ELSEVIER

Blood 142 (2023) 1819–1821

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Low Thrombosis Risk CALR Mutations Confer Higher Risk of Essential Thrombocythemia Progression

Katie Erdos[1], *Neville Lee Jr.*[1], *Ahamed Lebbe*[2], *Imane Bouhali*[2], *Mohammed Khalid*[2], *Ghaith Abu-Zeinah, MD*[1], *Richard T. Silver, MD*[1], *Joseph M. Scandura, MDPhDMS*[1]

[1] Richard T. Silver, MD Myeloproliferative Neoplasms Center, Weill Cornell Medicine, New York, NY
[2] Weill Cornell Medicine - Qatar, Doha, Qatar

Background: Patients (pts) with essential thrombocythemia (ET) face increased risk of thrombosis and the prospect of progression to myelofibrosis (MF) or acute leukemia. ET treatment recommendations from ELN [1] and NCCN [2] are largely governed by the revised IPSET-thrombosis score that identifies 4 risk categories from "very low" to "high" based on age, thrombosis history, and the presence of a JAK2 ^{V617F} mutation [3]. Pts with CALR-mutated ET are known to have a lower risk of thrombosis than those with a JAK2 mutation, and for this reason, are often considered to have lower risk ET. Yet previous study of pts with clinically diagnosed ET found that CALR mutations may negatively impact progression risk [4]. For this reason, we evaluated the impact of driver mutations on the risks of thromboembolic events, disease progression, and overall mortality for a cohort of pts with rigorously defined WHO ET treated at our institution.
Methods: Medical records were queried for pts with the diagnosis (dx) of ET, as per ICD, code versions 9-10. The dx of ET and dx date were confirmed by manual review. All pts met the 2022 WHO criteria for ET, including a diagnostic marrow in all cases. Confounding diagnoses, including pre-fibrotic MF, polycythemia vera, or presumed ET in pts lacking a marrow biopsy, were strictly excluded by thorough review of the rich data available. Structured query language supplemented by manual review was used to extract clinical, laboratory, molecular, and marrow findings and treatment course. Overall (OS), MF-free (MFS), and thrombosis-free (TFS) survival were estimated using Kaplan-Meier methods. Univariable and multivariable analysis of post-ET MF (PETMF), thrombosis and mortality risk were performed using Cox proportional-hazards models using IPSET-survival [5] and revised IPSET-thrombosis variables as covariates.
Results: The query returned 751 pts but only 338 met our strict criteria for ET with diagnostic marrows and had annotated driver mutations. Of these, 216 (64%) were positive for JAK2 ^{V617F}, 85 (25%) CALR, 19 (6%) MPL, and 18 (5%) triple negative (TN). We identified no significant differences among the driver mutation cohorts in dx age, sex, or median follow up duration. Semi-quantitative features of the diagnostic marrow biopsies, including age-adjusted cellularity and reticulin fibrosis score, were not significantly different among the groups. Red cell parameters at dx were mildly higher in the JAK2 pts (HCT, HGB, RBC all with $p<0.001$), WBC count was highest in TN pts ($p=0.012$), and PLT count was not significantly different ($p=0.064$). 20-year TFS for JAK2 was 71%, CALR 100%, MPL 90% and TN 83% ($p=0.0027$, Figure 1); 20-year MFS for JAK2 was 87%, CALR 48%, MPL 65% and TN 94% ($p=0.00053$, Figure 2); 20-year OS for JAK2 was 76%, CALR 86%, MPL 89% and TN 90% ($p=0.66$). Multivariable analysis showed that CALR was associated with a significantly higher risk of PETMF as compared to JAK2 (HR 11.52, CI 1.88-70.51, $p=0.008$), independent of age, sex, WBC, and thrombosis history. Conversely, CALR was associated with a lower risk of thrombosis (HR 0.08, CI 0.01-0.58, $p=0.013$) when adjusting for sex and revised-IPSET thrombosis parameters.
Discussion: We found that although pts with CALR-mutated ET have lower thrombosis risk, they experience higher risk of progression to MF. Current risk models for thrombosis yield treatment recommendations well suited to reducing thrombosis risk [3]. With this success, pts are expected to live with ET for decades, thereby exposing them to other ET risks, most notably that of malignant disease progression. These risks are of particular concern for younger pts who suffer the greatest relative risk [6]. It is important that thrombosis risk and fibrosis risk are not conflated as our data suggest that pts with low or very low risk CALR-mutated ET can be at higher risk of progression. Our findings reinforce the need for long-term data to guide therapy for ET based not only on the near-term thrombotic risk, but also on the long-term risk of progression.

References

1. Barbui et al. *Leukemia* 2018.
2. Gerds et al. NCCN Guidelines Recommendations Version 1.2023 Myeloproliferative Neoplasms. 2023 May 19.
3. Haider et al. *Am J Hematol, 2016.*
4. Loscocco et al. *Am J Hematol*, 2021.

5. Passamonti et al. *Blood* 2012.
6. Abu-Zeinah et al. *Leukemia & Lymphoma*, 2022.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-188952

Figure 1. Thrombosis free survival of ET patients by driver mutation

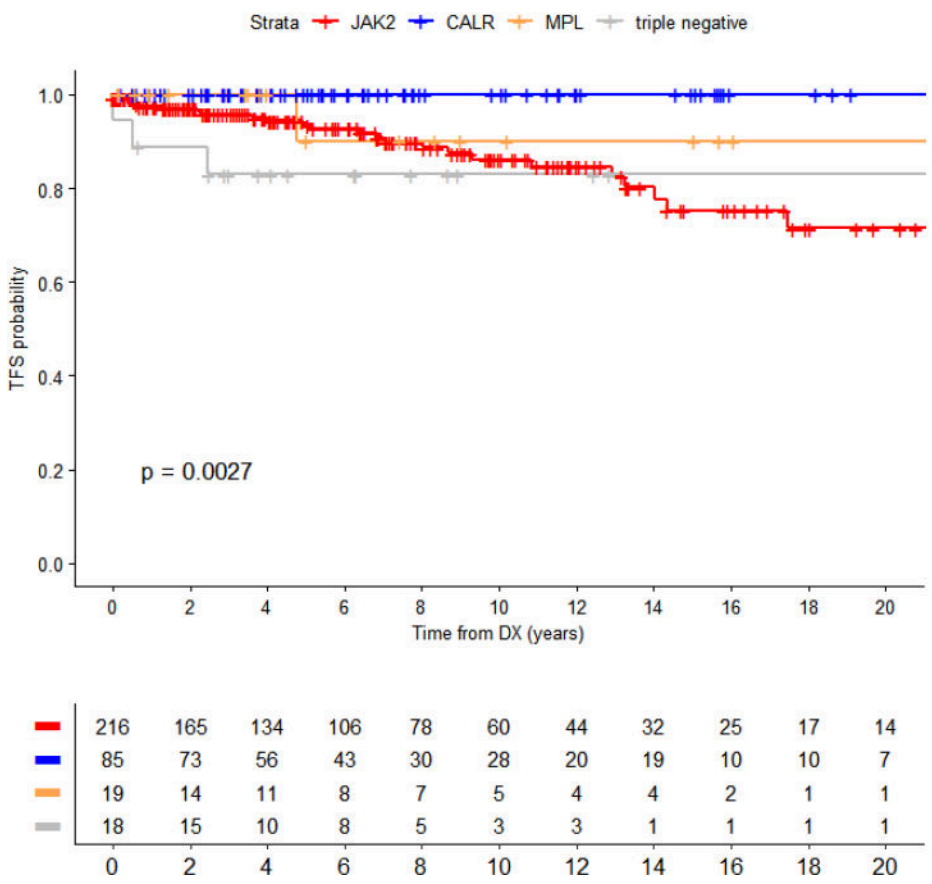

Figure 2. PETMF free survival of ET patients by driver mutation

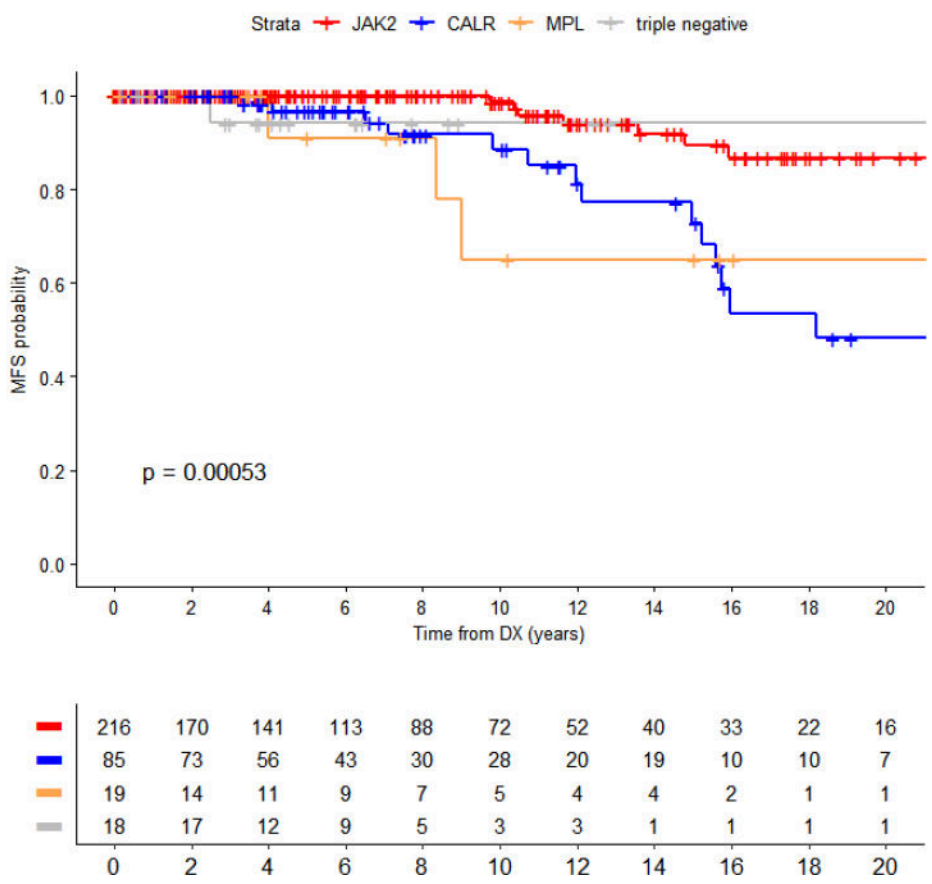

Figure 1