When is molecular analysis useful in MDS ?

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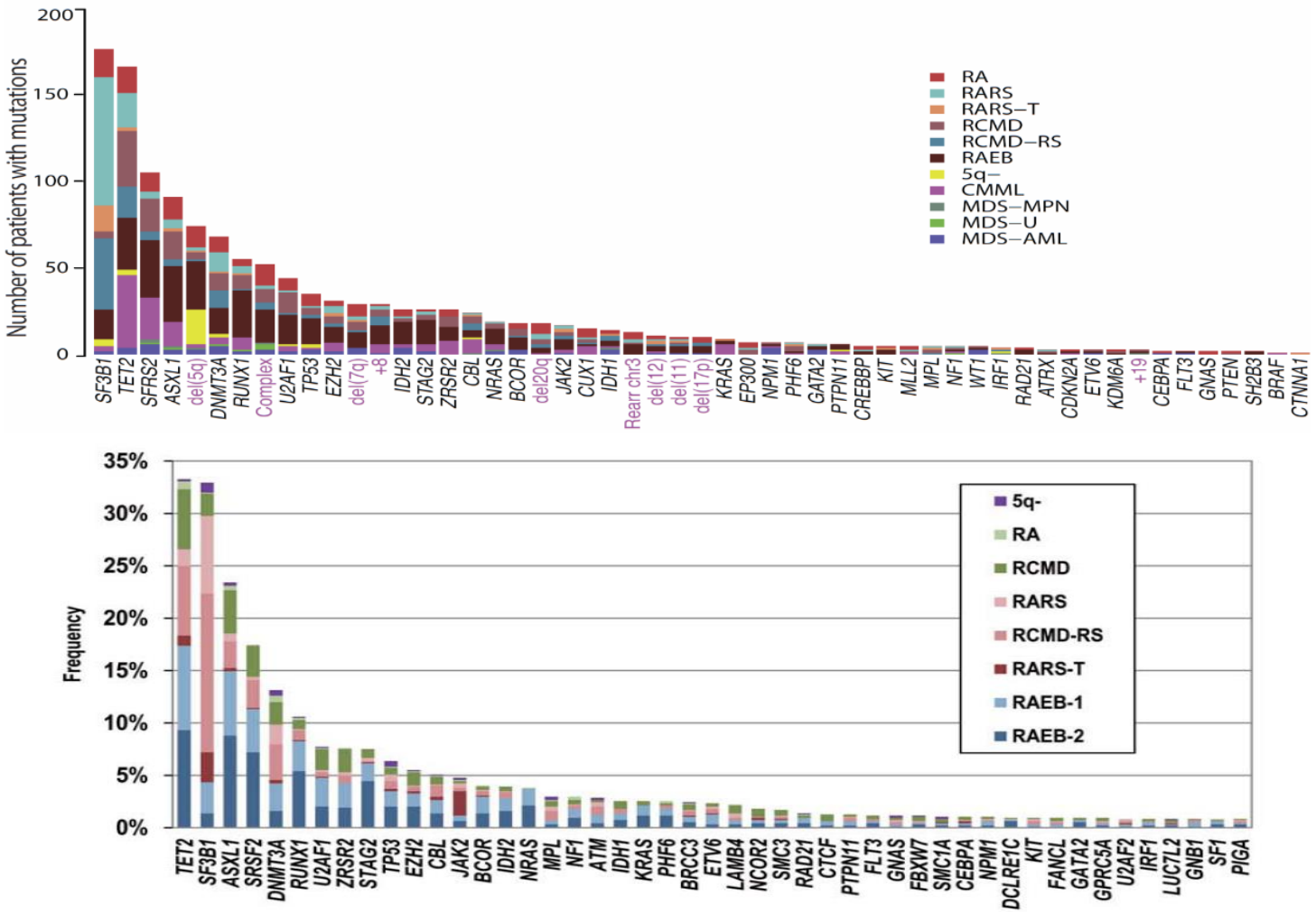
Disclosures of Valeria Santini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS CELGENE	x					x	
GERON						x	
GILEAD						x	
OTSUKA			x				
NOVARTIS						x	
TAKEDA						x	
ABBVIE						x	
SYROS						x	
SERVIER						x	

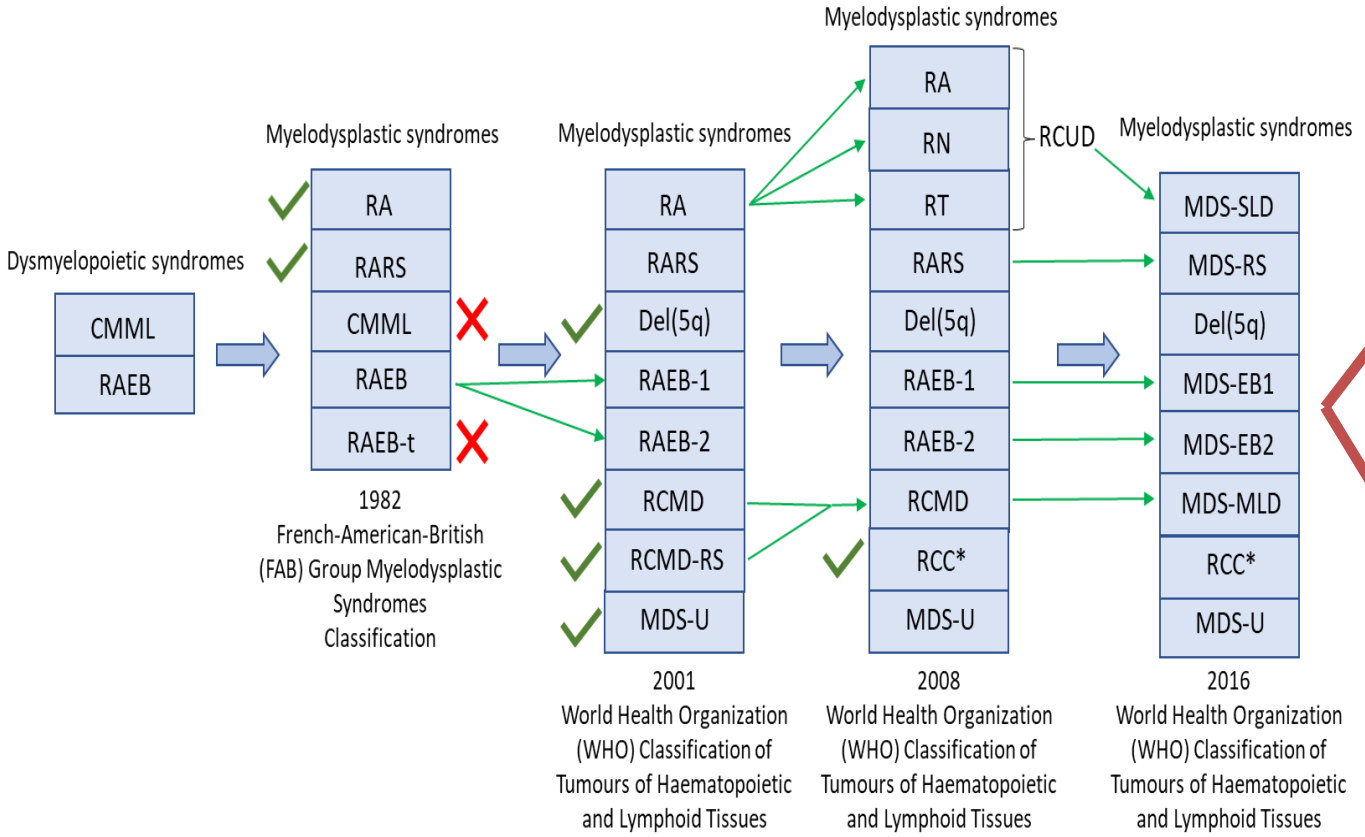
Somatic Mutations in MDS are very frequent



Papaemmanuil et al. *Blood*. 2013.

Haferlach et al. *Leukemia*. 2014.

MDS classification has evolved over time



WHO 2022


Leukemia

www.nature.com/leu

REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

ICC 2022

The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data

Daniel A. Arber, Attilio Orazi, Robert P. Hasserjian, Michael J. Borowitz, Katherine R. Calvo, Hans-Michael Kvasnicka, Sa A. Wang, Adam Bagg, Tiziano Barbui, Susan Branford, Carlos E. Bueso-Ramos, Jorge E. Cortes, Paola Dal Cin, Courtney D. DiNardo, Herve' Dombret, Eric J. Duncavage, Benjamin L. Ebert, Elihu H. Estey, Fabio Facchetti, Kathryn Foucar, Naseema Gangat, Umberto Gianelli, Lucy A. Godley, Nicola Gökbuget, Jason Gotlib, Eva Hellström-Lindberg, Gabriela S. Hobbs, Ronald Hoffman, Elias J. Jabbour, Jean-Jacques Kiladjian, Richard A. Larson, Michelle M. Le Beau, Mignon L-C. Loh, Bob Löwenberg, Elizabeth Macintyre, Luca Malcovati, Charles G. Mullighan, Charlotte Niemeyer, Olatoyosi M. Odenike, Seishi Ogawa, Alberto Orfao, Elli Papaemmanuil, Francesco Passamonti, Kimmo Porkka, Ching-Hon Pui, Jerald P. Radich, Andreas Reiter, Maria Rozman, Martina Rudelius, Michael R. Savona, Charles A. Schiffer, Annette Schmitt-Graeff, Akiko Shimamura, Jorge Sierra, Wendy A. Stock, Richard M. Stone, Martin S. Tallman, Jürgen Thiele, Hwei-Fang Tien, Alexandar Tzankov, Alessandro M. Vannucchi, Paresh Vyas, Andrew H. Wei, Olga K. Weinberg, Agnieszka Wierzbowska, Mario Cazzola, Hartmut Döhner and Ayalew Tefferi

Zeidan A et al, Blood Reviews, 2019; Khoury J et al, Leukemia; Arber D et al, Blood 2022

The 2022 WHO classification

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury JD Leukemia. 2022 Jun 22.

The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data

Pre-malignant clonal cytopenias and myelodysplastic syndromes

Clonal cytopenia of undetermined significance

Myelodysplastic syndrome with mutated *SF3B1*

Myelodysplastic syndrome with del(5q)

Myelodysplastic syndrome, not otherwise specified (MDS, NOS)

- MDS, NOS without dysplasia
- MDS, NOS with single lineage dysplasia
- MDS, NOS with multilineage dysplasia

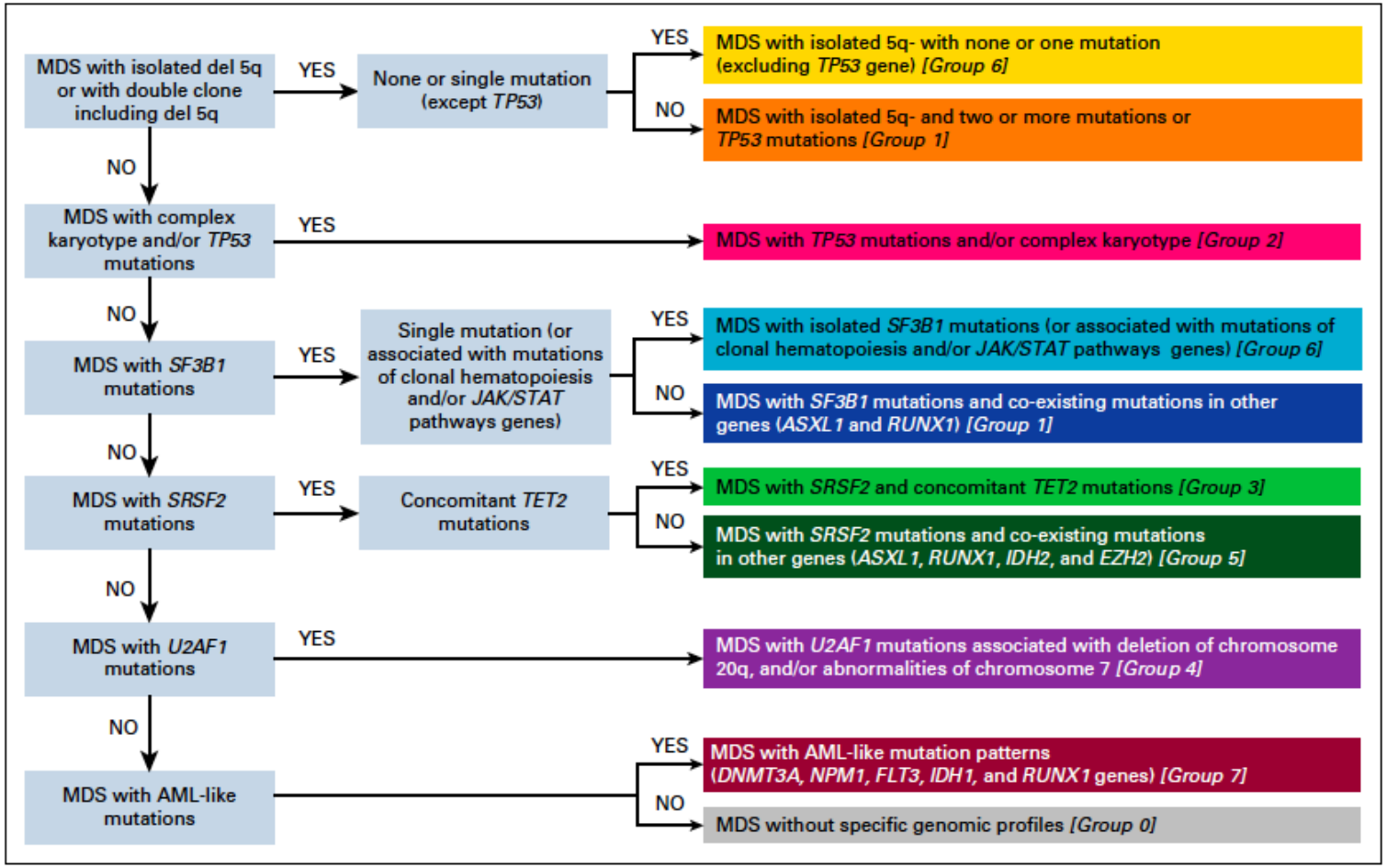
Myelodysplastic syndrome with excess blasts

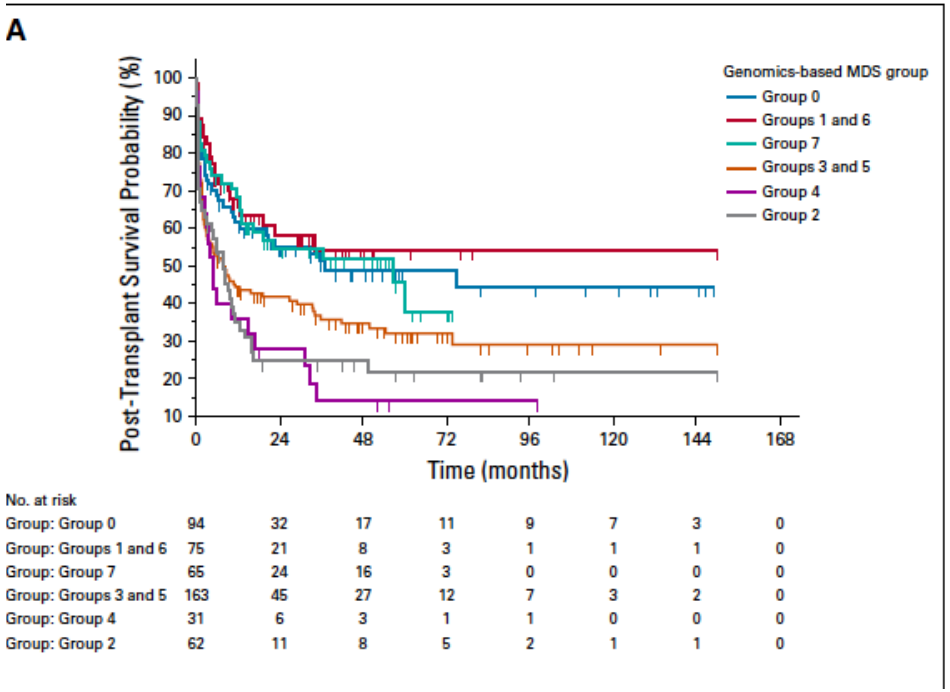
Myelodysplastic syndrome /acute myeloid leukemia (MDS/AML)

- MDS/AML with mutated *TP53*
- MDS/AML with myelodysplasia-related gene mutations
- MDS/AML with myelodysplasia-related cytogenetic abnormalities
- MDS/AML, not otherwise specified

Arber D et al, Blood 2022

Integration of somatic mutations in prognostication





Bersanelli et al, JCO 2021

The model consisted of

1) hemoglobin, platelets and bone marrow blasts (neutrophil number not significant)

2) IPSS-R cytogenetic category

3) 17 binary features derived from the presence of mutations in 16 predictive genes

(*ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *IDH2*, *KRAS*, MLL^{PTD}, *NPM1*, *NRAS*, *RUNX1*, $SF3B1^{5q}$, $SF3B1^{\alpha}$, *SRSF2*, $TP53^{multihit}$, and *U2AF1*);

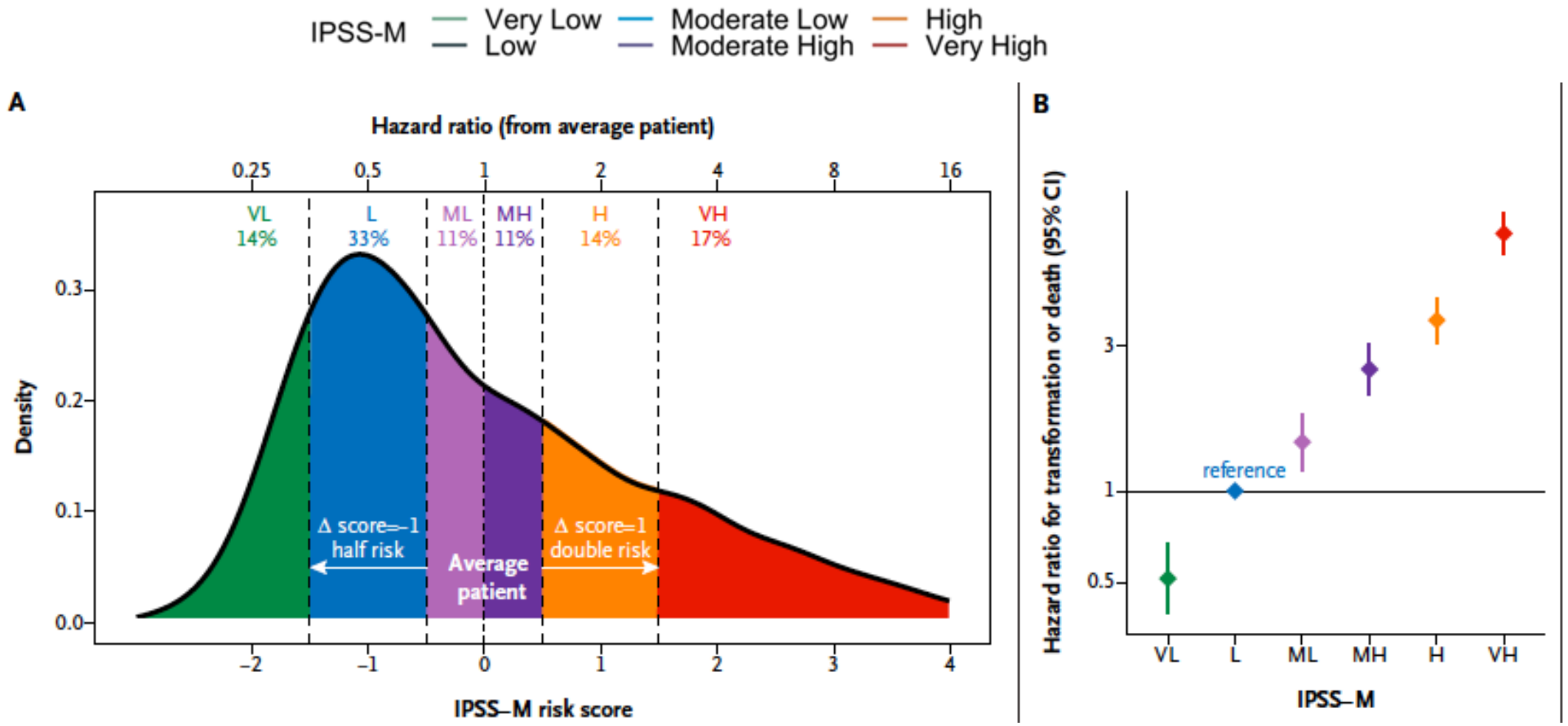
4) one feature representing the number of mutations from a group of 15 genes.

15 additional genes (*BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*) on the basis of adverse effects

Molecular International Prognostic scoring system for myelodysplastic syndromes IPSS-M

Bernard e et al, NEJM Evid 2022; 1 (7) June 12

IPSS-M patient-specific risk score & risk categories



score value of 0 represented the average patient (i.e., a hypothetical patient with mean values for all variables),

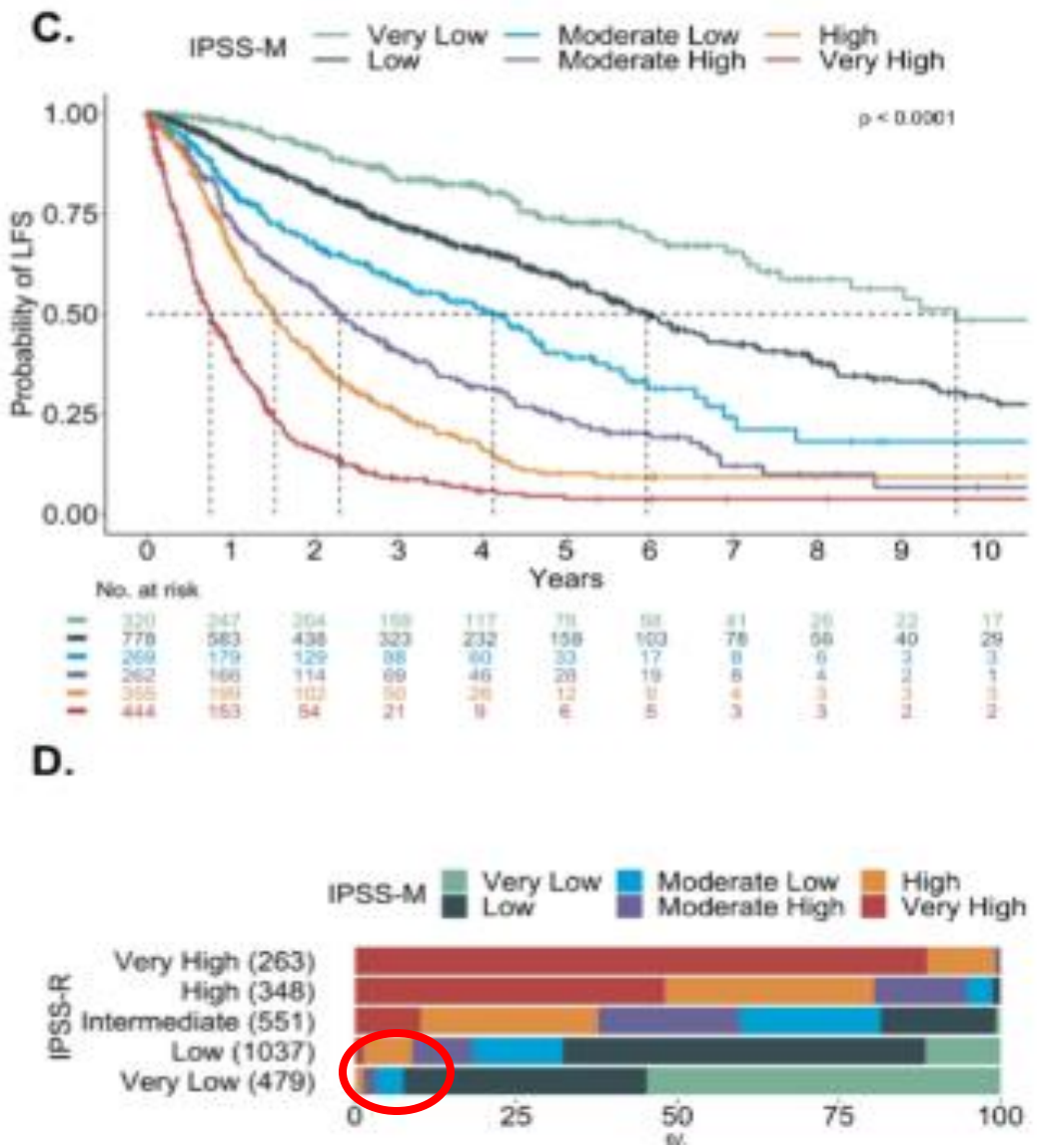
Continuous risk score

Patient-specific score

Reproducible and Interpretable

Bernard e et al, NEJM Evid 2022; 1 (7) June 12

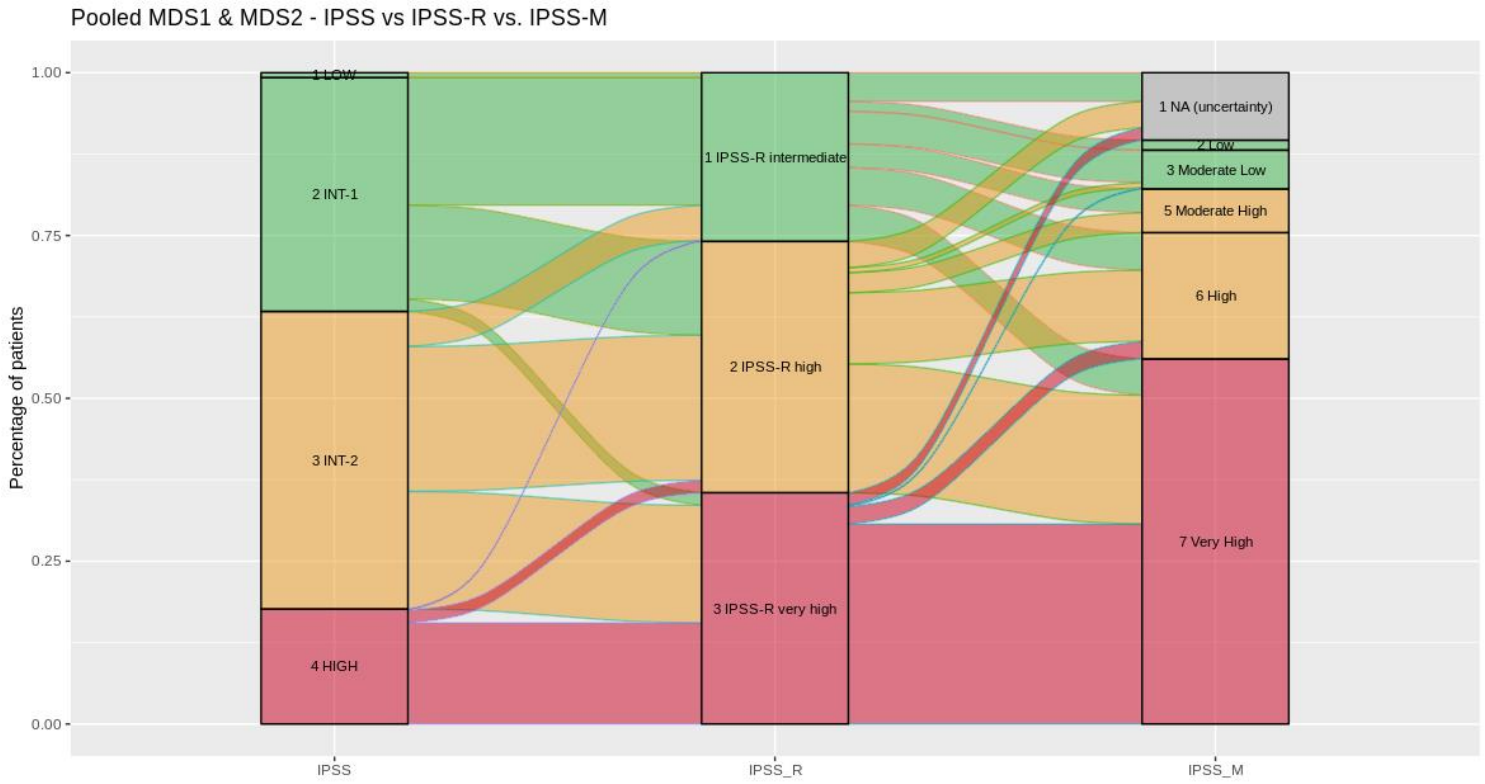
IPSS-M patient-specific risk score & risk categories



Bernard et al, NEJMevidences 2022

Correlative analysis between IPSS, IPSS-R, and IPSS-M[a]

IPSS-M frequently uptages MDS



- Upstaging was observed from derived former IPSS criteria to IPSS-R
- Comparing IPSS-R and IPSS-M
  - Of patients with IR IPSS-R, 22.2% and 21.5% were upstaged to HR and vHR IPSS-M, respectively
  - 51.2% of patients with HR IPSS-R were upstaged to vHR IPSS-M
  - 86.5% of patients with vHR IPSS-R remained vHR and 7.6% were downstaged to HR IPSS-M

Santini et al, EHA 2023

HR, high risk; INT, intermediate; IPSS, International Prognostic Scoring System, IPSS-R, revised IPSS; IPSS-M, molecular IPSS; IR, intermediate risk; MDS, myelodysplastic syndromes; MDS1, STIMULUS-MDS1; MDS2, STIMULUS-MDS2; NA, not available; vHR, very high risk.

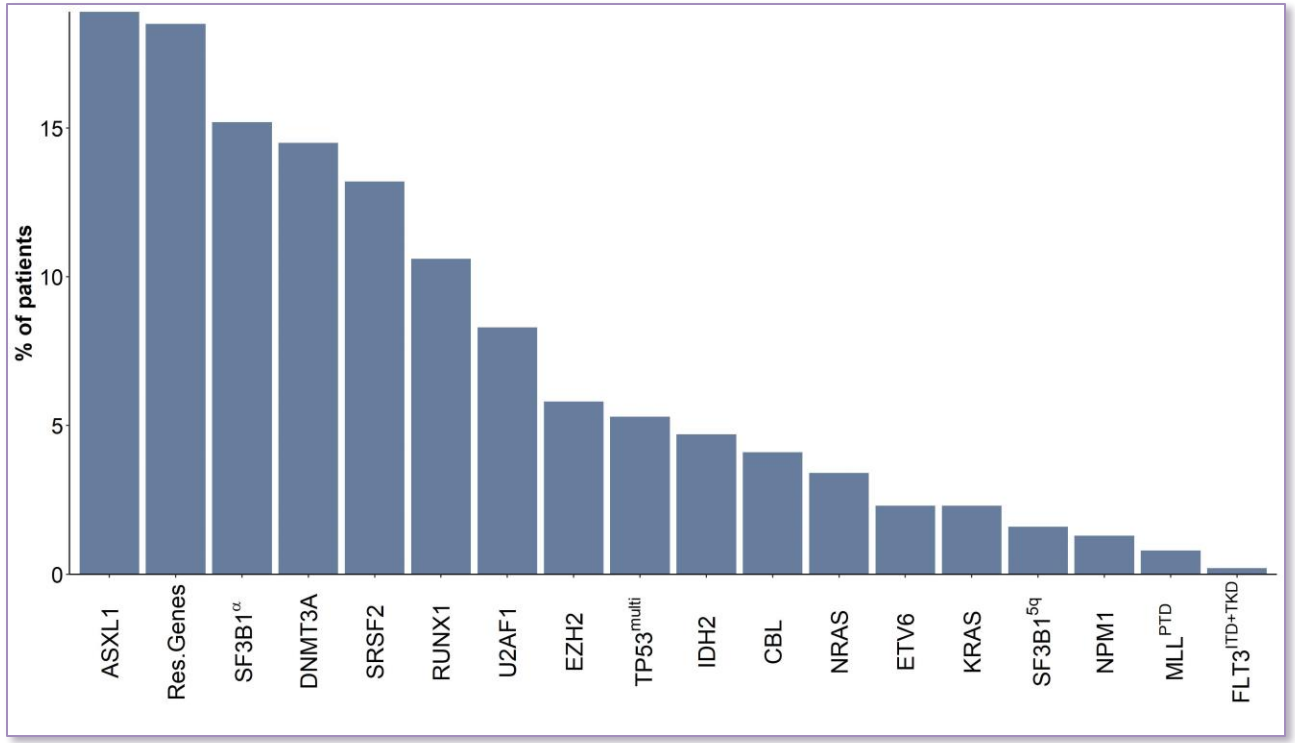
[a]Based on N=512 MDS patients with mutation data available from pooled studies (N=118 from MDS1; N=403 from MDS2).

Validation of IPSS-M- Real world data.

- 2,876 patients with primary MDS from GenoMed4All consortium with clinical and molecular data available from 21 European affiliated centers (retrospective analysis)

Genomed4All Cohort Characteristics	All Patients (n = 2,876)
Age (yrs), median (range)	68 (18-96)
Gender (Male/Female), %	1133/1743, 39% ; 61%
Median follow-up (months)	37.5 (36.2-38.8)
≥1 somatic mutations on 31 IPSS-M genes, %	82.4
≥1 oncogenic lesions, %	84
Number oncogenic lesions per patient, median (range)	3 (0-12)

DISTRIBUTION OF MUTATIONS ON THE IPSS-M GENES IN THE STUDY POPULATION

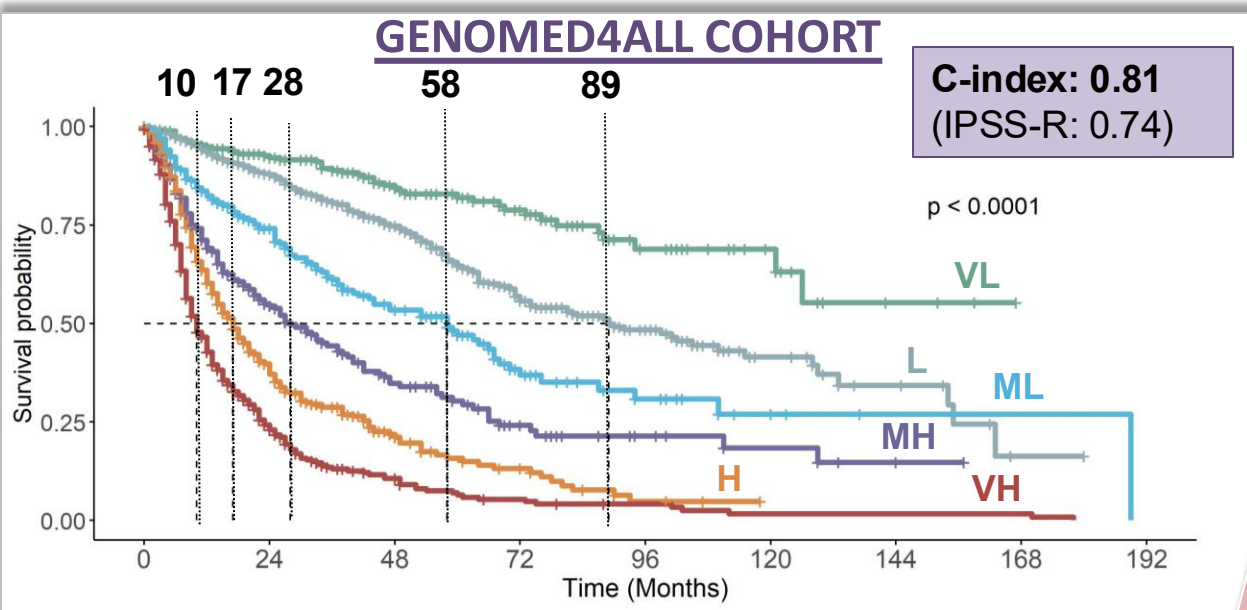


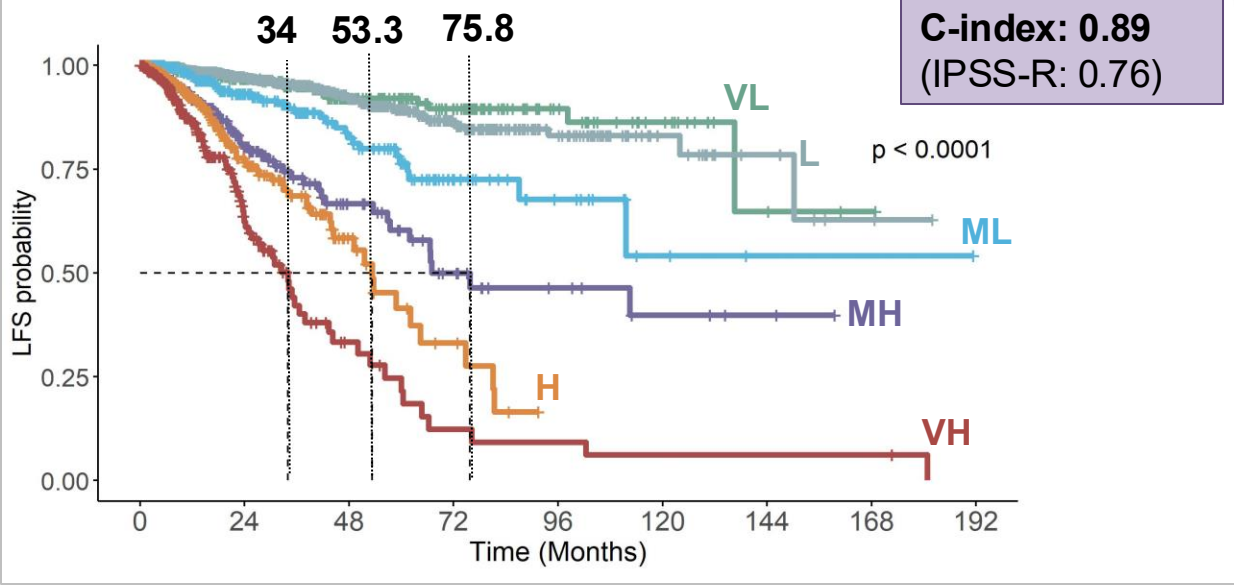
Sauta et al, JCO 2023

GENOMED4ALL

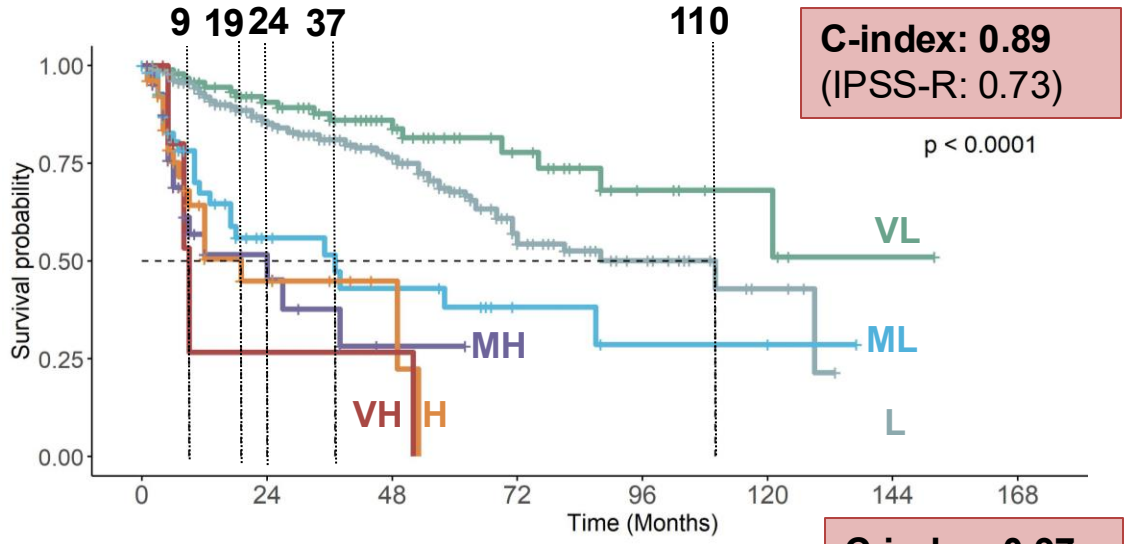
AIM 1: Extensive Real-World Validation

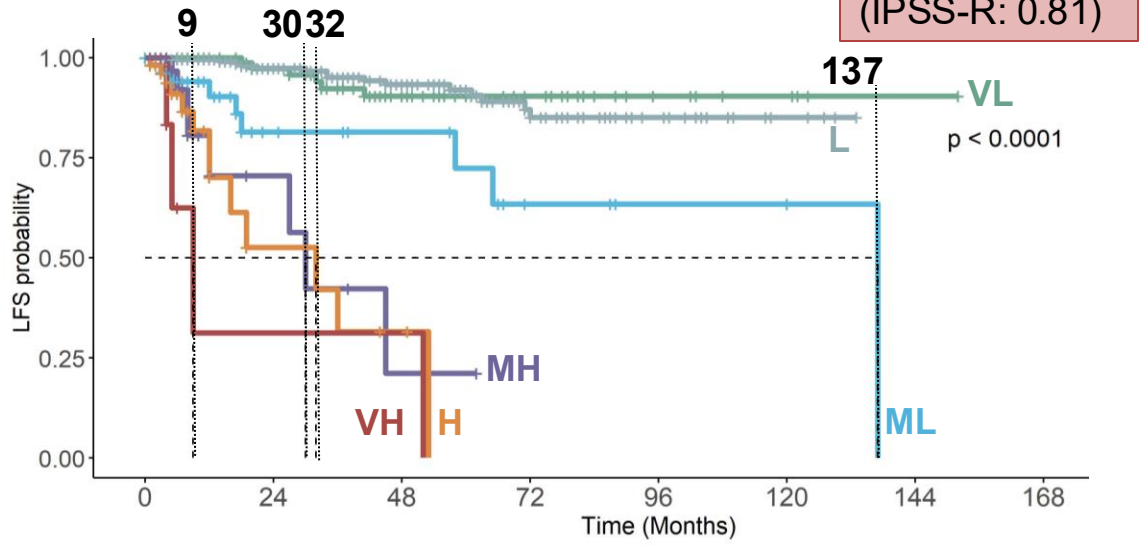
GENOMED4ALL COHORT





PATIENTS WITHOUT DETECTABLE IPSS-M MUTATIONS



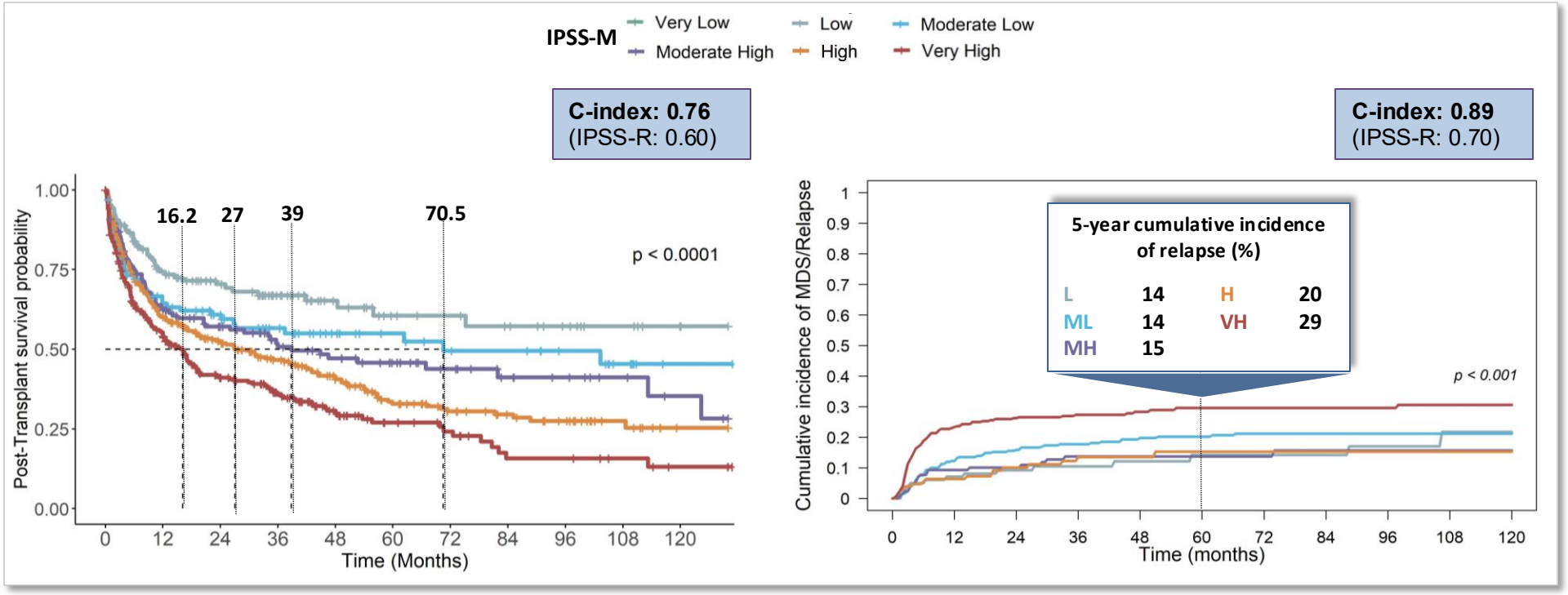


Sauta et al, JCO 2023

GENOMED4ALL

Validation in Patients Receiving HSCT

- 964 patients of the GenoMed4All cohort were treated with **allo-HSCT**



Sauta E et al J Clin Oncol 2023 Mar 17;JCO2201784.

Data-driven, harmonised classification system for myelodysplastic syndromes: a consensus paper from the International Consortium for Myelodysplastic Syndromes

Rami S Komrokji, Luca Lanino*, Somedeb Ball*, Jan P Bewersdorf*, Monia Marchetti, Giulia Maggioni, Erica Travaglino, Najla H Al Ali, Pierre Fenaux, Uwe Platzbecker, Valeria Santini, Maria Diez-Campelo, Avani Singh, Akriti G Jain, Luis E Aguirre, Sarah M Tinsley-Vance, Zaker I Schwabkey, Onyee Chan, Zhouer Xie, Andrew M Brunner, Andrew T Kuykendall, John M Bennett, Rena Buckstein, Rafael Bejar, Hetty E Carraway, Amy E DeZern, Elizabeth A Griffiths, Stephanie Halene, Robert P Hasserjian, Jeffrey Lancet, Alan F List, Sanam Loghavi, Olatoyosi Odenike, Eric Padron, Mrinal M Patnaik, Gail J Roboz, Maximilian Stahl, Mikkael A Sekeres, David P Steensma, Michael R Savona, Justin Taylor, Mina L Xu, Kendra Sweet, David A Sallman, Stephen D Nimer, Christopher S Hourigan, Andrew H Wei, Elisabetta Sauta, Saverio D'Amico, Gianluca Asti, Gastone Castellani, Mattia Delleani, Alessia Campagna, Uma M Borate, Guillermo Sanz, Fabio Efficace, Steven D Gore, Tae Kon Kim, Navel Daver, Guillermo Garcia-Manero, Maria Rozman, Alberto Orfao, Sa A Wang, M Kathryn Foucar, Ulrich Germing, Torsten Haferlach, Phillip Scheinberg, Yasushi Miyazaki, Marcelo Iastrebner, Austin Kulasekararaj, Thomas Cluzeau, Shahram Kordasti, Arjan A van de Loosdrecht, Lionel Ades, Amer M Zeidan†, Matteo G Della Porta†, on behalf of the International Consortium on Myelodysplastic Syndromes*

Komrokij , Lancet Haematol. 2024 Nov;11(11):e862-e872.

Characteristics of icMDS patient Population

	MOFFITT	GenoMed4all
No. of MDS patients	**2237**	**4780**
Age at diagnosis, median (range)	70 (18-97) years	69.4 (18-98) years
Male sex, n (%)	1419 (63%)	2896 (60.5%)
Non-Hispanic White, n (%)	2019 (90%)	
Hemoglobin (gm/dl), median (range)	9.5 (3-17.1)	9.7 (2.1-19.6)
WBC count (x10^9/L), median (range)	3.38 (0.09-76.8)	3.8 (0.1-121.0)
ANC (x10^9/L), median (range)	1.50 (0-47.9)	1.8 (0-104)
Platelet count (x10^9/L), median (range)	105 (2-1280)	120 (2-1491)
Peripheral blast (%), median (range)	2% (0%-19%)	0% (0%-19%)
Bone marrow blast (%), median (range)	3% (0%-19%)	4% (0%-19%)
Transfusion dependent, n (%)	741 (33%)	1094/4497 (24.3%)
Cytogenetic abnormalities, n (%)		
Deletion 5q/ -5	458 (21%)	645/4457 (14.5%)
Deletion 7q/ -7	337 (15%)	432/4457 (9.7%)
Complex karyotype	391 (**18%**)	482/4457 (**10.8%**)

	MOFFITT	GenoMed4all
Somatic mutations, n (%)		
ASXL1	463 (21%)	1091/4779 (22.8%)
TP53	438 (**20%**)	549/4768 (**11.5%**)
Multi-hit TP53*	211 (**9%**)	443/4780 (**9.3%**)
SF3B1	376 (**17%**)	1022/4773 (**21.4%**)
RUNX1	249 (11%)	577/4780 (12.1%)
IDH1 and IDH2	150 (7%)	342/4780 (7.2%)
EZH2	125 (6%)	283/4770 (5.9%)
IPSS-R Categories, n (%)		tot=4780
Very low	309 (14%)	592(12.4%)
Low	723 (32%)	1490 (31.2%)
Intermediate	424 (19%)	898 (18.8%)
High	315 (**14%**)	676 (**14.2**%)
Very high	432 (**19%**)	563 (**11.8%**)
Karyotype not available		561 (11.7%)
Treatment modalities, n (%)		
ESA	687 (31%)	1290 (27.0%)
Lenalidomide	339 (15%)	397 (8.3%)
ATG	35 (2%)	NA
HMA	1265 (**57%**)	1065 (**22%**)
Allogeneic HSCT	344 (**16%**)	1160 (**24.3%**)
Median FU	60.3 months	23.8 months
Rate of AML transformation, n (%)	554 (25%)	851 (17.8%)
Median OS	40.9 months	51.0 months
Median LFS	30.9 months	38.6 months

Komrokij , Lancet Haematol. 2024 Nov;11(11):e862-e872.

MDS-*SF3B1* genetically defined group has best outcome

	MCC Cohort		GM Cohort	
	WHO	ICC	WHO	ICC
n (%)	294 (13%)	277 (12%)	654 (13.9%)	594 (12.6%)
OS	101.8	111.6	104.9	101.9
LFS	100.6	109.4	102.2	101.9

- MDS-*SF3B1* accounts for 12-13% of all MDS cases (slight difference between WHO and ICC given VAF difference definition).
- Median OS and LFS exceeds 8 years.

Komrokij , Lancet Haematol. 2024 Nov;11(11):e862-e872.

MDS del5q is associated with favorable outcomes

	MCC Cohort		GM Cohort	
	WHO	ICC	WHO	ICC
n (%)	107 (5%)	108 (5%)	219 (4.6%)	223 (4.7%)
OS	75.6	75.6	82.1	82.1
LFS	65	65	68.2	69.4

- MDS-del5q accounts for 5% of all MDS cases.
- Median OS 6-7 years and median LFS 5-6 years.

Komrokij , Lancet Haematol. 2024 Nov;11(11):e862-e872.

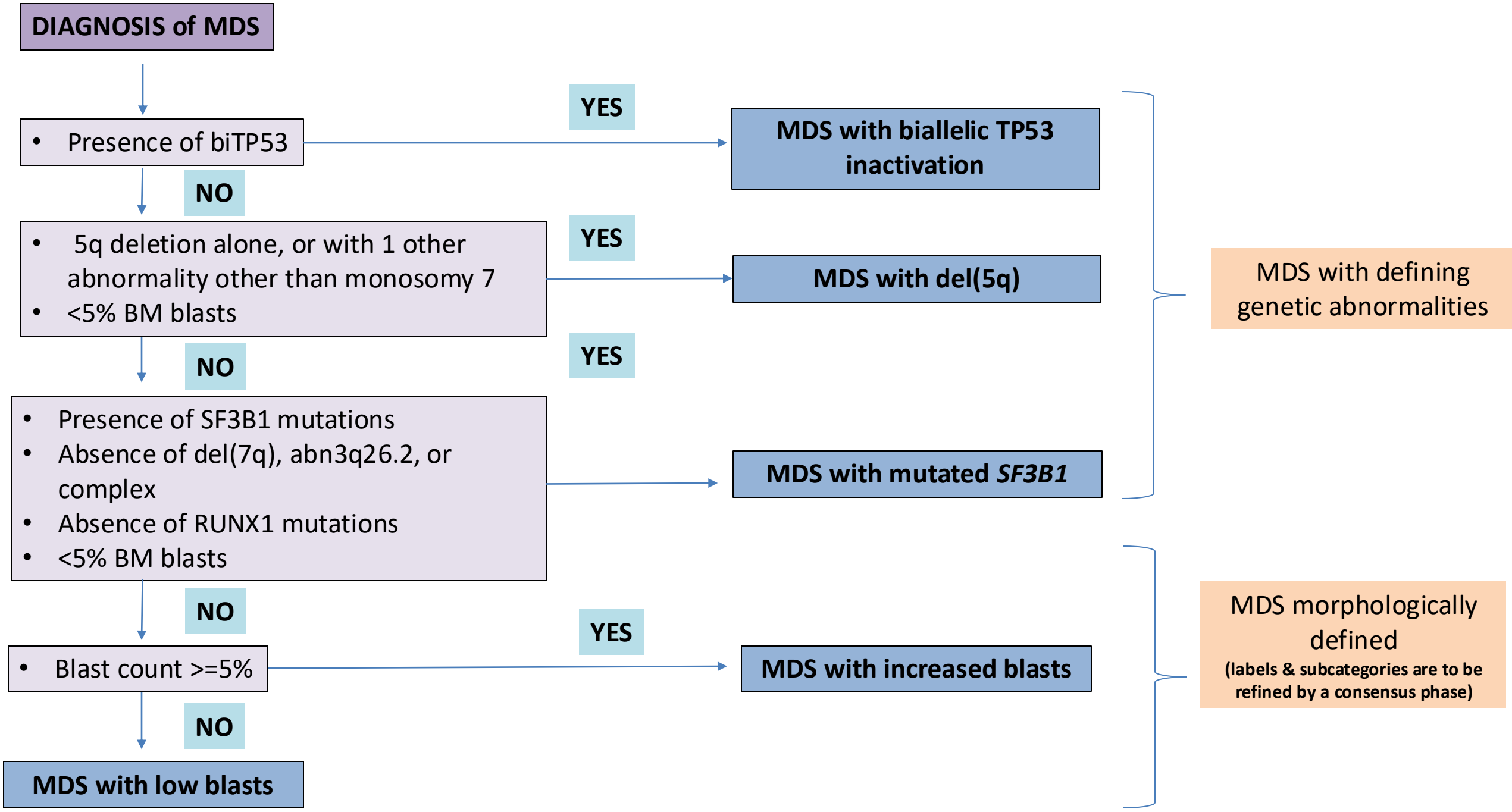
TP53-mutated MDS has the worst outcome

MDS-bi *TP53*	MCC Cohort		GM Cohort	
	WHO	ICC	WHO	ICC
n (%)	214 (10%)	194 (9%)	443 (9.4%)	290 (6.2%)
OS	13.2	14.2	14	17.6
LFS	10	11.5	13.4	16.3

MDS/AML-m *TP53*	MOFFITT	GM
	ICC	ICC
n (%)	115 (5%)	146 (3.1%)
OS	11	10
LFS	6.4	9.7

- WHO 2022 MDS bi-allelic *TP53* inactivation accounted for ≈ 10% of MDS cases with median OS ≈ 1-1.5 years .
- ICC 2022 MDS/AML m-*TP53 (+≥10% myeloblasts) accounted for 3-5% of MDS cases* with median OS < 1 year. (worse outcome driven by increased myeloblasts).

Komrokij , Lancet Haematol. 2024 Nov;11(11):e862-e872.


DIAGNOSIS of MDS
• Presence of biTP53
YES
MDS with biallelic TP53 inactivation
NO
• 5q deletion alone, or with 1 other abnormality other than monosomy 7
• <5% BM blasts
YES
MDS with del(5q)
NO
• Presence of SF3B1 mutations
• Absence of del(7q), abn3q26.2, or complex
• Absence of RUNX1 mutations
• <5% BM blasts
YES
MDS with mutated SF3B1
NO
• Blast count >=5%
YES
MDS with increased blasts
NO
MDS with low blasts
MDS with defining genetic abnormalities
MDS morphologically defined
(labels & subcategories are to be refined by a consensus phase)

Conceptual classification of MDS

Chronic phase MDS

- MDS-SF3B1
- MDS-del5q
- MDS-LB

Accelerated phase MDS

- 5-19% myeloblasts (cutoff to be refined)
- Bi-allelic TP53 MDS
- MDS-f

Blast phase MDS

- ≥20% myeloblasts (cutoff to be refined)
- AML with MDS defining cytogenetic abnormalities or gene mutations.

WHO 2022 classification of myeloid neoplasms associated with germline predisposition

• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

A new scalable model

Khoury JD Leukemia. 2022 Jun 22.

The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: Integrating Morphological, Clinical, and Genomic Data

Table 25. ICC of hematologic neoplasms with germline predisposition

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *CEBPA* mutation
Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Myeloid or lymphoid neoplasms with germline *TP53* mutation

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms with germline *SAMD9* mutation
Myeloid neoplasms with germline *SAMD9L* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
- Fanconi anemia
- Shwachman-Diamond syndrome
- Telomere biology disorders including dyskeratosis congenita
- Severe congenital neutropenia
- Diamond-Blackfan Anemia

Juvenile myelomonocytic leukemia associated with neurofibromatosis
Juvenile myelomonocytic leukemia associated with Noonan-syndrome-like disorder (CBL-syndrome)
Myeloid or lymphoid neoplasms associated with Down syndrome

Acute lymphoblastic leukemia with germline predisposition*
Acute lymphoblastic leukemia with germline *PAX5* mutation
Acute lymphoblastic leukemia with germline *IKZF1* mutation

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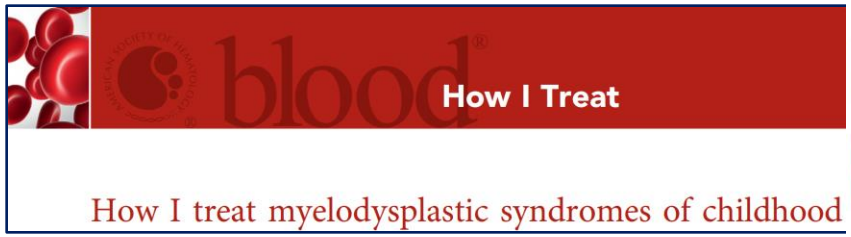
*Down syndrome, and germline mutations in *ETV6* or *TP53*, also predispose to acute lymphoblastic leukemia.

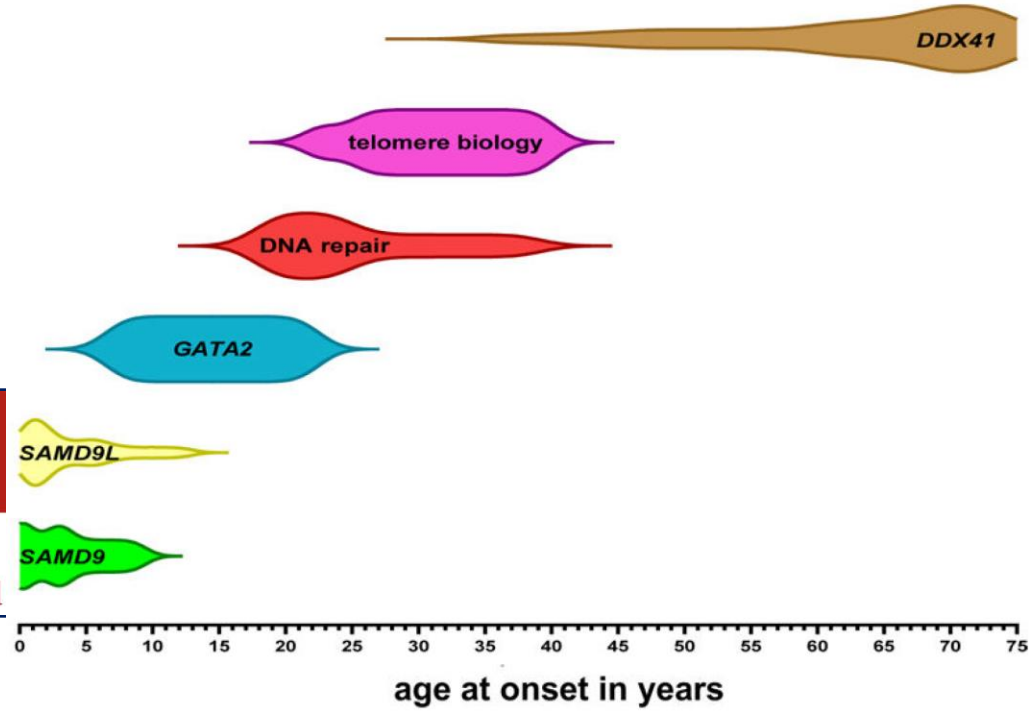
Arber D et al, Blood 2022

Do we know the age of manifestation of MDS in GM predisposition?

From childhood to late onset of germline predisposition MDS



Locatelli F, Strahm B; Blood. 2018



Feurstein S et al. Germline variants drive MDS in young adults. Leukemia. 2021.

Is Germline evaluation useful in “younger” MDS patients?

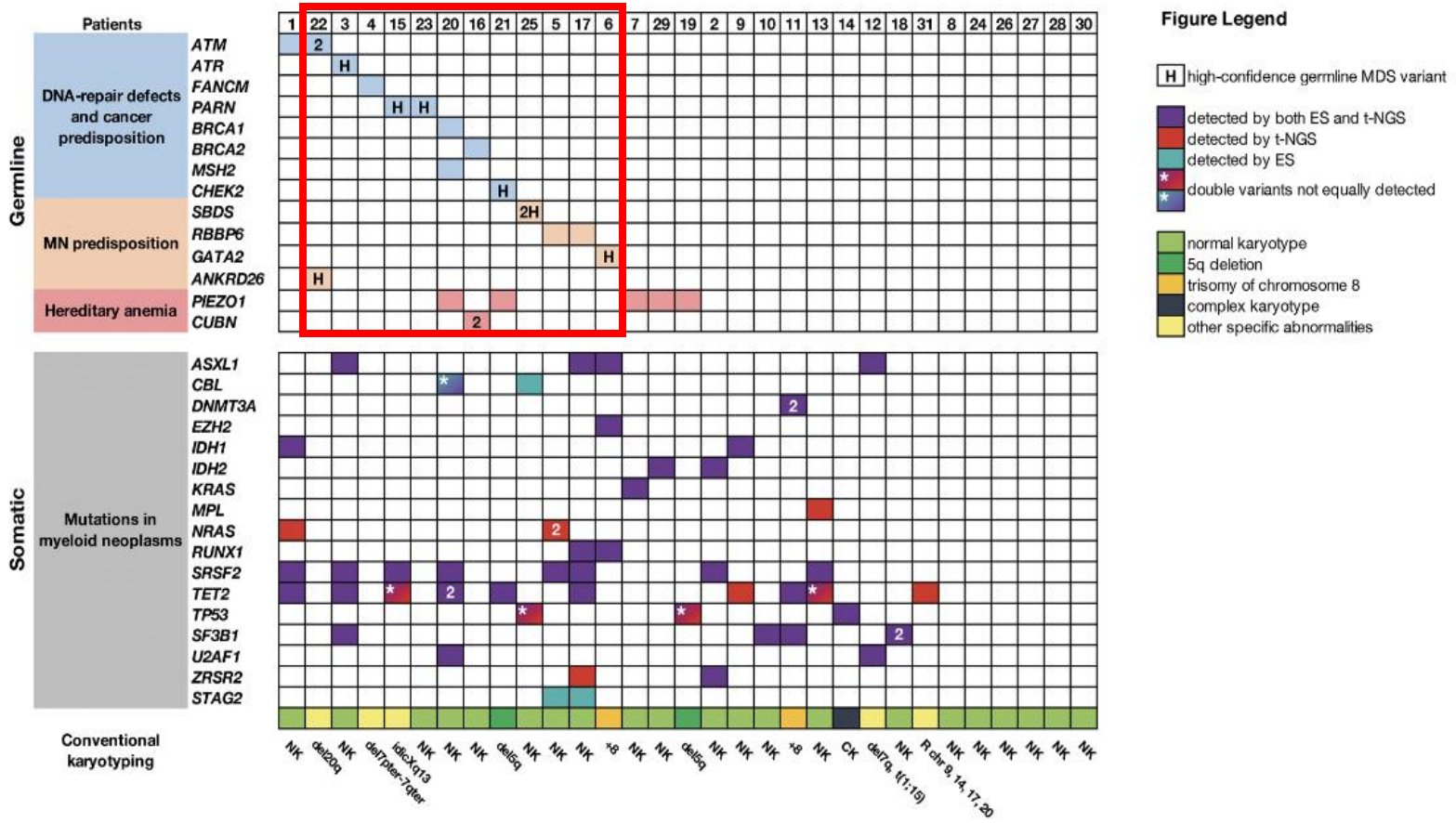
31 MDS cases aged <60 yrs

Exome sequencing

- Bone marrow/Peripheral blood (31/31)
- Saliva (23/31)
- GL status validation with Sanger on nails (18/31)

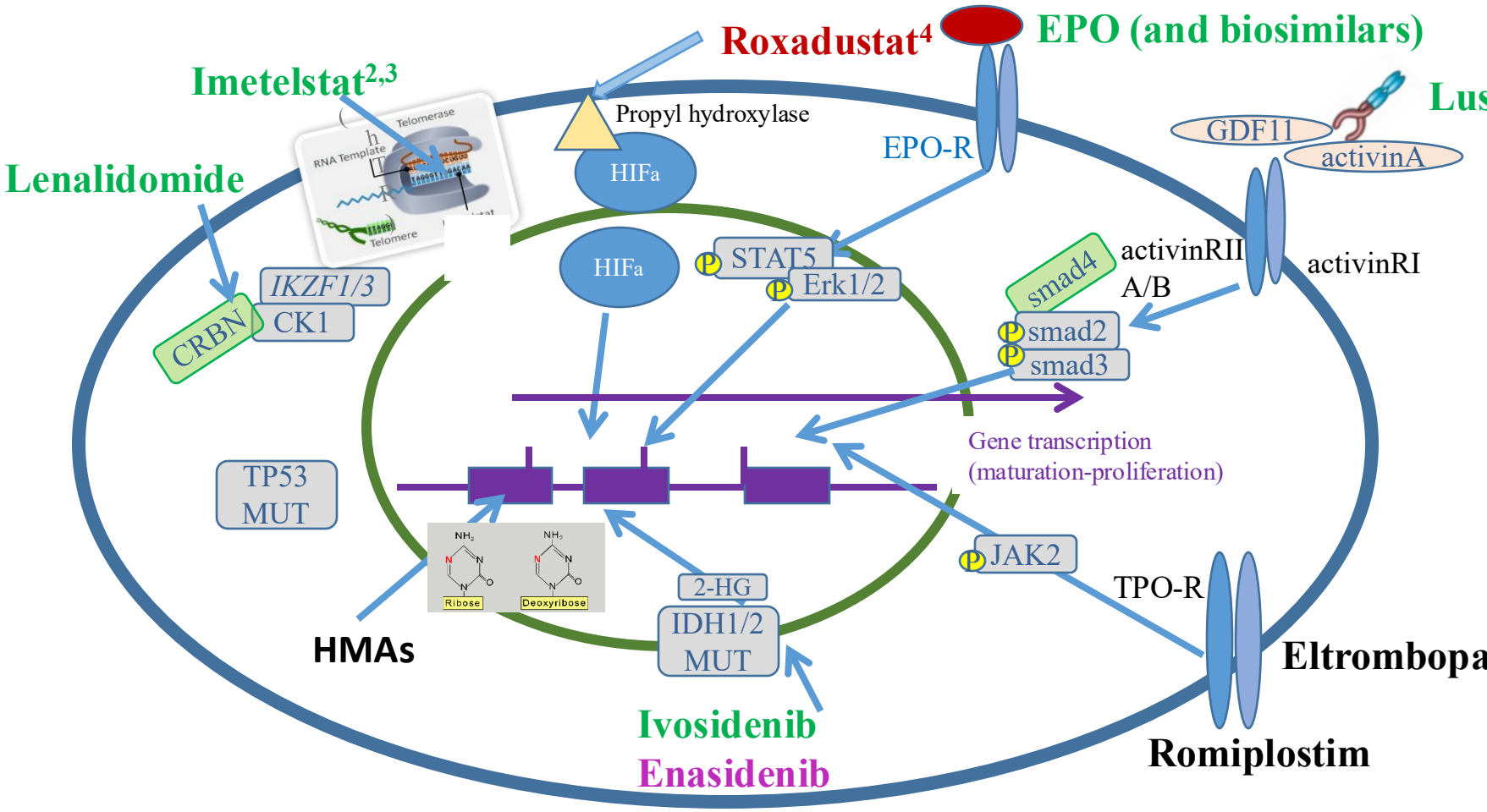
22.6% cases carried GL P/LP variants (high confidence GL MDS variant)

29% cases carried GL VUS



Attardi E. et al, HemaSphere, 2024;8:e112.

A constellation of agents for MDS treatment: …. But few target drugs



Additional targets:

TP53 mut (APR246)[5]
BCL2 (Venetoclax)[6]
NEDD8NAE (Pevonedistat)[7]
Tim-3 (Sabatolimab)[8]
CD47 (Magrolimab)[9]
Irak-4 (R289)[10]

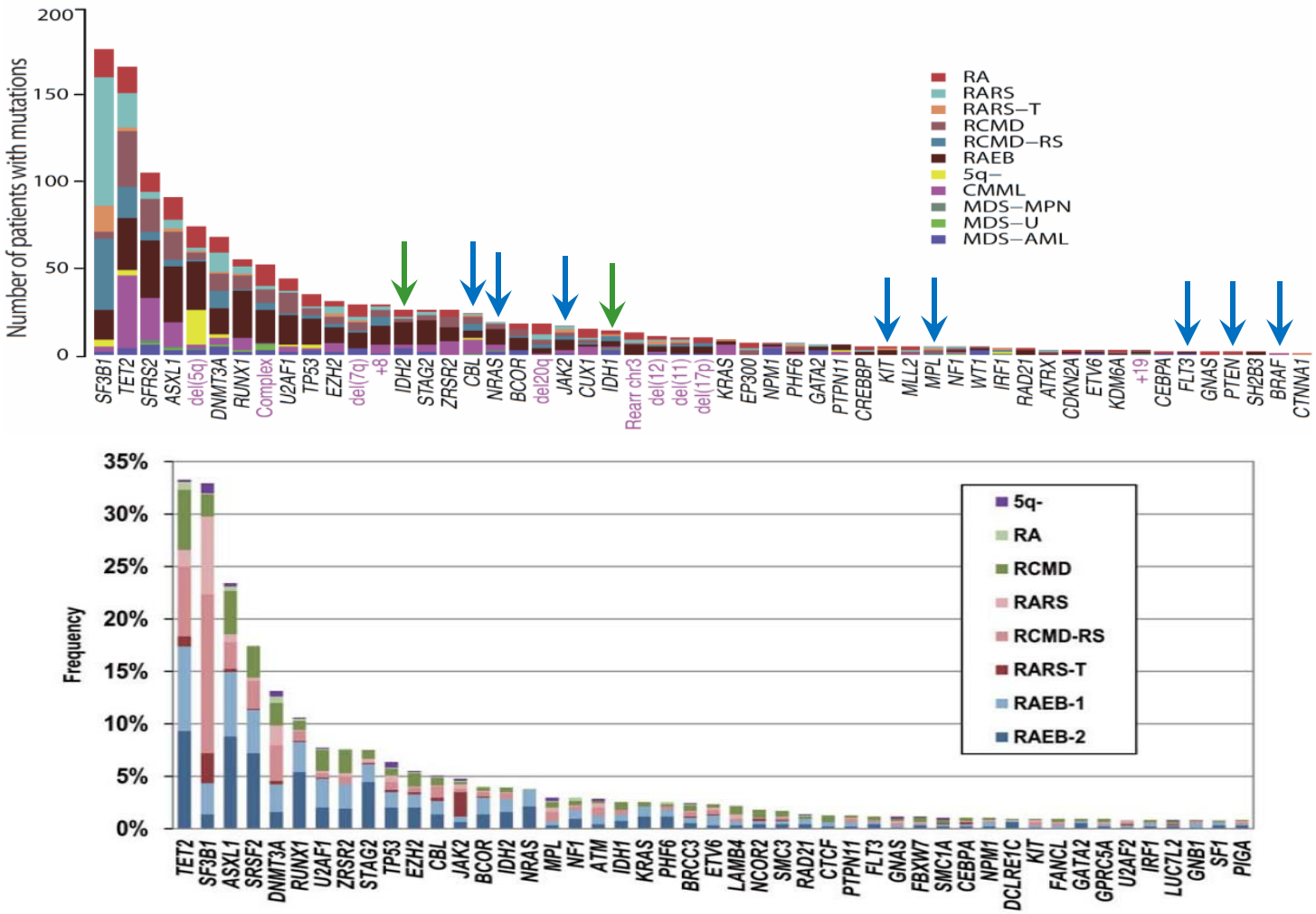
Approved drugs
Failed studies
Successful studies
Under investigation

EPO: erythropoietin; EPO-R: erythropoietin receptor; HMA: hypomethylating agents; MDS: myelodysplastic syndrome; MUT: mutation; TPO-R: plasma thrombopoietin receptor.
1. Santini V. *Hemato* 2022;3:153–162. 2. Santini V, et al. EHA 2024; (Abstract S184). 3. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-imetelstat-low-intermediate-1-risk-myelodysplastic-syndromes-transfusion-dependent (Accessed Jun 2024)
3. https://www.targetedonc.com/view/tvardi-imetelstat-misses-efficacy-endpoint-for-its-3-phase-mds-study (Accessed Jun 2024). 4. https://www.targetedonc.com/view/mn-nimal-efficacy-observed-with-epigenetherapy-plus-azacitidine-in-tp53-mutant-mds (Accessed Jun 2024).
5. EPCterakh I, et al. *Clin Hematol Int* 2023;5:143–154. 6. https://ascopost.com/issues/february-25-2022/no-significant-benefit-for-pevonedistat-plus-azacitidine-in-higher-risk-myelodysplastic-syndrome/ (Accessed Jun 2024). 7. Zeidan AM, et al. *Future Oncol* 2023;19:631–642.
8. https://www.gilead.com/news-and-press/press-room/press-releases/2023/7/gilead-to-discontinue-phase-3-enhance-study-of-magrolimab-plus-azacitidine-in-higher-risk-mds (Accessed Jun 2024).
9. https://clinicaltrials.gov/study/NCT05308264 (Accessed Jun 2024). 8. https://www.gilead.com/news-and-press/press-room/press-releases/2023/7/gilead-to-discontinue-phase-3-enhance-study-of-magrolimab-plus-azacitidine-in-higher-risk-mds (Accessed Jun 2024).

Three possible approaches to optimize therapy of MDS through molecular characterization:

1)Target single mutation
2)Base therapeutic choice on molecular pattern
3)Identify mutations conferring enhanced sensitivity

Somatic Mutations in MDS are very frequent



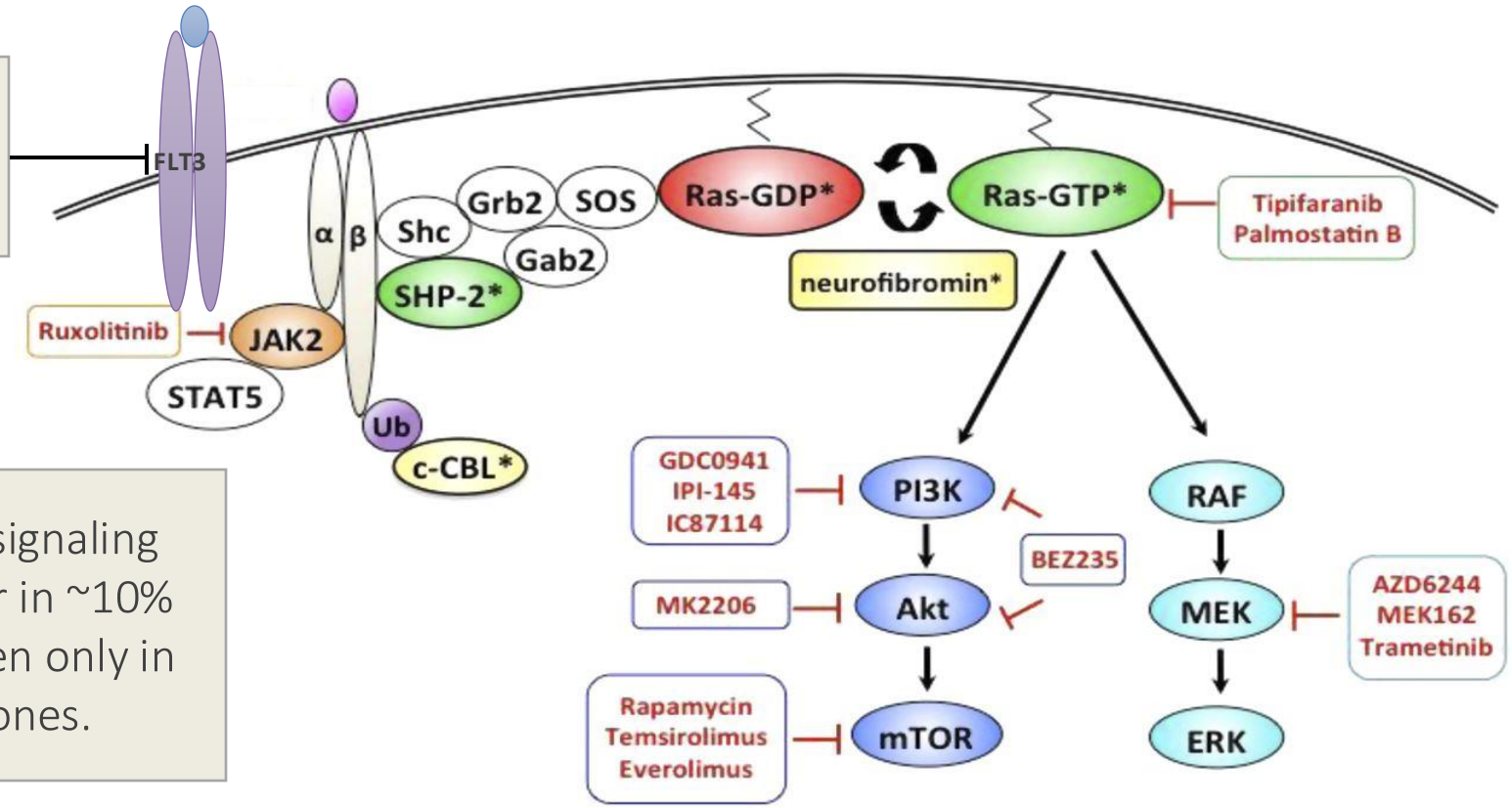
Papaemmanuil et al. *Blood*. 2013.

Haferlach et al. *Leukemia*. 2014.

Mutations as Drug Targets

Activated kinases and other gain-of-function enzymatic mutations are RARE in MDS

Midostaurin
Sorafenib
AC220
Ponatinib



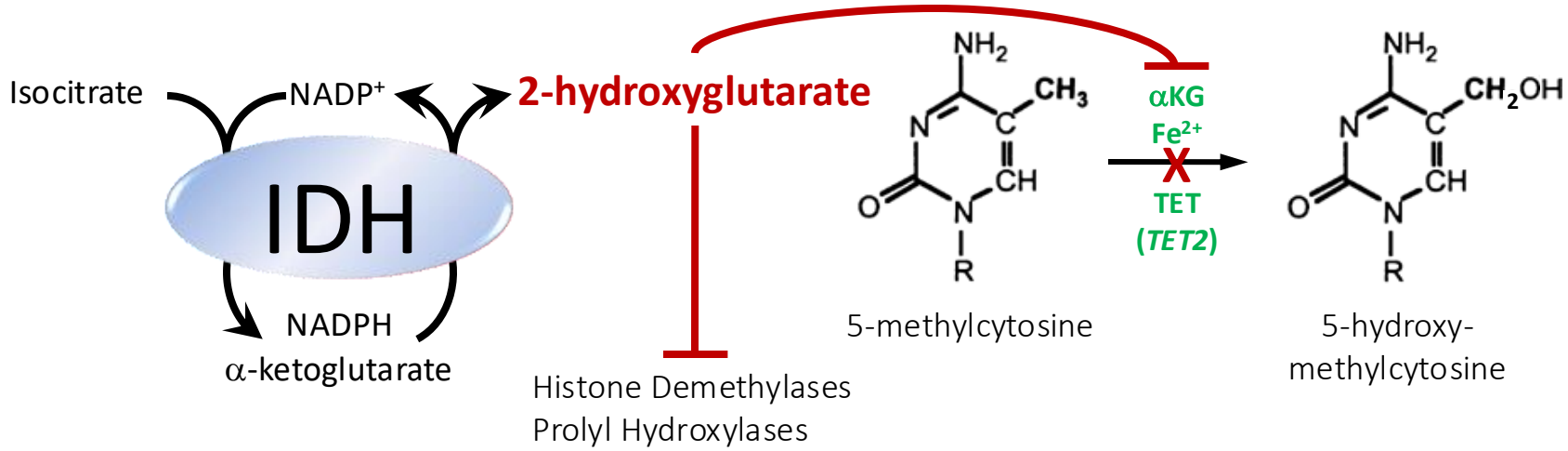
Growth factor signaling mutations occur in ~10% of MDS and often only in small subclones.

Chang et al. Blood, 124(16), 2487-2497.

Midostaurin, AC220, tipifarnib, palmostatin B, GDC0941, IPI-145, IC87114, MK2206, BEZ235, AZD6244, MEK162 and temsirolimus are all investigational molecules and are not approved by any Health Authority

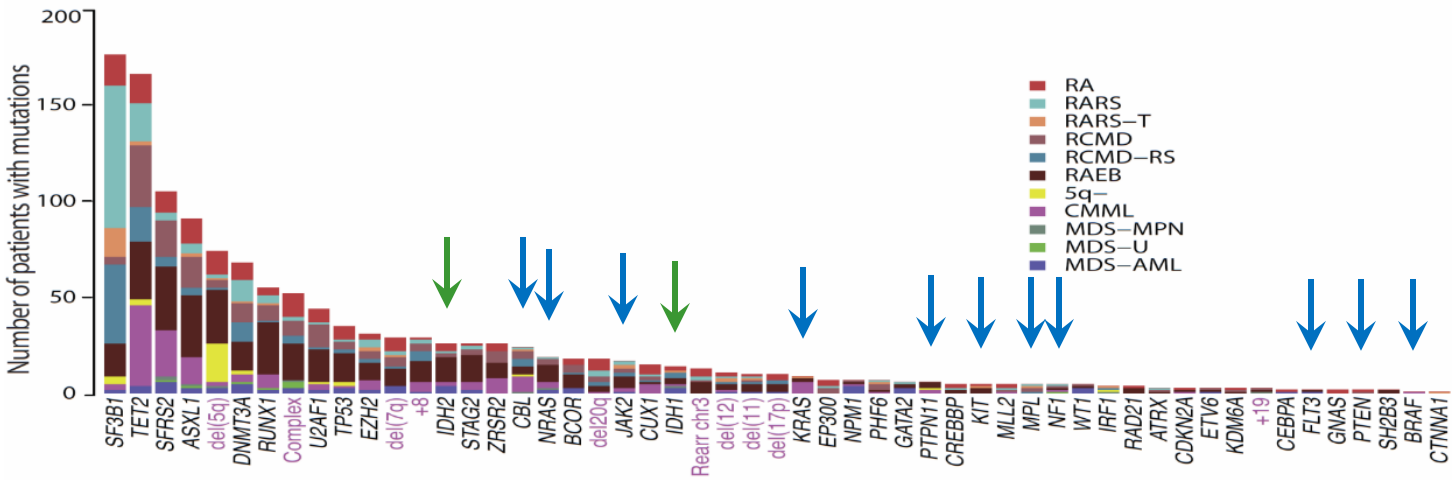
Midostaurin, AC220, tipifarnib, palmostatin B, GDC0941, IPI-145, IC87114, MK2206, BEZ235, AZD6244, MEK162 y temsirolimus son todas moléculas en investigación y no están aprobadas por ninguna autoridad sanitaria

Mutations as Drug Targets



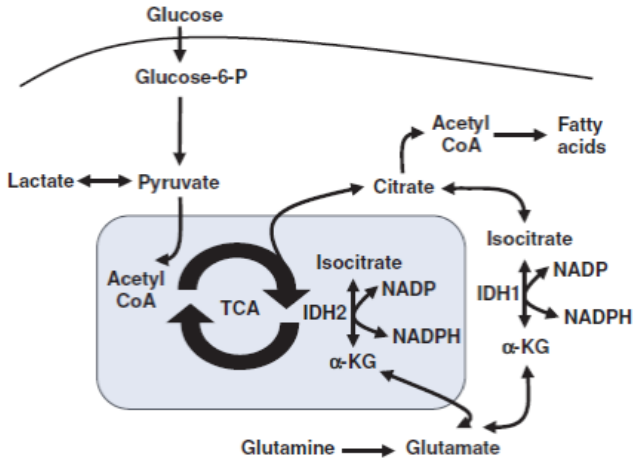
Xu et al. *Cancer Cell.* **19**:17-30, 2011.

Sasaki et al. *Nature*. **488**:656-9, 2012

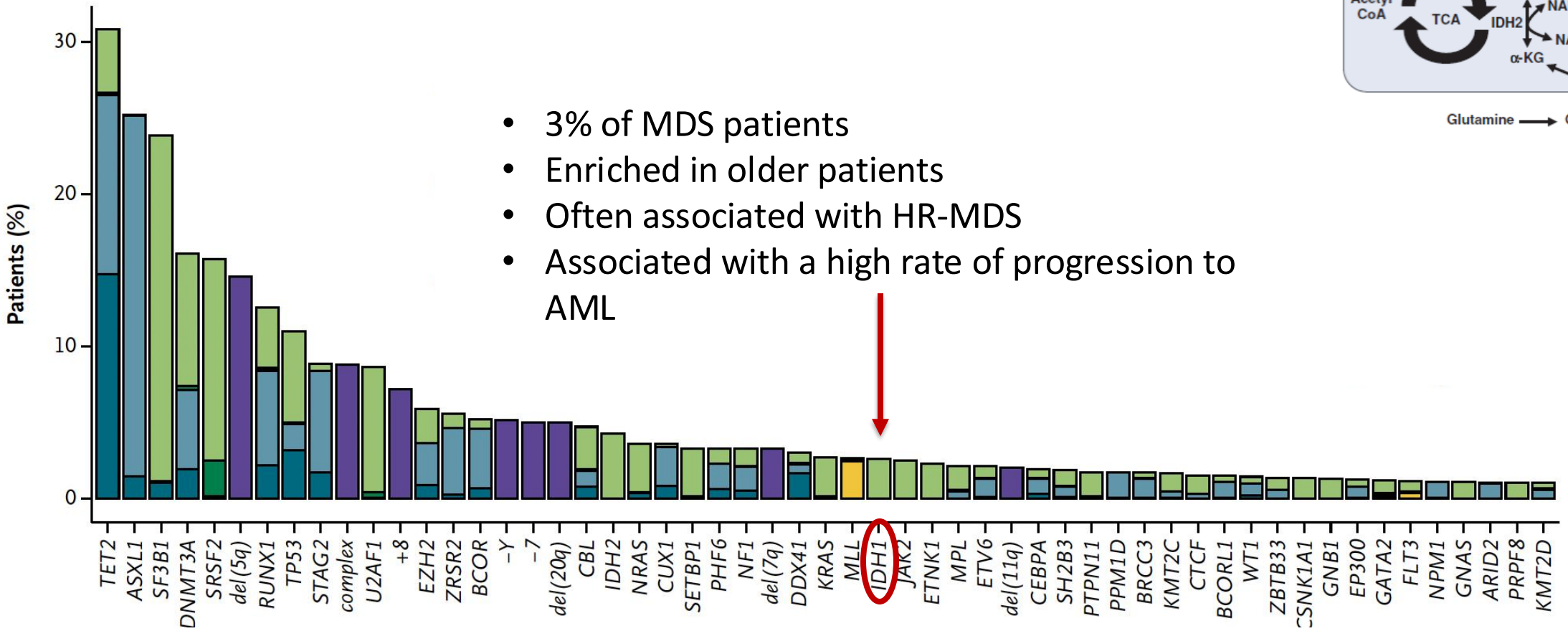


Papaemmanuil et al. *Blood*. 2013.

- The mutant IDH1 enzymes has gain of function activity, catalyzing the reduction of alpha-ketoglutarate in the oncometabolite 2-HG (2-HG)
- 2-HG accumulation leads to metabolic dysregulation, driving oncogenesis via epigenetic dysregulation and a block in cellular differentiation

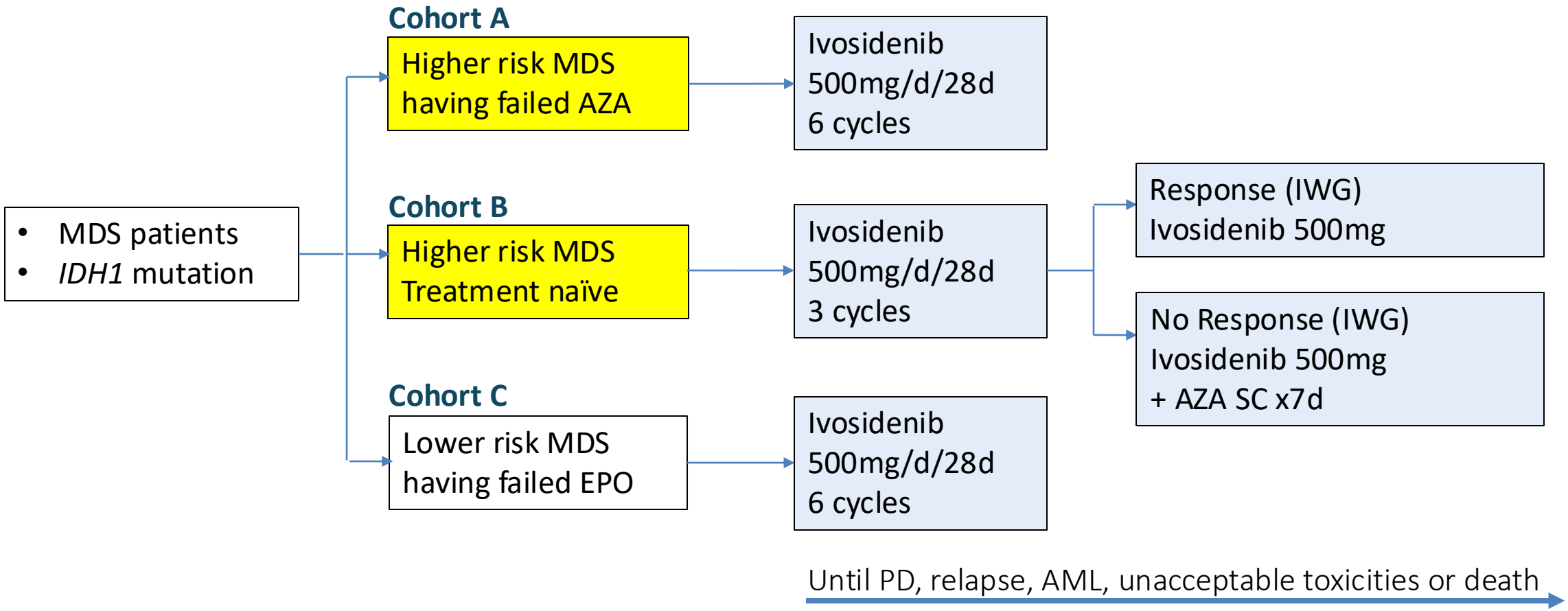


- 3% of MDS patients
- Enriched in older patients
- Often associated with HR-MDS
- Associated with a high rate of progression to AML



E. Bernard et al, NEJM ev. 2022

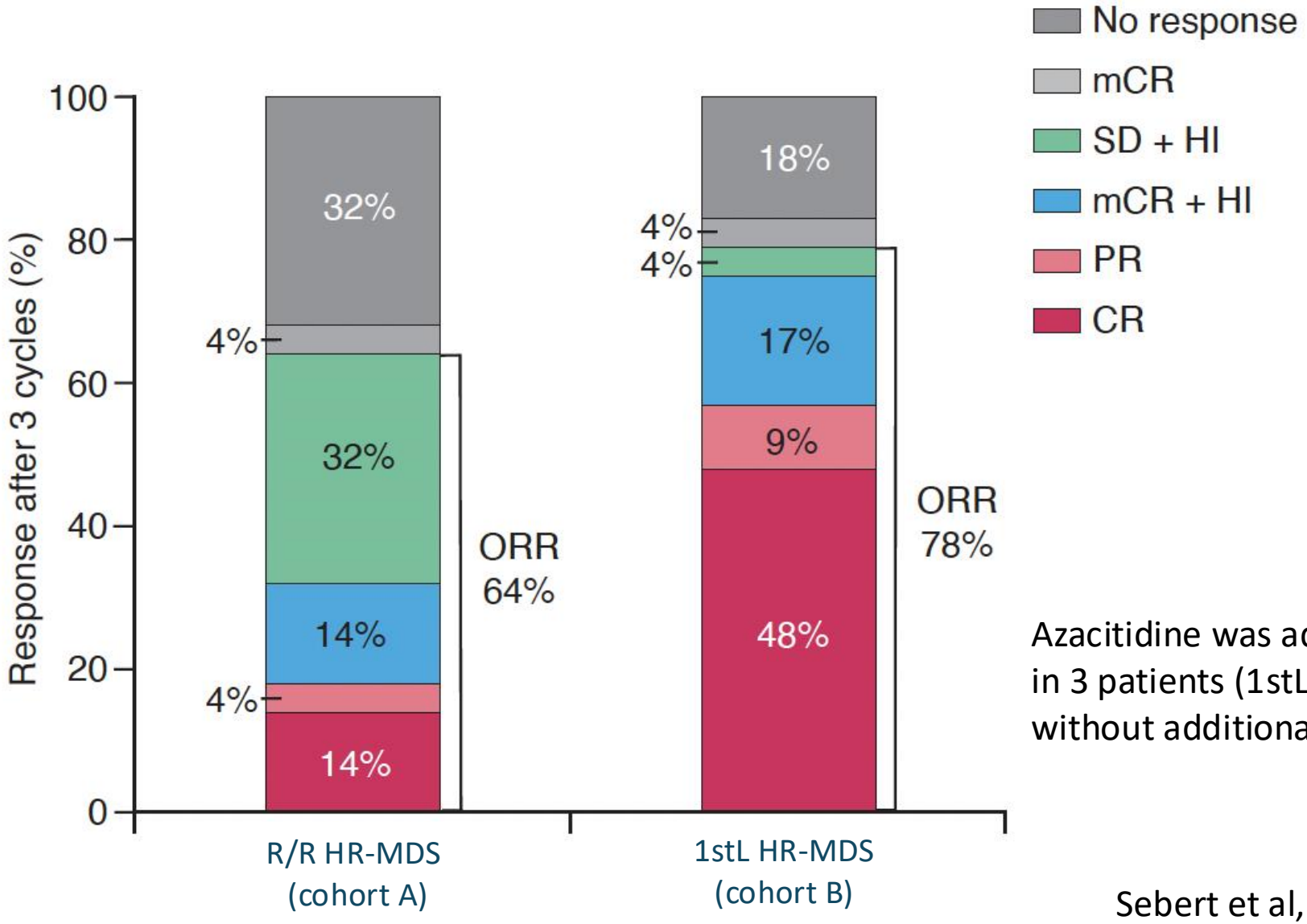
Ivosidenib in MDS



- Primary endpoint:
  - ORR at 3 and 6 months (including CR, PR, SD with HI according to IWG 2006) for HR-MDS
  - Safety for LR-MDS
- Secondary endpoints: Response duration, OS, prognostic factor of response, evolution of IDH1 VAF, AE and toxicity

Sebert et al, EHA 2024

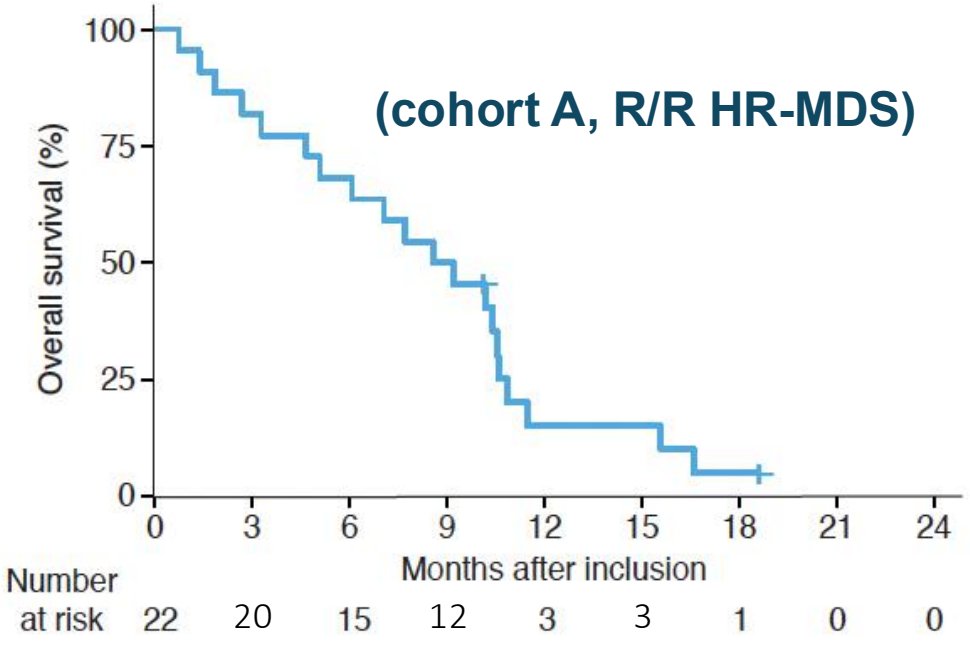
Overall response rate (Cohort A and B)



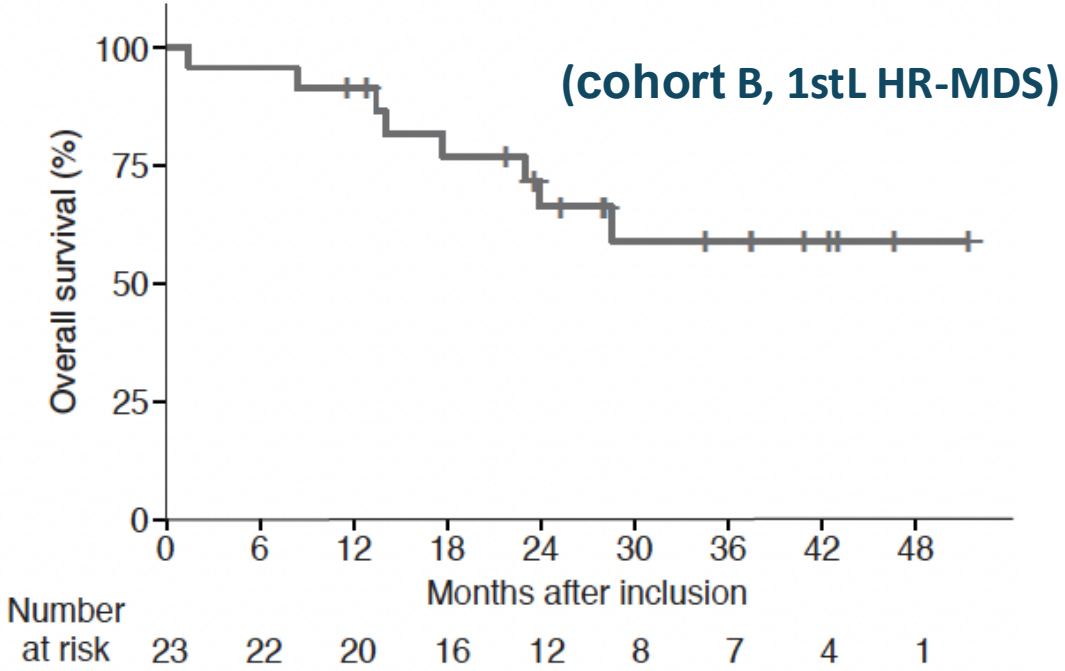
Azacitidine was added to Ivosidenib after 3 cycles in 3 patients (1stL HR-MDS), without additional response

Sebert et al, EHA 2024

Duration of responses and survival



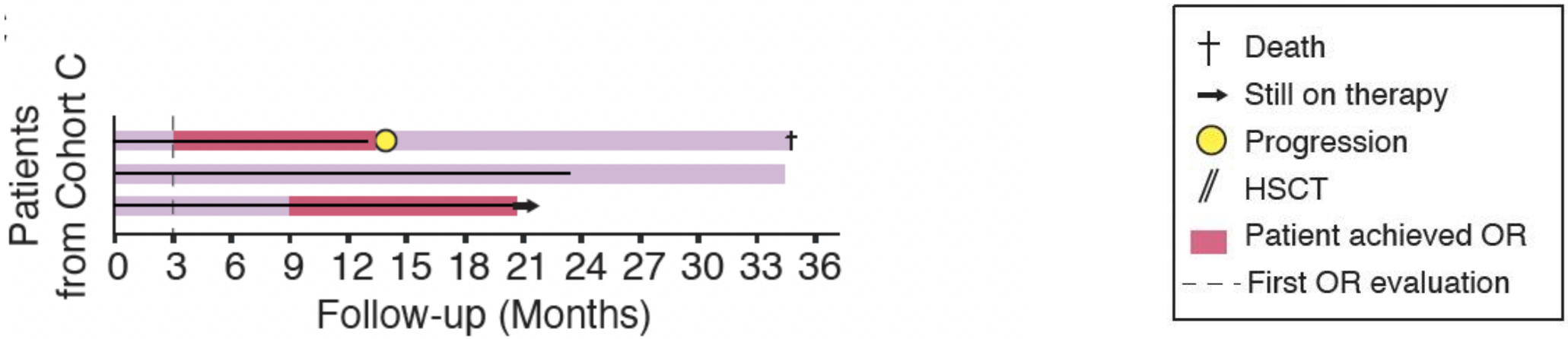
- Median OS was 8.9 months
- 12-month OS rate was 15.2% (95%CI, 5.4-42.5)
- 2 patients are still alive on therapy
- 14 progressed
- 20 died



- Median FU: 25.2 months
- Median OS and DOR were not reached
- 12-month OS rate was 91.3% (95%CI, 80.5-100)
- 5 patients (22%) have been bridged to transplant
- 8 patients progressed
- 8 patients still on therapy

Sebert et al, EHA 2024

Cohort C, EPO R/R LR-MDS (n=3)



- Two of the 3 patients achieved CR, with transfusion independency, one after 3 cycles, one after 9 cycles
- One patient died 2 years after inclusion from progression after 13 cycles (DOR, 10 months)
- Two others are still alive without progression, one still in CR on therapy (20 cycles)
- No toxicity

Sebert et al EHA abs 182

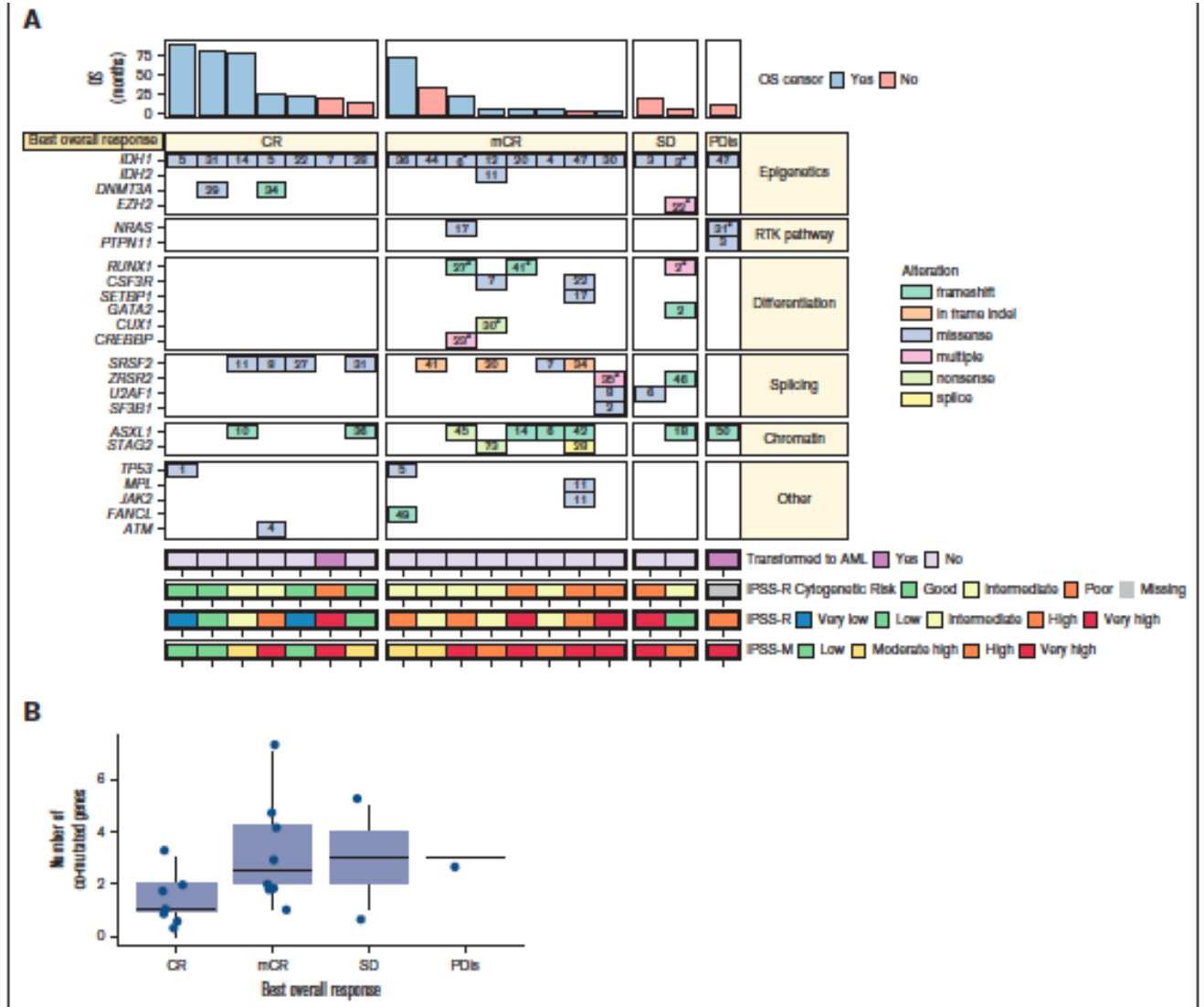
Ivosidenib in mutant IDH1 relapsed/refractory myelodysplastic syndrome

Ivosidenib resulted in a

CR 38.9%
ORR 83.3% in
median duration of response was not reached.

- **Median OS in this R/R MDS cohort was ~36 months;**

~75% of RBC- and platelet TD patients became TI



Di Nardo et al, Blood Advances 2024

Three approaches to optimize therapy of MDS through molecular characterization:

1)Target single mutation

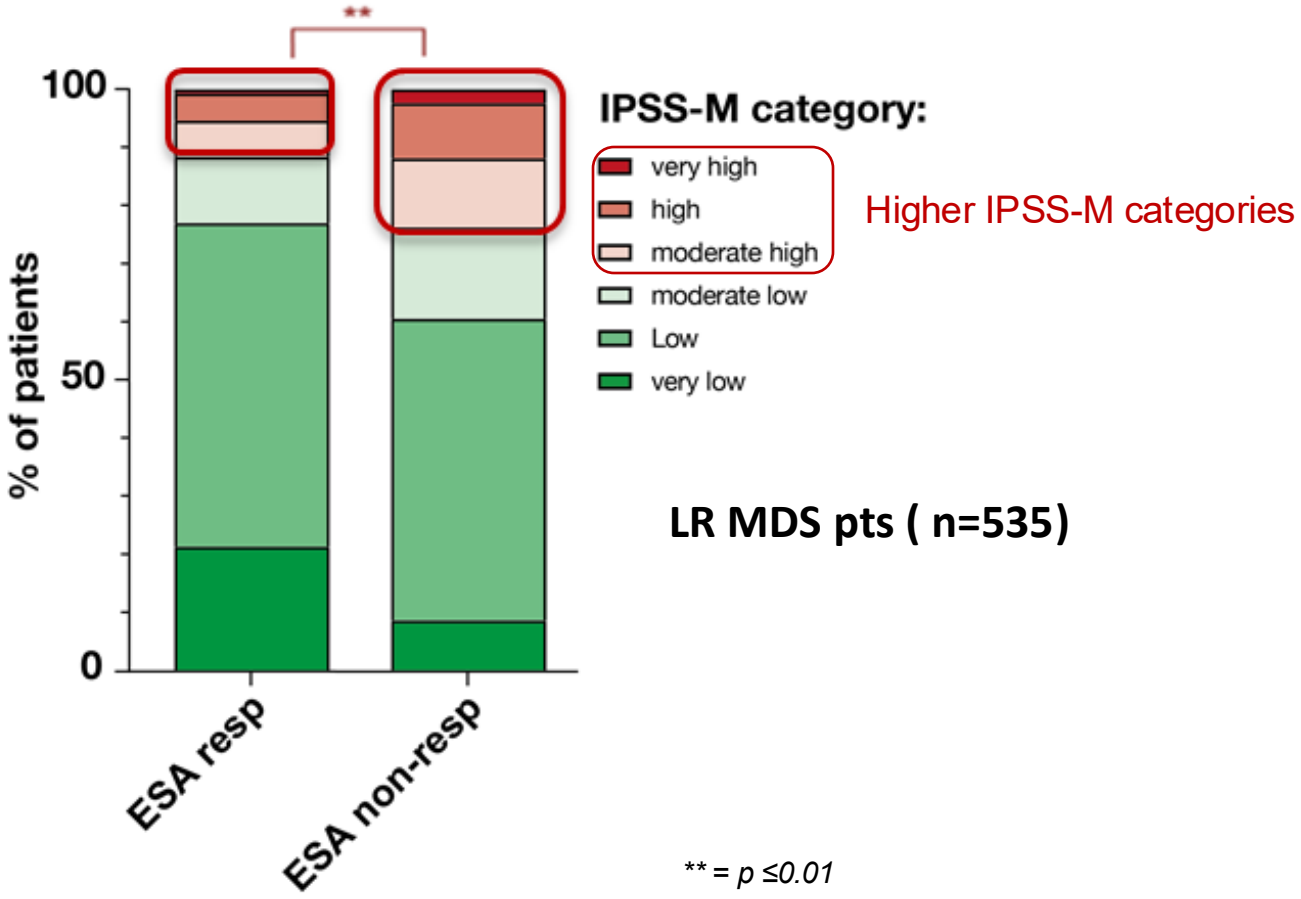
2)Base therapeutic choice on molecular pattern

3)Identify mutations conferring enhanced sensitivity

Select MDS patients to be treated : Erythropoietic stimulating agents

IPSS-M and Response to ESAs

Significantly increased fraction of cases transitioning from lower IPSS-R categories to **higher IPSS-M** risk categories among non-responders compared to responders

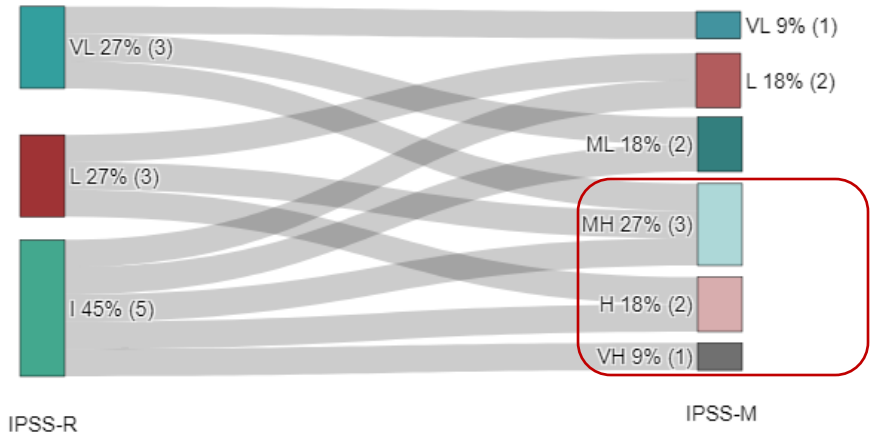


Higher IPSS-M categories

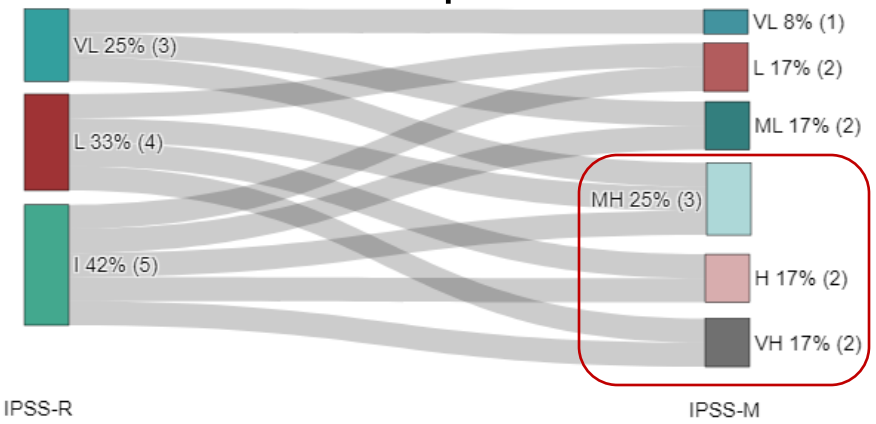
LR MDS pts (n=535)

** = p ≤0.01

ESA responders

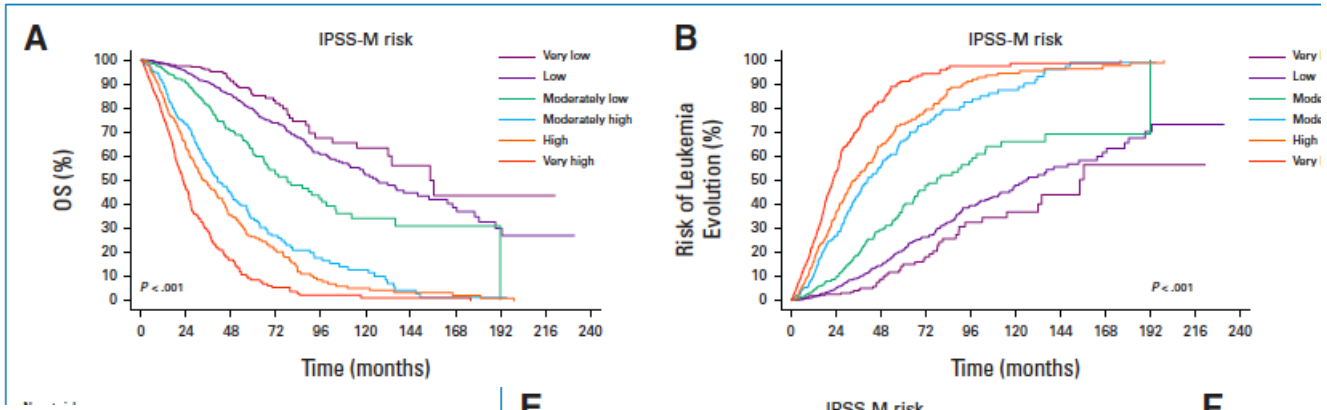


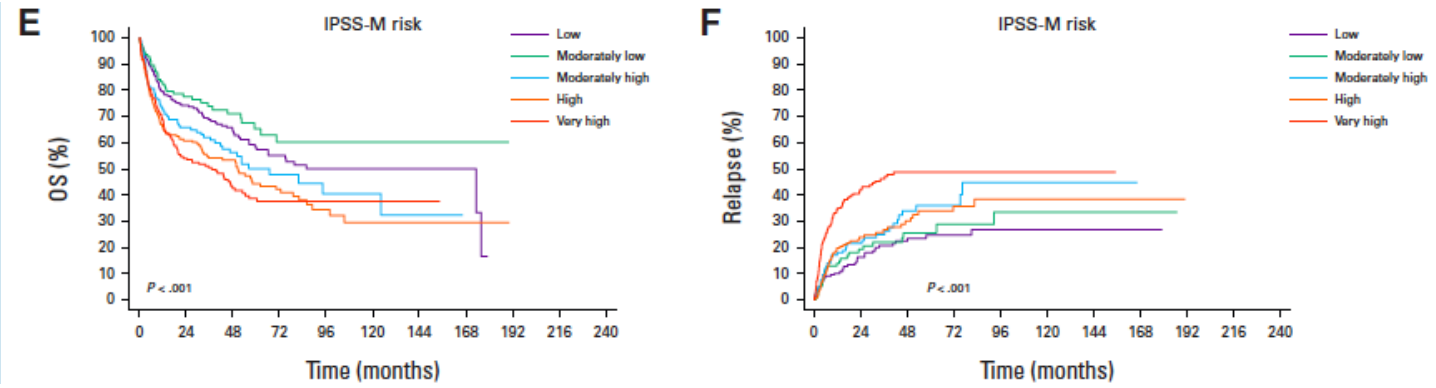
ESA non-responders



Raddi et al, poster ASH 2023 (manuscript in preparation)

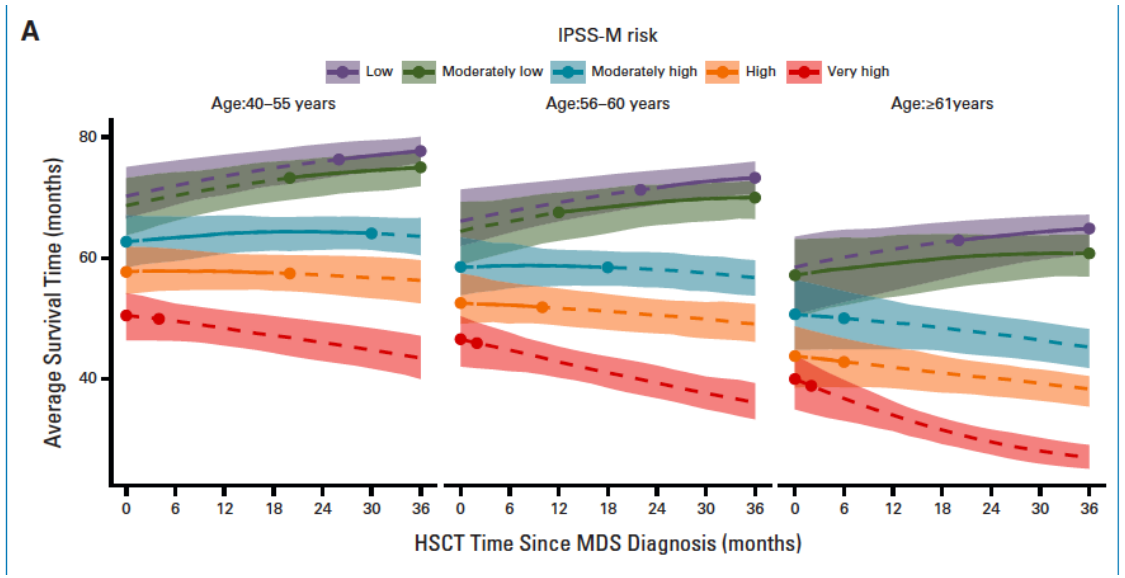
Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes

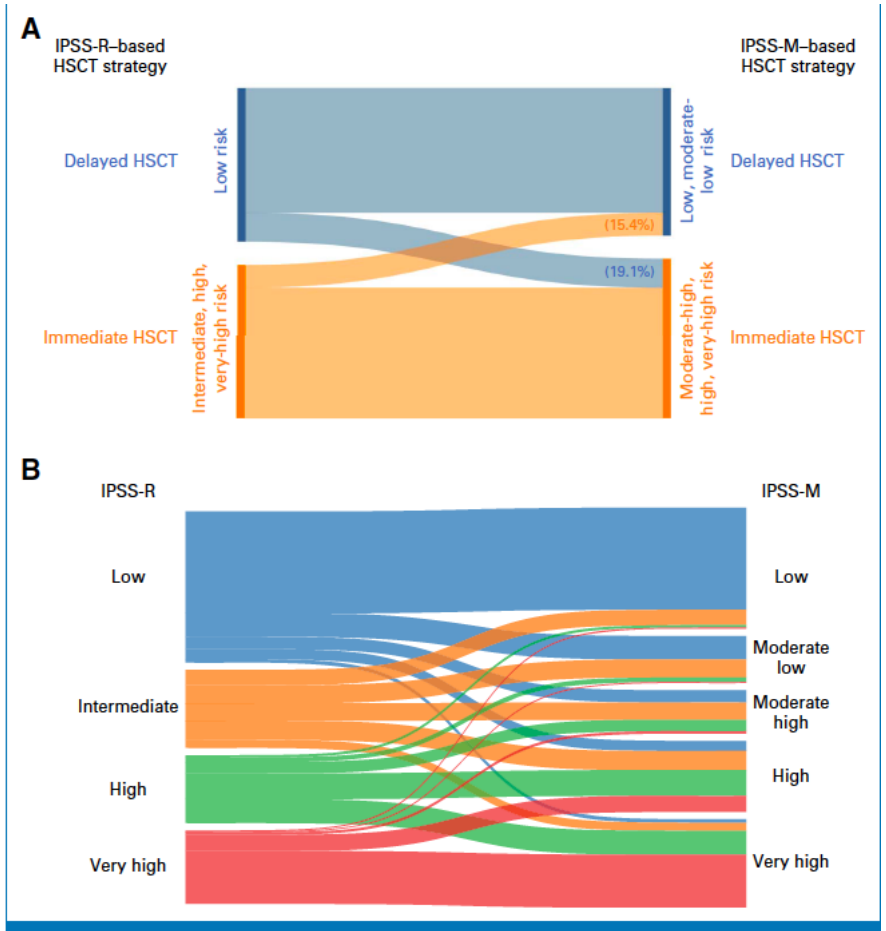




Tentori CA et al , JCO 2024

Clinical and Genomic-Based Decision Support System to Define the Optimal Timing of Allogeneic Hematopoietic Stem-Cell Transplantation in Patients With Myelodysplastic Syndromes





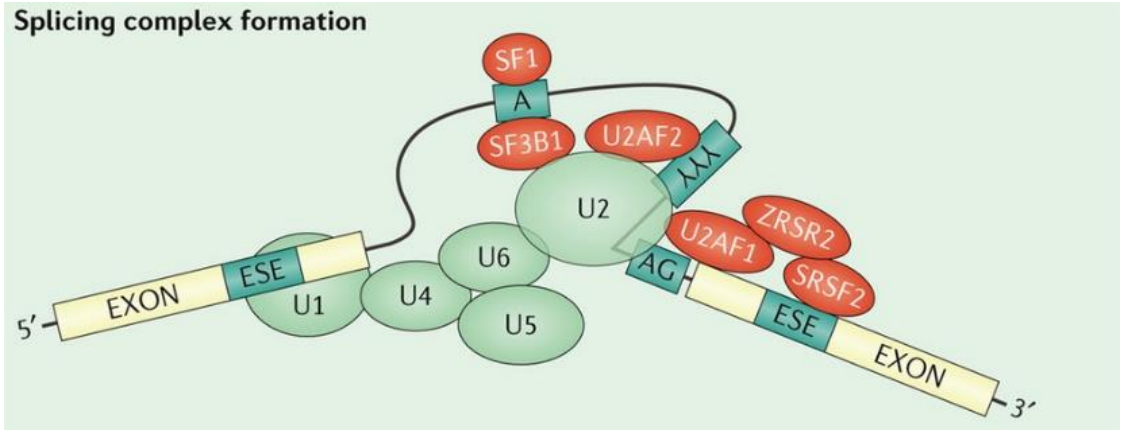
Tentori CA et al , JCO 2024

Three approaches to optimize therapy of MDS through molecular characterization:

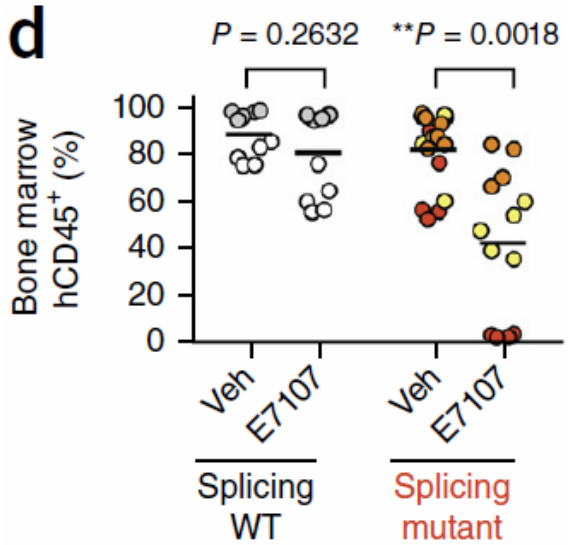
1)Target single mutation
2)Base therapeutic choice on molecular pattern
3)Identify mutations conferring enhanced sensitivity

Associations of molecular alteration with with Response

Splicing Factor Mutations – Present in >65% of MDS

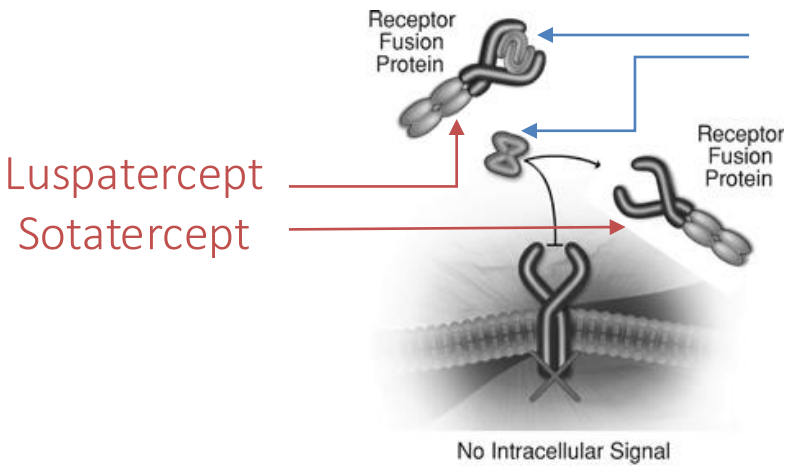


Sperling et al. *Nat Rev Cancer*. 2017;17(1):5-19.



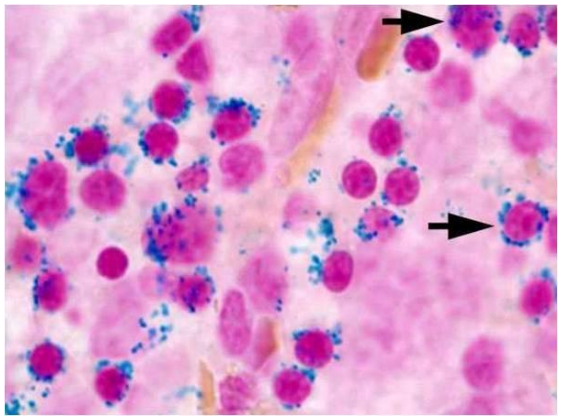
Lee et al. *Nat Med*. 2016;22(6):672-8.

SF3B1 Mutations – Present in >30% of Lower Risk MDS



TGFβ

+



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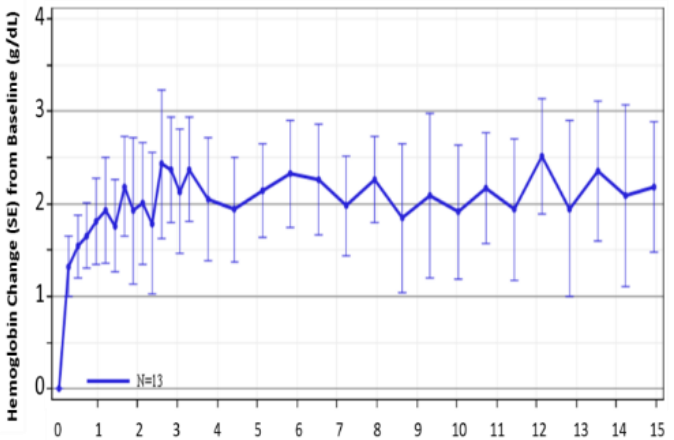

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Welch et al., *NEJM*. 2017;375(21):2023-36

MEDALIST study design

MEDALIST (NCT02631070)

LTFU (NCT04064060)

Screening (5 weeks)

Double-blind treatment phase

Primary phase (24 weeks)

Extension phase

MEDALIST patient population (N = 229)

- Age ≥ 18 years
- IPSS-R Very low-, Low-, or Intermediate-risk
- MDS-RS (WHO 2008):
  - ≥ 15% RS or ≥ 5% with *SF3B1* mutation
  - < 5% bone marrow blasts
- Non-del(5q) MDS
- **Average RBC transfusion burden ≥ 2 units/8 weeks**
- **ESA history:**
  - **Refractory, intolerant, or no prior ESAs (ineligible due to sEPO > 200 U/L)**
- No prior treatment with disease-modifying agents (eg, IMiDs, HMAs)

R 2:1

Luspatercept
Starting dose
1.0 mg/kg
s.c. Q3W
(n = 153)

No crossover allowed

Placebo
s.c. Q3W
(n = 76)

MDS disease assessment Week 25

Patients continue double-blind treatment if experiencing clinical benefit and without disease progression per IWG 2006 criteria

Luspatercept

Placebo

Post-treatment follow-up

Patients monitored for ≥ 3 years post last dose

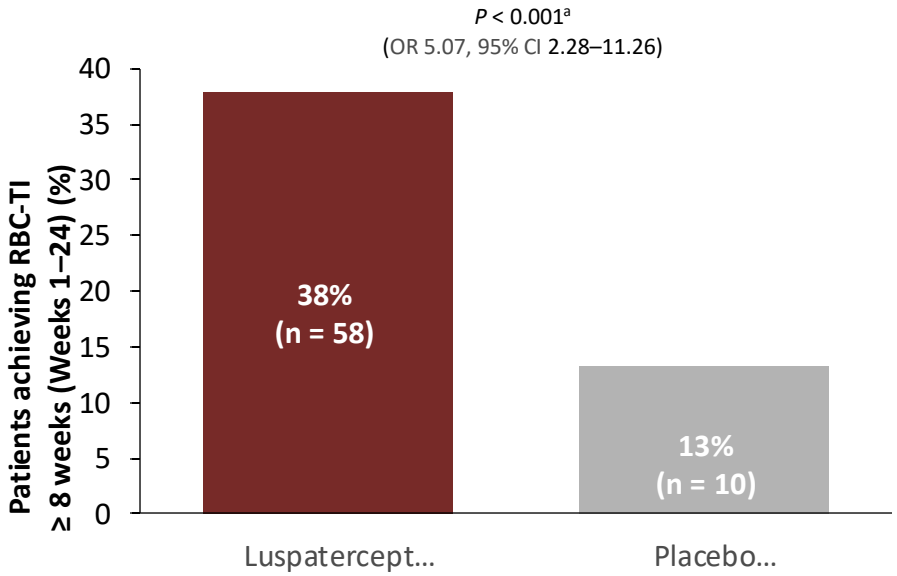
Patients could continue treatment on the long-term follow-up study

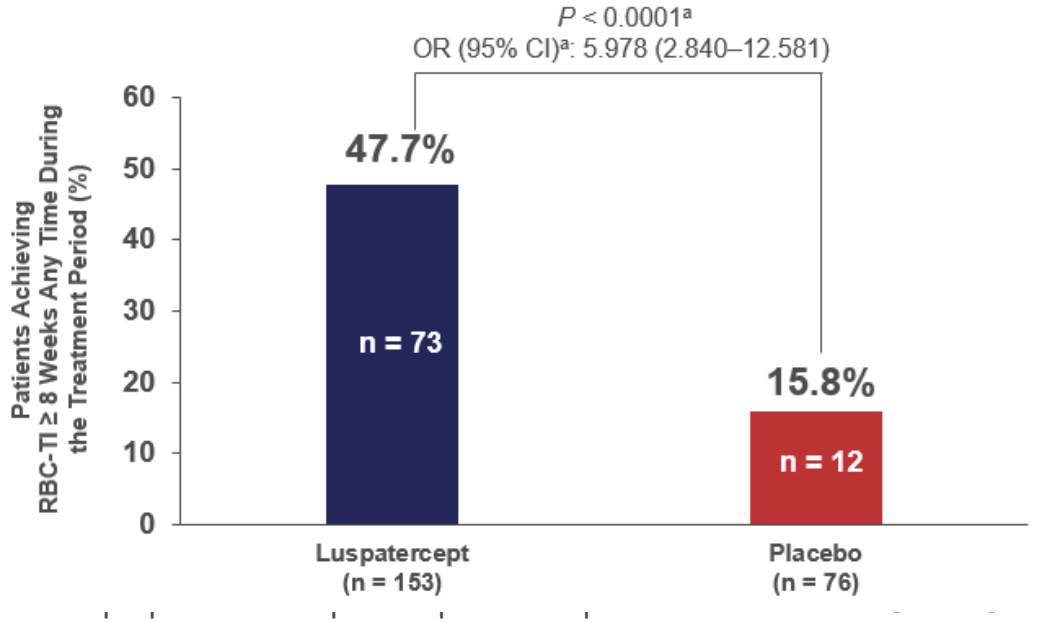
At rollover:
Luspatercept (n = 52)
Placebo (n = 21)

As of Jan 2, 2023:
Luspatercept (n = 19)
Placebo (n = 0)

Santini V, et al. ASH 2023 [Abstract #915]

Luspatercept induces Transfusion independence in *RS(+)* LR-MDS





weeks compared with placebo than previously reported (37.9% of patients receiving luspatercept achieved RBC-TI ≥ 8 weeks during Weeks 1–24 of treatment vs 13.2% of placebo-treated patients; *P* < 0.0001)[1]

Fenaux et al, N Engl J Med. 2020 Jan 9;382(2):140-151.

Luspatercept has been approved by FDA and EMA in 2020 for TD MDS-RS

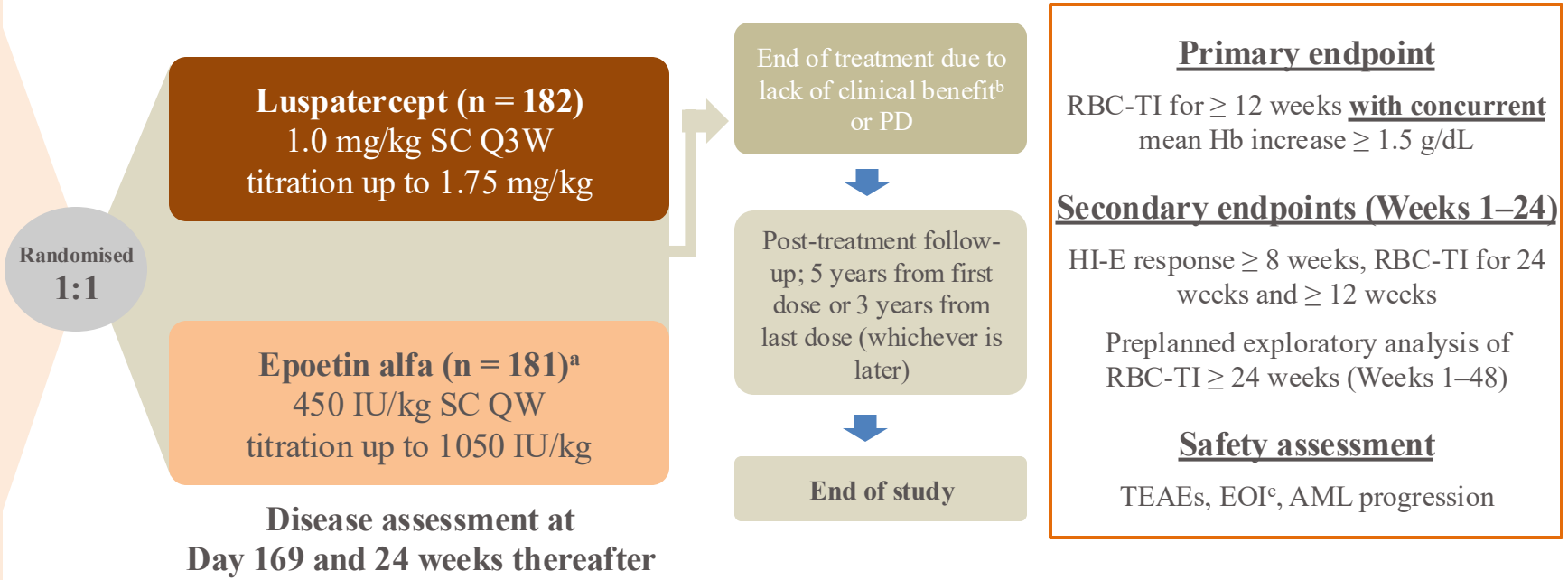
Luspatercept vs. epoetin alfa in ESA-naïve, lower-risk MDS COMMANDS Phase 3 global trial[1,2]

Key patient eligibility criteria

- IPSS-R very low-, low- or intermediate-risk MDS (with or without RS), with < 5% blasts in bone marrow
- Required RBC transfusions (2–6 units/8 weeks for a minimum of 8 weeks immediately prior to randomisation)
- Endogenous sEPO < 500 U/L
- ESA-naïve
- Patients with del(5q) were excluded

Patients stratified by:

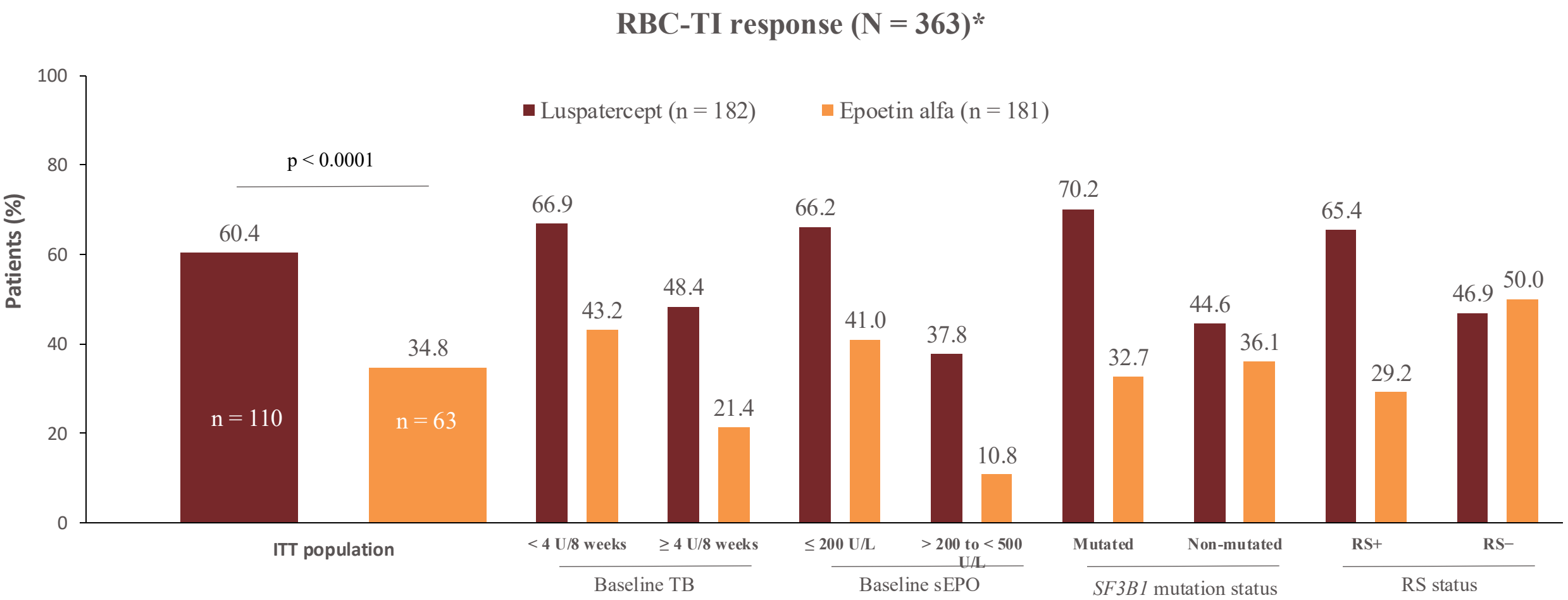
- Baseline RBC transfusion burden
- Baseline sEPO level
- RS status



[a] Two patients randomised to the epoetin alfa arm withdrew consent prior to receiving their first dose; [b] Clinical benefit defined as transfusion reduction of ≥ 2 units/8 weeks vs. baseline; [c] EOI are safety events selected based on findings from nonclinical or clinical phase 2 and 3 luspatercept trials.
AML: acute myeloid leukaemia; del(5q): deletion 5q; ESA: erythropoiesis-stimulating agent; EOI: events of interest; Hb: haemoglobin; HI-E: haematological improvement – erythroid response; IPSS-R: Revised International Prognostic Scoring System; MDS: myelodysplastic syndromes; PD: progressive disease; QW: every week; Q3W: every 3 weeks; RBC: red blood cell transfusion independence; RS: ring sideroblasts; SC: subcutaneous; sEPO: serum erythropoietin; TEAE: treatment-emergent adverse event.
1. Platzbecker U, et al. *Lancet* 2023;402:373–385. 2. Garcia-Manero G, et al. ASH 2023; (Abstract 193; oral).

Della Porta MG , Garcia Manero G et al, Lancet Hematol 2024

First line treatment with Luspatercept significantly improved RBC-TI vs. EPO alfa



Della Porta MG , Garcia Manero G et al, Lancet Hematol 2024

Three approaches to optimize therapy of MDS through molecular characterization:

1)Target single mutation
2)Base therapeutic choice on molecular pattern
3)Identify mutations conferring enhanced sensitivity

4)Possible molecular markers of response

Imetelstat in TD LR MDS
IMerge Phase 3 Trial Design (MDS3001; NCT02598661)

Phase 3
Double blind, randomized
118 Clinical sites in 17 countries

Patient Population (ITT N = 178)

- IPSS low- or intermediate 1- risk MDS
- relapsed/refractory[a] to ESA or EPO >500 mU/mL (ESA ineligible)
- **Transfusion dependent: ≥4 units RBCs/8 weeks over 16-week pre-study**
- Non-deletion 5q
- No prior treatment with lenalidomide or HMAs

R 2:1

Imetelstat
7.5 mg/kg IV/4 weeks
(N = 118)

Stratification:

- Transfusion burden (4-6 vs >6 units)
- IPSS risk category (low vs Intermediate 1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (e.g., G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

Placebo
(N = 60)

Safety population (treated) N = 177

Imetelstat N = 118

Placebo N = 59

Primary endpoint:

- 8-week RBC-TI[b]

Key secondary endpoints:

- 24-week RBC-TI[b]
- Duration of TI
- Hematologic improvement-erythroid
- Safety

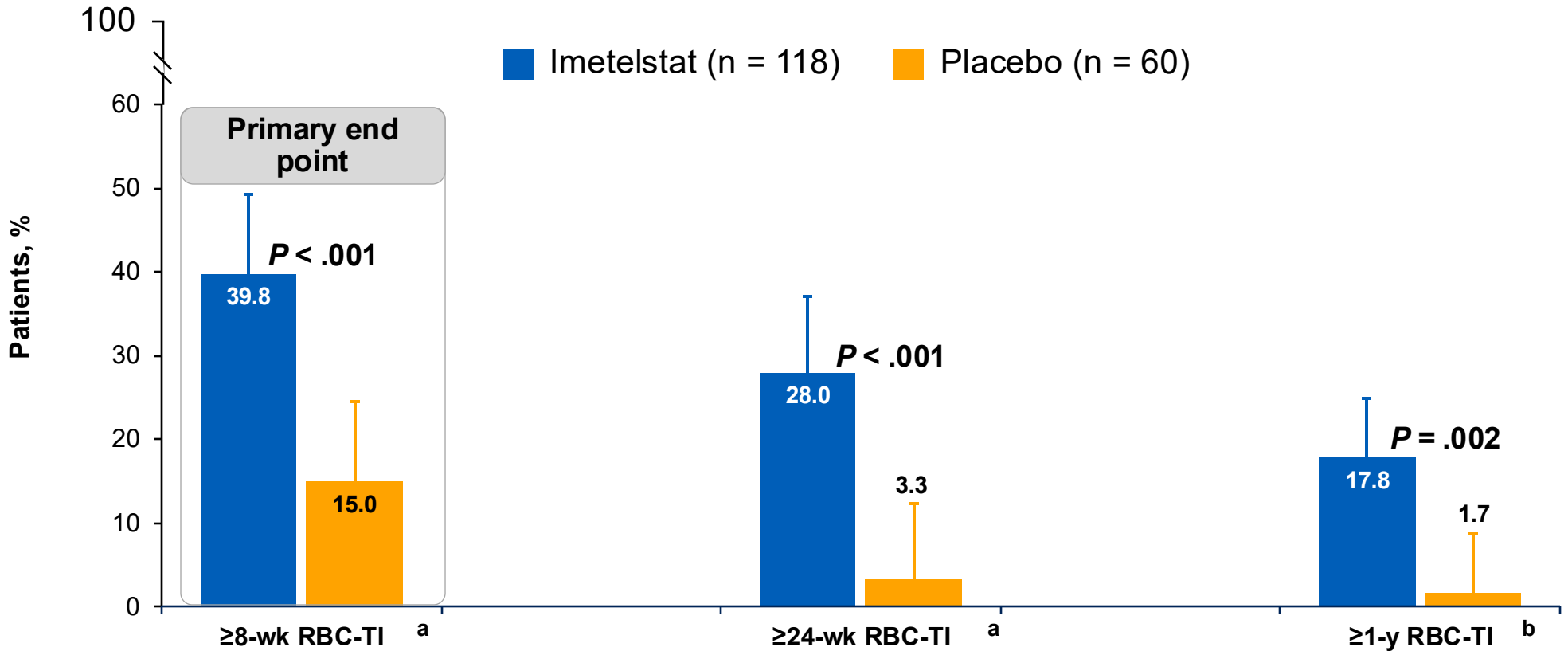
Key exploratory endpoints:

- VAF changes
- Cytogenetic response
- PRO: fatigue measured by FACIT-Fatigue

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 units, epoetin beta ≥30,000 units or darbepoetin alfa 150 µg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 units/8 weeks or transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. [b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI)
EPO, erythropoietin; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hgb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; R, randomization; RBC, red blood cell; TI, transfusion independence, VAF, variant allele frequency.

Platzbecker , Santini et al, in press Lancet 2023

RBC-TI With Imetelstat vs Placebo in LR MDS



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.

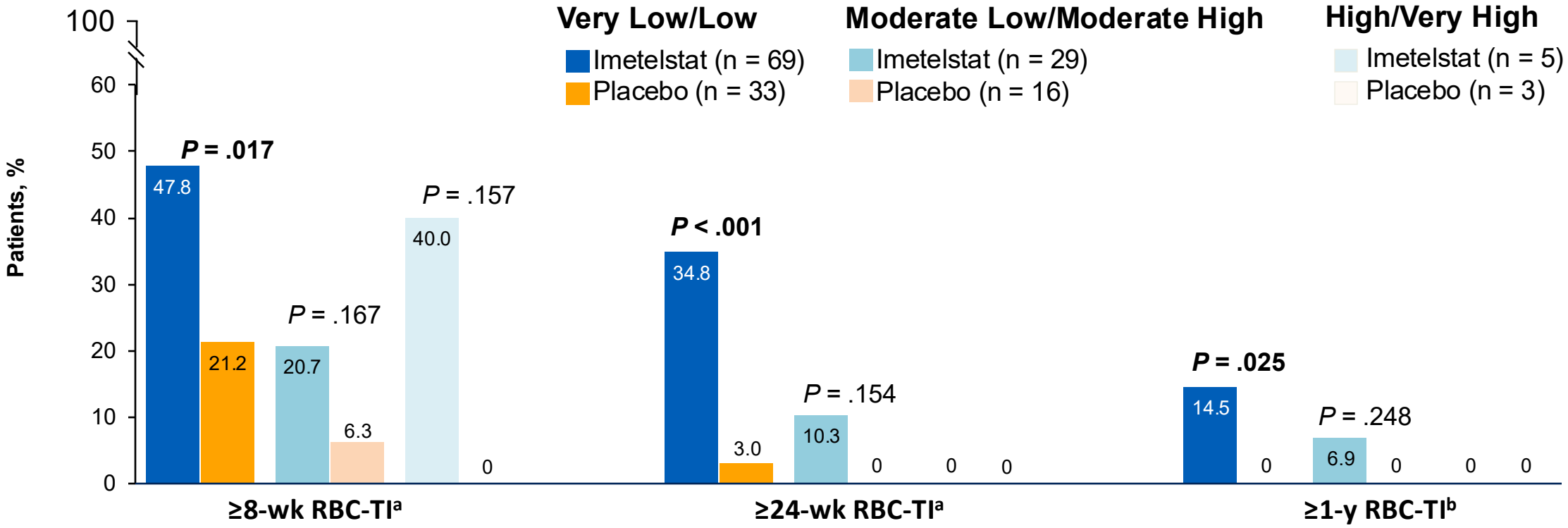
The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.

IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

Platzbecker U, et al. Oral presentation at: EHA 2023; June 6, 2023; Frankfurt, Germany. Presentation S165.

RBC-TI by IPSS-M Subgroup

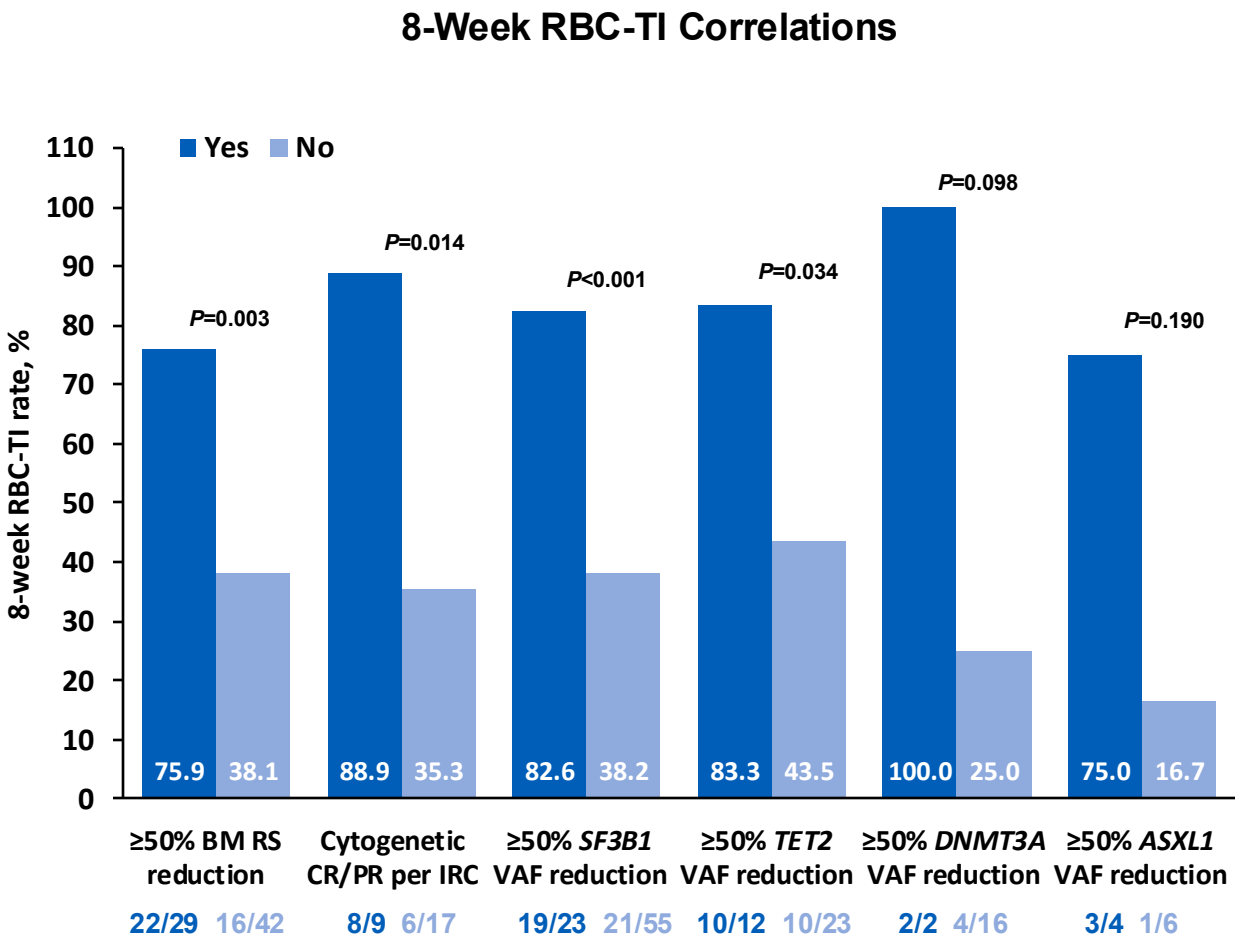
- Imetelstat treatment had higher RBC-TI response rates than placebo, regardless of IPSS-M risk group

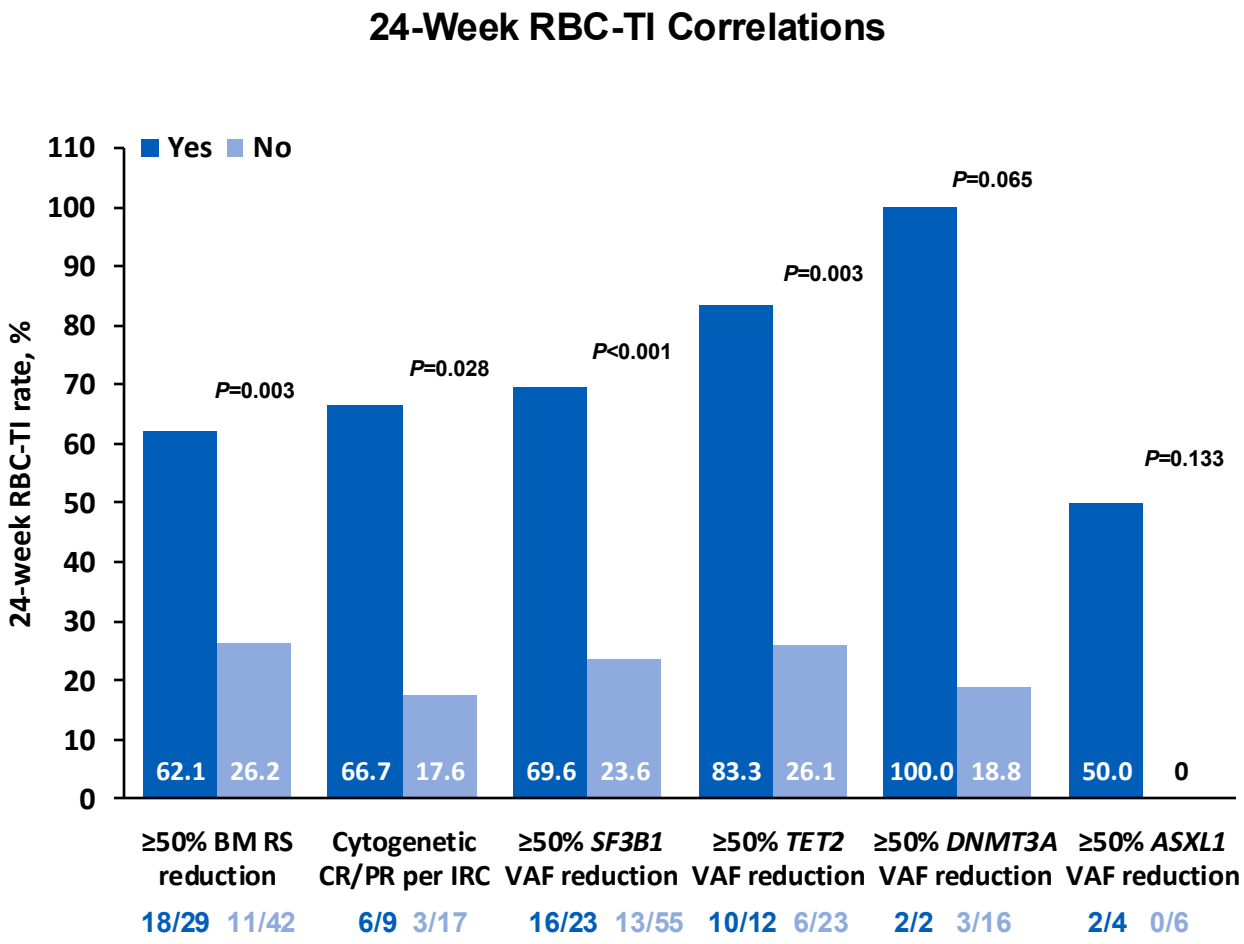


[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.

IPSS-M, molecular International Prognostic Scoring System; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.

8-Week and 24-Week RBC-TI Correlated With Reduction in RS+ Cells, Cytogenetic Responses, and VAF Reduction in Patients Treated With Imetelstat





Data cutoff: October 13, 2022.

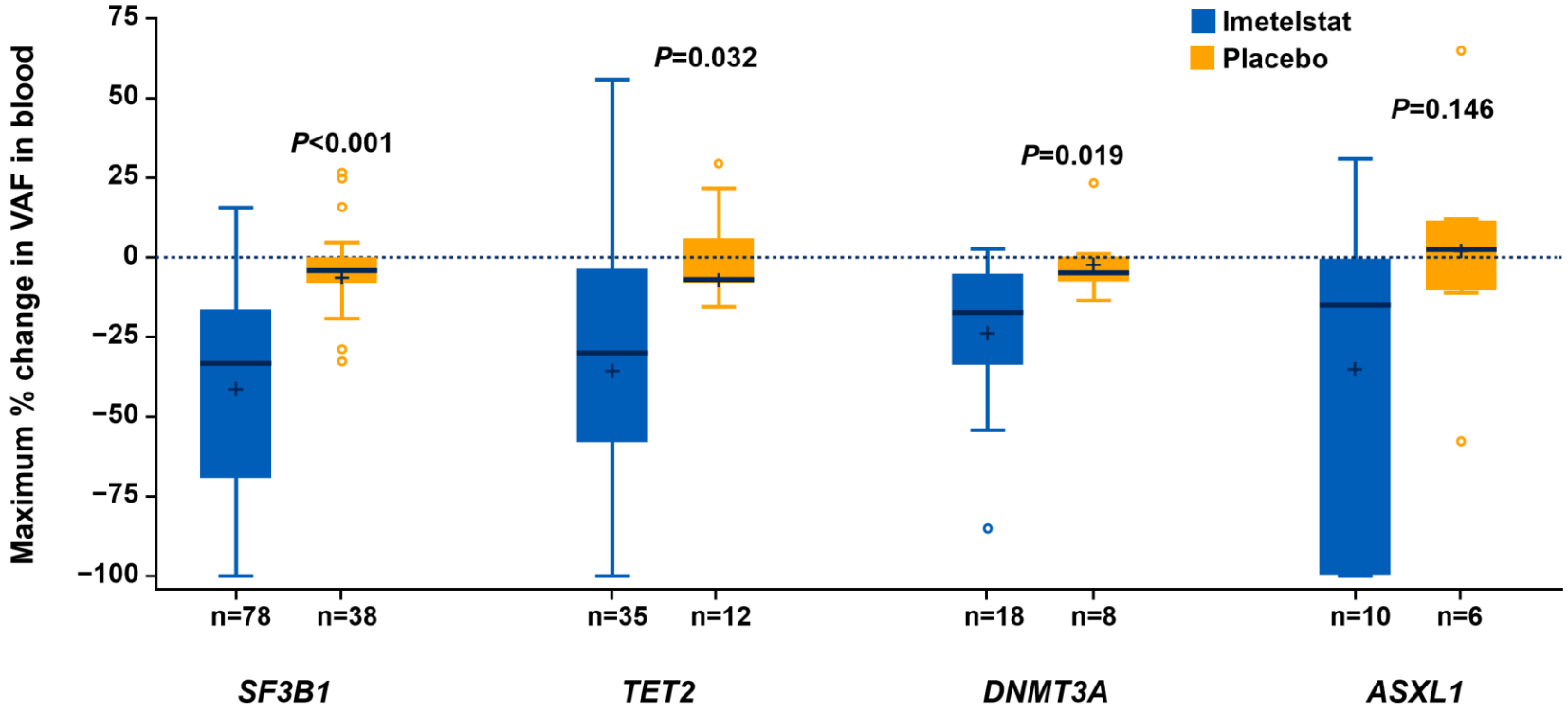
Note: *P* value calculated using Fisher exact test between yes vs no in each outcome.

ASXL1, additional sex combs like-1; BM, bone marrow; CR, complete response; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IRC, independent review committee; PR, partial response; RBC, red blood cell; RS, ring sideroblasts; TET2, Tet methylcytosine dioxygenase 2; SF3B1, splicing factor 3b subunit 1; TI, transfusion independence; VAF, variant allele frequency.

Santini et al , EHA 2023

Reductions in VAF of Genes Frequently Mutated in MDS Were Greater With Imetelstat vs Placebo

- Mutations on 36 genes associated with MDS were tested by NGS on samples taken from baseline and post-treatment
- Among patients with evaluable mutation data, the maximum reductions in VAF of the *SF3B1*, *TET2*, *DNMT3A, and ASXL1* genes were greater with imetelstat than placebo



Data cutoff: October 13, 2022.

Note: Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of theindicated gene. *P* value based on the two-sample *t*-test. Analyses included patients in the intent-to-treat population with a detectable mutant allele for the indicated gene (≥5%)prior to treatment and ≥1 postbaseline mutation assessment.

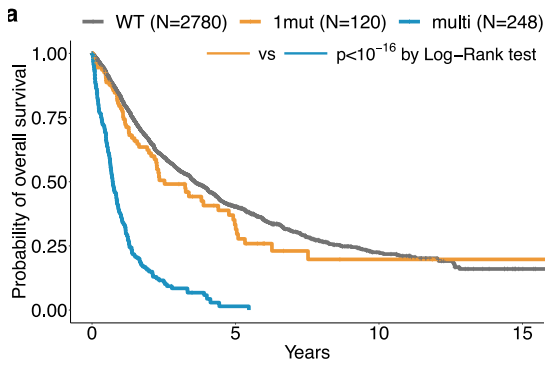
ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; MDS, myelodysplastic syndromes; NGS, next-generation sequencing; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

TP53 mutation in MDS:

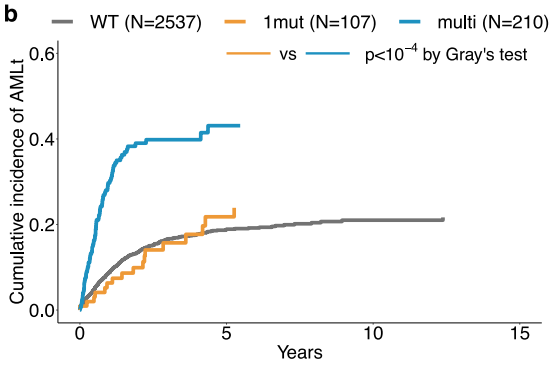
a world apart

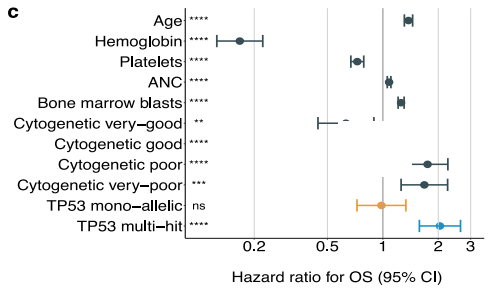
TP53 allelic state shapes clinical outcomes

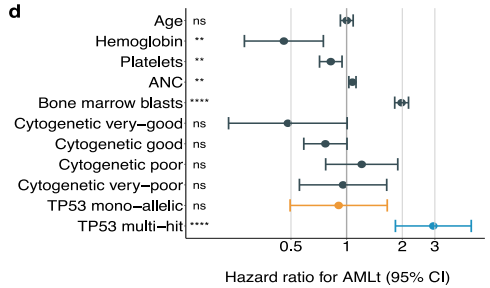
Overall Survival



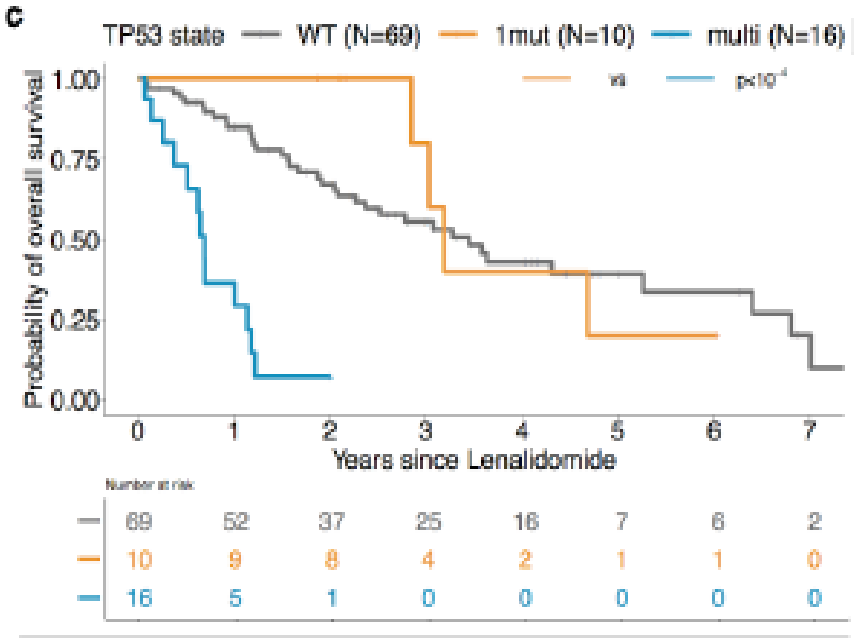
AML Transformation







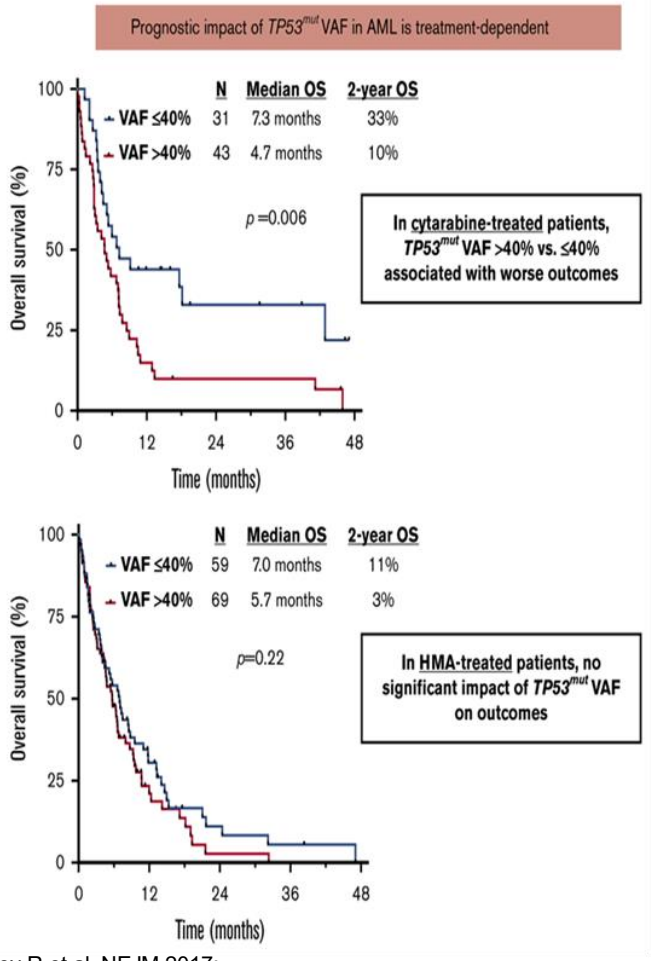
Overall Survival after LEN

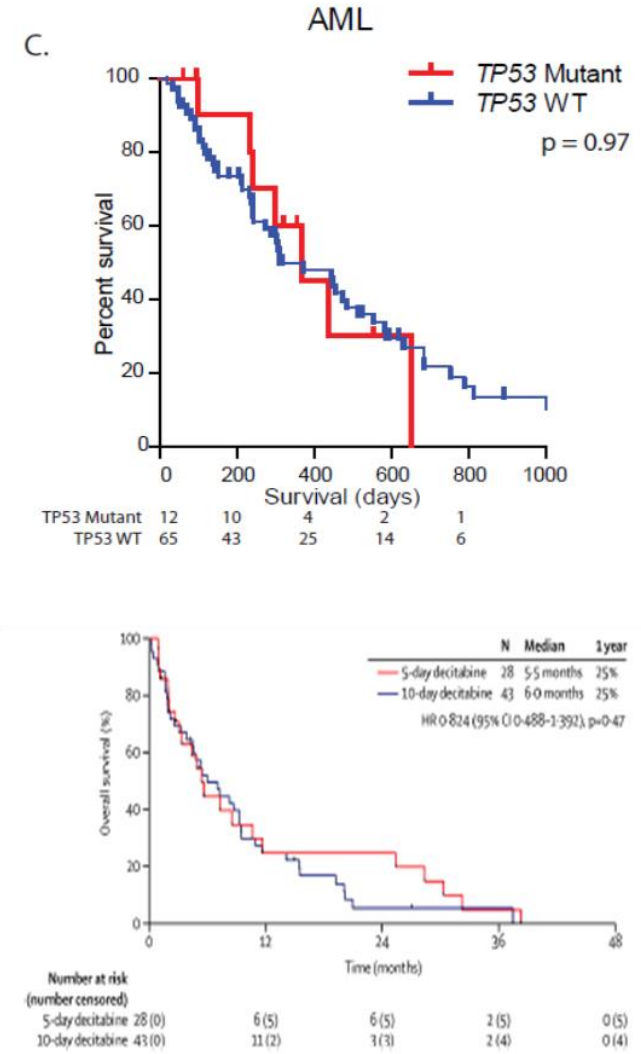


E.Bernard et al, Nat Med. 2020 Oct;26(10):1549-1556

Outcomes to Therapy in *TP53* MDS/AML

- Current therapies in *TP53* mutant MDS/AML
  - Hypomethylating agents (HMA) result in 15-20% CR and 40-45% ORR, similar to *TP53* wildtype patients
  - Despite HMA responses, significantly inferior OS in *TP53* mutant patients (6-12 months)
  - No Improvement in extended decitabine duration +/- venetoclax in AML
    - OS < 6 months
  - IC maybe an option for patients with *TP53* subclone

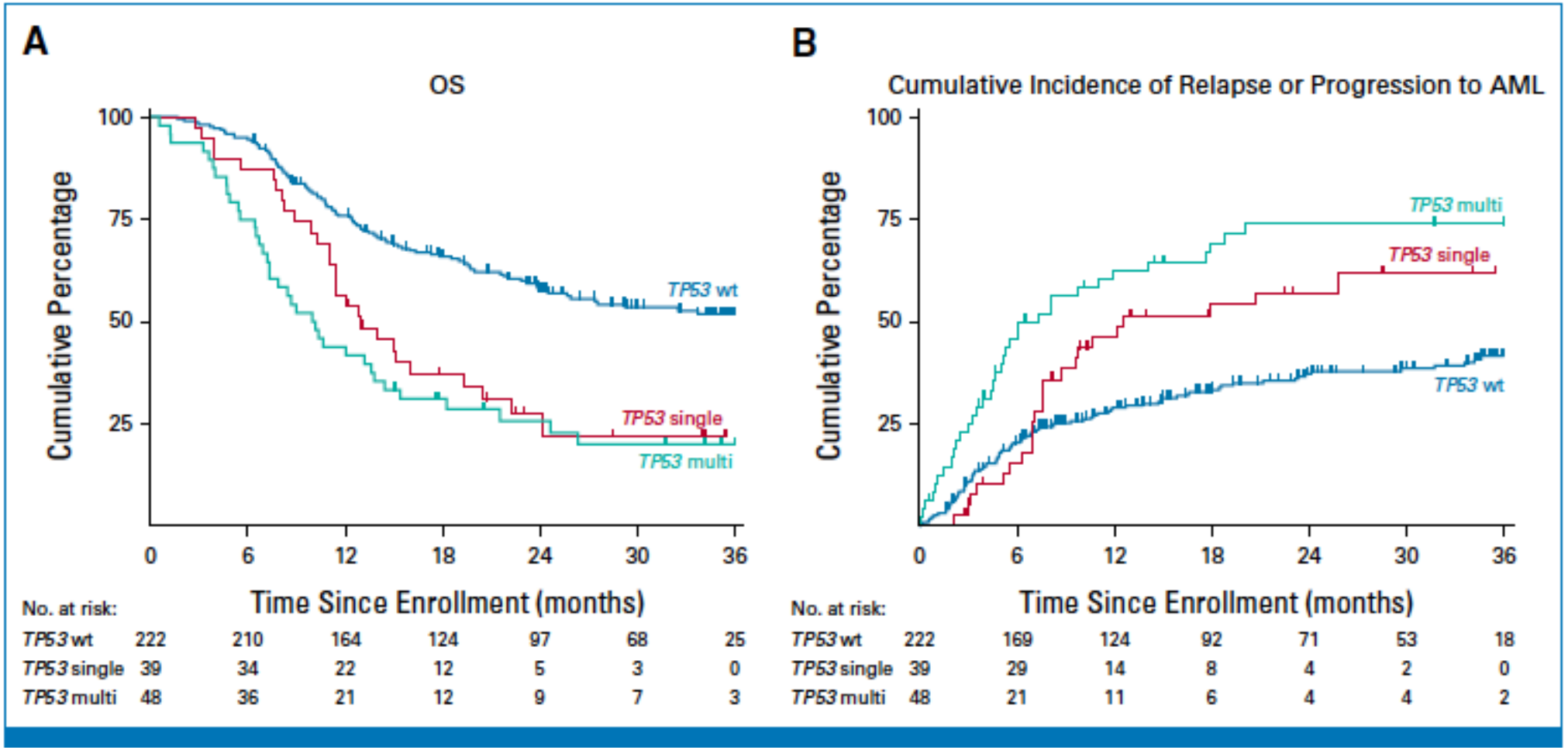




Bally C, et al. Leuk Res. 2014; Welch JS, et al. NEJM 2016; Haase D, et al. Leukemia 2019; Bejar R, et al. JCO. 2014; Lindsley R et al. NEJM 2017; Sallman et al. Leukemia 2016; DiNardo C ,et al. Blood 2019; Wei A, et al. J Clin Oncol, 2019. Della Porta MG et al. JCO 2016; Yoshizato T, et al. Blood 2017; Hunter A et al., Blood Advances 2021; Short et al., Lancet Haematology 2019; Short N et al., Blood Adv 2020

Courtesy David A. Sallman MD

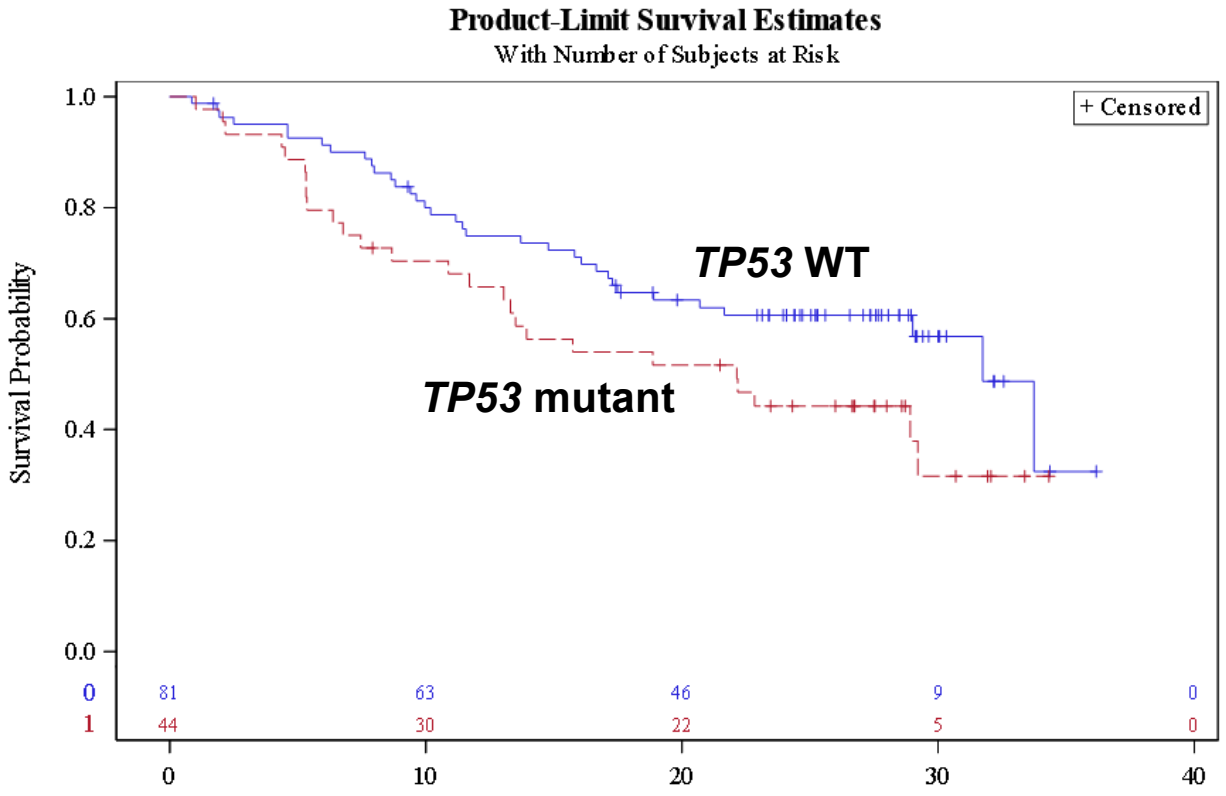
Outcomes to HSCT in *TP53* MDS/AML



VERSLUIS J ET AL, JCO 2023

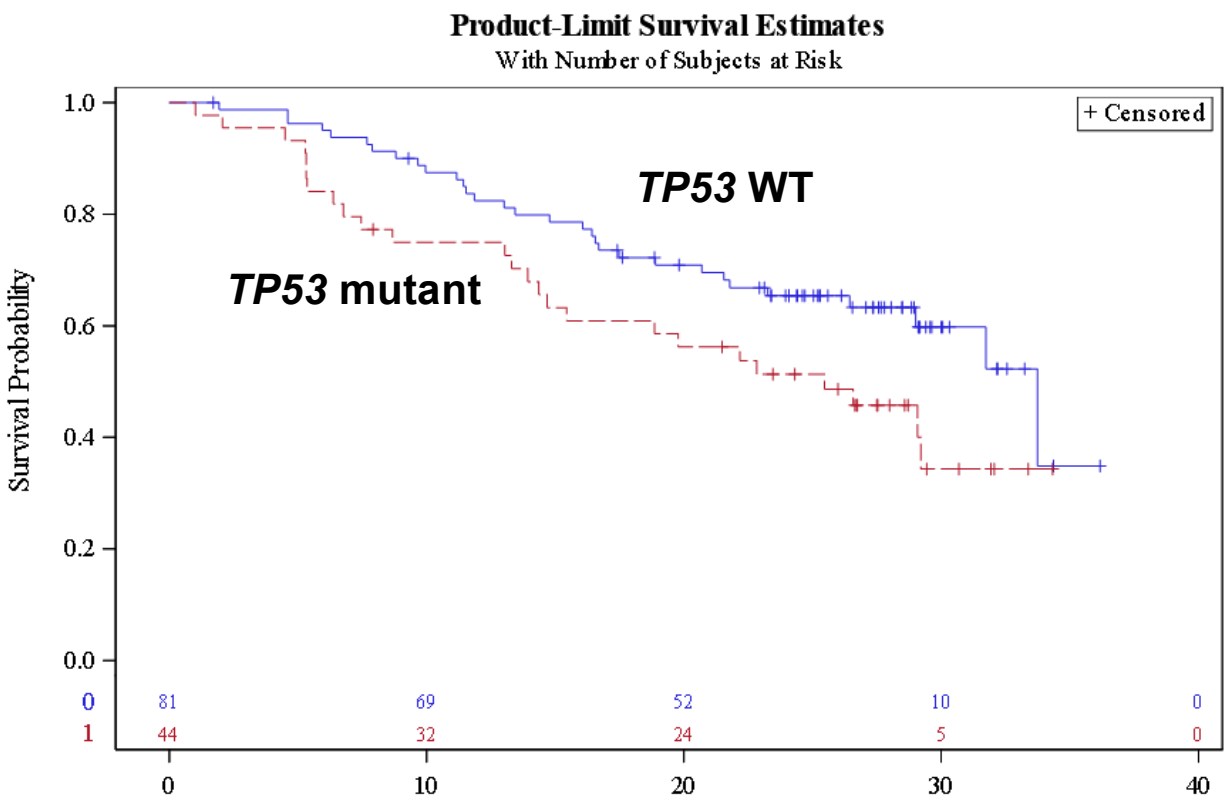
Survival in Bi-Allelic TP53-Mutated (*TP53*^{mut}) MDS Subjects Treated with Oral Decitabine/Cedazuridine in the ASCERTAIN Trial (ASTX727-02)

Leukemia-Free Survival



LFS: WT 31.7 months (21.7, NE)
Mut 22.1 months (11.7, 29.2)

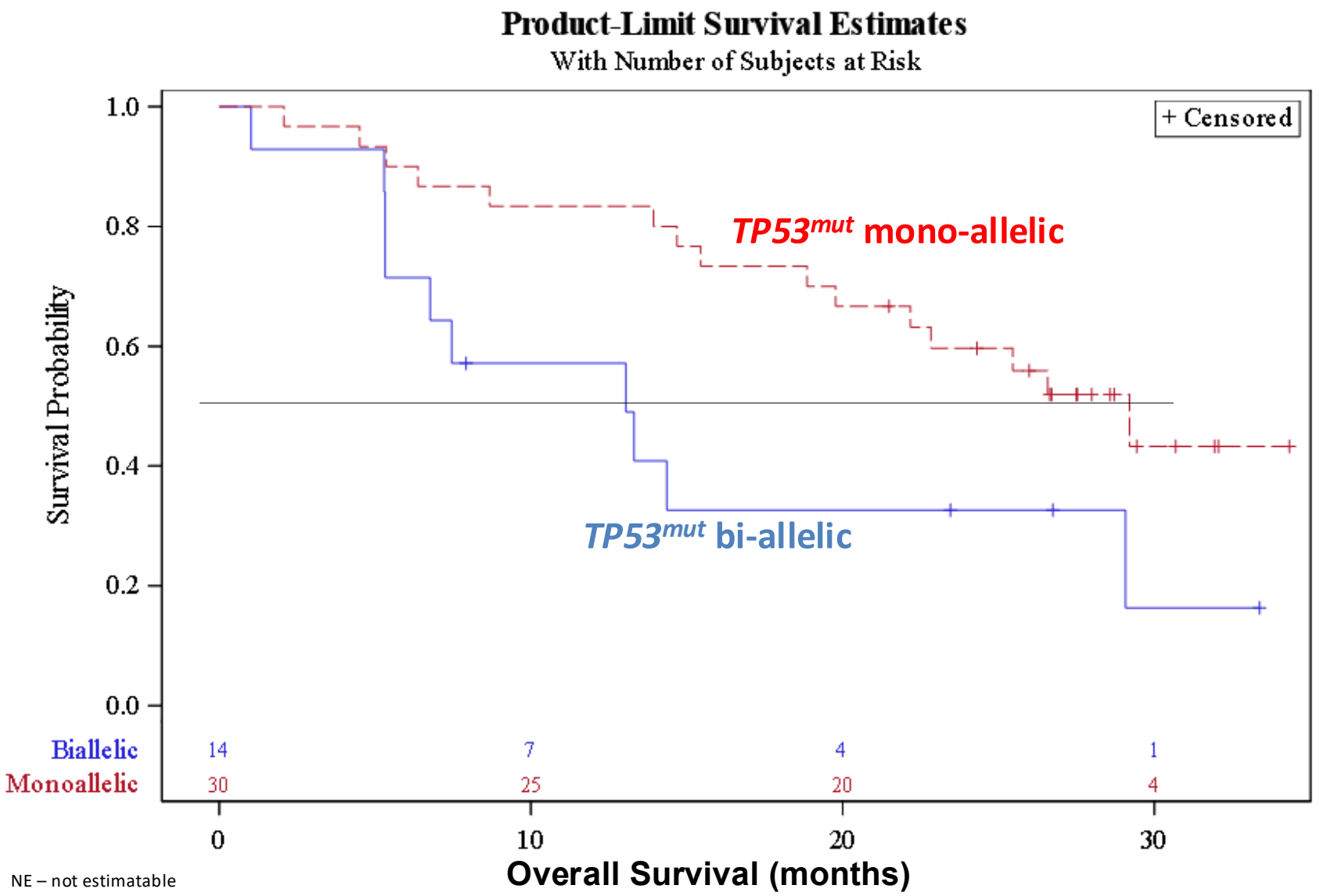
Overall Survival



OS: WT 33.7 months (29.0, NE)
Mut 25.5 months (14.4, NE)

NE – not estimatable

Survival in *TP53*^{mut} (Mono- vs. Bi-allelic)



NE – not estimatable

Mono-allelic OS:

mOS: 29.2 months

95% CI (19.7 months, NE)

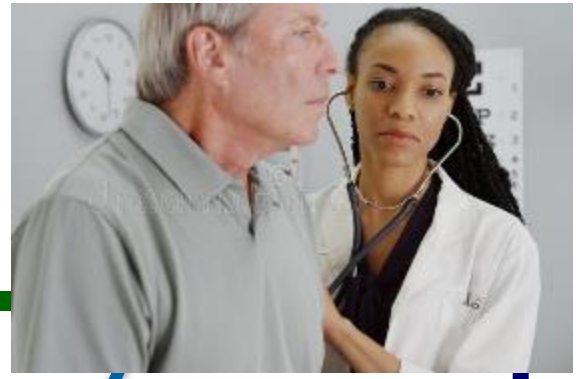
Bi-allelic OS:

mOS: 13.0 months

95% CI (5.3 months, 29.0)

Usefulness of molecular analysis in MDS

Level of anemia shapes symptoms,
but the disease charcaterization is complex



WBC counts and PB smear

BM aspirate
+ Perls staining

Karyotype

Flow cytometry

NGS- somatic+germline

Family and
patient history

Comorbidity
CGA

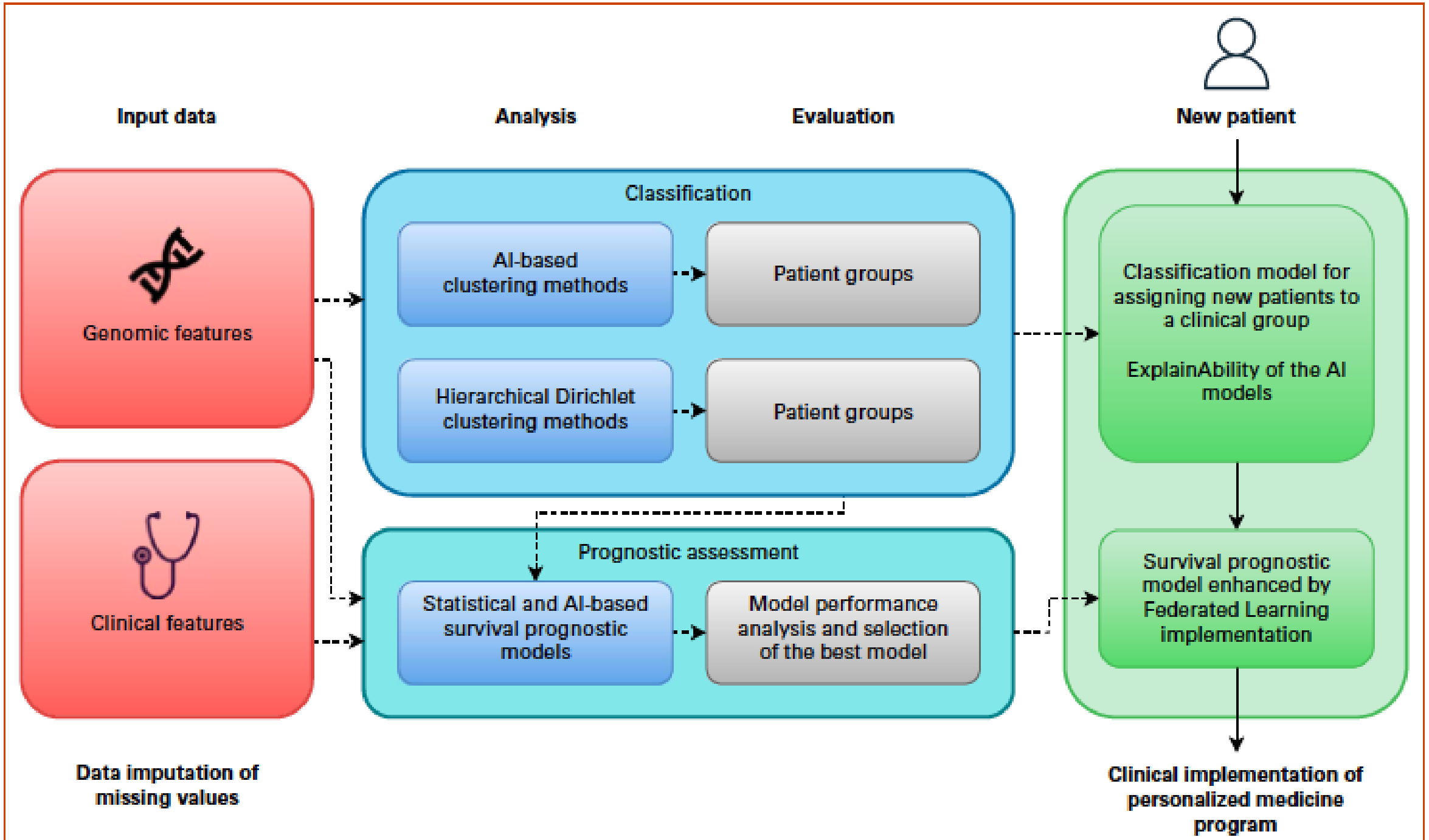
Iron balance, TSH, creatinine,
sEPO, HLA typing

MOSAIC: An Artificial Intelligence–Based Framework for Multimodal Analysis, Classification, and Personalized Prognostic Assessment in Rare Cancers

Saverio D'Amico, MEng[1,2]; Lorenzo Dall'Olio, PhD[3]; Cesare Rollo, PhD[4]; Patricia Alonso, PhD[5]; Iñigo Prada-Luengo, PhD[6]; Daniele Dall'Olio, PhD[3]; Claudia Sala, PhD[7]; Elisabetta Sauta, PhD[1]; Gianluca Asti, MSc[1]; Luca Lanino, MD[1]; Giulia Maggioni, MD[1]; Alessia Campagna, MD[1]; Elena Zazzetti, MEng[1]; Mattia Delleani, MSc[1]; Maria Elena Bicchieri, PhD[1]; Pierandrea Morandini, MEng[1]; Victor Savevski, MEng[1]; Borja Arroyo, PhD[5]; Juan Parras, PhD[5]; Lin Pierre Zhao, MD[8]; Uwe Platzbecker, MD[9]; Maria Diez-Campelo, MD[10]; Valeria Santini, MD[11]; Pierre Fenaux, MD[8]; Torsten Haferlach, MD[12]; Anders Krogh, PhD[6]; Santiago Zazo, PhD[5]; Piero Fariselli, PhD[4]; Tiziana Sanavia, PhD[4]; Matteo Giovanni Della Porta, MD[1,13]; and Gastone Castellani, PhD[3,7]

DOI https://doi.org/10.1200/CCI.24.00008

JCO CCI 2024


Input data
Analysis
Evaluation
New patient
Genomic features
Clinical features
Classification
AI-based clustering methods
Patient groups
Hierarchical Dirichlet clustering methods
Patient groups
Prognostic assessment
Statistical and AI-based survival prognostic models
Model performance analysis and selection of the best model
Classification model for assigning new patients to a clinical group
ExplainAbility of the AI models
Survival prognostic model enhanced by Federated Learning implementation
Data imputation of missing values
Clinical implementation of personalized medicine program

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

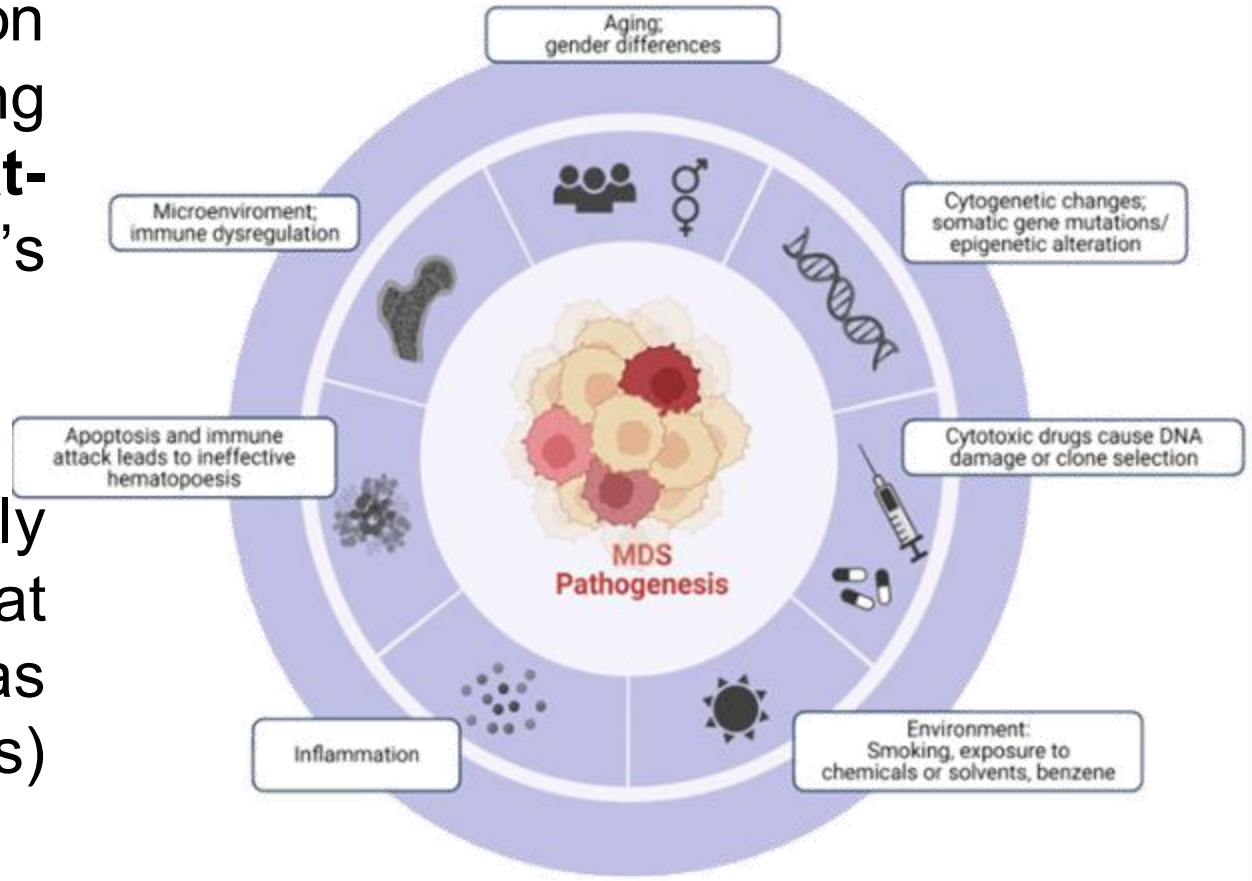
Elisabetta Sauta, PhD

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

Background

Advancements in genome characterization have transformed the study of MDS, moving from traditional classification to **next-generation systems**, incorporating patient's genomic profiles.

However, genetic abnormalities partially explain patients' heterogeneity, indicating that other non-mutational factors (such as transcriptomic and immune-related features) may play a crucial role.



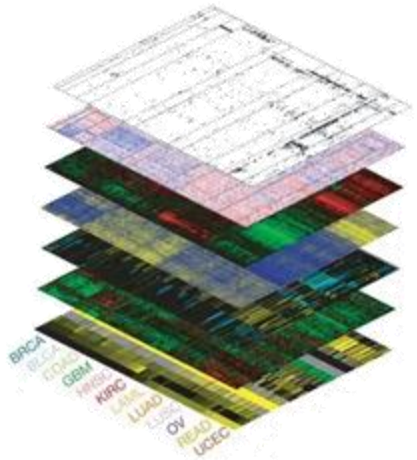
Bewersdorf JP et al. Blood Rev. 2023

Rationale

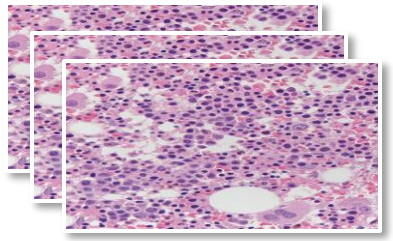
PATIENTS DATA MODALITIES

- OMICS LAYERS

CLINICAL



DIGITAL PATHOLOGY



INTEGRATIVE MODEL

DEEP FUSION MODEL

CLINICAL DECISION MAKING

PATIENT'S TAILORED ...

DIAGNOSIS

PROGNOSIS

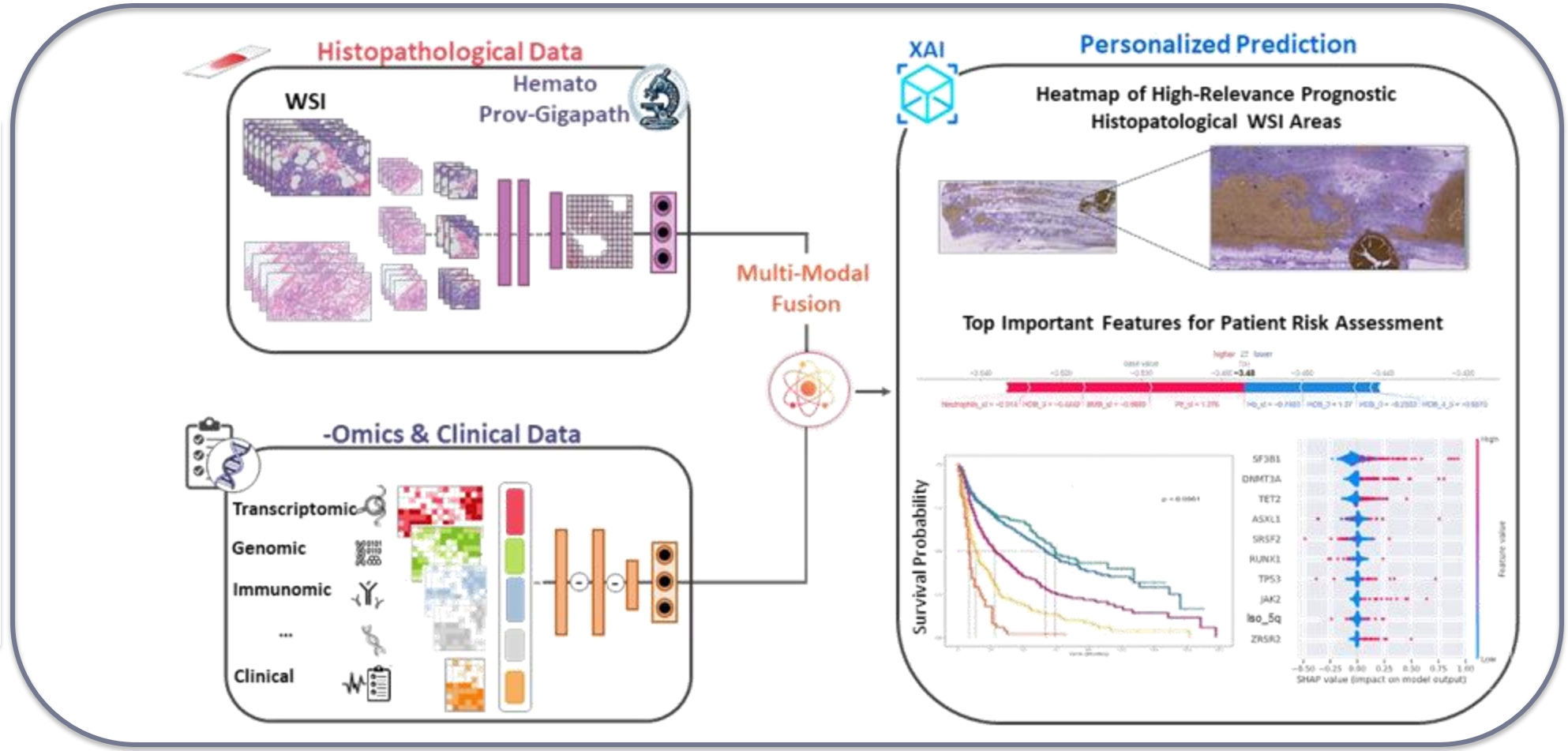
- Survival
- Disease Progression

TREATMENT

- HMA Response

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

MEGAERA

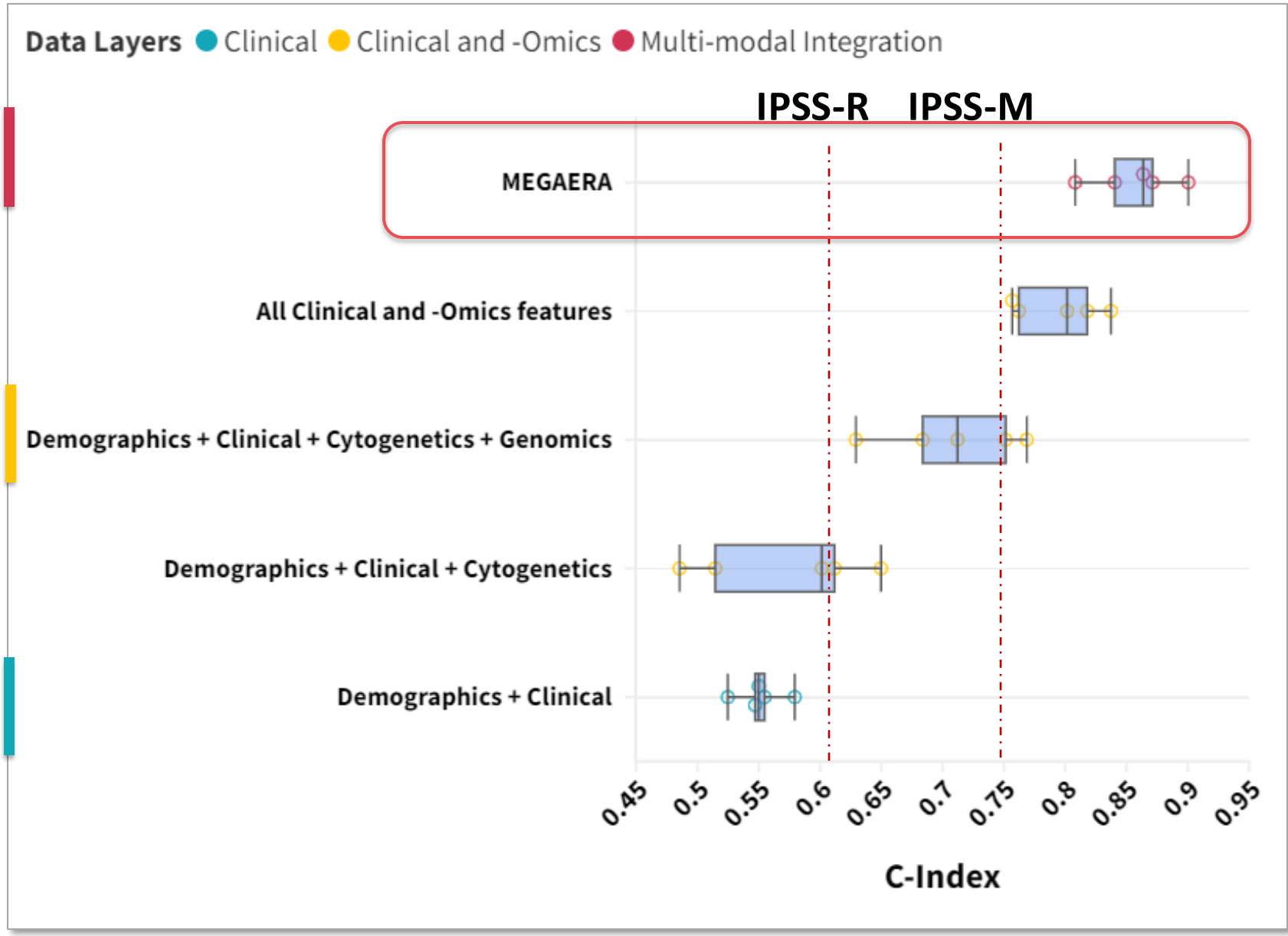


Results MEGAERA PREDICTIVE PERFORMANCE

Aim: Overall Survival Risk Prediction

Schema:

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

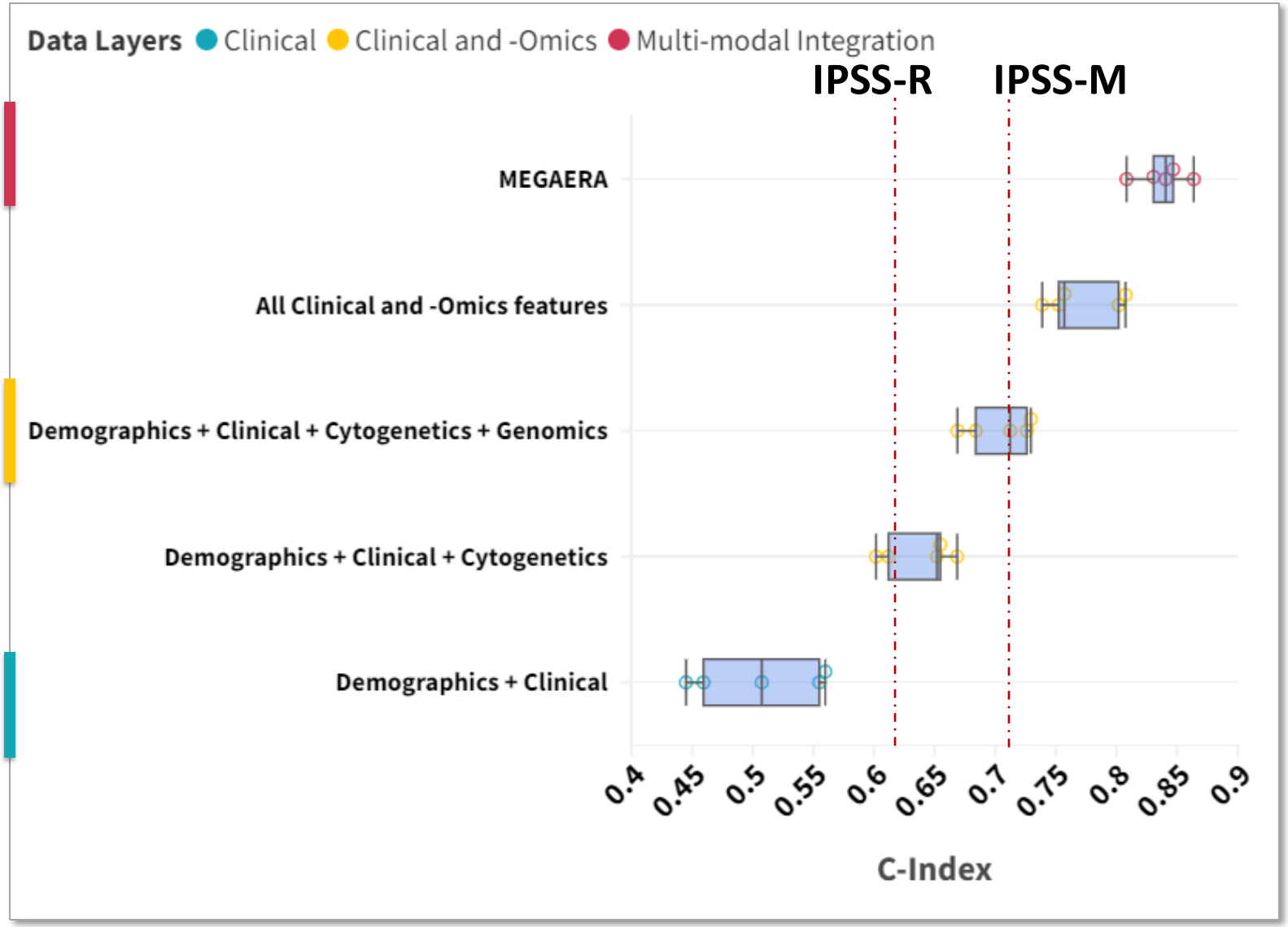


Results MEGAERA PREDICTIVE PERFORMANCE

Aim: Overall Survival post-HMA Risk Prediction

Schema:

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



Thanks!

MDS Unit, DMSC

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Barbara Caciagli

UNIVERSITÀ DEGLI STUDI FIRENZE
DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

EMSCO MYELODYSPLASTIC SYNDROMES

AIRC

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

INTERCEPT-MDS

GEN-MED-ALL
Horizon 2020
European Union Funding for Research & Innovation

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