Myelodysplastic Syndromes
" ASH 2024 Highlights"

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COI disclosures

BMS: Research Grant, Advisory board

DSI: Advisory board

Geron: Consultancy

Genentech: consultancy

Pharma Essentia: Speaker Bureau, Advisory board

Rigel: Speaker Bureau, Advisory board

Servier: Speaker Bureau, Advisory board

Sobi: Speaker Bureau, Advisory board

Sumitomo Pharma: consultancy, Advisory board

Myelodysplastic Syndromes (MDS) in the United States

10-20K **New cases per year, although some estimates are much higher**

1 in 3 patients will progress to AML

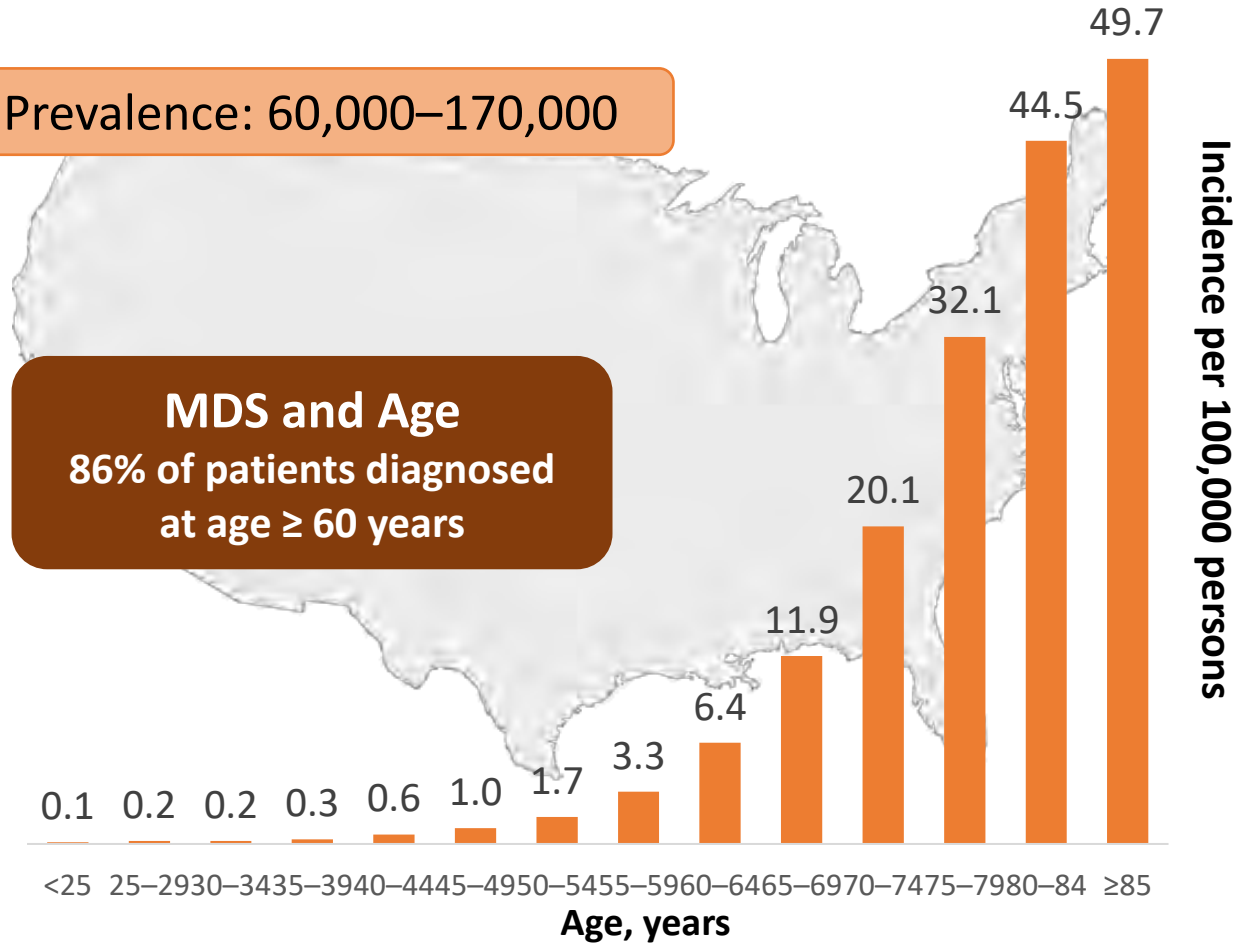
Approximately 5%-10% of cases occur after exposure to previous radiation/chemotherapy

More than 90% of patients harbor somatic mutations

Anemia is the most common clinical feature

Prevalence: 60,000–170,000

MDS and Age
86% of patients diagnosed at age ≥ 60 years



AML = Acute Myeloid Leukemia

Ma X. *Am J Med*. 2012;125(7):S2–S5; Cogle CR. *Curr Hematol Malig Rep.* 2015;10(3):272-281; American Cancer Society. www.cancer.org. Accessed 10/24/23. Leukemia and Lymphoma Society. www.lls.org Accessed 10/24/23.

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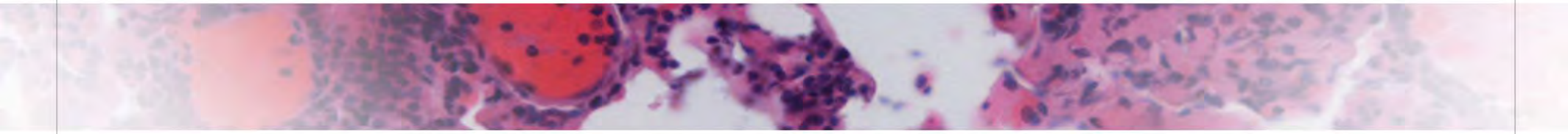


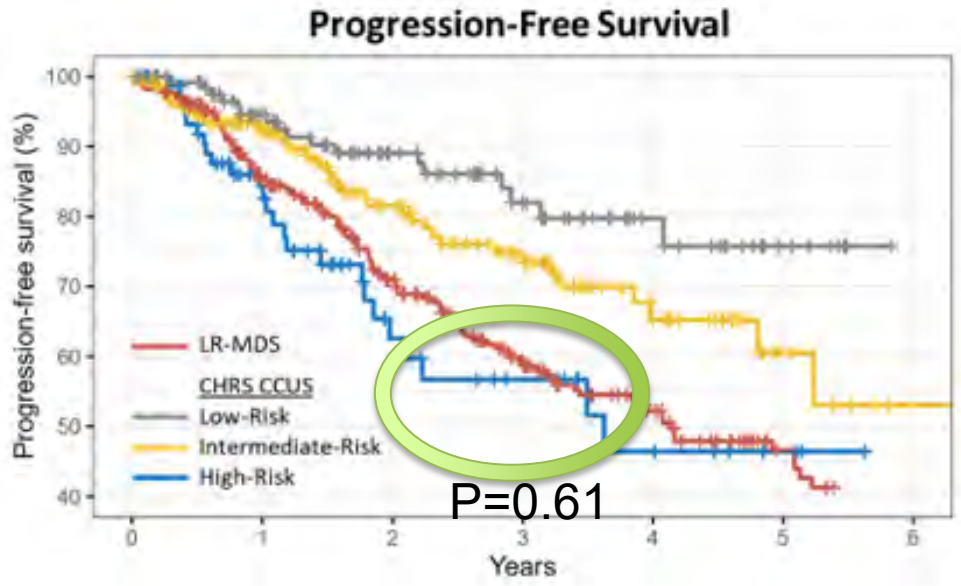
High-Risk CCUS is Clinically Indistinguishable from Low-Risk Myelodysplastic Syndromes/Neoplasms

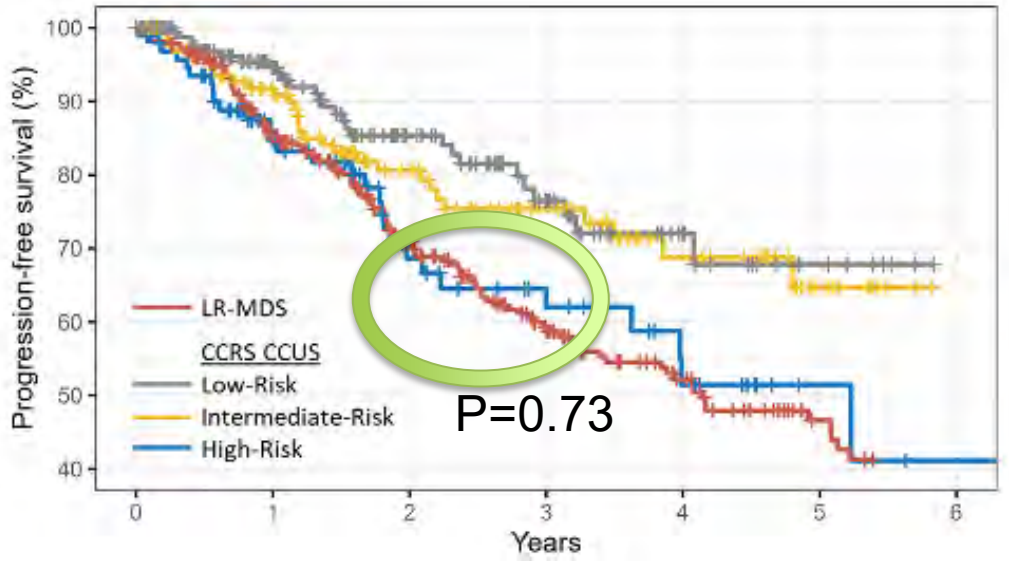
Zhuoer Xie, MD, MS, Zena Komrokji, Michael Otterstatter, PhD, Ling Zhang, MD, Lynn C. Moscinski, MD, Najla H. Al Ali, David A Sallman, MD, Jeffrey Lancet, MD, Amy E. DeZern, MD, MHS, Mikkael A. Sekeres, MD, Rami S. Komrokji, MD, **Nancy K Gillis, PhD and Eric Padron, MD**

Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The Emmes Company, LLC, Rockville, MD; Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; Sylvester Cancer Center, University of Miami Health System, Miami, FL

Progression free survival

- High-Risk CCUS were more similar to LR-MDS in terms of median (IQR) hemoglobin, platelets and absolute neutrophil count (ANC)

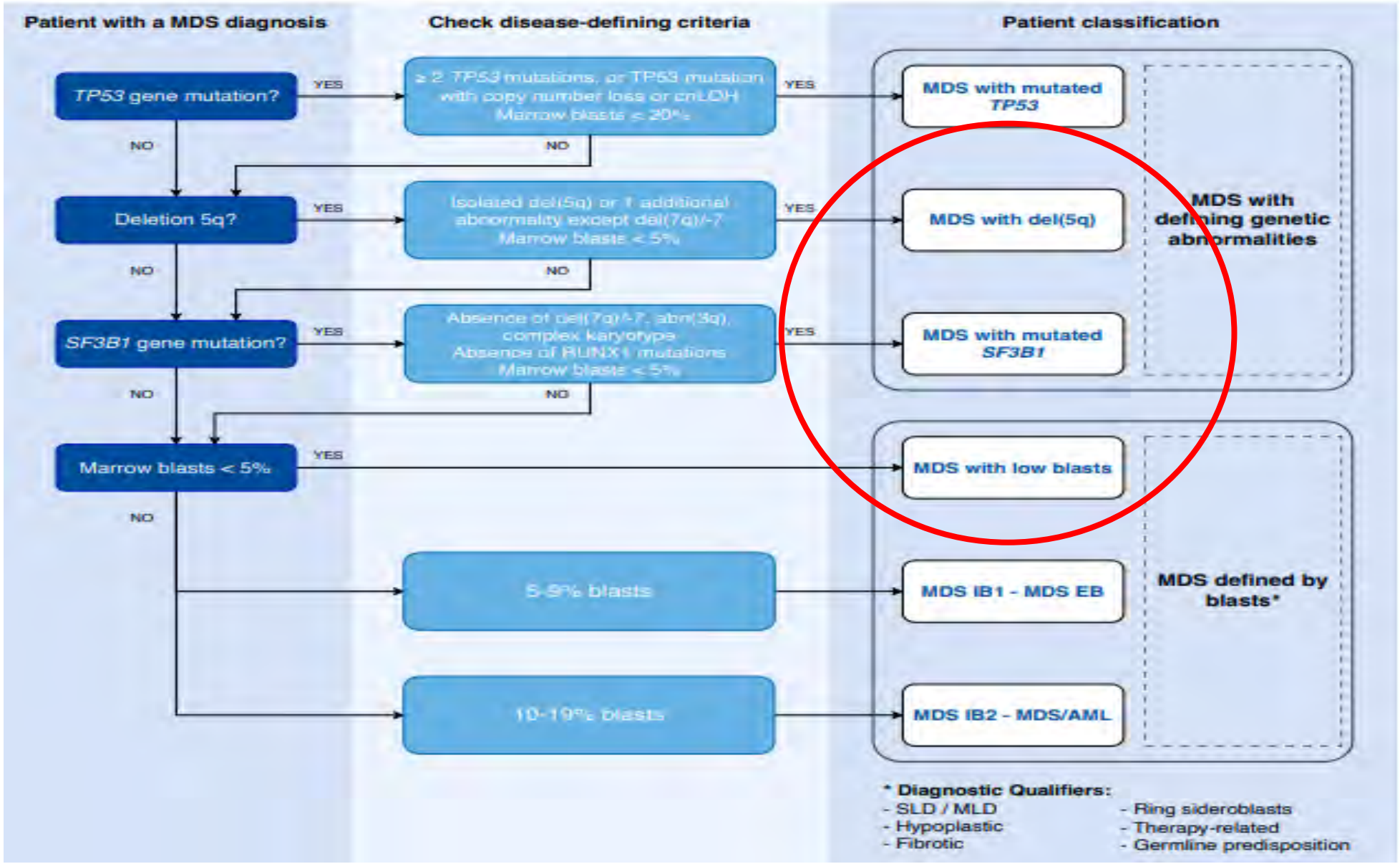




	CHRS CCUS vs LR-MDS	
CCUS Risk Category	**HR**	**P-value**
Low-Risk	0.36 (0.21-0.61)	< 0.001
Intermediate-Risk	0.62 (0.44-0.89)	0.01
High-Risk	1.12 (0.72-1.73)	0.611

	CCRS CCUS vs LR-MDS	
CCUS Risk Category	**HR**	**P-value**
Low-Risk	0.49 (0.32-0.75)	< 0.001
Intermediate-Risk	0.58 (0.39-0.88)	0.009
High-Risk	0.93 (0.62-1.40)	0.726

Harmonized WHO/ICC 2022 classification



Komrokji et al, Lancet Hematology 2024 Dec;11(12):e886. doi: 10.1016/S2352-3026(24)00339-9

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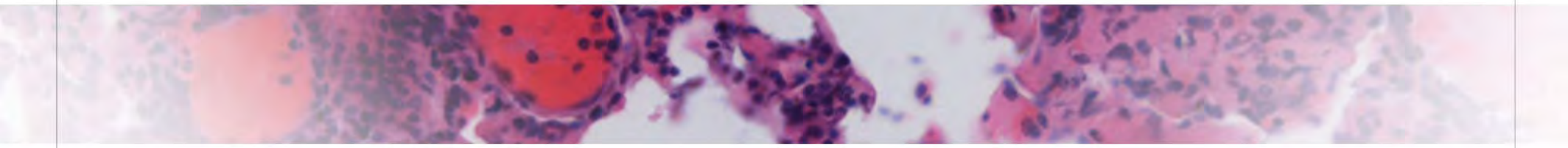


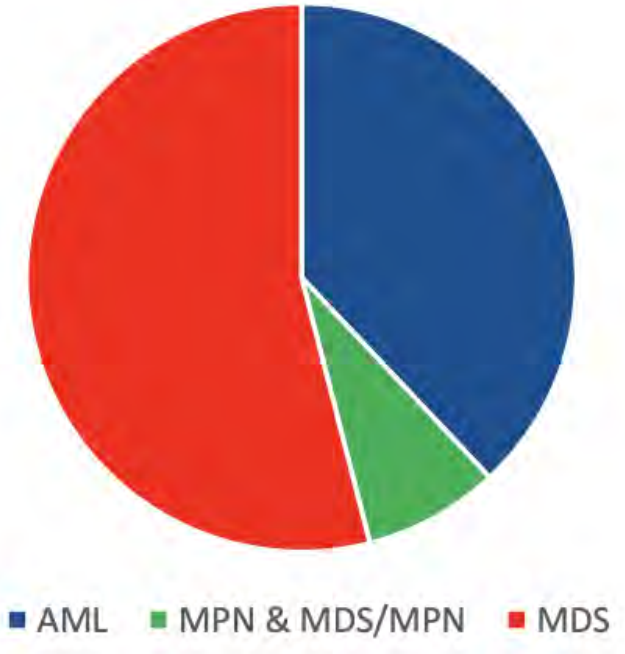
AI, Data-Driven, Comprehensive Classification of Myeloid Neoplasms Based on Genomic, Morphological and Histological Features

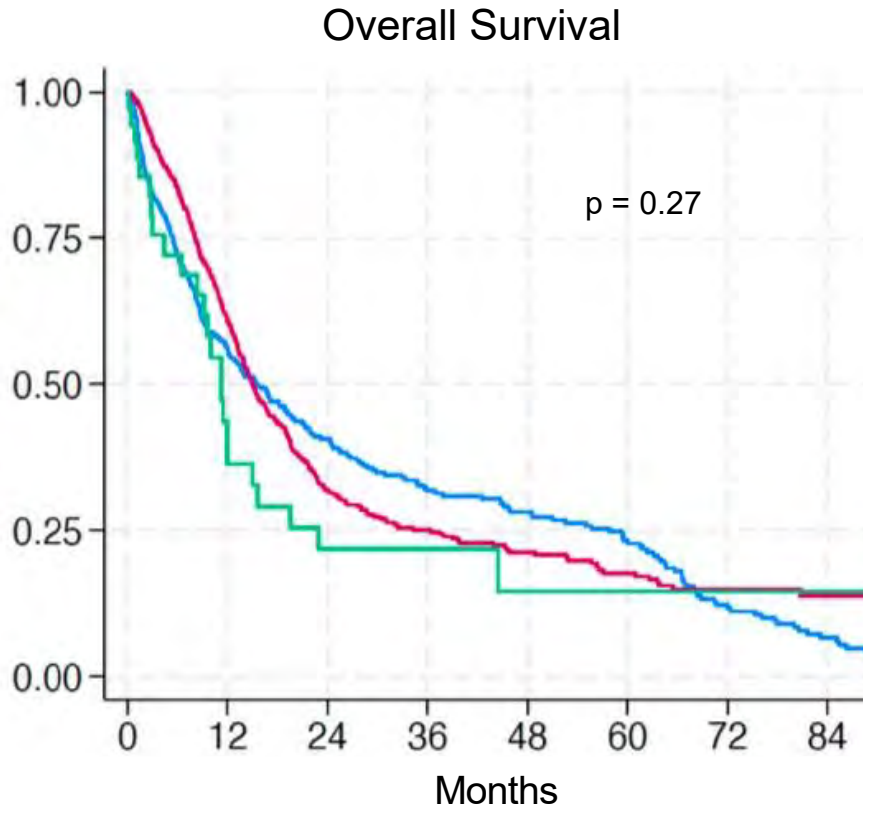
Luca Lanino, S D'Amico, G Maggioni, N Al Ali, YH Wang, C Gurnari, N Gagelmann, JP Bewersdorf, S Ball, P Guglielmelli, M Meggendorfer, A, AS Kubasch, E Travaglino, A Campagna, M Ubezio, A Russo, G Todisco, C Tentori, A Buizza, E Sauta, M Zampini, E Riva, G Asti, M Delleani, F Ficara , A Santoro, C Sala,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

Results 2 - Splicing Mutations Are Shared Across Multiple Entities

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

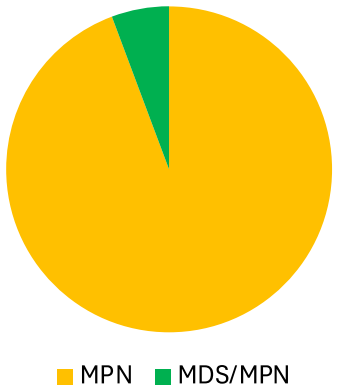
Results 3 - *TP53* Drives Cluster Assignment Irrespective of Diagnostic Entity



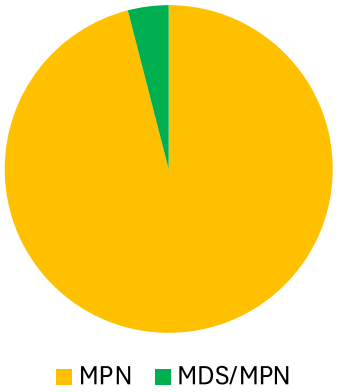


- Biallelic inactivation was identified in most cases (>65%)
- Monoallelic *TP53* MNs showed progression to biallelic at leukemic evolution

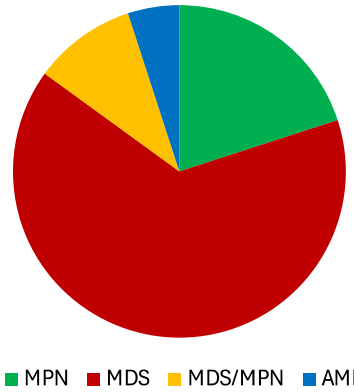
Results 4 - Fibrosis identifies distinct clusters with diverse features and survival



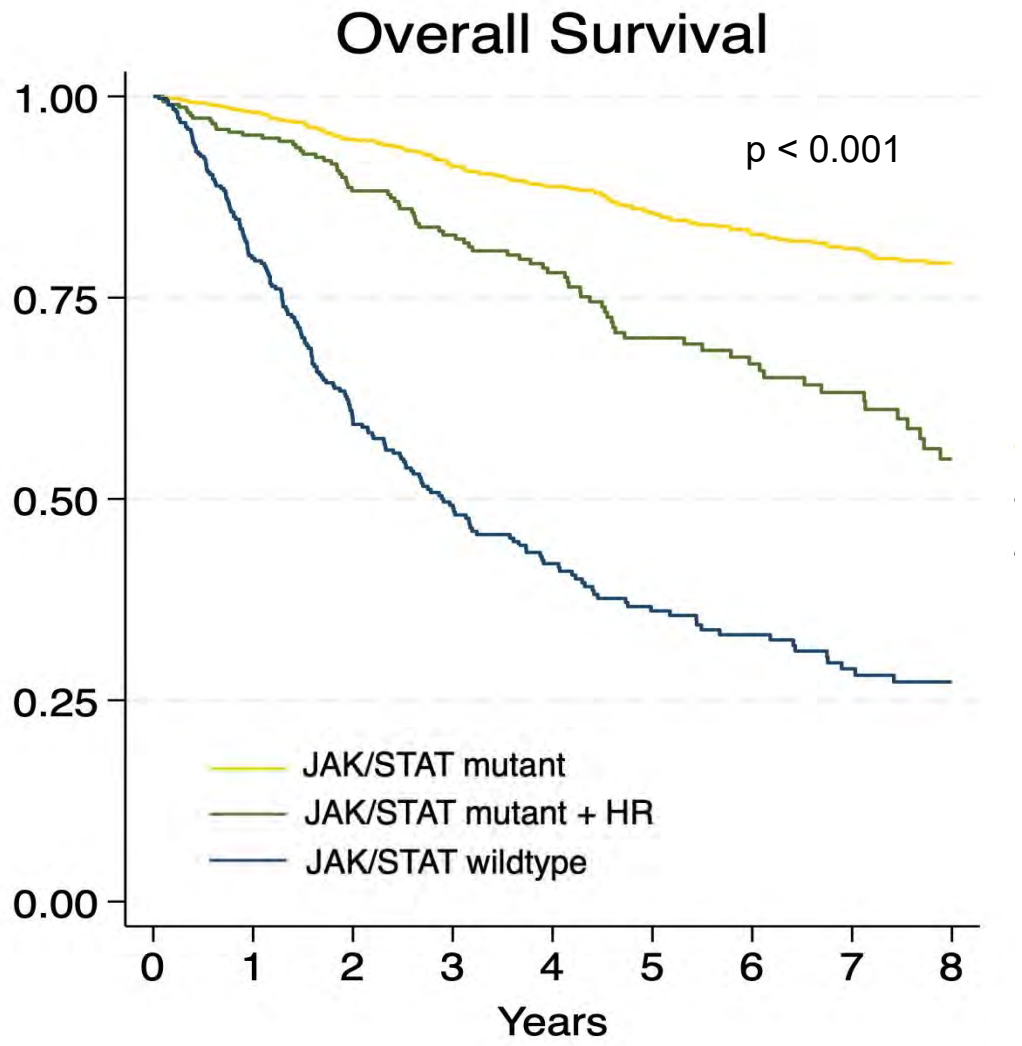
JAK/STAT mutations
No HR Features*
n = 1143



JAK/STAT mutations
+ HR Features*
n = 305



JAK/STAT wildtype
n = 381



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

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

Case :

- 68-year-old female past medical history of HTN presented to ER with shortness of breath. CBC WBC 4.0/ANC 2.0/HGB 7.0 g/dl/plat 270
- The patient received 2 units PRBC and hematology consulted.
- A bone marrow aspirate and biopsy performed revealing hypercellular bone marrow, erythroid dysplasia, no increased myeloblasts, and 30% ring sideroblasts.
- Karyotype was normal. NGS revealed *SF3B1* K700E VAF 30%, *TET-2* VAF 30%.
- IPSS-M: -0.87 (Low), IPSS-R 2.5 (low)
- Endogenous erythropoietin level is 225 U/L.

CASE-

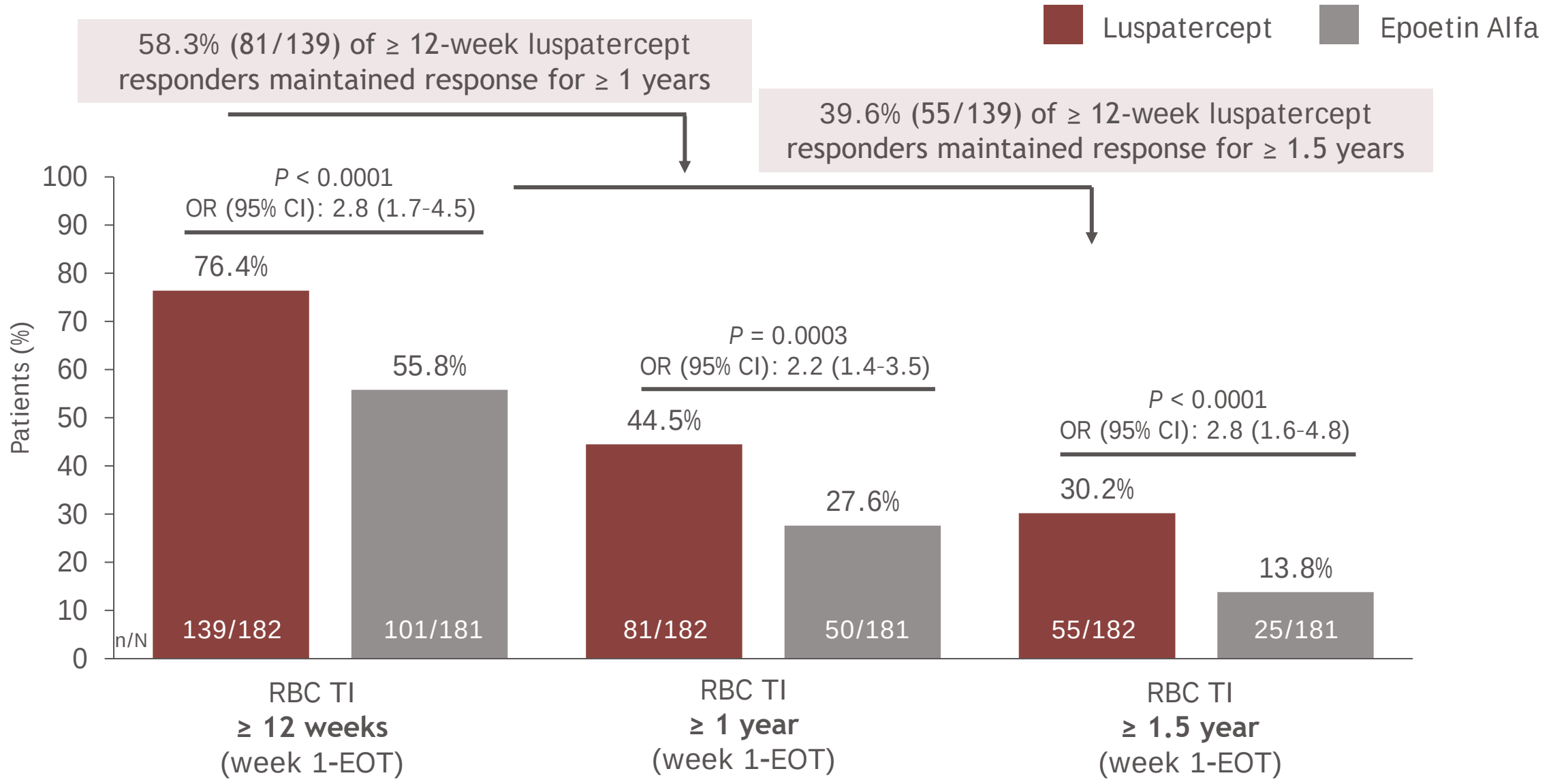
- How should this patient be treated?
  A. ESA
  B. Luspatercept
  C. Imetelstat
  D. Lenalidomide

Long-term response analysis of transfusion independence in erythropoiesis stimulating agent-naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes treated with luspatercept versus epoetin alfa in the COMMANDS trial

Guillermo Garcia-Manero,[1] Valeria Santini,[2] Amer M. Zeidan,[3] Rami S. Komrokji,[4] Veronika Pozharskaya,[5] Karen Keeperman,[5] Shelonitda Rose,[5] Yinzhi Lai,[5] Barkha Aggarwal,[5] Dimana Miteva,[6] David Valcárcel,[7] Pierre Fenaux,[8] Jake Shortt,[9] Matteo Giovanni Della Porta,[10] Uwe Platzbecker[11]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]AOUC, University of Florence, Florence, Italy; [3]Yale School of Medicine, New Haven, CT, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Bristol Myers Squibb, Princeton, NJ, USA; [6]Bristol Myers Squibb, Boudry, Switzerland; [7]Vall d'Hebron Hospital, Barcelona, Spain; [8]AP-HP St Louis, Paris, France; [9]Monash Health & Monash University, Clayton, VIC, Australia; [10]Humanitas University, Milan, Italy; [11]University Hospital Leipzig, Leipzig, Germany

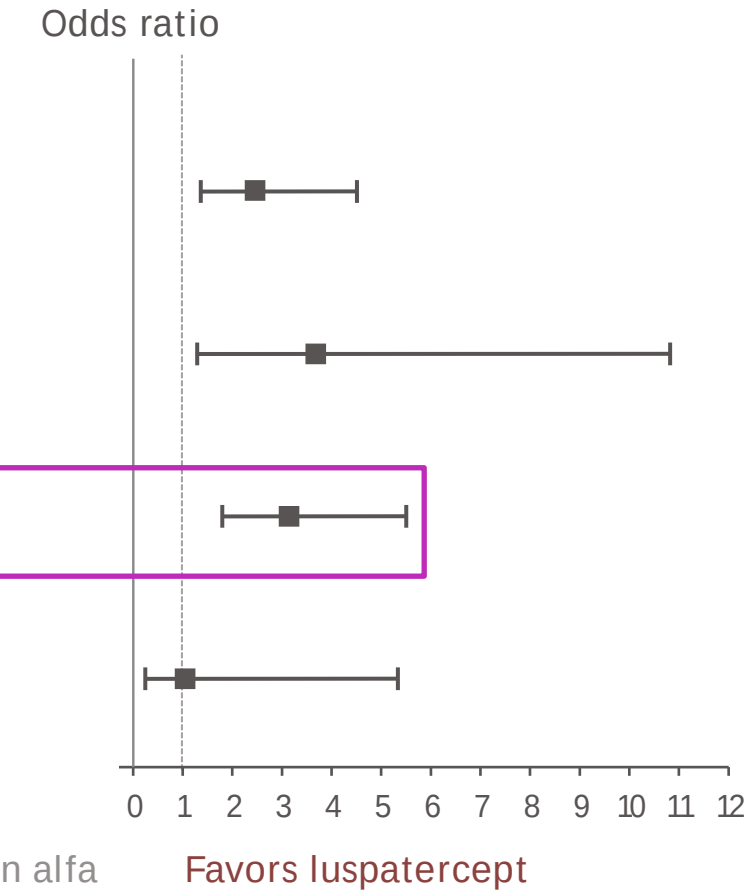
COMMANDS: RBC-TI responses of ≥ 12 weeks, ≥ 1 years, and ≥ 1.5 years



Data cutoff: September 22, 2023.
OR, odds ratio.

COMMANDS: continuous RBC-TI ≥ 1.5 years[a] across patient subgroups

	Luspatercept n/N (%) [95% CI]	Epoetin Alfa n/N (%) [95% CI]
Baseline transfusion burden		
< 4 units	41/118 (34.7%) [26.2-44.1]	20/111 (18.0%) [11.4-26.4]
≥ 4 units	14/64 (21.9%) [12.5-34.0]	5/70 (7.1%) [2.4-15.9]
Baseline serum EPO		
≤ 200 U/L	52/145 (35.9%) [28.1-44.2]	22/144 (15.3%) [9.8-22.2]
> 200 U/L	3/37 (8.1%) [1.7-21.9]	3/37 (8.1%) [1.7-21.9]

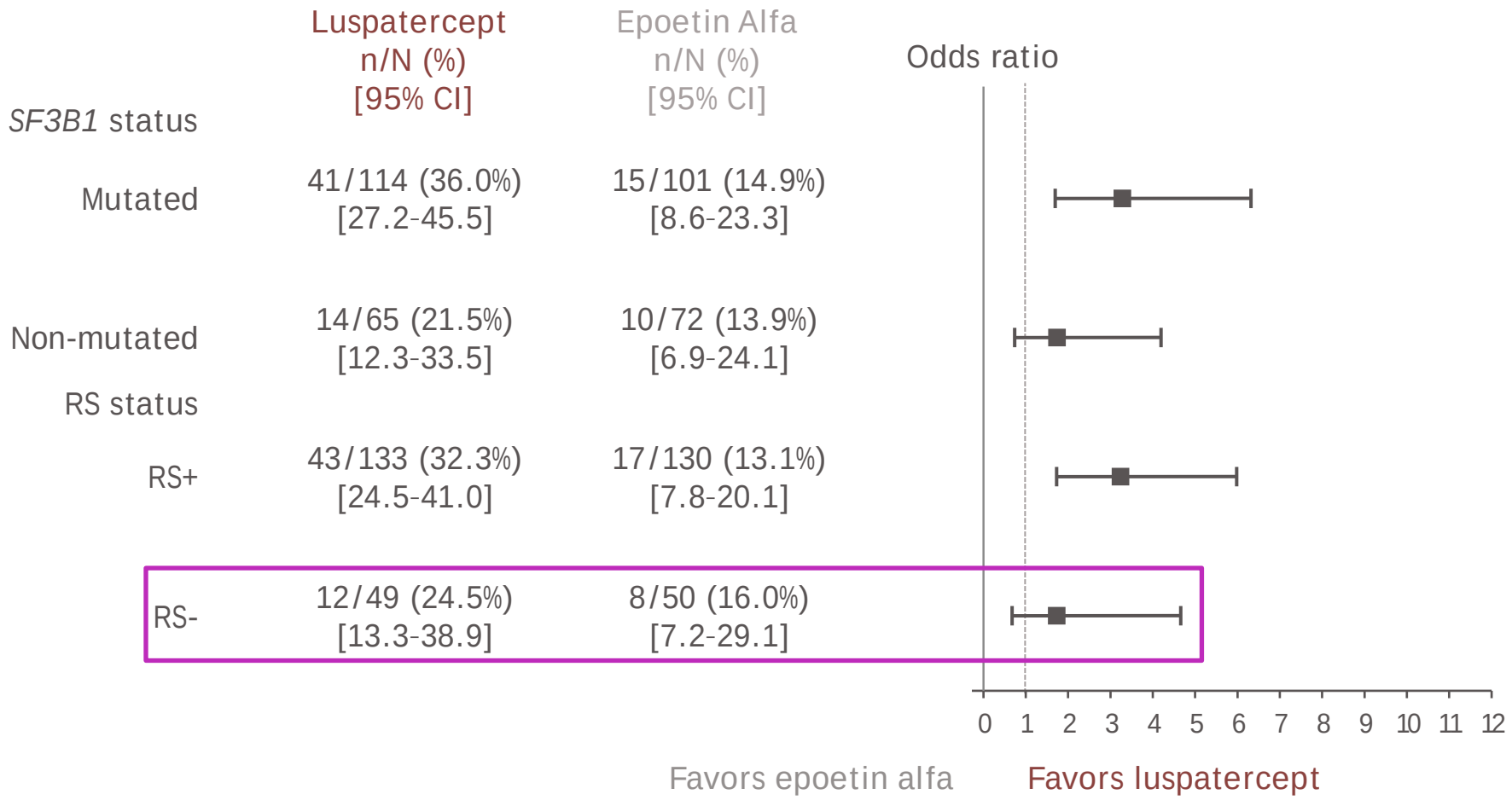


Patients with baseline serum erythropoietin ≤ 200 U/L had a 2.3 x greater response rate for RBC-TI ≥ 1.5 years with luspatercept compared with epoetin alfa

Data cutoff: September 22, 2023.

[a]Defined as patients achieving a single, uninterrupted period of RBC-TI for ≥ 1.5 years from week 1-EOT.

COMMANDS: continuous RBC-TI ≥ 1.5 years[a] across patient subgroups



Superior RBC-TI benefit with luspatercept versus epoetin alfa was observed across prespecified subgroups, including those who were RS- who had 1.5 x greater response rate

Data cutoff: September 22, 2023.

[a]Defined as patients achieving a single, uninterrupted period of RBC-TI for ≥ 1.5 years from week 1-EOT.

Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes

Baseline characteristics (n=28)	% (n)
Age (median)	72 (51-94)
Gender (male)	68(19)
Race (white)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dl	8 (6.6-9.4)
Platelets (mean) $x10^9$/L	259 (16-814)
ANC (mean) $x10^9$/L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n=18)
RBC transfusion Burden	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Prior ESA treatment	89 (24)
Prior HMA treatment	42 (12)
Prior Lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

	% (n)
Overall response (n=28)	36 (10)
Hgb increase more than 1.5 g/dl in NTD or Hgb increase more than 1.5 g/dl with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dl increase >50% reduction in RBC-TB	14 (4/28) 4 (1/28)
Response in NTD (n=3)	
Hgb increase more than 1.5 g/dl	33 (1/3)
Response in LTB (n=13)	38 (5/13)
Hgb increase more than 1.5 g/dl and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dl increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n=12)	33 (4/12)
Hgb increase more than 1.5 g/dl and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dl increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

Predictors of response included:

- Prior response to luspatercept monotherapy/or frontline combination compared to primary luspatercept failure.
- Endogenous serum epo levels < 500
- *SF3B1* mutation.
- HMA/Len treatment naïve.

Komrokji et al , Blood Advances 2023 April 14

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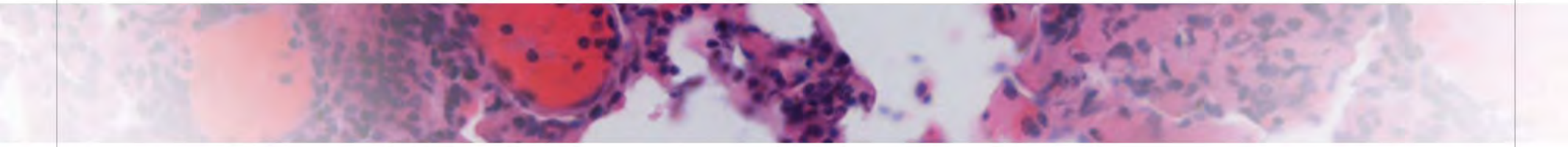


Combining ESA and Luspatercept in Non-RS MDS Patients Having Failed ESA - Results of the Phase 1-2 Part a of the GFM Combola Study

Lionel Ades, MD, PhD[1], *Thomas Cluzeau, MD, PhD*[2], *Thibault Comont*[3*], *Lorea Aguinaga, MD*[4*], *Aspasia Stamatoullas, MD*[5*], *Mathieu Meunier*[6*], *Emmanuel Gyan, MD, PhD*[7], *Alice Garnier, MD*[8*], *Maud D'Aveni, MD, PhD*[9*], *Sylvain Thépot, MD*[10*], *Marie Sebert, MD, PhD*[11*], *Marius Moldovan*[12*], *Anouk Walter Petrich, MD*[13*], *Karine Lemarie*[14*], *Fatiha Chermat*[15*], *Michaela Fontenay*[16*], *Sylvie Chevret*[17*] *and Pierre Fenaux, MD*[18]

GFM COMBOLA Part A: Efficacy

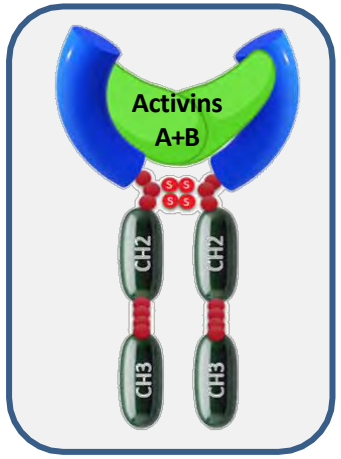
Outcome, n (%)	Low Transfusion Burden (n = 6)	High Transfusion Burden (n = 16)	Nontransfusion Dependent (n = 2)	Overall (N = 24)
Erythroid response* at Wk 25	2 (33)	4 (25)	1 (50)	7 (30)

*Per IWG 2018.

- Among 7 patients who achieved an erythroid response, 3 continue to respond to treatment
  - Median DoR: 9.18 mo
- 2 patients achieved a platelet response, and 1 achieved a neutrophil response
- In terms of survival, n = 2 experienced progression to AML, n = 5 died (n = 2 due to infection, n = 1 due to AML evolution; none deemed related to study drug)

Ades. ASH 2023. Abstr 351.

KER-050 (elritercept) is Designed to Target Bone Marrow Disorders of Ineffective Hematopoiesis Including MDS



KER-050 (elritercept)

- **Designed to inhibit select TGF-beta ligands, including Activin A, which has been associated with ineffective hematopoiesis, disease pathogenesis and progression[1,2]**

Domain	Effect
Erythropoiesis	ALL stages of differentiation and maturation
Thrombopoiesis	ALL stages of differentiation and maturation
Bone	Increased bone formation
Iron Metabolism	Improved iron utilization

- Preclinical data showed that **KER-050 (elritercept) acts on early and late stages of hematopoiesis**, supporting a differentiated MOA[3]

- KER-050 has the potential to:
  - Treat a broad range of patients with lower-risk (LR) MDS
  - Provide clinical benefit beyond improving hematopoiesis (Chee, et al. ASH 2023 Poster #1089)

Preliminary results from an ongoing open- label Phase 2 trial evaluating KER-050 (elritercept) in participants with LR-MDS Presented ASH 2023 Diez-Campelo et al

[1]Verma A, et al. *J Clin Inv* 2020; [2]Portale F, et al., *Haematologica*. 2019; [3]Feigenson, M et al. European Hematology Association. 2021

Hematological Responses Observed in Broad Array of Participants

Responders/N (%)	$mITT_{24}$[a]		$mITT_{24}$ + EPO n < 500 U/L[b]	
	All (N=87)	HTB (N=51)	All (N=71)	HTB (N=39)
Overall Response[c]	48/87 (55.2)	25/51 (49)	43/71 (60.6)	22/39 (56.4)
Modified IWG 2006 HI-E[d]	42/87 (48.3)	24/51 (47.1)	37/71 (52.1)	21/39 (53.8)
RS+	33/59 (55.9)	19/35 (54.3)	29/52 (55.8)	16/30 (53.3)
non-RS	9/28 (32.1)	5/16 (31.3)	8/19 (42.1)	5/9 (55.6)
TI ≥8 weeks[e]	27/69 (39.1)	16/51 (31.4)	26/55 (47.3)	15/39 (38.5)
RS+	22/47 (46.8)	13/35 (37.1)	21/41 (51.2)	12/30 (40.0)
non-RS	5/22 (22.7)	3/16 (18.8)	5/14 (35.7)	3/9 (33.3)

- Overall response rates in participants with HTB were similar to those observed in the overall ($mITT_{24}$) population.
- Higher response rate was observed in the EPO < 500 U/L population, particularly in non-RS participants.

[a]Includes data for Weeks 0–24 in $mITT_{24}$ participants; [b]Includes data for Weeks 0–24 in $mITT_{24}$ participants with baseline EPO < 500 U/L, excluding one participant with del5q MDS. 9 $mITT_{24}$ participants (2 LTB RS+, 1 LTB non-RS, 4 HTB RS+, 2 HTB non-RS) had missing Baseline EPO measures and were conservatively classified as having EPO < 500 U/L. Two (both HTB, 1 RS+, 1 non-RS) of these 9 participants had EPO values ≥ 500 U/L post-baseline; both achieved a HI-E response, but not TI; [c]Defined as achieving modified IWG 2006 HI-E and/or TI; [d]Modified IWG 2006 HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC U/8 Wks (HTB) on treatment compared to 8-week pre-treatment period; [e]TI-evaluable participants received at least 2 RBC units in the 8-wk pre-treatment period.

Giagounidis et al, ASH 2024

Case :

- 74-year-old gentleman past medical history of CAD diagnosed originally with MDS-MLD, blasts 3%; normal karyotype, *NGS TET-2/DNMT3A.* CBC at diagnosis Hgb 9 g/dl, plat 200, ANC 2000. EPO 64 U/L
- *IPSS-M: -0.99 (low), IPSS-R (AA) 3.14 (INT)*
- The patient was started on erythropoietin 40,000. Hgb improved originally but after one year on escalated dose treatment Hgb progressively decreased, and patient became RBC-TD requiring 2 Units PRBC every 3 weeks.
- Repeat bone marrow no disease progression or clonal evolution.

CASE

- How would you treat this patient at this point
  A. Azacitidine 5days regimen
  B. Decitabine 3 days regimen
  C. Lenalidomide
  D. Imetelstat
  E. Luspatercept

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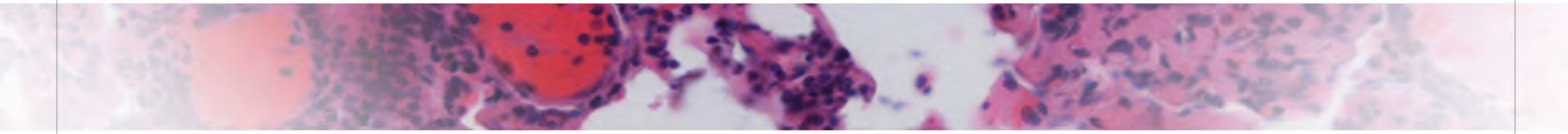

Effect of Prior Treatments on the Clinical Activity of Imetelstat in Transfusion-Dependent Patients with Erythropoiesis-Stimulating Agent, Relapsed or Refractory/Ineligible Lower-Risk Myelodysplastic Syndromes

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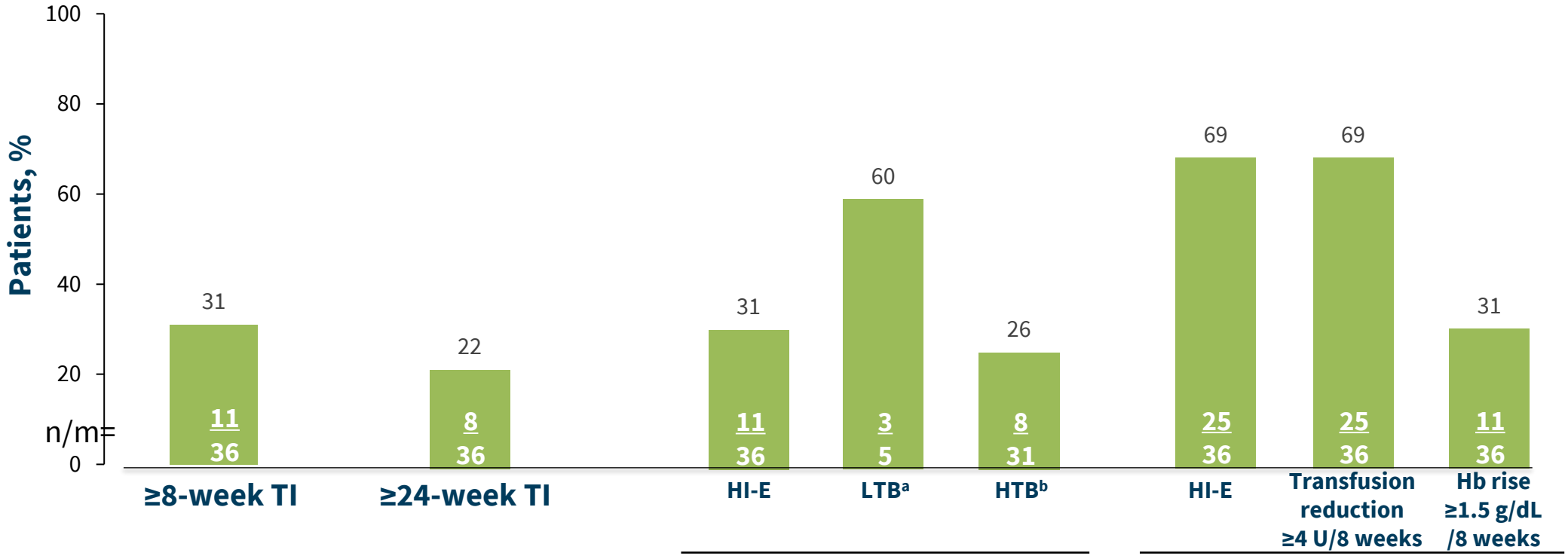
Results: Imetelstat Shows Clinical Activity in Patients With Prior LUSP (n=36)

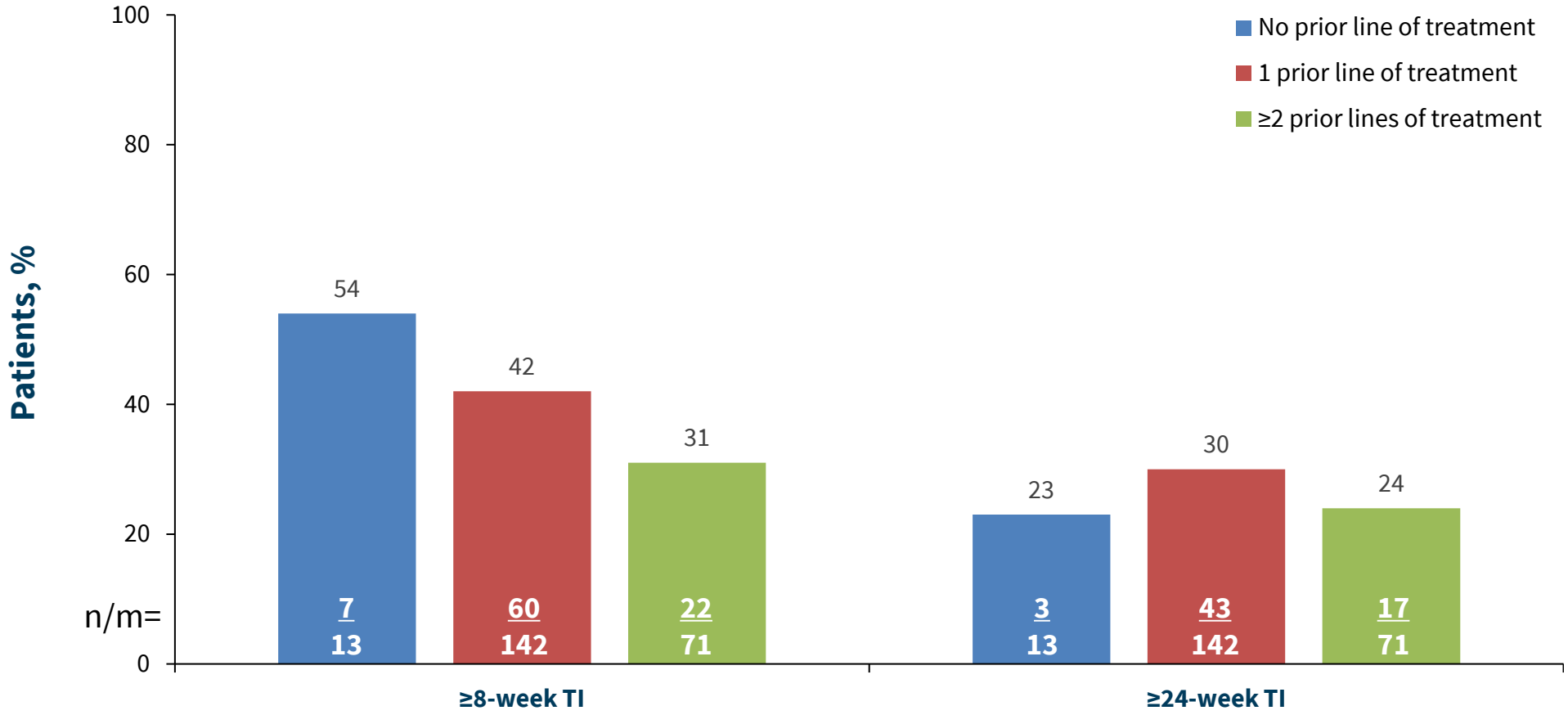


	≥8-week TI	≥24-week TI	IWG 2018 HI-E	IWG 2018 LTB[a]	IWG 2018 HTB[b]	IWG 2006 HI-E	IWG 2006 Transfusion reduction ≥4 U/8 weeks	IWG 2006 Hb rise ≥1.5 g/dL /8 weeks
With RS+ status, n/N (%)	10/31 (32)	8/31 (26)	10/31 (32)	3/5 (60)	7/26 (27)	22/31 (71)	22/31 (71)	10/31 (32)
With prior ESA and LUSP, n/N (%)	11/32 (34)	8/32 (25)	11/32 (34)	3/5 (60)	8/27 (30)	23/32 (72)	23/32 (72)	11/32 (34)
With prior ESA and no LUSP, n/N (%)	70/172 (41)	52/172 (30)	78/172 (45)	13/30 (43)	65/142 (46)	111/172 (65)	107/172 (62)	58/172 (34)

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; LUSP, luspatercept; n/m, number with event/number in population; RBC, red blood cell; RS, ring sideroblast; TI, transfusion independence.

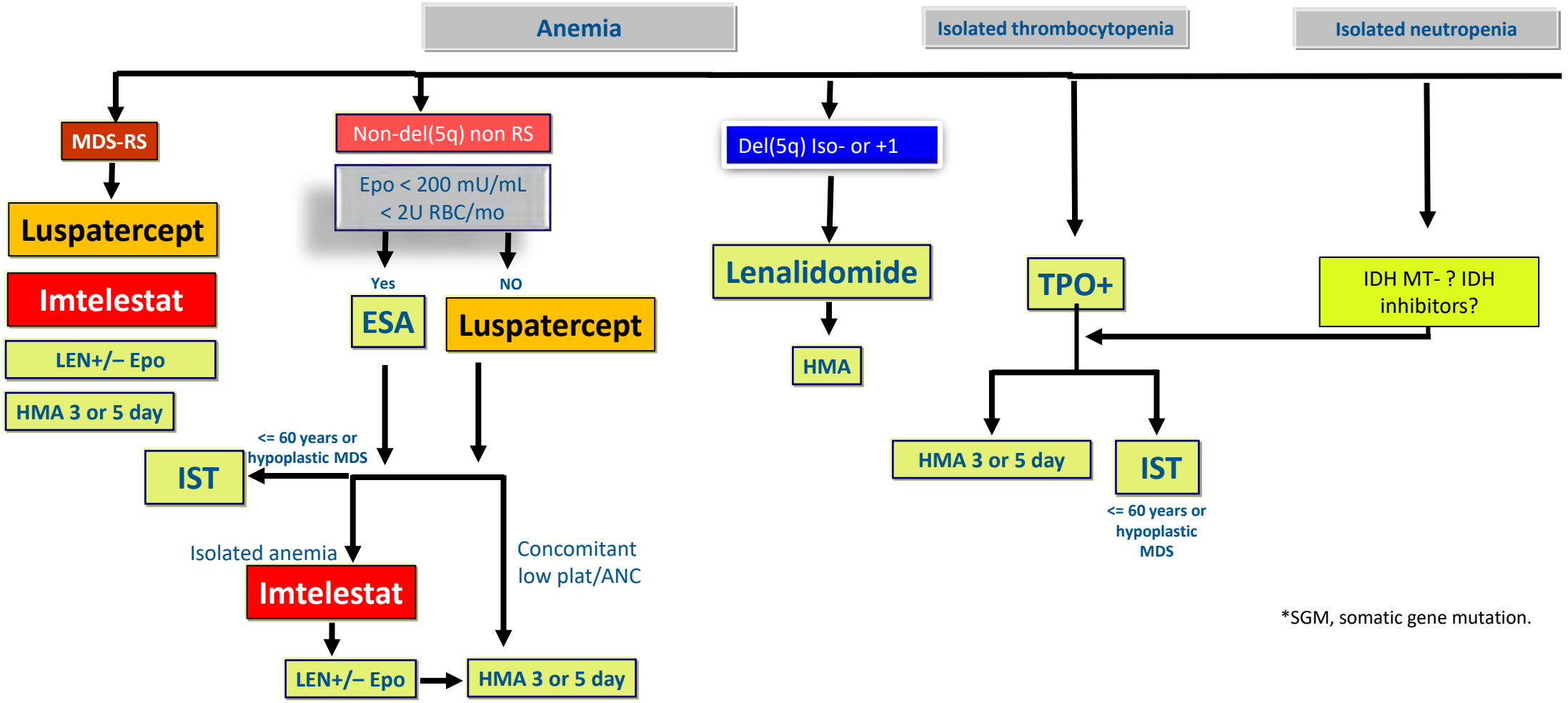
[a]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [b]HTB defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks.

Results: Imetelstat Clinical Activity by Number of Prior Lines of Therapy (N=226)



n/m, number with event/number in population; TI, transfusion independence.

How I treat LR-MDS in 2025



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

Case :

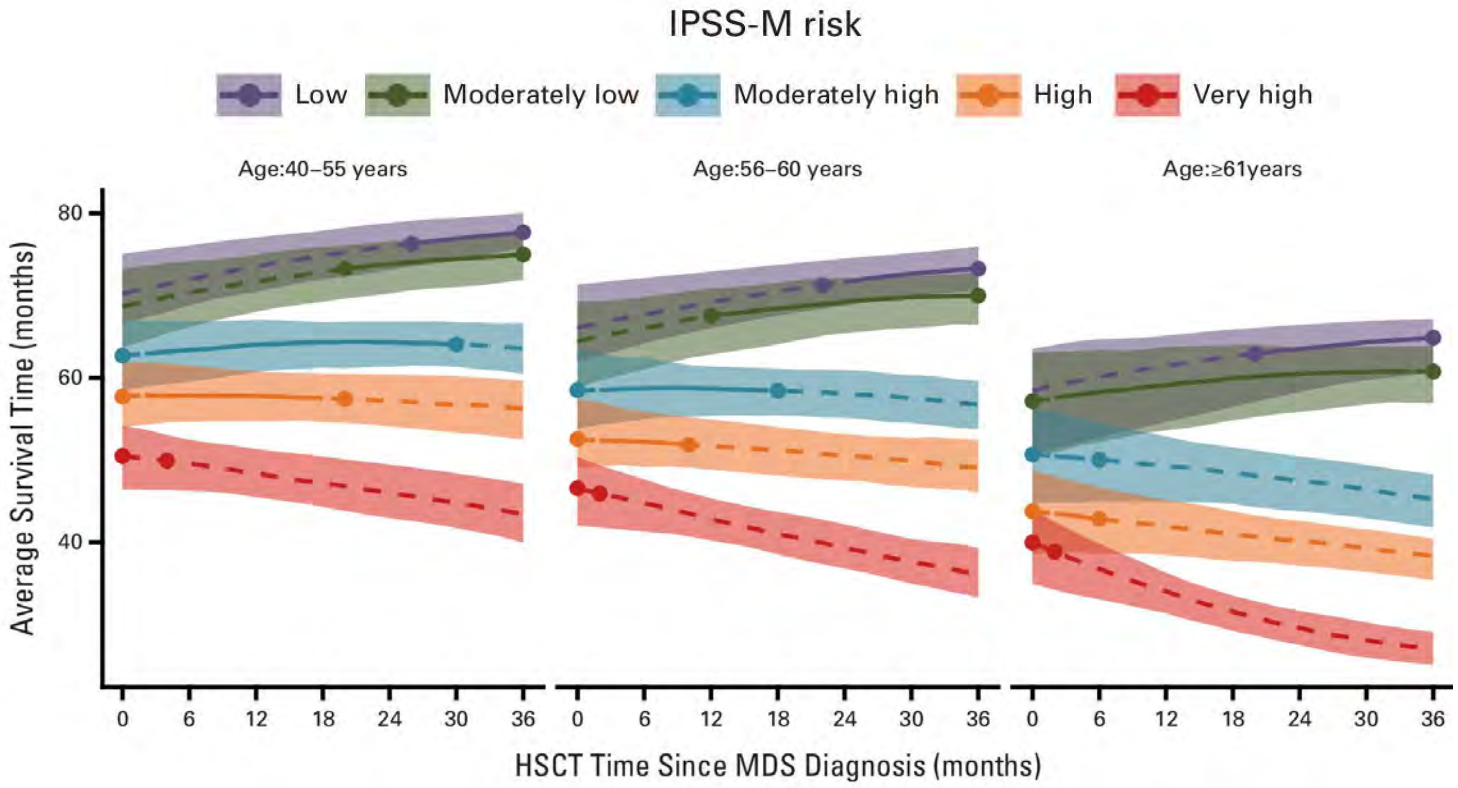
- 63-year-old gentleman no significant past medical history presented with fatigue, and SOB to local ER. CBC revealed WBC 3000, ANC 2.0, Hgb 7.2 g/dl, platelets 30.
- A bone marrow aspirate and biopsy was obtained, hypercellular bone marrow, 8% myeloblasts, karyotype del 12p (good)
- NGS: *TET-2* mutation VAF 30%; *RUNX1* mutation VAF 20%

Case

- How do you treat this patient?
  A. ESA
  B. Luspatercept
  C. Imetelstat
  D. Hypomethylating agent
  E. Hypomethylating agent and consideration of AHSCT

IPSS-M for AHSCT

Time to allo-SCT



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J Clin Oncol., 42(24):2873-2886, doi:10.1200/JCO.23.02175.

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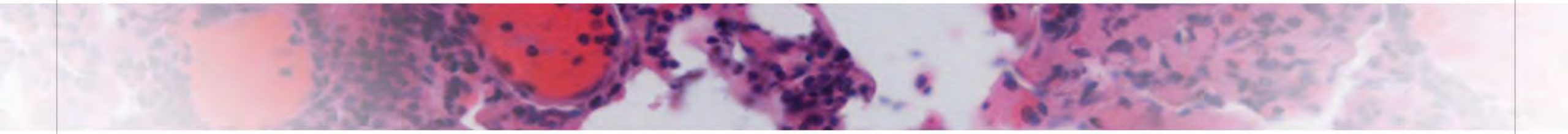

Impact of Response to Hypomethylating Agent-Based Therapy on Survival Outcomes in the Context of Baseline Clinical-Molecular Risk and Transplant Status in Patients with Myelodysplastic Syndromes/Neoplasms (MDS): An Analysis from the International Consortium for MDS (icMDS) Validate Database

Benjamin Rolles[1,2], Jan Philipp Bewersdorf[3,4], Tariq Kewan[3], Ondrej Blaha[5], Jessica M. Stempel[3], Luca Lanino[6], Najla H. Al Ali[7], Amy E. DeZern[8], Mikkael A. Sekeres[9], Geoffrey L. Uy[10], Hetty E. Carraway[11], Pinkal Desai[12], Elizabeth A. Griffiths[13], Eytan M. Stein[4], Andrew M. Brunner[14], Christine McMahon[15], Rory M. Shallis[3], Joshua F. Zeidner[16], Michael R. Savona[17], Stacey M. Frumm[1], Shougat Barua[2], Namrata S. Chandhok[9], Constantine Logothetis[10], Aram Bidikian[3], Ted M. Getz[3], Gail J. Roboz[12], Eunice S. Wang[13], Amyah C. Harris[14], Maria L Amaya[15], Hayley Hawkins[17], Somedeb Ball[17], Justin Grenet[12], Zhuoer Xie[7], Yazan F. Madanat[18], Yasmin Abaza[19], Talha Badar[20], Torsten Haferlach[21], Jaroslaw Maciejewski[11], David A. Sallman[7], Anoop K Enjeti[22], Kamal Al-Rabi, MD[23], Khalid Halahleh[23], Devendra Hiwase[24], Maria Diez-Campelo[25], David Valcárcel[26], Claudia Haferlach[21], Lisa Pleyer[27], Ioannis Kotsianidis[28], Vassiliki Pappa[29], Valeria Santini[30], Angela Consagra[30], Aref Al-Kali[31], Seishi Ogawa[32], Yasuhito Nannya[32], Matteo Giovanni Della Porta[6], Rami S. Komrokji[7], Amer M. Zeidan[3] and Maximilian Stahl, MD[2]

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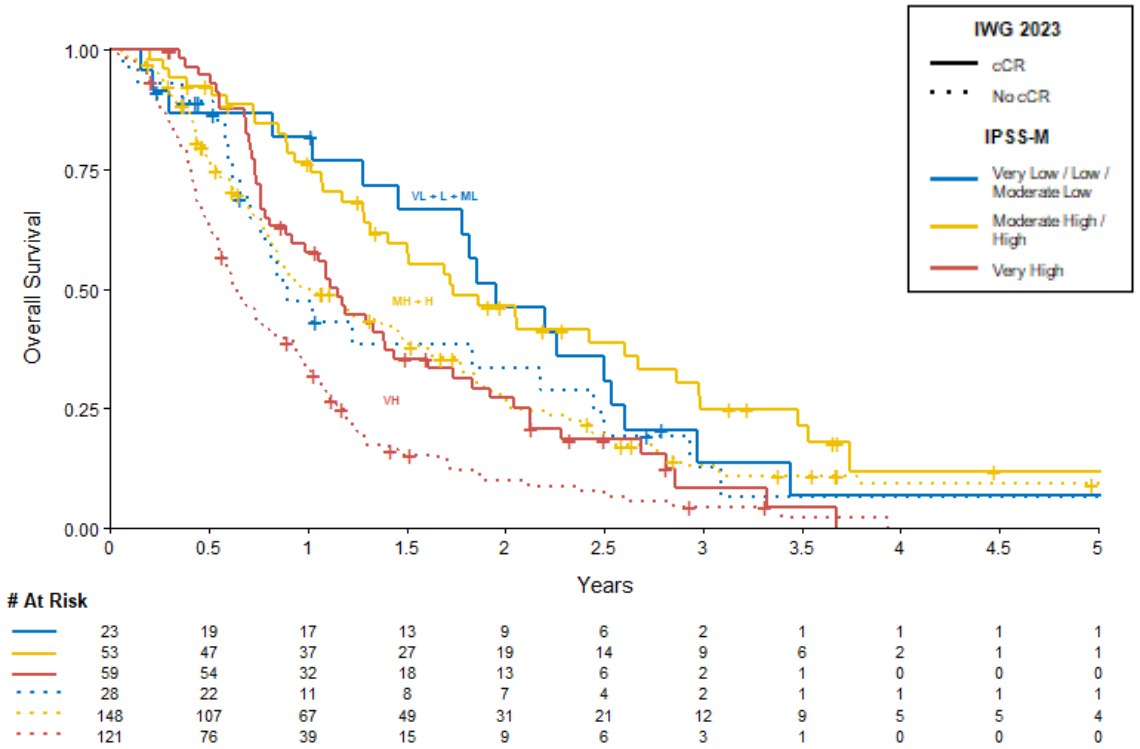
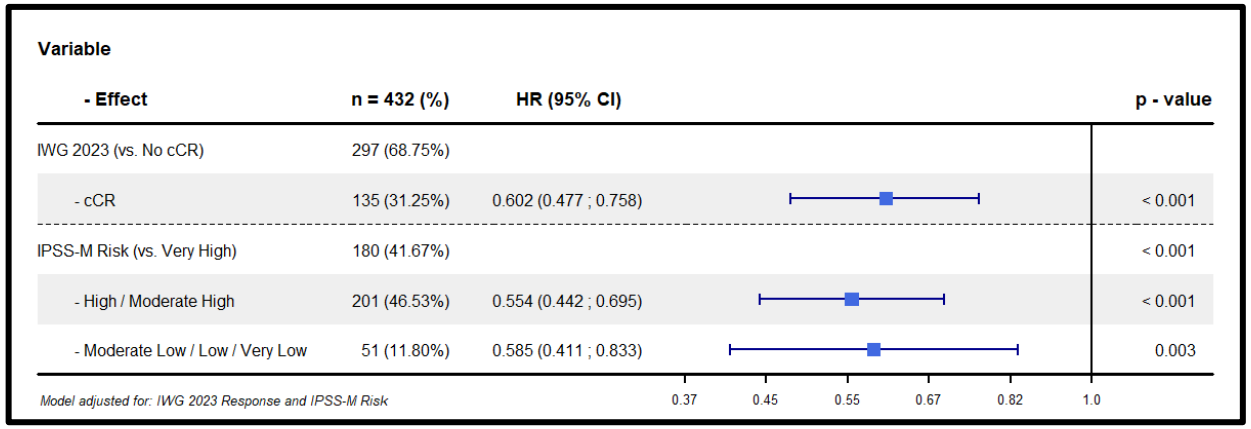
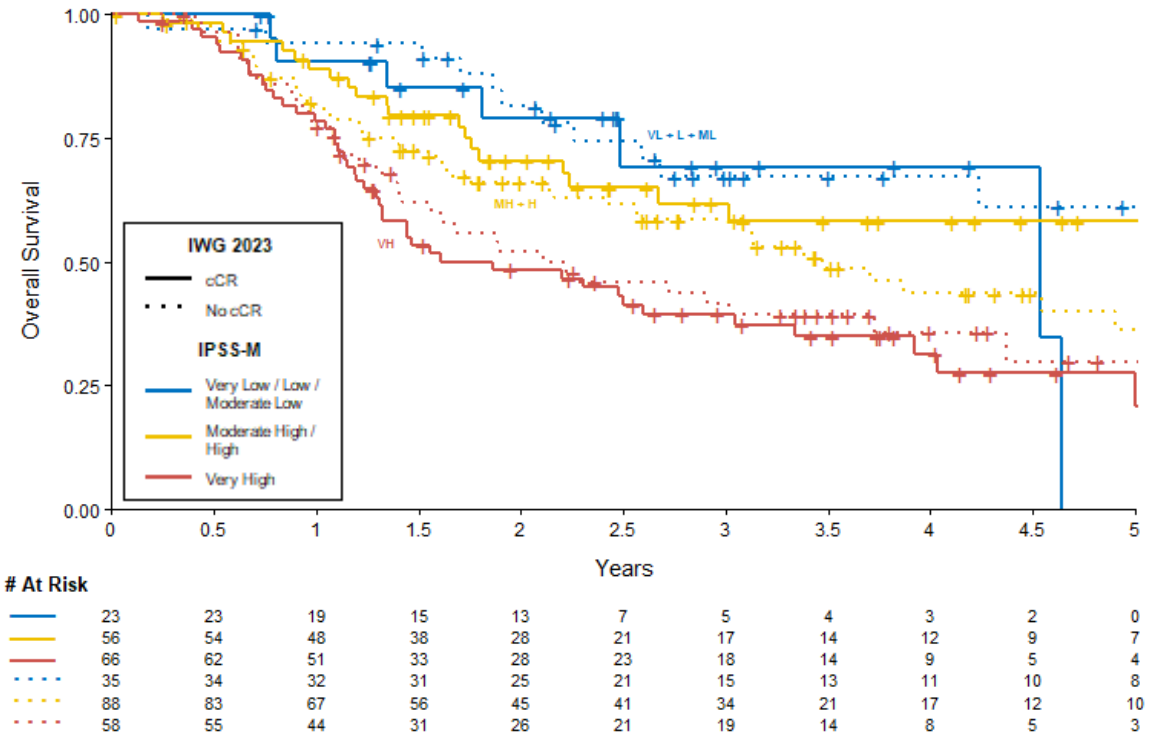
Treatment response in non-transplanted patients

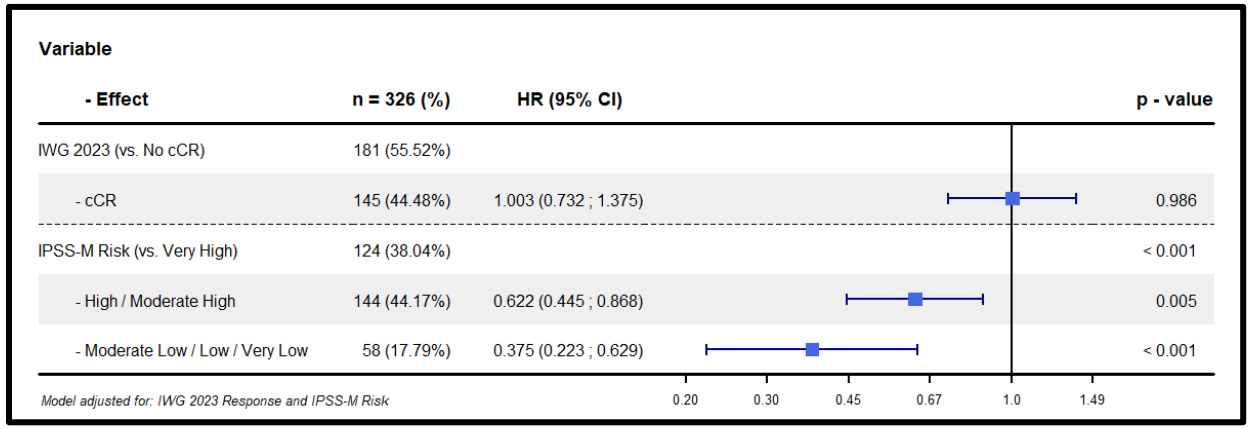




- **Within each pre-defined IPSS-M risk group, non-transplanted patients had improved median OS if they achieved a cCR compared to patients who did not.**
- **In non-transplanted patients who achieved cCR the median OS remained significantly different based on baseline IPSS-M.**

Treatment response in transplanted patients

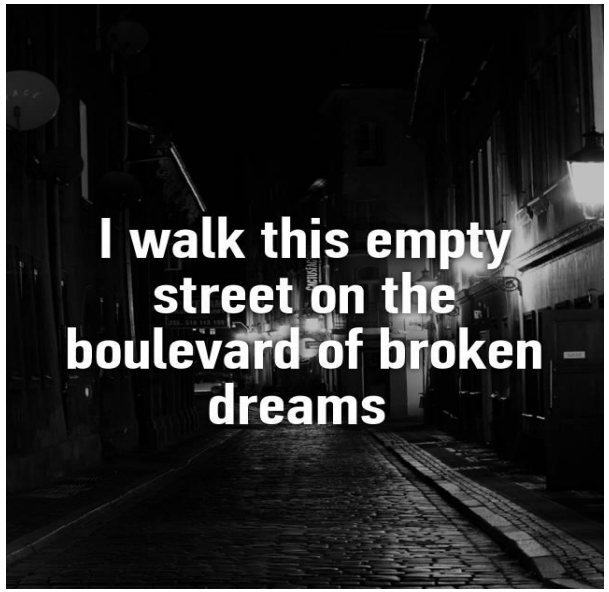




- **No effect of IWG 2023 response on OS in transplanted patients with MDS when adjusted for baseline IPSS-M risk.**
- **However, within transplanted patients OS was significantly different based on a patient's baseline IPSS-M.**

Lessons Learned from Phase III clinical trials in HR-MDS

Drug	Patient characteristics	Intervention	Study outcomes
Venetoclax	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)	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	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	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	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)	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



- Bi-allelic *TP53* MDS specific clinical trials.
- Survival= CR rate x duration
- Studies are under-powered to detect small improvements

A Retrospective Analysis of HMA + Venetoclax in Patients With MDS: Baseline Characteristics

Characteristic	HMA + VEN (n = 175)	HMA (n = 196)	Post-HMA failure VEN (n = 83)
Median age, yr (range)	66 (59-72)	69 (62-75)	71 (65-77)
Male, %	63	62	69
Race, %			
White	83	92	80
Black	5.7	5.1	8.4
Hispanic	7.4	0.5	8.4
IPSS-R, %			
Intermediate	16	34	28
High	26	36	36
Very High	58	30	35
Disease type, %			
De novo	67	82	83
Therapy-related	33	18	17
Del17p/TP53 mutated, %	49	22	25

Murthy. ASH 2024. Abstr 3206.

A Retrospective Analysis of HMA + Venetoclax in Patients With MDS: Efficacy and Safety

- Venetoclax mostly started in outpatient setting (78.6%) with TLS prophylaxis
  - 70-400 mg dosing range
- TLS rare: 6.2% lab-only; 1 pt with clinical TLS
- Neutropenic fever
  - HMA + VEN: 34.2%
  - HMA: 22.5%
  - Post HMA failure VEN: 44.5%

- HMA + VEN vs HMA
  - CR: 33% vs 12%
  - Marrow CR: 40% vs 27% (*P*<.001)
  - EFS: HR (95% CI) of 0.59 (0.44-0.78); *P* <.001
  - OS: HR (95% CI) of 0.77 (0.57-1.04); *P* = .08
- Post HMA failure VEN
  - CR: 10%
  - Marrow CR: 32%

Murthy. ASH 2024. Abstr 3206.

Olutasidenib for IDH1 Mutated MDS: Efficacy

	Olu (n = 5)	Olu + Aza (n = 14)	Pooled (n = 19)
ORR, n (%)	2 (40)	11 (79)	13 (68)
CR	1 (20)	5 (36)	6 (32)
Marrow CR	1 (20)	6 (43)	7 (37)
PR	0	0	0
SD, n (%)	1 (20)	3 (21)	4 (21)
Clinical benefit	1 (20)	0	1 (5)
PD	1 (20)	0	1 (5)

	Olu (n = 6)	Olu + Aza (n = 16)	Pooled (n = 22)
Time to CR, median mos	8.3	5.1	5.7
Duration of CR, median mos	NR	14.15	20.5
Time to CR/marrow CR, median mos	4.65	2	2
Duration of CR/marrow CR, median mos	NR	14.6	14.6
mOS, mos	14	27.5	27.2
12-mo OS rate, %	67	69	68

Cortes. ASH 2024. Abstr 4600.

IDEAL: Efficacy and Safety

	Cohort A	Cohort B	Cohort C
OR, %	42.9	43.3*	55
Median DoR, mos	6.9	12.2†	NR
Median OS, mos	14.9	25.5	NR

*4 patients received ENA + AZA after 3 cycles for 1 additional response
†2 patients went on to transplant

- Among 58 patients with HR-MDS in cohorts A and B
  - 45 (78%) experienced a total of 72 Grade ≥3 adverse events
  - No SAE related to enasidenib (total of 87 events)
  - 5 (8.6%) experienced differentiation syndrome which was manageable

Ades. ASH 2024. Abstr 1839.

Summary

- We keep learning about the spectrum of myeloid neoplasm
  - High risk CCUS=LR-MDS
  - Clinical phenotypes are reflection of underlying biology and genomics.
- Luspatercept is new standard of care as upfront therapy for LR-MDS RS+.
- Imetelstat is new approved option for treating anemia in LR-MDS, and activity is retained after Luspatercept failure.
- AHSCT remains only curative options and lack of response to treatment prior to transplant should not exclude patients.
- Hypomethylating agents remain the standard of care for HR-MDS, awaiting results of VERONA trial to confirm role of venetoclax.
- Post hypomethylating agent failure, targeted therapy such as IDH inhibitors remains best option.

Thank You

Rami.Komrokji@moffitt.org

Moffitt MDS team: Only perfect counts !!!

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