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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

The Significance of Variant Allele Frequency in *SF3B1* Mutated Myelodysplastic Neoplasms/Syndromes

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Introduction:
Recent iterations of the World Health Organization (WHO) and international consensus classification (ICC) guidelines for myelodysplastic neoplasms (MDS) refined disease defining characteristics through incorporation of morphologic and genetic criteria. Despite these welcome updates, discrepancies between the WHO and ICC remain, particularly with respect to variant allele frequency (VAF) threshold in disease defining mutations such as *SF3B1* and *TP53*. We evaluated patients with *SF3B1*-mutated MDS, a specific molecular class of MDS in both classification schemes , providing additional biologic and survival information to inform both diagnosis and prognosis.

Methods:
We queried the International Working Group for Prognosis in MDS (IWG-PM) cohort of adult (age ≥ 18 years) patients (pts) with MDS (N= 3,323; Bernard et al. *NEJM Evidence* 2022) for baseline clinical demographic, cytogenetic and molecular information, and clinical outcomes. *SF3B1* VAF was assessed using targeted next generation sequencing. Demographics were analyzed using descriptive statistics. Between group differences were assessed using the Wilcoxon rank-sum test or Fisher's exact test as appropriate. Time to event endpoints were analyzed using the log-rank method. Multivariate analysis utilized cox proportional hazards regression.

Results:
We identified 447 (14%) pts met WHO 5th criteria for MDS with low blasts and *SF3B1* mutation. Among these, 30 (7%) of pts had a *SF3B1* VAF < 10% (*SF3B1* ^{low};currently classified as MDS, not otherwise specified by ICC) while 93% (N=417/447) had *SF3B1* VAF of ≥ 10% (*SF3B1* ^{high}). Median VAF in pts with *SF3B1* ^{low} vs. *SF3B1* ^{high} was 6% (range: 2.2-9.9%) vs. 37% (range: 10.9-54.1%). Pts with *SF3B1* ^{low} vs. *SF3B1* ^{high} were older (median age 79 vs. 74, p=0.010), and had lower median platelet (185 x10 ^{9}/L vs. 264 x10 ^{9}/L, p < 0.001) and white blood cell levels (3.94 x10 ^{9}/L vs. 5.46 x10 ^{9}/L , p < 0.001).
The median number of mutations other than *SF3B1* in *SF3B1* ^{low} and *SF3B1* ^{high} was 2 (range: 0-5 vs. 0-8, p=0.42), and *SF3B1* was the sole genetic alteration in 10% vs. 20%, respectively (OR=2.2, p=0.24). Common *SF3B1* variants in *SF3B1* ^{low} vs. *SF3B1* ^{high} included p.K666 (27% vs. 10%, OR: 0.31, p=0.01) and p.K700 (50% vs. 59%, OR: 1.42, p=0.44).
In pts with *SF3B1* ^{low}, single-hit mutations in *TP53* (13% vs. 3%, OR: 0.21, p=0.021), *SRSF2* (10% vs. 3%, OR: 0.25, p=0.06), and *RUNX1* (7% vs. 4%, OR: 0.60, p=0.37) were more frequent (Fig. A). Other co-mutations had similar frequencies in *SF3B1* ^{low} vs. *SF3B1* ^{high} MDS: *TET2* (33% vs. 42%, OR: 1.45, p=0.44), *DNMT3A* (23% vs. 27%, OR 1.22, p=0.83), *ASXL1* (17% vs. 13%, OR:

0.71, p=0.57).The distribution of *SF3B1* VAF, and observed patterns of co-mutations did not differ by sample type (peripheral blood or bone marrow).
More pts with *SF3B1* ^{low} vs. *SF3B1* ^{high} (76% vs. 46%, p: 0.0011) had a subclonal *SF3B1* mutation compared with other co-occurring mutations. In the 213 (48%) pts with subclonal *SF3B1*, the most frequent dominant mutations included *TET2* (35%, N=75), *DNMT3A* (21%, N=45), and *ASXL1* (4%, N=8). Among the top co-mutations in *SF3B1* ^{low} vs. *SF3B1* ^{high}, *SF3B1* ^{low} was more frequently subclonal to *TP53* (50% vs. 0%, p=0.04), *SRSF2* (33% vs. 0%, p=0.2), and *RUNX1* (50% vs. 0%, p=0.1). As anticipated, *SF3B1* ^{high} cases were enriched for very-low/low risk IPSS-M subtypes (78% vs. 43%, OR: 2.9, p=0.011) compared to *SF3B1* ^{low} cases which had an increased frequency of moderate IPSS-M subtypes (30% vs. 14%, OR: 0.39, p=0.03; Fig.B).
Median leukemia free survival (LFS; 5 vs. 6 years, p=0.10) was not significantly different between pts with *SF3B1* ^{low} vs. *SF3B1* ^{high} MDS. Median overall survival (OS; 5 vs. 6.2 years, p=0.04) was significantly shorter in pts with *SF3B1* ^{low}, however after adjusting for *SF3B1* VAF, age, and IPSS-M score, only age (HR: 1.05 95% CI: 1.03-1.07, $p < 0.0001$), and increasing IPSS-M score (HR: 2.60 95% CI: 2.10-3.20, $p < 0.0001$) significantly associated with OS.

Conclusion:

Patients with MDS with *SF3B1*-mutation VAF < 10% are older and have an increased frequency of other clonally dominant co-mutations in adverse risk genes (i.e., *TP53*, *SRSF2, RUNX1*). Despite more adverse disease biology, LFS and OS were similar between pts with *SF3B1* ^{low} vs. *SF3B1* ^{high} with respect to *SF3B1* VAF after accounting for age and IPSS-M score. Future diagnostic and prognostic schema could account for differences in *SF3B1* ^{low}disease biology through use of comprehensive prognostic tools such as the IPSS-M score.

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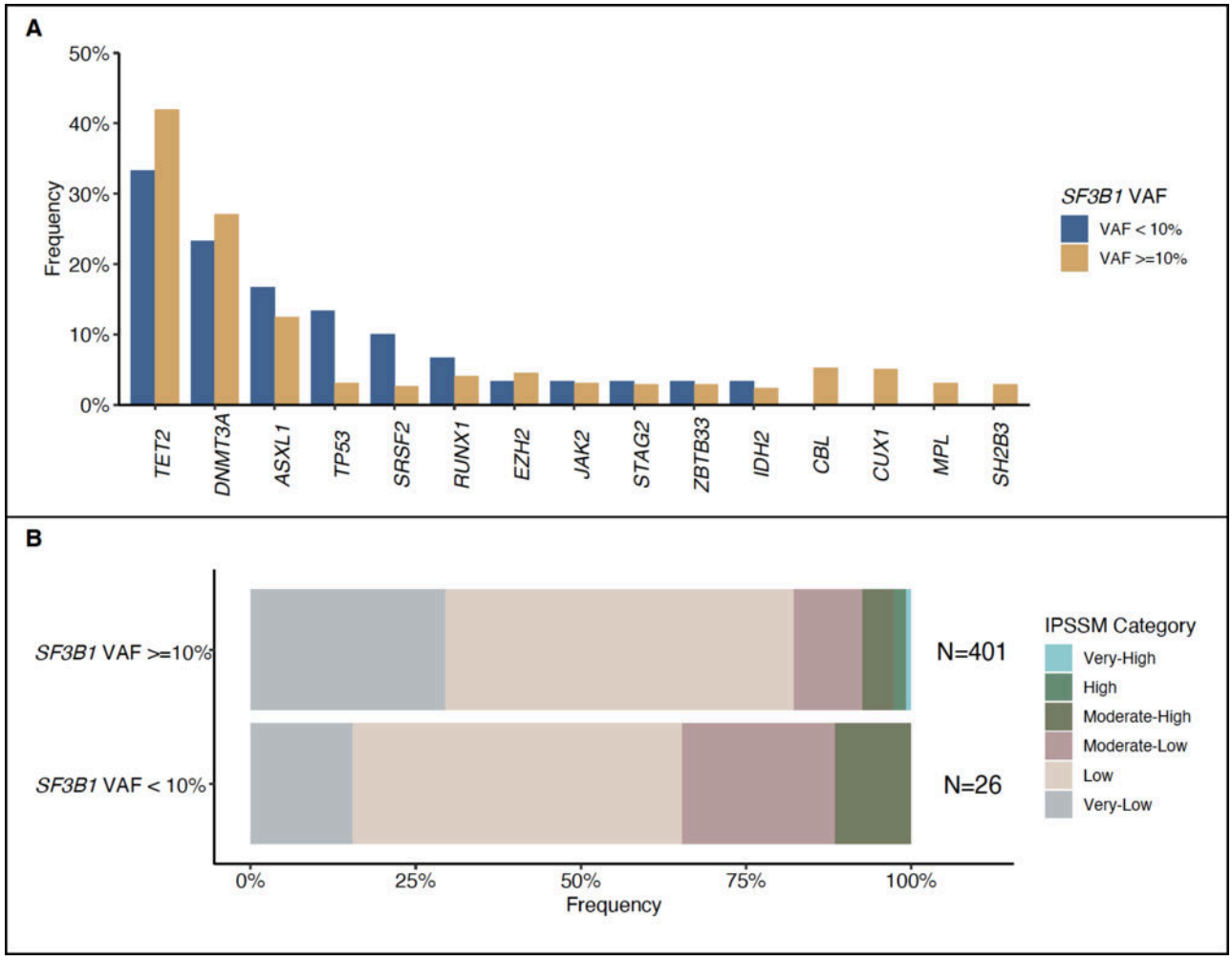

Figure 1

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