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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

STAG2 and *PHF6*: Comparison of 2 X-Linked Gene Mutations in Myeloid Neoplasms

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INTRODUCTION:
The Stromal Antigen 2 (*STAG2*), on Xq25, is the most common cohesin complex gene mutated in myeloid neoplasms (MN) (5-10%). *STAG2* mutations (*STAG2*m) were incorporated in the ELN2022 as AML-MDS defining genetic mutations inferring poor prognosis and is a genetic marker in IPSS-M risk stratification. The PHD-finger protein 6 (*PHF6*) gene, on Xq26.3, is a tumor suppressor gene, mutated in 3% of MN, and is more common in T-ALL. *PHF6*m is believed to be a late event in MN with little data on its prognostic implications in MN. Both *STAG2*m and *PHF6*m are more prevalent in males, but their implications on the clinical presentation of MN have not been compared prior.

METHOD:
Our study is a multicenter study at Mayo Clinic (Rochester, Florida, Arizona). After IRB approval, we retrospectively analyzed charts of 7935 patients who had NGS between 2016-2022. *STAG2*m was found in 96 patients, and *PHF6*m in 116 (including 3 with concurrent *STAG2*m and *PHF6*m). We excluded 4 PHF6m patients who had T-ALL. Data was captured at time of NGS. MDS risk stratification was by IPSS-M and AML by ELN2022. Overall survival (OS) was calculated from date of NGS to date of last follow-up. BlueSky Software was used for statistical analysis.

RESULTS:
Characteristics: We compared 96 *STAG2*m vs 112 *PHF6*m MN patients. Of *STAG2*m cases, 78% were male vs 76% in *PHF6*m MN. Median age was 72 vs 73 years, respectively. Diagnoses included AML (29% of *STAG2*m vs 34% of *PHF6*m MN), MDS (54% vs 28%), MDS/MPN (10% vs 21%) and MPN (3% vs 9%). MDS was more common among *STAG2*m MN (p<.001) while MDS/MPN was more common among *PHF6*m MN (=.05). MDS-IB was the most common subtype in both (69% vs 52% in *STAG2*m vs *PHF6*m MDS). MDS-LB and 5q subtypes were only found in *PHF6*m MDS, and there was more *PHF6*m MDS-RS (13% vs 2%). Median IPSS-M score was 0.9 vs 0.8 in *STAG2*m vs *PHF6*m MDS (both high-risk). Majority of *STAG2*m AML were adverse risk (96%) while *PHF6*m AML were intermediate (79%) (p<.001). AML cases included 43% vs 30% secondary AML (sAML) in *STAG2*m vs *PHF6*m AML. Among *STAG2*m and *PHF6*m MN, 17% of each were tMN. Cytogenetic abnormalities were more common in *PHF6*m MN (50% vs 31%, p=.005). The median bone marrow (BM) blasts count among *STAG2*m MN was 7% vs 4% in *PHF6*m MN (p=.03).
Genetic characteristics: *STAG2*m were nonsense, frameshift and splice site (54%, 36% and 11%). *PHF6*m were nonsense, frameshift, splice site, missense and start loss variant mutations (44%, 33%, 12%, 10% and 1%). The median variant allele frequency (VAF) of *STAG2*m MN was 50% compared to 32% in *PHF6*m MN (p=.008).
Co-mutations: The median number of co-mutations was 3 in *STAG2*m and 4 in *PHF6*m MN (p=.04). The most common were *TET2*m (37% in *STAG2*m MN vs 45% in *PHF6*m MN), *RUNX1*m (31% in both), *SRSF2*m (39% vs 20%), *ASXL1*m (66% vs 38%), *BCOR*m (19% vs 6%), *U2AF1*m (13% vs 14%) and *IDH2*m (18% vs 7%). *ASXL1*m, *SRSF2*m, *BCOR*m, *IDH2*m and *SF3B1*m were more common among *STAG2*m MN (p=<.001, .003, .006, .02, .09). *JAK2*m, *IDH1*m are more common among *PHF6*m MN (p=.02, .06).
Survival: Of *STAG2*m and *PHF6*m MN, 70% and 72% of patients received treatment. HSCT was performed in 23 (24%) and 23 (21%) of *STAG2*m and *PHF6*m patients, including AML (n=9, n=10), MDS (n=12, n=8), MDS/MPN (n=2, n=2). OS among

*STAG2*m and *PHF6*m MN was 20.5 and 22.1 months, respectively. OS among AML cases was 13.5 vs 21 months (p=.6) in *STAG2*m vs *PHF6*m, was NR vs 22 months (p=.4) in MDS, 11.7 vs 17.6 months in MDS/MPN (p=.4), and 10.4 vs 27.4 months (p=.5) in MPN. There was no difference between males and females in either *STAG2*m or *PHF6*m MN. HSCT led to longer OS among both *STAG2*m (NR vs 19.9 months, p=.01) and *PHF6*m MN patients (NR vs 17.6 months, p=.07). Among AML patients, HSCT did not significantly impact OS (18 vs 9.6 months, p=.3 and 25.1 vs 21 months, p=.2, in *STAG2*m and *PHF6*m). HSCT improved OS in *STAG2*m MDS (NR vs 20.5 months, p=.03). In *PHF6*m MDS, OS was 22.1 vs 13.1 months in HSCT vs non-HSCT (p=.3).

CONCLUSION:

*STAG2*m and *PHF6*m are 2 X-linked mutations that occur in MN. Both commonly occur in elderly males. MDS was the most common diagnosis in *STAG2*m MN. *STAG2*m co-occurred particularly with *SRSF2*m *ASXL1*m and *BCOR*m, which are associated with poor prognosis. In our cohort, *STAG2*m AML carried a poorer prognosis than *PHF6*m AML. Our study confirms the ELN2022 AML risk stratification. MDS risk classification and OS did not differ between *STAG2*m and *PHF6*m in our cohort. A larger cohort is required to confirm our findings and may provide stronger validation.

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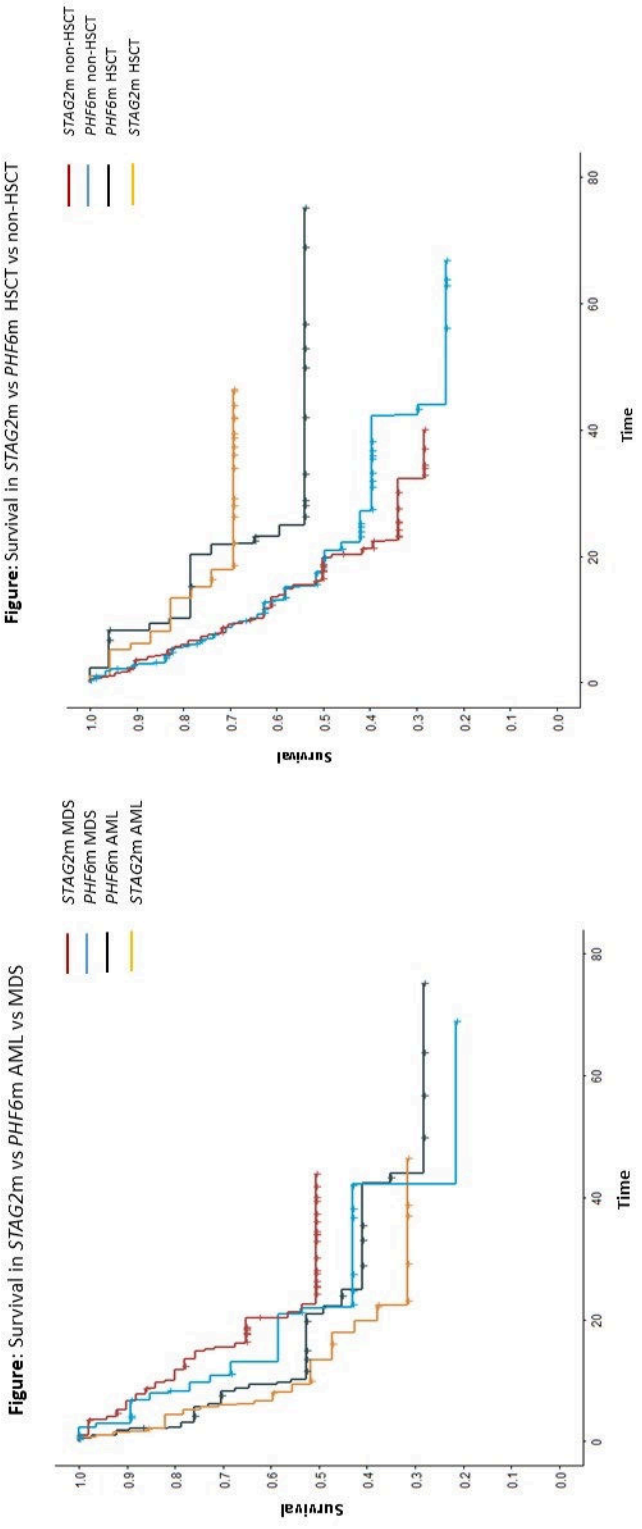

Figure 1