Poor Prognosis of SRSF2 Gene Mutations in Patients Treated with Venetoclax-Azacitidine (VEN-AZA) for Newly Diagnosed Acute Myeloid Leukemia. a Multicentric Real-Life Study of 117 Patients

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INTRODUCTION

- **Spliceosomes** are complexes composed of small nuclear RNA that remove introns in protein-encoding genes
- Spliceosome mutations (***SRSF2***, ***SF3B1***, ***U2AF1***, ***ZRSR2***[1]) are encountered in ~50% of secondary AML cases
- Splicing mutations (splice-mut), in particular *SRSF2*, correlate with **inferior outcomes to standard induction therapy**
- A recent report reported the **lack of impact of splice-mut** on prognosis of AML patients treated upfront with **Hypomethylating agents (HMA) + VEN** in clinical trials[2]

AIM

To assess the impact of splicing mutations in a population of patients with newly diagnosed acute myeloid leukemia (ND-AML), treated with VEN-AZA.

METHOD

We performed **a retrospective multicentric study**

Included patients were treated in **three centers** :
- Institut Paoli-Calmettes
- CHU La Conception
- Hôpital L'Archet

Inclusion criterias were :
- **ND-AML** adult patients
- Treatement with **VEN and AZA**
- Available **NGS** at diagnosis

RESULTS

117 ND-AML patients were included
34 patients (29%) had at least 1 splice-mut

Best overall response rate was 72.6%
CR, CRi and MLFS were 54%, 14% and 5%

Only **prior HMAs and *TET2* mutation** were predictive of **lower response rates**
(42% vs 82%, p=0.004, and 64% vs 85%, p=0.025)

Only ***IDH2* mutation** was predictive of **better response** (100%vs 75%, p=0.037)

In multivariate analysis, **SRSF2** mutation was predictive of **worse OS and LFS**

SRSF2mut patients had 4.8mos OS and 5mos LFS versus 11.3 and 8mos, respectively
(p=0.034 and p=0.037)

Splice-mut were predictive of **worse LFS**
(5.1mos vs 10.4 mos, p= 0.0045) but not worse OS

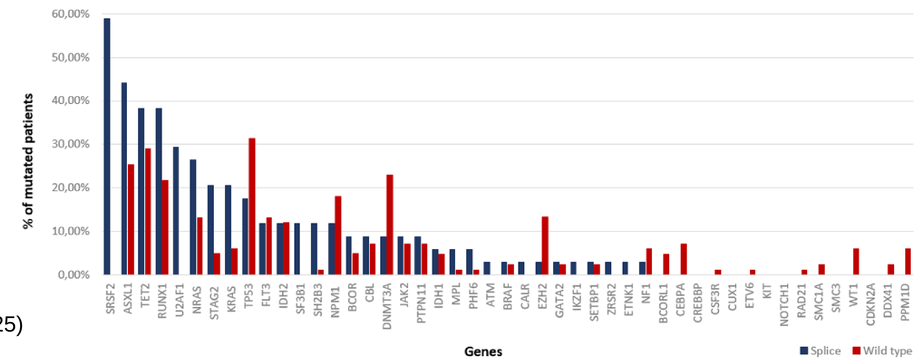

Fig.1 Proportion of mutations in Splice-mut and Splice-wt cohorts

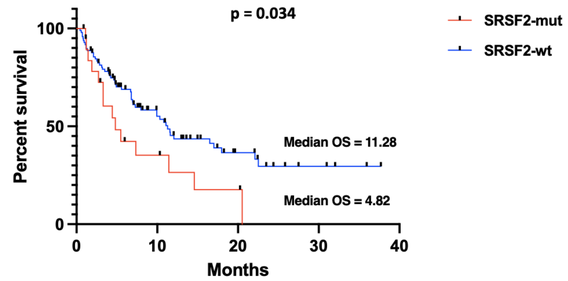

Fig.2 Overall Survival for SRSF2-mut and SRSF2-wt patients

	Splice-mut (N = 34)	Splice-wt (N = 83)
Median age at diagnosis	75 (57-85)	75 (32-89)
Prior MDS	11 (32.4%)	12 (14.5%)
Therapy related	5 (14.7%)	15 (18.1%)
Prior HMAs	7 (20.6%)	6 (7.2%)
Cytogenetics		
Complex	7 (20.6%)	28 (33.7%)
del5q	4 (11.8%)	20 (24.1%)
del7	2 (5.9%)	16 (19.3%)
del17	1 (2.9%)	9 (10.8%)

CONCLUSIONS

***SRSF2* mutation** seems to be **predictive of worse survival in ND-AML** patients treated with **VEN-AZA**

This finding warrants further exploration in larger cohorts

REFERENCES

1 **Papaemmanuil, E. et al.** Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N. Engl. J. Med.* **374**, 2209–2221 (2016)

2 **Lachowiez, C. A. et al.** Impact of splicing mutations in acute myeloid leukemia treated with hypomethylating agents combined with venetoclax. *Blood Adv.* 5, 2173–2183 (2021)

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