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# POSTER ABSTRACTS

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

### The Genomic Landscape and Its Clinical Implication in *NPM1*-Mutated AML Patients: A Study within the AMLSG 09-09 Clinical Trial

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**Background:** Mutations in the *Nucleophosmin* 1 gene ( *NPM1* $^{mut}$ ) represent one of the most common genetic lesions in acute myeloid leukemia (AML).Based on its characteristic clinico-pathologic features, *NPM1* $^{mut}$AML has been recognized as a distinct entity among the category "AML with recurrent genetic abnormalities". According to the ELN 2022 genetic risk-stratification, *NPM1* $^{mut}$ AML, in the absence of *FLT3*-ITD mutation, is associated with a favorable prognosis. However, a significant proportion of these patients (pts) relapse after intensive therapy suggesting that other co-mutations may have an impact on outcome.
**Aims:** To comprehensively characterize the genomic landscape and leukemogenic trajectoriesin a large cohort of *NPM1* $^{mut}$ AML pts and to investigate its prognostic and predictive impact on outcome.
**Methods**: Targeted DNA sequencing (mean read depth: 1817) on the entire coding region of 263 genes was performed in 568 *NPM1* $^{mut}$ AML pts (median age: 58.7 years; 18-60 years, n=317; >60 years, n=251). All pts were enrolled in the randomized open-label Phase 3 AMLSG 09-09 trial [NCT00893399; Döhner H et al. Lancet Haematol 2023]. In this trial, pts were assigned to intensive chemotherapy plus all- *trans* retinoic acid with or without gemtuzumab ozogamicin; none of the pts received midostaurin.
**Results**: In total n=3,058 variants (variant allele frequency of ≥1%) were identified in 195/263 genes. The median number of co-mutations was 3 (range 0-11). The most common co-mutated genes were *DNMT3A* (49.5%), *FLT3*-TKD (42.8%) *PTPN11* (24.8%), *NRAS* (22.7%) *TET2* (21.7%), *IDH2* (21.3%), *IDH1* (18%), and *FLT3*-ITD (17.3%). *DNMT3A* $^{R882}$ hotspot mutations occurred more frequently in younger pts (36.6% vs 17.1%), while there was no difference for *DNMT3A* $^{nonR882}$ mutations between the two age groups (21.8% and 21.9%). An age-dependent difference was also identified for mutations in myelodysplasia-related genes ( *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and ZRSR2)* as defined by the ICC, occurring with a higher incidence in older pts (30.3% vs 12.3% in younger pts).
Analyzing the mutational pattern of co-mutations, we found statistically significant tertiary gene-gene interactions: e.g., *NPM1- NFE2- STAG2* (p<.001), *NPM1- IDH2- SRSF2* (p<.001), *NPM1- CEBPA- TET2* (p<.001), *NPM1- DNMT3A* $^{R882}$*- NRAS* (p=.002), and *NPM1- ASXL1- SRSF2* (p=.004); mutual exclusivities were identified for *NPM1- DNMT3A* $^{R882}$*- DNMT3A* $^{nonR882}$ (p<.001), *NPM1- IDH2- TET2* (p<.001), *NPM1- DNMT3A* $^{R882}$*- SRSF2* (p<.001), *NPM1- IDH1- TET2* (p<.001), and *NPM1- FLT3*-ITD- *KRAS* (p<.002). Correlating co-mutation data with outcome, we found that *DNMT3A* $^{R882}$ hotspot mutations confer inferior

event-free (EFS) and overall survival (OS) only in younger pts (EFS, p<.001 vs p=.11, Figure 1a; OS, p=.003 vs p=.8), whereas *DNMT3A* $^{nonR882}$ mutations did not impact prognosis within the two age groups. We also found a negative prognostic impact of *IDH1* mutations which was restricted to younger pts (EFS, p=.05), whereas *IDH2* mutations were associated with superior EFS in older pts (p=.04) and superior OS in both groups (p=.05 and p=.03). Of note, co-mutations occurring in one or more of the myelodysplasia-related genes did not impact EFS or OS (Figure 1b). In multivariable analysis (all pts) including age, WBC, LDH, allogeneic transplantation in CR1, and mutations with an incidence of at least 3% as covariables, age (HR,1.03; p<.001), *DNMT3A* $^{R882}$ (HR, 1.86; p<.001), *FLT3*-ITD (HR, 1.54; p=.012), *IDH1* (HR, 1.48; p=.009), *MYC* (HR, 1.83; p=.032), and *WT1* (HR, 1.73; p=.012), were associated with an inferior EFS, while *SMC3* mutation showed favorable EFS (HR, 0.44; p=.019). To further study the leukemogenic trajectories, we used an oncogenetic tree modeling algorithm, which yielded a tree with several main branches including *DNMT3A* $^{R882}$, *DNMT3A* $^{nonR882}$, *FLT3*-TKD , *IDH1*, *IDH2*, *PTPN11*, and *TET2*. These mutations might represent initiating events which predispose to additional events with further distinct branches.

**Conclusions:** Our study provides comprehensive data on the genomic landscape and its clinical impact in pts with *NPM1* $^{mut}$ AML fit for intensive chemotherapy. The co-mutational pattern clearly differs between younger and older *NPM1* $^{mut}$AML pts. Using this large dataset allowed the identification of secondary and tertiary gene-gene interactions with significant impact on outcome. Further data analysis is ongoing and will be presented at the meeting.



**Disclosures Gaidzik:** *Abbvie:* Membership on an entity's Board of Directors or advisory committees, Other: Travel Support, Speakers Bureau; *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Other: Travel Support; *Pfizer:* Speakers Bureau; *Janssen:* Speakers Bureau. **Theis:** *SOBI:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory committees. **Fiedler:** *Jazz Pharmaceuticals:* Consultancy, Other: Support for meeting attendance; *Apis:* Research Funding; *Clinigen:* Consultancy; *Stemline:* Consultancy; *Morphosis:* Consultancy; *Servier:* Consultancy, Other: Support for meeting attendance; *AbbVie:* Consultancy, Honoraria, Other: Support in medical writing; *Pfizer:* Consultancy; *Amgen:* Consultancy, Other: Support for meeting attendance, Patents & Royalties. **Kühn:** *Pfizer:* Consultancy, Honoraria; *Kura Oncology:* Consultancy, Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria; *Bristol-Myers Squibb / Celgene:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Gilead:* Speakers Bureau; *Daiichi Sankyo:* Other: Travel support. **Lübbert:** *Syros:* Membership on an entity's Board of Directors or advisory committees; *Otsuka:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Cheplapharm:* Other: Study drug; *Astex Pharmaceuticals, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Janssen-Cilag:* Research Funding; *Imago Blosciences:* Other: study drug. **Thol:** *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Heuser:** *BergenBio:* Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Glycostem:* Consultancy, Research Funding; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Janssen:* Honoraria; *Karyopharm:* Research Funding; *Sobi:* Honoraria; *Servier:* Consultancy; *Amgen:* Consultancy; *Certara:* Honoraria; *Pfizer:* Consultancy, Honoraria; *Novartis:* Honoraria; *PinotBio:* Consultancy, Research Funding; *Loxo Oncology:* Research Funding; *Astellas:* Research Funding; *Agios:* Research Funding; *Abbvie:* Consultancy, Research Funding; *LabDelbert:* Consultancy. **Bullinger:** *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; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Benner:** *Sanofi:* Other: Travel, Accomondations, Expenses. **Döhner:** *Celgene:* Consultancy, Honoraria, Research Funding; *Gilead:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria, Research Funding; *Pfizer:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Syndax:* Honoraria; *Kronos-Bio:* Research Funding; *Agios:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Berlin-Chemie:* Consultancy, Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria; *Stemline:* Consultancy, Honoraria. **Döhner:** *Agios:* Research Funding; *Astellas:* Research Funding; *Roche:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Ulm University Hospital:* Current Employment.

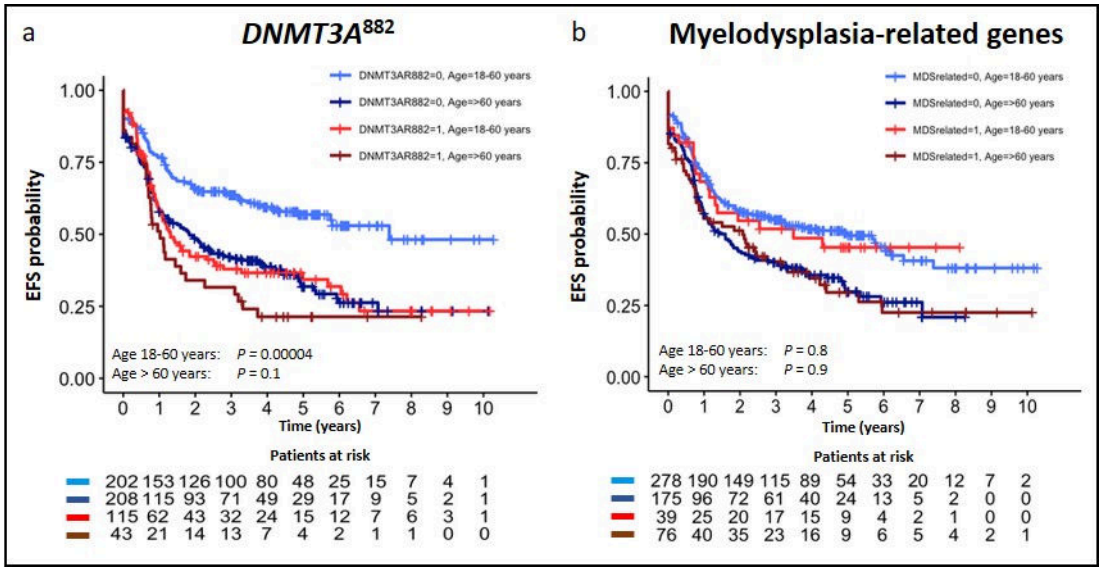


**Figure 1**

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