.1 years, p=0.35).
In MVA of *NPM1* ^{mut}AML adjusted for MR ^{mut}, BM blast percentage, age, performance status, baseline WBC, hemoglobin, platelet count, *NPM1* ^{mut} VAF, and treatment setting (AMLSG or UKNCRI), the presence of an MR ^{mut} (HR 1.39 [95% CI: 1.0-1.9], p=0.04), age < 60 (HR 0.43 [95% CI: 0.32-0.56], p < 0.001), and performance status (HR 1.35 [95% CI: 1.14-1.60], p=0.0004) retained statistical significance.

Conclusion

Pts with low blast *NPM1* ^{mut} MN have outcomes similar to pts with *NPM1* ^{mut} AML, supporting *NPM1* ^{mut} as an AML defining event irrespective of BM blast enumeration. In patients with ELN favorable risk *NPM1* ^{mut} AML, co-occurrence of MR ^{mut} is independently associated with inferior survival, comparable to ELN intermediate risk AML. These results may inform future refinements of current consensus guidelines.

Disclosures Lachowiez: *COTA Healthcare:* Consultancy; *Rigel Pharmaceuticals:* Other: Advisory board. **Bullinger:** *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Astellas:* Honoraria; *Gilead:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bayer Oncology:* Research Funding; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria; *Bristol-Myers Squibb:* Honoraria; *Daiichi Sankyo:* Honoraria; *Sanofi:* Honoraria. **Döhner:** *BMS:* Consultancy, Research Funding, Speakers Bureau; *Celgene:* Consultancy, Research Funding, Speakers Bureau; *CTI:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Research Funding, Speakers Bureau; *Roche:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy; *Daiichi Sankyo:* Consultancy; *Janssen:* Consultancy; *Jazz:* Consultancy; *Astellas:* Research Funding; *Agios:* Research Funding. **Dohner:** *AbbVie:* Consultancy, Research Funding; *Agios:* Consultancy, Research Funding; *Amgen:* Consultancy, Research Funding; *Astellas:* Consultancy, Research Funding; *AstraZeneca:* Consultancy; *Berlin-Chemie:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding; *Celgene:* Consultancy; *GEMoaB:* Consultancy; *Gilead:* Consultancy; *Janssen:* Consultancy; *Jazz Pharmaceuticals:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Syndax:* Consultancy; *Kronos-Bio:* Research Funding. **Russell:** *Pfizer:* Honoraria, Research Funding, Speakers Bureau; *Jazz Pharma:* Research Funding; *Servier:* Honoraria; *Astellas:* Honoraria. **Loghavi:** *QualWorld:* Consultancy; *Guidepoint:* Consultancy; *Astellas:* Research Funding; *Amgen:* Research Funding; *Daiichi Sankyo:* Consultancy; *Caris Diagnostics:* Consultancy; *Gerson Lehrman Group:* Consultancy; *Abbvie:* Consultancy; *Blueprint Medicine:* Consultancy; *Recordati/ EUSA Pharma:* Consultancy; *Abbvie:* Current equity holder in publicly-traded company. **Papaemmanuil:** *TenSixteen Bio:* Current equity holder in private company; *Isabl Inc.:* Current equity holder in private company, Current holder of *stock options* in a privately-held company, Other: CEO, Patents & Royalties: Whole genome cancer analysis.

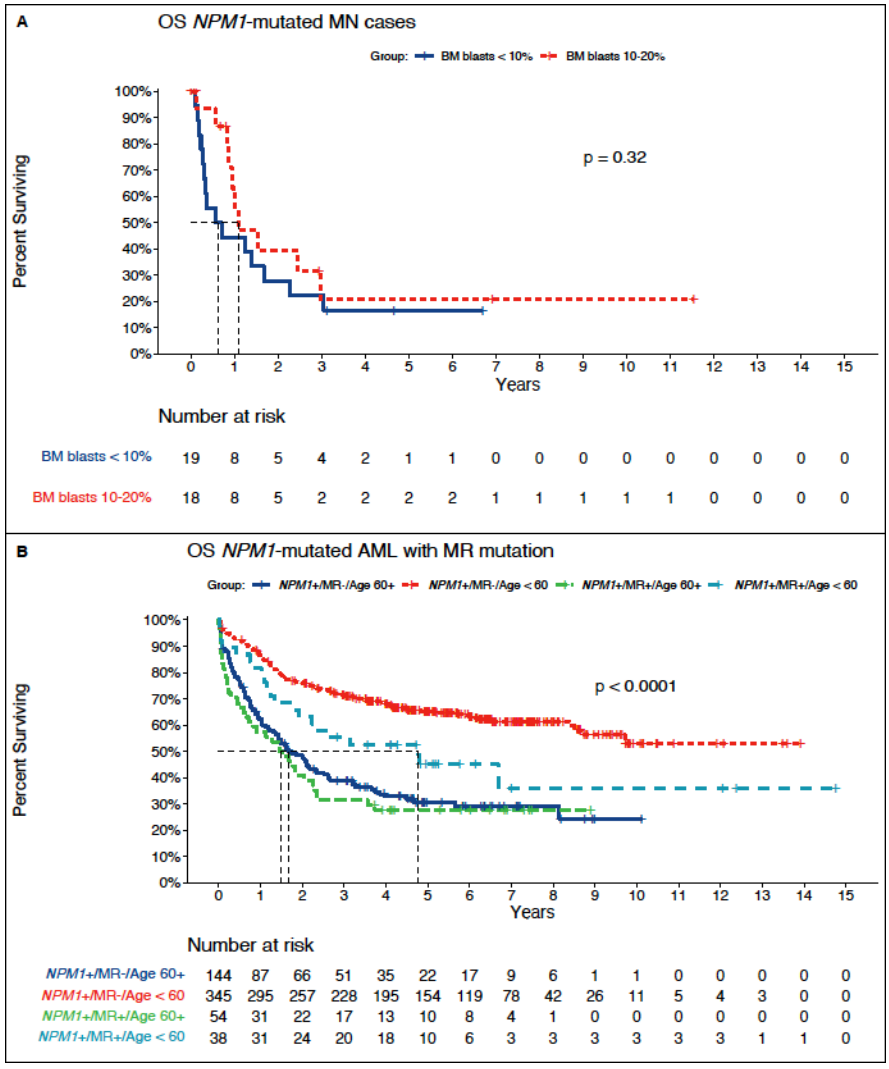

Figure 1

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