POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Sindromi Mielodisplastiche - Biologia e prognosi

Humanitas Research Hospital - MILANO

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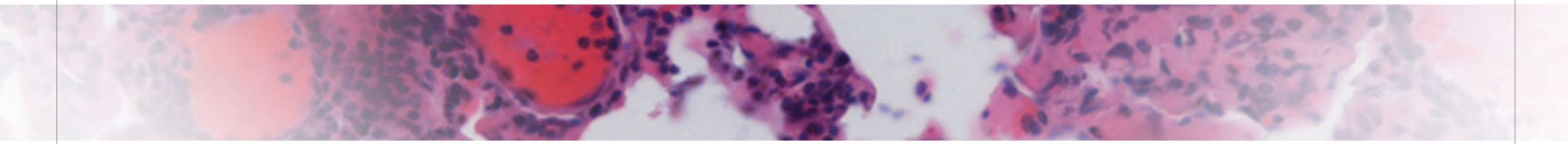
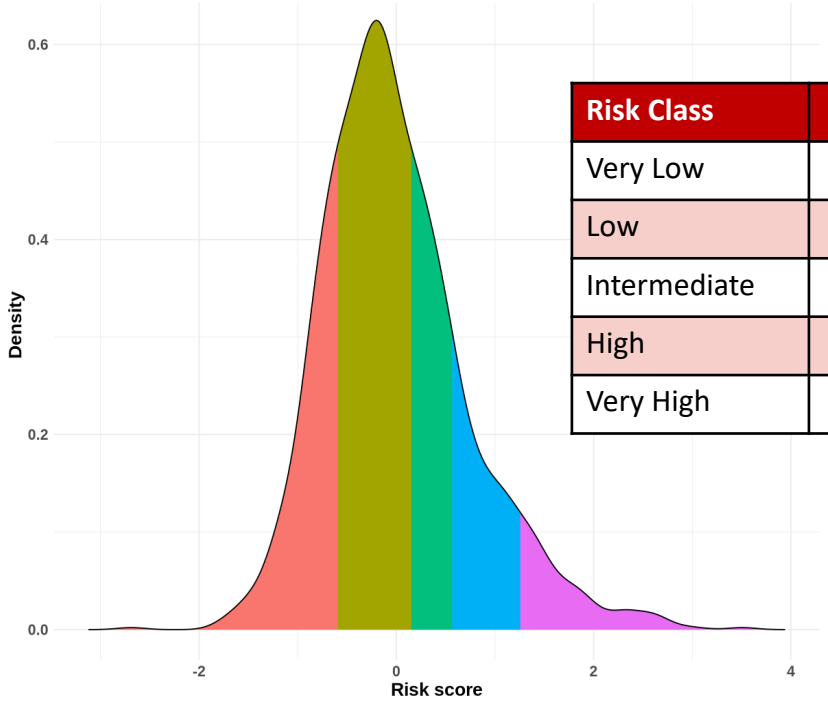


A Molecular-Based Ecosystem to Improve Personalized Medicine in Chronic Myelomonocytic Leukemia

Luca Lanino, AM Hunter, N Gagelmann, M Robin, C Sala, D Dall'Olio, C Gurnari, L Dall'Olio, YH Wang, L Pleyer, B Xicoy, G Montalban-Bravo, LY Shih, T Haque, O Abdel-Wahab, K Geissler, A Bataller, A Bazinet, M Meggendorfer, I Casetti, E Sauta, E Travaglino, L Palomo, L Zamora, D Quintela, A Jerez, E Cornejo, PG Martin, Marina Diaz-Beya, Alejandro Avendano Pita, Veronica Roldan, Dolly Viviana Fiallo Suarez, Estefania Cerezo Velasco, Marisa Calabuig, Esperanza Such, Guillermo Sanz, AS Kubasch, C Castilla-Llorente, C Bulabois, L Souchet, H Awada, M Bernardi, P Chiusolo, A Curti, L Giaccone, F Onida, LM Borin, F Passamonti, E Diral, V Vucinic, GM Bergonzi, MT Voso, HA Hou, WC Chou, CY Yao, CC Lin, HF Tien, A Campagna, M Ubezio, A Russo, G Todisco, G Maggioni, CA Tentori, A Buizza, G Asti, M Zampini, E Riva, M Delleani, A Consagra, F Ficara, A Santoro, L Carota, T Sanavia, C Rollo, A Kiwan, J VanOudenhove, P Fariselli, NH Al Ali, D Sallman, W Kern, G Garcia-Manero, S Thota, EA Griffiths, M Yung Follo, C Finelli, U Platzbecker, F Sole, M Diez-Campelo, J Maciejewski, R Bejar, FR Thol, N Kroger, P Fenaux, R Itzykson, TA Graubert, M Fontenay, AM Zeidan, RS Komrokji, V Santini, T Haferlach, U Germing, S D'Amico, G Castellani, MM Patnaik, , E Solary, **E Padron, MG Della Porta**

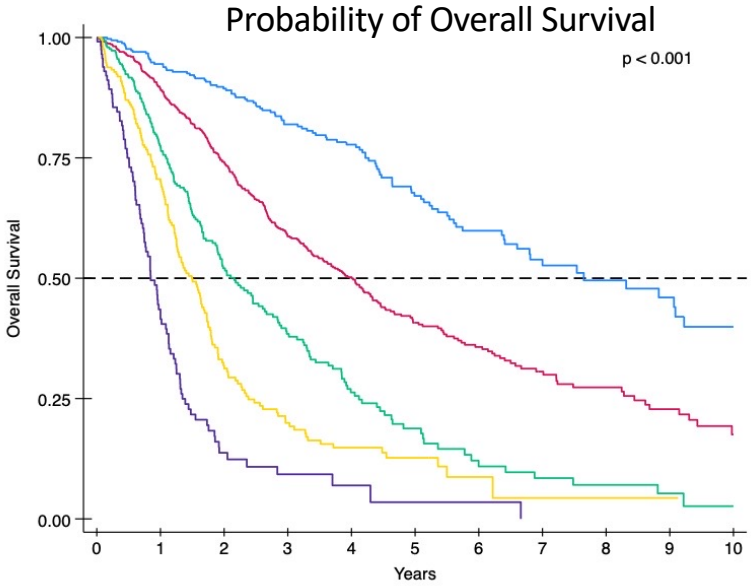
Development of the International CMML Prognostic Score (iCPSS)

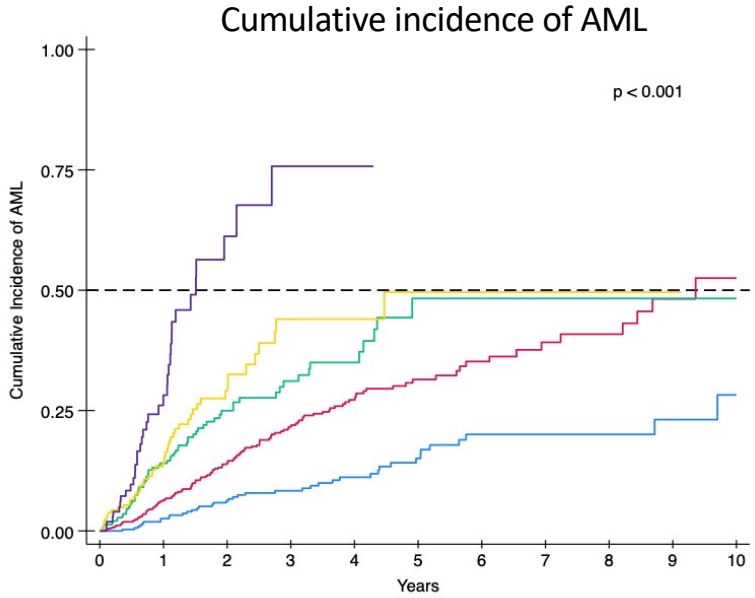
- **Laboratory parameters:**
  - WBC
  - Hb
  - PLT
  - BM Blasts
- **CPSS cytogenetic stratification**
- **Mutational status (n=9)**
  - *ASXL1*
  - *DNMT3A*
  - *EZH2*
  - *RUNX1*
  - *SETBP1*
  - *STAG2*
  - *TET2*
  - *TP53*
  - *U2AF1*



Risk Class	Risk Score	%
Very Low	< -0.594	21%
Low	[-0.594, 0.147]	43%
Intermediate	[0.147, 0.566]	18%
High	[0.566, 1.258]	12%
Very High	≥1.258	7%

Results – iCPSS Performances (N = 3,565)





	C-INDEX
iCPSS	0.75
CPSS-mol[1]	0.63
GFM[2]	0.60
MMM[3]	0.61

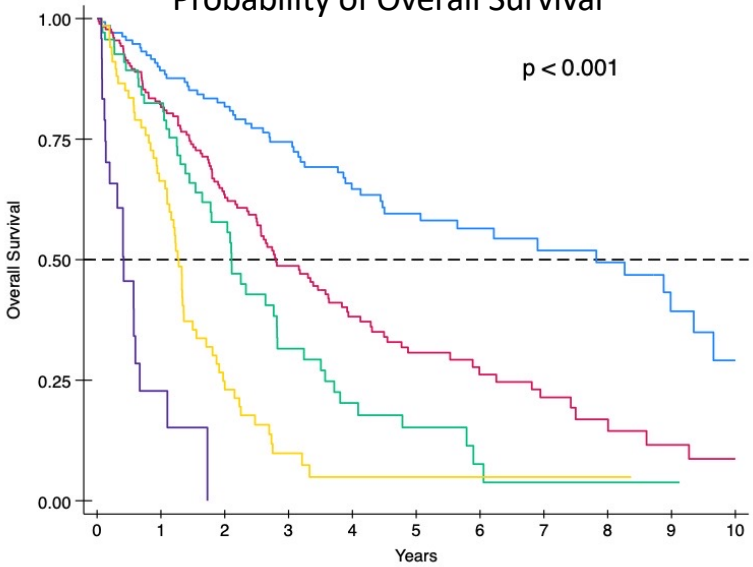
Very Low Low Intermediate High Very High

	C-INDEX
iCPSS	0.71
CPSS-mol[1]	0.62
GFM[2]	0.59
MMM[3]	0.58

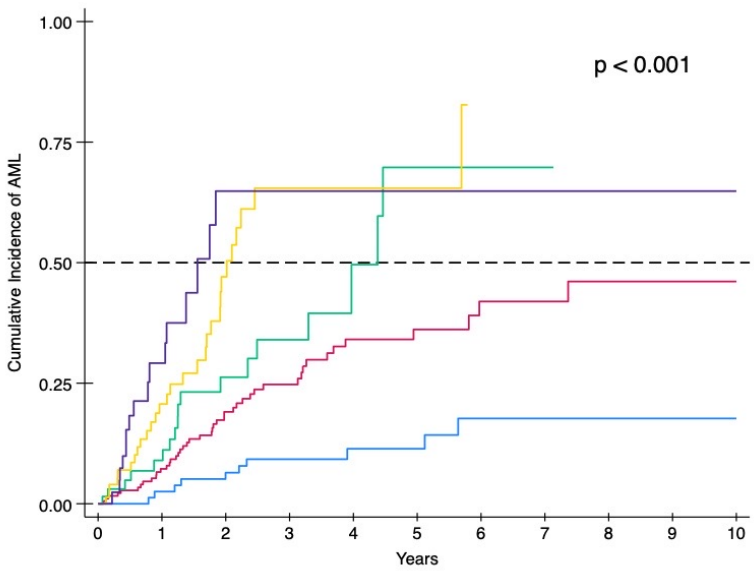
1: Elena et al., Blood 2016, PMID 27385790
2: Itzykson et al., JCO 2013, PMID: 23690417
3: Patnaik et al., Leukemia 2013, PMID: 24695057

Results – iCPSS External Validation (N=516)

Probability of Overall Survival



Cumulative incidence of AML



	C-INDEX
iCPSS	0.70
CPSS-mol[1]	0.61
GFM[2]	0.59
MMM[3]	0.56

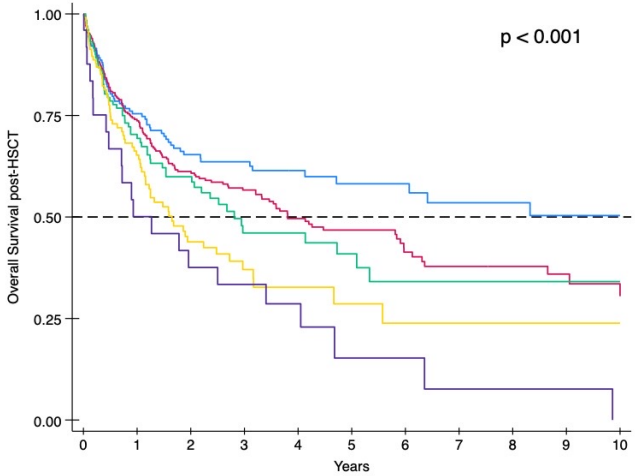
Very Low Low Intermediate High Very High

	C-INDEX
iCPSS	0.69
CPSS-mol[1]	0.62
GFM[2]	0.58
MMM[3]	0.57

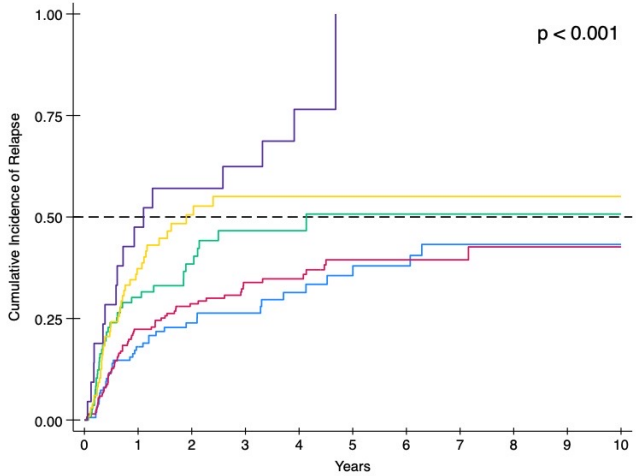
1: Elena et al., Blood 2016, PMID 27385790
2: Itzykson et al., JCO 2013, PMID: 23690417
3: Patnaik et al., Leukemia 2013, PMID: 24695057

Results – iCPSS for Transplant Outcomes (N=769)

Probability of Overall Survival



Cumulative Incidence of Relapse



Very Low Low Intermediate High Very High

	HR*	p
Low	1.32	0.06
Intermediate	1.53	0.01
High	1.99	< 0.01
Very High	2.97	< 0.01

	HR*	p
Low	1.08	0.69
Intermediate	1.71	0.01
High	2.01	< 0.01
Very High	3.40	< 0.01

- Adjusted for status at HSCT, donor and conditioning

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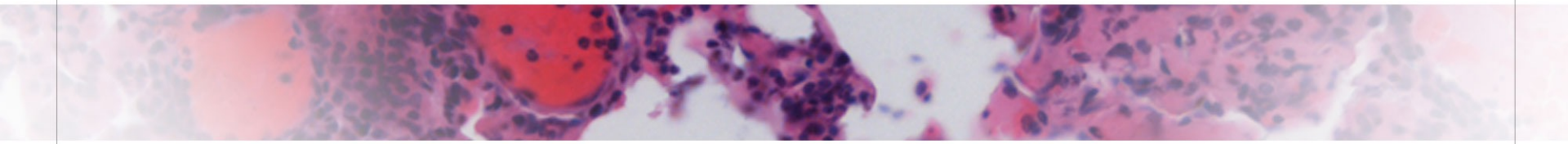


AI, Data-Driven, Comprehensive Classification of Myeloid Neoplasms Based on Genomic, Morphological and Histological Features

Luca Lanino, S D'Amico, G Maggioni, N Al Ali, YH Wang, C Gurnari, N Gagelmann, JP Bewersdorf, S Ball, P Guglielmelli, M Meggendorfer, A, AS Kubasch, E Travaglino, A Campagna, M Ubezio, A Russo, G Todisco, C Tentori, A Buizza, E Sauta, M Zampini, E Riva, G Asti, M Delleani, F Ficara , A Santoro, C Sala, D Dall'Olio, L Dall'Olio, T Kewan, I Casetti, H Awada, B Xicoy, V Vucinic, HA Hou, WC Chou, CY Yao, CC Lin , HF Tien, A Consagra, D Sallman, W Kern, M Bernardi, P Chiusolo, LM Borin, MT Voso, L Pleyer, L Palomo, D Quintela, A Jerez, E Cornejo, P Garcia Martin, M Díaz-Beyá, A Avendaño Pita, V Roldan, D Fiallo Suarez, E Cerezo Velasco, Marisa Calabuig, Guillermo Garcia-Manero, Sanam Loghavi, Uwe Platzbecker, Francesc Sole, Maria Diez-Campelo, J Maciejewski, N Kroger, P Fenaux, M Fontenay, V Santini, T Haferlach, U Germing, E Padron, M Robin, F Passamonti, E Solary, A Vannucchi, G Castellani, AM Zeidan, RS Komrokji, **MG Della Porta**

The TITAN Study

- A collaborative, world-wide effort to collect and analyze clinical and genomic information from real-world patients affected by myeloid neoplasms.

GENOMED4ALL

SYNTHEMA

EuroBloodNet

MDS

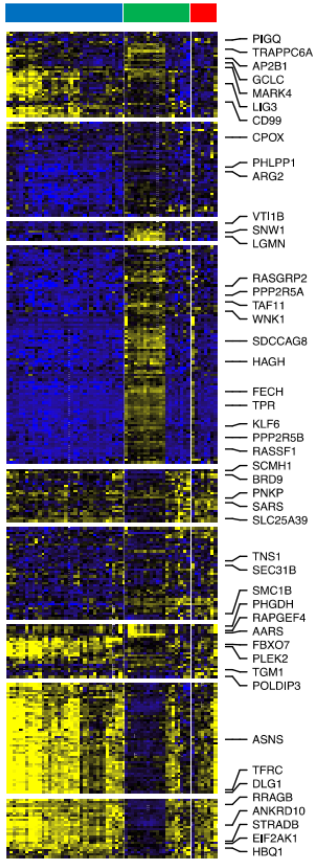
- 103 Hospitals and Cancer Centers
- 20,012 retrospective patients with clinical and genomic information from local sequencing facilities:
  - **6,311 AML**
  - **8,378 MDS**
  - **2,720 MDS/MPN**
  - **1,597 MPN (Myelofibrosis)**

- 1,482 patients with matched RNAseq information from bone marrow progenitors for correlative analyses

Results 2 - Splicing Mutations Are Shared Across Multiple Entities

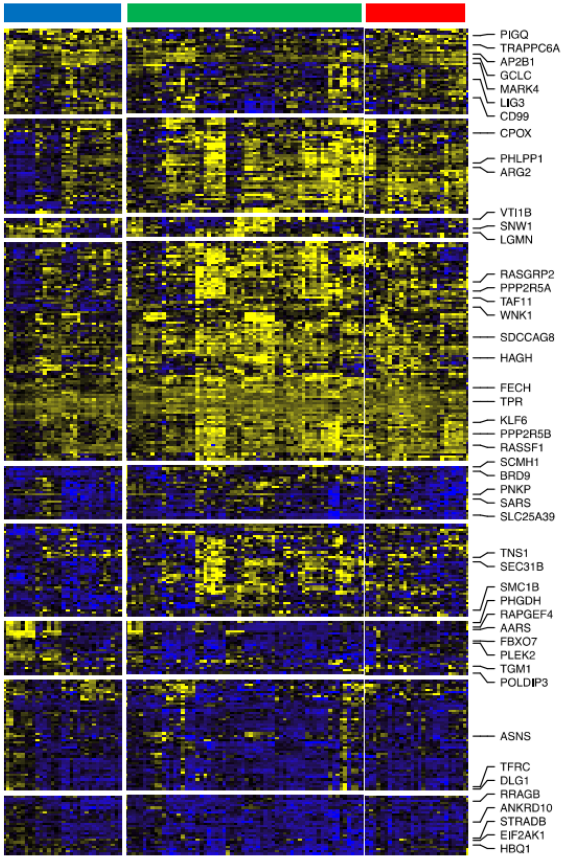
Disease Entity	**Early Disease:** - Absence of High-Risk Features - No Excess Blasts	**High-Risk Features:** - RUNX1/ASXL1 mutations - del(7)/-7, abn(3q) or CK **Advanced Disease:** - Excess Blasts
MN with ***SF3B1*** mutation (n=1991)	MDS: 88.1% MDS/MPN: 11.9%	MDS: 40.8% MDS/MPN: 8.4% AML: 50.8%
MN with ***SRSF2*** mutation (± *TET2*) (n=1447)	MDS: 54.5% MDS/MPN: 45.5%	MDS: 25.6% MDS/MPN: 22.2% AML: 52.1%
MN with ***U2AF1*** mutation (n=1118)	MDS: 87.5% MDS/MPN: 12.5%	MDS: 34.8% MDS/MPN: 4.6% AML: 60.6%

Results 2 – RNAseq analysis of Splicing Mutant Patients



Splicing Mutations without HR Features

- SF3B1 mutation
- SRSF2 mutation
- U2AF1 mutation

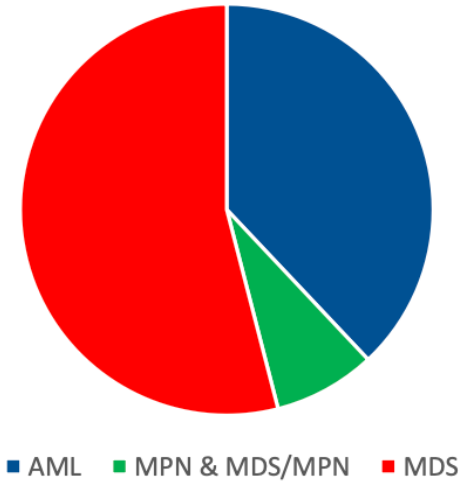


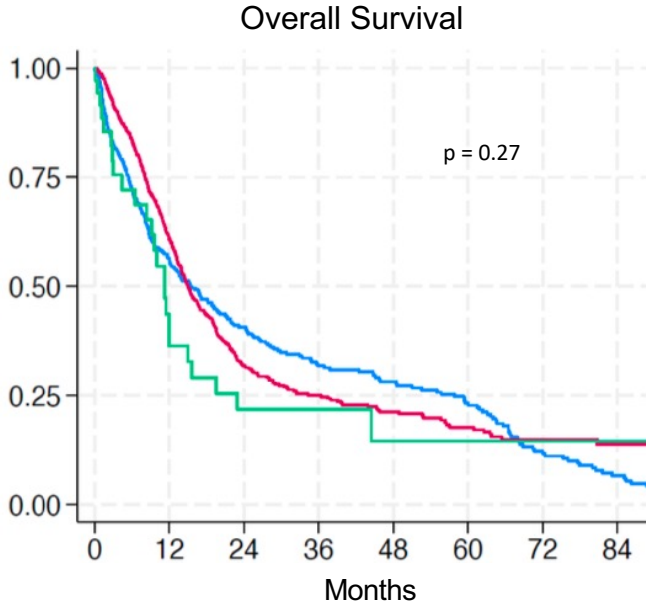
Splicing Mutations with HR Features*:

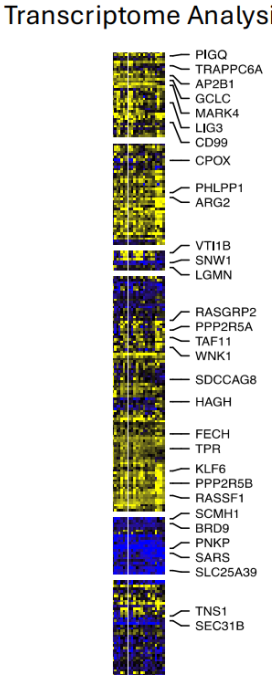
- SF3B1 mutation
- SRSF2 mutation
- U2AF1 mutation

*: $RUNX1^{mut}$, $ASXL1^{mut}$ del(7)/-7, abn(3q), complex karyotype, excess blasts

Results 3 - *TP53* Drives Cluster Assignment Irrespective of Diagnostic Entity

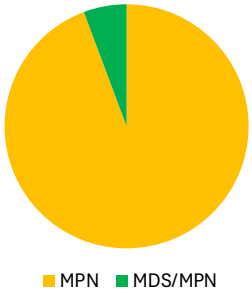




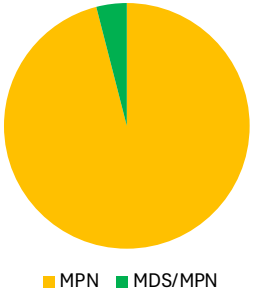


- Biallelic inactivation was identified in most cases (>65%)
- Monoallelic *TP53* MNs showed progression to biallelic at leukemic evolution

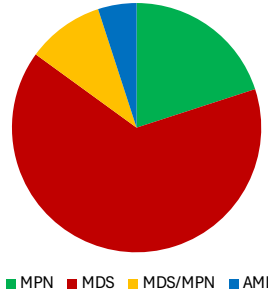
Results 4 - Fibrosis identifies distinct clusters with diverse features and survival



JAK/STAT mutations
No HR Features*
n = 1143

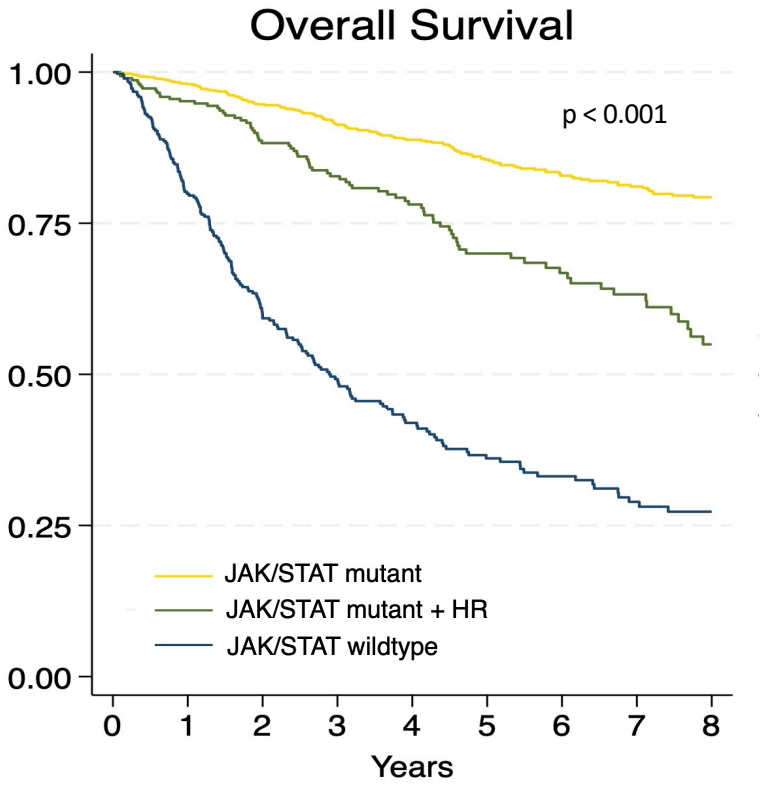


JAK/STAT mutations
+ HR Features*
n = 305



JAK/STAT wildtype
n = 381

- SHAP analysis identified marrow fibrosis (MF2+) as a relevant features for cluster assignment
- Triple-negative MNs with fibrosis had the worst prognosis and a high prevalence of HR features



*: ASXL1, BCOR, EZH2, RUNX1 mutations
del(7)/-7, complex karyotype

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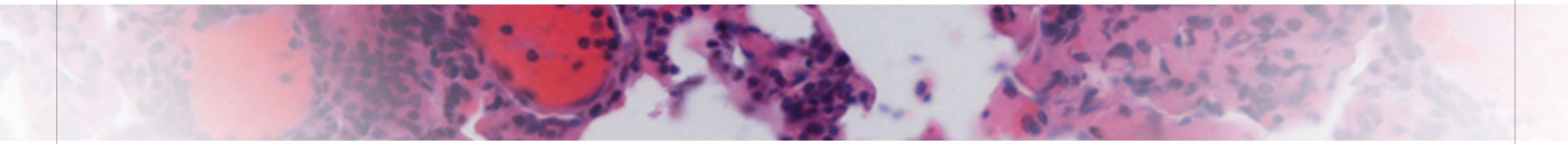
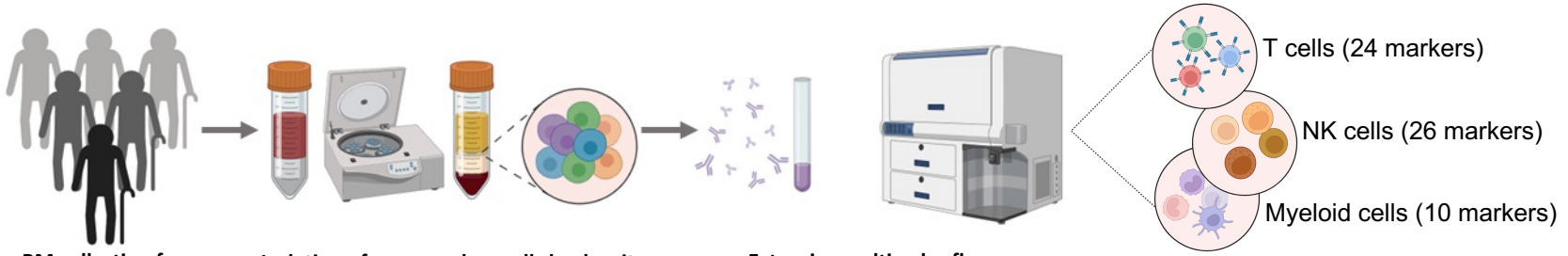


Landscape of immune cell states and ecosystems in patients with Myelodysplastic Syndrome to refine prognostic assessment and predict treatment response.

A study by i4MDS Consortium

Elena Riva, M Calvi, M Zampini, L Dall'Olio, A Merlotti, A Russo, G Maggioni, L Orlandi, A Frigo, F Ficara, L Crisafulli, E Sauta, S D'Amico, E Lugli, A Campagna, M Ubezio, CA Tentori, G Todisco, L Lanino, A Buizza, D Ventura, N Pinocchio, E Saba, A Santoro, V Santini, A. van de Loosdrecht, RS Komrokji, G Garcia-Manero, P Fenaux, L Ades, U Platzbecker, T Haferlach, A Medina Almeida, AM. Zeidan, S Kordasti, D Remondini, G Castellani, C Di Vito, D Mavilio, and **Matteo Giovanni Della Porta**

Prospective study population (n=211) and study design



BM collection from patients

Isolation of mononuclear cells by density gradient centrifugation

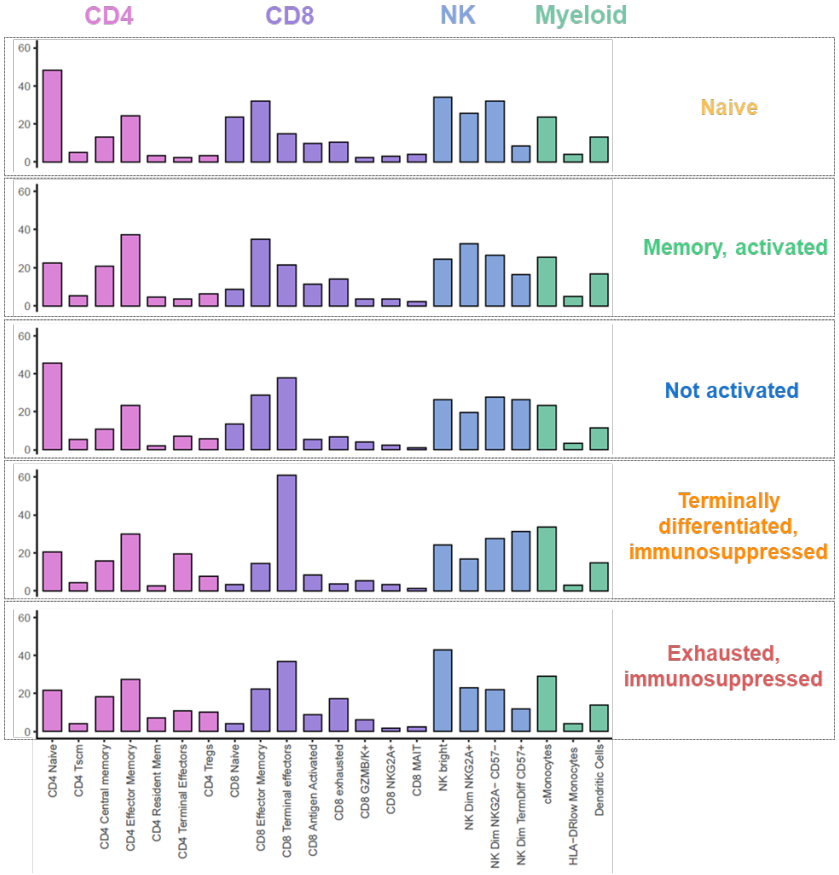
Extensive multi-color flow cytometry

Panels designed according to i4MDS reccomendations (Tentori et al., Hemasphere 2024)

IPSS-R	#PATIENTS
Age-matched controls	21
Very Low/Low	67
Intermediate	26
High/Very High	39
AML post MDS	58
	211

IPSS-R	BM PRE THERAPY	BM POST HMAs	#SAMPLES
Age-matched HC	21	-	21
Very low/Low	65	-	65
Intermediate	18	9	27
High/Very high	25	20	45
AML post MDS	45	37	82
	174	66	**240**

Characterization of immune ecosystems



Immune Dysfunction

- High CD4 and CD8 Naive
- High CD56^{bright} NK cells with conventional phenotype
- Low Tregs and exhausted T cells
- Low CD8 and CD4 Terminal effectors

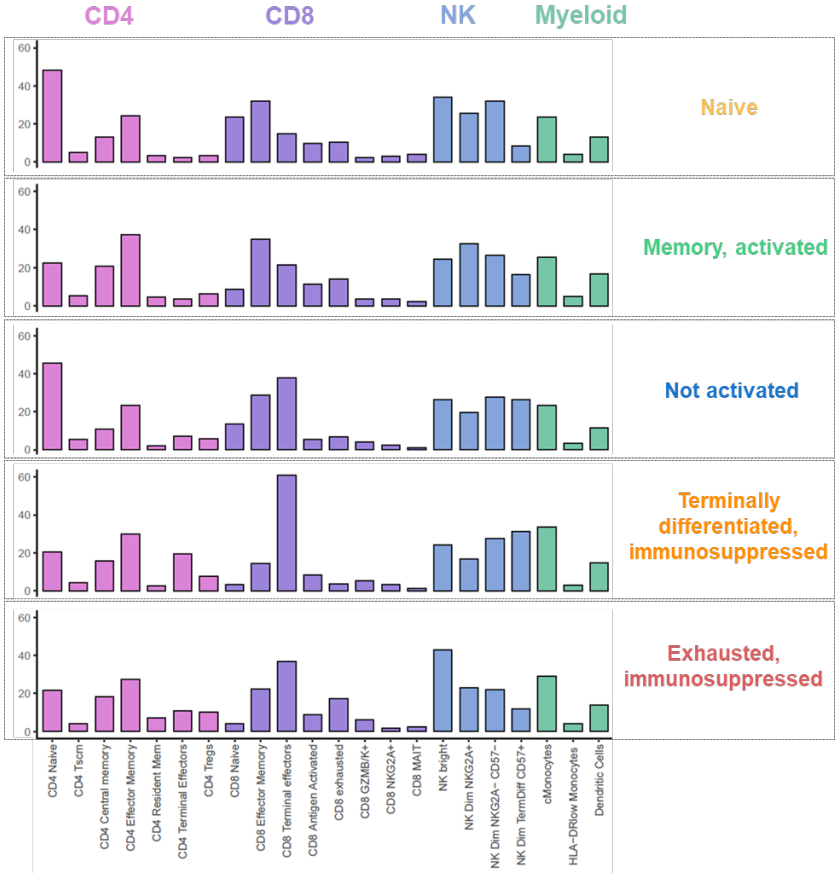
- Low CD4 and CD8 Naive
- High central and effector memory T cells
- High antigen-activated T cells
- Low CD4 and CD8 Terminal effectors
- High HLA-DR^{low} monocytes and Dendritic cells

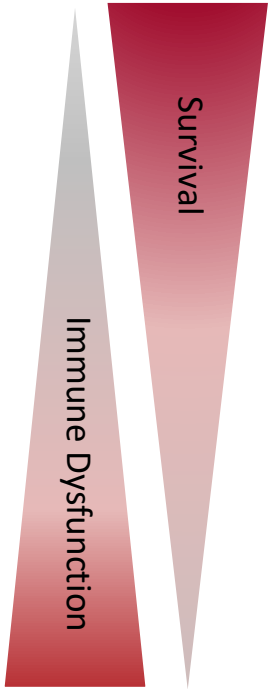
- High CD4 and CD8 Naive
- High terminally differentiated T and NK cells
- Low Tregs and exhausted T cells
- Low Antigen-activated T cells

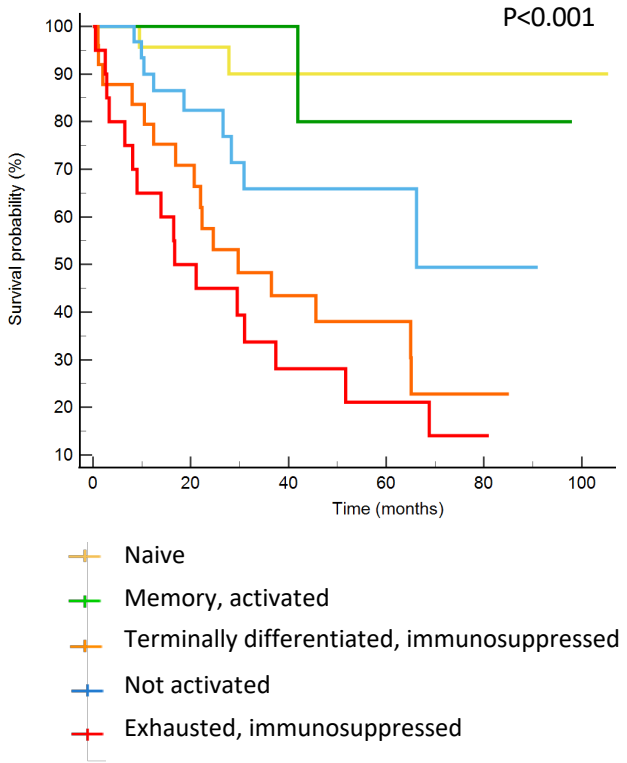
- High terminally differentiated T and NK cells
- Low exhausted T cells
- High Tregs
- High Monocytes

- High terminally differentiated T and NK cells
- High Tregs
- High T exhausted
- Low mature CD56^{dim} NK cells
- High expression of PD1 and low expression of Nkp30/46 on NK cells

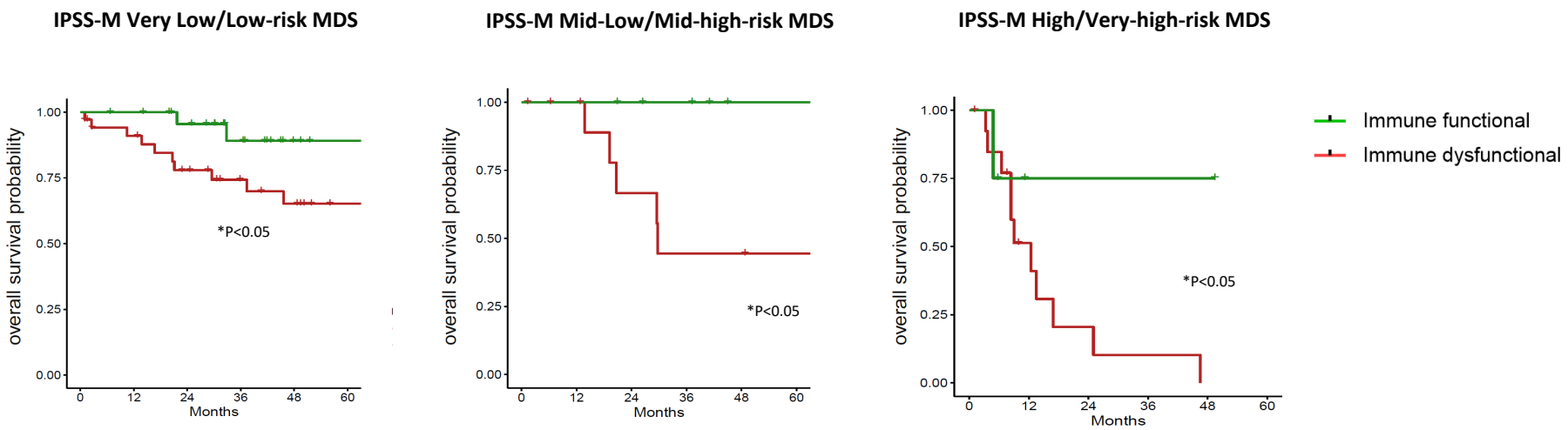
Prognostic relevance of immune ecosystems





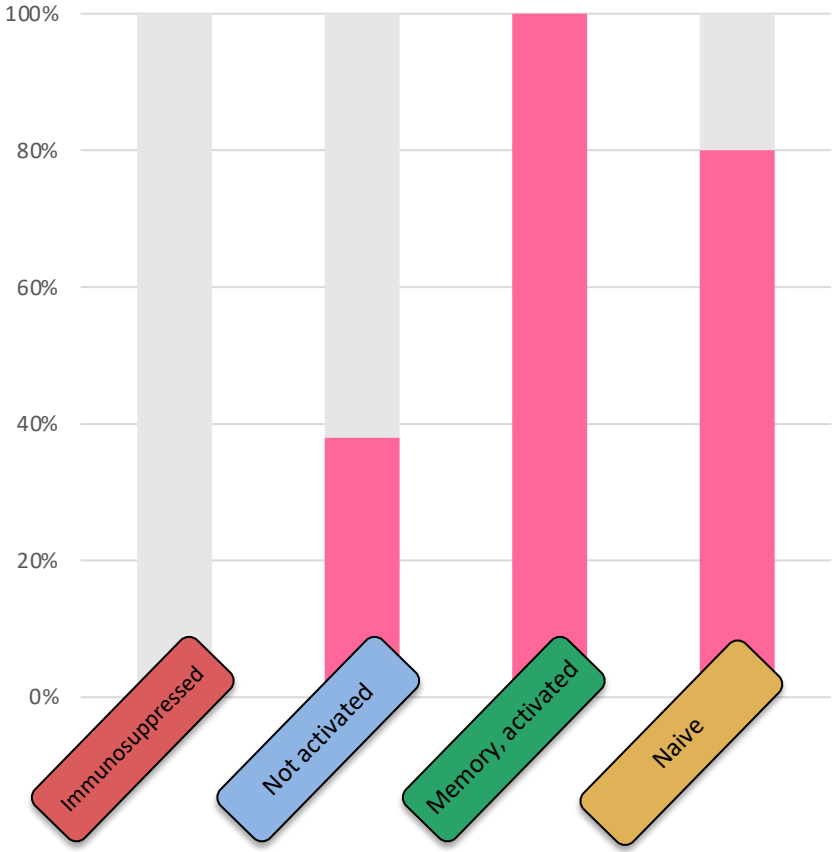


Immunological profiles improve MDS patients' prognosis



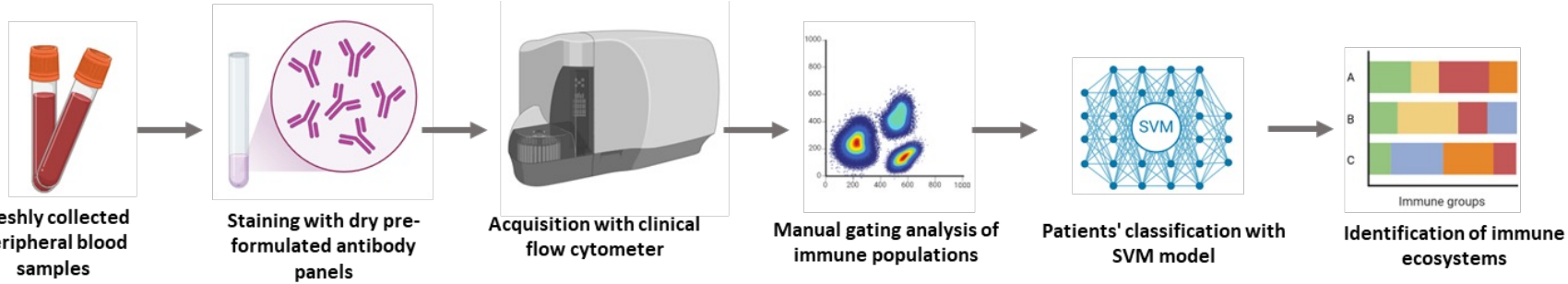
- The immune signatures were able to further refine the prognosis of patients stratified according to IPSS-R (P<0.05) and IPSS-M risk groups (P<0.05).
- In a multivariable model adjusted for age, sex and IPSS-M score, the immune signatures retained an independent prognostic impact (P<0.001, HR 1.46).
- Integrating immune cell signatures with molecular profiles improved the accuracy of predicting patient outcomes (CI 0.76 vs. 0.84 for IPSS-M alone vs IPSS-M and immune signatures).

Prediction of HMAs therapy outcome by exploiting immune profile at diagnosis

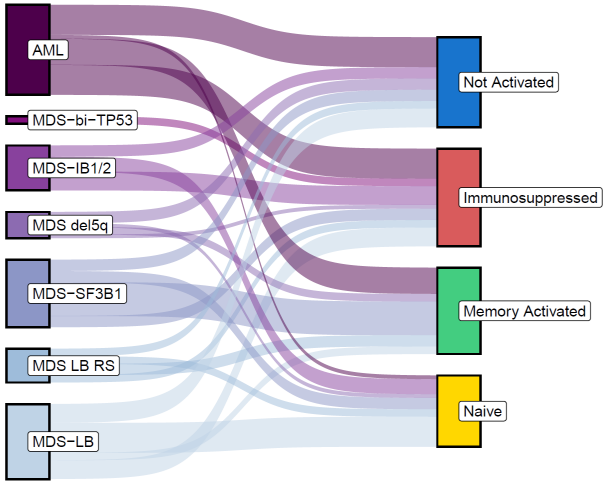


- Evaluation of immune ecosystems enrichment in the BM of **40 MDS patients** subsequently treated with HMAs
- At diagnosis, patients that exhibited functional immune ecosystems were associated with higher probability of overall response (80-100%) to HMAs treatment compared to dysfunctional ones (0-38%)

Integration of immune ecosystems evaluation in a clinical setting



- Design of 4 dry pre-formulated antibody panels for the characterization of T lymphocytes, NK and Myeloid cells in peripheral blood samples by using a routine flow cytometer
- Support Vector Machine (SMV) model was trained to automatically classify patients into immune groups, resulting into a very high precision rate (>95%)
- Validation cohort was an independent population of 100 MDS and AML patients



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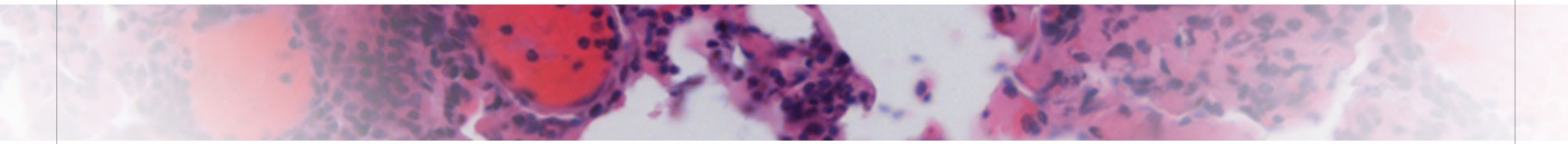


Enhancing Personalized Prognostic Assessment of Myelodysplastic Syndromes through a Multimodal and Explainable Deep Data Fusion Approach (MEGAERA)

Elisabetta Sauta, PhD

Sartori F, Lanino L, Asti G, D'Amico S, Delleani M, Riva E, Zampini M, Zazzetti E, Bicchieri M, Maggioni G, Campagna A, Todisco G, Tentori CA, Ubezio M, Russo A, Buizza A, Ficara F, Crisafulli C, Brindisi M, Ventura D, Pinocchio N, Bonometti A, Di Tommaso L, Savevski V, Santoro A, Derus NR, Dall'Olio D, Santini V, Solé F, Platzbecker U, Fenaux P, Campelo MD, Komrokji RS, Garcia-Manero G, Haferlach T, Kordasti S, Zeidan AM, Castellani G, Sanavia T, Fariselli P and Della Porta MG

Study Population

Retrospective patients cohort with primary MDS from Humanitas Research Hospital

Humanitas MDS Cohort Characteristics	All Patients (n = 605)
Age (yrs), median (range)	70 (19-93)
Gender (Male/Female), %	381 / 224, 63% ; 37%
MDS (median follow-up, months)	363 25 (0.2-181)
AML from MDS (median follow-up, months)	242 (0.1-117)
Number oncogenic lesions per patient, median (range)	3 (0-10)

CLINICAL

- Demographic information
- Blood parameters
- Treatments & Clinical outcomes

GENOMIC

- Chromosomal alterations
- Somatic mutation screening of 31 target genes

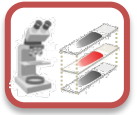
TRANSCRIPTOMIC

- Bulk RNA-seq of CD34⁺ bone marrows cells

IMMUNOMIC

- Bone marrow and peripheral bloods of 3 marker panels for T, NK and Myeloid cells

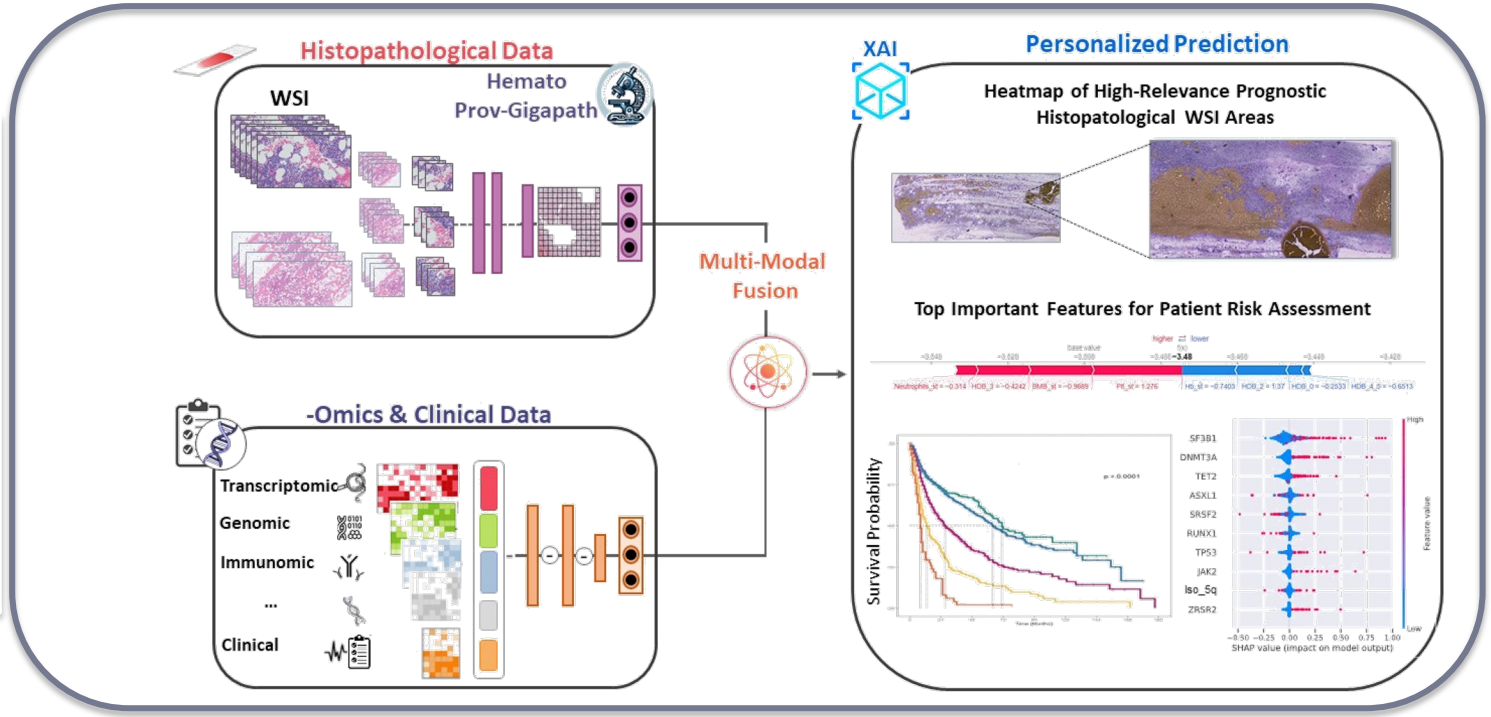
DIGITAL PATHOLOGY



- Digitalized H&E and MGG images of biopsy and cytological bone marrow smears

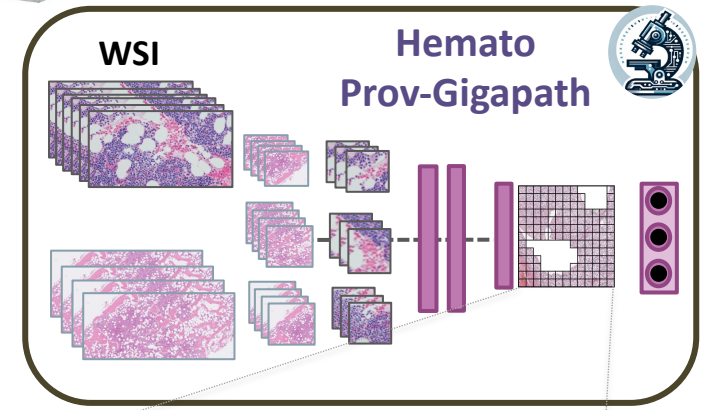
MEGAERA: **M**ulti-modal **E**xplainable and **G**rounded AI-based **E**ngine for **R**esearch **A**dvancements in personalized care in hematology

MEGAERA

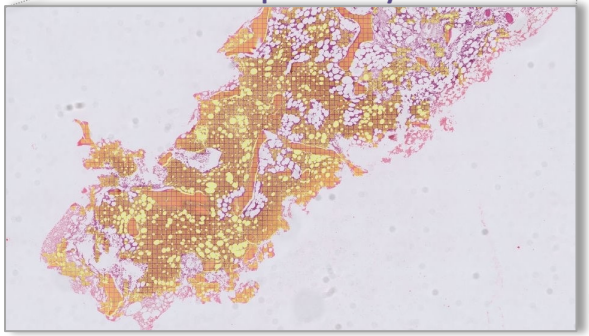


MEGAERA 1 — DEFINITION OF A FOUNDATION MODEL IN HEMATOLOGY

Histopathological Data



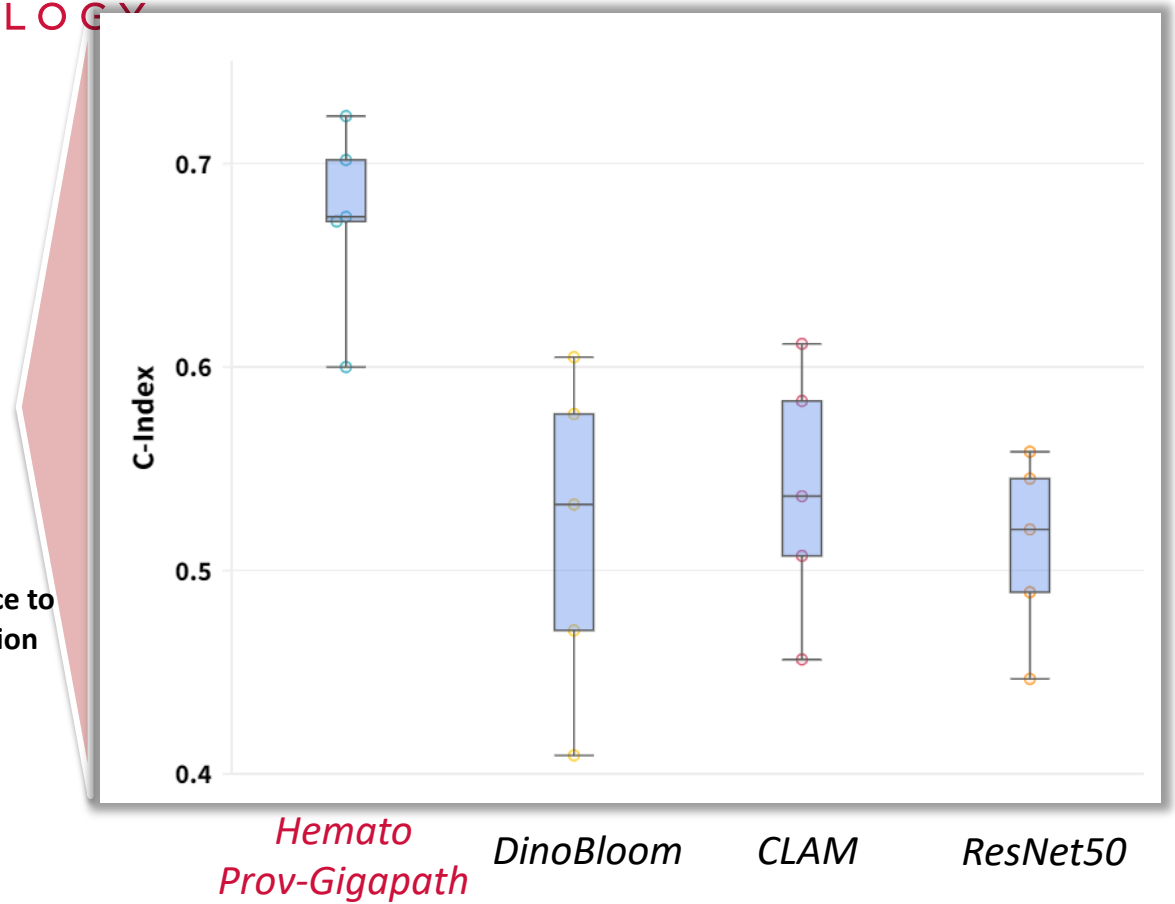
WSI Explainability



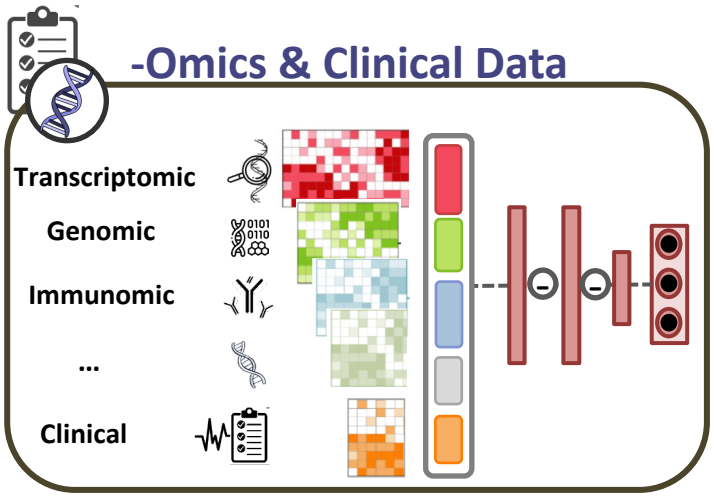
Relevance to Prediction

High

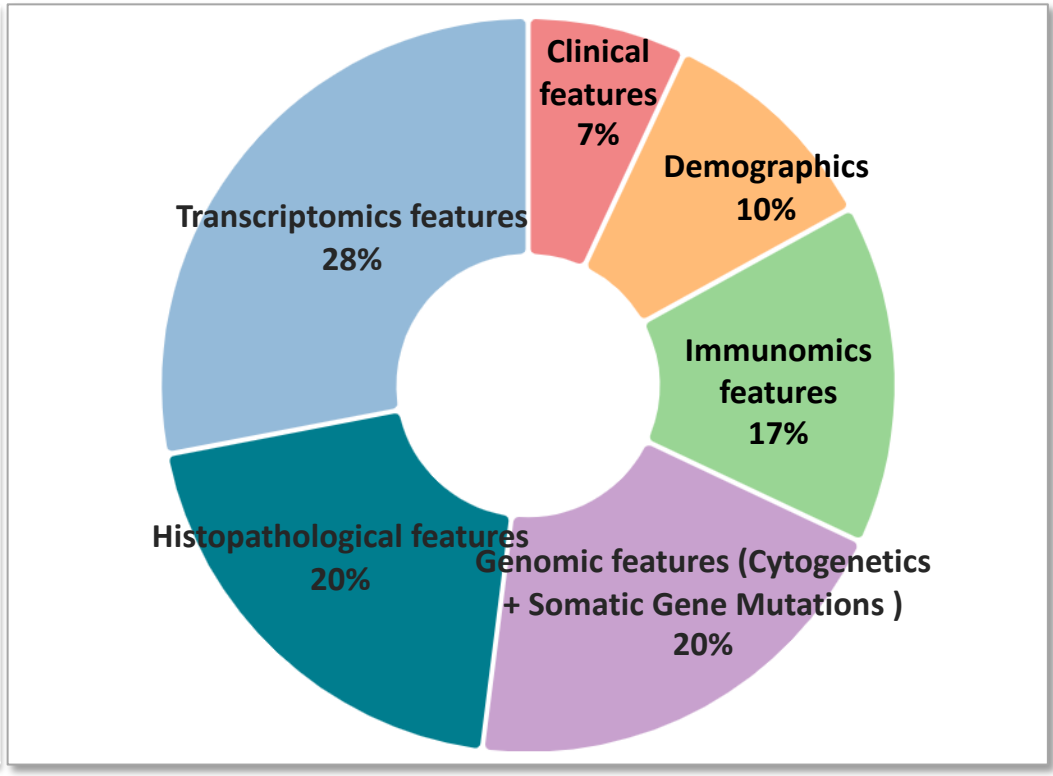
Low



MEGAERA² DEFINITION OF AN INTEGRATIVE DEEP MODEL FOR CLINICAL AND-OMICS DATA



Explained Variance of Probability of Survival



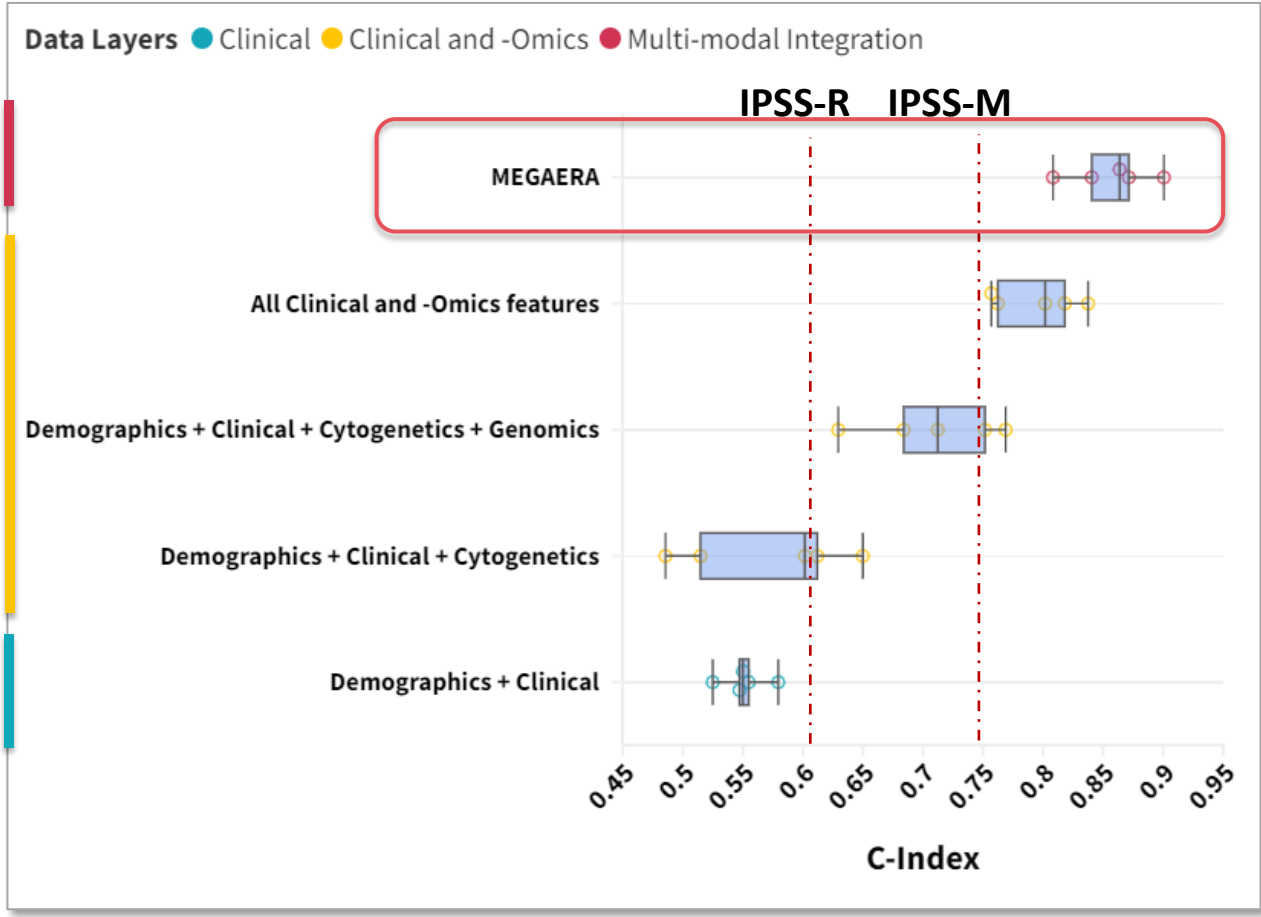
Results

MEGAERA PREDICTIVE PERFORMANCE

Aim: Overall Survival Risk Prediction

Schema:

- 5-fold Cross-Validation
- Ablation analyses to evaluate the contribution of each modality



Results

MEGAERA MODEL INTERPRETABILITY

SHAP Explainability on MDS patients treated with HMA: the most relevant features associated with treatment failure

- Clinical
- Genomic
- Transcriptomics
- Immunomics