Prognostic effect of co-mutations on patients with *NPM1*+ acute myeloid leukemia enrolled in the Connect® Myeloid Registry

AML-547

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Introduction

- Mutations in nucleophosmin-1 (*NPM1*+) occur in ~30% of patients with acute myeloid leukemia (AML)[1-3]
- The 2017 World Health Organization classification of myeloid neoplasms and AML recognizes AML with mutated *NPM1* as a distinct entity with favorable prognosis[4]
- However, presence of mutations other than *NPM1* may further influence disease prognosis[4]
  - Unlike *NPM1*-mutated AML, AML with mutations in *RUNX1* or *TP53* is associated with poor prognosis[2,4]
- *NPM1*+ has been associated with favorable outcomes following intensive chemotherapy (IC) and positive prognostic value[1,3,5,6]
- As gene-gene interactions may have a pronounced effect on prognosis, understanding how patterns of co-mutations affect clinical outcomes may help improve AML management

Objective

- This study aimed to better understand the prognostic effect of *NPM1* co-mutations and primary induction therapy in patients with AML enrolled in the Connect® Myeloid Registry (NCT01688011)

Methods

Connect® Myeloid Registry

- The Connect® Myeloid Registry is a large, US, multicenter, prospective observational cohort study of patients with newly diagnosed AML, myelodysplastic syndromes, idiopathic cytopenia of undetermined significance, or myelofibrosis[7,8]
  - Enrollment of eligible patients with newly diagnosed AML ≥ 55 years of age began in December 2013; data were collected up to the data cutoff date for this analysis of February 2022
  - Patients were grouped according to known *NPM1* mutational status (*NPM1*+ vs *NPM1*−)

Analyses

- Demographics and patient characteristics at baseline were summarized by group
- The frequency of gene mutations was analyzed among patients with *NPM1*+ and *NPM1*− AML
- Overall survival (OS) from the date of AML diagnosis was evaluated in each group using the Cox model adjusted for age and/or mutations in *TP53* and *RUNX1*

Results

Patient characteristics

- Overall, 483 patients with a diagnosis of AML and known *NPM1* mutational status in the Connect® Myeloid Registry were assessed, including 123 with *NPM1*+ AML and 360 with *NPM1*− AML (**Table 1**)
- Baseline demographic and clinical characteristics were similar across *NPM1*+ and *NPM1*− groups

Table 1. Demographics and patient characteristics at baseline

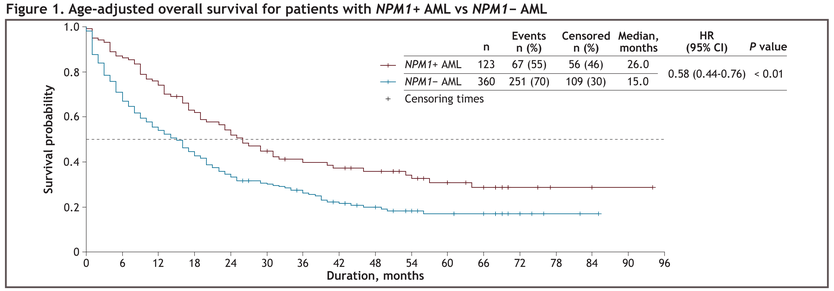
	NPM1+ AML (n = 123)	*NPM1*− AML (n = 360)
Age, years, median (range)	67.0 (55-87)	71.0 (55-97)
Sex, n (%)	117 (100.0)	351 (100.0)
Male	72 (61.5)	213 (60.7)
Female	45 (38.5)	138 (39.3)
Ethnicity, n (%)	123 (100.0)	360 (100.0)
Hispanic/Latino	6 (4.9)	24 (6.7)
Non-Hispanic/Latino	108 (87.8)	304 (84.4)
Not specified	9 (7.3)	32 (8.9)
Race, n (%)	123 (100.0)	360 (100.0)
White	96 (78.0)	308 (85.6)
Black	10 (8.1)	20 (5.6)
Pacific Islander	0	3 (0.8)
American Indian/Alaskan Native	0	1 (0.3)
Asian	0	4 (1.1)
Other	1 (0.8)	0
Not specified	16 (13.0)	24 (6.7)
US geographic region, n (%)	117 (100.0)	351 (100.0)
Northeast	25 (21.4)	73 (20.8)
Midwest	33 (28.2)	101 (28.8)
South	45 (38.5)	115 (32.8)
West	14 (12.0)	62 (17.7)
ECOG, n (%)	97 (100.0)	304 (100.0)
0	15 (15.5)	67 (22.0)
1	55 (56.7)	153 (50.3)
≥ 2	27 (27.8)	84 (27.6)
Frailty group, n (%)	76 (100.0)	219 (100.0)
Mild	63 (82.9)	179 (81.7)
Moderate	11 (14.5)	33 (15.1)
Severe	2 (2.6)	7 (3.2)
ELN risk score, n (%)	123 (100.0)	360 (100.0)
Favorable/Intermediate-1	99 (80.5)	125 (34.7)
Intermediate-2/Adverse	18 (14.6)	218 (60.6)
Not completed	6 (4.9)	17 (4.7)
Induction regimen, n (%)	123 (100.0)	360 (100.0)
IC	38 (30.9)	90 (25.0)
Low IC	85 (69.1)	270 (75.0)

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; IC, intensive chemotherapy; US, United States.

Overall survival analysis by *NPM1* mutation status

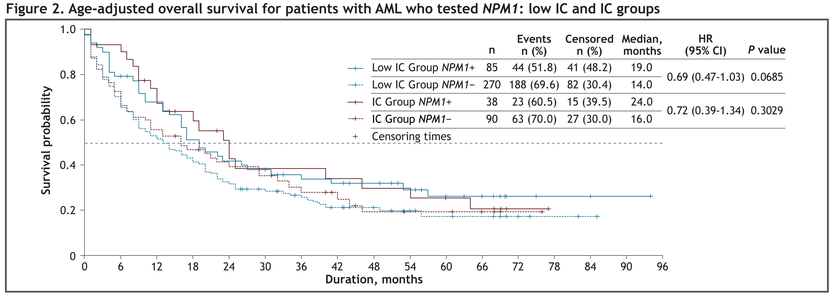
- Consistent with previous findings,[9-11] age-adjusted median OS was significantly longer in patients with *NPM1*+ AML vs *NPM1*− AML (26 vs 15 months; HR [95% CI]: 0.58 [0.44-0.76]; *P* < 0.01; **Figure 1**)

Figure 1. Age-adjusted overall survival for patients with *NPM1*+ AML vs *NPM1*− AML



- Regardless of whether they received a low IC or IC regimen, patients with *NPM1*+ AML had longer median OS than patients with *NPM1*− AML, although the difference was not statistically significant (**Figure 2**)
  - Among patients who received low IC regimens, median OS was 19 and 14 months in the *NPM1*+ and *NPM1*− groups, respectively
  - Among patients who received IC regimens, median OS was 24 and 16 months in the *NPM1*+ and *NPM1*− groups, respectively

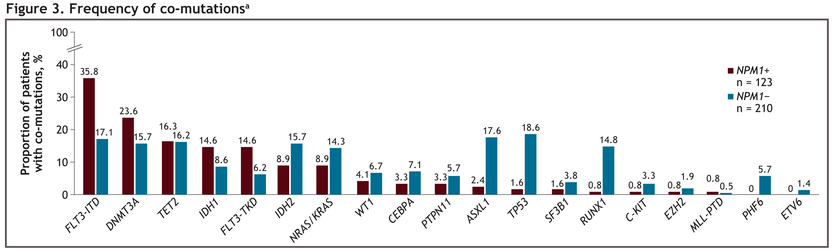
Figure 2. Age-adjusted overall survival for patients with AML who tested *NPM1*: low IC and IC groups



Analysis of co-mutational burden

- Patients with *NPM1*+ AML vs *NPM1*− AML had a lower frequency of certain key mutations typically associated with poor prognosis, such as *TP53* and *RUNX1* (**Figure 3**)

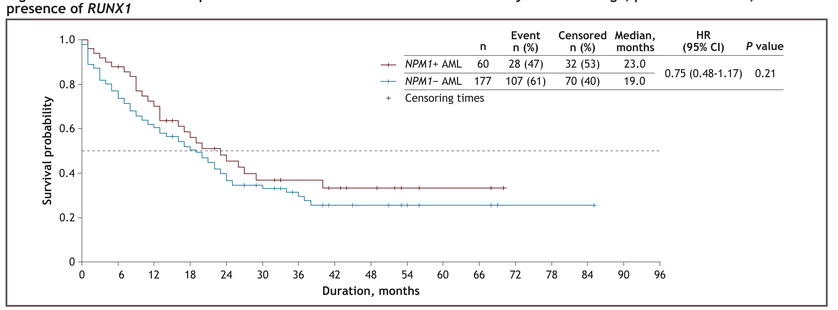
Figure 3. Frequency of co-mutations[a]



AML, acute myeloid leukemia.
[a]Co-mutations other than those listed were present in 24% of patients with *NPM1*+ AML and 54% of patients with *NPM1*- AML.

- Longer median OS was observed in patients with *NPM1*+ AML compared with *NPM1*− AML after adjusting for the presence of *TP53* and *RUNX1* mutations, although the difference was not statistically significant (23 vs 19 months; HR [95% CI]: 0.75 [0.48-1.17]; *P* = 0.21) (**Figure 4**)

Figure 4. Overall survival for patients with *NPM1*+ AML vs *NPM1*− AML after adjustment for age, presence of *TP53*, and presence of *RUNX1*



Strengths and limitations

- Because enrollment in the Registry is still ongoing, factors associated with therapy or diagnosis may change as more patients enroll
- As there were no scheduled clinic visits, evaluation intervals may have varied between patients. This could impact the assessment of outcome measures and limit comparisons of observational data with clinical trial results
- The Registry provides the opportunity to observe real-world patterns of treatment, diagnosis, and the changes that occur over time as treatment options and diagnostic testing guidelines evolve
- Furthermore, the Registry has the ability to query sites for more information on questionable data

Conclusions

- Consistent with observations in the clinical trial setting, in this analysis of patients with AML treated in real-world clinical practice, longer OS overall was observed in patients with *NPM1*+ AML compared to *NPM1*− AML
  - Patients with *NPM1*+ AML had longer OS with both low IC and standard IC induction regimens than patients with *NPM1*− AML
- These analyses did not consider co-mutations, which could also affect outcomes
- Patterns of co-mutations differed between the *NPM1*+ and *NPM1*− groups such that fewer patients in the *NPM1*+ group had mutations associated with poor prognosis including *TP53* and *RUNX1*
  - *FLT3-ITD* and *FLT3-TKD* mutations were present in 36% and 15% of patients with *NPM1*+ AML, respectively
  - Next-generation FLT3 inhibitors that are approved or currently under development may improve clinical outcomes of patients with *FLT3*+ AML[12,13]
- The co-mutational pattern of favorable and unfavorable mutations may contribute to the improved OS of patients with *NPM1*+ AML and poorer OS of patients with *NPM1*- AML; this was supported by the observation that the median OS of patients with *NPM1*+ AML was not significantly longer after adjusting for *TP53* and *RUNX1* mutations

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