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## S130 NPM1 MUTATED AML: IMPACT OF CO-MUTATIONAL PATTERNS - RESULTS OF THE EUROPEAN HARMONY ALLIANCE

**Topic:** 04. Acute myeloid leukemia - Clinical

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### Background:

Acute myeloid leukemia (AML) is a heterogeneous disease in terms of clinical features, outcomes and genetics. While mutations of *NPM1* are usually considered as a favorable prognostic marker, the vast majority of the patients carry several co-mutations that might influence the prognosis. Therefore, a better understanding of the *NPM1*<sup>mut</sup> AML mutational landscape is warranted. The large cohort of AML patients collected within the European HARMONY Alliance provides an excellent basis for this purpose.

### Aims:

To identify clinically significant co-mutational patterns in *NPM1*<sup>mut</sup> AML in order to establish a revised risk stratification model.

### Methods:

From the HARMONY Alliance AML database, a total of 1001 *NPM1*<sup>mut</sup> intensively treated patients were selected. Clinically significant co-mutations were evaluated using graphical patterns created with the Gephi tool and confirmed by detailed survival analysis using Kaplan-Meier and Cox regression models. Finally, a novel multi-state risk stratification model for *NPM1*<sup>mut</sup> AML was established.

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## Results:

The study population of 1001 *NPM1*<sup>mut</sup> AML patients included 57% females and median age was 53 years. Regarding ELN2017 classification, 68% of patients were classified into the favorable, 29% intermediate and 3% adverse risk groups. The most frequent co-mutations were *DNMT3A* (54%), followed by *FLT3-ITD* (38%). In total, 24% of patients presented with a high allelic mutant-to-wildtype ratio  $\geq 0.5$  (*FLT3-ITD*<sup>high</sup>) while 14% had low allelic ratio  $< 0.5$  (*FLT3-ITD*<sup>low</sup>). Other frequent co-mutations were *NRAS* (21%), *TET2* (20%) and *PTPN11* (15%).

The triple mutation pattern of *NPM1*<sup>mut</sup> + *FLT3-ITD*<sup>high</sup> + *DNMT3A*<sup>mut</sup> identified a subgroup with adverse prognosis (2-year OS of 25%), similar to *NPM1*<sup>mut</sup> + *TP53*<sup>mut</sup>. The combination of *FLT3-ITD*<sup>low</sup> + *DNMT3A*<sup>mut</sup> or *FLT3-ITD*<sup>high</sup> + *DNMT3A*<sup>wt</sup> was associated with intermediate prognosis (2-year OS of 45% and 53% respectively). Notably, mutations of *NRAS*, *KRAS*, *PTPN11* or *RAD21* were identified to be associated with better OS. However, in the context of *NPM1*<sup>mut</sup> + *DNMT3A*<sup>mut</sup> these mutations did not affect the prognosis when a *FLT3-ITD* was present. This information is summarized in a 3-category risk classification model (**Figure 1**).

The revised *NPM1*<sup>mut</sup> favorable group presented with a 2-year OS of 73%, while for intermediate and adverse groups the OS was 54% and 27% respectively ( $p < 0.001$ ). Regarding relapse free survival (RFS), the median was not reached in the favorable group, while it was 23 months for intermediate and 6 months for adverse group ( $p < 0.001$ ). It should be noted that 171 patients in the *NPM1*<sup>mut</sup> intermediate group would be considered as favorable according to the ELN2017 criteria, as well as 162 patients in the *NPM1*<sup>mut</sup> adverse group were previously classified as intermediate risk. Therefore, our model was able to reclassify 33% of *NPM1*<sup>mut</sup> AML patients in comparison to ELN2017 criteria.

Multivariate analysis of OS in *NPM1*<sup>mut</sup> AML identified the following independent prognostic factors: *NPM1*<sup>mut</sup> model (taking favorable group as reference, HR 1.6 for intermediate and HR 2.7 for adverse group,  $p < 0.001$ ); secondary or therapy-related AML (HR 1.8,  $p < 0.001$ ), WBC at diagnosis  $> 100 \times 10^3 / \mu\text{L}$  (HR 1.5,  $p < 0.001$ ) and age  $> 60$  years (HR 1.4,  $p < 0.001$ ).

## Image:

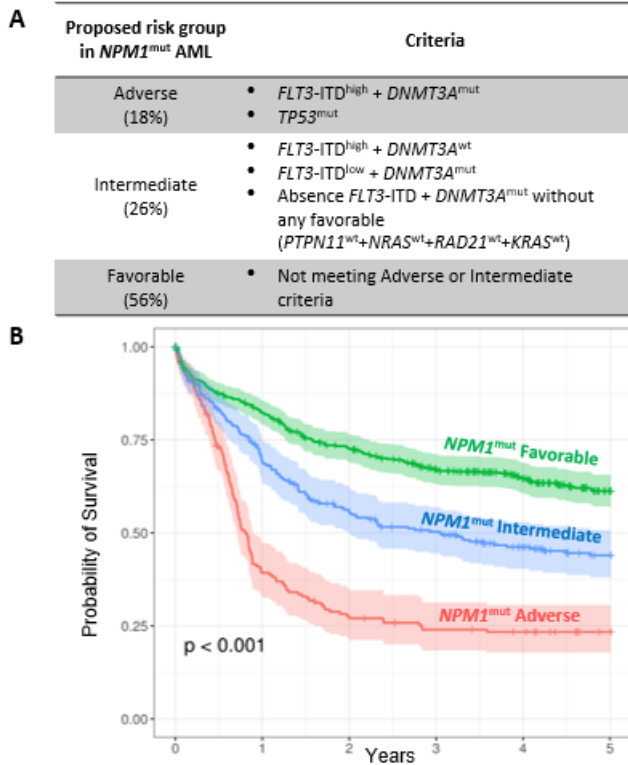
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Figure 1. Classification criteria for *NPM1*<sup>mut</sup> AML (A) and Kaplan-Meier OS analysis in each group (B)



## Summary/Conclusion:

Analysis of large *NPM1*<sup>mut</sup> AML cohorts allows the discovery of co-mutation patterns associated with prognostic outcome. In accordance, we propose a new genetic stratification model for *NPM1*<sup>mut</sup> AML that identifies 3 groups with different OS and RFS. This model improves ELN2017 criteria as it is able to correctly reclassify 33% of *NPM1*<sup>mut</sup> AML patients.

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