



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

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*), 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 in a cohort of 119 patients, of whom 33 had splice mutations and 24 were *SRSF2* mutated, reported the lack of impact of splice-mut on prognosis of AML patients treated upfront with Hypomethylating agents (HMA) + VEN in clinical trials (Lachowicz, C. A. et al Blood Adv. 2021).

Aims

We aimed to assess the impact of splice-mut in a population of patients with newly diagnosed acute myeloid leukemia (ND-AML), treated with VEN-AZA.

Methods

We performed a retrospective multicentric study including patients treated in three French centers in Marseille (Institut Paoli-Calmettes, CHU La Conception) and Nice (Hôpital L'Archet). Inclusion criterias were ND AML adult patients treated with VEN (7 to 28 days per cycle) and AZA at conventional doses. Next Generation Sequencing (NGS) was performed at diagnosis and was available for all patients. Data were collected from patients' electronic medical records. Statistical analyses were performed using GraphPad Prism v9.5.1

Results

We included 117 ND-AML patients (median age = 75 yo; range, 32-89) treated with VEN-AZA between October 2019 and March 2023. The five most frequently mutated genes in the whole cohort were *TET2*, *ASXL1*, *TP53* and *RUNX1* in thirty-seven (32%), 36 (31%), 32 (27%) and 31 (26%) patients, respectively. Thirty-four patients (29%) had a mutation in at least one of the spliceosome genes (=Splice-mut), including 20 (17%), 11 (9%), 4 (3%) and 1 (1%) mutations in *SRSF2*, *U2AF1*, *SF3B1* and *ZRSR2*, respectively (**Fig.1**). Median variant allele frequency (VAF) was 42%, 43% and 26% for *SRSF2*, *U2AF1* and *SF3B1* respectively. Secondary AML was found in 18 (53%) of the splice-mut AML and 21 (25.3%) of the splice-wt AML groups of patients. Prior

HMA was given in seven (20.6%) patients in the splice-mut versus 6 (7.2%) in the splice-wt cohort. Complex cytogenetics was identified in 7 (20.6%) patients in the splice-mut cohort and 28 (33.7%) in the splice-wt cohort. We found a *TP53* mutation in 17.6% and 31.3% of splice-mut and wt cohorts, respectively. Best overall response rate (= CR, CRi and MLFS) was 72.6%; with CR, CRi and MLFS observed in 63 (54%), 16 (14%) and 6 (5%) patients, respectively. We did not find any difference in response rate between the splice-mut (=73.5%) and splice-wt (72.3%) AML. Prior treatment with hypomethylating agents and *TET2* mutation were the only factors significantly associated with lower response rates (42% vs 82%, $p=0.004$, and 64% vs 85%, $p=0.025$, respectively), while *IDH2* mutation was predictive of a better response (100% vs 75%, $p=0.037$, OR: 9.9 [CI 95% 0.57-173]). Median overall survival (OS) and leukemia-free survival (LFS) for the whole cohort was 10.8 and 7.1 months, respectively. In multivariate analysis taking into account *TP53* and/or del17p, *NRAS*mut and/or *FLT3-ITD*, *IDH2*mut, complex karyotype, and *SRSF2*, the only factors predicting OS and LFS were mutations in *TP53* and *SRSF2* genes. Patients mutated for *SRSF2* had a 4.8 months OS and a 5 months LFS compared to 11.3 and 8 months, respectively ($p=0.034$ and $p=0.037$), comparable with *TP53*mut AML patients (**Fig.2**).

Conclusions

*SRSF2*mut seems to be predictive of a worse survival in ND AML treated with VEN-AZA. This finding warrants further exploration in larger cohorts.

Disclosures Loschi: AstraZeneca: Honoraria; BMS: Honoraria; Gilead: Honoraria; GSK: Honoraria; Jazz: Honoraria; Kartos: Honoraria; Medac: Honoraria; MSD: Honoraria; Novartis: Honoraria; Pfizer: Honoraria; Sanofi: Honoraria; Sobi: Honoraria; Telios: Honoraria; Alexion: Honoraria. **Charbonnier:** Pfizer, Novartis, Incyte Biosciences: Honoraria. **Venton:** Novartis, Abbvie, Jazz, BMS, Janssen, GSK, Astrazeneca, Gilead: Consultancy. **Cluzeau:** Novartis: Consultancy, Speakers Bureau; Abbvie: Consultancy, Speakers Bureau; Jazz Pharma: Consultancy, Speakers Bureau; Syros: Speakers Bureau; Keros: Speakers Bureau; Servier: Consultancy, Speakers Bureau; Incyte: Speakers Bureau; BMS: Consultancy, Speakers Bureau.

Fig.1

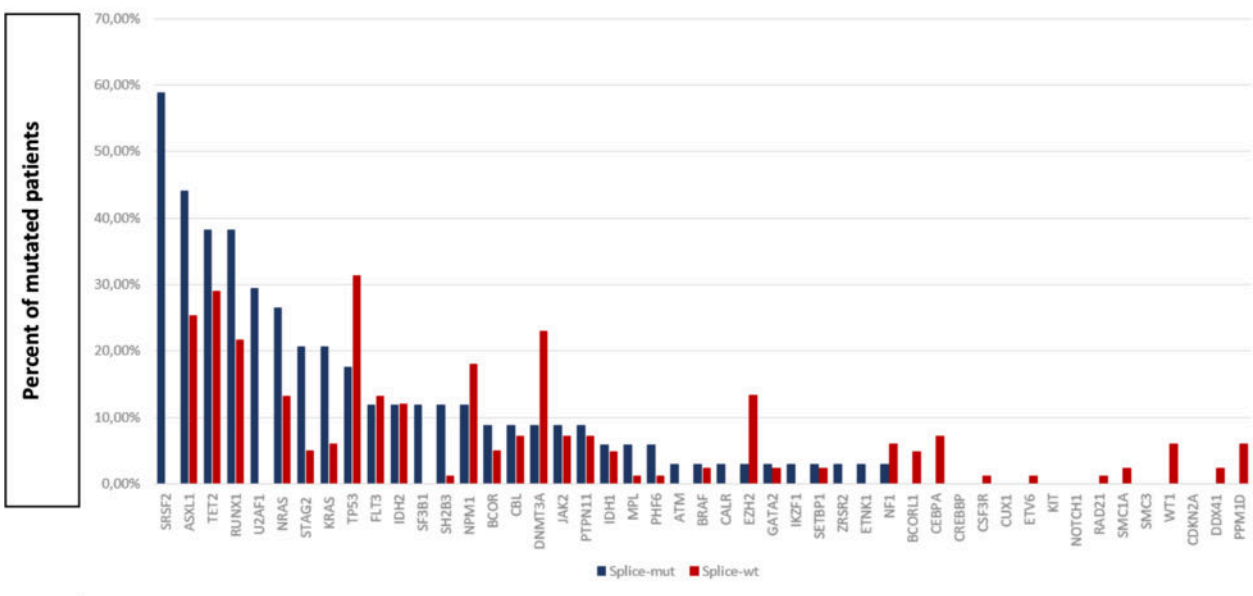


Fig.2

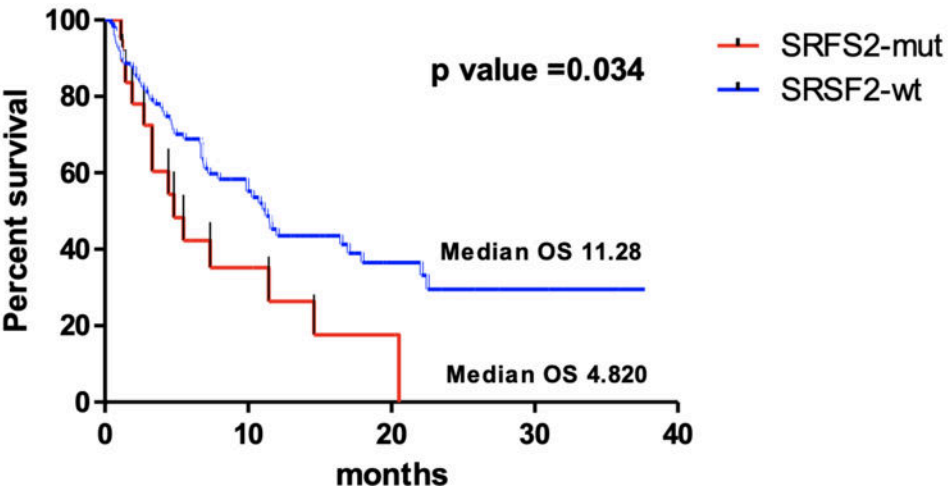


Figure 1

<https://doi.org/10.1182/blood-2023-180733>