XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. B7

Myeloproliferative disorders

MOLECULAR RISK PROFILING IN MYELOPROLIFERATIVE NEOPLASMS BLAST PHASE (MPN-BP) TREATED WITH VENETOCLAX AND DECITABINE: A THREE-GENE SCORE FOR SURVIVAL PREDICTION

F. Crupi[1|2|3], P. Guglielmelli[1|2|3], F. Mannelli[1|2|3], J. Caroprese[1|2|3], M. Lomi[1|3], G. G. Loscocco[2|3], N. Bartalucci[1|3], S. Soddu[4], C. Maccari[1|3], A. Enderti[1|3], L. Signori[1|3], A. Piciocchi[4], P. Fazi[4], A. M. Vannucchi[1|2|3]

[1]Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze; [2]SOD Ematologia, AOU Careggi; [3]Centro Ricerca e Innovazione Malattie Mieloproliferative CRIMM, AOU Careggi; [4]Fondazione GIMEMA.

Background: Myeloproliferative Neoplasm-Blast Phase (MPN-BP) has poor outcome with overall survival (OS) <6 months (mo), and limited responses to intensive chemotherapy. Venetoclax (VEN) plus hypometilating agents, effective in unfit or relapsed/refractory de-novo AML, is increasingly considered for MPN-BP. However, MPN-BP's distinct molecular profile may not be adequately captured by current risk models (ELN24/mPRS, ELN24-refined).

Aim: To define a prognostic risk profile using clinical data from ENABLE, a phase 2 trial exploring VEN and decitabine in MPN-BP.

Patients and Methods: 101 pts were enrolled in ENABLE trial, with 80 having samples for translational analyses. DNA was extracted from purified blasts at diagnosis and driver, and myeloid mutations (mut) were assessed by PCR and NGS.

Results: Pts were *JAK2*^{mut} (n=64, 80%), *CALR*^{mut} (n=10, 12.5%), *MPL*^{mut} (n=2, 2.5%); 92.5% had >1 (median 4) additional myeloid gene mut. ELN24/mPRS separated the favorable category (54% of the pts; median OS, 20.7mo, p=0.0041) from the intermediate (17%, OS 8.9mo) and the adverse one (29%; OS 5.1mo); though the latter two were almost superimposable (p=0.35). ELN24-ref system favorable category (9% of the pts) showed median OS not reached (p=0.012) compared to 14mo in intermediate (57%) and 10-mo in adverse (24%), with the latter two overlapping (p=0.10). In our cohort, predictors of OS identified in univariable analysis included achievement of CR/PR within two cycles (55%; p = 0.02), mut in *SRSF2* (25%; p = 0.048), *U2AF1* (7.5%; p < 0.001), *EZH2* (16.3%; p = 0.047), and *TP53* (28.8%; p = 0.01), irrespective of multihit status (17.5%). In multivariable analysis *SRSF2*^{mut} (HR 3.0; 95%CI 1.4-6.3; p=0.004), *U2AF1*^{mut} (HR 4.2, 1.6-10.7; p=0.003) and *TP53*^{mut} (HR 2.7, 1.3-5.3; p=0.005) maintained independent impact on OS. We thus created a 3-gene score assigning 2 points each to *SRSF2*^{mut} and *U2AF1*^{mut} and 1 point to *TP53*^{mut}, separating three risk groups: in the favorable (point 0; n=38 pts, 47.5%) OS was 20.7 mo (95%CI 17-24) compared to 10.8 mo (3-18.6) in the intermediate (point 1; n= 16 pts, 20%) and 3.7 mo (0-10.8) in the adverse (≥2 points, n26 pts, 32.5%) risk category (p=0.001). C-index for the 3-gene model was 0.68 compared to 0.59 for ELN24 and 0.57 for ELN24-ref. Reclassification of pts according to 3-gene model as compared to ELN24 mainly regarded intermediate pts, half of whom were reclassified as favourable and half as adverse. Additionally, 32% of pts initially classified as favourable were reassigned to the adverse category. The improved stratification by 3-gene model may reflect unique molecular features of MPN-BP pts compared to *de novo* AML: notably, 78% of *TP53*^{mut} pts (n=23) had additional mut beyond driver mut, a distinct figure from pts enrolled in the mPRS cohort (n=63, 35%).

Conclusions: The 3-gene score outperforms de-novo AML genetic models in our cohort of MPN-BP pts treated with VEN/DEC. Validation in independent series is warranted.

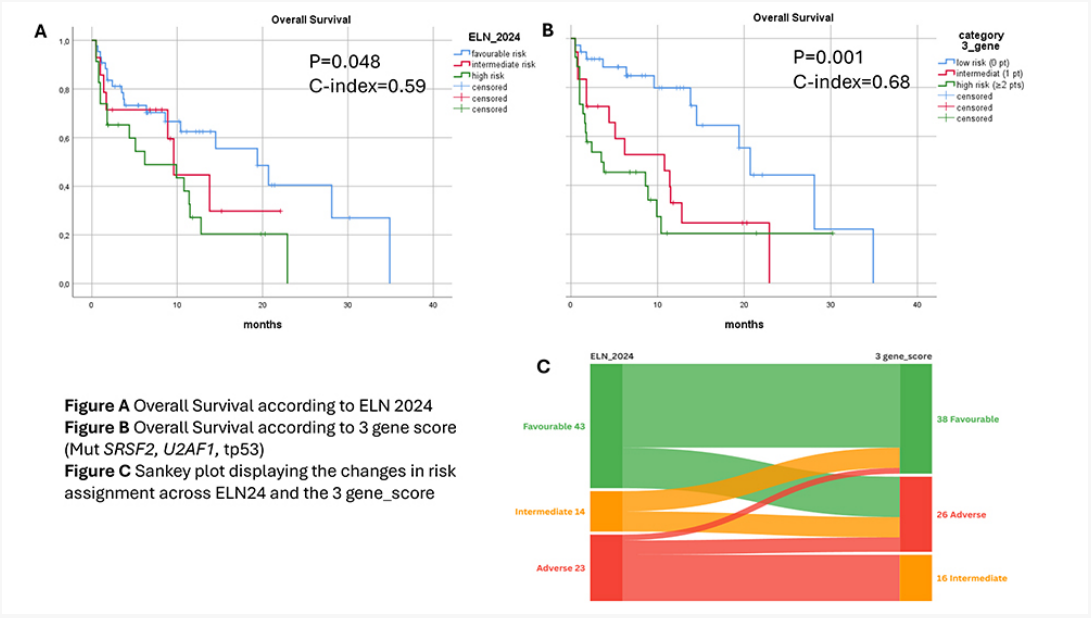

Figure A Overall Survival according to ELN 2024
Figure B Overall Survival according to 3 gene score (Mut *SRSF2, U2AF1,* tp53)
Figure C Sankey plot displaying the changes in risk assignment across ELN24 and the 3 gene_score