XIX CONGRESSO NAZIONALE SIES 2026

Molecular Risk Profiling in MPN-BP pts treated with Venetoclax and Decitabine

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Firenze | 4-6 marzo 2026

Palazzo degli Affari

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Background:

- MPN-BP is characterized by **dismal outcome**, with OS below 6 months
- Intensive chemotherapy has shown disappointing results in this setting of pts
- There is increasing interest for non-intensive regimens, such as **venetoclax (VEN) plus hypomethylating (HMA)** agents, successfully used in unfit, untreated, as well as relapsed/refractory, pts with de-novo AML
- However, data in this setting of pts were largely retrospective as these patients were excluded from clinical trials (i.e., VIALE-A)
- **Genetic risk score** specific for de-novo AML receiving VEN/HMA were developed:

	ELN24/mPRS *Dohner H, Blood 2024*	**ELN24 refined** *Lachowiez CA, Blood 2024*	**Beat AML** *Hoff FW, BloodAdv2024*	**Mayo Genetic Risk Score** *Gangat N, AJH 2025*
Favourable	*FLT3-ITD* neg, *NRAS/KRAS* wt, *TP53* wt	Mut *NPM1*, *IDH1/2*, or *DDX41*	ELN22 fav- and int-risk	*IDH2* mut; *KRAS* mut: ELN22 adverse karyotype = 1 pt *KMT2A*r= 2 pts Stratification of pts achieving CR/Cri in: Low risk (0 pt); Int risk (1 pt); High risk (>1 pt)
Intermediate	*FLT3-ITD* pos and/or *NRAS/KRAS* mut	Mut *FLT3-ITD*, *NRAS*, or other mut	ELN22 adv- and mut score≤0 point	
Adverse	Mut *TP53*	Mut *KRAS, PTPN11,* or *TP53;*	ELN22 adv- and mut score ≥1 point *(TP53, KRAS, MLL)*	

Aim:

- Since MPN-BP's distinct molecular profile may not be adequately captured by current risk models (ELN24/mPRS, ELN24-refined) we aimed to define a prognostic risk profile taking advantage of data from **ENABLE, a prospective multi-center phase 2 clinical trial of VEN and decitabine in MPN-BP** (ASH meeting 2025, AM Vannucchi et al)

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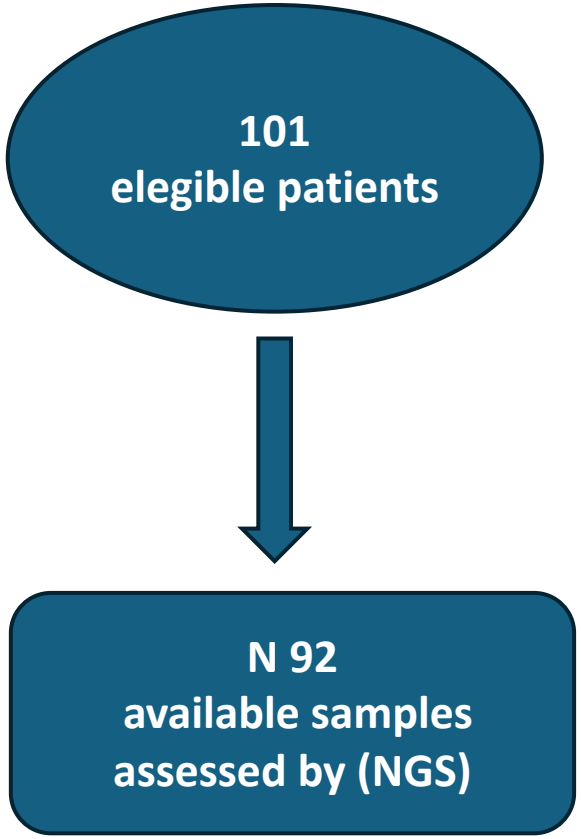
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

A Phase 2, prospective, multi-center intervention trial in patients with acute myeloid leukemia secondary to myeloproliferative neoplasms unfit for intensive chemotherapy investigating a treatment combination including decitabine and venetoclax

ENABLE (vENetoclax plus decitAbine treatment in Blastic phase of myeLoproliferative nEoplasms)

GIMEMA AML2420

Patients and Methods:



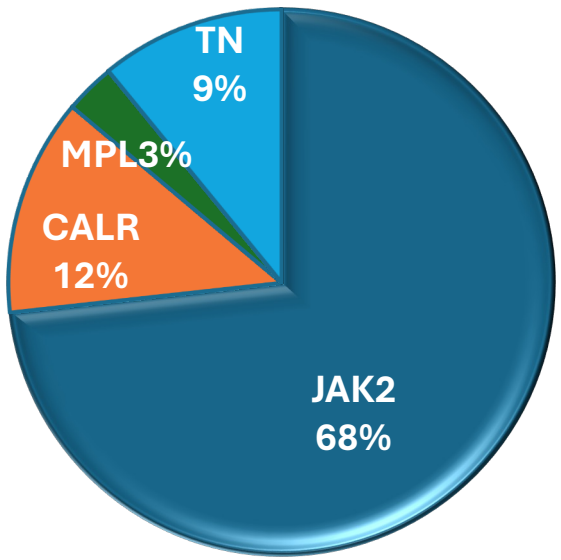
Oral communication ASH 2025 (*Vannucchi et al)*

Results (part 1):

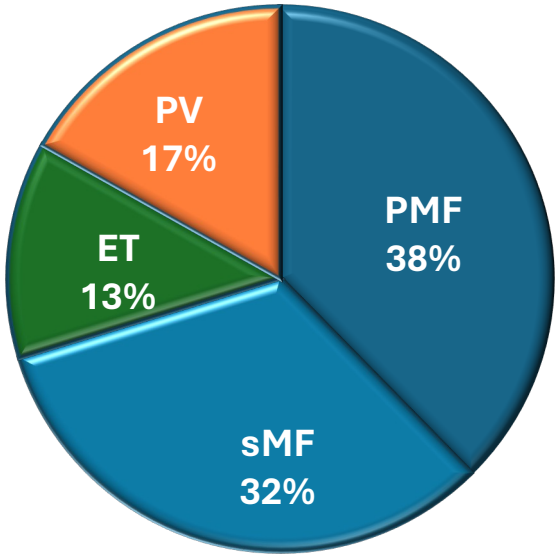
	mPRS/ELN 2024	ENABLE
Patients (N)	279	101
Age (median)	76	71
CR (%)	43.4%	36%
OS (months) **OS probability 12 mo (%)**	14.7 37.5%	10.8 47.2%

- An abnormal karyotype was found in 59% of the pts, classified as poor in 17% and complex in 23% according to ELN22.
- Non-driver myeloid mutations were found in 95%, with a median of 4 mutations (IQ range 3 to 5).
- 79% of TP53^{mut} pts (n=26) had additional mut beyond driver mutation, a higher prevalence than that observed in pts enrolled in the mPRS cohort (n=63, 35%).
- Among the 26 TP53^{mut} pts, 54% were multi-hit.

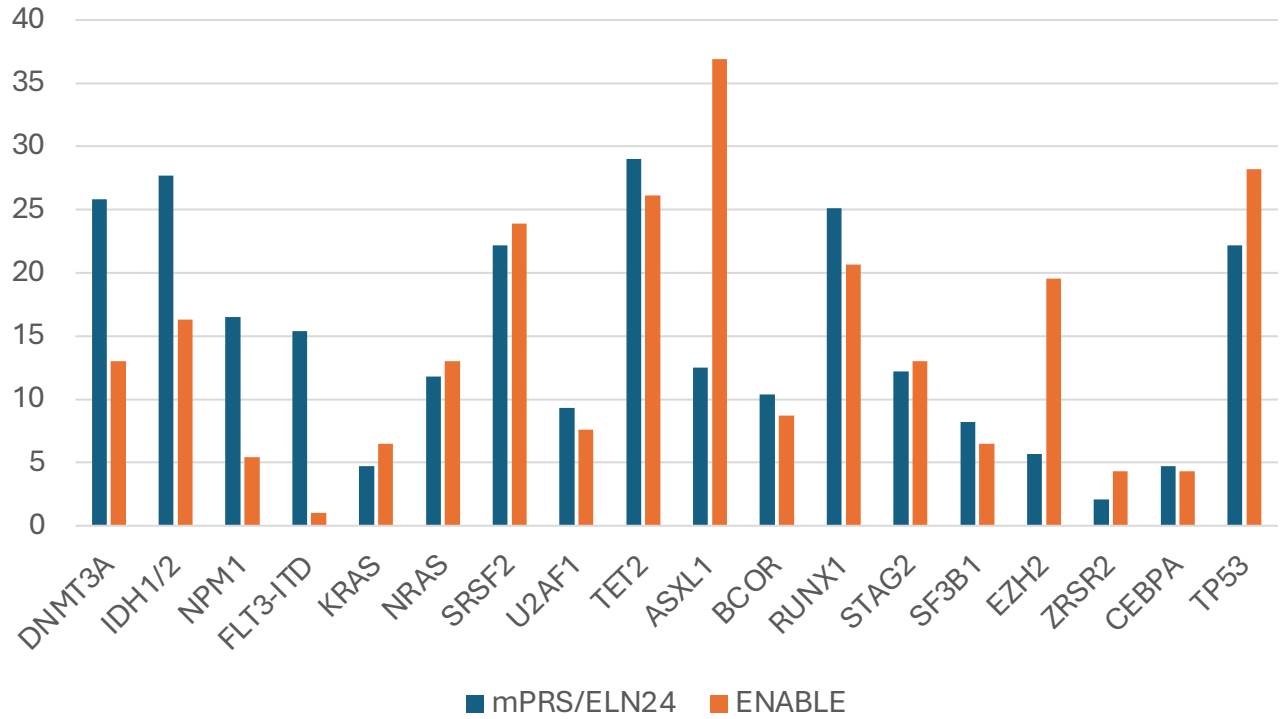
Distribution of driver mutations



Distribution of MPN variants



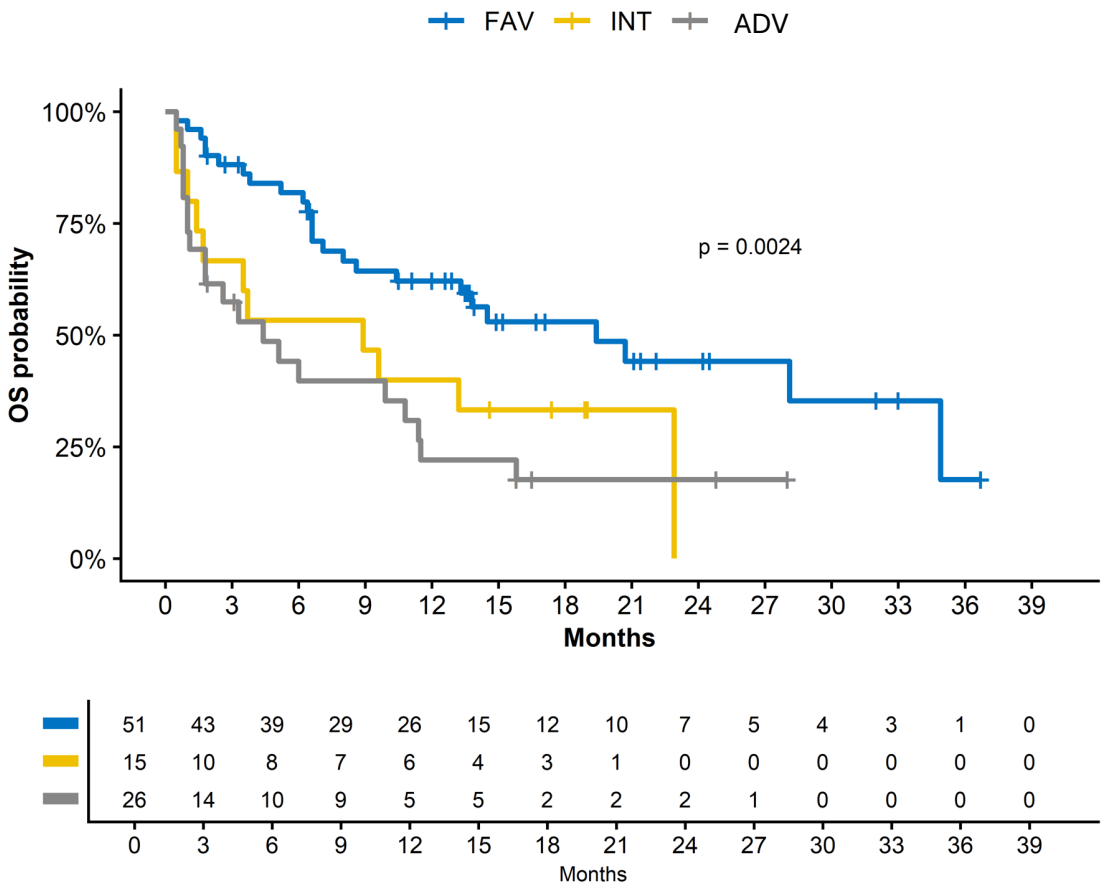
Distribution of mutations in mPRS/ELN24 vs ENABLE pts



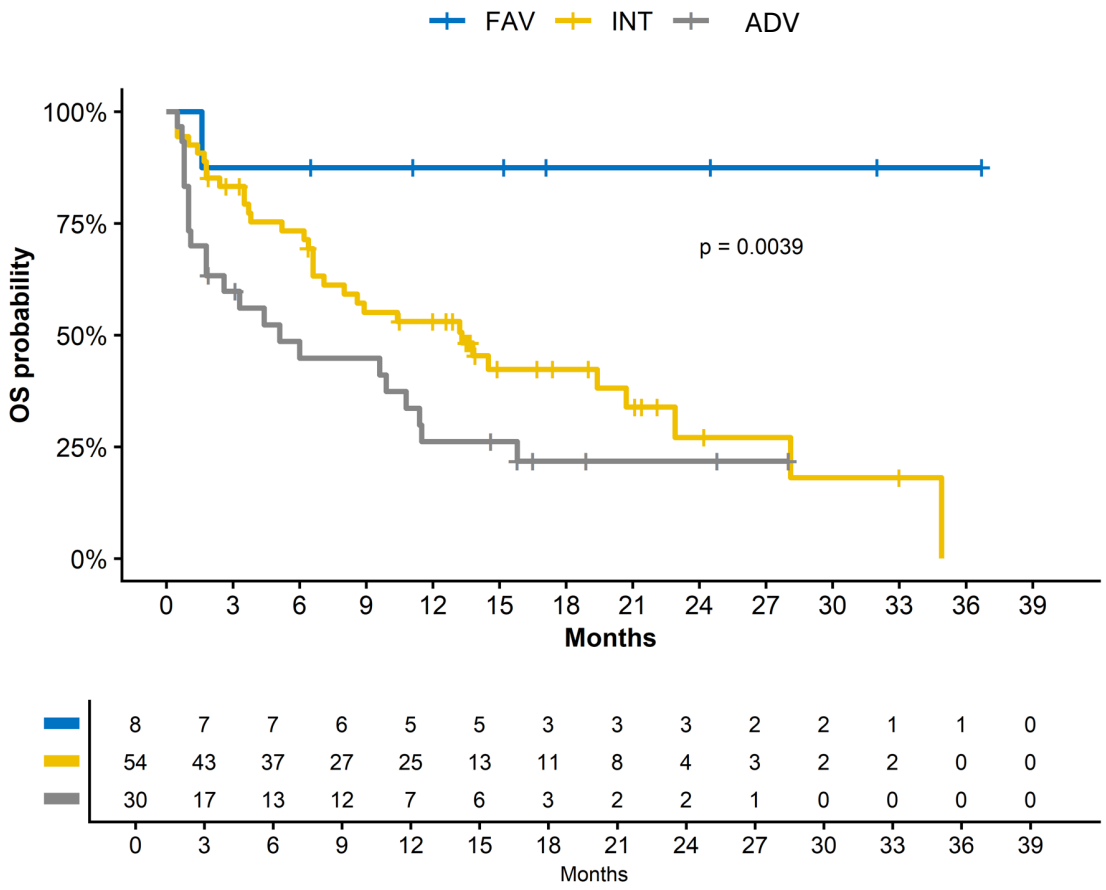
Results (part 2):

- We evaluated the performance of available prognostic models in our cohort of 92 pts:

OS by ELN24



OS by ELN24 refined



Results (part 3):

- **Variables included in univariate analysis:**
- ✓ NGS mutations, including *TP53* any and *TP53* multi-hit;
- ✓ HMR (according MYPSS70plus)
- ✓ Karyotype (poor and complex according to ELN2022)

- Variables with a **p-value < 0.20 in univariable analysis** were included in the multivariable analysis.

Variable	n (%)	HR (95% CI)	*P*
***DNMT3*^{mut}**	12 (13%)	0.17 (0.04-0.7)	**0.015**
***SRSF2*^{mut}**	22 (23.9%)	1.5 (0.8-2.6)	0.185
***U2AF1*^{mut}**	7 (7.6%)	2.5 (1.1-6)	**0.038**
TP53*^{mut} *(any)	26 (28%)	2.2 (1.3-3.9)	**0.005**
***SF3B1*^{mut}**	6 (6.5%)	2.0 (0.8-5.3)	0.140
***IDH1*^{mut}**	5 (5.4%)	4.9 (0.7-36.1)	0.113
***IDH2*^{mut}**	10 (10.9%)	2.3 (0.8-6.3)	0.120
***PTPN11*^{mut}**	6 (6.52%)	3.3 (1.3-8.6)	**0.013**
***NRAS*^{mut}**	12 (13%)	1.8 (0.9-3.6)	0.094

- In **multivariable analysis** maintained independent impact on OS:

Variable	HR (95% CI)	*P*
***DNMT3*^{mut}**	0.2 (0.05-0.9)	**0.038**
***SRSF2*^{mut}**	3.0 (1.4-6.3)	**0.027**
***U2AF1*^{mut}**	2.5 (1.0-6.1)	**0.049**
***TP53*^{mut}** (any)	2.9 (1.5-5.3)	**0.001**

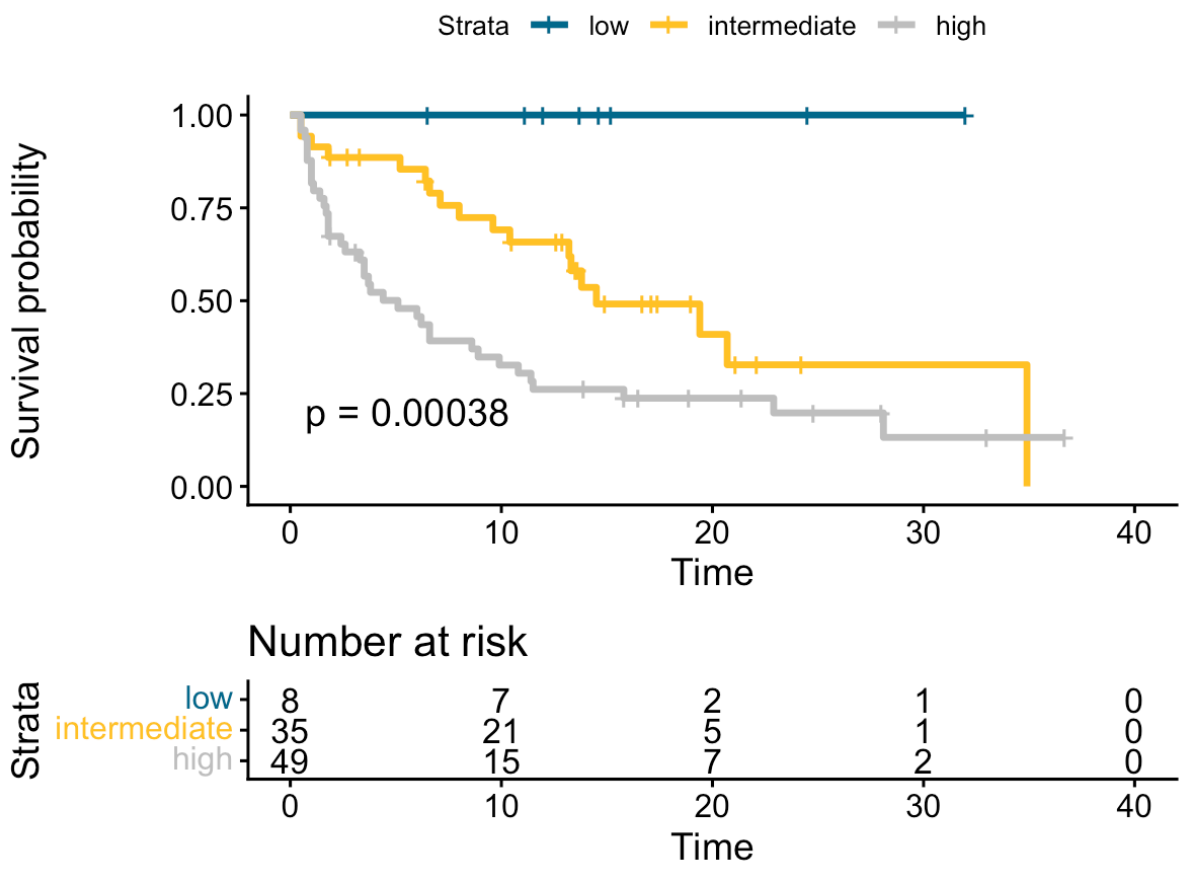
Results (part 3):

- **OS by ENABLE score**
- **Categories:**

Low: *DMT3A*^{mut} (and *TP53/SRSF2/U2AF1*^{wt})

Intermediate:
DNMT3A^{wt} (and *TP53/SRSF2/U2AF1*^{wt})

High: *TP53*^{mut} or *SRSF2/U2AF1*^{mut} and *DNMT3A*^{wt}



Discussion:

- ***DMT3A^{mut}* controversial prognostic role:**
  - ✓ Not included among adverse mutations in ELN 2022
  - ✓ Associated with unfavorable outcomes in many studies of intensively treated patients especially in triple-mutated cases (*NPM1/FLT3-ITD/ DMT3A^{mut}*)

    (Othman J, et al Blood. 2024; Papaemmanuil E, et al NEJM. 2016; Patel JL, et al Leuk Res. 2017)

- **Limited evidence in non-intensively treated patients**
  - ✓ Prognostic impact still poorly explored

    In some report associate with increase response to HMA+Ven

    (Boisclair S et al Blood (2023) 142 (Supplement 1):2904.; Miyashita N et al BJH 2023; Metzeler KH et al Leukemia2012)
  - ✓ However, not incorporated in mPRS/ELN24 or ELN24 refined

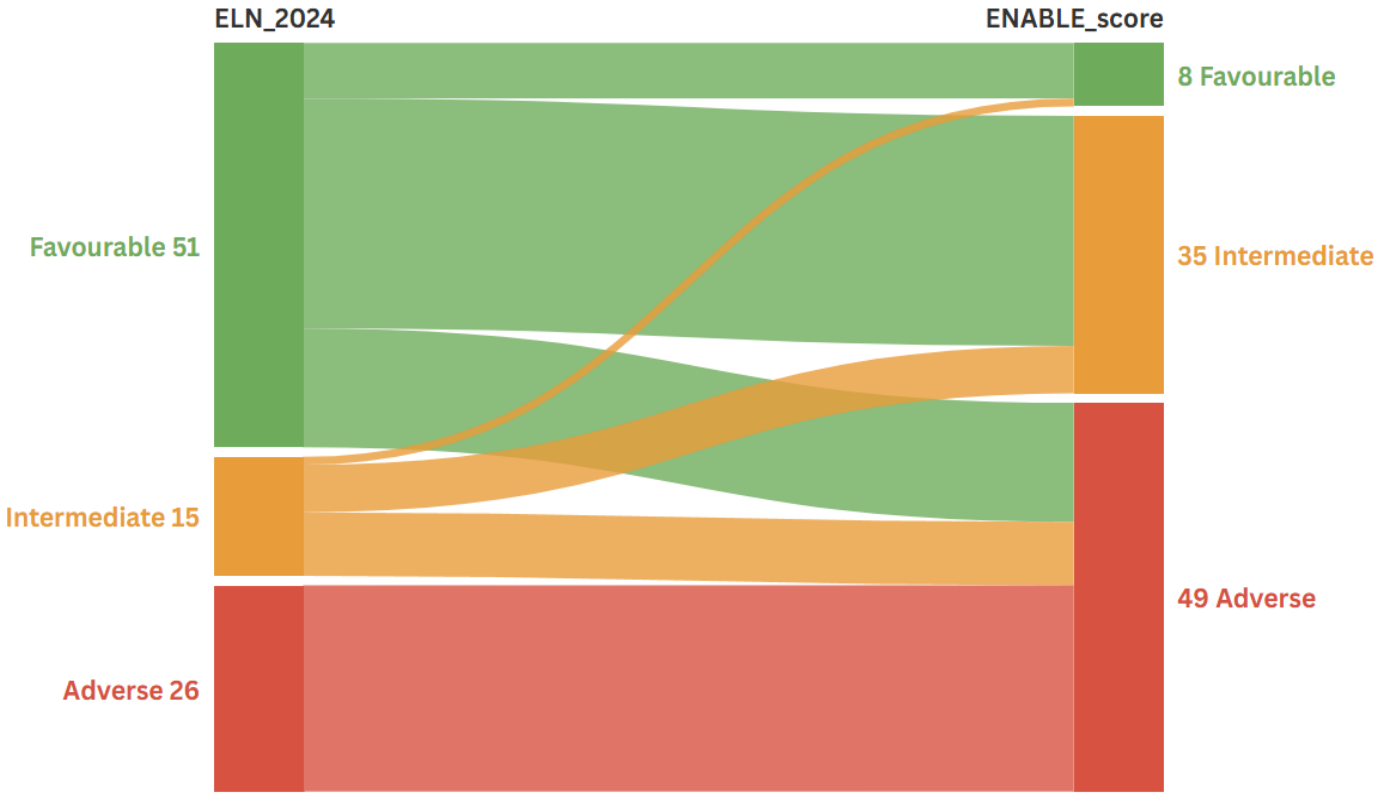
- **Context-dependent effect** in *de novo* AML
  - ✓ Frequently co-occurs with mutations with favorable (ie: *NPM1*
    IDH1/2) or intermediate (ie: *FLT3-ITD*) impact
  - ✓ These co-mutations may modulate or mask its prognostic role

	Higher benefit (n = 145)	Intermediate benefit (n = 71)	Lower benefit (n = 63)
DNMT3A	40 (27.6)	25 (35.2)	7 (11.1)

ELN24/mPRS
Dohner H, Blood 2024

- **Potentially distinct role in MPN-BP**
  - ✓ Co-mutations with *NPM1* or *FLT3-ITD* are rare
  - ✓ *DMT3A^{mut}* may therefore exert a different and independent prognostic effect

Conclusions:



Sankey plot displaying the changes in risk assignment across ELN24 and the ENABLE-gene score

- **Reclassification** of pts according to **our model** as compared to ELN24 mainly regarded favourable pts, 57% of whom were reclassified as intermediate and 29% as adverse
- Additionally, 50% of pts initially classified as intermediate were reassigned to the adverse category
- The stratification by our model may reflect **unique molecular features of MPN-BP** pts compared to de novo AML
- Validation in independent series is warranted

Thanks to

Participating Centers:

- ***Alessandro Rambaldi, Marco Frigeni, Monica Rondi*** : Azienda Socio-Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo
- ***Giovanni Caocci, Olga Mulas, Marco Sanna****:* Ematologia e Centro Trapianti Midollo Osseo Ospedale "A. Businco", ARNAS "G. Brotzu"
- ***Monica Bocchia, Corrado Zuanelli Brambilla:*** Hematology Unit, Azienda Ospedaliero-Universitaria Senese, University of Siena
- ***Antonio Curti, Cristina Papayannidis*** : IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna
- ***Fabrizio Pane, Francesco Grimaldi :*** Department of Clinical Medicine and Surgery, Hematology Division, University of Napoli "Federico II"
- ***Erika Borlenghi, Lorenzo Masina***: ASST Spedali Civili di Brescia
- ***Chiara Frairia:*** Ematologia Città della Salute e della Scienza di Torino
- ***Prassede Salutari:*** UOC Ematologia, Azienda USL di Pescara, Pescara, Italy
- ***Patrizia Chiusolo:*** Hematology Department, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy
- ***Elisa Coviello:*** Ematologia e Terapie Cellulari IRCCS Ospedale Policlinico San Martino Genova Italy
- ***Maria Teresa Voso:*** *Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome*
- ***Pellegrino Musto*****:** Unit of Hematology and Stem Cell Transplantation, Bari, Italy
- ***Massimo Breccia:*** Department of Translational and Precision Medicine, Sapienza University, Rome, Italy
- ***Mario Luppi***: University of Modena and Reggio Emilia, Modena, Italy
- ***Daniela Cilloni :*** Department of Clinical and Biological Sciences, University of Turin, Largo Filippo Turati 62, Turin 10128, Italy
- ***Maria Paola Martelli:*** Institute of Hematology and Center for Hemato-Oncology Research, University of Perugia and Santa Maria della Misericordia Hospital, Perugia, Italy
- ***Matteo Giovanni Della Porta:*** IRCCS Humanitas Research Hospital & Humanitas University, Rozzano - Milan, Italy
- ***Rossella Manfredini :*** Interdepartmental Centre for Stem Cells and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
- ***Luca Malcovati:*** Department of Hematology Oncology, IRCCS Policlinico San Matteo, Pavia, Italy

Fondazione GIMEMA Franco Mandelli Onlus, GIMEMA Data Center:

- Alfonso Piciocchi
- Paola Fazi
- Marco Vignetti

SOD Ematologia , CRIMM, Università di Firenze, AOU Careggi:

- Alessandro Maria Vannucchi
- Francesco Mannelli
- Paola Guglielmelli
- Jessica Caroprese
- Niccolò Bartalucci
- Alessio Enderti
- Leonardo Signori
- Mirko Lomi
- Chiara Maccari
- Giuseppe Gaetano Loscocco

Metastatic disease: the key unmet need in oncology

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