Myelodysplastic Syndrome
Challenges, Current Standard Therapy and Future Directions.

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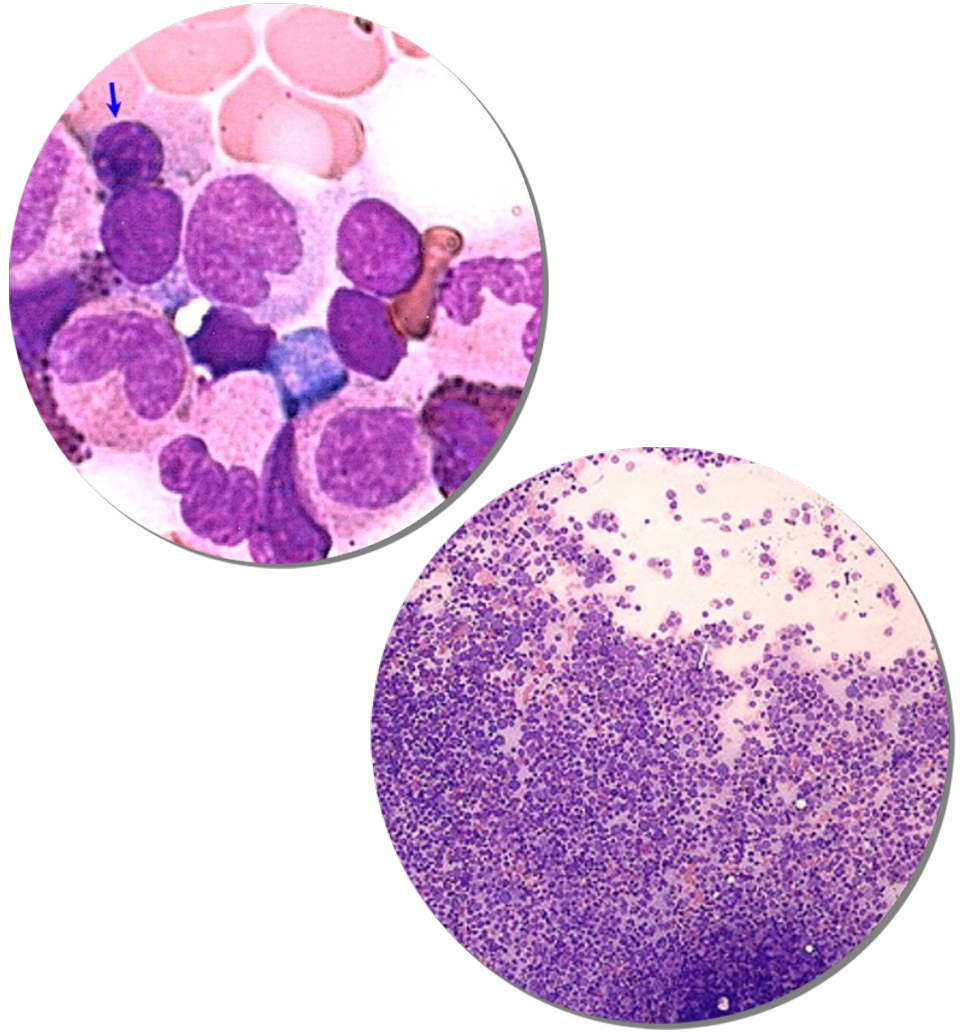
Myelodysplastic Syndromes (MDS)

- A group of malignant hematopoietic neoplasms characterized by[1]:
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000[2]
  - In US (true estimates ≈37,000-48,000)
- Median age: 70 yrs; incidence: 34-47/100,000 >75 yrs[3]



1. Bennett J et al. *Clinical Oncology*. New York, NY: Churchill Livingstone; 2004:2849-2881; 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.

MDS Minimal Diagnostic Criteria

Prerequisite Criteria

Both 1 and 2 must be fulfilled

1. Cytopenia(s)

2. EXCLUDE other causes of cytopenias and morphological changes:

- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE etc.)*
- *Hereditary BMF syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

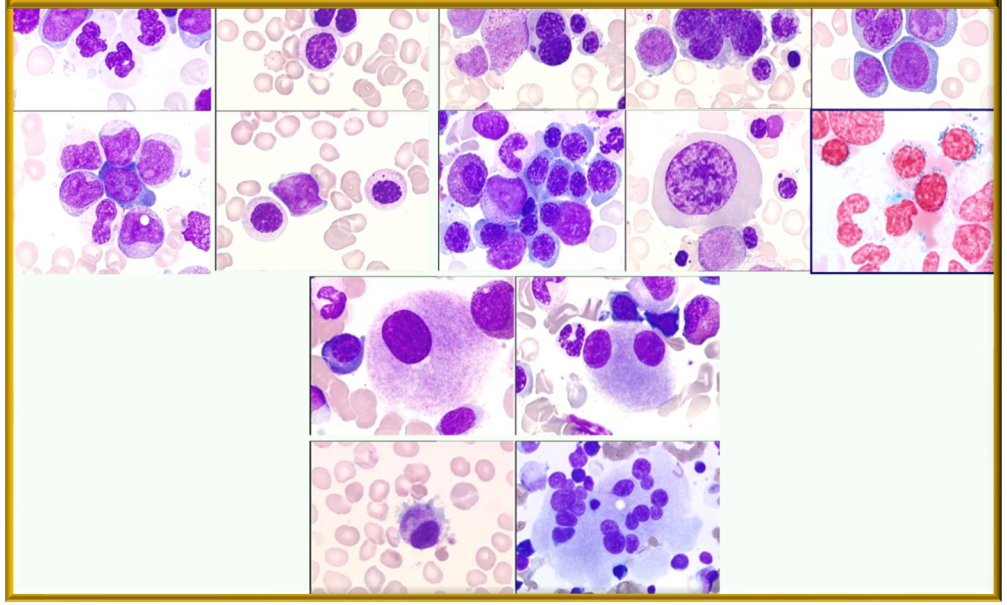
MDS Major Criteria

i. Dysplasia of at least 10% of cells in one or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in ring sideroblasts (RS) of ≥ 15% (or ≥ 5% in the presence of a SF3B1 mutation)

ii. An increase in myeloblasts of 5-19% in dysplastic BM smears or 2-19% myeloblasts in peripheral blood smears

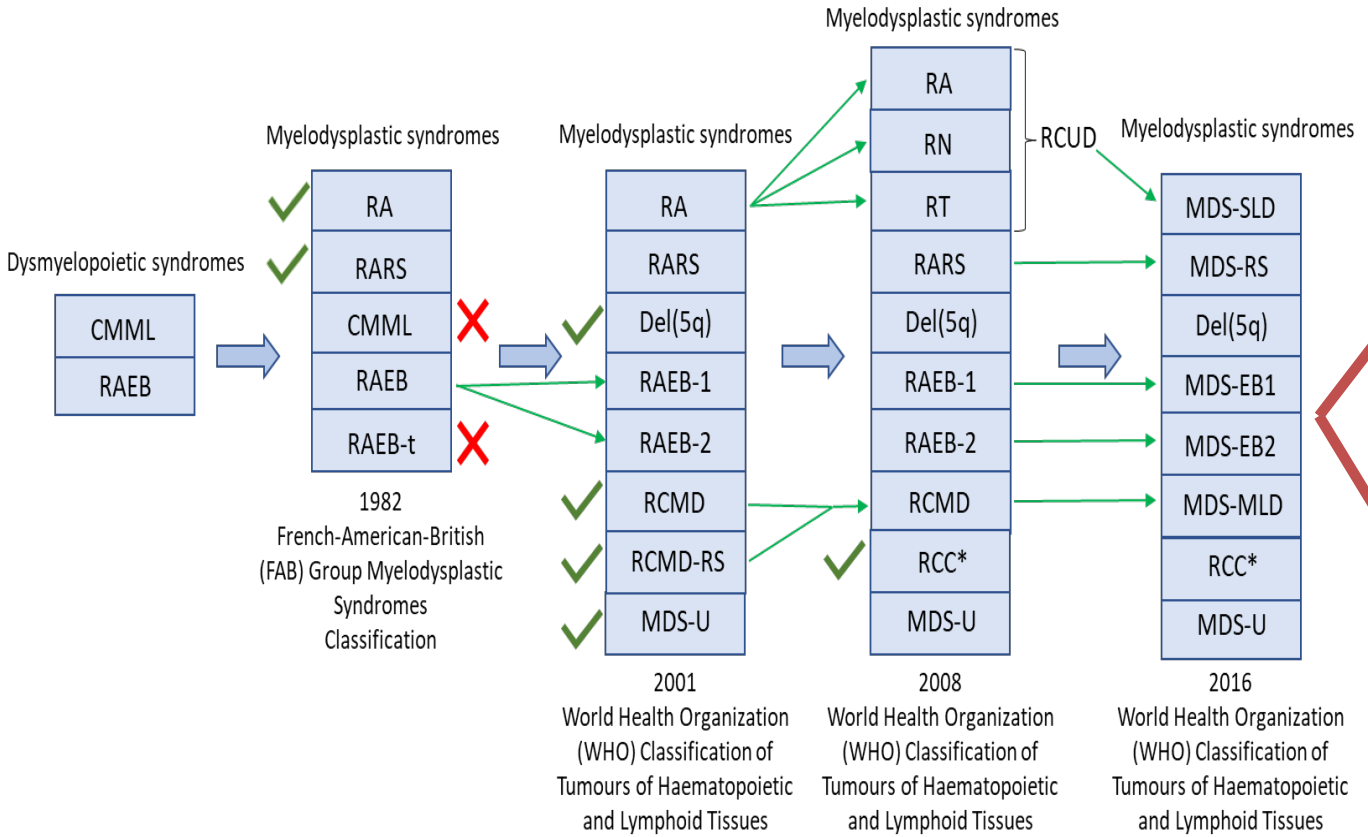
iii. An MDS-related (5q-, -7, complex….) karyotype

At least one of these major MDS criteria has to be met (together with pre-requisite-criteria) to arrive at the diagnosis of MDS



Valent, et al. *Oncotarget*. 2017 Sep 26; 8(43): 73483–73500.

MDS classification has evolved over time



WHO 2022

Leukemia www.nature.com/leu

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

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

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

Similarities and Differences: WHO and ICC 2022 for MDS

Genetically Defined Subgroups	*SF3B1*	No specific category	**MDS-*SF3B1*:** MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - No del 5q, -7, complex karyotype - No biallelic *TP53*	**MDS-*SF3B1*:** MDS with low blasts (BM <5%, PB <2%) and *SF3B1* mutation - *SF3B1* VAF ≥10% - No del 5q, -7, inv3/t(3;3), complex karyotype - No multi-hit *TP53* or *RUNX1* mutations
	Del 5q	MDS with isolated del(5q)	**MDS-5q:** MDS with low blasts and isolated del 5q or with 1 other cytogenetic abnormality except -7/del(7)	**MDS del(5q):** MDS with isolated Del 5q or with 1 other cytogenetic abnormality except -7/del(7)
	TP53 mutation (supersedes all other MDS categories)	Not included	**MDS-bi*TP53:*** MDS with biallelic *TP53* inactivation - ≥2 *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH	**MDS with mutated *TP53*** **MDS/AML with mutated *TP53*** - MDS (blast <10%): Criteria same as WHO or, 1 *TP53* mutation plus complex karyotype - MDS/AML (blast 10-19%): Any *TP53* mutation (VAF ≥10%)
Other genetic Subgroups	MDS-related gene mutations and cytogenetic abnormalities	Not included		**MDS/AML with myelodysplasia related gene mutations** **MDS/AML with myelodysplasia related cytogenetic abnormalities**

Arber et al. Blood. 2016; Khoury et al. Leukemia. 2022; Arber et al. Blood. 2022.

Similarities and Differences: WHO and ICC 2022 for MDS

MORPHOLOGY		WHO 2016	WHO 2022	ICC 2022
Ring Sideroblasts	RS ≥15%	MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD) and multi-lineage dysplasia (MDS-RS-MLD)	MDS with ring sideroblasts (**MDS-RS**): Low blast, *SF3B1* wild-type	No RS specific category
Number of Dysplastic Lineages	1 vs. >1	MDS with single lineage dysplasia (MDS-SLD) and multi-lineage dysplasia (MDS-MLD)	Dysplastic lineages are removed MDS with low blasts (**MDS-LB**): <5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (**MDS, NOS-SLD**) and multi-lineage dysplasia (**MDS, NOS-MLD**)
Blasts	5-9%	MDS with excess blasts-1 (MDS-EB1): 5-9% BM blasts	MDS with increased blasts-1 (**MDS-IB1**): 5-9% BM and/or 2-4% PB blasts	MDS with excess blasts (**MDS-EB**; 5-9% BM and/or 2-9% PB blasts or Auer rods)
	10-19%	MDS excess blasts-2 (MDS-EB2): 10-19% BM or PB blasts or Auer rods	MDS with increased blasts-2 (**MDS-IB2**): 10-19% BM or 5-19% PB blasts or Auer rods	**MDS/AML** (10-19% BM or PB blasts)
Added Subgroup	WHO	Not included	MDS, hypoplastic (**MDS-h**): Hypocellular marrow (age-adjusted)	Not included
		Not included	MDS with fibrosis (**MDS-f**): BM blasts 5-19%, PB blasts 2-19%; BM Fibrosis- grade ≥ 2	Not included
Removed		MDS unclassifiable	Not included	Not included

Arber et al. Blood. 2016; Khoury et al. Leukemia. 2022; Arber et al. Blood. 2022.

MYELODYSPLASTIC NEOPLASMS (MDS) CLASSIFICATION FROM WHO 2017 TO WHO 2022 AND ICC 2022:

AN EXPANDED ANALYSIS OF 7017 PATIENTS ON BEHALF OF THE INTERNATIONAL CONSORTIUM FOR MDS (icMDS)

Rami S Komrokji*, Somedeb Ball*, Giulia Maggioni, Erica Travaglino, Najla Al Ali, Pierre Fenaux, Uwe Platzbecker, Maria Diez-Campelo, Torsten Haferlach, Avani M Singh, Luis E Aguirre, Akriti G Jain, Sara M Tinsley, Zaker I Schwabkey, Onyee Chan, Zhuoer Xie, Andrew Kuykendall, Andrew Brunner, John Bennett, Rena Buckstein, Rafael Bejar, Jan Philipp Bewersdorf, Hetty Carraway, Amy E. DeZern, Elizabeth A. Griffiths, Stephanie Halene, Robert Hasserjian, Sanam Loghavi, Olatoyosi Odenike, Mrinal Patnaik, Gail Roboz, Valeria Santini, Maximilian Stahl, Mikkael A Sekeres, David Steensma, Michael R. Savona, Justin Taylor, Mina Xu, Kendra Sweet, Jeffrey lancet, Alan List, Eric Padron, David A Sallman, Amer M Zeidan#, Matteo G Della Porta #

Date: 10/06/2023

Program section:**Session: s424 Clinical updates in MDS**

Twitter: @ic_MDS

Conceptual classification of MDS

Chronic phase MDS

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

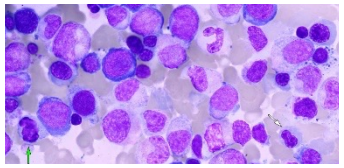
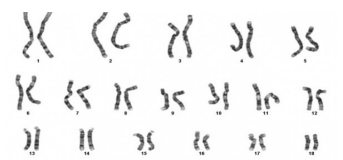
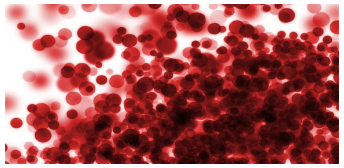
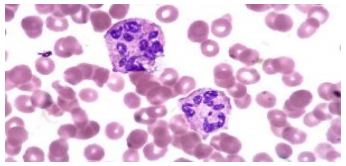
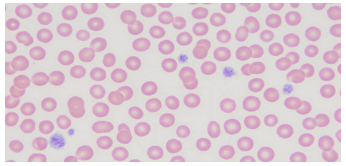
Accelerated phase MDS

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

AML-MDS related (AML-MR)

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

Risk stratification and clinical decisions in MDS – pre-2022

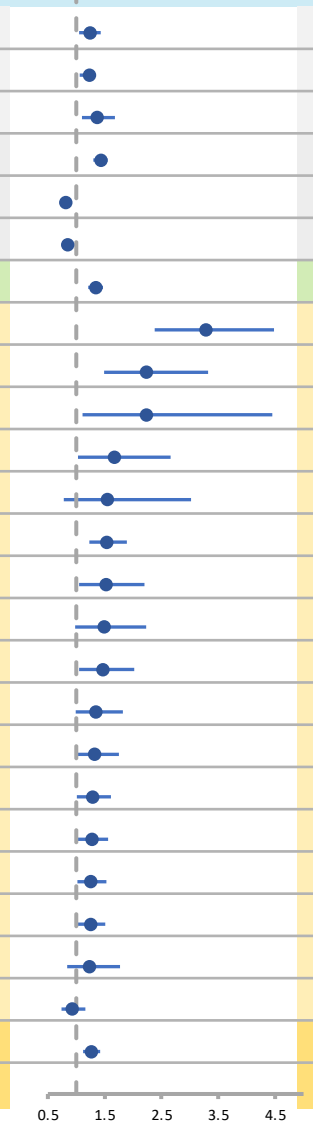
Diagnosis[1]	IPSS-R classification[1]	Incidence (%)[1]	Median OS (yrs)[1]	Progression risk (yrs)*,[1]	Treatment goal[2]	Current SoC[2]
	Very low *(Low)*	19	8.8	N/A	Hematologic improvement (lower risk of infection & bleeding)	Transfusion ESAs Watch & wait
	Low *(Low/int-1)*	38	5.3	10.8†		
	Intermediate *(Int-1/int-2)*	20	3.0	3.2		
	High *(Int-1/int-2/high)*	13	1.6	1.4	Alter disease natural history (higher risk of infection & bleeding)	HMAs/ICT +/- ASCT
	Very high *(Int-2/high)*	10	0.8	0.7		

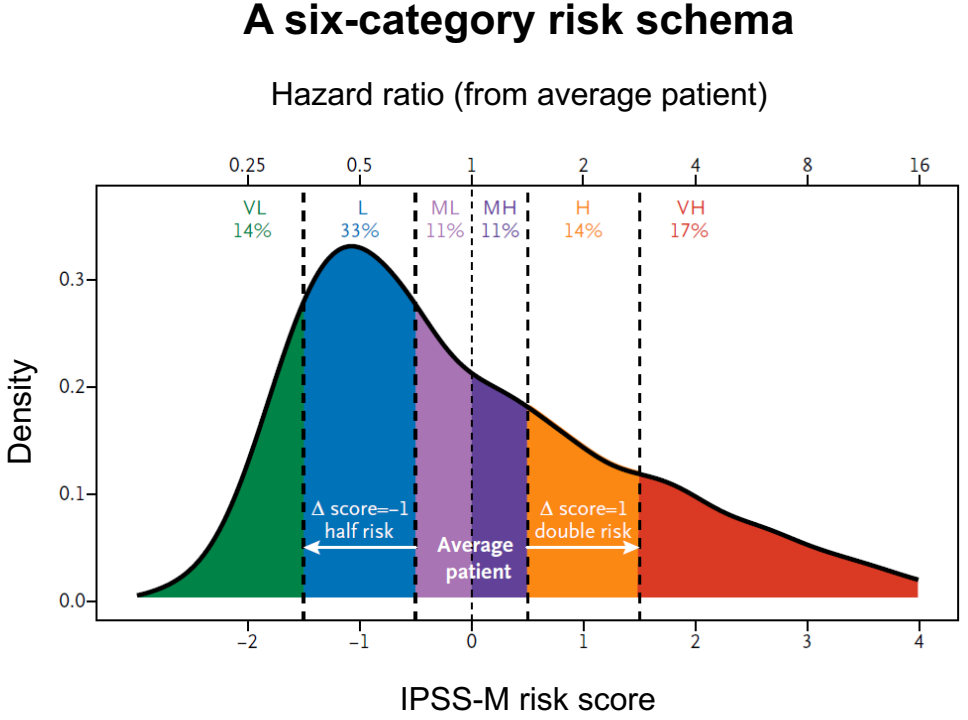
* Time to 25% AML transformation.

1. Greenberg PL, *et al. Blood* 2012; **120:**2454–2465;
2. Fenaux P, *et al. Ann Oncol* 2021; **32:**142–156.

Clinical and molecular variables defining IPSS-M

Category	Variable	Multivariable model: hazard ratio (95% CI)	Weight w	Scaling x^{mean}
Confounder	**Age**, in years	1.23 (1.05–1.43)	N/A	N/A
	Sex: Male	1.22 (1.06–1.41)	N/A	N/A
	Type: Secondary/Therapy-related	1.36 (1.10–1.68	N/A	N/A
clinical	**Bone marrow blasts**, in %	1.07 (1.05–1.09)	0.352	0.922
	(**Platelets**, 250), in $x10^9$/L	0.80 (0.72–0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81–0.88)	-0.171	9.87
cytogenetics	**IPSS-R category vector**	1.33 (1.21–1.47)	0.287	1.390
gene main effects 17 variables, 16 genes	***TP53*^{multi}**	3.27 (2.38–4.48)	1.18	0.0710
	***MLL*^{PTD}**	2.22 (1.49–3.32)	0.798	0.0247
	***FLT3*$^{ITD+TKD}$**	2.22 (1.11–4.45)	0.798	0.0108
	***SF3B1*^{5q}**	1.66 (1.03–2.66)	0.504	0.0166
	NPM1	1.54 (0.78–3.02)	0.430	0.0112
	RUNX1	1.53 (1.23–1.89)	0.423	0.126
	NRAS	1.52 (1.05–2.20)	0.417	0.0362
	ETV6	1.48 (0.98–2.23)	0.391	0.0216
	IDH2	1.46 (1.05–2.02)	0.379	0.0429
	CBL	1.34 (0.99–1.82)	0.295	0.0473
	EZH2	1.31 (0.98–1.75)	0.270	0.0588
	U2AF1	1.28 (1.01–1.61)	0.247	0.0866
	SRSF2	1.27 (1.03–1.56)	0.239	0.158
	DNMT3A	1.25 (1.02–1.53)	0.221	0.161
	ASXL1	1.24 (1.02–1.51)	0.213	0.252
	KRAS	1.22 (0.84–1.77)	0.202	0.0271
	SF3B1	0.92 (0.74–1.16)	-0.0794	0.186
gene residuals 1 variable, 15 genes	Min(**Nres**,2)	1.26 (1.12–1.42)	0.231	0.388
	Possible values are 0,1 or 2			

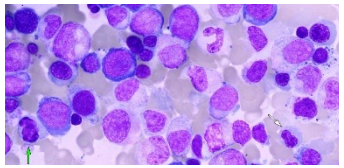
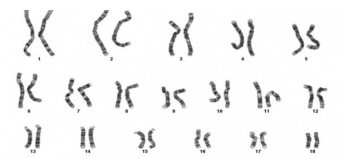
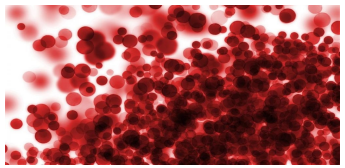
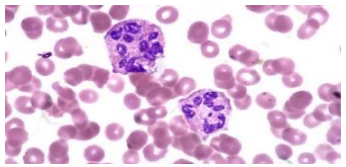
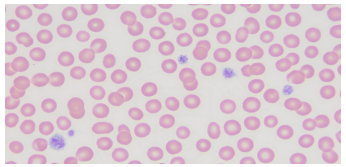




^residual genes: *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*

Bernard E, et al. *NEJM Evidence* 2022; 1:7

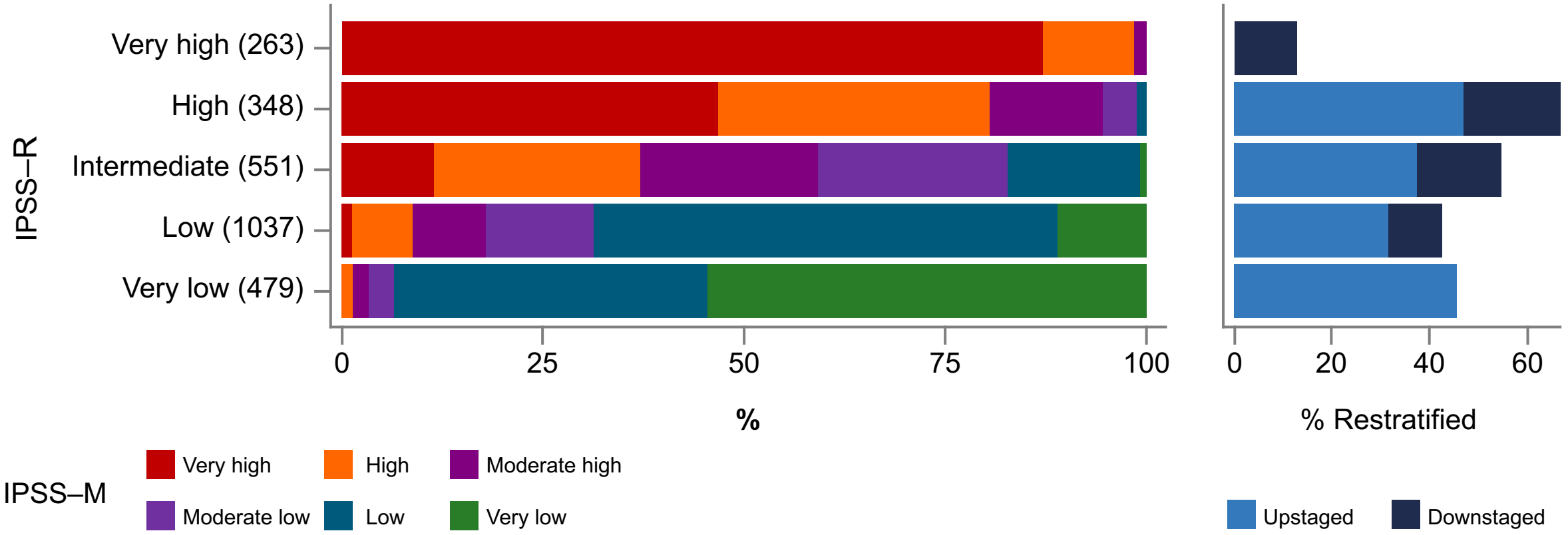
Risk stratification and clinical decisions in MDS – IPSS-M

Diagnosis[1]	Classification[1]	Incidence (%)[1]	Median OS (yrs)[1]	Progression risk (yrs)*,[1]	Treatment goal[2]	Current SoC[2]
	Very low *(Very low/low)*	14	10.6	2.8	Hematologic improvement (lower risk of infection & bleeding)	Transfusion ESAs Watch & wait
	Low *(Very low/low/int)*	33	6.0	5.1		
	Moderate low *(Low/int)*	11	4.6	11.4	?	
	Moderate high *(Low/int/high)*	11	2.8	18.9	Alter disease natural history (higher risk of infection & bleeding)	HMAs/ICT +/- ASCT
	High *(Int/high/very high)*	14	1.7	29.2		
	Very high *(High/very high)*	17	1.0	42.8		

* 4 years

1. Bernard E, *et al. NEJM Evid* 2022; **1**:7; 2. Fenaux P, *et al. Ann Oncol* 2021;**32:1**42–156.

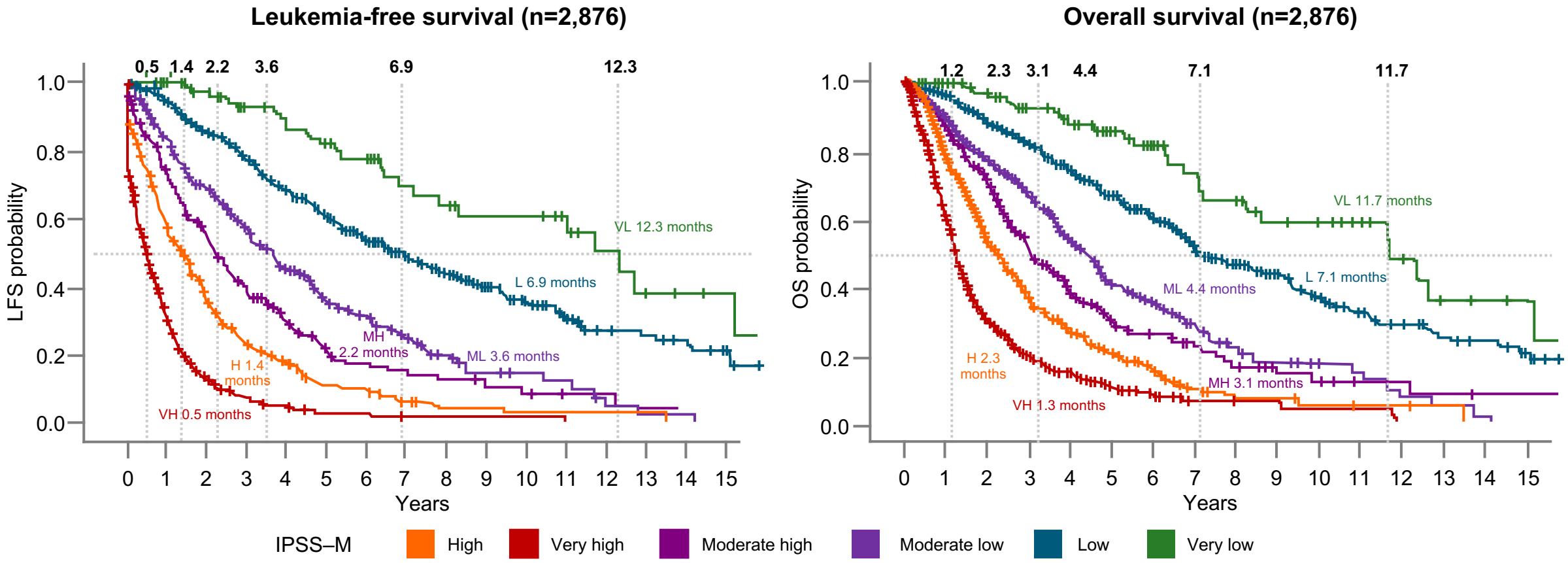
IPSS-M: Improves risk stratification of patients with MDS, providing a valuable tool for clinical decision making



Categorization by IPSS-M and restratified 46% of patients (n=1,223/2,678) and of these, 74% (n=911) were upstaged vs IPSS-R

Bernard E, *et al. NEJM Evid* 2022; **1**:7

IPSS-M improved discrimination of MDS vs IPSS-R Moffitt Cancer Center



IPSS-M improved discrimination of LFS, OS, and leukemic transformation vs IPSS-R with 2.3-, 2.0-, and 1.5-point increases in C-index

Aguirre et al, *et al. Blood* 2022; **140**(Suppl 1):1121–1124.

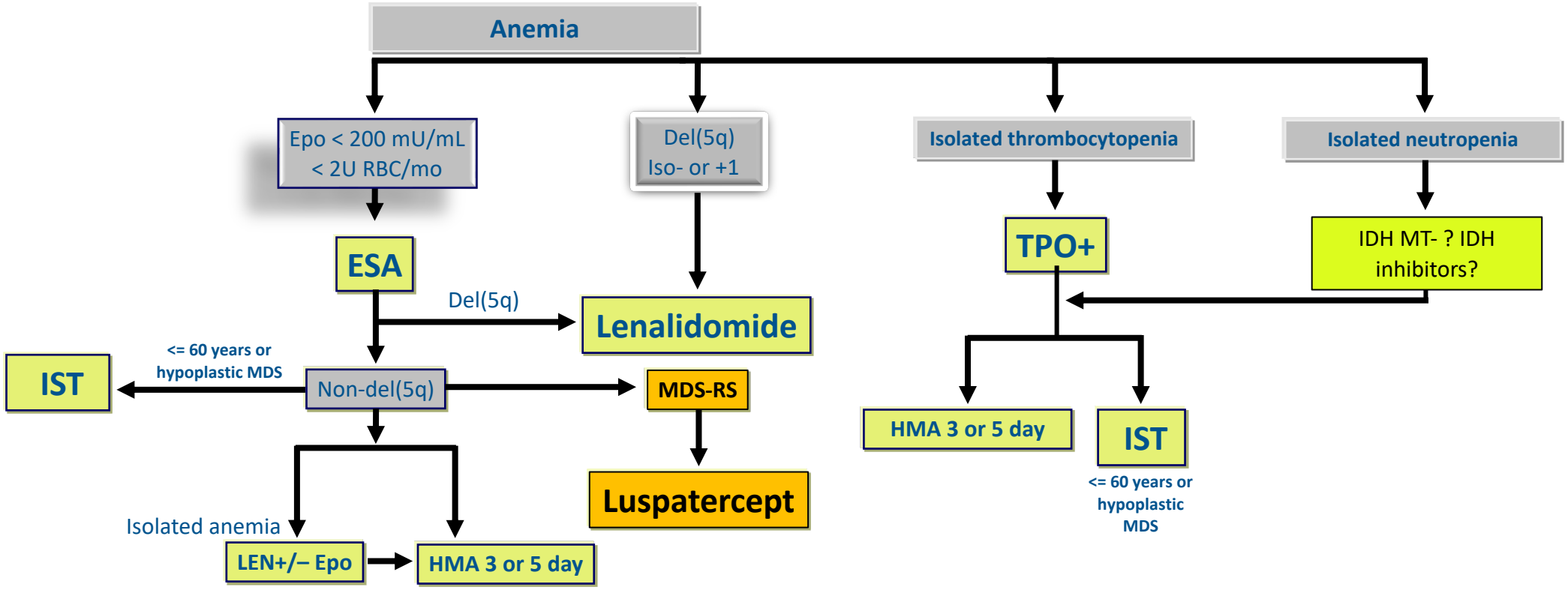
Natural History of LR-MDS

- LR-MDS conventionally defined as IPSS ≤ 1 or IPSS-R ≤ 3.5
- 2396 patients in European MDS Registry with IPSS ≤ 1
  - Median OS 4.7 years; most common causes of death were MDS/AML (20%), infection (18%), and cardiovascular disease (10%)
- Patterns of progression in 1914 patients with LR-MDS by IPSS-R at Moffitt
  - 68% remained LR, 17% LR→high-risk (HR), 7% LR→HR→AML, 9% LR→AML
- Reducing transfusion dependence is associated with improved QOL in LR-MDS & HR-MDS

Prognostic Score	Median OS (years)
IPSS	Low: 5.7 Int-1: 3.5
IPSS-R	Very low: 8.8 Low: 5.0 Int: 3.0
IPSS-M	Very low: 10.6 Low: 6.0 Moderate Low: 4.6

Greenberg et al, Blood 1997; Greenberg et al, 2012; Bernard, NEJM Evidence 2022; Pfeilstöcker et al, Blood 2016; Madry et al, BJH 2023; Jain et al, ASH 2021; Oliva et al, JCM 2022; Zeidner et al, Haematologica 2023

How Do I Manage LR-MDS in 2023



*SGM, somatic gene mutation.

- **Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features.**
- **Iron chelation should be considered in patients with evidence of iron overload.**

Adapted from Volpe VO, Komrokji RS. Ther Adv Hematol 2021;12:1-10.

Luspatercept versus epoetin alfa for treatment of anemia in ESA-naive lower-risk myelodysplastic syndromes patients requiring RBC transfusions: data from the phase 3 COMMANDS study

Matteo Giovanni Della Porta,[1,2] Uwe Platzbecker,[3] Valeria Santini,[4] Amer M. Zeidan,[5] Pierre Fenaux,[6] Rami S. Komrokji,[7] Jake Shortt,[8] David Valcarcel,[9] Anna Jonasova,[10] Sophie Dimicoli-Salazar,[11] Ing Soo Tiong,[12] Chien-Chin Lin,[13] Jiahui Li,[14] Jennie Zhang,[14] Ana Carolina Giuseppi,[14] Sandra Kreitz,[15] Veronika Pozharskaya,[14] Karen L. Keeperman,[14] Shelonitda Rose,[14] Jeevan K. Shetty,[15*] Sheida Hayati,[14] Sadanand Vodala,[14] Andrius Degulys,[16,17] Stefania Paolini,[18] Thomas Cluzeau,[19] Guillermo Garcia-Manero[20]

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*At the time of the study

EHA 2023, Presentation S102

The COMMANDS study

The COMMANDS study (NCT03682536) is a phase 3, global, open-label, randomized trial comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R LR-MDS in ESA-naive patients who require RBC transfusions

Key eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low, or intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2–6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

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

Randomized 1:1

Luspatercept (N = 178)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 178)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG criteria

Post-treatment safety follow-up

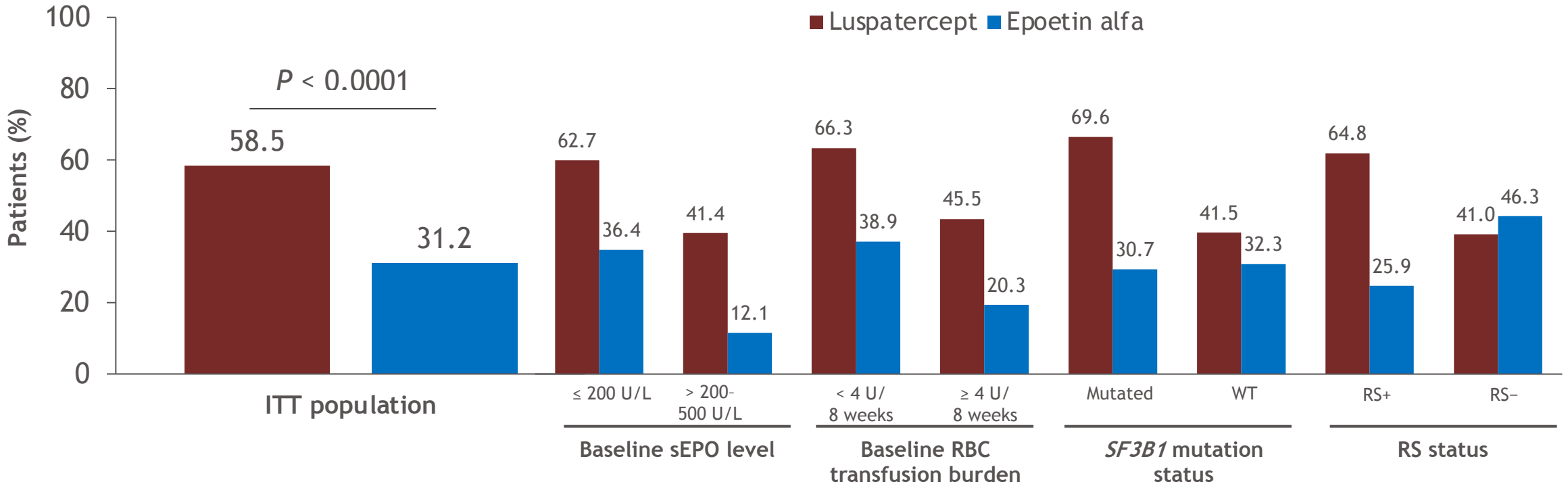
- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

[a]MDS with del(5q) were excluded. [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline; AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndromes; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

Primary endpoint: luspatercept superior to epoetin alfa

- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
  - Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed

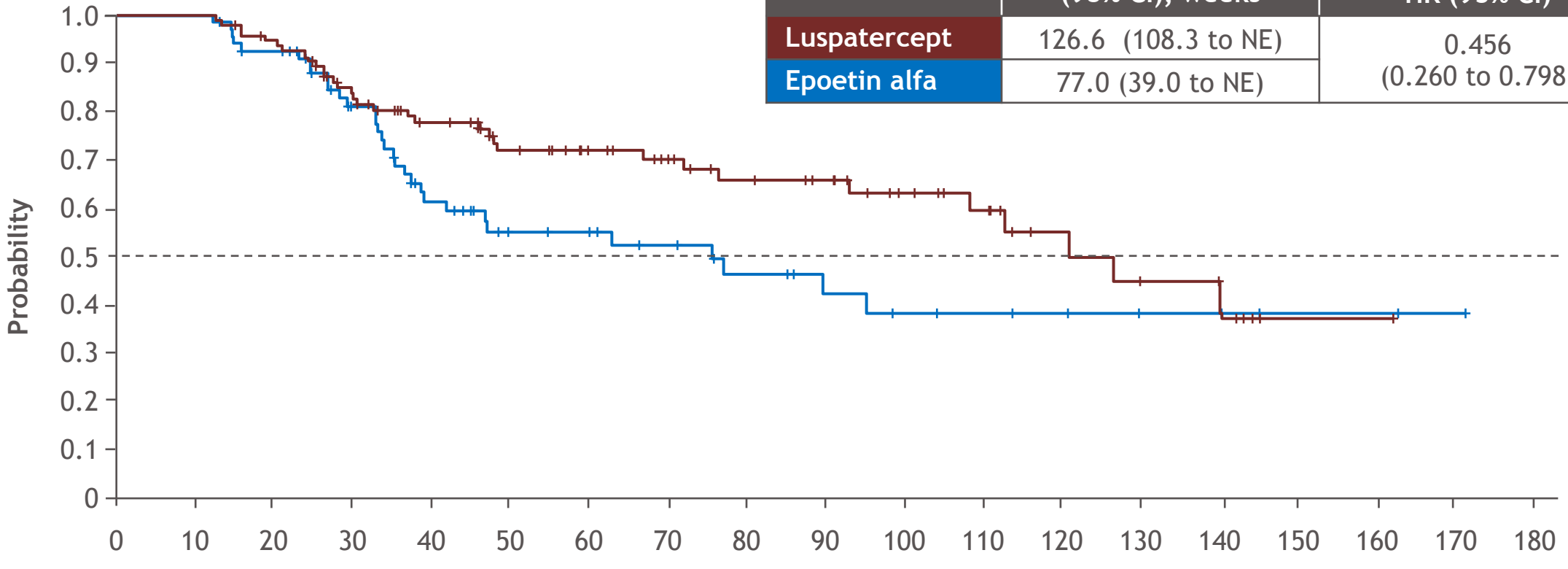


This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

Duration of RBC-TI ≥ 12 weeks[a] longer with luspatercept

	Median duration (95% CI), weeks	HR (95% CI)
Luspatercept	126.6 (108.3 to NE)	0.456 (0.260 to 0.798)
Epoetin alfa	77.0 (39.0 to NE)	



No. at risk																			
Luspatercept	98	98	91	74	61	49	42	37	31	28	21	17	11	8	6	1	1	0	
Epoetin alfa	71	71	63	47	33	24	23	19	15	11	9	8	7	5	5	2	2	1	0

EOT, end of treatment; NE, not estimable; RBC-TI, red blood cell transfusion independence.
[a]In ITT responders during weeks 1–EOT.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

CONTINUOUS TRANSFUSION INDEPENDENCE WITH IMETELSTAT IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS STIMULATING AGENTS IN IMERGE PHASE 3

Uwe Platzbecker,[1] Valeria Santini,[2] Pierre Fenaux,[3] Mikkael A. Sekeres,[4] Michael Robert Savona,[5] Yazan F. Madanat,[6] Maria Diez-Campelo,[7] David Valcárcel-Ferreiras,[8] Thomas Illmer,[9] Anna Jonášová,[10] Petra Bělohlávková,[11] Laurie Sherman,[12] Tymara Berry,[12] Souria Dougherty,[12] Sheetal Shah,[12] Qi Xia,[12] Lixian Peng,[12] Libo Sun,[12] Ying Wan,[12] Fei Huang,[12] Annat Ikin,[12] Shyamala Navada,[12] Rami S. Komrokji,[13] Amer M. Zeidan[14]

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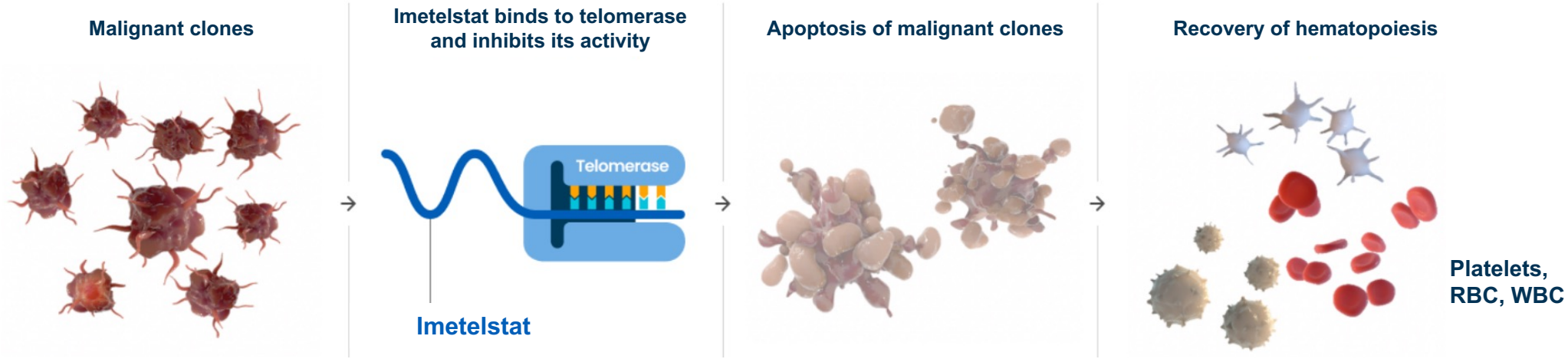
09/06/2023

Session: s417 MPN and MDS Targeting red cells and platelets

Imetelstat in Lower Risk MDS



- Imetelstat is a first-in class direct and competitive inhibitor of telomerase activity that specifically targets malignant clones with abnormally high telomerase activity, enabling recovery of effective hematopoiesis[1-4]
- In the phase 2 part of the IMerge study (NCT02598661), patients with LR-MDS who were heavily RBC transfusion dependent, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA achieved durable and continuous RBC-TI when treated with imetelstat[5]
  - Specifically, 8-week RBC-TI rates were 42% with a median TI duration of 86 weeks
- This analysis reports phase 3 results from IMerge in the same patient population

ESA, erythropoiesis stimulating agent; HMA, hypomethylating agent; LR-MDS, lower risk myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388.
5. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56.

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:

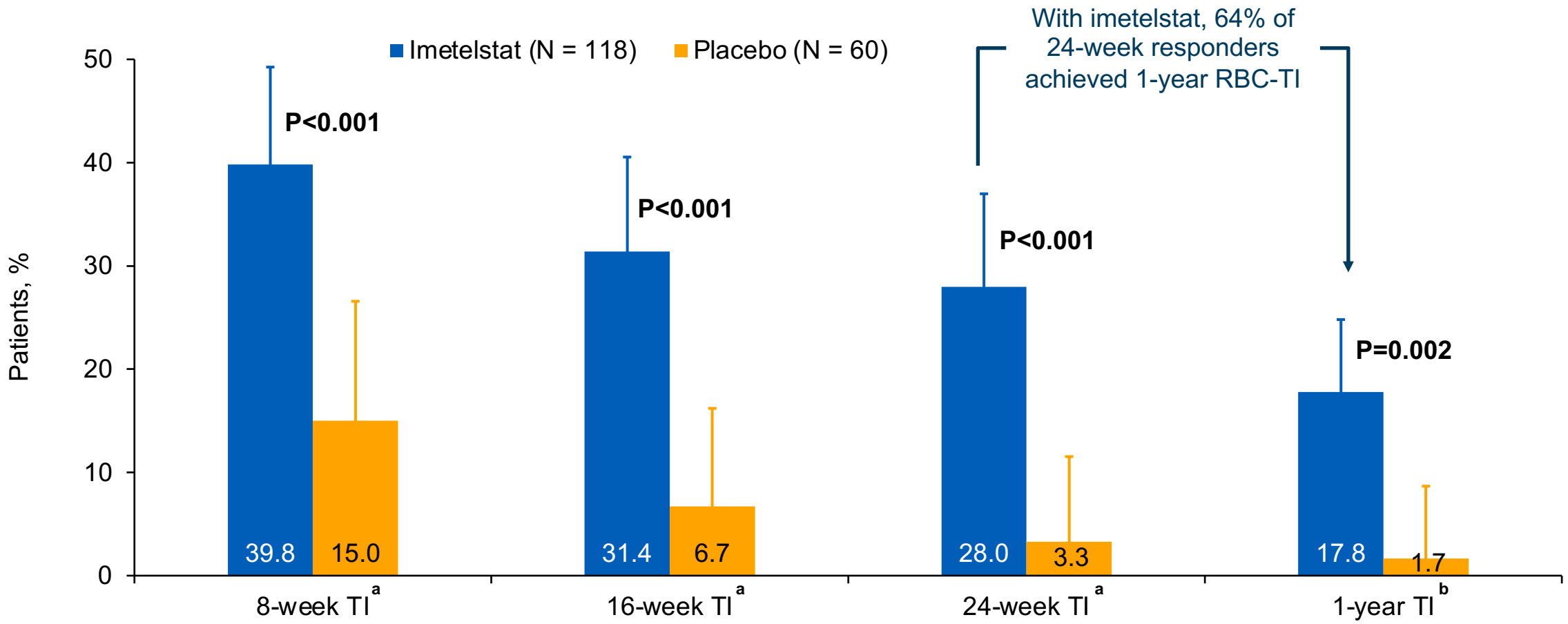
- 24-week RBC-TI[b]
- Duration of TI
- Hematologic improvement-erythroid
- Safety

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.

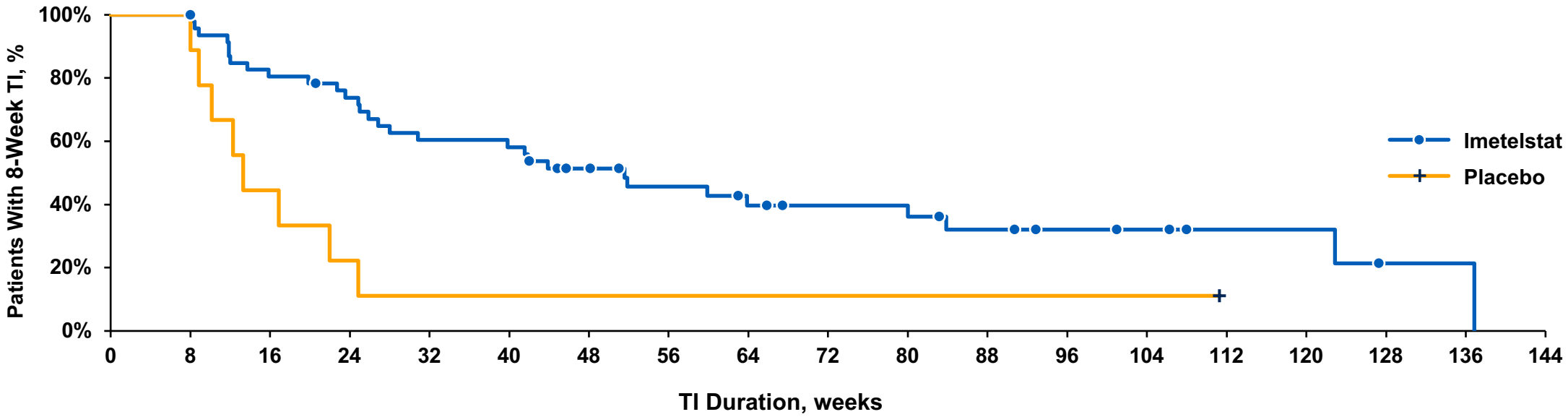
Higher Rates of Longer-Term Duration of RBC TI Observed With Imetelstat vs Placebo, Including 1-year RBC TI With Additional 3 Month Follow-up



[a]Data cutoff: October 13, 2022. [b]Data cutoff: January 13, 2023.
P-values were determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs. >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline International Prognostic Scoring System risk category (low vs. intermediate-1) applied to randomization.
RBC, red blood cell; TI, transfusion independence.

Imetelstat 8-Week RBC-TI Responders Have Significantly Longer Duration of Transfusion Independence vs Placebo

8-Week TI Responders	Imetelstat (N = 47)	Placebo (N = 9)	HRa (95%CI)	P-Value
Median duration of RBC-TI, weeks (95% CI)	51.6 (26.9–83.9)	13.3 (8.0–24.9)	0.23 (0.09–0.57)	<0.001



Patients, N																			
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

Data cutoff: October 13, 2022.

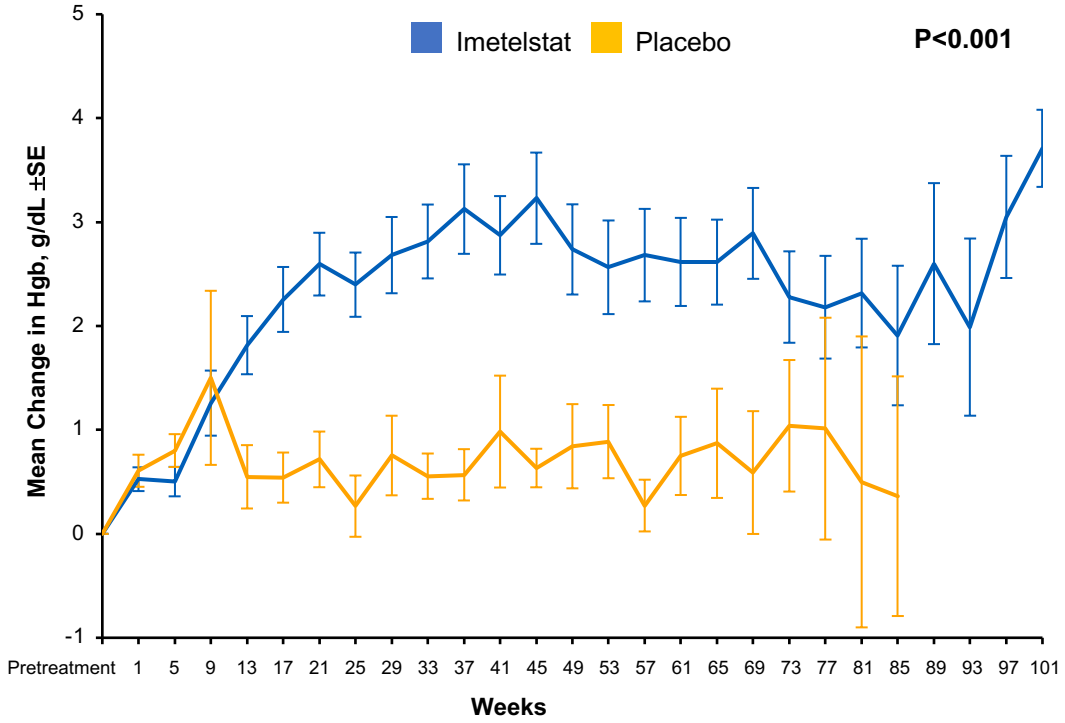
[a]HR (95% CI) from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. [b]P value (2-sided) for superiority of imetelstat vs placebo in HR based on stratified log-rank test.

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

Significant and Sustained Increase in Hemoglobin Among Patients Treated With Imetelstat

8-Week TI Responders[a]	Imetelstat (N = 47)	Placebo (N = 9)
Median Hgb rise, g/dL (range)	3.6 (−0.1 to 13.8)	0.8 (−0.2 to 1.7)
Median Hgb peak, g/dL (range)	11.3 (8.0–21.9)	8.9 (7.9–9.7)

Mean Change in Hgb Over Time[b]



Patients, N

Imetelstat	118	59	53	54	47	42	48	48	43	43	31	37	31	35	32	25	26	24	23	21	19	18	11	11	9	9	5
Placebo	60	37	29	17	16	18	15	8	10	10	11	7	3	9	8	9	7	7	5	5	4	2	4				

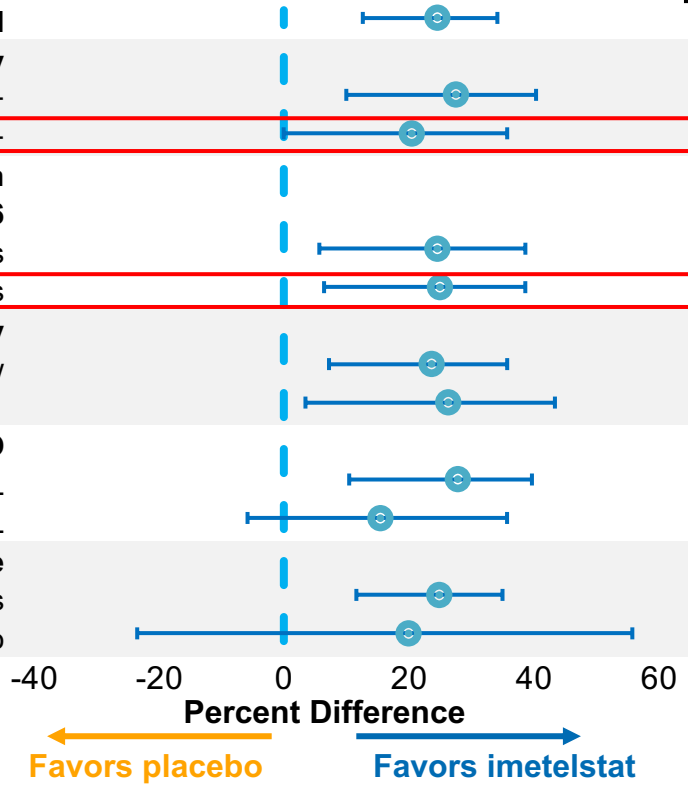
Data cutoff: October 13, 2022.

[a]Among patients achieving 8-week TI, analysis performed during TI. Hgb rise is defined as the maximum Hgb value in the longest TI interval excluding the first 2 weeks minus the pretreatment Hgb level. [b]Mean changes from the minimum Hgb of the values that were after 14 days of transfusions in the 8 weeks prior to the first dose date are shown. P-value based on a mixed model for repeated measures with Hgb change as the dependent variable, week, stratification factors, minimum Hgb in the 8 weeks prior to the first dose date, treatment group, and treatment and week interaction term as the independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

Hgb, hemoglobin; RBC, red blood cell; SE, standard error; TI, transfusion independence.

Comparable 24-Week RBC TI Rate Across Key LR-MDS Subgroups

	Imetelstat, n/N (%)	Placebo, n/N (%)	% Difference (95% CI)	P-value
Overall	33/118 (28.0)	2/60 (3.3)	24.6 (12.64–34.18)	**<0.001**
WHO category				
RS+	24/73 (32.9)	2/37 (5.4)	27.5 (10.00–40.37)	**0.003**
RS−	9/44 (20.5)	0/23 (0.0)	20.5 (−0.03–35.75)	**0.019**
Prior RBC transfusion burden per IWG 2006				
4–6 units / 8 weeks	19/62 (30.6)	2/33 (6.1)	24.6 (5.68–38.66)	**0.006**
>6 units / 8 weeks	14/56 (25.0)	0/27 (0)	25.0 (6.44–38.65)	**0.012**
IPSS risk category				
Low	23/80 (28.8)	2/39 (5.1)	23.6 (7.23–35.75)	**0.003**
Intermediate-1	10/38 (26.3)	0/21 (0)	26.3 (3.46–43.39)	**0.009**
Baseline sEPO				
≤500 mU/mL	29/87 (33.3)	2/36 (5.6)	27.8 (10.46–39.71)	**0.002**
>500 mU/mL	4/26 (15.4)	0/22 (0)	15.4 (−5.81–35.73)	**0.050**
Prior ESA use				
Yes	31/108 (28.7)	2/52 (3.8)	24.9 (11.61–35.00)	**<0.001**
No	2/10 (20)	0/8	20.0 (-23.47–55.78)	0.225



- Similar trends were observed across subgroups for 8-week RBC TI rates

Data cutoff: October 13, 2022.
P-values were determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs. intermediate-1) applied to randomization.
IPSS, International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TI, transfusion independence.

Consistent With Prior Clinical Experience, the Most Common AEs Were Hematologic

- Grade 3–4 thrombocytopenia and neutropenia were the most frequently reported AEs, most often reported during Cycles 1–3
  - There were no fatal hematologic AEs
- Nonhematologic AEs were generally low grade
- No cases of Hy's Law or drug-induced liver injury observed
  - The incidence of grade 3 liver function test laboratory abnormalities was similar in both treatment groups

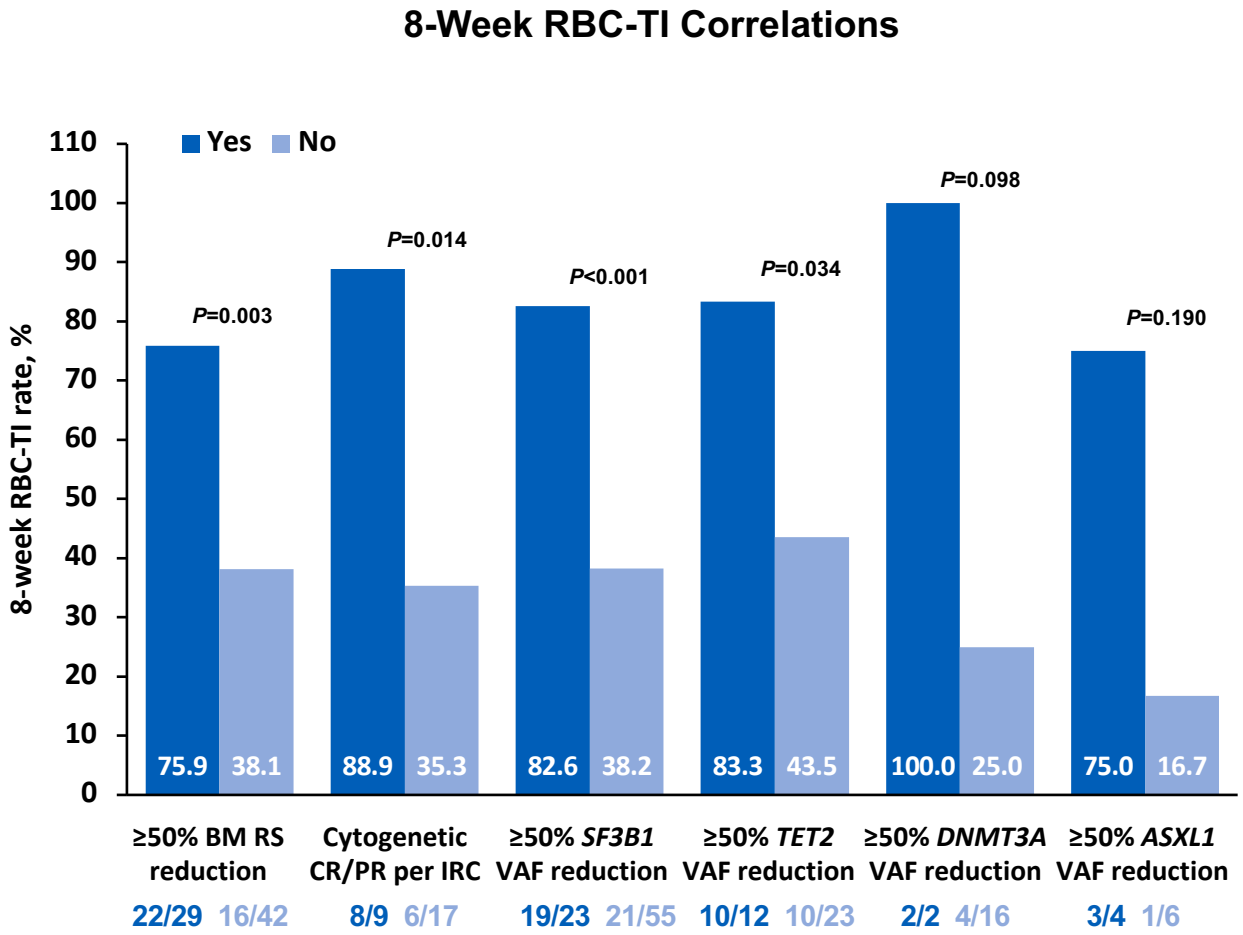
AE (≥10% of patients), n (%)	Imetelstat (N = 118)		Placebo (N = 59)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Thrombocytopenia	89 (75)	73 (62)	6 (10)	5 (8)
Neutropenia	87 (74)	80 (68)	4 (7)	2 (3)
Anemia	24 (20)	23 (19)	6 (10)	4 (7)
Leukopenia	12 (10)	9 (8)	1 (2)	0
Other				
Asthenia	22 (19)	0	8 (14)	0
COVID-19	22 (19)[a]	2 (2)[b]	8 (14)[a]	3 (5)[b]
Headache	15 (13)	1 (1)	3 (5)	0
Diarrhea	14 (12)	1 (1)	7 (12)	1 (2)
ALT increased	14 (12)	3 (3)	4 (7)	2 (3)
Edema peripheral	13 (11)	0	8 (14)	0
Hyperbilirubinemia	11 (9)	1 (1)	6 (10)	1 (2)
Pyrexia	9 (8)	2 (2)	7 (12)	0
Constipation	9 (8)	0	7 (12)	0

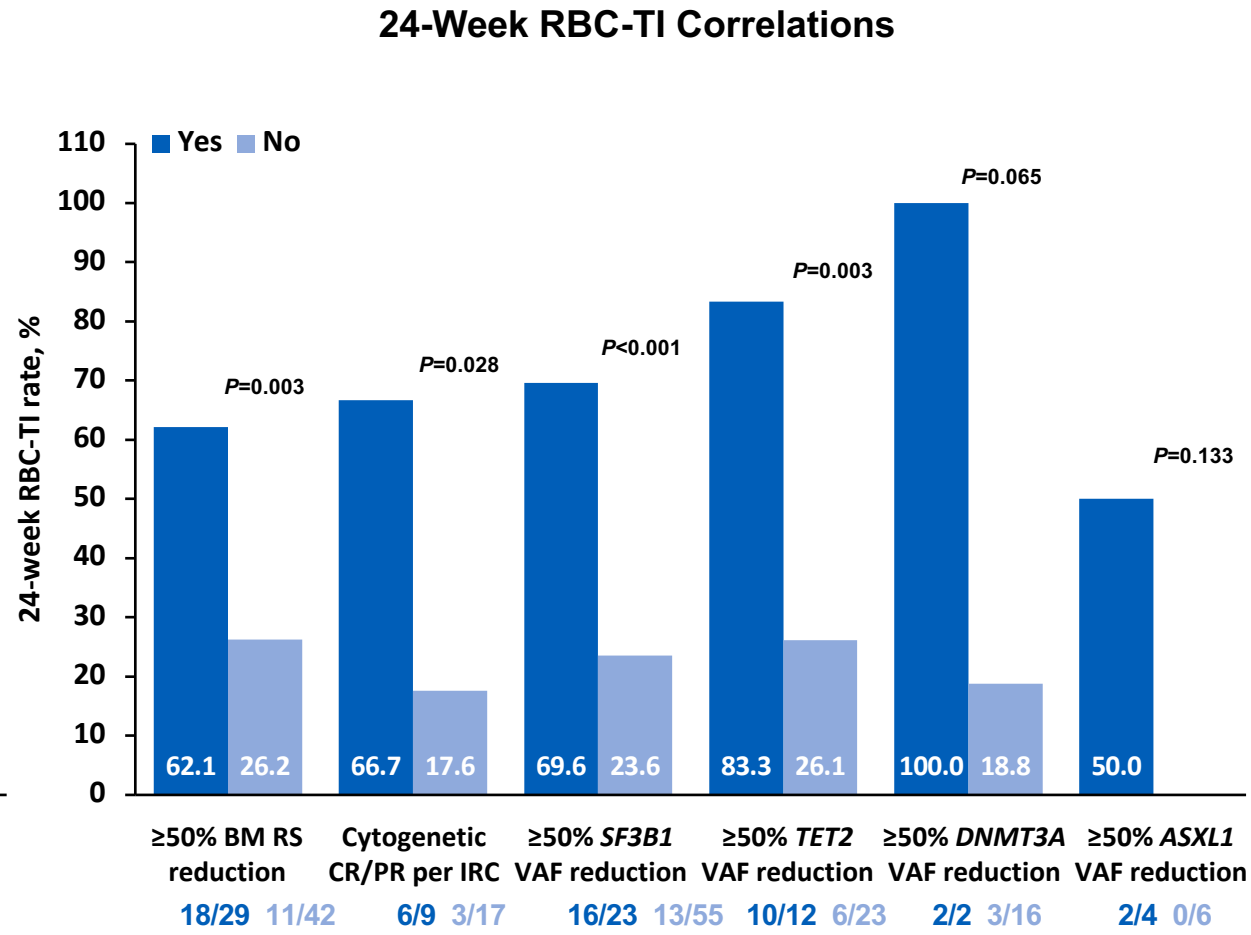
Data cutoff: October 13, 2022.

[a]Included COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. [b]Only COVID-19 pneumonia events were grade 3–4 COVID-19.

AE, adverse event; ALT, alanine aminotransferase.

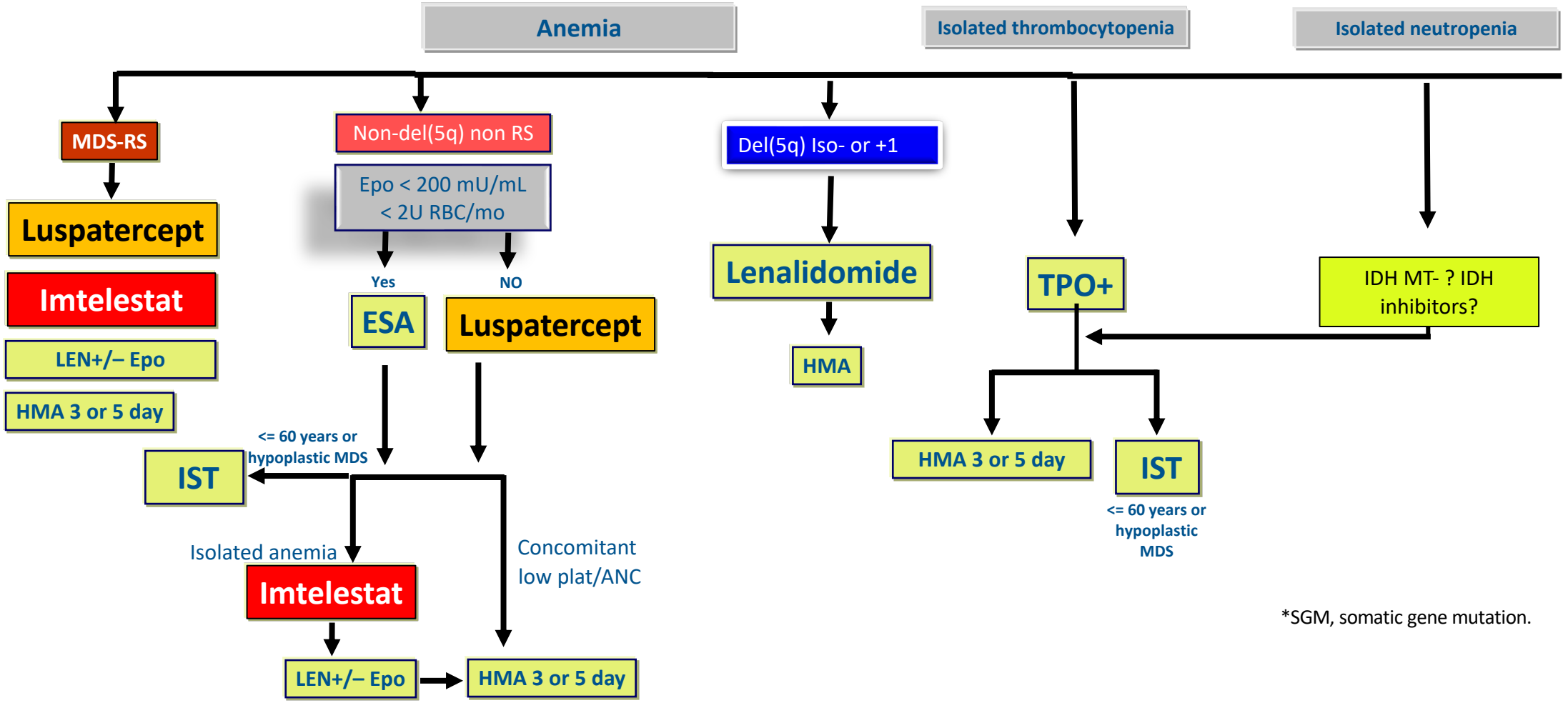
8-Week and 24-Week RBC-TI Correlated With Reduction in RS+ Cells, Cytogenetic Responses, and VAF Reduction in Patients Treated With Imetelstat





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.

How Do I Manage LR-MDS in 2024



*SGM, somatic gene mutation.

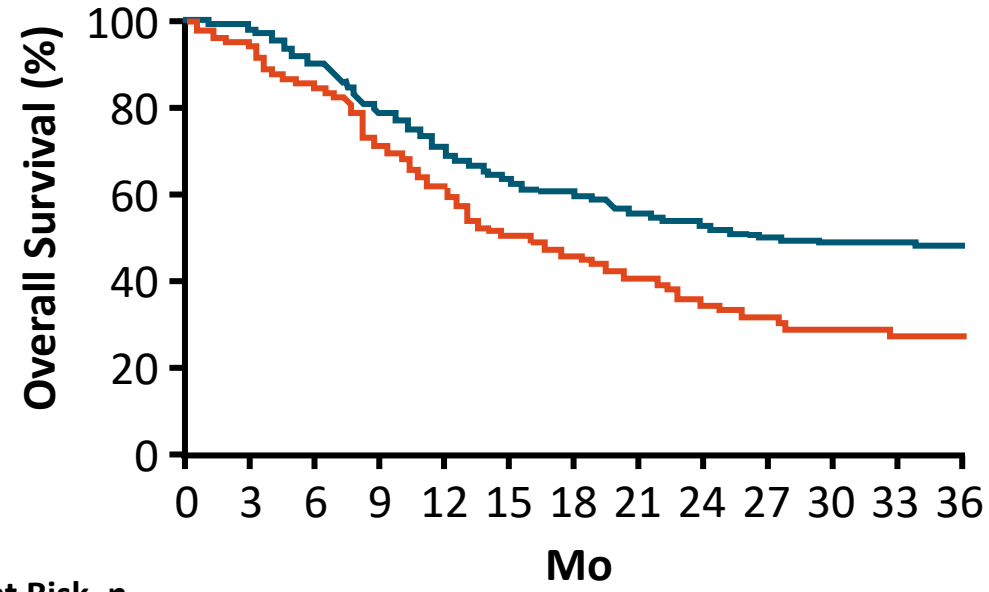
- **Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features by IPSS-M.**
- **Iron chelation should be considered in patients with evidence of iron overload.**

Adapted from Volpe VO, Komrokji RS. Ther Adv Hematol 2021;12:1-10.

BMT CTN 1102: RIC Plus Allo-HSCT vs BSC in Older Patients With Higher-Risk MDS

Overall Survival

	Donor	No Donor
3-yr estimate, %	47.9	26.6
95% CI	41.3-54.1	18.4-35.6

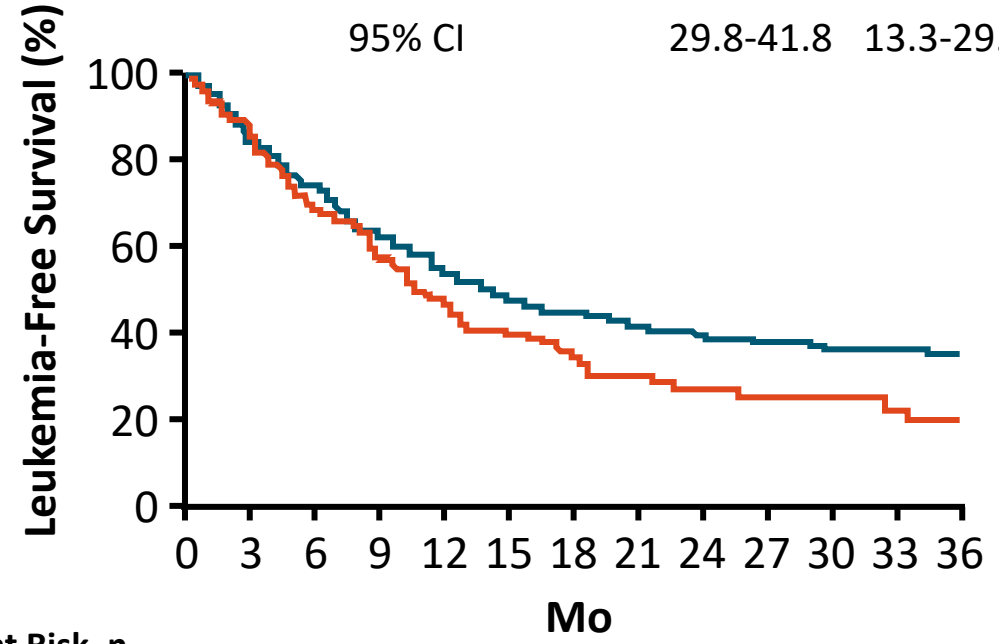


Patients at Risk, n

Donor	260	253	233	201	176	155	129	117	102	86	76	72	27
No donor	124	116	103	84	71	56	49	40	30	22	15	14	7

Leukemia-Free Survival

	Donor	No Donor
3-yr estimate, %	35.8	20.6
95% CI	29.8-41.8	13.3-29.1

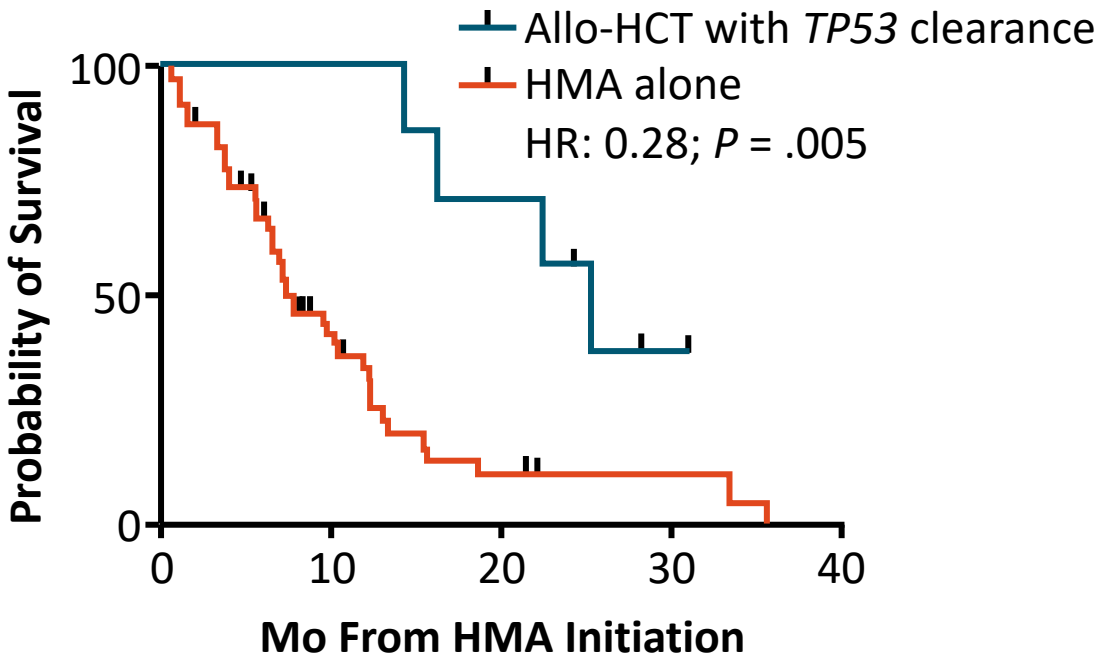


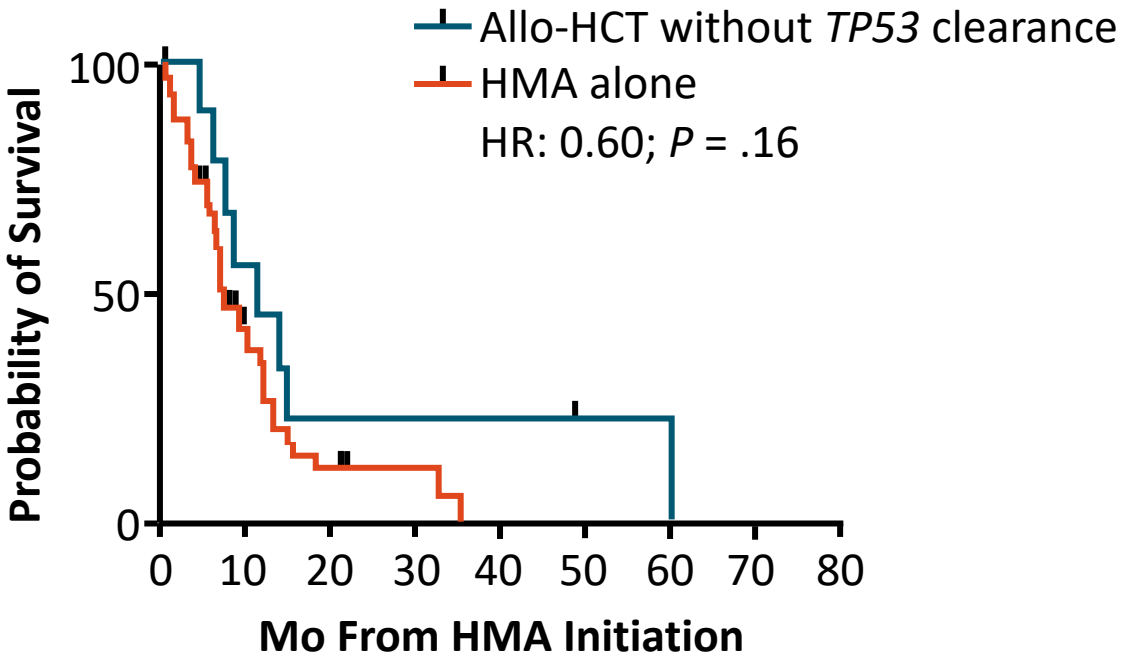
Patients at Risk, n

Donor	260	219	192	160	135	119	97	88	76	66	58	56	22
No donor	124	106	83	68	56	44	37	29	24	18	14	12	5

Nakamura. JCO. 2021;39: 3328.

Baseline and Serial Molecular Profiling Predicts Outcomes With HMAs in MDS





Proposed treatment algorithm for *TP53* mutated MDS:

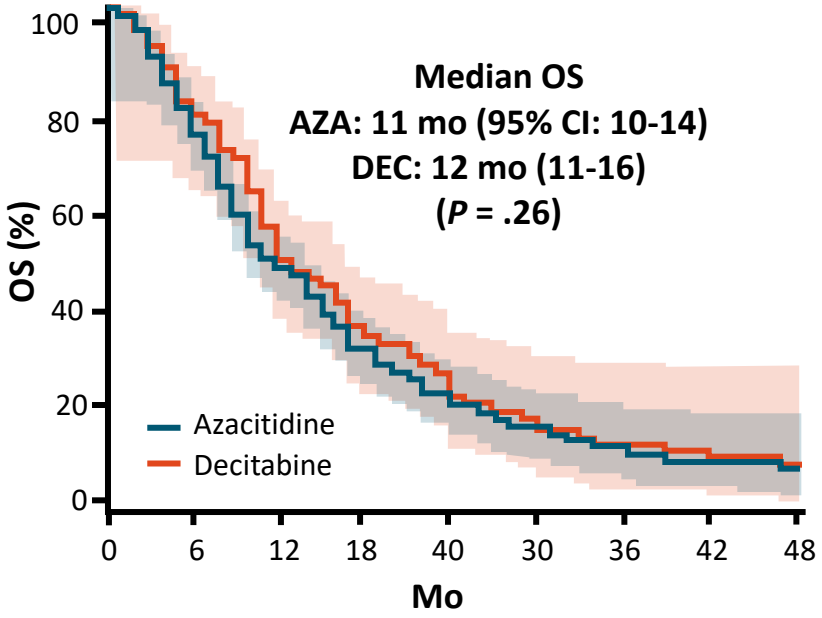
TP53 mutated, higher-risk MDS → Frontline therapy with a hypomethylating agent → Serial next generation sequencing to assess molecular response

- Clearance of *TP53* mutation → Proceed to allogeneic transplant (if candidate)
- Persistent *TP53* mutation detected → Clinical trial evaluating novel therapy

Hunter. Blood Adv. 2021;5:1017.

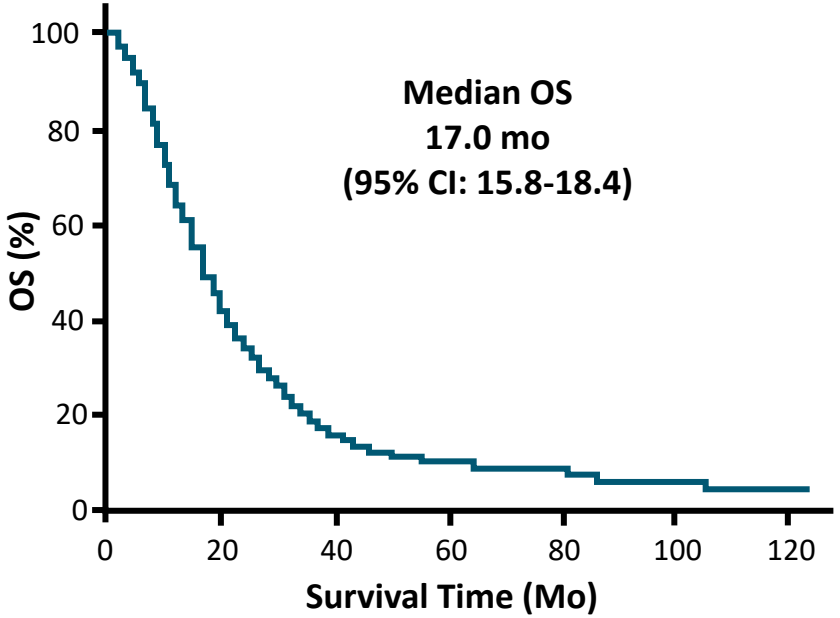
Survival of Patients With HR-MDS Remains Poor Despite Use of HMAs

OS: AZA vs DEC



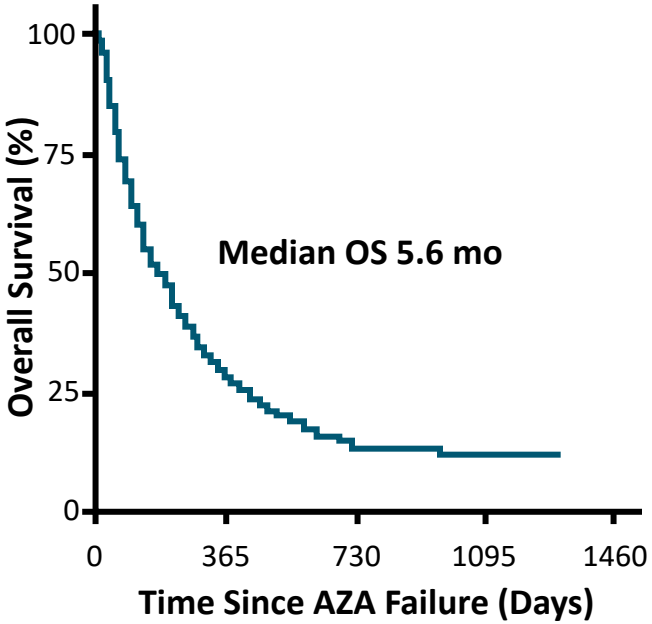
532 patients ≥66 yr at diagnosis who received ≥10 days of HMA therapy

OS: Median 5 Cycles HMA



636 HR-MDS of all ages in the MDS Clinical Research Consortium who received HMA (median 5 cycles), 72% received ≥4 cycles. 68% received AZA.

OS: Post-AZA Failure



Survival post-AZA failure for patients with HR-MDS

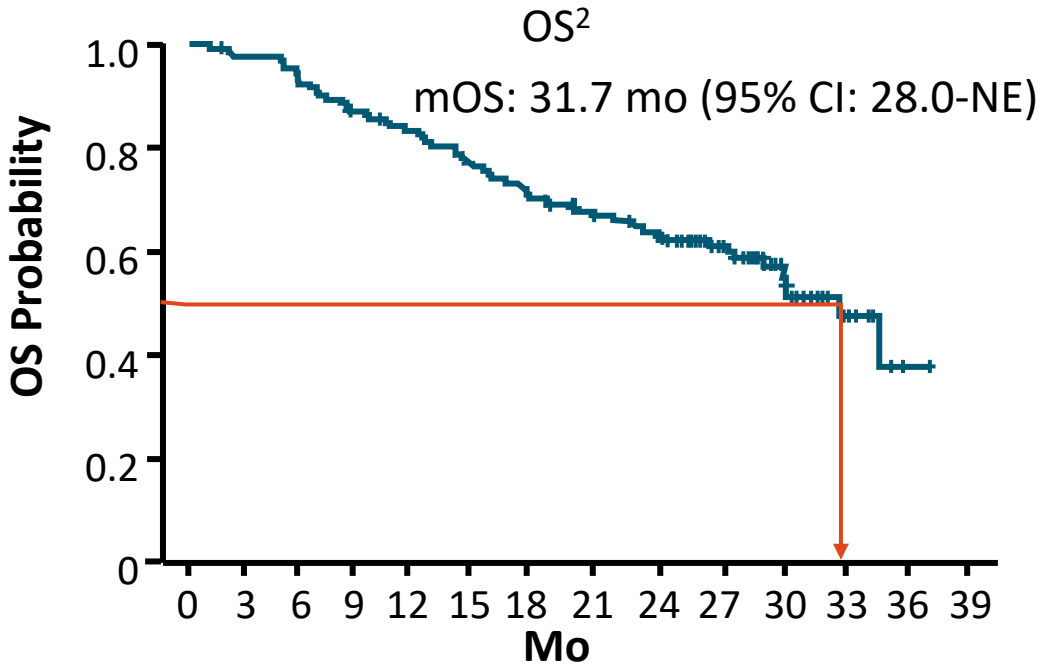
Zeidan. Br J Haematol. 2016;175:829. Zeidan. Leukemia. 2016;30:649. Prebet. JCO. 2011;29:3322.

ASCERTAIN: Update on Efficacy and Safety of Oral Decitabine/Cedazuridine in Patients With MDS and CMML

Response Category[1,2]	Treated Patients (N = 133)
CR, n (%)	29 (22)
PR, n (%)	0
mCR, n (%)	43 (32.3)
▪ mCR with HI	22 (16.5)
HI, n (%)	10 (7.5)
▪ HI-erythroid	2 (1.5)
▪ HI-neutrophils	1 (0.8)
▪ HI-platelet	7 (5.3)
Overall response (CR + PR + mCR + HI), n (%)	82 (61.7)
RBC transfusion independence, n/N (%)*	27/53 (51)
Platelet transfusion independence, n/N (%)*	6/12 (50)

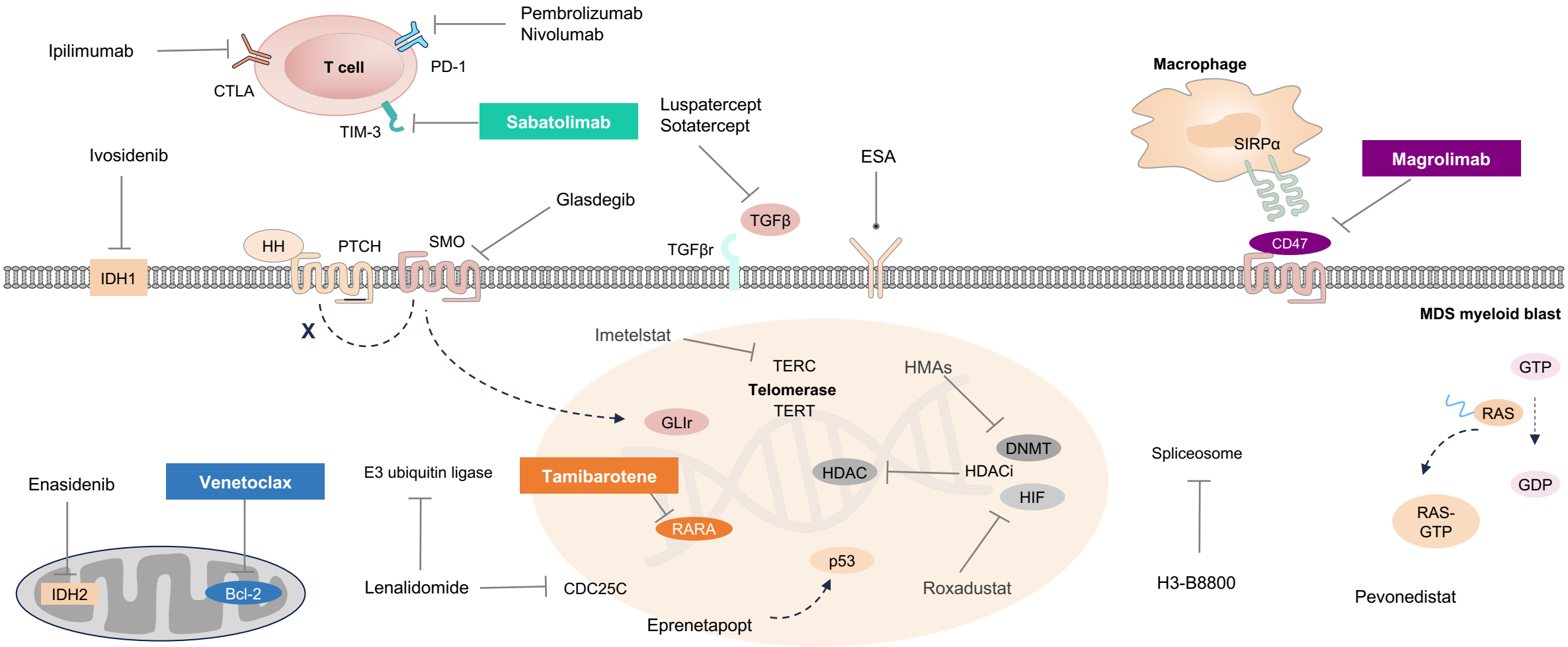
*# patients TI/# patients TD at baseline.

- Median CR duration: 14.0 mo (range: 2-29)
- Median duration of best response: 12.7 mo (range: 1-33)
- Number of patients proceeding to HCT: 34 (26%)
- Leukemia-free survival: 29.1 mo (95% CI: 22.1-NE)



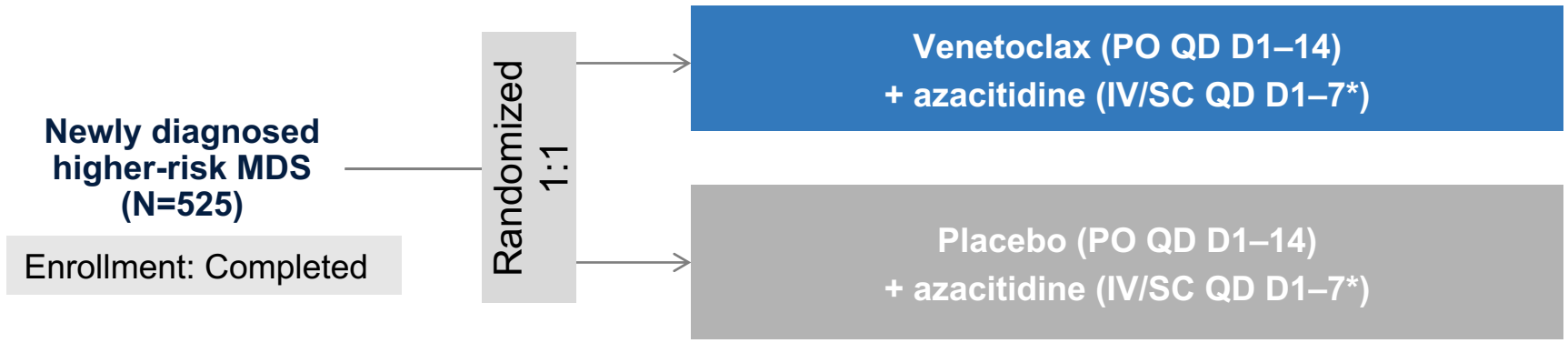
1. Savona. ASH 2020. Abstr 1230. 2. Savona. MDS 2021. Abstr P48.

Novel MoA of late phase therapies for higher-risk MDS



Adapted from Pagliuca S, *et al. Cancers* 2021; **13**:784

VERONA: Phase 3 study of Ven+Aza in higher-risk MDS



Key inclusion criteria

- ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
- <20% BM blasts
- ECOG PS 0–2
- IPSS-R score of >3 (Intermediate, high, very high)
- No planned HSCT at the time of C1D1

Primary endpoints

- CR
- OS

Secondary endpoints

- Modified overall response (mOR)
- Transfusion independence (TI)
- ORR
- QoL

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04401748 (accessed June 2023)

Venetoclax and HMA in Higher-Risk MDS: Efficacy of First-line Therapy

Best Response, %	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
ORR	77	40	<.005
▪ CR	34	13	
▪ mCR	37 (62 + HI)	11	
▪ PR	3	1	
▪ HI	3	15	
***ASXL-1* mut**	**(n = 16)**	**(n = 106)**	
ORR	87	32	<.005
▪ CR	44	8	
***TP53* mut**	**(n = 12)**	**(n = 137)**	
ORR	75	44	.038
▪ CR	25	17	.47

Outcome	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
Median OS, mo			
▪ From diagnosis (95% CI)	21 (11-32)	20 (19-22)	.86
▪ From start of treatment*	19.4	17.2	.88
AML transformation, %	23	37	.08
AHSCT cohort†	**(n = 13)**	**(n = 256)**	
Median OS, mo (95% CI)	NR	38 (27-50)	.20
2-yr OS, %	91	51	

*Median time from diagnosis to treatment was 1 mo in both arms.
†Patients who went on to AHCST.

Oral decitabine/cedazuridine + venetoclax in 1L HR MDS or CMML

Key eligibility criteria

- ≥ 18 years of age
- IPSS intermediate 2 or high risk
- WHO 2016, with > 5% blasts in bone marrow
- Treatment-naive MDS or CMML

Phase 1: dose escalation
3 pts ASTX727 100/35mg day 1-5 + VEN 200mg 1-14

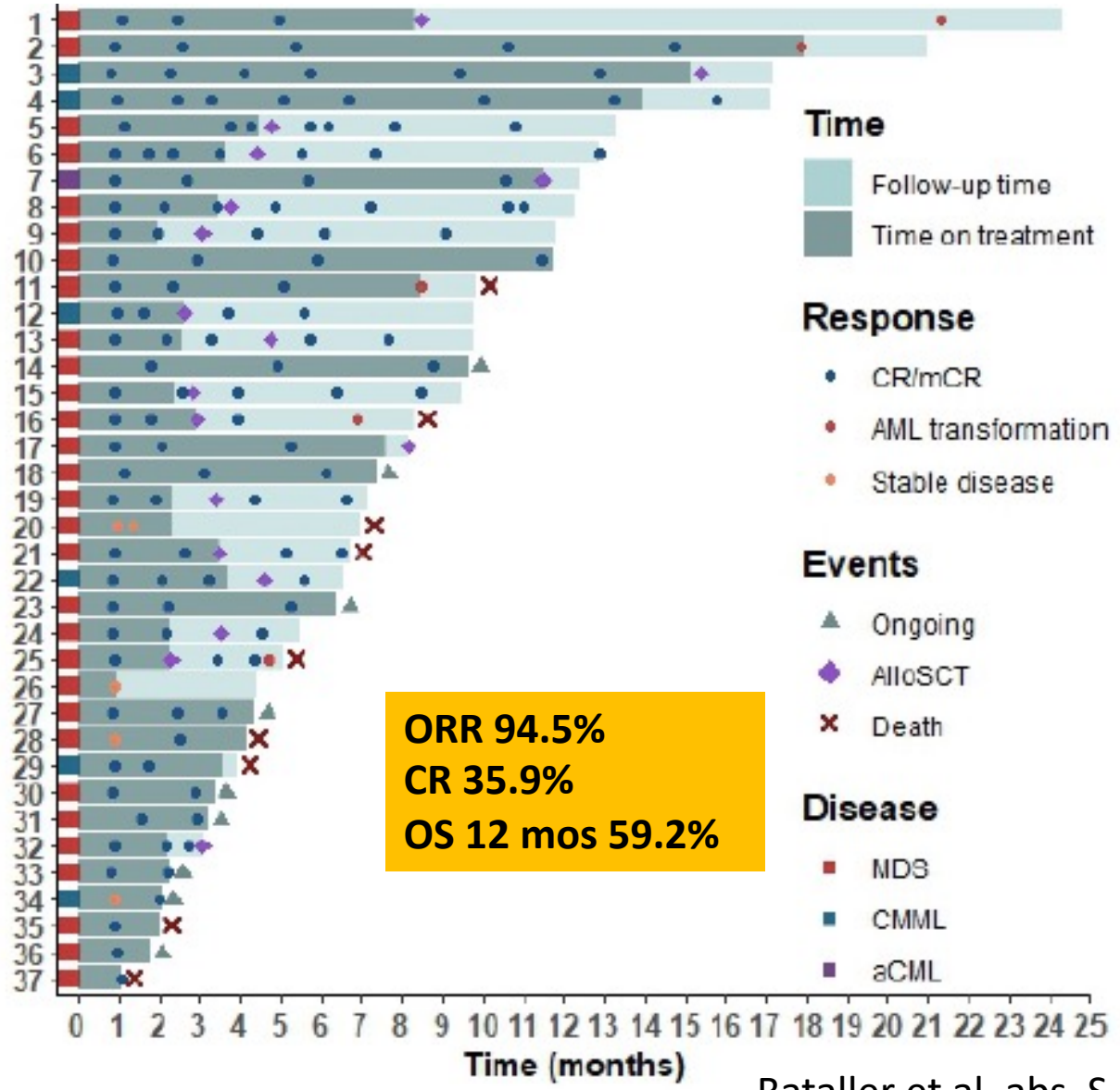
6 pts ASTX727 100/35mg day 1-5 + VEN 400mg 1-14

Phase 2: dose expansion

28 pts ASTX727 100/35mg day 1-5 + VEN 400mg 1-14

ORR

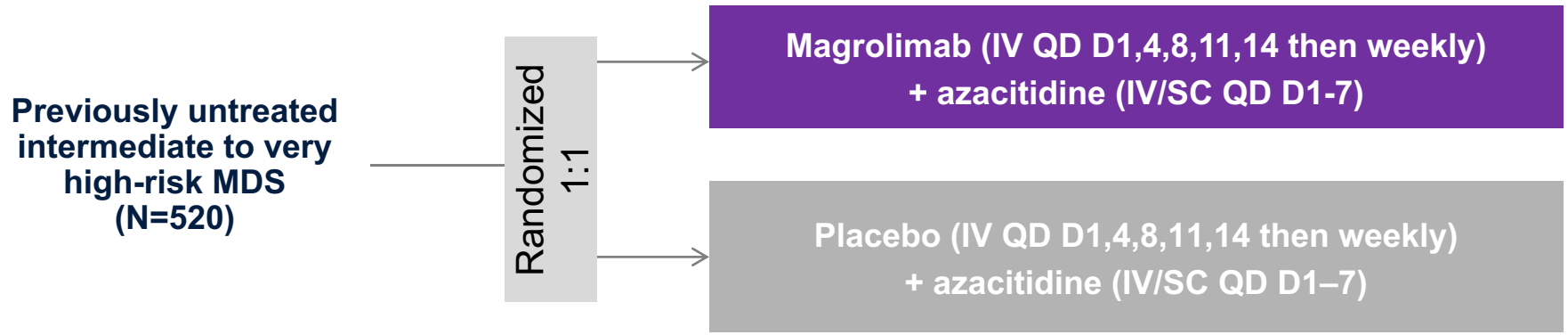
Median age 71 yrs
MDS EB2 65%, CMML 2 16%
IPSS-M very high 68.7%
mTP53 20%. 7/8 multiallelic
Median n cycles 2
Median Time to response 1 cycle



ORR 94.5%
CR 35.9%
OS 12 mos 59.2%

Bataller et al, abs S 172

ENHANCE: Phase 3 study of Magro+Aza in higher-risk MDS



Key inclusion criteria

- ≥18 years old with diagnosed intermediate to high-risk MDS according to 2016 WHO classification
- Adequate performance status and hematologic, liver, and kidney function

Key exclusion criteria

- Immediate eligibility for alloSCT

Primary endpoints

- CR
- OS

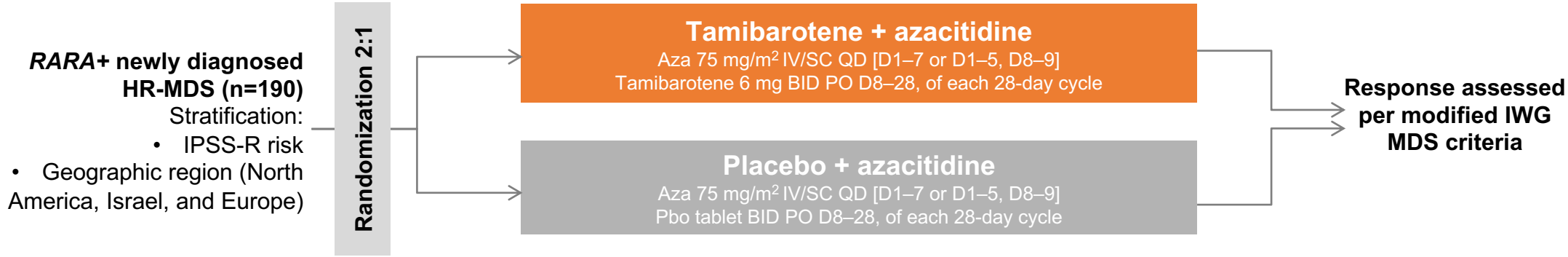
Key secondary endpoints

- Duration of CR
- ORR
- DoR
- RBC TI rate

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04313881 (accessed April 2023)

Tamibarotene + Aza vs Pbo+Aza

Phase 3, double-blind, randomized trial in patients with *RARA+* newly diagnosed HR-MDS



Key inclusion criteria

- Adults ≥18 years old
- *RARA*+ based on the investigational biomarker test
- Newly diagnosed with HR-MDS by 2016 WHO classification and classified by IPSS-R as very high, high, or intermediate risk
- Blast count >5% at study entry

Key exclusion criteria

- Patients suitable for transplant at the time of screening

Primary endpoint

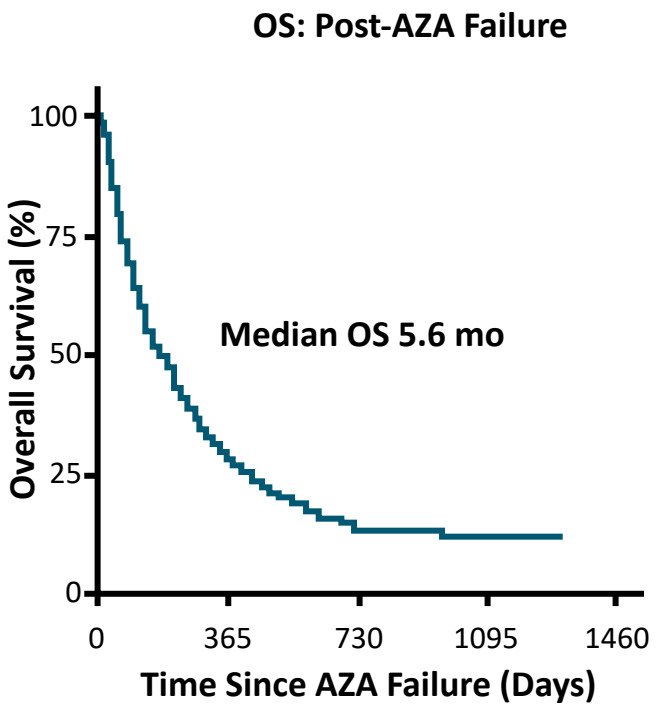
- Proportion of participants with CR [Timeframe: up to 5 years]

Key secondary endpoints

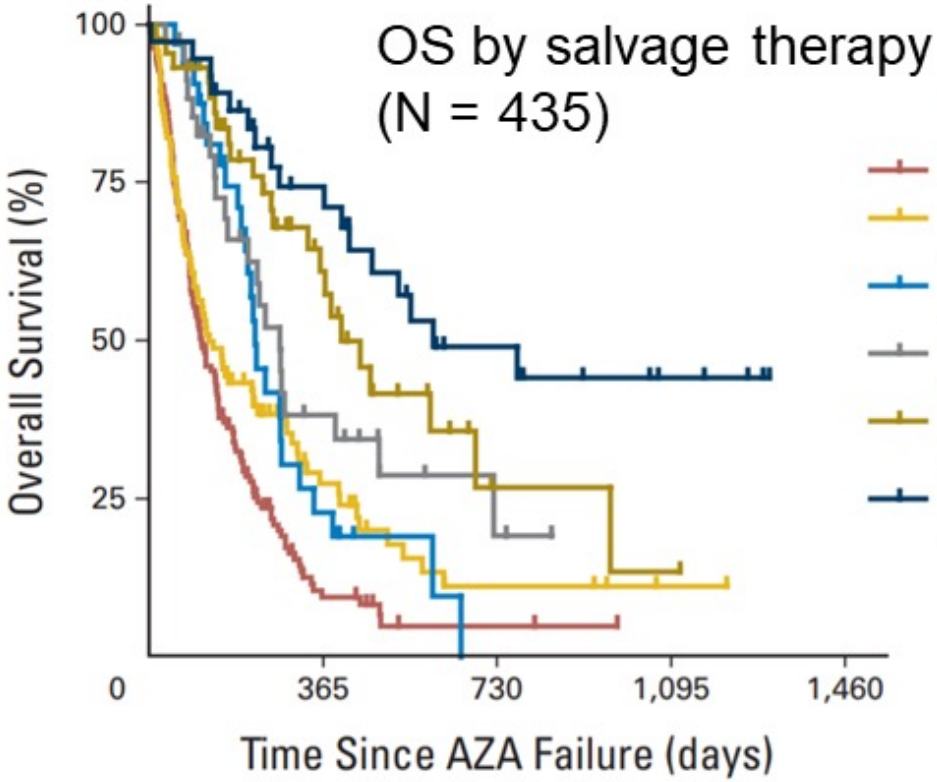
- ORR
- EFS, OS
- Transfusion independence

Adapted from Dezern AE, *et al. J Clin Oncol* 2022; 40(Suppl):TPS7075 (Poster)

AlloSCT and Investigational Agents Best Salvage Therapy for Patients With HR MDS After HMA Failure



Survival post-AZA failure for patients with HR-MDS



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Prebet. JCO. 2011;29:3322.

Treatment Options in MDS After HMA Failure

- Add additional agent to HMA
- Intensive chemotherapy
- Mini-CLA ± venetoclax: normal karyotype
- *IDH2* (5-10%): enasidenib
- *IDH1* (5%): ivosidenib
- *FLT3* (15%): multiple *FLT3* agents
- *NPM1* (1%): ara-C based

Venetoclax and HMA in Higher-Risk MDS: Efficacy in R/R MDS Population

Best Response, %	1L HMA (n = 1127)	HMA + Ven for R/R (n = 31)	1L HMA + Ven (n = 35)	*P* Value
ORR	77	61	40	
▪ CR	34	13	13	
▪ mCR	37 (62 + HI)	48	11	
Median OS from diagnosis, mo (95% CI)	20 (19-22)	33 (31-36)	21 (11-32)	.02

- 31 patients with R/R MDS received median 6 cycles of first-line HMA
- 9 patients who received HMA + venetoclax for R/R MDS underwent AHSCT
  - Median OS: 31 vs 33 mo with no AHSCT (*P* = .70)

Komrokji. ASH 2021. Abstr 536.

Targeting R/R *IDH1*/*IDH2*^{mut} MDS with ivosidenib/enasidenib

IDIOME: phase 2 study of Ivo in 3 cohorts (N=26)[1]

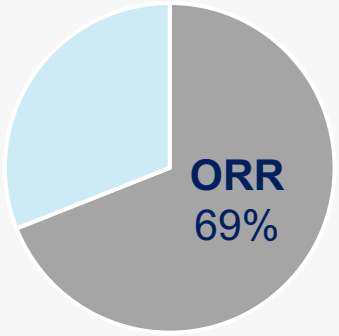
- **A**: HR-MDS, failed AZA (n=13)
- **B**: Untreated HR-MDS (n=11)
- **C**: LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

Differentiation syndrome, n=4, febrile neutropenia, n=1



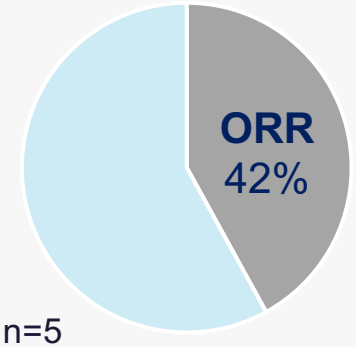
IDEAL: phase 2 study of Ena in 3 cohorts (N=26)[2]

- **A**: HR-MDS, failed AZA (n=11)
- **B**: Untreated HR-MDS (n=9)
- **C**: LR-MDS, failed ESA (n=6)

Median follow-up: 8.6 months

Median OS: 17.3 months

Differentiation syndrome, n=3; nausea/diarrhea, n=4; thrombocytopenia, n=5



Ivosidenib in R/R *IDH1*/*IDH2*^{mut} MDS[3]

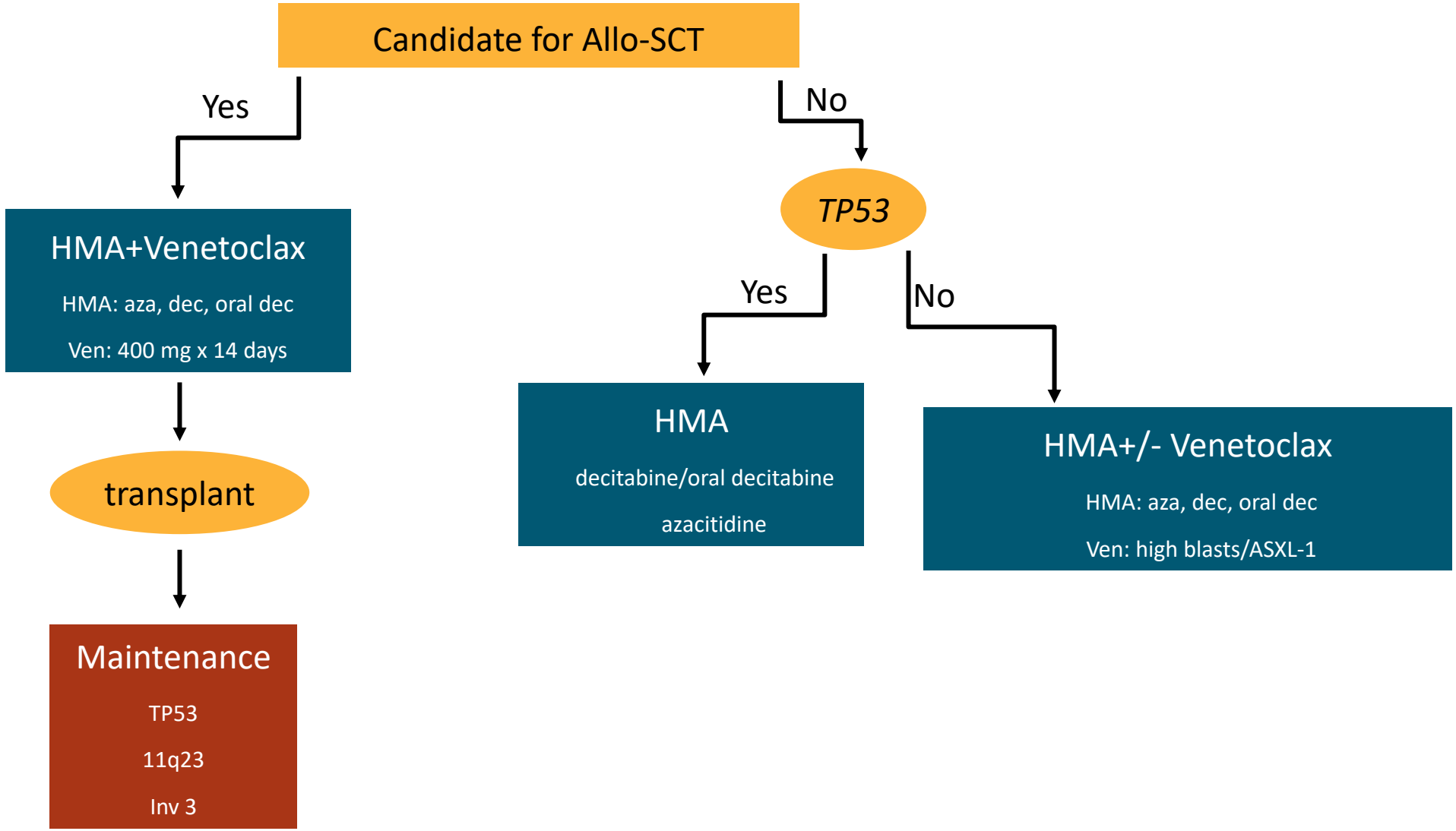
Updated results of a phase 1 dose-escalation study (500 mg QD)

Efficacy outcomes	N=16
ORR	81%
CR	44%
mCR	31%
PR	6%
HI	69%
12-month duration CR+PR	60%

Safety outcomes	N=16
Grade ≥3 AEs	69%
Grade ≥3 TRAEs	13%
SAEs	44%

1. Sebert M, *et al.* ASH 2021. Abstract 62 (oral presentation);
2. Ades L, *et al.* ASH 2021. Abstract 63 (oral presentation); 3. Sallman DA, *et al.* ASCO 2022. Abstract 7053 (Poster 284)

How do I treat Higher risk MDS?

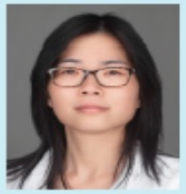


Thank You

Rami.Komrokji@moffitt.org

MEET THE TEAM


Dr. Rami Komrokji


Dr. Onyee Chan


Dr. Andrew Kuykendall


Dr. Jeffrey Lancet


Dr. Eric Padron


Dr. David Sallman


Dr. Kendra Sweet


Dr. Sara Tinsley

Moffitt MDS team: Only perfect counts !!!

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- Our patients and their caregivers
- Moffitt MDS team