

Mutations Highly Specific for Secondary AML are Associated with Poor Outcomes in Patients with *NPM1*-Mutated ELN Favorable Risk AML

Onyee Chan MD¹, Najla Al Ali M.Sc¹, Seongseok Yun MD, PhD¹, Chetasi Talati MD¹, Andrew Kuykendall MD¹, Eric Padron MD¹, David Sallman MD¹, Kendra Sweet MD¹, Rami Komrokji MD¹, Jeffrey Lancet MD¹

¹Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA



Introduction

- NPM1* is commonly mutated in AML and represents a distinct entity under the WHO 2016 classification [1].
- It is one of the few mutations that can potentially support favorable risk by ELN 2017 [2].
- Mutations that are highly specific for secondary AML including *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, and *STAG2* (sMut) have been shown to confer poor prognosis [3].

Objective

To assess what factors and mutations affect outcomes in patients with *NPM1*-mutated AML

Methods

- This was a retrospective study of *NPM1*-mutated AML patients who were treated at the Moffitt Cancer Center from 2013-2020.
- Only those with *NPM1* mutations and NGS performed at diagnosis were included in the study (n=115).
- Kaplan-Meier, univariate, and multivariate analyses were performed.

Results

Table 1. Baseline characteristics of the study cohort.

	All patients N (%)
Number of patients	115
Gender	
Male	54 (47)
Female	85 (53)
Median age at diagnosis (range)	61 (22-86)
Type of AML	
De Novo	96 (83.5)
Secondary	14 (12.2)
Therapy-related	5 (4.3)
ELN Risk	
Favorable	64 (55.7)
Intermediate	41 (35.6)
Adverse	10 (8.7)
Cytogenetics	
Normal	91 (79.1)
Complex karyotype	5 (4.3)
Most common mutations (Top 6)	
DNMT3A	55 (47.8)
FLT3-ITD	45 (39.1)
TET2	23 (20)
FLT3-TKD	21 (18.3)
IDH1	21 (18.3)
IDH2	19 (16.5)
^a Secondary AML related mutations	19 (16.5)
Mutation burden (average)	3.4
Treatment	
Frontline	
Intensive	96 (83.5)
Non-intensive	16 (13.9)
No treatment	3 (2.6)
No relapse after CR/CRi	55 (47.8)
Relapse after CR/CRi	42 (36.5)
Never achieved CR/CRi	18 (15.7)
Lines of therapy (average)	2.4
Allogeneic HCT	52 (45.2)
Median OS (months)	49.1

Table 2. Univariate analysis showed sMut and alloHCT significantly impacted OS. Multivariate regression confirmed their survival prognostic significance.

Variable	Overall Survival					
	HR	Univariate 95% CI	P	HR	Multivariate 95% CI	P
Age > 60 at diagnosis	2.26	0.94-5.41	0.068	0.69	0.23-2.12	0.521
^a Type of AML						
Secondary AML	0.78	0.23-2.68	0.689	1.00	0.27-3.70	0.998
Therapy-related AML	2.94	0.37-23.20	0.306	2.46	0.30-20.05	0.402
Mutation burden > 3	1.03	0.47-2.25	0.940	0.60	0.24-1.50	0.271
^a Mutations related to sAML	3.86	1.75-8.54	<0.001	5.12	1.72-15.22	0.003
HCT (Received)	0.24	0.09-0.65	0.005	0.26	0.09-0.76	0.014

More Results

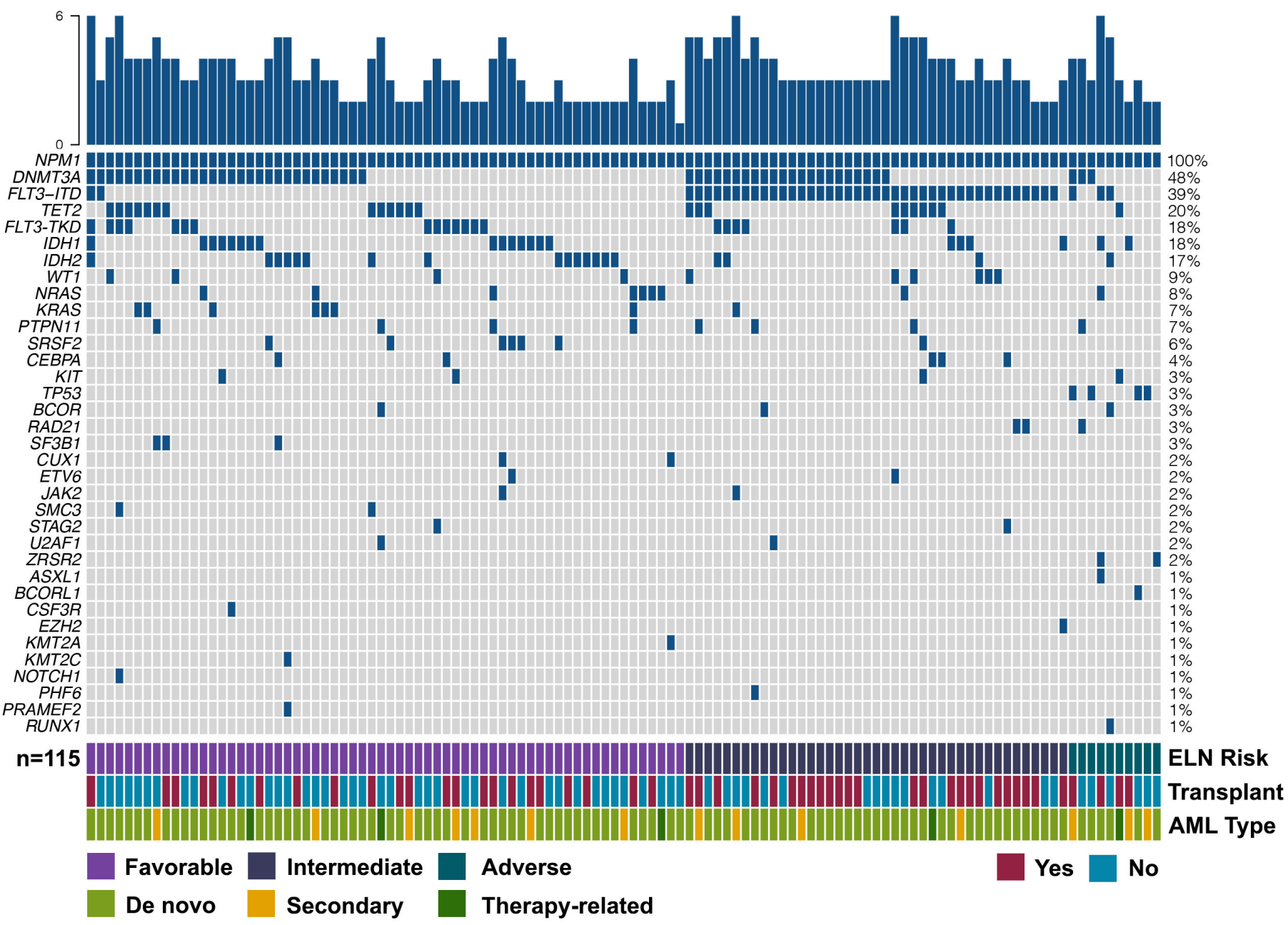


Figure 1. Mutation landscape of the entire cohort.

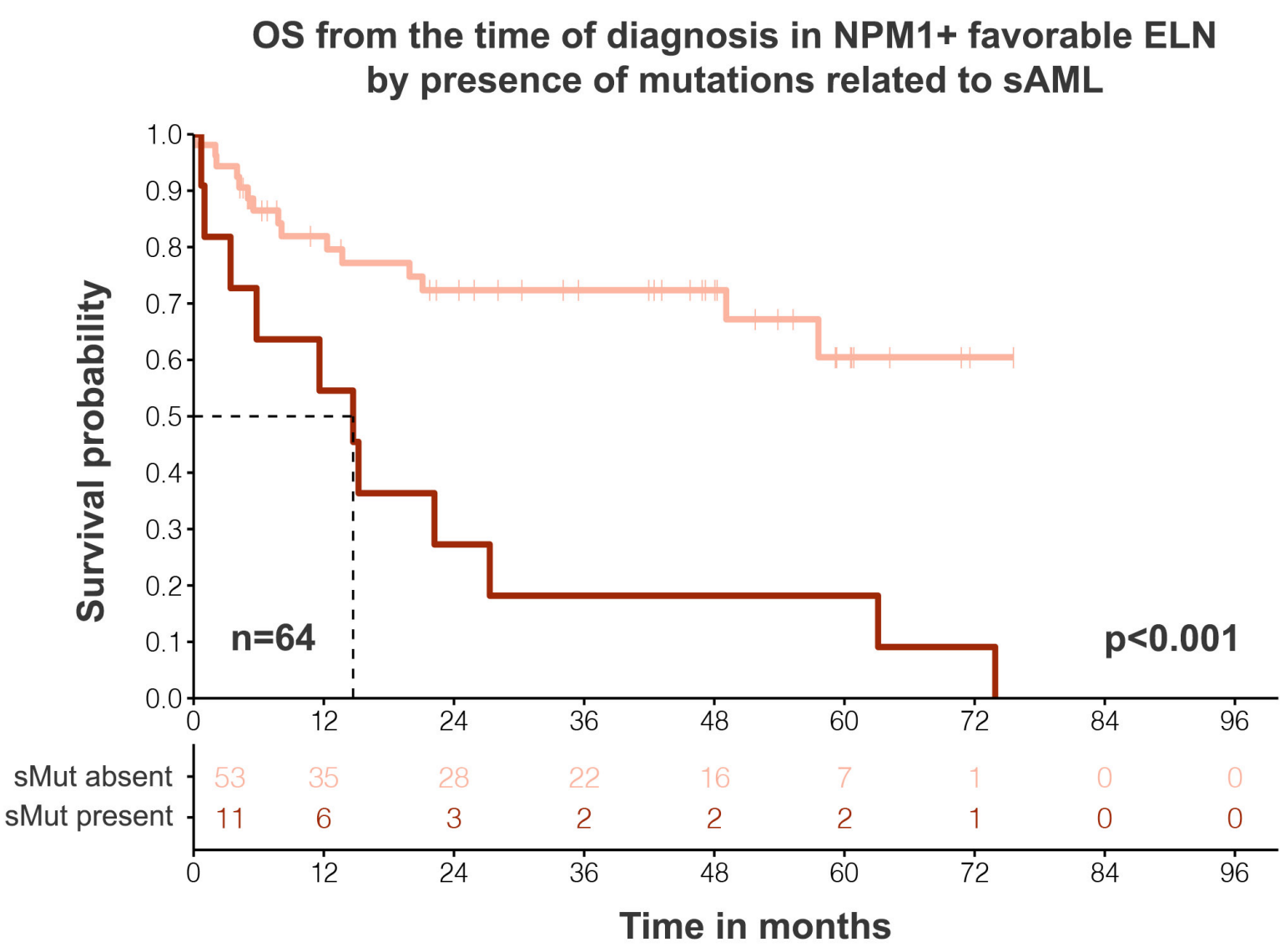


Figure 2. Overall survival from the time of diagnosis in *NPM1*+ favorable risk ELN patients by the presence of mutations related to secondary AML.

Conclusions

- NPM1*-mutated AML patients with sMut have significantly worse prognosis despite being classified as favorable risk by ELN 2017 at diagnosis.
- This may have treatment implications in the need for and/or timing of HCT.
- Further studies and larger datasets are needed to confirm these observations.

References

- Arber DA et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016.
- Dohner et al. Diagnosis and management of AML in adults: 2017 ELN... *Blood* 2017.
- Lindsley et al. AML ontogeny is defined by distinct somatic mutations. *Blood* 2015.