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P985 THE ALLELIC RATIO OF DRIVER AND ASXL1 MUTATIONS IS PROGNOSTICALLY RELEVANT IN PMF

Topic: 15. Myeloproliferative neoplasms - Biology & Translational Research

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Background: Primary myelofibrosis (PMF) is a clonal disorder driven by mutations in *JAK2*, *CALR*, and *MPL*. Somatic mutations in myeloid-associated genes were shown to impact prognosis of PMF patients (pts). Among these, *ASXL1* mutations (*ASXL1*^{mt}) are by far the most frequent and prognostically relevant, in fact they are included in the category of "high molecular risk" (HMR), along with *EZH2*, *IDH1/2*, *SRSF2*, and *U2AF1*^{Q157} mutations.

Aims: To investigate the phenotypic and prognostic implications of *ASXL1*^{mt} and variant allele frequency (VAF) in PMF.

Methods: After IRB approval, consecutive pts with WHO-defined PMF were included in the study. Mutational analysis by targeted NGS was performed by previously described methods (Guglielmelli P *et al.*, JCO 2017).

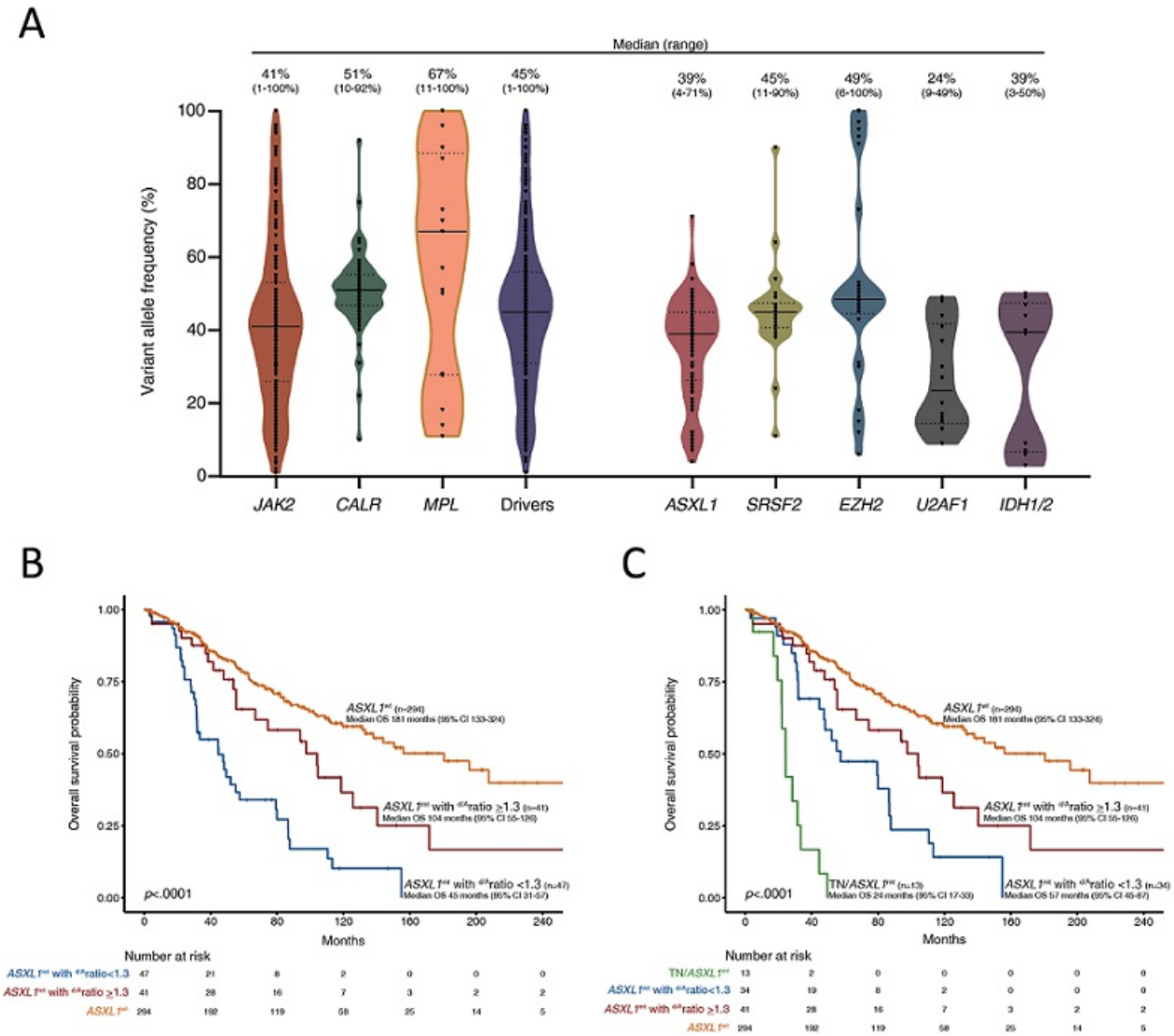
Results: The study enrolled a total of 384 pts, including 190 (49%) prefibrotic and 194 (51%) overt PMF. Median age was 60 (18-90) years, 236 (61%) were male. *JAK2*, *CALR* and *MPL* mutations were found in 255 (66%), 83 (22%), and 17 (4%) pts, respectively; 36 (9%) were triple negative (TN). Among HMR mutations, *ASXL1* was mutated in 88 (23%) pts, *SRSF2* in 35 (9%), *EZH2* in 32 (8%), *U2AF1* in 15 (5%), and *IDH1/2* in 11 (3%). VAF distribution of driver and HMR mutations was as reported in Fig.1A.

We did not find any significant correlation of *ASXL1*^{mt} VAF with other clinical and molecular characteristics, including PMF subtype, gender, age, hemoglobin, leukocyte, platelet and blast counts, splenomegaly, BM fibrosis grade, cytogenetics, mutational status for driver and other HMR genes and their VAFs. The only exception was the association of *CALR*-mutated PMF with lower *ASXL1* VAF (median 28% *vs* 40%, p=.0332).

Median overall survival (OS) was 120 (102-151) months. In univariate Cox analysis, *ASXL1*^{mt} VAF did not correlate with OS, nor did other single driver and HMR mutations. When considered as a whole (for the purpose of this study, TN pts were considered has having driver VAF equal to 0), the VAF of driver mutations inversely correlated with survival (HR 0.4 [0.2-0.9], p=.0219). We next investigated the allelic ratio between driver and *ASXL1* mutations ($^{d/A}$ratio) and its prognostic correlates. Median (range) of $^{d/A}$ratio was 1.24 (0-13), and ROC analysis with death as an endpoint identified 1.31 as the optimal cut-off value. In univariate analysis, pts with a $^{d/A}$ratio <1.31 had a significantly worse OS compared to those with a ratio ≥1.31 (median 45 *vs* 104 months, p=.0014; HR 2.4 [1.4-4.1]) (Fig.1B). When TN pts with *ASXL1*^{mt} were considered apart, having a $^{d/A}$ratio <1.31 retained its inferior prognostic impact compared to the $^{d/A}$ratio ≥1.31 group (median OS 57 *vs* 104 months, p<0.0453; HR 1.8 [1-3.2]), with TN/*ASXL1*^{mt} pts being associated with the worst outcome (median OS 24 months) (Fig.1C).

In a multivariate Cox model including VAF-adjusted *ASXL1* mutant status (*ASXL1*^{wt} *vs* *ASXL1*^{mt} with $^{d/A}$ratio ≥1.3 *vs* *ASXL1*^{mt} with $^{d/A}$ratio <1.3) and other HMR mutations, the former and mutated *SRSF2* were confirmed to be independent predictors of inferior OS. Both $^{d/A}$ratio <1.31 and ≥1.31 remained significant compared to *ASXL1*^{wt} with respective HRs of 3.4 (2.3-5.1; p<.0001) and 1.6 (1-2.6; p=.0342). Notably, $^{d/A}$ratio <1.31 still retained its inferior prognostic impact compared to $^{d/A}$ratio ≥1.31 (HR 2 [1.2-3.5]; p=.0095).

Image:



Summary/Conclusion: This study explores the implications of *ASXL1*^{mt} VAF and its interplay with driver mutant burden. The adverse prognosis of pts with a $^{d/A}$ratio <1.31 suggests that this disease entity is predominantly driven by *ASXL1*^{mt}-clones characterized by a more aggressive biology. Further research is needed.

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