Myelodysplastic Syndromes/Neoplasms 2023 Updates

Amer Zeidan, MBBS, MHS

Associate Professor of Medicine
Interim Chief, Division of Hematologic Malignancies
Director, Leukemia & Myeloid Malignancies Program
Leader, Leukemia & Myeloid Malignancies Clinical Research Team
Director, Hematology Early Therapeutics Research
Assistant Director, Clinical Trial Office

Section of Hematology,
Department of Internal Medicine
Yale University School of Medicine
Yale Comprehensive Cancer Center

Amer.Zeidan@yale.edu
Dr_AmerZeidan

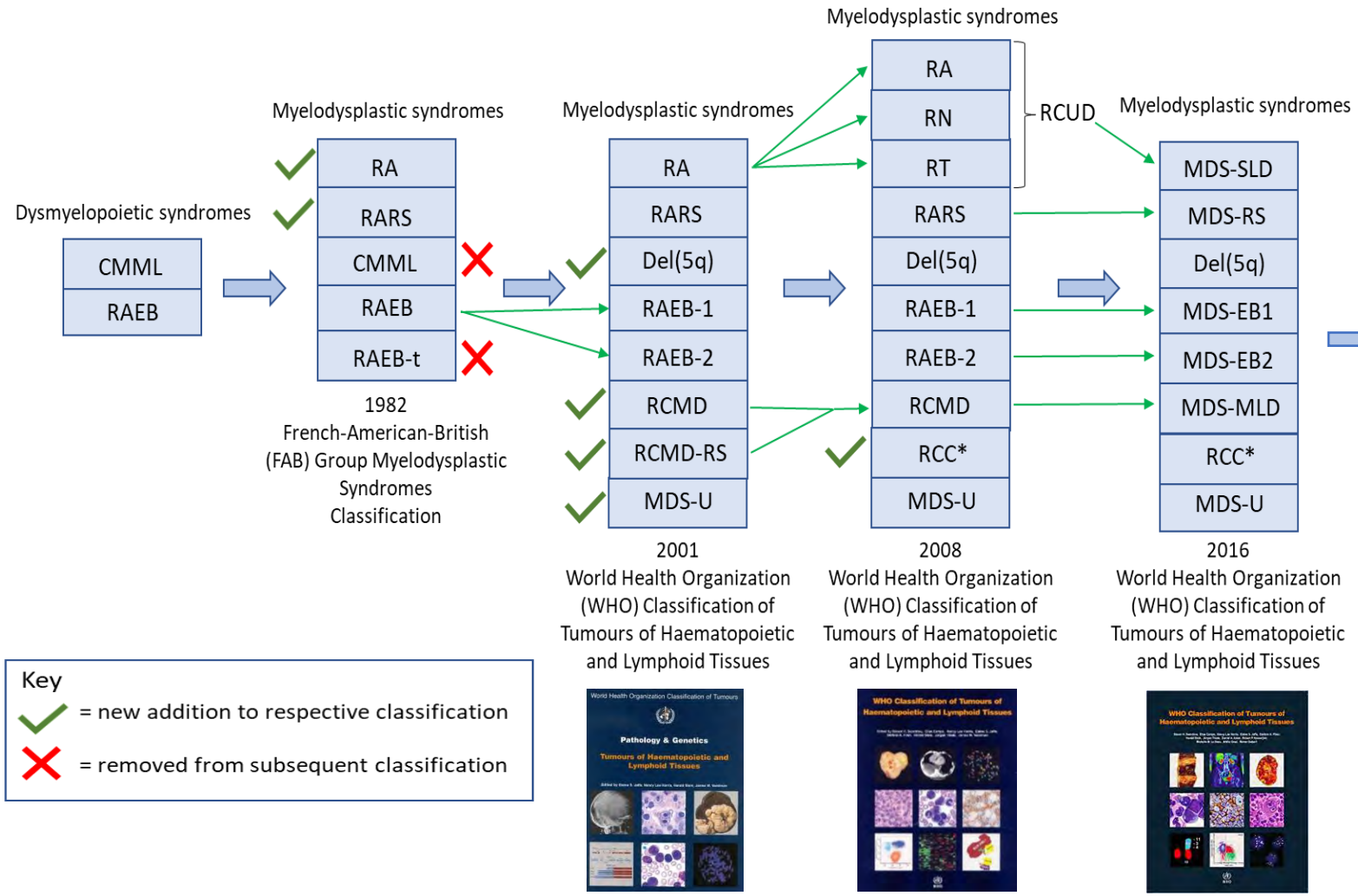
Disclosures

- A.M.Z. received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, AstraZeneca, Boehringer-Ingelheim, Cardiff Oncology, Takeda, Shattuck Labs, Novartis, Aprea, and ADC Therapeutics.
- A.M.Z participated in advisory boards, and/or had a consultancy/ and/or received honoraria from AbbVie, Genentech, Taiho, Otsuka, Pfizer, Celgene/BMS, Jazz, Agios, Novartis, Astellas, Daiichi Sankyo, Seattle Genetics, BeyondSpring, Takeda, Ionis, Amgen, Janssen, Aprea, Epizyme, Syndax, Kura, Janssen and Janssen, Regeneron, Gilead, BioCryst, Orum, Chiesi, Mendus, Notable Labs, and ALX Oncology.
- A.M.Z served on clinical trial committees for clinical trials for Novartis, Kura, Astex, Biocryst, ALX Oncology, Abbvie, Celgene/BMS, Gilead, and Geron.

Outline

- Updates in classification, risk stratification, & response assessment in MDS
- Updates in Current and investigational therapies for lower risk MDS
- Updates in Current and investigational therapies for higher risk MDS

MDS classification has evolved over time



Modified from Zeidan A et al, Blood Reviews 2019

REVIEW ARTICLE OPEN

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]

Leukemia. 2022 Jul;36(7):1703-1719

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Blood. 2022 Sep 15;140(11):1200-1228

A genetic-based diagnostic approach

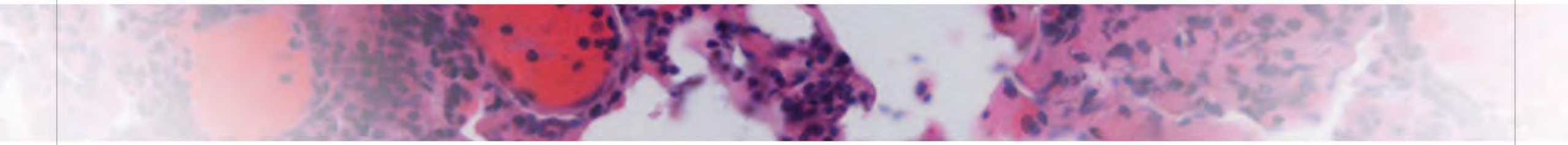
Evolving MDS classifications

WHO 2016	WHO 2022	ICC
MDS with single lineage dysplasia (MDS-SLD)	Not included MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
MDS with multi-lineage dysplasia (MDS-MLD)	MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
MDS with ring sideroblasts • With single lineage dysplasia (MDS-RS-SLD) • With multi-lineage dysplasia (MDS-RS-MLD)	MDS with low blasts and mutated *SF3B1* or MDS with ring sideroblasts (if ≥ 15% RS and *SF3B1* wild-type)	MDS with mutated *SF3B1*
MDS with isolated del(5q)	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)
MDS unclassifiable	Not included	Not included
Not included	Not included	MDS, not otherwise specified without dysplasia (e.g., monosomy 7/del(7q))[a]
MDS excess blasts-1 (MDS-EB1; 5–9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1; 5–9% bone marrow and/or 2–4% peripheral blood blasts)	MDS excess blasts (5–9% bone marrow and/or 2–9% peripheral blood blasts)
MDS excess blasts-2 (MDS-EB2; 10–19% bone marrow or peripheral blood blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2; 10–19% bone marrow or 5–19% peripheral blood blasts or Auer rods)	MDS/AML (10–19% bone marrow or peripheral blood blasts)
AML-defining genetics[b]	AML-defining genetics independent of bone marrow and peripheral blood blast count	AML-defining genetics with ≥10% bone marrow and peripheral blood blasts
AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)
Not included	MDS with biallelic *TP53* inactivation (Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH)	MDS with mutated *TP53* (Multi-hit *TP53* mutation, or *TP53* mutation (VAF > 10%) and loss of 17p) and MDS/AML with mutated *TP53* (Any somatic TP53 mutation (VAF > 10%)
Not included	MDS, hypoplastic (MDS-h)	Not included
Not included	MDS with fibrosis (MDS-f)	Not included
Not included	Clonal hematopoiesis (CHIP, CCUS)[c]	Pre-malignant clonal cytopenias and CCUS[c]

Zeidan A et al, Leukemia, 2023

American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



Data-Driven Harmonization of 2022 WHO and ICC Classifications of Myelodysplastic Syndromes/Neoplasms (MDS): A Study By the International Consortium for MDS (icMDS)

L Lanino*, S Ball*, JP Bewersdorf*, M Marchetti, G Maggioni, E Travaglino, NH Al Ali, P Fenaux, U Platzbecker, V Santini, M Diez-Campelo, AM Singh, A Gupta Jain, LE Aguirre, SM Tinsley-Vance, ZI Schwabkey, O Chan, Z Xie, AM Brunner, AT Kuykendall, JM Bennett, R Buckstein, R Bejar, HE Carraway, AE DeZern, EA Griffiths, S Halene, R Hasserjian, J Lancet, AF List, S Loghavi, O Odenike, E Padron, MM Patnaik, GJ Roboz, M Stahl, MA Sekeres, DP Steensma, MR Savona, J Taylor, M Xu, K Sweet, DA Sallman, SD Nimer, CS Hourigan, AH Wei, E Sauta, S D'Amico, G Asti, G Castellani, UM Borate, G Sanz, F Efficace, SD Gore, TK Kim, N Daver, G Garcia-Manero, M Rozman, A Orfao, SA Wang, MK Foucar, U Germing, T Haferlach, P Scheinberg, Y Miyazaki, M Iastrebner, A Kulasekararaj, T Cluzeau, S Kordasti, AA van de Loosdrecht, L Ades, **AM Zeidan#, RS Komrokji# and MG Della Porta#**

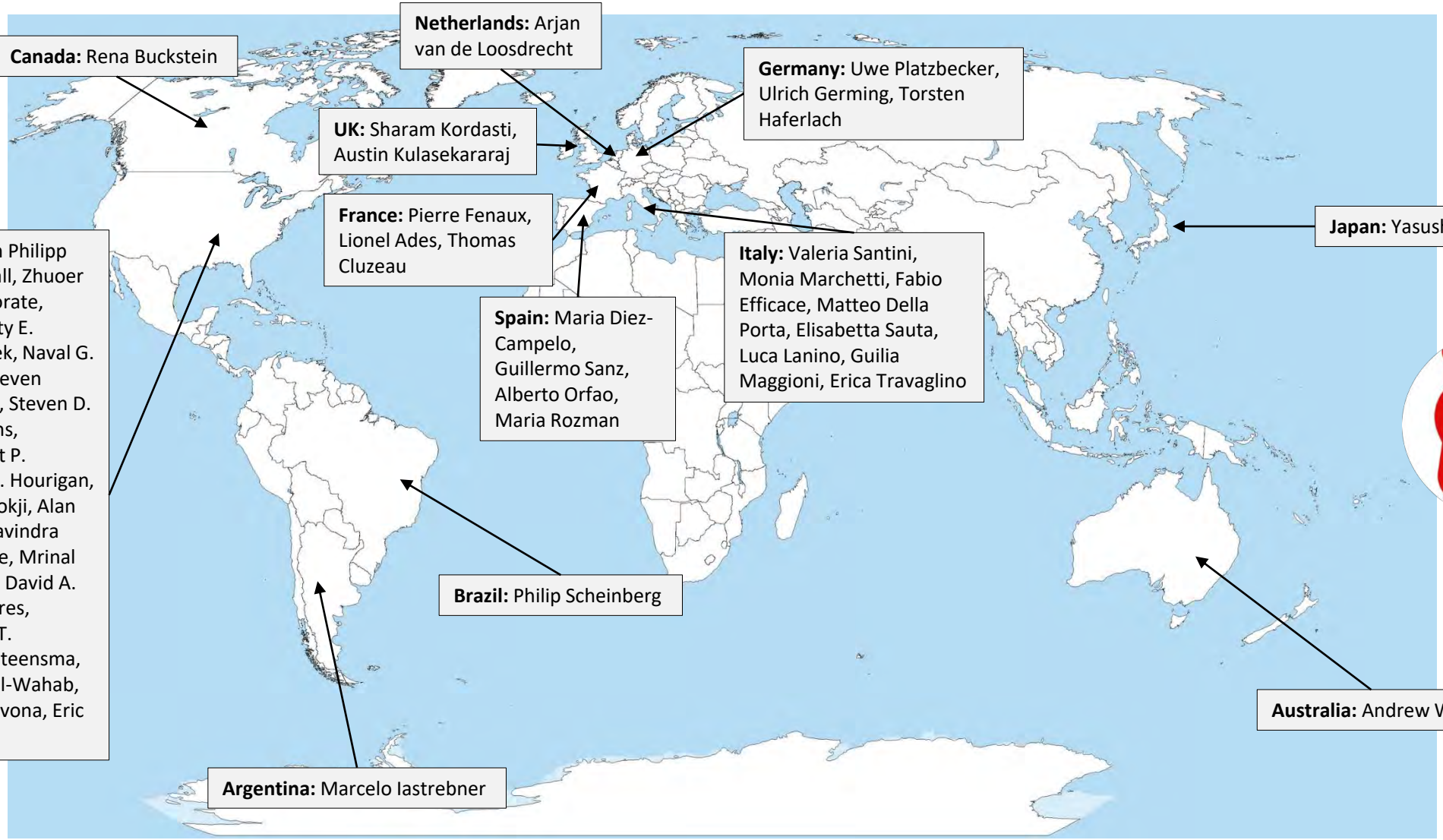
*co-first authors

#co-senior authors

MDS

Twitter (X):ic_MDS

INTERNATIONAL CONSORTIUM FOR MDS (icMDS)
A Global Expert Thinktank



Canada: Rena Buckstein

Netherlands: Arjan van de Loosdrecht

Germany: Uwe Platzbecker, Ulrich Germing, Torsten Haferlach

UK: Sharam Kordasti, Austin Kulasekararaj

France: Pierre Fenaux, Lionel Ades, Thomas Cluzeau

Japan: Yasushi Miyazaki

USA: Amer M Zeidan, Jan Philipp Bewersdorf, Somedeb Ball, Zhuoer Xie, Rafael Bejar, Uma Borate, Andrew M. Brunner, Hetty E. Carraway, Jane E. Churpek, Naval G. Daver, Amy E. DeZern, Steven Nimer, Maria E. Figueroa, Steven D. Gore, Elizabeth A. Griffiths, Stephanie Halene, Robert P. Hasserjian, Christopher S. Hourigan, Tae Kon Kim, Rami Komrokji, Alan F. List, Sanam Loghavi, Ravindra Majeti, Olatoyosi Odenike, Mrinal M. Patnaik, Gail J. Roboz, David A. Sallman, Mikkael A. Sekeres, Maximilian Stahl, Daniel T. Starczynowski, David P. Steensma, Justin Taylor, Omar Abdel-Wahab, Mina L. Xu, Michael R. Savona, Eric Padron, Sa Wang

Spain: Maria Diez-Campelo, Guillermo Sanz, Alberto Orfao, Maria Rozman

Italy: Valeria Santini, Monia Marchetti, Fabio Efficace, Matteo Della Porta, Elisabetta Sauta, Luca Lanino, Guilia Maggioni, Erica Travaglino

Brazil: Philip Scheinberg

Australia: Andrew Wei

Argentina: Marcelo Iastrebner

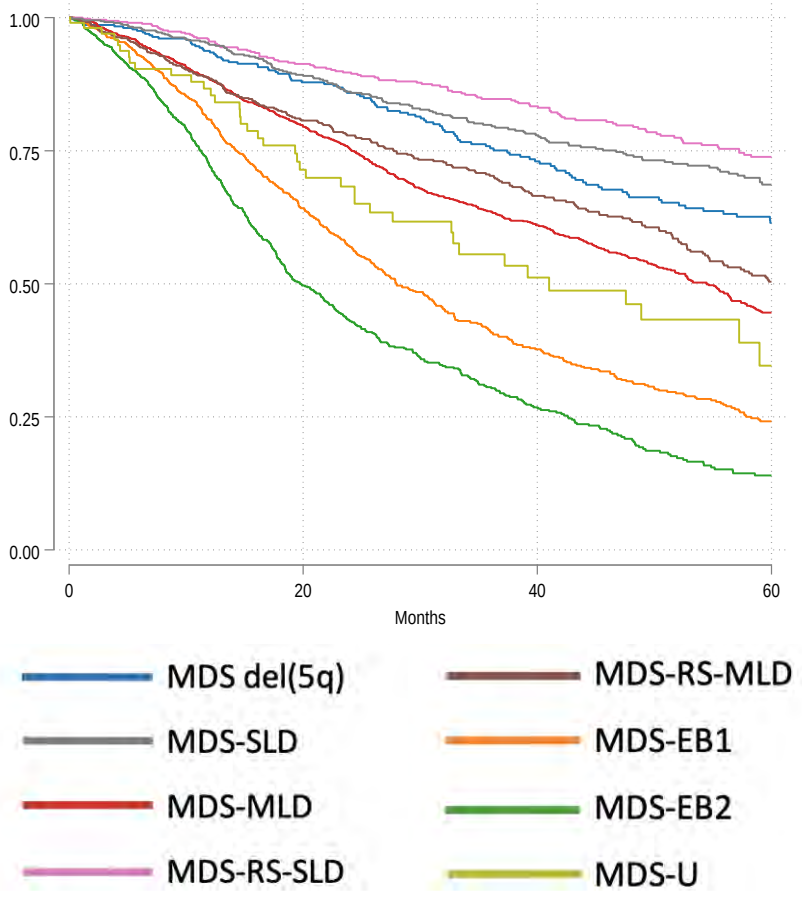
https://en.wikipedia.org/wiki/File:A_large_blank_world_map_with_oceans_marked_in_blue.PNG#filelinks

Data-Driven Harmonization of 2022 WHO and ICC (N=7017)

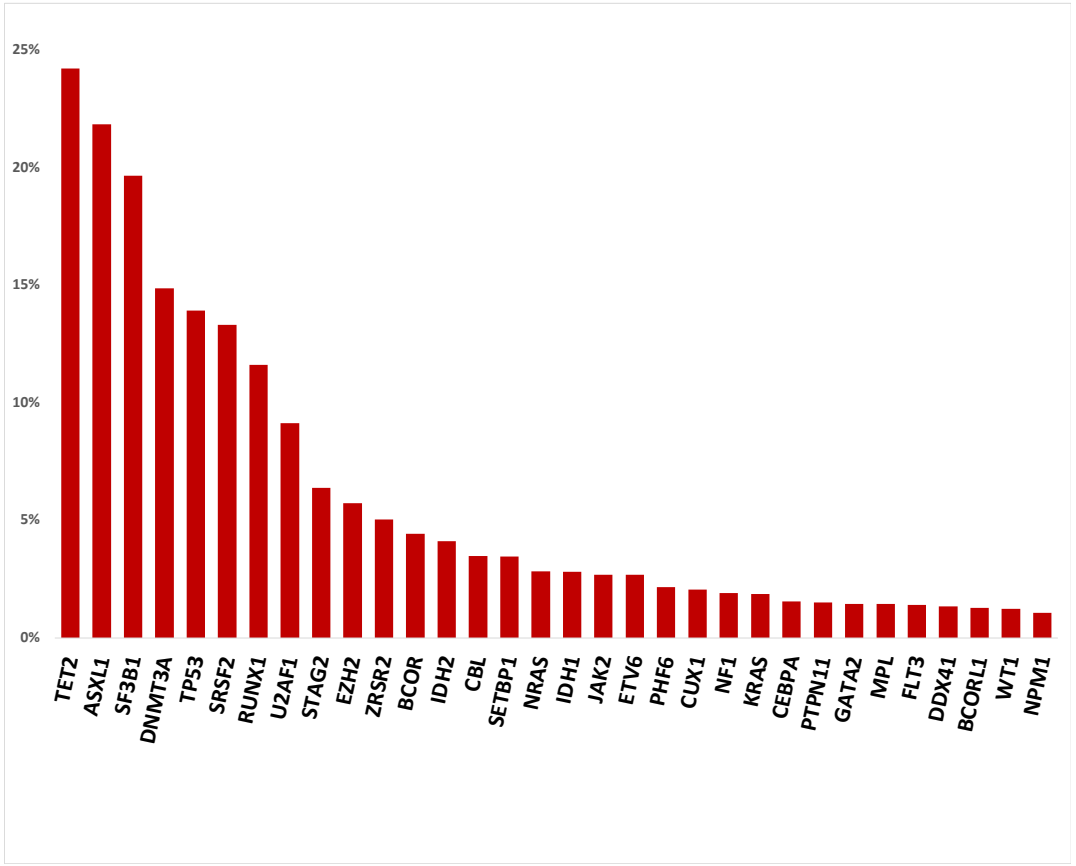
Aim: To create a hierarchical and WHO/ICC harmonized classification of MDS based on a comprehensive patients dataset, using advanced statistical methods of inference and explainable artificial intelligence

Demographics	
Age at diagnosis	69.6 (18-98)
Male sex	4315 (61.5)
WHO 2016 Classification	
MDS 5Q-	373 (5,3%)
MDS-EB1	1321 (18,8%)
MDS-EB2	1509 (21,5%)
MDS-MLD	1868 (26,6%)
MDS-RS-MLD	635 (9,1%)
MDS-RS-SLD	539 (7,7%)
MDS-SLD	666 (9,5%)
MDS-U	106 (1,5%)
IPSS-R Risk	
Very Low	980 (14%)
Low	2424 (34,5%)
Intermediate	1449 (20,6%)
High	1086 (15,5%)
Very High	1078 (15,4%)

Overall survival



Mutations frequency



HUMANITAS UNIVERSITY

Komrokji RK et al, Myelodysplastic Neoplasms Classification From WHO 2017 To WHO 2022 and ICC 2022, EHA 2023 Abstract

Proposal for a hierarchical harmonized MDS classification

2 or more ***TP53* mutations**, or 1 *TP53* mut with evidence of copy number loss or cnLOH
BM blasts < 20%

→ **MDS with biallelic inactivation of *TP53***

5q deletion alone, or with 1 other abnormality
Absence of -7
BM blasts < 5%

→ **MDS with del(5q)**

Mutated SF3B1, absence of del(7q), abn(3q), *RUNX1*^{mut} or complex karyotype
BM blasts < 5%

→ **MDS with mutated *SF3B1***

Blast count ≥5%

→ **MDS with 5-9% blasts**

→ **MDS with 10-19% blasts**

MDS with low blasts

MDS with defining genomic abnormalities

MDS morphologically defined

Reclassification according to this algorithm was concordant with ICC and WHO labels in 97.2% and 98.1%

IPSS-M

Bernard et al. NEJM Evidence 2021

Input:

- **Clinical variables:** age, sex, Hb, PLT, BM blasts%, IPSS-R cytogenetic risk.
- **Molecular variables:** 31 gene panel

  (17 genetic variables from 16 main effect genes: *TP53* allelic status, *SF3B1*^{5q}, *SF3B1*$^{\alpha}$, *SF3B1*$^{\beta}$- Number of additional mutations in *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*

  &

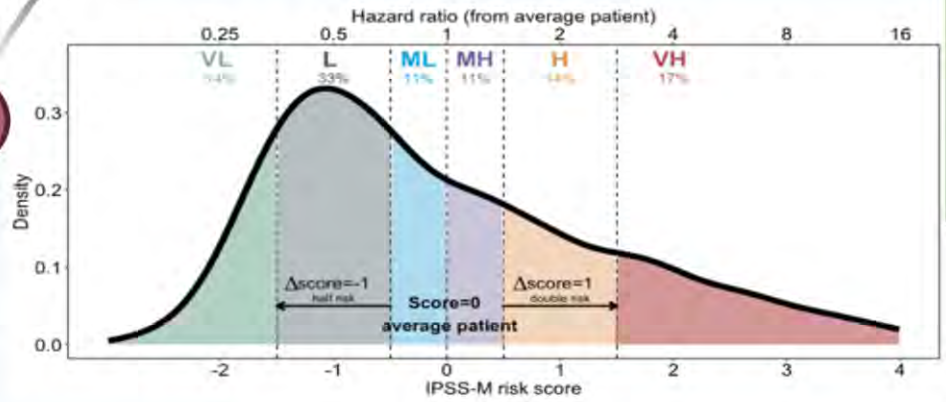
  1 genetic variable from 15 residual genes: *ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH2, KRAS, MLL-PTD, NPM1, NRAS, RUNX1, SRSF2,* and *U2AF1)*

2

3

Output: six risk strata

Very Low | Low | Moderate Low | Moderate High | High | Very High



Online calculator:

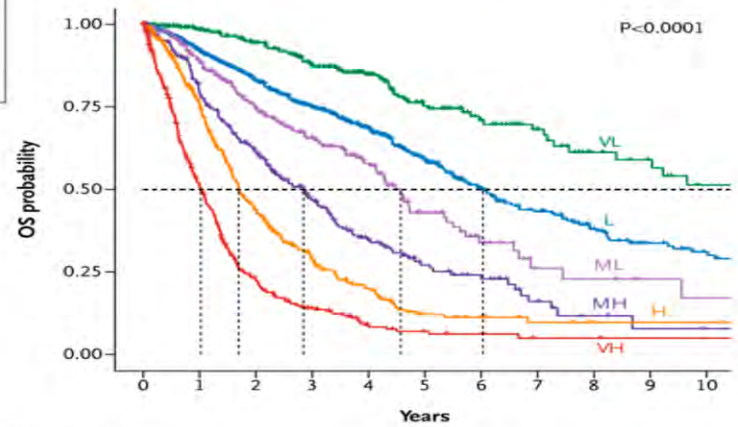
https://mds-risk-model.com/

1

Pt with MDS

4 **Information sharing with the patients**

Risk Score	VL	Low	ML	MH	H	VH
Median LFS, yrs	9.7	5.9	4.5	2.3	1.5	0.76
Median OS, yrs	10.6	6	4.6	2.8	1.7	1.0
AML transformation by 1yr, %	0	1.7	4.9	9.5	14.3	28.2



No. at risk

VL - 344	267	224	180	126	82	57	42	28	24	18
L - 852	640	496	382	270	176	112	83	57	40	31
ML - 295	214	152	111	72	35	18	8	7	4	3
MH - 278	191	134	80	48	27	20	9	4	2	1
H - 367	235	121	65	37	15	12	6	3	3	3
VH - 460	200	77	37	14	9	6	3	3	2	2

VALIDATE database: Validating IPSS-M & IWG 2023 HR-MDS response criteria

University of Colorado Cancer Center

Washington University in St. Louis School of Medicine

Dana-Farber Cancer Institute

Massachusetts General Hospital Cancer Center

Johns Hopkins Medicine — The Sidney Kimmel Comprehensive Cancer Center

Roswell Park Comprehensive Cancer Center

Yale Cancer Center — A Comprehensive Cancer Center Designated by the National Cancer Institute

Cleveland Clinic Taussig Cancer Institute

Memorial Sloan Kettering Cancer Center

Weill Cornell Medicine

Vanderbilt-Ingram Cancer Center

UNC Lineberger Comprehensive Cancer Center

Moffitt Cancer Center

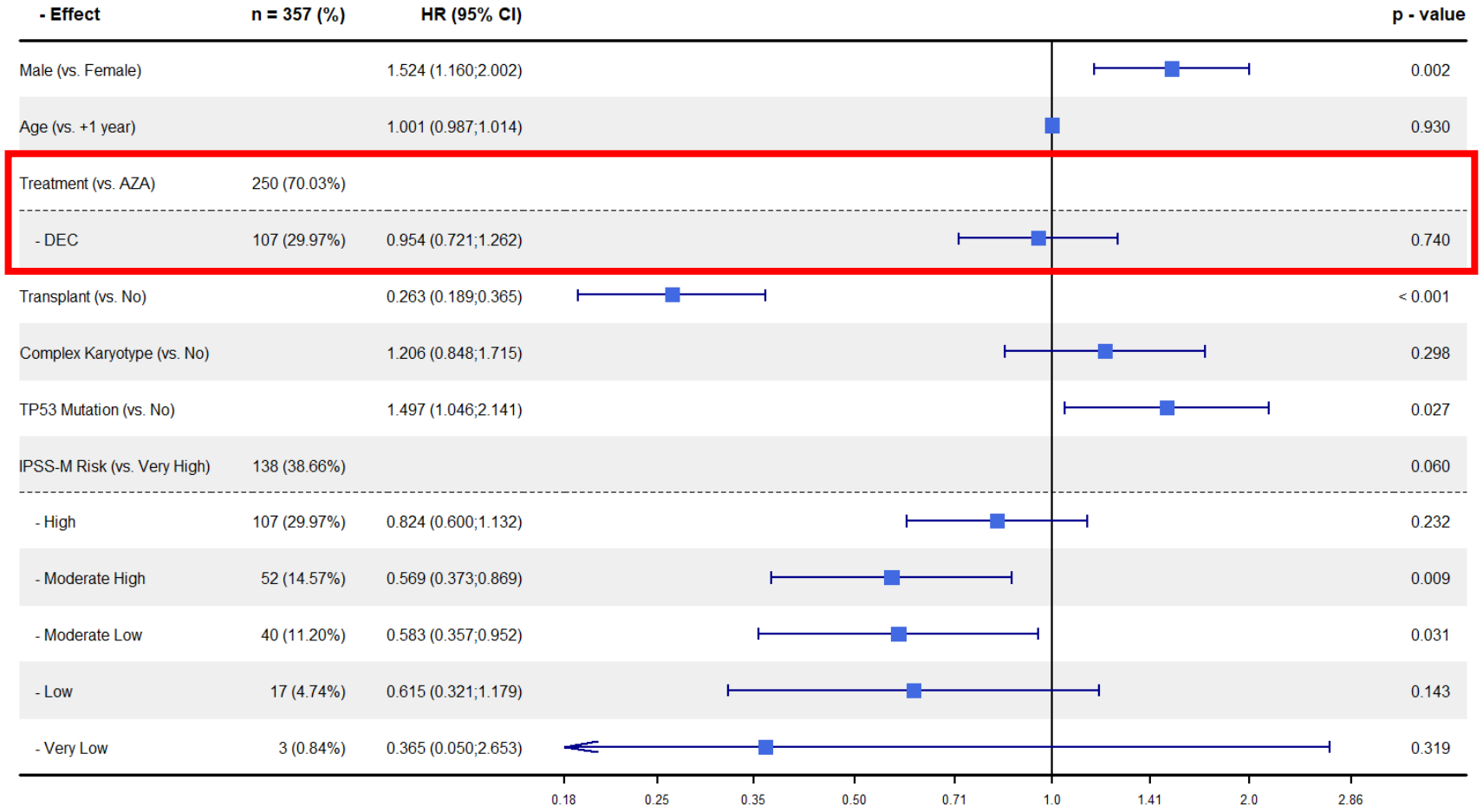
Sylvester Comprehensive Cancer Center — University of Miami Health System

https://commons.wikimedia.org/wiki/File:Blank_US_Map_%28states_only%29.svg

No difference in clinical outcomes between AZA and Dec (N=919)

- **No difference in response rates of OS between AZA and DEC monotherapy (Hazard ratio [HR]: 0.95, 95% CI: 0.72 – 1.26; p=0.740) in adjusted analyses**

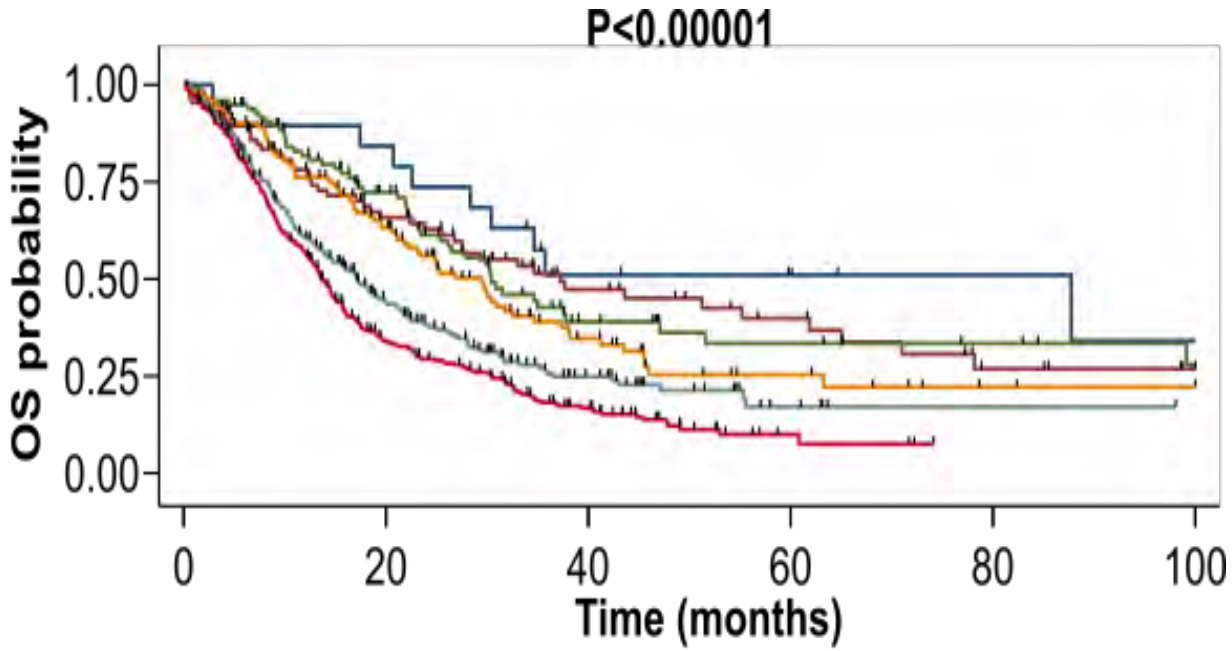
- **Other factors (e.g., *TP53* mutations, complex karyotype) are more relevant to outcomes than the type of HMA used.**



Bewersdorf J,,,,,Zeidan A. ASH 2023. Abstract 4613

IPSS-M remains prognostic among HMA-treated patients (N=925)

- IPSS-M groups showed significant differences for both **OS and LFS** (**p-value: <0.0001 for both**).
- The median OS (mo, 95%CI) based on IPSS-M categories were low (37, 25-62), moderate low (30, 23-47), moderate high (29, 22-35), high (17, 14-20), and very high (14, 12-15)



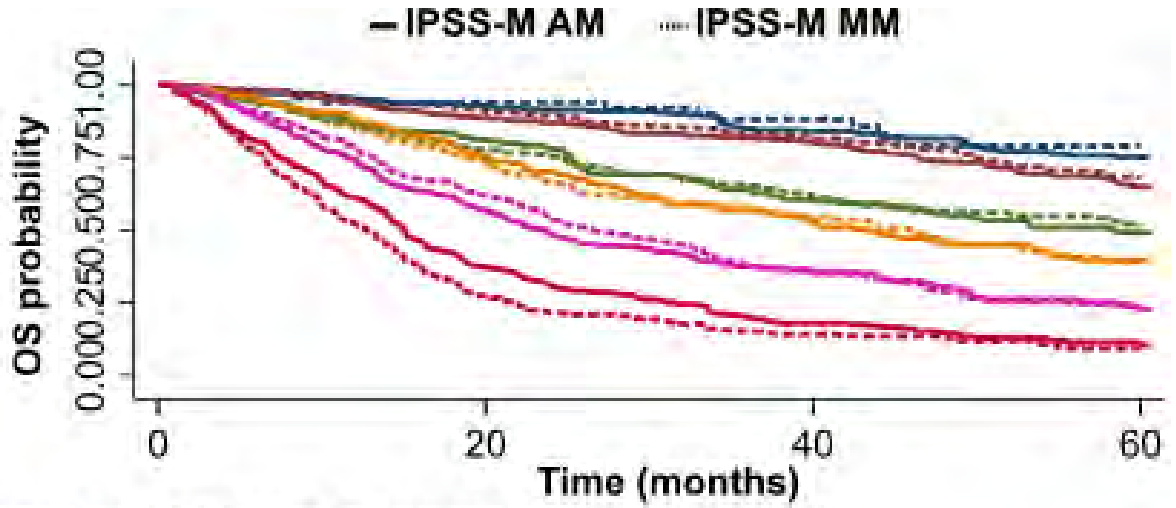
Number at risk

Very Low	19	16	7	5	3	2
Low	87	46	23	14	6	2
Moderate Low	97	55	18	12	8	5
Moderate High	123	65	23	9	3	2
High	260	90	27	6	1	0
Very High	325	95	33	4	0	0

Kewan T,,,,,Zeidan A. ASH 2023. Abstract 3240

Comparing IPSS-MM and IPSSM-AM (N=2,429)

- IPSS-M MM showed **comparable performance** to IPSS-M AM
- c-index (95%CI) for **OS**: **0.713** (0.697 - 0.728) vs. **0.714** (0.699-0.729).
- c-index (95%CI) for **LFS**: **0.645** (0.622-0.669) vs. **0.623** (0.599-0.647).
- When used as **continuous** scores, IPSSM MM continues to be **comparable** to IPSS-M AM for OS (c-index:0.721 vs. 0.730) and LFS (c-index:0.655 vs. 0.641).



Number at risk (IPSS-M missing molecular data [MM])

Very Low	75	53	39	26
Low	739	569	410	246
Moderate Low	428	281	172	95
Moderate High	310	191	103	52
High	396	208	88	35
Very High	332	72	25	5

Number at risk (IPSS-M available molecular data [AM])

Very Low	293	229	174	112
Low	679	513	370	217
Moderate Low	265	179	94	54
Moderate High	233	142	76	40
High	398	184	77	26
Very High	412	127	46	10

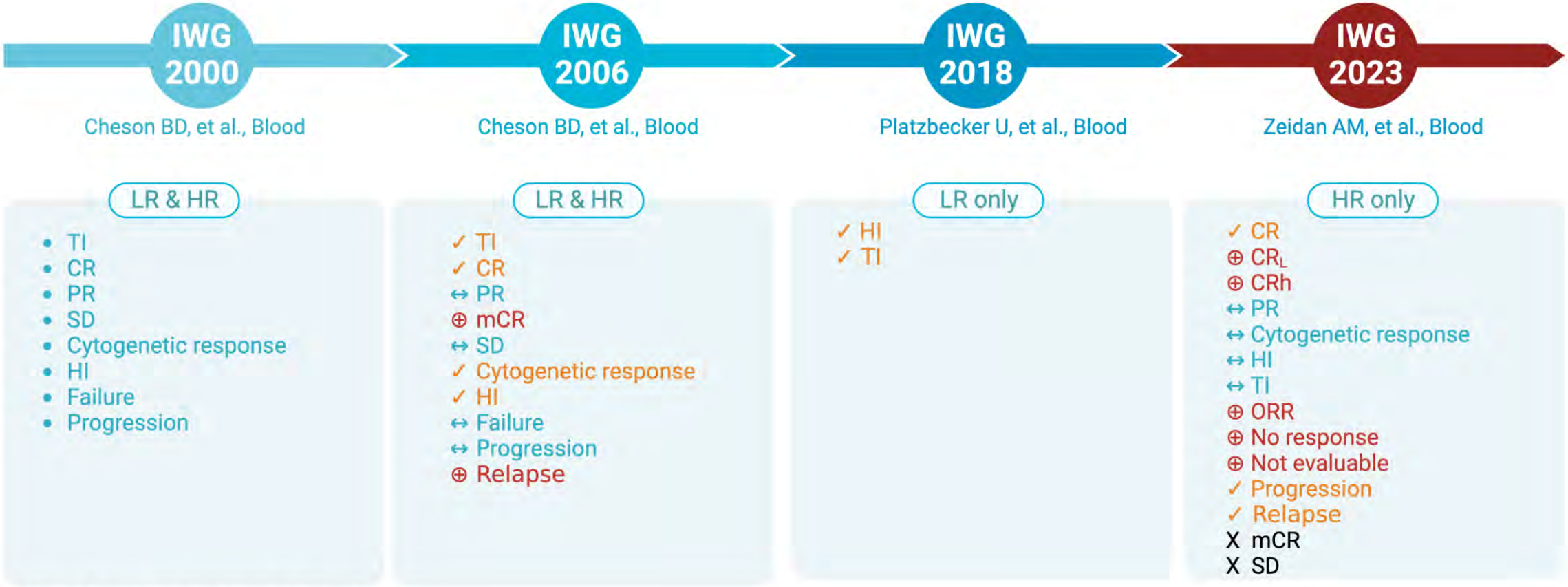
Kewan T,,,,,Zeidan A. ASH 2023. Abstract 4607

The Graveyard for HMA-based combinations: Are IWG 2006 response criteria moving agents with minimal clinical benefits to phase 3 trials?

- HMA + Lenalidomide
- HMA + Vorinostat
- HMA + volasertib
- HMA + Eltrombopag
- HMA + romiplostim
- HMA + Pracinostat
- HMA + Durvalumab
- HMA + Pevonedistat
- HMA + APR246
- HMA + Magrolimab

Last drug approved for higher risk MDS in the frontline setting was in 2006 (IV decitabine) - Aside from oral DEC/CED which was approved in 2020 based on PK equivalence to IV decitabine

Evolution of response criteria in MDS



↔ Item is carried forward from the last version
✓ Item is revised from the previous version
⊕ Item is not included in the previous version
X Item is removed from the current version

Abbreviations: **CR:** complete remission; **mCR:** marrow CR; **PR:** partial remission; **SD:** stable disease; **CR_L:** CR with limited count recovery; **CRh:** CR with partial hematologic recovery; **HI:** hematological improvement; **HR:** high risk; **LR:** low risk; **ORR:** overall response rate; **PRO:** patient-reported outcome; **TI:** tranfusion independence.

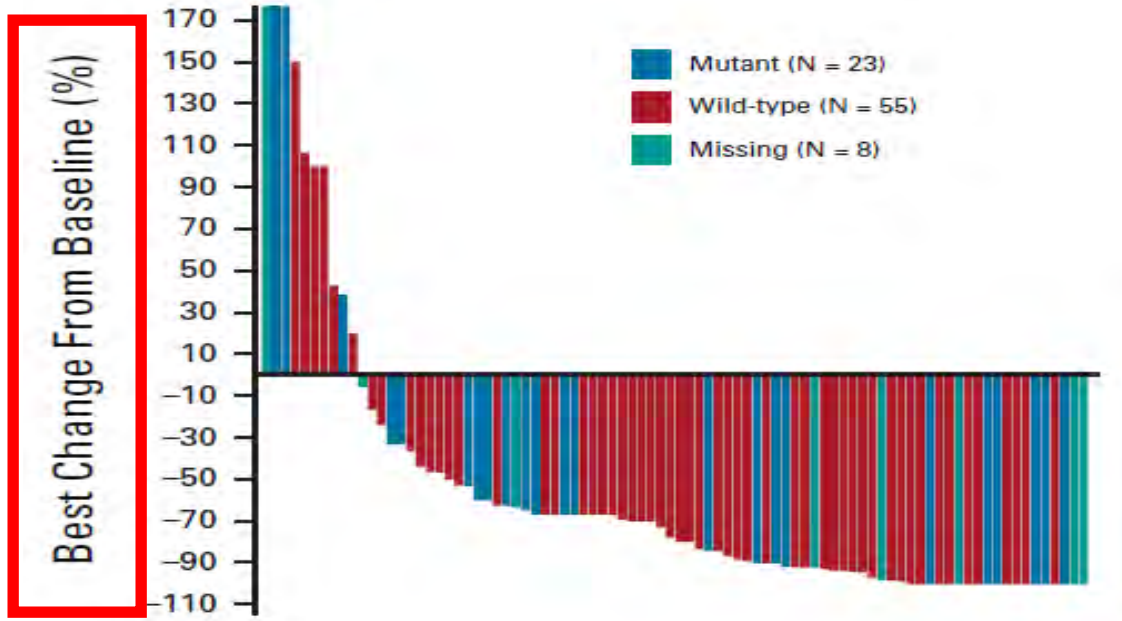
*IWG 2018 revised LR-MRS response criteria; IWG 2023 revised HR-MDS response criteria

Patient-reported outcome and molecular data assessment are encouraged; integrating these two into response criteria require further optimization and validation.

Stempel J,,,,,,Zeidan A, The Cancer Journal, 2023

How does reporting of responses look like currently in HR-MDS trials?

MDS risk category by IPSS-R, No. (%)	
Intermediate	26 (27.4)
High	49 (51.6)
Very high	20 (21.1)
WHO classification, No. (%)	
MDS-RS	2 (2.1)
MDS-RS with single lineage dysplasia	2 (2.1)
MDS-RS with multilineage dysplasia	6 (6.3)
MDS with multilineage dysplasia	12 (12.6)
MDS with excess blasts	64 (67.4)
MDS with isolated del(5q)	1 (1.1)
MDS, unclassifiable	



Outcome	All (N = 95[a])	*TP53*-wt MDS (N = 61)	*TP53*-mut MDS (N = 25)
OR rate, %[b]	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0

OR: [b]Defined as CR + PR + mCR + SD with HI in all patients who received at least one dose of magrolimab.

Sallman D et al. JCO 2023

IWG 2023 MDS Response Criteria – a Global Effort

blood

Special Report

azaki

USA (14 sites): Amer M Ze
Bewersdorf, Maximilian Sta
Andrew Brunner, Hetty E C
Daver, Amy E DeZern, Guill
Manero, Jacqueline S Garc
Griffiths, Robert P Hasserji
Komrokji, Olatoyosi Odenik
Sekeres

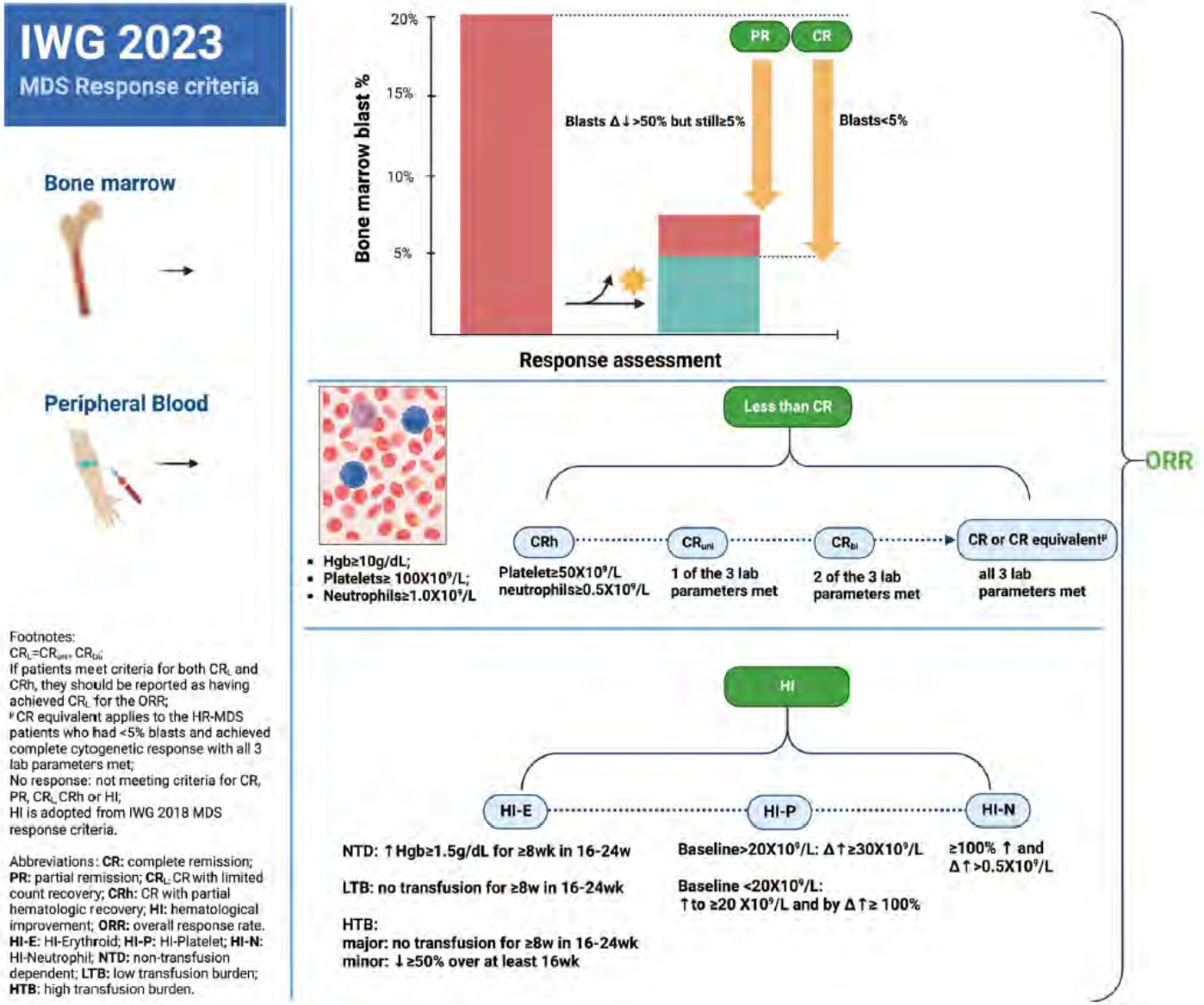
Arge

Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes

Amer M. Zeidan,[1,*] Uwe Platzbecker,[2,*] Jan Philipp Bewersdorf,[3] Maximilian Stahl,[4] Lionel Adès,[5] Uma Borate,[6] David Bowen,[7] Rena Buckstein,[8] Andrew Brunner,[9] Hetty E. Carraway,[10] Naval Daver,[11] Maria Díez-Campelo,[12] Theo de Witte,[13] Amy E. DeZern,[14] Fabio Efficace,[15] Guillermo Garcia-Manero,[11] Jacqueline S. Garcia,[4] Ulrich Germing,[16] Aristoteles Giagounidis,[17] Elizabeth A. Griffiths,[18] Robert P. Hasserjian,[19] Eva Hellström-Lindberg,[20] Marcelo Iastrebner,[21] Rami Komrokji,[22] Austin G. Kulasekararaj,[23] Luca Malcovati,[24] Yasushi Miyazaki,[25] Olatoyosi Odenike,[26] Valeria Santini,[27] Guillermo Sanz,[28] Phillip Scheinberg,[29] Reinhard Stauder,[30] Arjan A. van de Loosdrecht,[31] Andrew H. Wei,[32] Mikkael A. Sekeres,[33,†] and Pierre Fenaux[5,†]

https://en.wikipedia.org/wiki/File:A_large_blank_world_map_with_oceans_marked_in_blue.PNG#filelinks

Key changes in IWG 2023 response criteria for HR-MDS



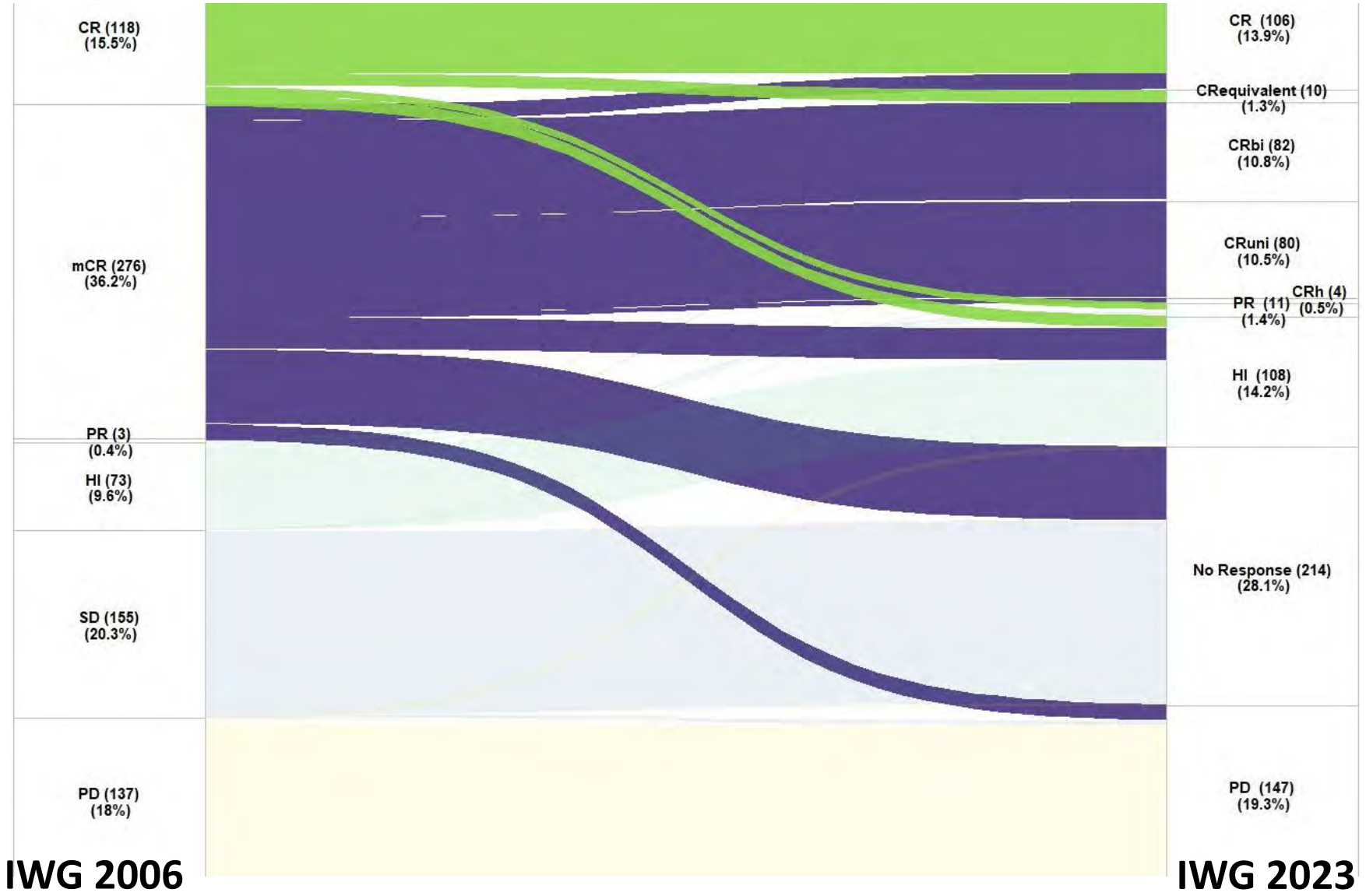
Footnotes:
CR_L=CR_{uni}, CR_{bi};
If patients meet criteria for both CR_L and CRh, they should be reported as having achieved CR_L for the ORR;
#CR equivalent applies to the HR-MDS patients who had <5% blasts and achieved complete cytogenetic response with all 3 lab parameters met;
No response: not meeting criteria for CR, PR, CR_L, CRh or HI;
HI is adopted from IWG 2018 MDS response criteria.

Abbreviations: **CR:** complete remission; **PR:** partial remission; **CR_L:** CR with limited count recovery; **CRh:** CR with partial hematologic recovery; **HI:** hematological improvement; **ORR:** overall response rate. **HI-E:** HI-Erythroid; **HI-P:** HI-Platelet; **HI-N:** HI-Neutrophil; **NTD:** non-transfusion dependent; **LTB:** low transfusion burden; **HTB:** high transfusion burden.

- Updated definition of CR (lower Hb threshold to 10g/dL; BM blasts <5%)
- Introduction of "less-than-CR" CRh & CRL as provisional endpoints
- Introduction for "CR equivalent" for patients with baseline < 5% BM blasts
- mCR and SD eliminated as formal response categories
- Added "No response" & "Non-evaluable" response categories and clearly defined ORR
- Molecular responses added as provisional endpoints
- Clarified relapse & PD definitions and organized by blast increase, worsening cytopenias, or progression to AML
- Clarified definitions of time-to-event endpoints
- Emphasis on measuring and reporting patient-reported outcomes (PROs)
- Emphasis on practicality and maximizing consistency & reproducibility of measurements & clarity in reporting

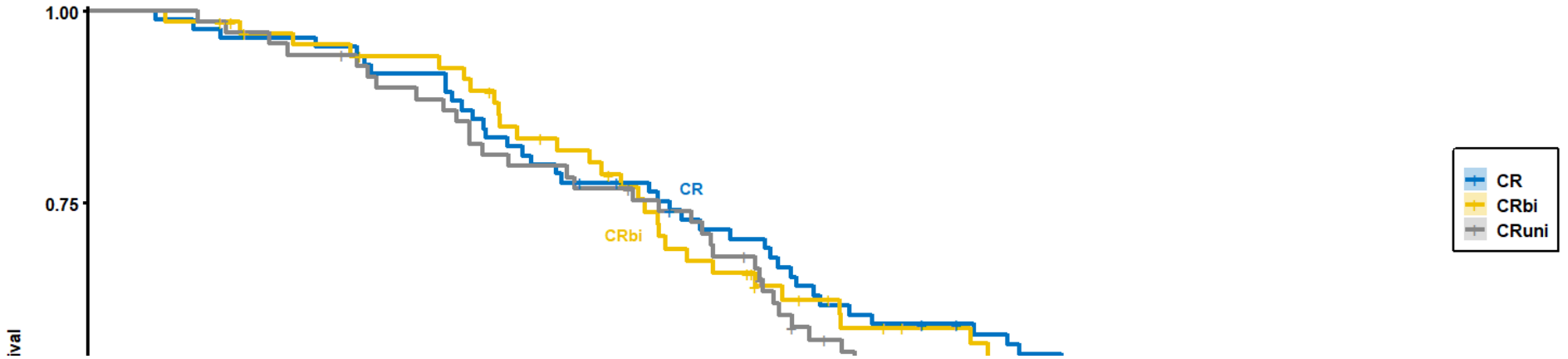
Zeidan A et al, Blood 2023; Stempel J,,,Zeidan A, The Cancer Journal, 2023

Reclassification of CR and mCR based on IWG 2023 criteria (N=726)



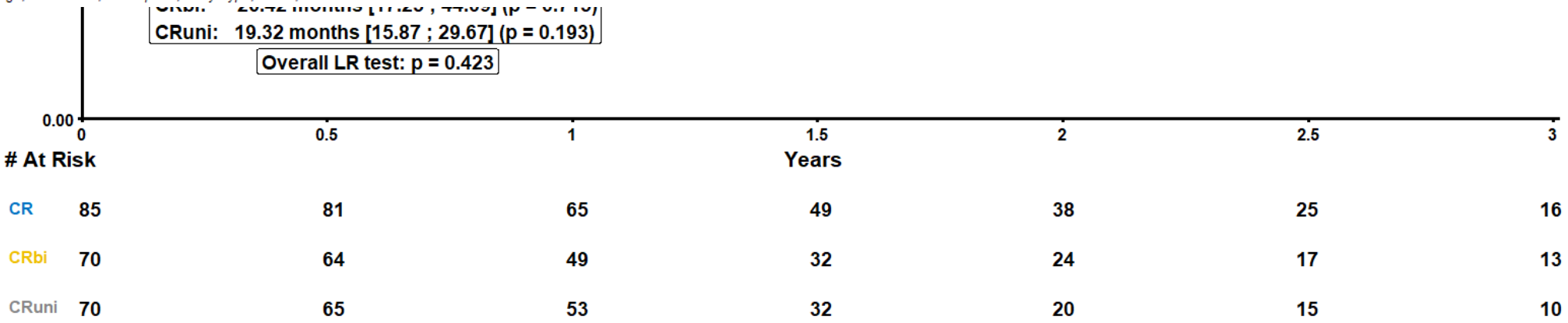
Bewersdorf J,,,,,Zeidan A. ASH 2023. Abstract 324

Overall survival by type of CR per IWG 2023 criteria



Variable - Effect	n = 225 (%)	HR (95% CI)	p - value
IWG 2023 (vs. CR)	85 (37.78%)		0.423
- CRbi	70 (31.11%)	1.085 (0.700 ; 1.683)	0.715
- CRuni	70 (31.11%)	1.322 (0.869 ; 2.011)	0.193

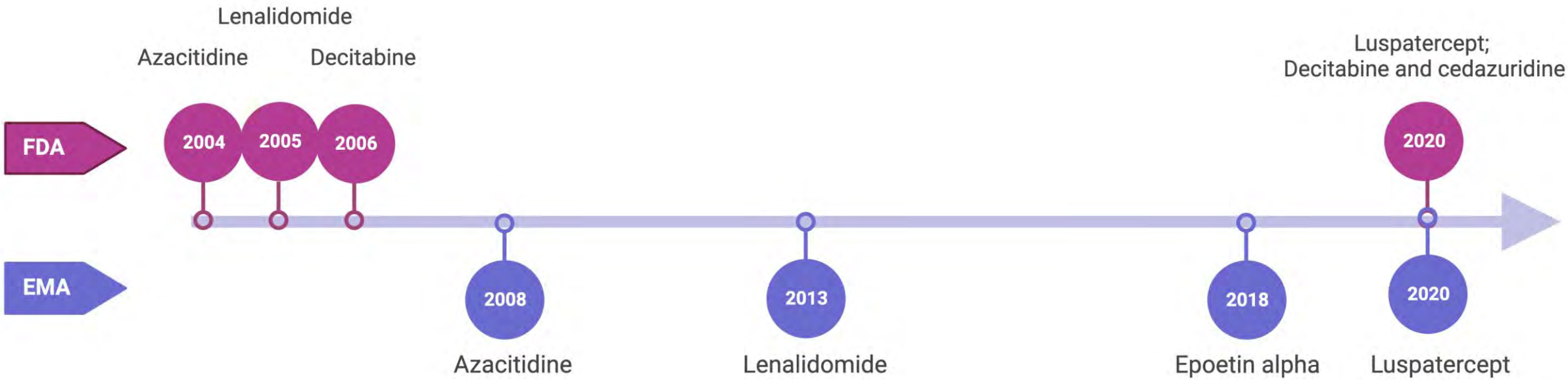
Model adjusted for: Sex, Age, Treatment, Transplant, Karyotype, TP53, and IPSS-M Risk



# At Risk							
CR	85	81	65	49	38	25	16
CRbi	70	64	49	32	24	17	13
CRuni	70	65	53	32	20	15	10

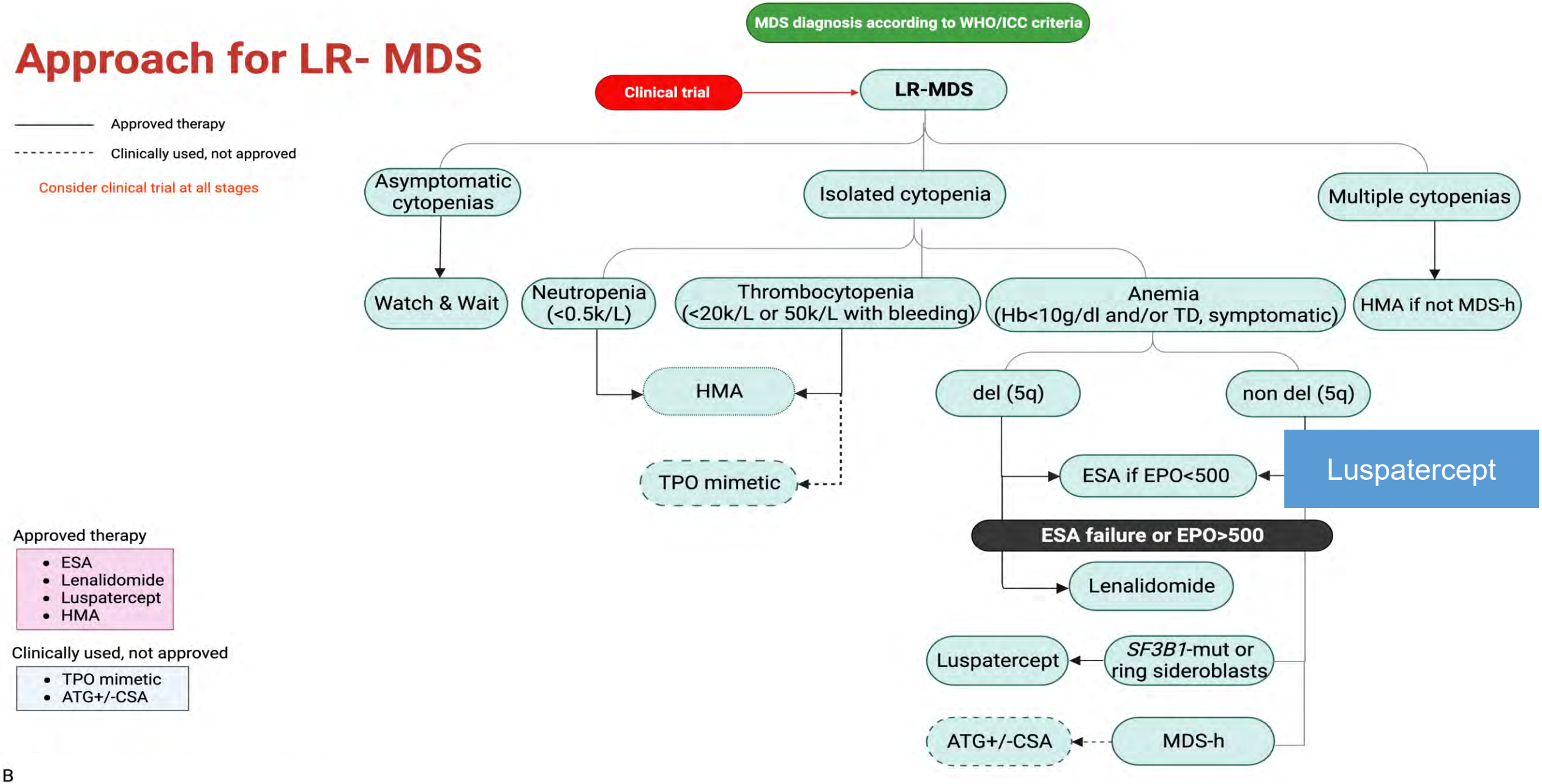
Bewersdorf J,,,,,Zeidan A. ASH 2023. Abstract 324

Approved therapy for MDS



Madanat F, Xie Z, Zeidan AM, Expert Rev Hematol 2023

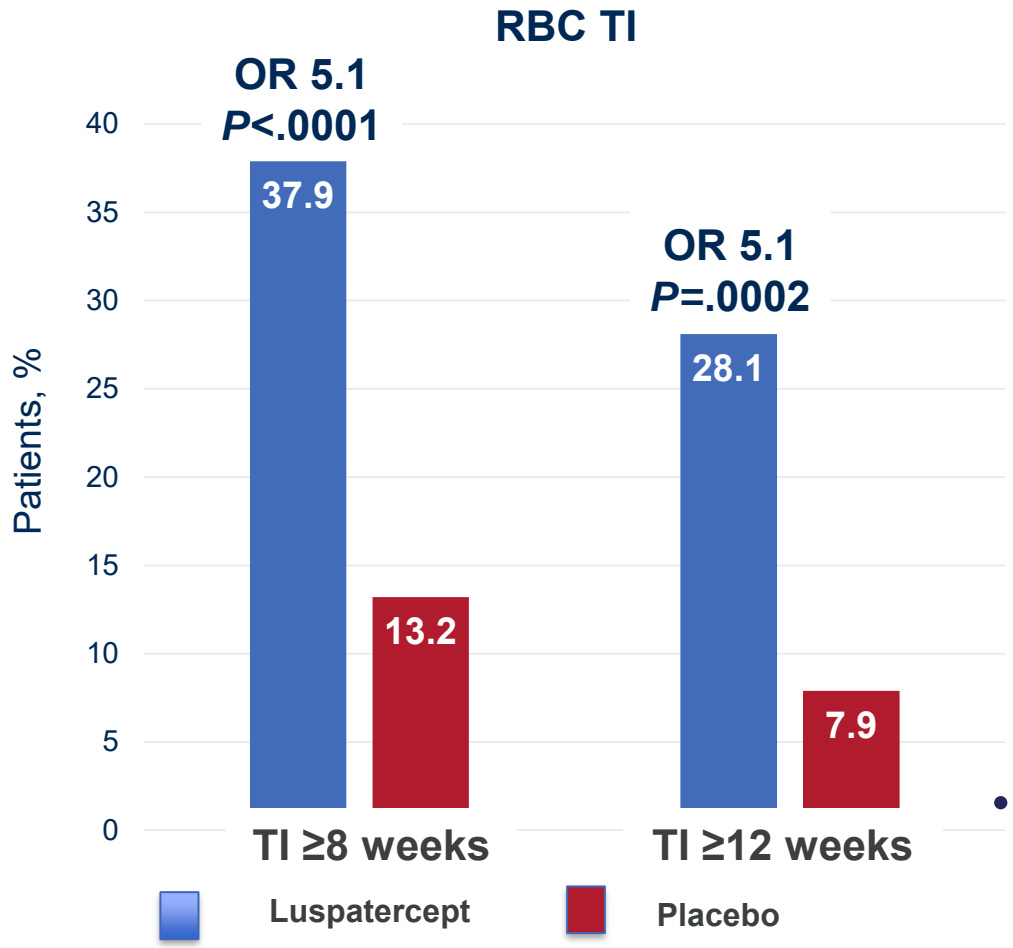
Approach for LR- MDS



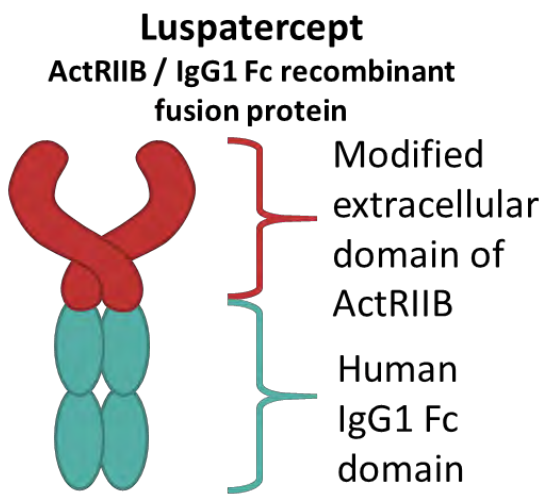
B

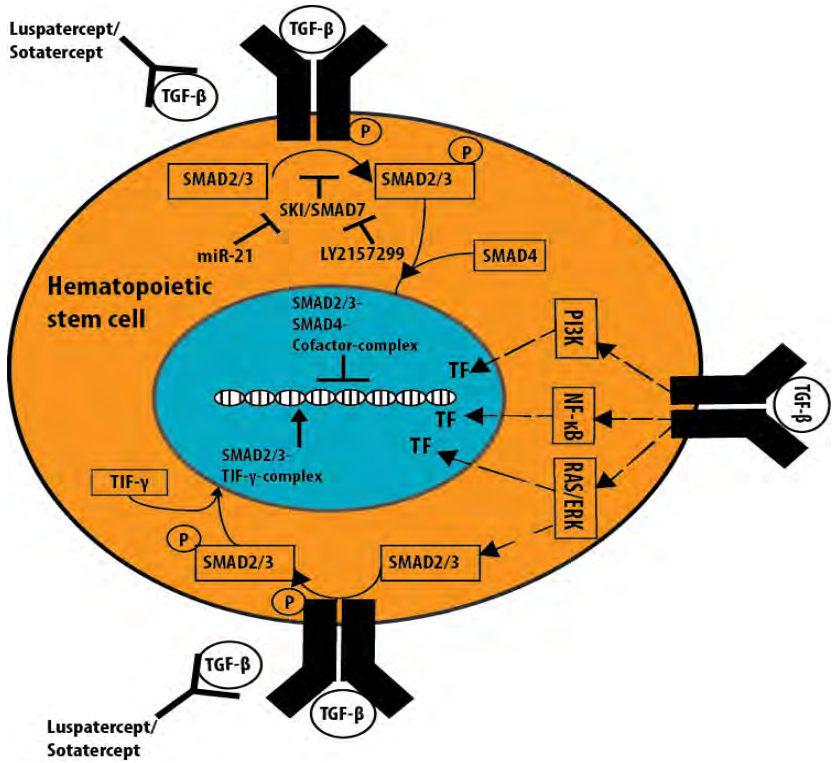
Bewersdorf J, Xie Z, Zeidan AM. The Cancer Journal 2023

The MEDALIST trial
Luspatercept significantly improved RBC TI rate compared to placebo



[a]Defined as a reduction in transfusion of ≥4 RBC units/8 weeks or a mean Hb increase of ≥1.5 g/dL/8 weeks in the absence of transfusions.

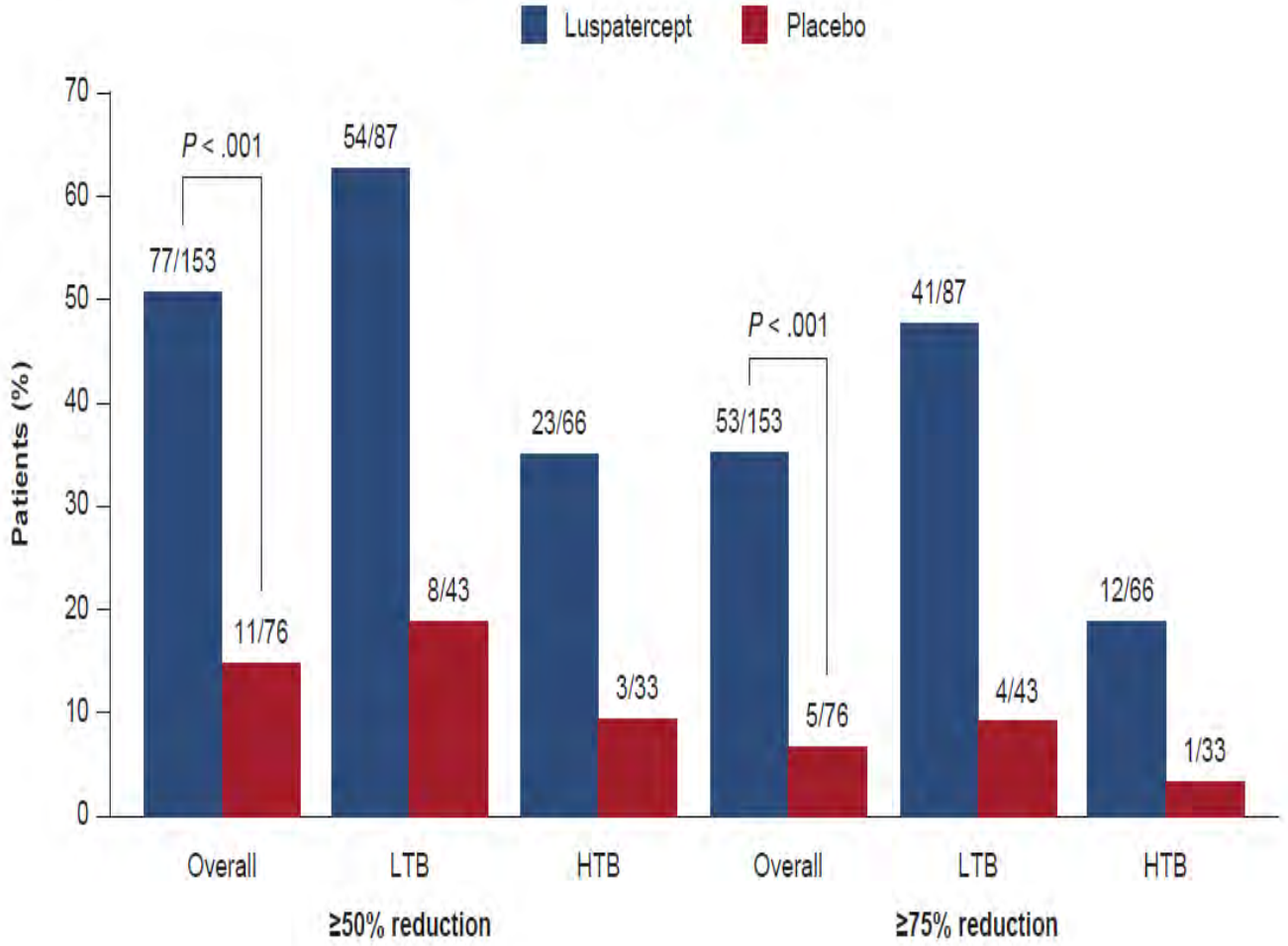




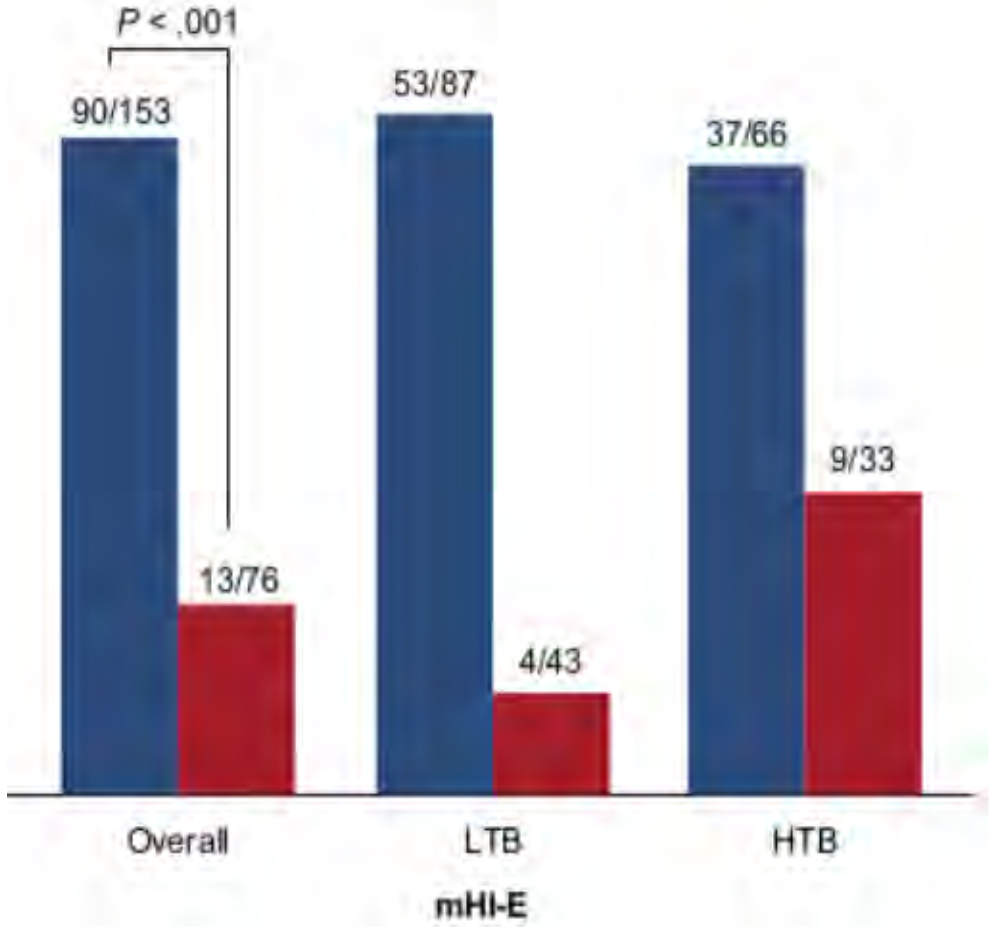
- Luspatercept is a first-in-class erythroid maturation agent (EMA) that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis

Fenaux P et al, NEJM 2020; Bewersdorf and Zeidan, Leukemia 2019

Luspatercept vs Placebo in MDS (MEDALIST): Reduction in RBC transfusion burden and improvement in HI-E



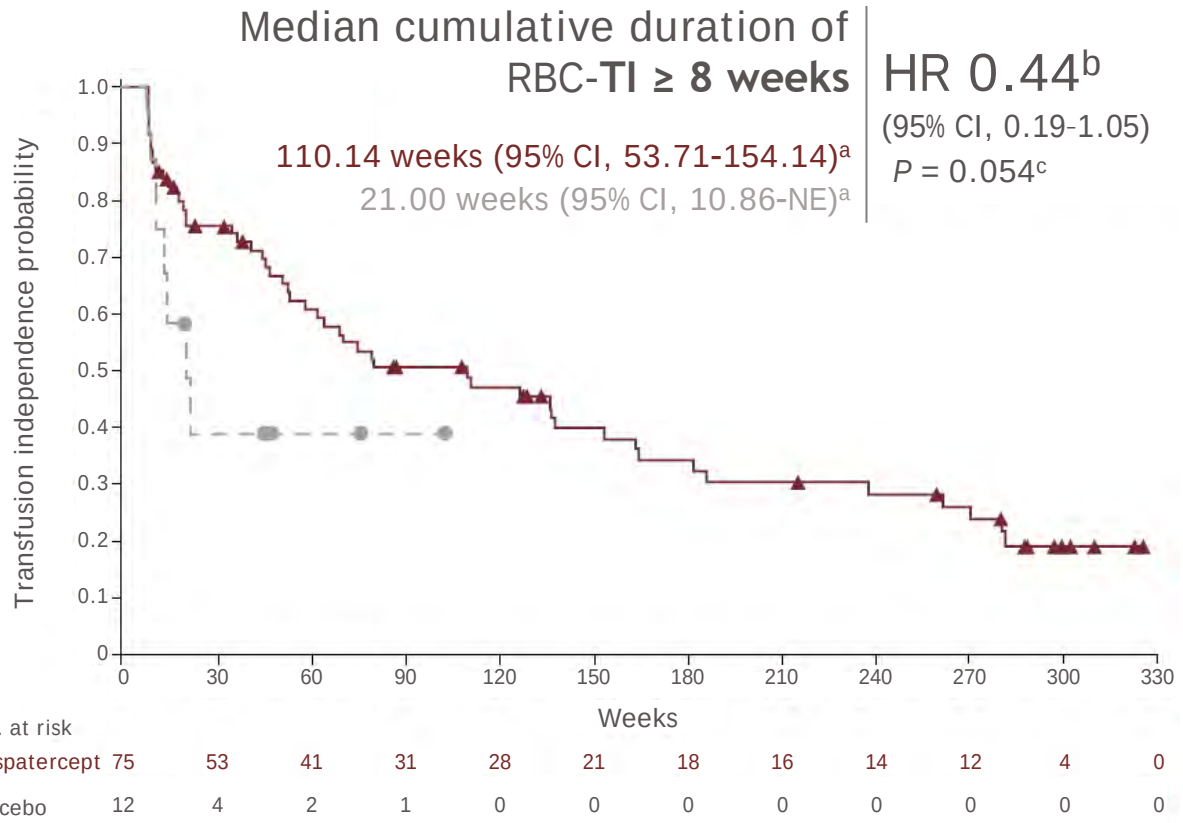
Change in RBC transfusion burden (TB): L: Low, H: High

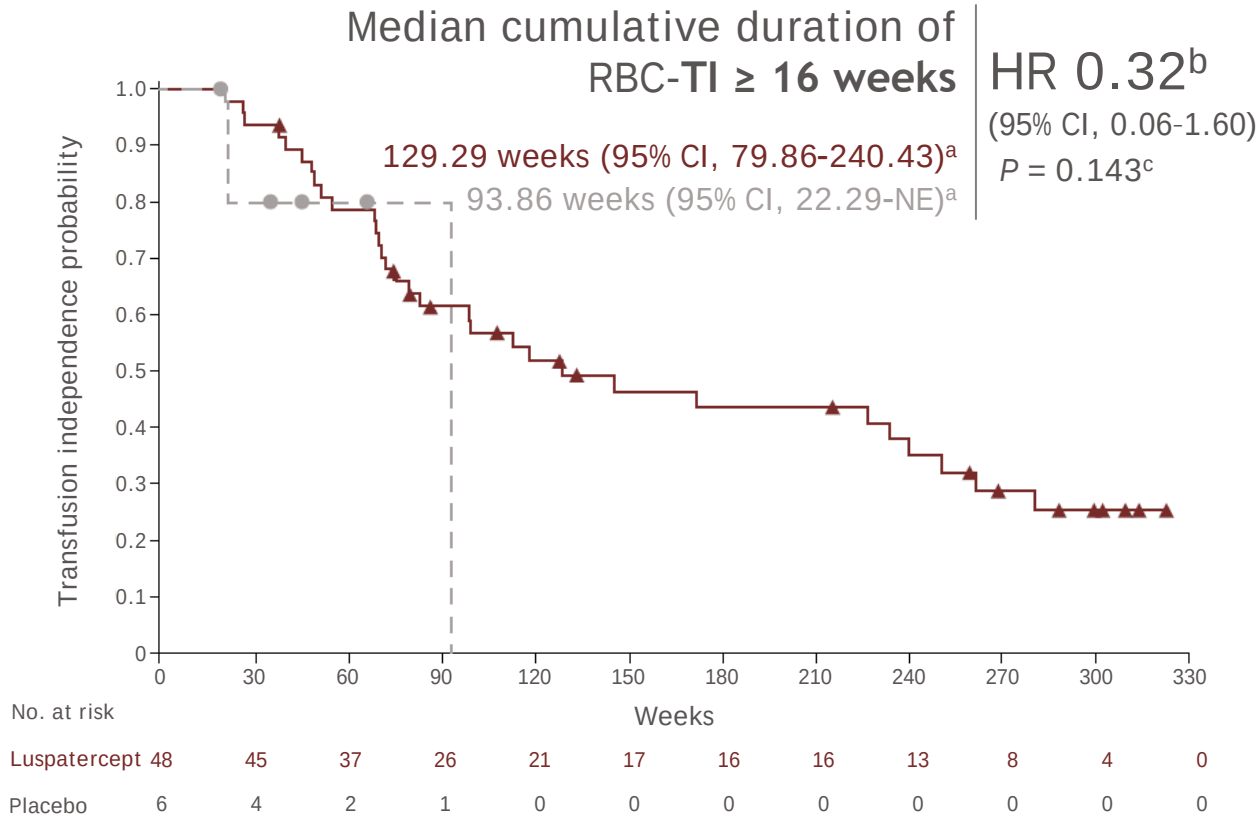


Change in erythroid hematologic improvement (HI-E)

Zeidan A et al, Blood 2022

Final analysis of the MEDALIST Trial
Efficacy





After more than 6 years of follow-up, patients with LR-MDS who received luspatercept for > 2 years longer than in the original MEDALIST study still experienced sustained RBC-TI

41.3% and 64.6% of patients who achieved RBC-TI ≥ 8 weeks and RBC-TI ≥ 16 weeks, respectively, achieved uninterrupted RBC-TI ≥ 1 year

Rates of RBC-TI response increased with treatment time

Santini V,,,,,,,,,Zeidan A, ASH 2023, Abstract 915

The COMMANDS Trial

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

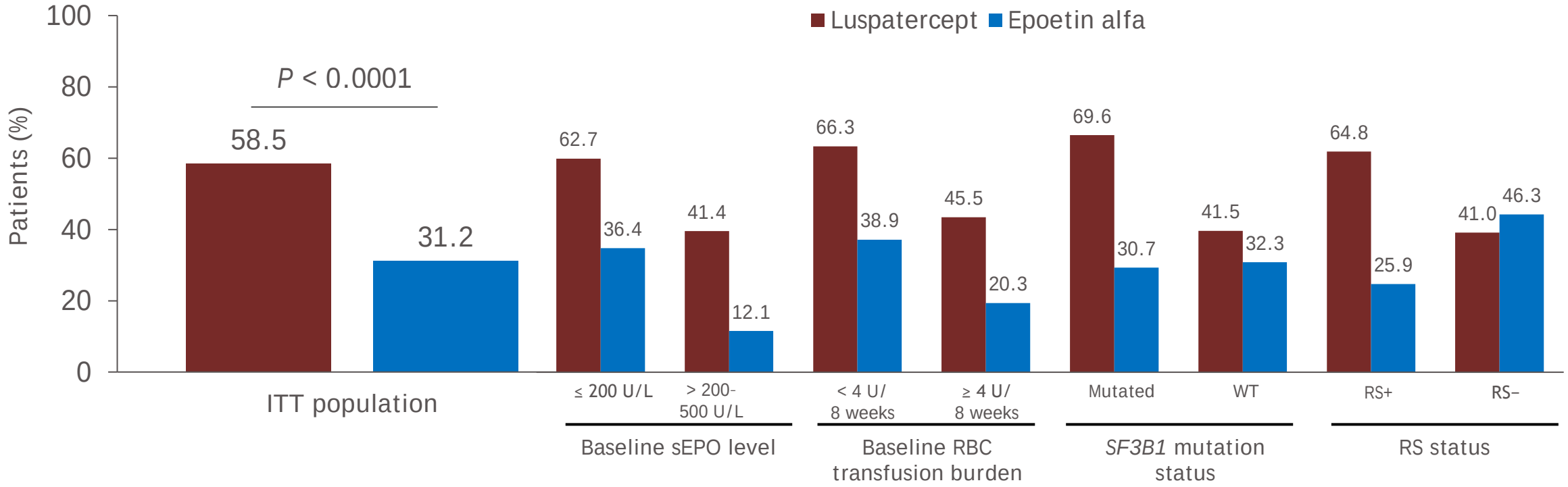
Post-treatment safety follow-up

- 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 randon 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 mye kemia; 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.

COMMANDS Trial Interim Analysis: Efficacy

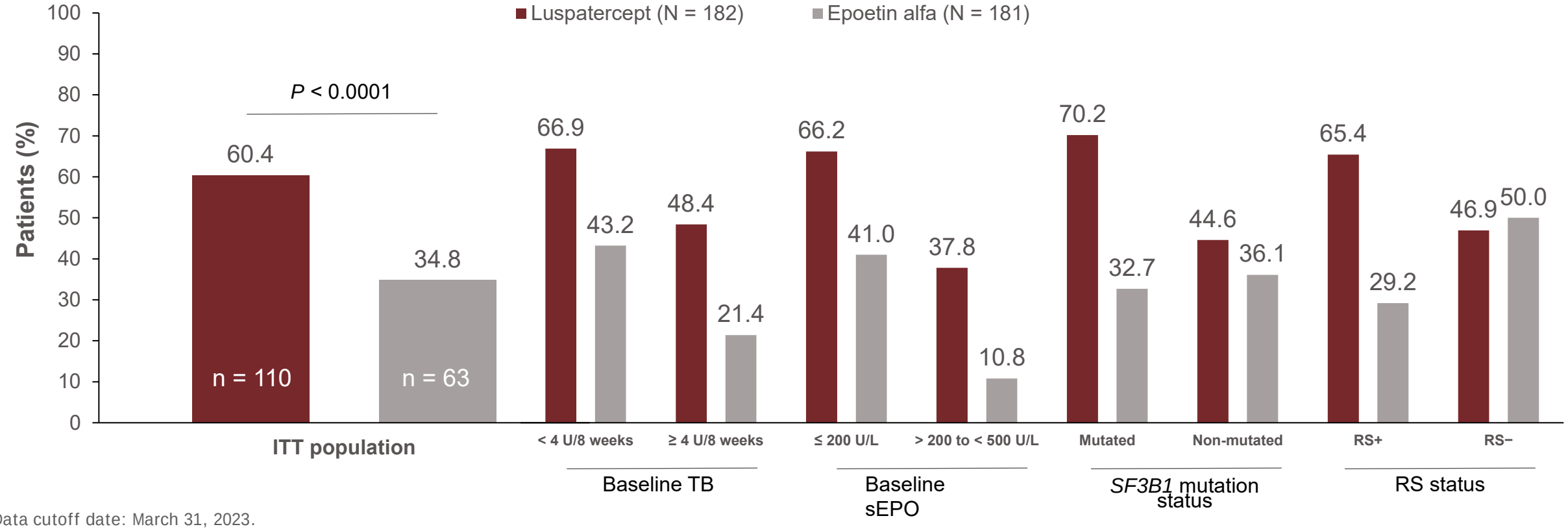
- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
  - Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed



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

COMMANDS Trial Full Analysis: Efficacy

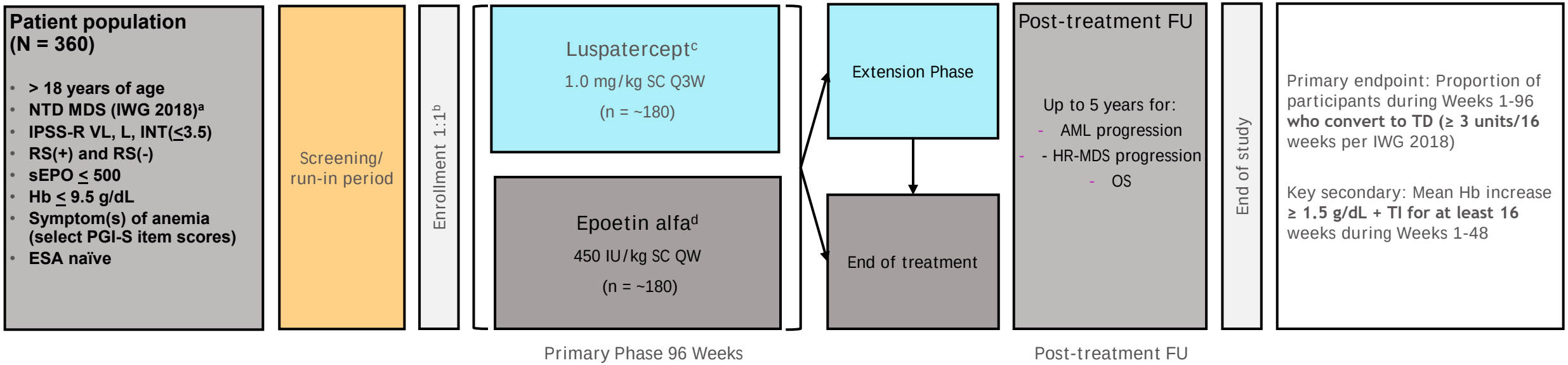
- The primary endpoint was achieved by 110 (60.4%) patients in the luspatercept arm versus 63 (34.8%) patients in the epoetin alfa arm ($P < 0.0001$)
  - Subgroup analysis of the primary endpoint showed greater response rates with luspatercept regardless of baseline TB, sEPO category, or *SF3B1* mutation status



Data cutoff date: March 31, 2023.
ITT, intent to treat.

ELEMENT MDS Trial

A Phase 3 registrational trial of luspatercept vs epoetin alfa in first-line non-RBC transfusion dependent lower risk MDS (N=360)



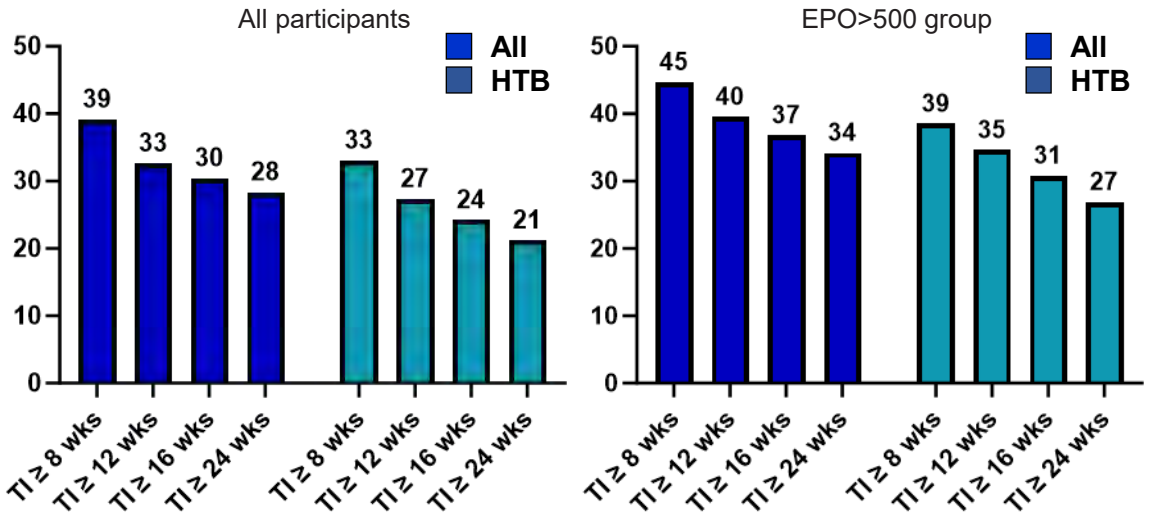
Steering Committee chair: Amer Zeidan

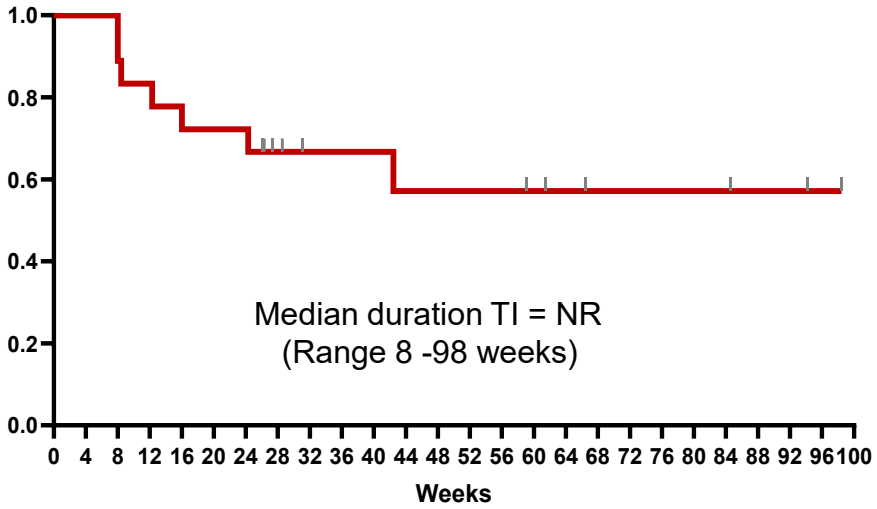
Zeidan A et al, ASH, 2023; Clinicaltrials.Gov : NCT05949684

New TGF pathway targeting agents: A phase 2 of KER-050 (elritercept)

Responders N (%)	$mITT_{24}$[a]		
	All (N=60)	HTB (N=33)	EPO<500 (N=50)
Overall Response[a,b]	**30/60 (50)**	**15/33 (45.5)**	**28/50 (56.0)**
Modified IWG 2006 HI-E[c]	**28/60 (47)**	**15/33 (45.5)**	**26/50 (52.0)**
RS+	23/40 (58)	12/23 (52.2)	21/36 (58.3)
non-RS	5/20 (25)	3/10 (30)	5/14 (35.7)
TI ≥8 weeks[d]	**18/46 (39.1)**	**11/33 (33.3)**	**17/38 (44.7)**
RS+	15/32 (46.9)	8/23 (34.8)	14/29 (48.3)
non-RS	3/14 (21.4)	3/10 (30)	3/9 (33.3)

[a] Includes data for weeks 0-24 in $mITT_{24}$ participants.
[b] Defined as achieving modified IWG 2006 HI-E and/or TI.
[c] Modified HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on treatment compared to 8-week pre-treatment period.
[d] TI-evaluable participants received at least 2 RBC units in the 8-week pre-treatment period.





KER-050 achieved important hematologic response: 50% HI-E;39% TI≥8 weeks.

- **Response rate similar in HTB subgroup**
- **Higher responses in EPO<500 U/L**
- **Among responders, >50% durable TI≥52 weeks**

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

RANDOMIZE

2:1

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

Placebo
(N = 60)

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

Safety population (treated) N = 177
Imetelstat N = 118
Placebo N = 59

Primary End Point:
- 8-week RBC-TI[b]

Key Secondary End Points:
- 24-week RBC-TI[b]
- Duration of TI
- Hematologic Improvement-Erythroid
- Safety

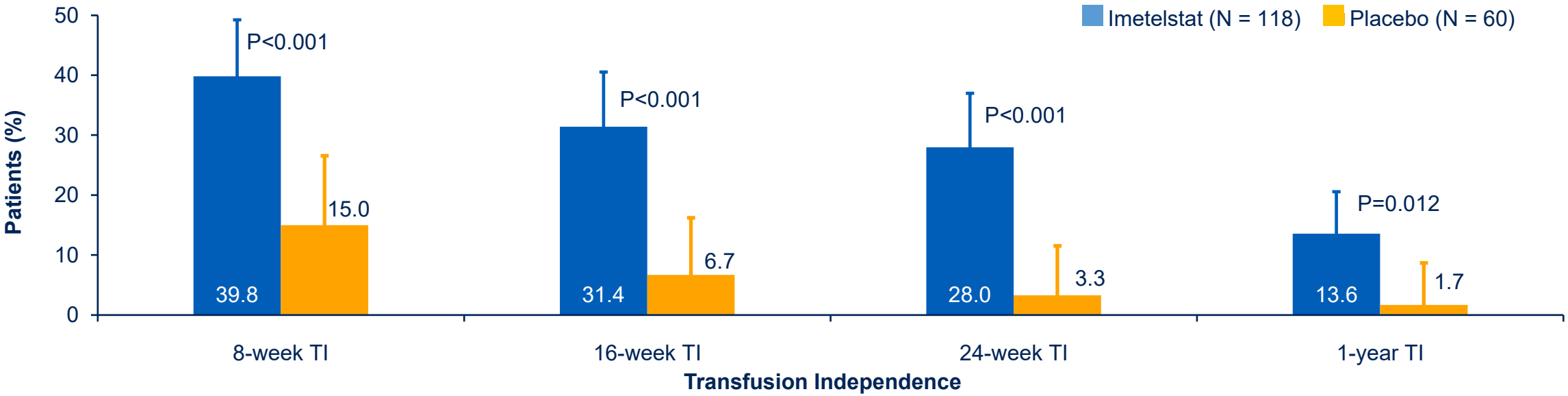
Key Exploratory End Point:
- VAF changes
- PRO (fatigue measured by FACIT-Fatigue)

[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U or darbepoetin alfa 150 µg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/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)

Zeidan A, et al. Presented at: ASCO;2023. NCT02598661. Accessed June 19, 2023. https://clinicaltrials.gov/ct2/show/NCT02598661. Platzbecker U et al, Lancet 2023

Higher Rates of Longer-Term Duration of RBC TI Observed with Imetelstat vs Placebo



Patients With Response, n (% [95% CI])

Imetelstat	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
Placebo	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])

Data cutoff: October 13, 2022.

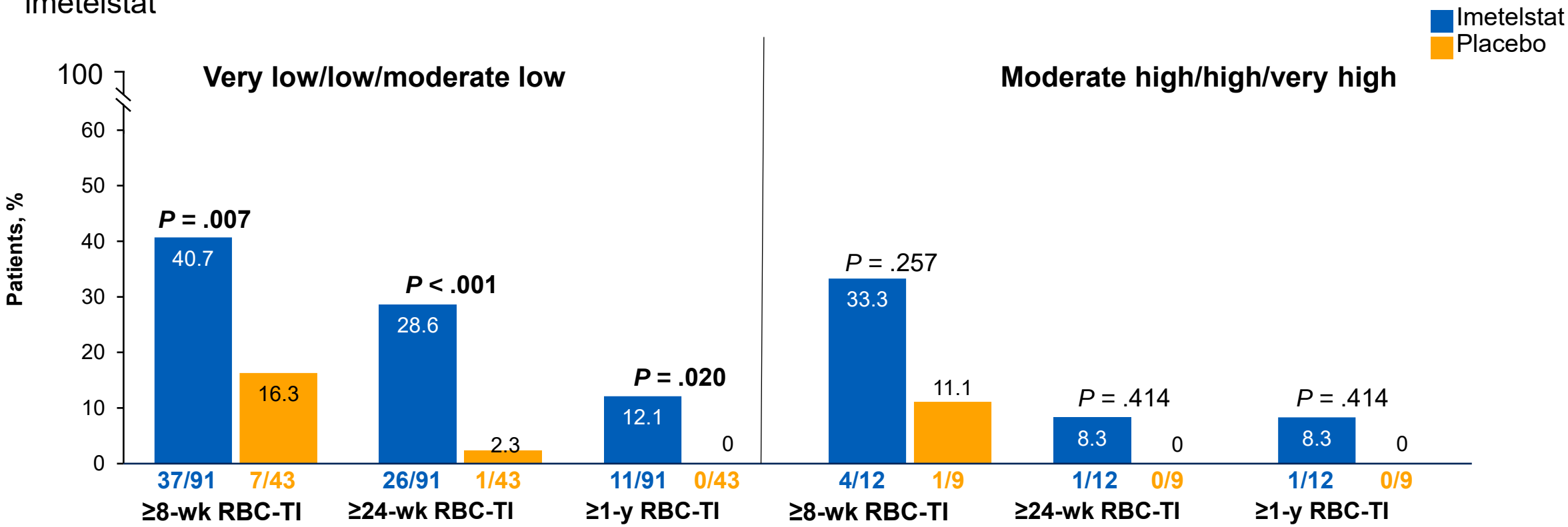
[a]Primary end point 8-week and the first secondary end point 24-week TI are statistically significant by study prespecified gatekeeping testing procedure. One-year TI represented a preliminary assessment. P-values determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion 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; RBC, red blood cell; TI, transfusion independence.

Zeidan A, et al. Presented at: ASCO;2023. NCT02598661. Accessed June 19, 2023. https://clinicaltrials.gov/ct2/show/NCT02598661. Platzbecker U et al, Lancet 2023

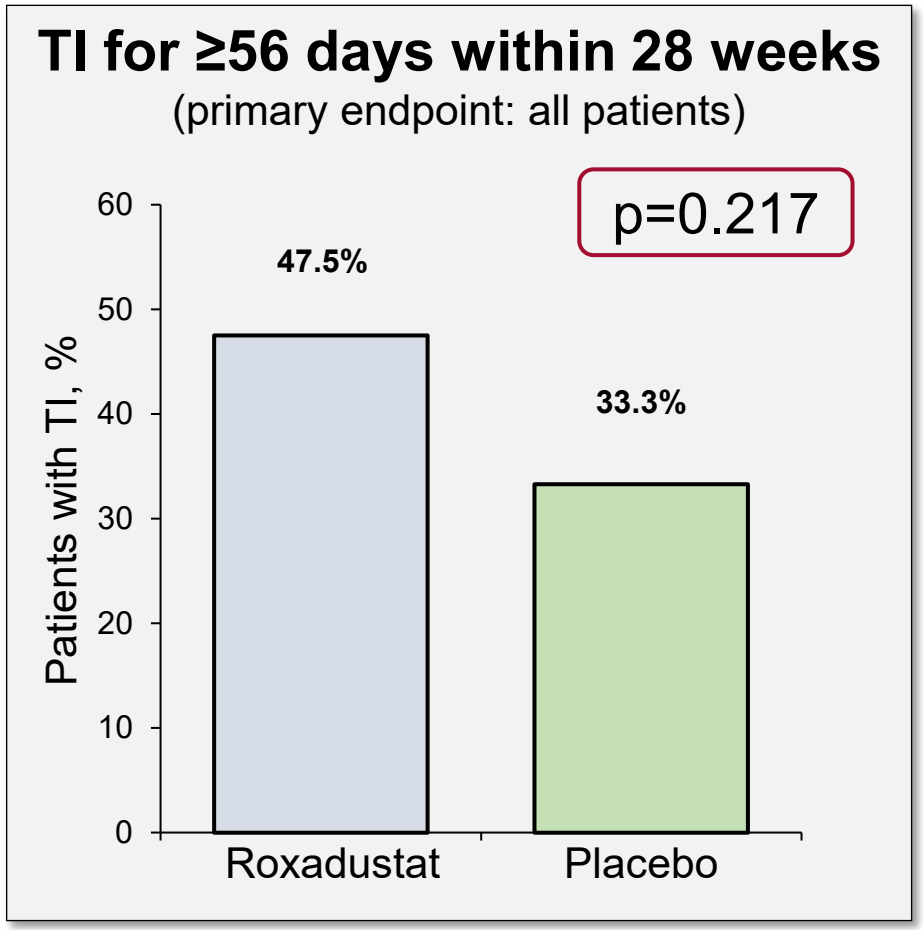
RBC-TI by IPSS-M Subgroup

- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-M risk group
- 4 out of 12 patients (33%) reclassified as having higher risk MDS by IPSS-M had ≥8-week RBC-TI with imetelstat



Data cutoff date: October 13, 2022.
Hb, hemoglobin; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

Roxadustat for Treatment of Anemia in Patients with LR-MDS with Low RBC Transfusion Burden: Results of Phase III Matterhorn Study

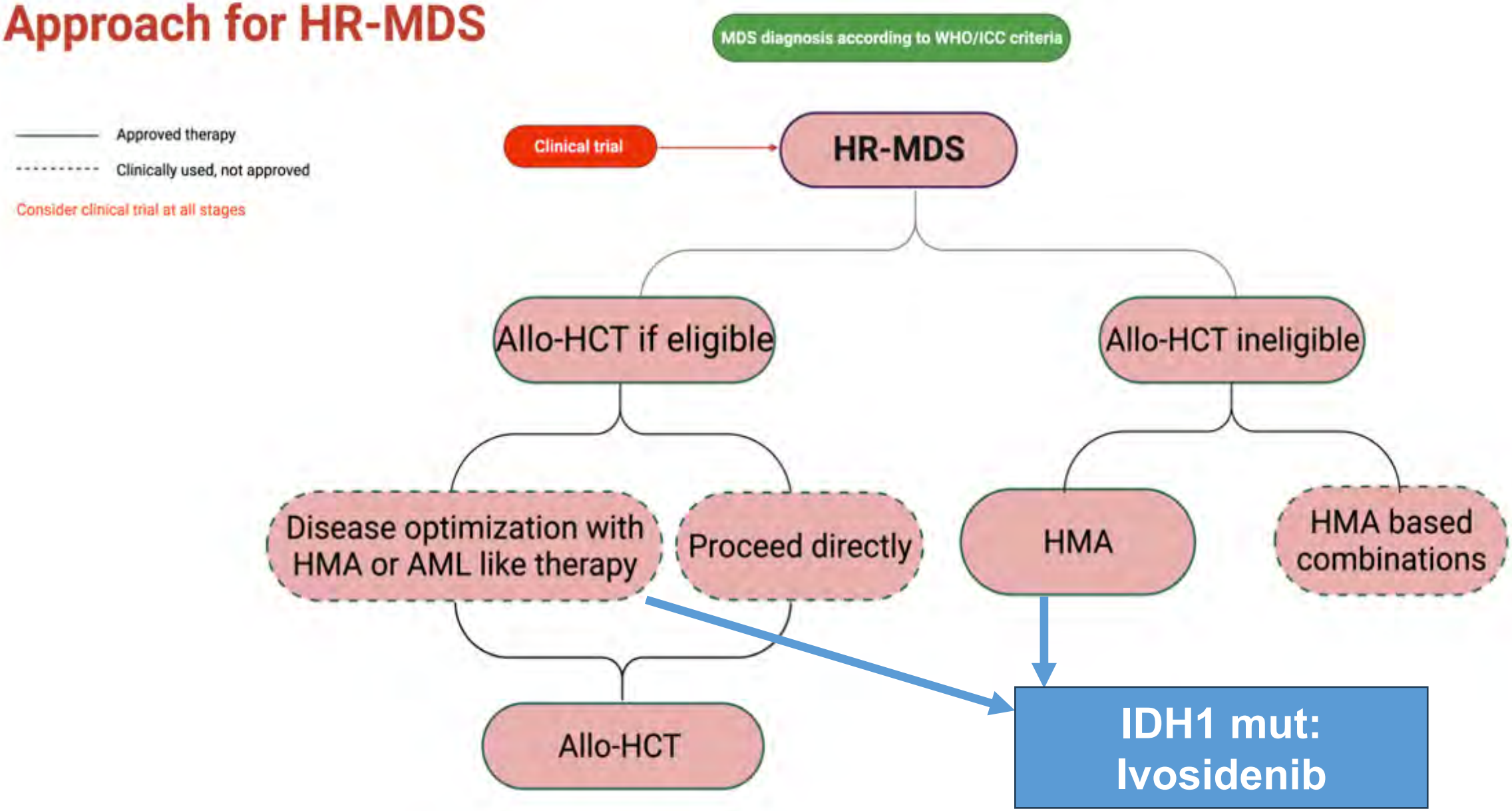


% (95% CI)	Roxadustat (n=80)	Placebo (n=57)	Roxadustat vs placebo
TI for ≥56 days within 28 weeks	47.5% (36.2–59.0)	33.3% (21.4–47.1)	OR: 1.582 (0.761–3.290) p=0.217

Study status: MATTERHORN was terminated because the primary endpoint outcomes did not meet statistical significance at 28 weeks

Final analysis (data cut-off date: Aug 2, 2023). Full analysis population (all randomized patients who received ≥1 dose of study drug and had ≥1 corresponding on-treatment Hb assessment). Pre-specified analysis. CI, confidence interval; Hb, hemoglobin; OR, odds ratio; TI, transfusion independence.

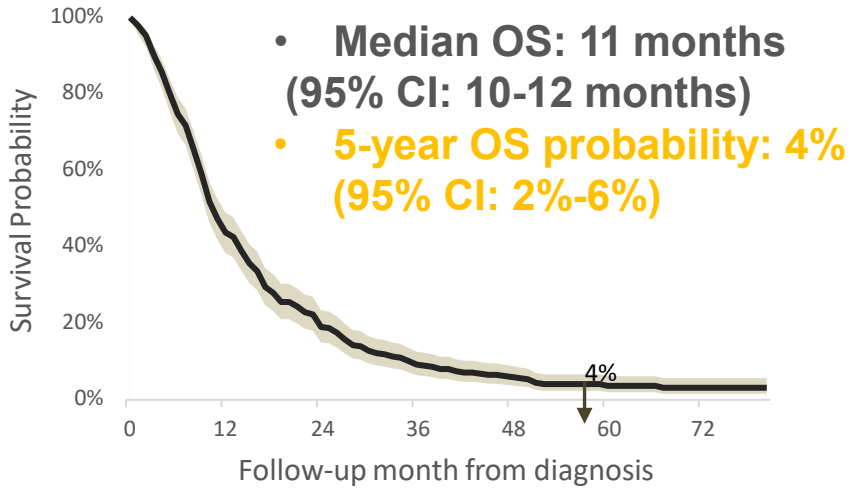
Approach for HR-MDS



Bewersdorf J, Xie Z, Zeidan AM. The Cancer Journal 2023

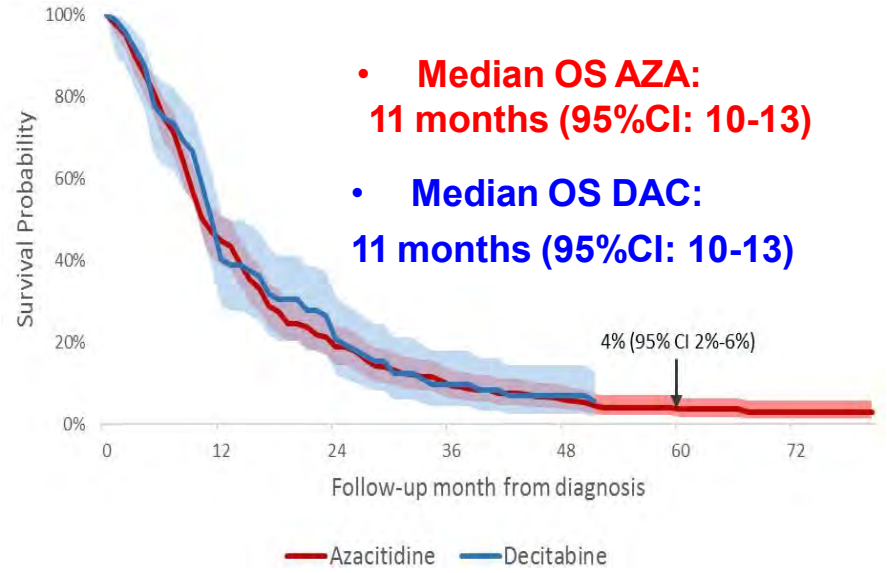
Long-term survival of MDS patients treated with HMAs who do not undergo transplantation

- 1187 total MDS patients
- RAEB: 336 (23.8% of all MDS patients)
- Age: 77 years (IQR 72-81)
- AZA: 79% DAC: 21%
- Median 5 cycles of HMA therapy
- ≥4 / ≥ 6 cycles of HMA therapy: 73%/ 50%
- AZA vs DAC: No difference in median HMA cycles



- Median OS: 11 months (95% CI: 10-12 months)
- 5-year OS probability: 4% (95% CI: 2%-6%)

Even among patients who received at least 6 cycles of HMA therapy:
Five-year OS probability 6%
(95% CI: 3 -11%)

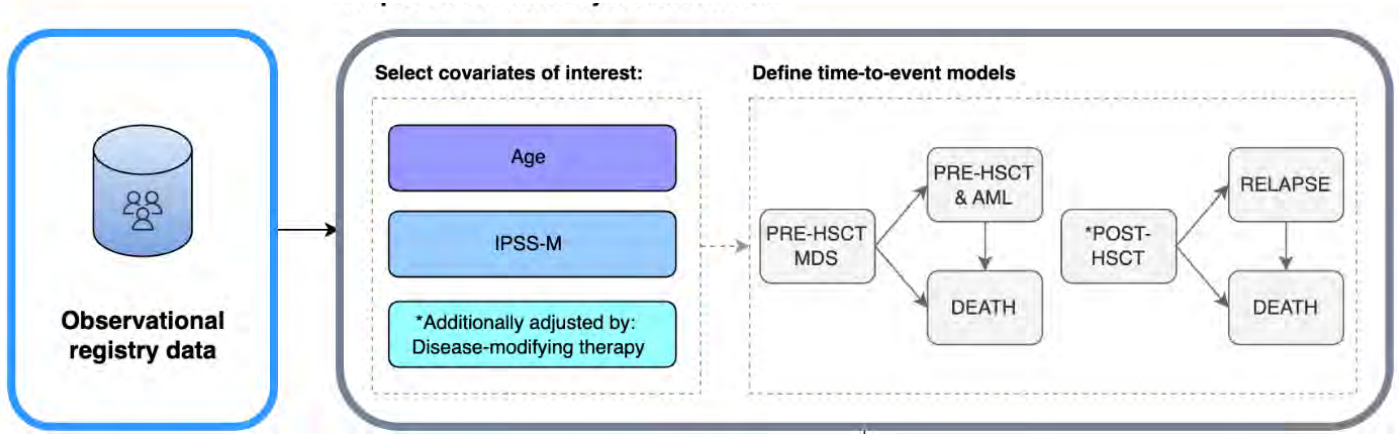


- Median OS AZA: 11 months (95%CI: 10-13)
- Median OS DAC: 11 months (95%CI: 10-13)

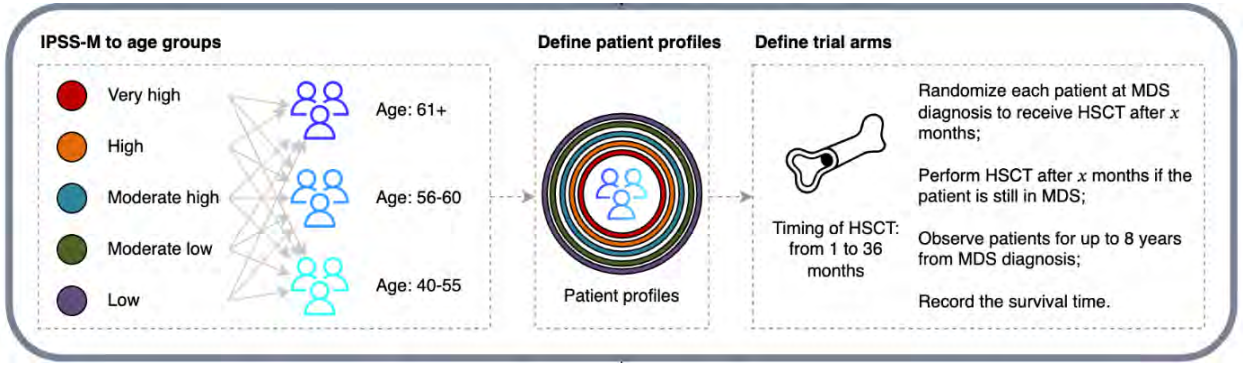
Zeidan et al, Blood, 2018

Clinical and genomic-based Decision Support System to define the optimal timing of allogeneic transplantation in MDS (N=7,118)

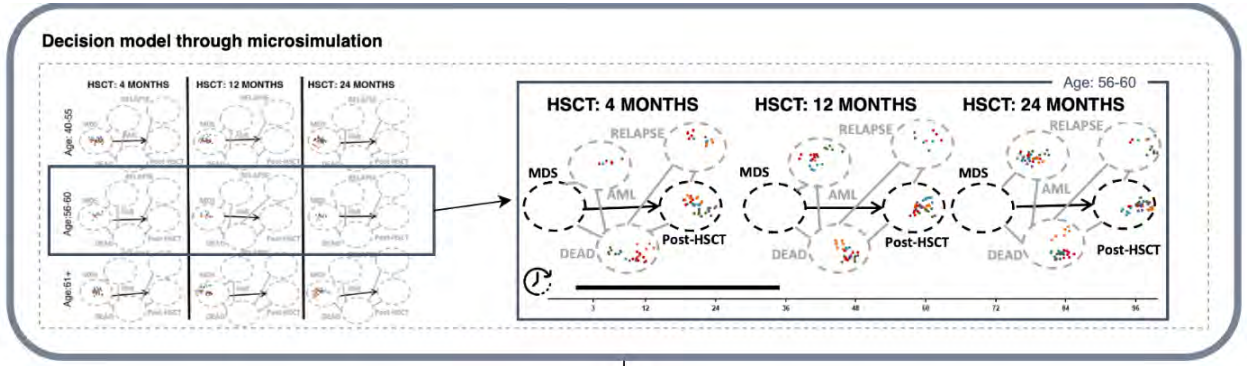
STEP 1 – Model of the disease natural history



STEP 2 Simulation of the target trial

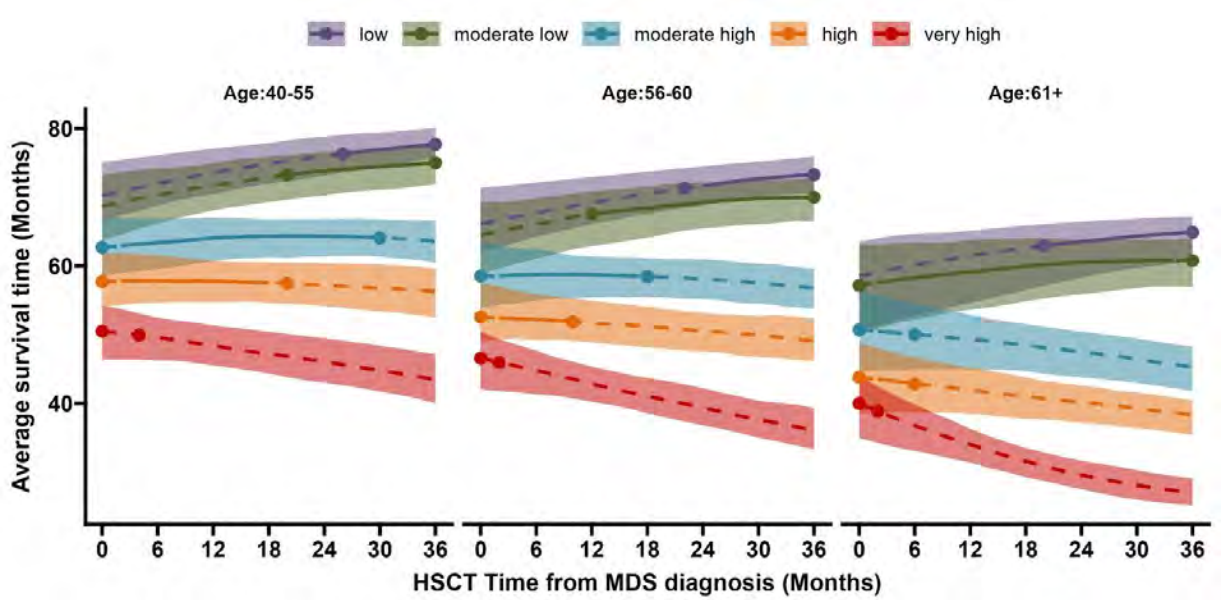


STEP 3 Scenario analysis - microsimulation

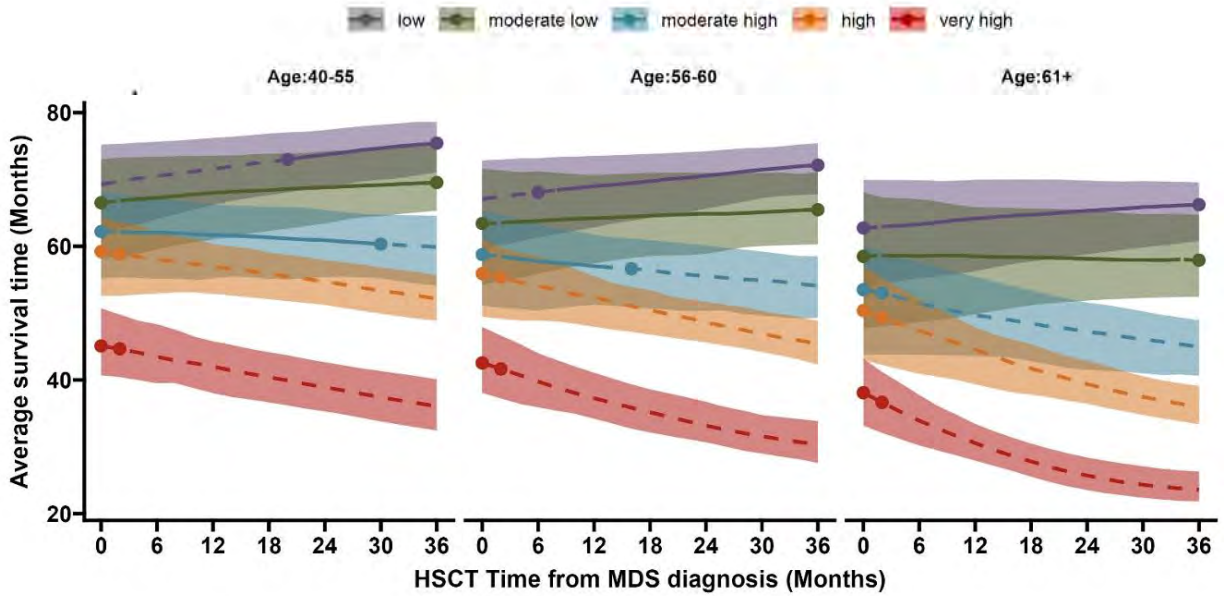


IPSS-M based transplantation policy

A – TRAINING COHORT



B – VALIDATION COHORT



- Under an IPSS-M based policy, in the training cohort, **patients with either low- and moderate-low risk benefited from a delayed transplantation policy, while in those belonging to moderate-high, high- and very-high risk categories immediate transplantation was associated with a prolonged RMST**. All these results were confirmed in the validation cohort.

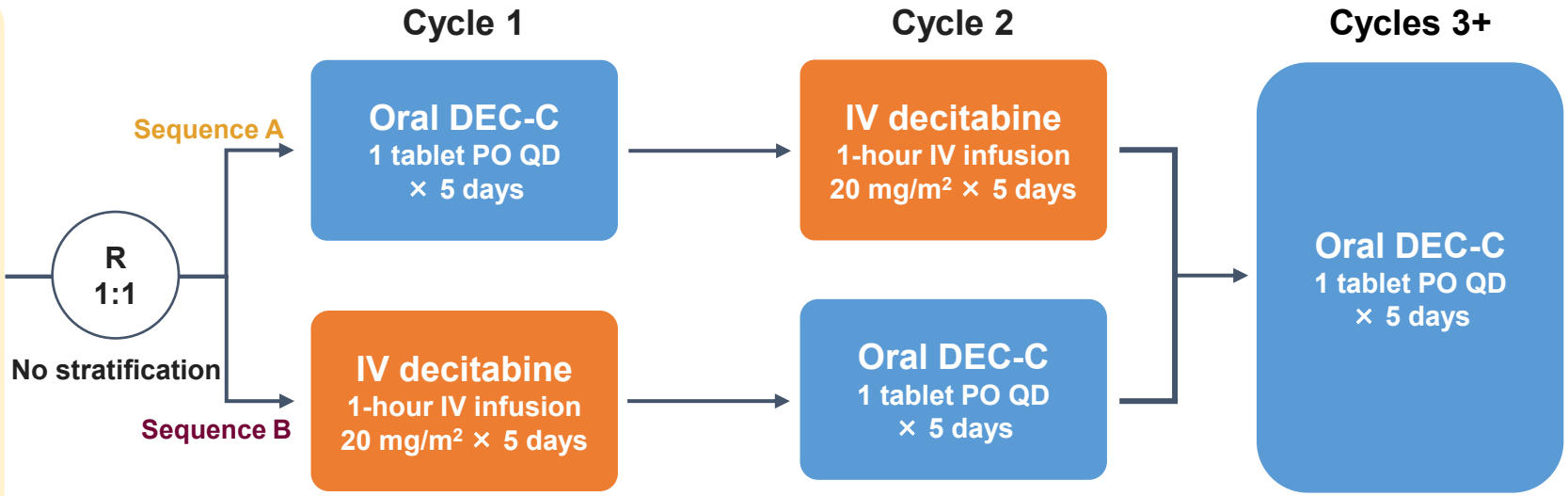
- Modelling decision analysis on IPSS-M vs conventional revised-IPSS (IPSS-R) changed transplantation policy in a relevant proportion of patients, resulting in a significant gain in life expectancy under an IPSS-M based policy

ASCERTAIN: Phase 3 Study (ASTX727-02) of DEC-C in Patients With MDS or CMML

Study design (NCT03306264): Multicenter, open-label, randomized, 2-cycle, 2-sequence, crossover study of oral DEC-C vs IV decitabine[1–3]

Ascertain MDS and CMML

N=133
- Age ≥18 years
- MDS, including all FAB subtypes and CMML, or IPSS intermediate-1, intermediate-2, or high-risk
- ECOG PS 0–1
- Adequate organ function
- 1 prior cycle of HMA allowed



Each cycle is 28 days; treatments are administered QD on days 1–5

Primary endpoint[1]
- Total 5-day decitabine AUC equivalence (oral/IV 90% CI: 80%, 125%)

Decitabine 5-day $AUC_{0\text{-}24}$ (h·ng/mL)		IV DEC N	IV DEC Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (% CV)
Primary Analysis	Paired*	123	864.9	123	855.7	98.9 (92.7-105.6)	31.7

Garcia-Manero G, McCloskey J, Griffiths E, Lee K, Zeidan A, et al, Lancet Haematology 2023

ASCERTAIN Trial: Efficacy Data

Response, n (% [95% CI])	All patients (n=133)
Complete response	29 (22 [15.1, 29.8])
Partial response	0
Marrow complete response	43 (32.3 [24.5, 41.0])
Marrow complete response with hematologic improvement	22 (16.5 [10.7, 24.0])
Hematologic improvement	10 (8 [3.7, 13.4])
Erythroid response	2 (2 [0.2, 5.3])
Neutrophil response	1 (1 [0.0, 4.1])
Platelet response	7 (5 [2.1, 10.5])
Total responders[a]	82 (62 [52.8, 69.9])
Progressive disease	6 (5 [1.7, 9.6])
No response[b]	29 (22 [15.1, 29.8])
Not evaluable	16 (12 [7.0, 18.8])

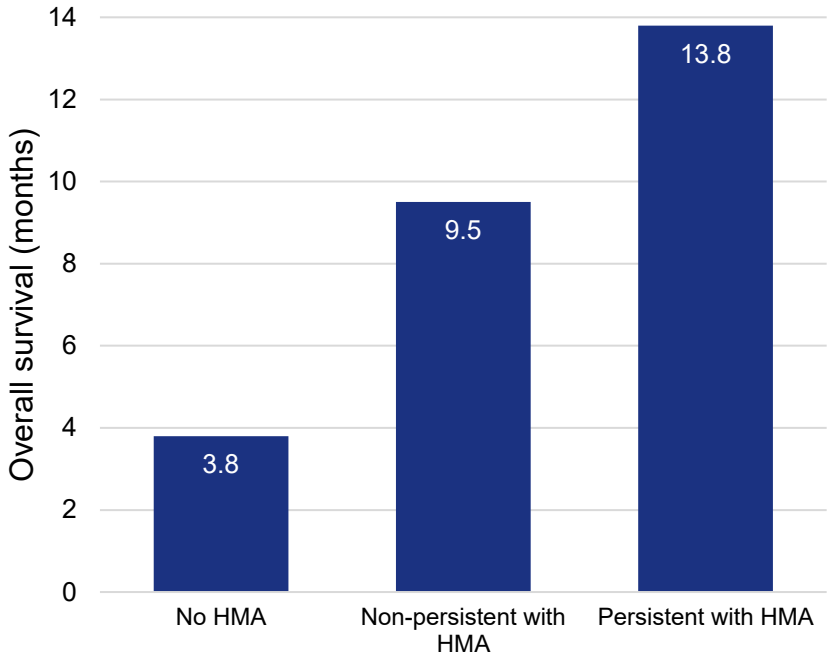
- Median follow up time 2.6 years
- Overall response rate was 62% among the total population (82/133) with a CR of 22%
- Median durations of best and complete response were ~1 year and ~14 months, respectively
- Transfusion dependence for RBC and platelets declined by 52% and 50%, respectively, over baseline
  - RBC: 28/54 (52%) becoming transfusion-independent
  - Platelets: 6/12 (50%) becoming transfusion-independent
- Median number of cycles: nine
- 27 (20%) patients proceeded to HSCT
- Median OS for the 133 patients was 31.8 months (95% CI: 28, NE)

Garcia-Manero G, McCloskey J, Griffiths E, Lee K, Zeidan A, et al, Lancet Haematology 2023

Real-life analyses suggest a negative impact of non-persistence on HMA therapy among patients with HR-MDS

- IV/SC HMAs are underutilized in clinical practice[1,2]
- In real-world studies (2010–2020), 44–65% of patients with HR-MDS did not receive HMA therapy[1–4]
- 44% of patients receiving HMAs were non-persistent with therapy[1,4,a]
- Underuse of HMA therapy has been associated with higher HCRU and worse survival outcomes[1,3-5]

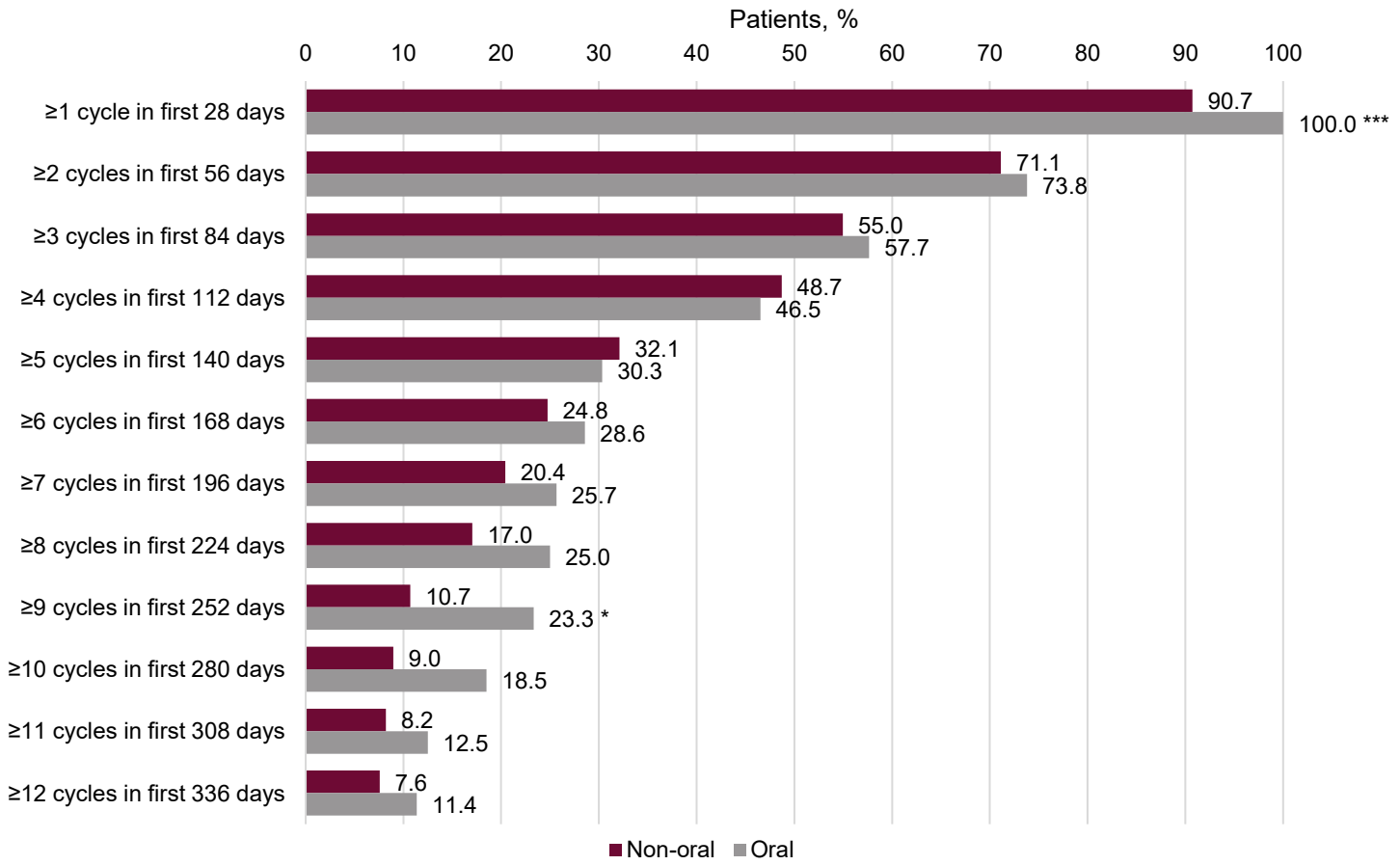
OS according to HMA use (N=1190)[1]



Non-persistent: Received <4 cycles of HMA therapy or a gap of ≥90 days between cycles. HCRU, healthcare resource utilization; HMAs, hypomethylating agents; HR-MDS, higher-risk myelodysplastic syndromes; IV/SC, intravenous and subcutaneous; OS, overall survival.

1. Corman S, et al. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):e206-e211. **2**. Zeidan AM, et al. Presented at the AMCP 2022 Congress, McCormick Place Convention Center, Chicago, IL, March 29–April 1, 2022. Poster D1. **3.** Zeidan AM, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(9):670-679. **4.** Joshi N, et al. *Clin Lymphoma Myeloma Leuk*. 2021;21(3):e248-e254. **5.** Cheng WY, et al. *Hematology.* 2021;26(1):261-270.

Real-World Treatment Patterns Among Patients With MDS Initiating Oral DEC-C or IV/SC HMAs

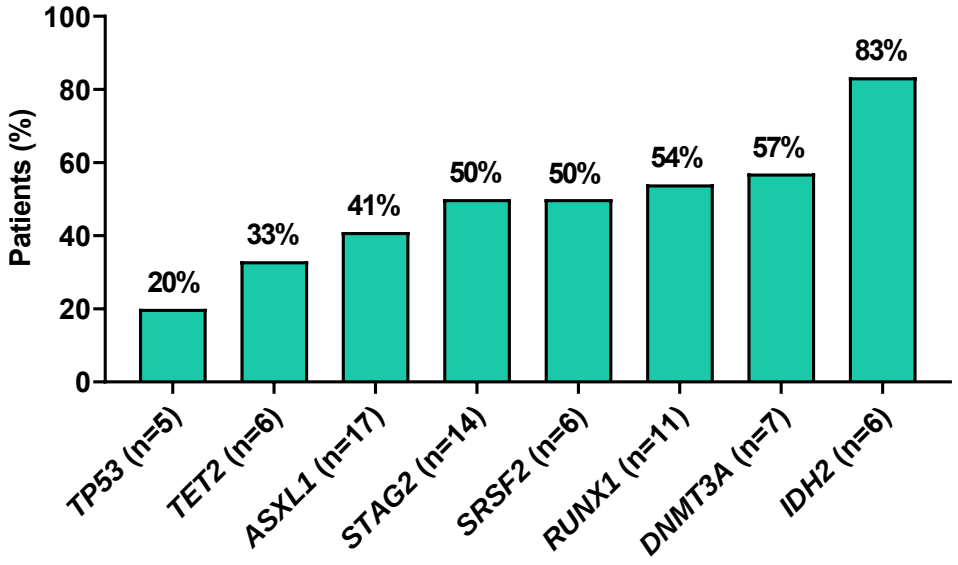


- Longitudinal persistence was comparable between the oral DEC-C and IV/SC HMA cohorts during the first 6 months after the index date
- A trend towards improved persistence with oral DEC-C vs IV/SC HMAs was observed in patients receiving treatment beyond 6 months
- Mean time to discontinuation of treatment was numerically higher for the oral DEC-C cohort vs the IV/SC HMA cohort (87.7 vs 82.0 days); however, differences were not statistically significant

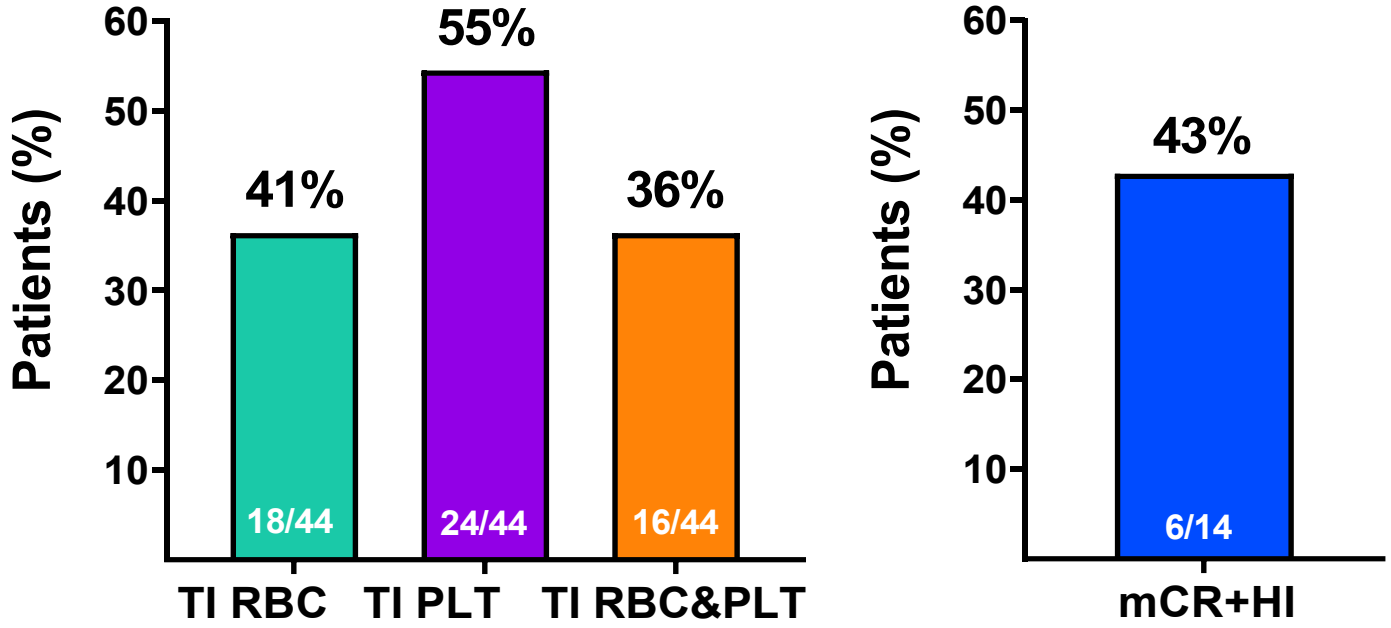
Zeidan A, et al, ASH 2023, abstract 548

A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine for the Treatment of Relapsed/Refractory MDS

CR+mCR by baseline mutations



Transfusion independence and Hematological Improvement

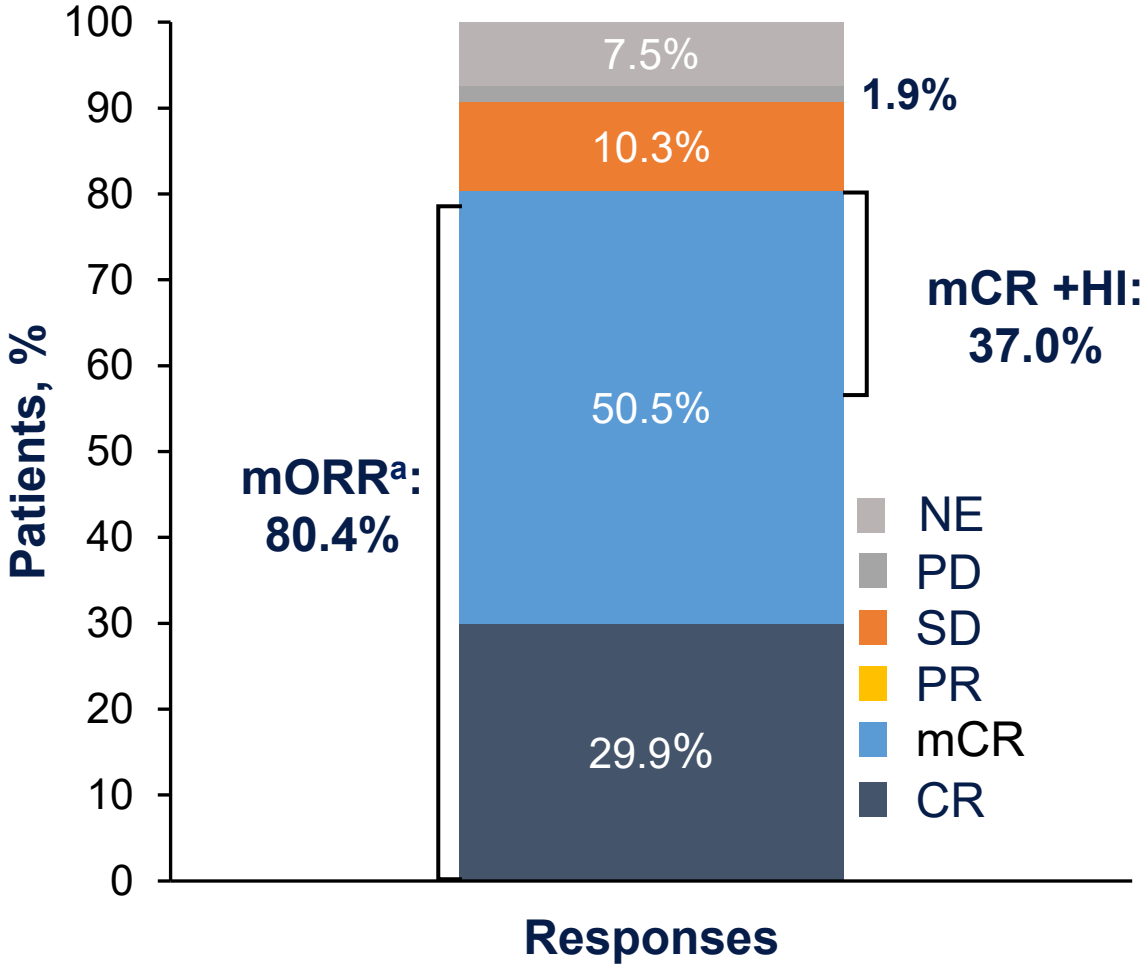


- Post-baseline TI (RBC or PLT) was achieved by 10/32 (31%) patients who were transfusion dependent at baseline

Zeidan A et al, AJH 2023

A Phase 1b/2 Study Evaluating Venetoclax in Combination with Azacitidine for frontline Treatment of higher risk MDS (N= 107): Response rate

>80% of Patients Who Received Ven + Aza Responded



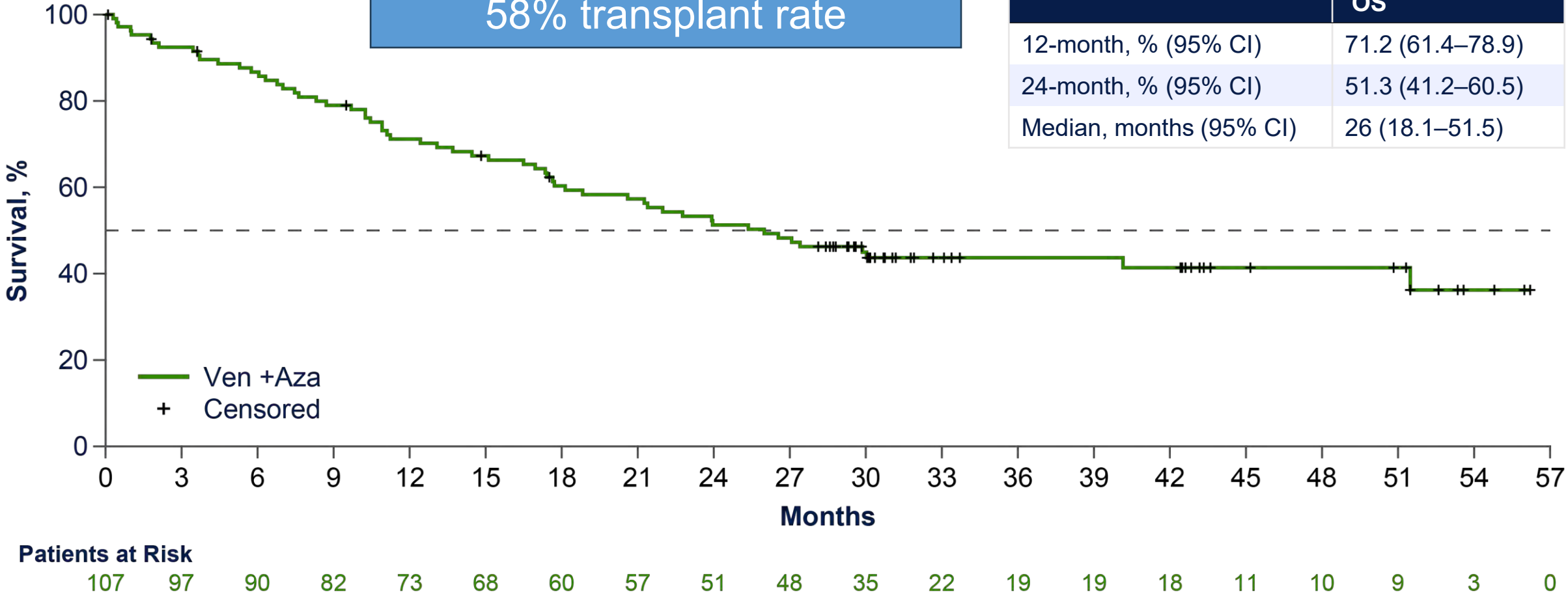
- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

[a]mORR=CR+mCR+PR; PR, n=0; response rates based on International Working Group 2006 response criteria.
AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; MDS, myelodysplastic syndromes; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

A Phase 1b/2 Study Evaluating Venetoclax in Combination with Azacitidine for frontline Treatment of higher risk MDS (N= 107): Overall survival

58% transplant rate

	OS
12-month, % (95% CI)	71.2 (61.4–78.9)
24-month, % (95% CI)	51.3 (41.2–60.5)
Median, months (95% CI)	26 (18.1–51.5)



[a]Overall survival was defined as the number of months from the date of the first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Aza, azacitidine; OS, overall survival; Ven, venetoclax.

Trial In Progress: VERONA
Design

P3
Phase 3

Double-blind Placebo-controlled

Randomized

International ~210 sites 23 countries

Multicenter

Up to **500** patients are planned for enrollment

NCT04401748

First Subject Dosed October 4, 2020

~500 patients newly diagnosed with higher–risk MDS

1:1 Randomization

Stratification factors:
- **IPSS-R**
- **HSCT Transplant eligible vs. ineligible**
- **Geographical region**

Ven 400 mg QD (days 1-14/cycle) + Aza 75 mg/m² (7 days within 9 calendar days/cycle)

Placebo for Ven 400 mg QD (days 1-14/cycle) + Aza 75 mg/m² (7 days within 9 calendar days/cycle)

Primary endpoints (PE):
- Dual PE are CR and OS

Secondary endpoints:
- RBC and Platelet TI for patients who are transfusion dependent at baseline
- Change from baseline in fatigue (by the PROMIS Fatigue SF 7a)
- Time to deterioration of physical functioning (by EORTC QLQ-C30)
- Overall response (OR): CR + PR
- Modified OR: CR + PR + mCR

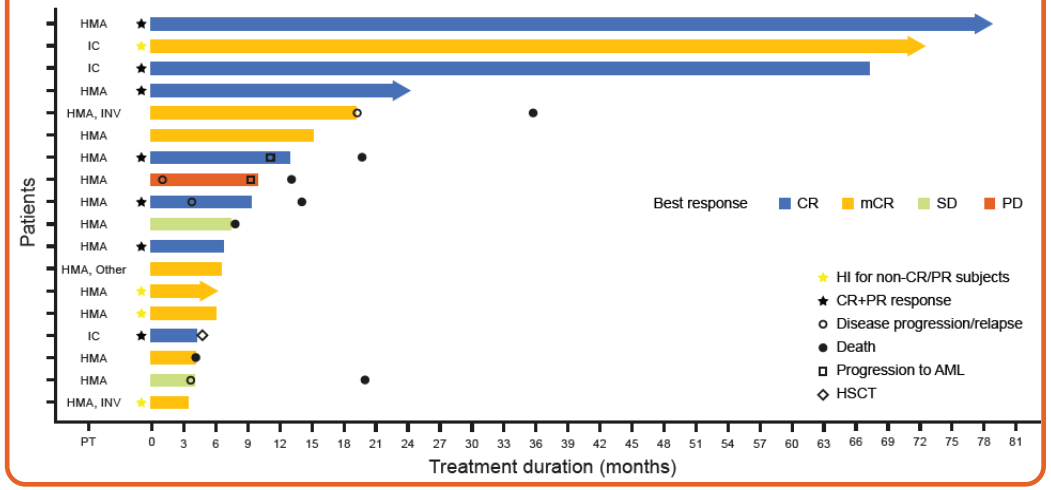
ivosidenib in mIDH1 R/R MDS

- In the efficacy analysis set (N=18)[a], the CR rate and ORR[b] were 38.9% and 83.3%, respectively; there were no PRs
- Median durations of CR and overall survival were not reached (range: 1.9–80.8[c]) and 35.7 (3.7[c]–88.7[c]) months, respectively, according to KM analyses
- One (5.6%) pt underwent a stem cell transplant; two (11.1%) progressed to AML
- Eight (44.4%) pts experienced mCR, four (50.0%) of whom had HI in at least one lineage (erythroid, platelet, and/or neutrophil)
- 71.4% and 75.0%, respectively, of pts who were RBC or platelet transfusion-dependent at baseline became TI (no transfusion for ≥56 days)
- 81.8% and 100%, respectively, of pts who were RBC- or platelet-TI at baseline remained TI at data cut off

[a]One pt was excluded from the efficacy analysis due to not meeting an inclusion criterion; [b]ORR=complete remission + partial remission + marrow complete remission; [c]censored observation; [d]Reported by investigators using IWG 2006 MDS response criteria.

AML, acute myeloid leukemia; CR, complete remission; HI, hematologic improvement; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IWG, International Working Group; KM, Kaplan-Meier; mCR, marrow complete remission; MDS, myelodysplastic syndrome; ORR, objective response rate; PD, progressive disease; PR, partial remission; PT, prior therapy; RBC, red blood cell; SD, stable disease; TI, transfusion independent.

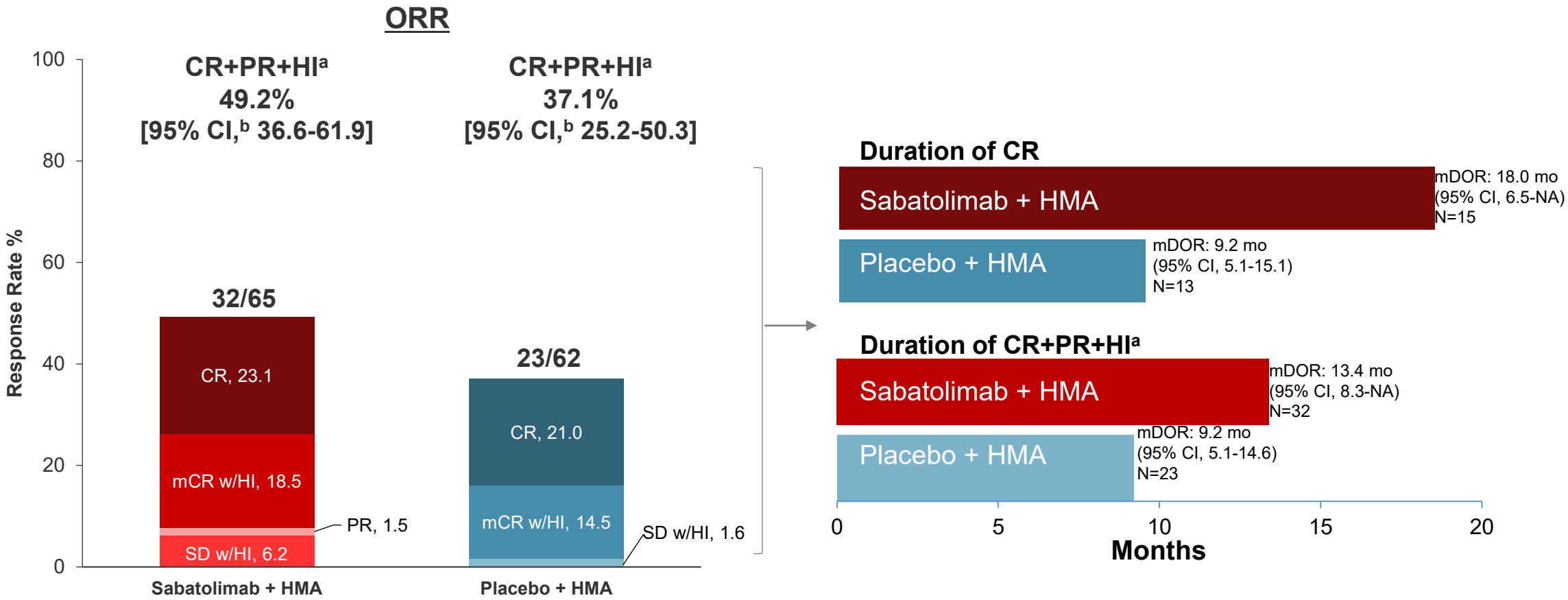
Treatment duration and best overall response in the efficacy analysis set (N=18)



Best overall response outcomes

Response, n (%)[d]	Efficacy analysis set (N=18)	95% CI
CR+PR rate	**7 (38.9)**	17.3–64.3
CR	**7 (38.9)**	
PR	0 (0.0)	
mCR	8 (44.4)	
SD	2 (11.1)	
PD	1 (5.6)	

Sabatolimab + HMA demonstrated a potential benefit in duration of response



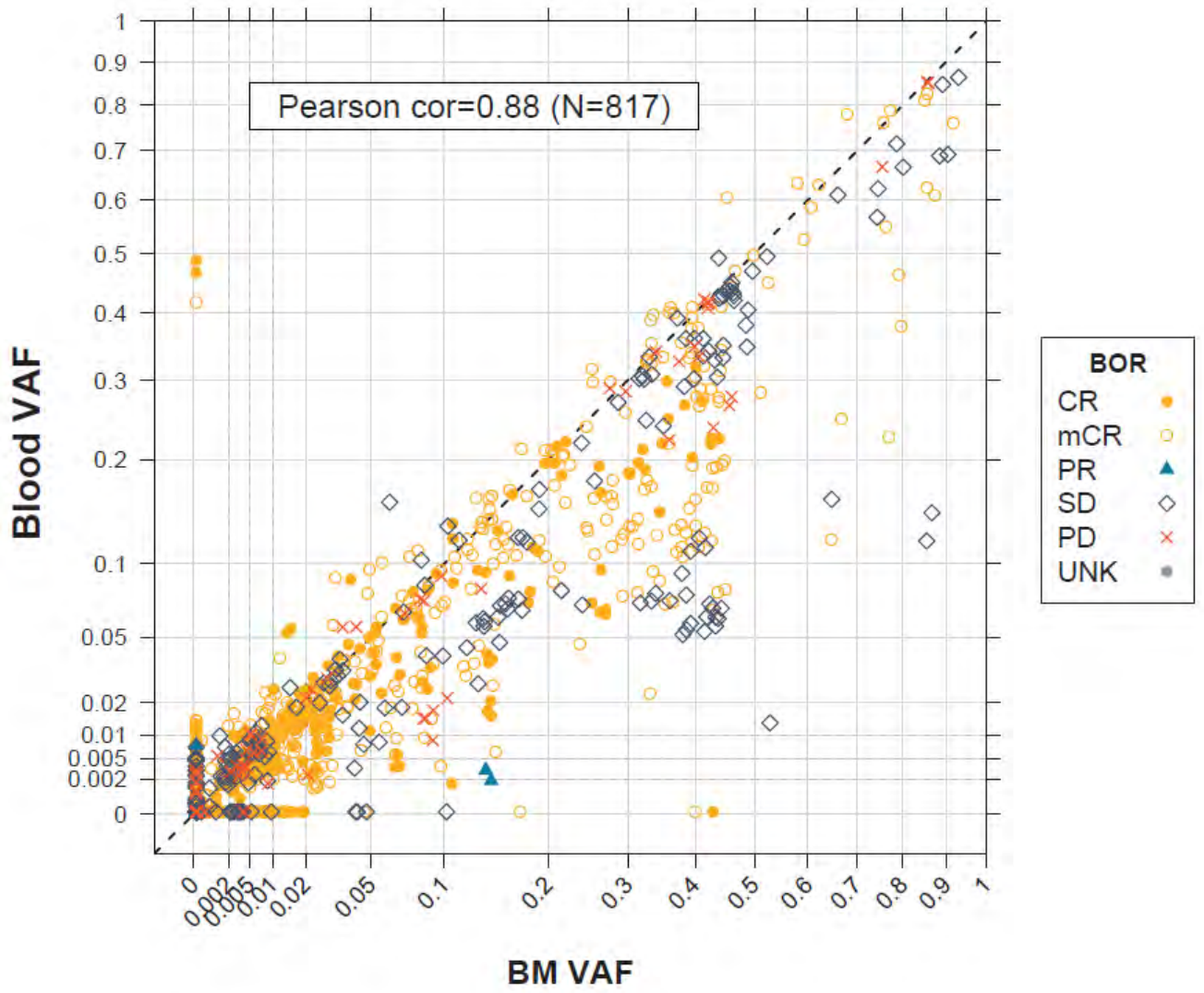
- Updated CR rate assessed at primary analysis (data cutoff March 1, 2022).

HI, hematologic improvement; HR, hazard ratio; mCR, marrow CR; mDOR, median duration of response; NA, not available; ORR, overall response rate; PR, partial remission; SD, stable disease.
[a]HI includes marrow CR with HI and SD with HI, and HI must be concurrent with best overall response. [b]The 95% CIs were computed using exact Clopper-Pearson 1934.

STIMULUS MDS-1 trial: Correlation in VAF between BM and PB samples

- Linear concordance at variant level between BMMC and PBMC of 88% evaluated per Pearson correlation coefficient (Figure)
- When considering all paired samples at the patient level, concordance of best MRD status using PBMC or BMMC results anytime on treatment was:
  - MRD-0.2%: 97%
  - MRD-0.5%: 89%
  - MRD-1%: 90%

Correlation in VAF between BM and PB samples (all reported VAFs)



BM, bone marrow; BMMC, bone marrow mononuclear cell; BOR, best overall response; CR, complete remission; mCR, marrow CR; MRD, measurable residual disease; PB, peripheral blood; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown; VAF, variant allele frequency.

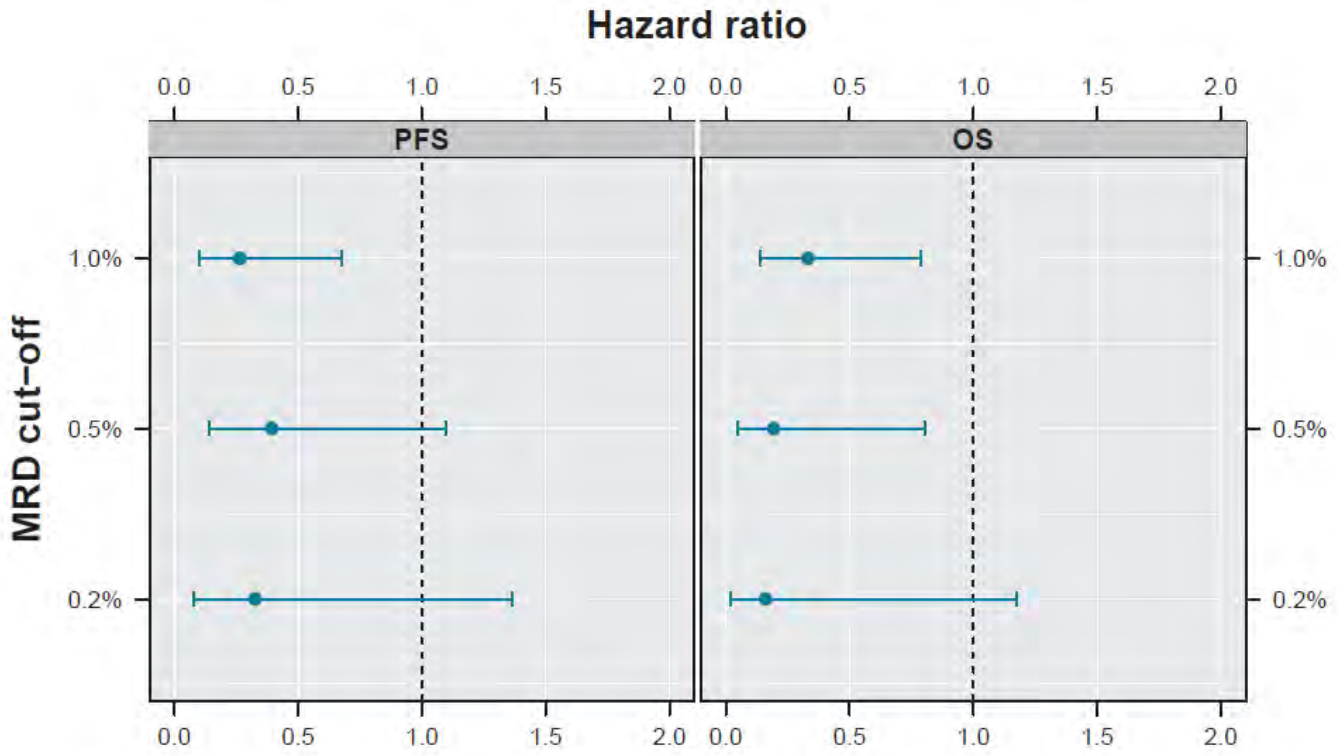
Oral presentation at: 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, CA, and online.

Zeidan A et al, ASH 2023

MRD-0.2%, -0.5% and -1% associated with lower PFS and OS hazard ratios

- A time-dependent Cox-model was conducted to rule out immortal bias
- MRD-0.2%, -0.5% and -1% negativity were associated with a lower hazard ratio for PFS and OS vs MRD-0.2%, -0.5% and -1% positivity (Figure)

PFS and OS hazard ratios at different MRD cut-offs



Time-varying covariate Cox model hazard ratios of clinical endpoints in all patients (N=112) who were MRD-positive at baseline at different MRD cut-offs. MRD was calculated at each visit using highest VAF with combined BMMC and PBMC samples. Bars represent 95% confidence intervals. BMMC, bone marrow mononuclear cell; MRD, measurable residual disease; OS, overall survival; PBMC, peripheral blood mononuclear cell; PFS, progression-free survival; PR, partial response.

Oral presentation at: 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, CA, and online.

Zeidan A et al, ASH 2023

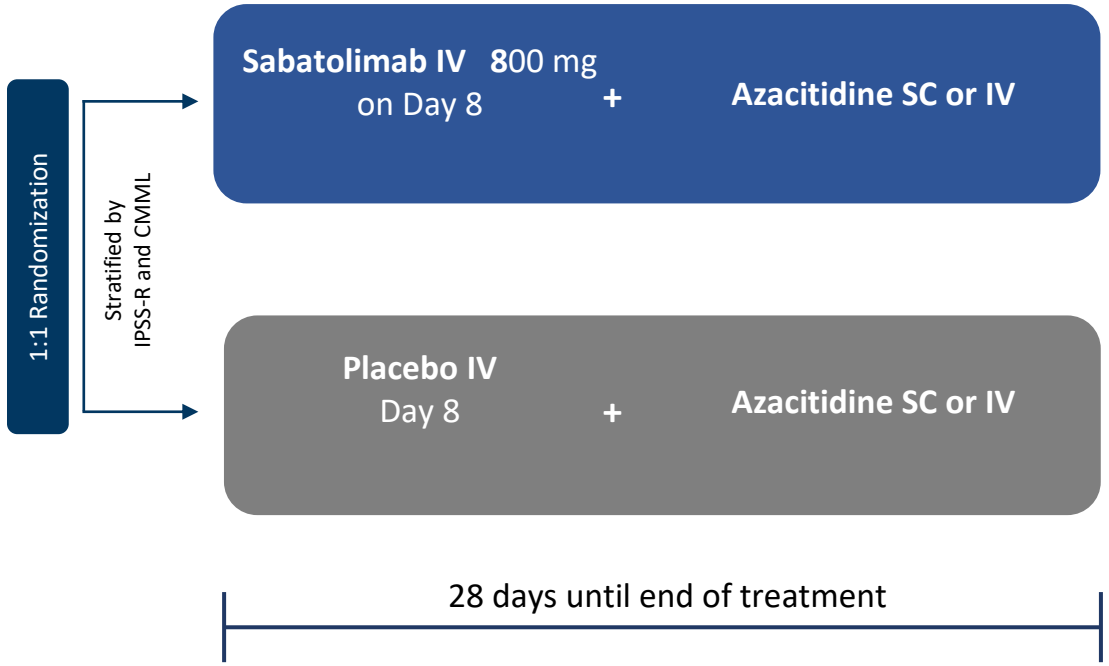
STIMULUS-MDS2: A Randomized Phase 3 trial of Sabatolimab+AZA vs. PBO+AZA in Patients With Higher Risk MDS

Primary objective:
Evaluate overall survival of patients with intermediate-, high-, or very high-risk MDS or CMML-2 treated with sabatolimab + azacitidine or azacitidine alone as a first-line therapy

I/H/vHR-MDS or CMML-2
N~500

Key Inclusion Criteria
- IPSS-R I/H/vHR-MDS or CMML-2
- Ineligibility for intensive chemotherapy or HSCT
- Indication for treatment with azacitidine

Key Exclusion Criteria
- Prior TIM-3–directed therapy
- Prior immune checkpoint therapy or cancer vaccine within 4 months
- Prior antineoplastic agent for first-line treatment of I/H/vHR-MDS or CMML
- Systemic steroids or immunosuppressive therapy within 2 weeks
- Investigational treatment within 4 weeks



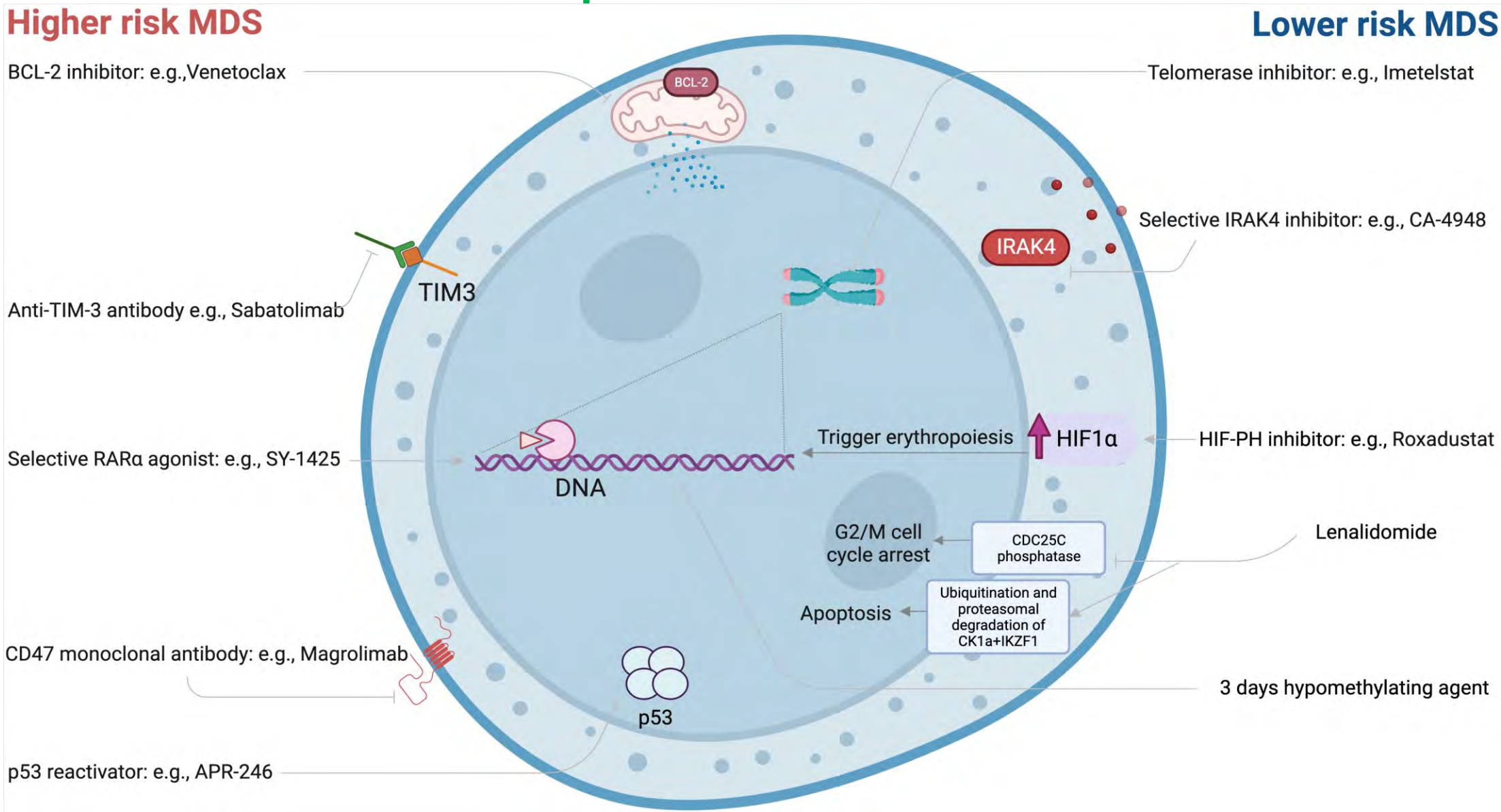
OS follow-up period: OS assessed every 12 weeks up to 5 years
Secondary endpoints: FACIT-Fatigue and EORTC QLQ-C30 (emotional and physical functioning), RBC transfusion-free intervals, RBC/platelet transfusion independence, CR/mCR/PR/HI, PFS, LFS, safety, PK, immunogenicity, EQ-5D-5L
Estimated primary completion: January 2027

Selected Randomized Phase III Trials in frontline management of HR-MDS

Drug	NCT	Patient characteristics	Intervention	Study outcomes
Venetoclax	NCT04401748 (VERONA) Estimated primary completion date: 02/2025	Newly-diagnosed HR-MDS Estimated enrollment: 500	Venetoclax + AZA vs. placebo + AZA	Primary Outcome: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 36 Months) - Overall survival (OS) (Up to 5 years)
MBG453 (Sabatolimab)	NCT04266301 (STIMULUS-MDS2) Estimated primary completion date: 05/2027	Newly-diagnosed HR-MDS or CMML-2 Estimated enrollment: 500	MBG453+ AZA vs. placebo + AZA	Primary Outcome: - Overall Survival (Up to 5 years after last patient randomized)
Pevonedistat	NCT03268954 (PANTHER) Estimated Primary completion date: 07/2023	Newly-diagnosed HR-MDS, CMML, or Low-Blast AML Estimated enrollment: 502	Pevonedistat + AZA vs. AZA alone Open-label	Primary Outcome: - Event-Free Survival (From randomization until transformation to AML, or death due to any cause; up to 6 years)
Magrolimab	NCT04313881 (ENHANCE) Estimated primary completion date: 08/2022	Newly-diagnosed HR-MDS Estimated enrollment: 520	Magrolimab + AZA vs. AZA + placebo	Primary Outcomes: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 24 Months) - Overall survival (OS) (Up to 5 years)
APR-246	NCT03745716 Actual primary completion date: 11/2020	Newly-diagnosed TP53-mutated HR-MDS Estimated enrollment: 154	APR-246 + AZA Vs. AZA alone Open-label	Primary Outcome: - Complete response rate (CR) with APR 246 + azacitidine vs. azacitidine only
SY-1425 (Tamibarotene)	NCT04797780 Estimated Primary completion date: 07/2023	Newly-diagnosed RARA-positive HR-MDS Estimated enrollment: 190	SY-1425 + AZA Vs. placebo + AZA	Primary outcome: - Complete response rate (CR) with SY-1425 + azacitidine vs. azacitidine only

Source: Clinicaltrials.gov

Novel therapies in trials for MDS

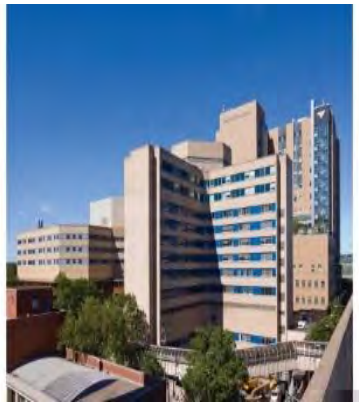


Bewersdorf J,,,,,Zeidan A on behalf of icMDS, Blood Reviews, 2023

Acknowledgements

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

someday is today®



Yale NewHaven Health
Smilow Cancer Hospital
Yale CANCER CENTER

The Ed Evans FOUNDATION
Registered Charity No. 1126226

Aplastic Anemia & MDS INTERNATIONAL FOUNDATION

CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology
YOUNG INVESTIGATOR AWARD

MDS Clinical Research Consortium

Dennis Cooper Award

COPPER MDS

Questions?
Amer.Zeidan@yale.edu
Dr_AmerZeidan

ETCTN
Experimental Therapeutics Clinical Trials Network
Team Driven. Cancer Therapy Focused.
National Cancer Institute at the National Institutes of Health