RAS mutations negate the favorable impact of *NPM1* in older patients with newly diagnosed acute myeloid leukemia treated with HMA+VEN

Blood Cancer United

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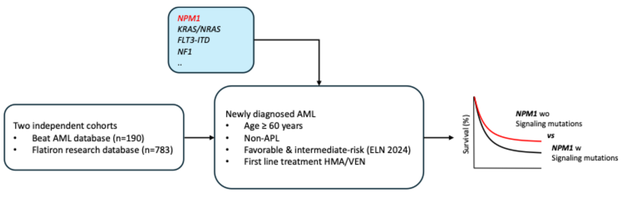
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Background

- Activating *RAS* mutations occur in approximately 15-20% of patients with newly diagnosed (ND) acute myeloid leukemia (AML)
- The ELN 2024 classifies *RAS* and/or *FLT3*-ITD mutations as intermediate risk in patients treated with venetoclax (VEN) and azacitidine.
- The ELN 2024 no longer classifies *NPM1* mutations as favorable risk when co-occurring with signaling gene (SG) mutations (i.e., *FLT3*, *NRAS*, *KRAS*).
- Given the small number of patients with a co-occurring *NPM1* and *RAS* mutation (n=8) or *FLT3*-ITD (n=16) in the original study, it is unclear whether these patients truly have worse outcome compared with those without SG mutations.
- We aimed to investigate the prognostic impact of *NPM1* alone and in the co-presence of SG mutations, among older patients (≥60 years) with favorable- or intermediate-risk AML per ELN 2024 who were treated with VEN in combination with a hypomethylating agent (HMA).

Methods



- Mutation analysis (next-generation sequencing or polymerase chain reaction) was performed at diagnosis.
- Overall survival (OS) was estimated using the Kaplan-Meier method. OS was defined as the date of consent (Beat AML) or start of 1L (Flatiron) to the date of death, allogeneic stem cell transplantation, or last follow-up.

Results

BEAT AML DATABASE (N=190)

Variable	All (N=190)	*NPM1*^{mut} (n=40)	*NPM1*^{wt} (n=150)	*P*
Age				
Median (range)	74 (61-89)	73 (62-89)	74 (61-87)	0.596
ELN 2024				
Favorable	130 (68)	20 (50)	110 (73)	0.009
RAS/MAPK mutations				
NRAS	30 (16)	8 (20)	22 (15)	0.563
KRAS	17 (9)	4 (9)	13 (10)	0.760
PTPN11	23 (12)	9 (23)	14 (9)	0.031
CBL	20 (11)	3 (8)	17 (11)	0.577
NF1	10 (5)	0 (0)	10 (7)	0.124
≥ 1 mutation	80 (42)	19 (48)	61 (41)	0.550
Tyrosine kinase receptor				
FLT3-ITD				
KIT	21 (11)	12 (30)	9 (6)	0.001
≥ 1 mutation	9 (5)	2 (5)	7 (5)	1.000
	29 (15)	13 (33)	16 (11)	0.002
JAK/STAT				
JAK2	26 (14)	2 (5)	24 (16)	0.117
MPL	8 (4)	0 (0)	8 (5)	0.207
CSF3R	6 (3)	1 (3)	5 (3)	1.000
≥ 1 mutation	36 (19)	3 (8)	33 (22)	0.064

FLATIRON HEALTH RESEARCH DATABASE (N=783)

Variable	All (N=783)*	*NPM1*^{mut} (n=120)	*NPM1*^{wt} (n=654)	*P*
Age				
Median (range)	76 (60-84)	75 (60-84)	76 (60-84)	0.333
ELN 2024				
Favorable	629 (80)	97 (81)	525 (80)	0.987
RAS/MAPK mutations				
NRAS (n=774)	110 (14)	16 (13)	92 (14)	1.000
KRAS (n=774)	64 (8)	8 (7)	56 (9)	0.715
NF1 (n=518)	37 (7)	8 (7)	28 (4)	0.341
≥ 1 mutation (n=565)	175 (31)	26 (22)	146 (22)	1.000
Tyrosine kinase receptor				
FLT3-ITD (n=472)	95 (20)	30 (25)	65 (10)	<0.001
KIT (n=766)	19 (2)	3 (3)	16 (3)	1.000
≥ 1 mutation (n=469)	112 (24)	32 (27)	80 (12)	<0.001
JAK/STAT				
JAK2 (n=753)	52 (7)	2 (2)	49 (7)	0.023
MPL (n=665)	12 (2)	3 (3)	9 (1)	0.398
CSF3R (n=740)	11 (1)	1 (1)	10 (2)	1.000
≥ 1 mutation (n=662)	70 (11)	6 (5)	63 (10)	0.153

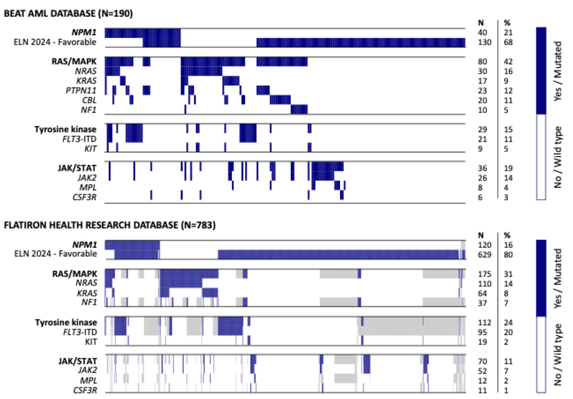
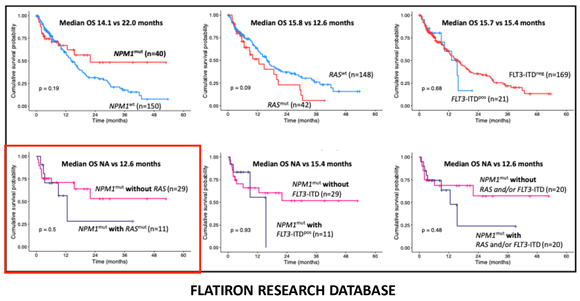
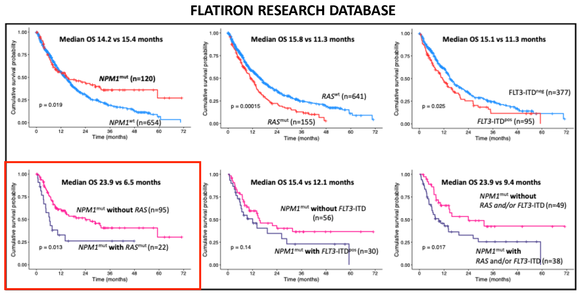


Figure. Categorical heatmap showing relevant myeloid signaling mutations. Each horizontal line represents an individual patient.

BEAT AML DATA BASE



FLATIRON RESEARCH DATABASE



- In patients enrolled on the Beat AML trial, *NPM1*^{mut} (n=40) was associated with a trend toward increased OS compared to *NPM1*^{wt} (n=150) (2-yr OS 49% vs 31%, p=0.19).
- *NPM1*^{mut} without *RAS*^{mut} (n=29) had a non-significant superior 2-yr OS compared to *NPM1*^{mut} with *RAS*^{mut} (n=11) (2-yr OS 53% vs 28%, p=0.50).
- In patients included in the real-world Flatiron database, *NPM1*^{mut} (n=120) was associated with a superior median OS compared to *NPM1*^{wt} (n=654) (2-yr OS 43% vs 31%, p=0.01).
- Median OS of *NPM1*^{mut} in the presence of *RAS*^{mut} (n=22) was significantly shorter compared to *NPM1*^{mut} with wildtype *RAS* (n=95). *FLT3*-ITD did not impact outcome of *NPM1*.

Conclusions & discussion

- We demonstrated that while *NPM1*^{mut} were prognostically favorable among patients treated with HMA+VEN, the presence of co-occurring RAS mutations, rather than *FLT3*-ITD, negates the favorable effect of *NPM1*^{mut} in ND older adults with AML.
- Further investigation of the prognostic impact of other signaling mutations, such as *NF1* and *PTPN11* is needed
- Given that the 4-gene risk model showed improvement with VEN+AZA over AZA among all prognostic risk groups, further investigation of triplets with an HMA+VEN as the backbone is warranted for patients with *NPM1*^{mut}*RAS*^{mut} AML

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