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Dr. Komrokji is a clinical investigator at H. Lee Moffitt Cancer Center. His research focus is on clinical trials in Myelodysplastic syndromes (MDS) and acute myeloid leukemia. He is the lead clinical investigator for the MDS Program at Moffitt and has conducted several translational clinical trials. He has also developed the MDS database, one of the largest is the world. Finally he serves as the Moffitt Cancer Center PI for the MDS Clinical Consortium, an agreement between 6 largest MDS Program in the country for conducting clinical trials in MDS. He serves as a member on the MDS NCCN committee and on the NIH MDS natural history study committee. His work is well recognized internationally and has collaborated with MDS programs worldwide.

Best of ASCO & EHA 2023
MDS & AML

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MYELODYSPLASTIC NEOPLASMS (MDS) CLASSIFICATION FROM WHO 2016 TO WHO 2022 AND ICC 2022:
AN EXPANDED ANALYSIS OF 7017 PATIENTS ON BEHALF OF THE INTERNATIONAL CONSORTIUM FOR MDS (icMDS)

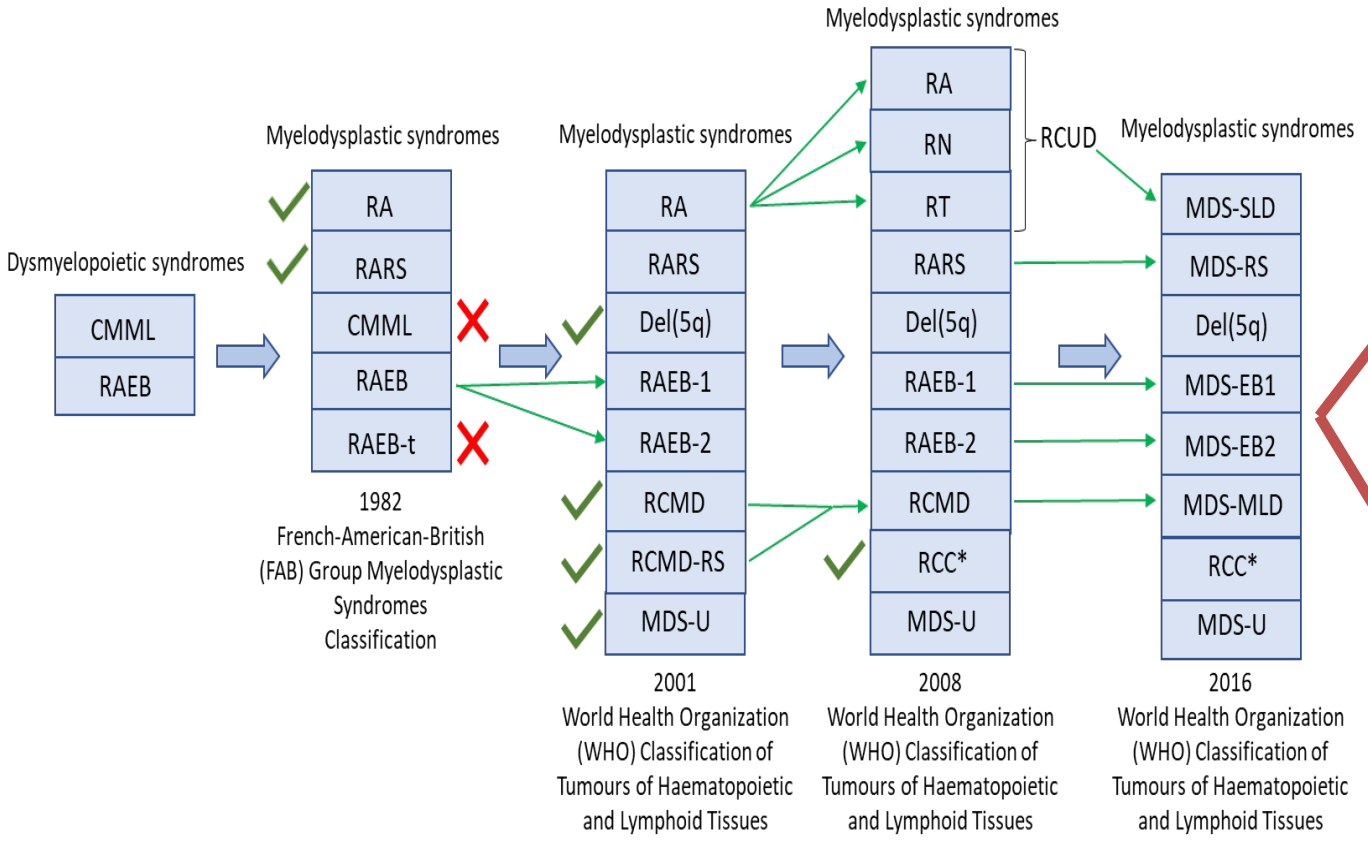
Rami S Komrokji*, Somedeb Ball*, Giulia Maggioni, Erica Travaglino, Najla Al Ali, Pierre Fenaux, Uwe Platzbecker, Maria Diez-Campelo, Torsten Haferlach, Avani M Singh, Luis E Aguirre, Akriti G Jain, Sara M Tinsley, Zaker I Schwabkey, Onyee Chan, Zhuoer Xie, Andrew Kuykendall, Andrew Brunner, John Bennett, 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

MDS classification has evolved over time



Key

✓ = new addition to respective classification

✗ = removed from subsequent classification

WHO 2022

Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

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

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

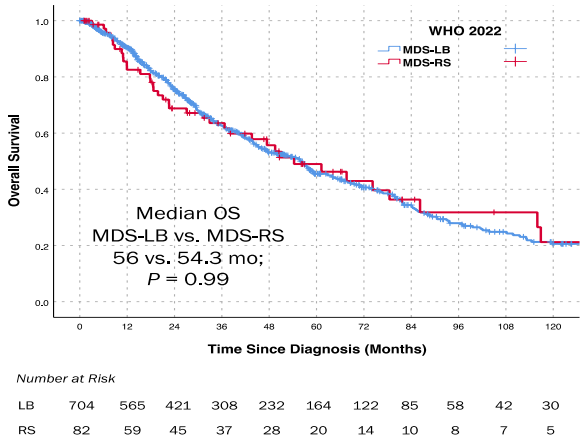
MDS-*SF3B1* genetically defined group has best outcome

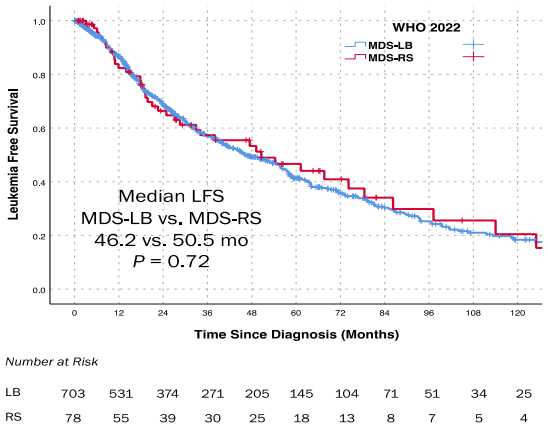
	MCC Cohort		GM Cohort	
	WHO	ICC	WHO	ICC
n (%)	294 (13%)	277 (12%)	654 (13.9%)	594 (12.6%)
OS	101.8	111.6	104.9	101.9
LFS	100.6	109.4	102.2	101.9

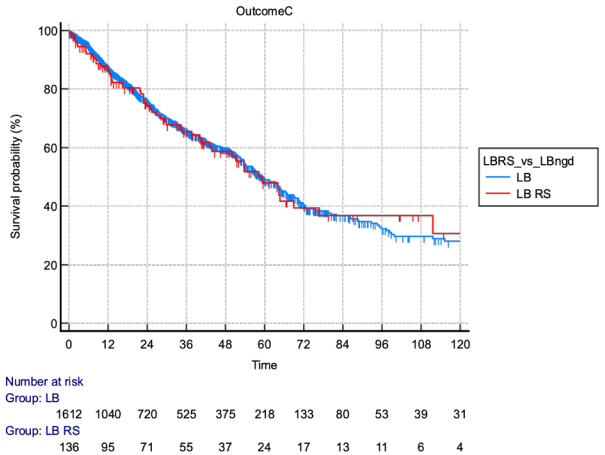
- MDS-*SF3B1* accounts for 12-13% of all MDS cases.
  (slight difference between WHO and ICC given definitions)
- Median OS and LFS exceeds 8 years.

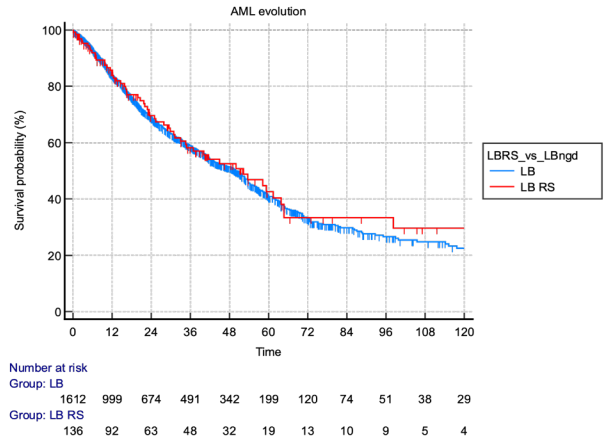
MDS-RS *SF3B1* WT uncommon but similar outcome to MDS-LB

	MCC Cohort			GM Cohort		
	MDS-RS-*SF3B1* WT	MDS-LB	P value	MDS-RS-*SF3B1* WT	MDS-LB	P value
n (%)	78 (4%)	704 (31%)		126 (4%)	1612 (34.3%)	
OS	54.3	56	.99	58.2	59.5	.82
LFS	50.5	46.2	.72	50.3	52.3	.79









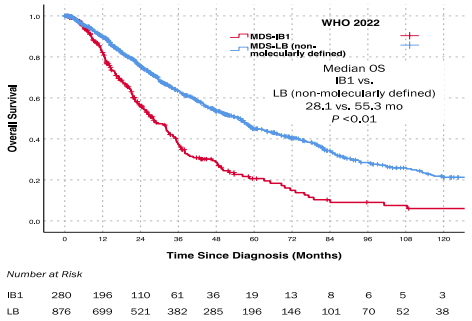
TP53-mutated MDS has the worst outcome

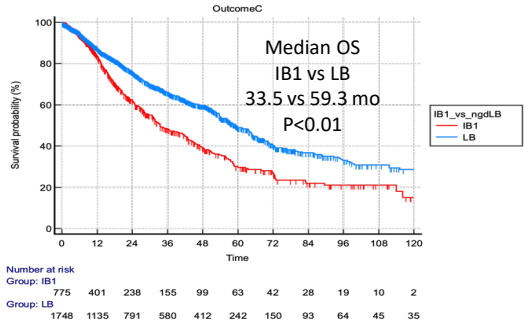
MDS-bi *TP53*	MCC Cohort		GM Cohort	
	WHO	ICC	WHO	ICC
n (%)	214 (10%)	194 (9%)	443 (9.4%)	290 (6.2%)
OS	13.2	14.2	14	17.6
LFS	10	11.5	13.4	16.3

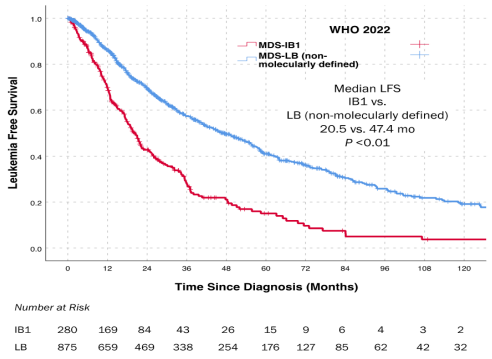
MDS/AML-m *TP53*	MOFFITT	GM
	ICC	ICC
n (%)	115 (5%)	146 (3.1%)
OS	11	10
LFS	6.4	9.7

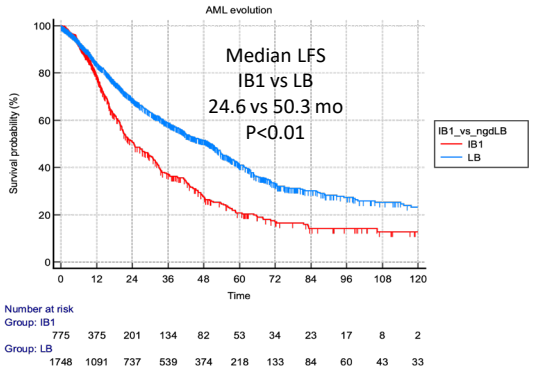
- WHO 2022 MDS bi-allelic *TP53* inactivation accounted for ~ 10% of MDS cases with median OS ~ 1-1.5 years .
- ICC 2022 MDS/AML m-*TP53 (≥10% myeloblasts) accounted for 3-5% of MDS cases* with median OS < 1 year.
- (worse outcome driven by increased myeloblasts).

Increased myeloblasts are associated with worse outcome but the exact cut off is not clear









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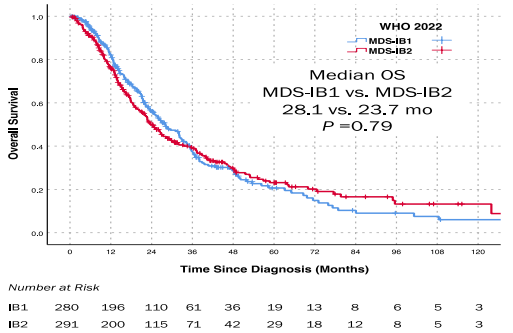
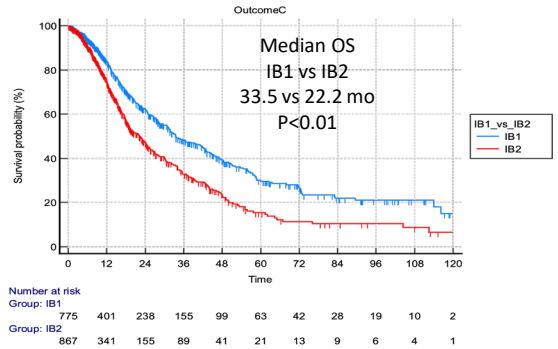
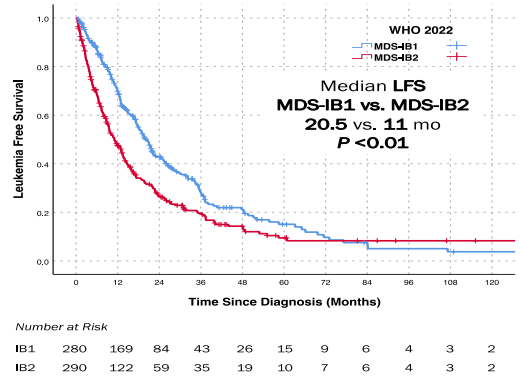
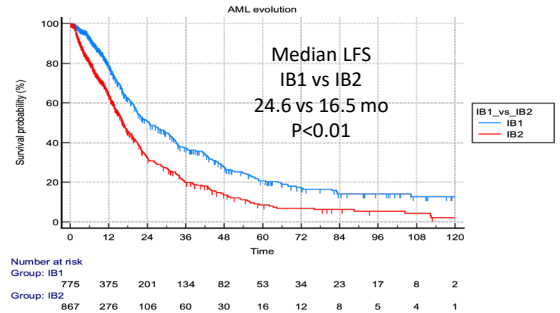
MDS-IB1 vs MDS-LB









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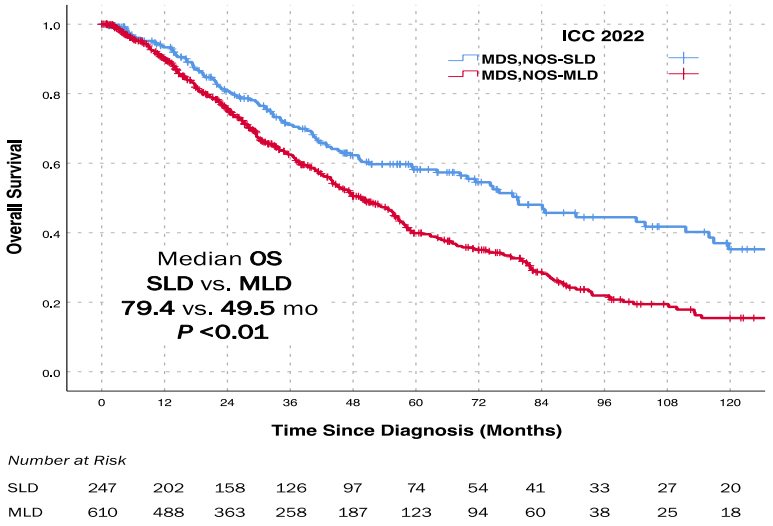
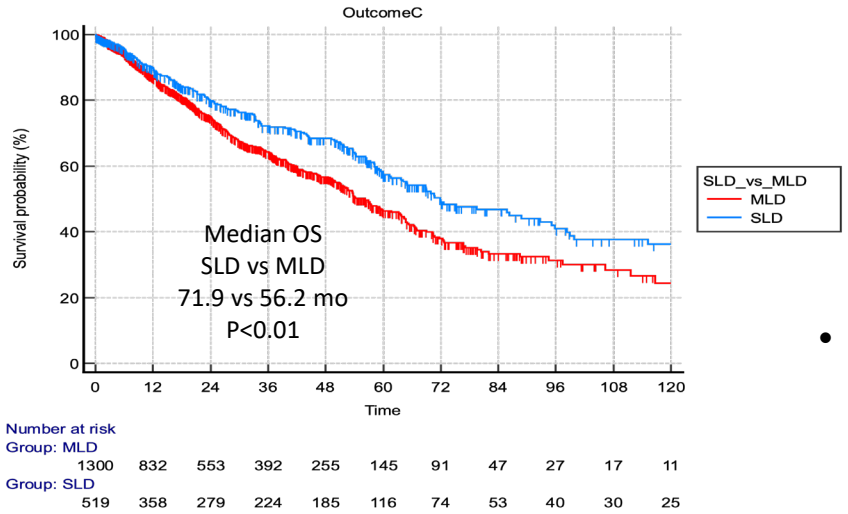
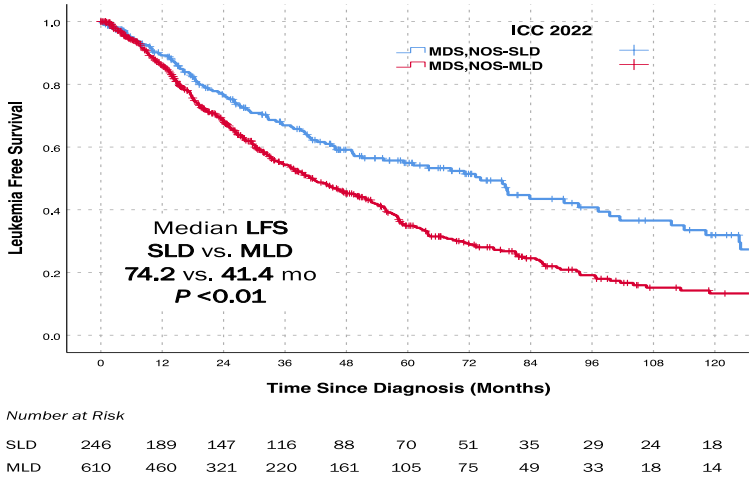
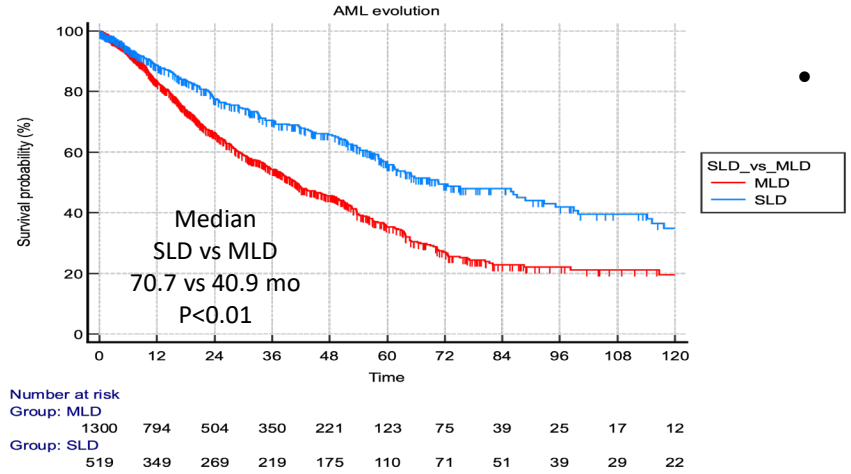
MDS-IB2 vs MDS-IB1

MDS MLD confers worse LFS and OS compared to MDS SLD

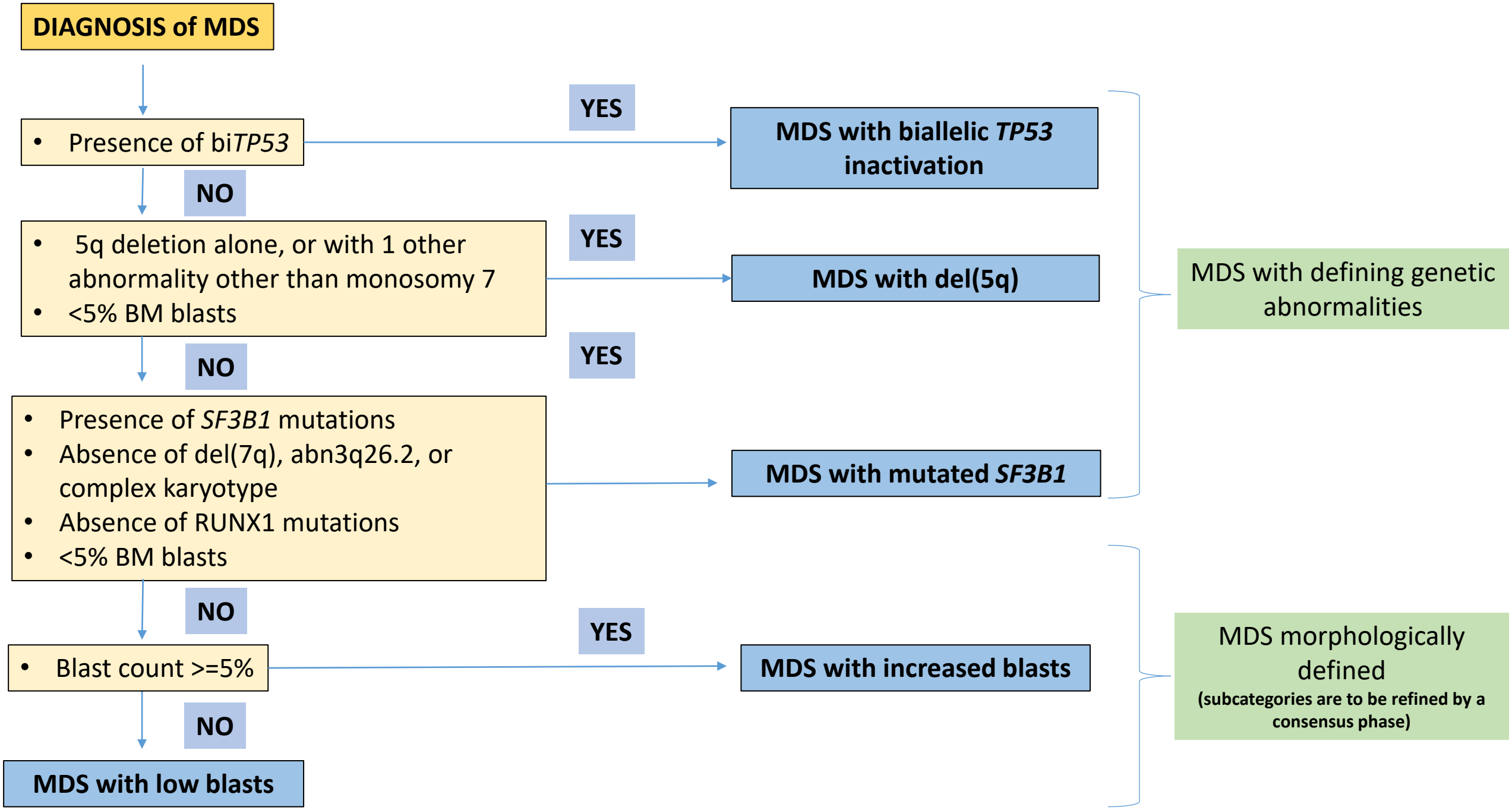








- MDS, SLD accounts for less than 30% of MDS-LB and had a significantly better median LFS and median OS compared to MDS, MLD
- No characteristics molecular profile.


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

2022 ELN Risk Categorization for AML

- The ELN AML risk classification is based on data from intensively treated patients and may need modifications for less-intensive therapies
- Initial risk assignment may change during the treatment course based on MRD analyses

Risk Category	Genetic Abnormalities
Favorable	▪ t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ▪ Mutated *NPM1* without *FLT3*-ITD ▪ bZIP in-frame mutated *CEBPA*
Intermediate	▪ Mutated *NPM1* with *FLT3*-ITD ▪ Wild-type *NPM1* with *FLT3*-ITD ▪ t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ▪ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Risk Category*	Genetic Abnormalities
Adverse	▪ t(6;9)(p23;q34.1)/*DEK*::*NUP214* ▪ t(v;11q23.3)/*KMT2A*-rearranged ▪ t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* ▪ t(8;16)(p11;p13)/*KAT6A*::*CREBBP* ▪ inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*,*MECOM(EVI1)* ▪ t(3q26.2;v)/*MECOM*(*EVI1*) rearranged ▪ -5 or del(5q); -7; -17/abn(17p) ▪ Complex karyotype, monosomal karyotype ▪ Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* ▪ Mutated *TP53*

Döhner. Blood. 2022:[Epub].

Slide credit: clinicaloptions.com

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

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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]

Study endpoints

Composite primary endpoint (weeks 1–24)

- RBC-TI for ≥ 12 weeks **WITH CONCURRENT** mean hemoglobin increase ≥ 1.5 g/dL

Secondary endpoints (weeks 1–24)

- HI-E response ≥ 8 weeks per IWG criteria
- RBC-TI for 24 weeks
- RBC-TI for ≥ 12 weeks

Secondary and exploratory endpoints

- Duration of RBC-TI for ≥ 12 weeks (week 1–EOT)
- Impact of baseline mutations on response
- Subgroup analyses

- The data cutoff date for this planned interim analysis was August 31, 2022
  - This prespecified interim analysis was planned for when ~300 patients had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment (at 85% of information for the primary endpoint)

Safety

- Treatment discontinuation
- TEAE
- HR-MDS/AML progression
- Death

HI-E, hematological improvement-erythroid; RBC-TI, RBC transfusion independence; TEAE, treatment-emergent adverse event.

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

Demographics and baseline patient characteristics

	Luspatercept (N = 178)	Epoetin alfa (N = 178)
Age, median (range), years	74.0 (46.0–93.0)	75.0 (33.0–91.0)
Female, n (%)	71 (39.9)	87 (48.9)
Time since original MDS diagnosis, median (range), months[a]	8.0 (−0.4 to 243.1)	5.2 (−0.3 to 171.6)
Baseline transfusion burden, median (range), pRBC units	3.0 (1–10)	3.0 (0–14)
Baseline transfusion burden category, n (%)		
< 4 pRBC units	114 (64.0)	109 (61.2)
2 pRBC units	80 (44.9)	79 (44.4)
≥ 4 pRBC units	64 (36.0)	69 (38.8)
IPSS-R risk classification at baseline, n (%)		
Very low	16 (9.0)	17 (9.6)
Low	126 (70.8)	131 (73.6)
Intermediate	34 (19.1)	28 (15.7)
Other[b]	1 (0.6)	0
Missing[c]	1 (0.6)	2 (1.1)

[a]Number of months from date of original diagnosis to date of informed consent. [b]The central pathology laboratory confirmed the MDS diagnosis with an IPSS-R score of intermediate at screening for 1 patient in the luspatercept arm; at the next bone marrow assessment, the central laboratory sent the report with an IPSS-R score of high, confirmed that the score at screening was also high, and acknowledged the mistake. [c]For 3 patients (1 in the luspatercept arm and 2 in the epoetin alfa arm) the risk score could not be calculated.

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

Demographics and baseline patient characteristics

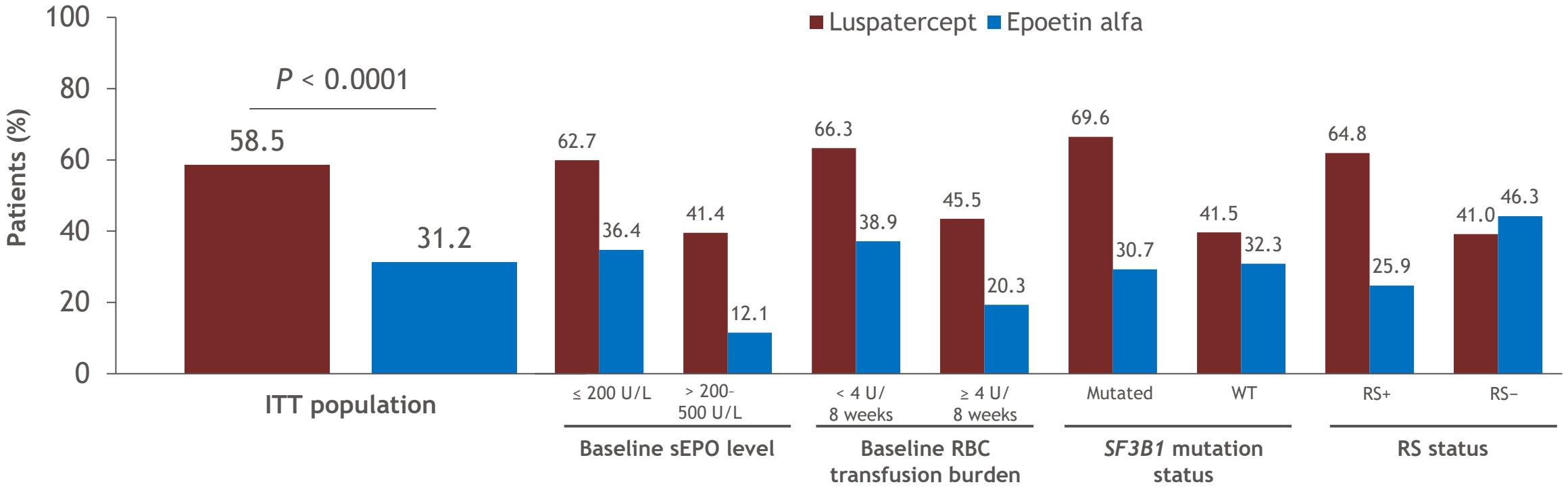
	Luspatercept (N = 178)	Epoetin alfa (N = 178)
Ring sideroblast status, n (%)		
RS+	130 (73.0)	128 (71.9)
RS−	48 (27.0)	49 (27.5)
Missing[d]	0	1 (0.6)
***SF3B1* mutation status, n (%)**		
Mutated	111 (62.4)	99 (55.6)
Non-mutated	65 (36.5)	72 (40.4)
Missing	2 (1.1)	7 (3.9)
Hemoglobin, median (range), g/dL	7.80 (4.7-9.2)	7.8 (4.5-10.2)
Serum erythropoietin, median (range), U/L	78.71 (7.8-495.8)	85.9 (4.6-462.5)
Platelet count, median (range), 10^9/L	230.0 (38-770)	234.5 (47-715)
Absolute neutrophil count, median (range), 10^9/L	2.4 (0.4-9.1)	2.3 (0.5-13.3)
Serum ferritin, median (range), µg/L	626.2 (12.4-3170.0)	651.3 (39.4-6960.5)

[d]1 patient in the epoetin alfa arm had a bone marrow biopsy assessed by the central lab with a diagnosis of MDS with multilineage dysplasia and RS status was not provided.

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

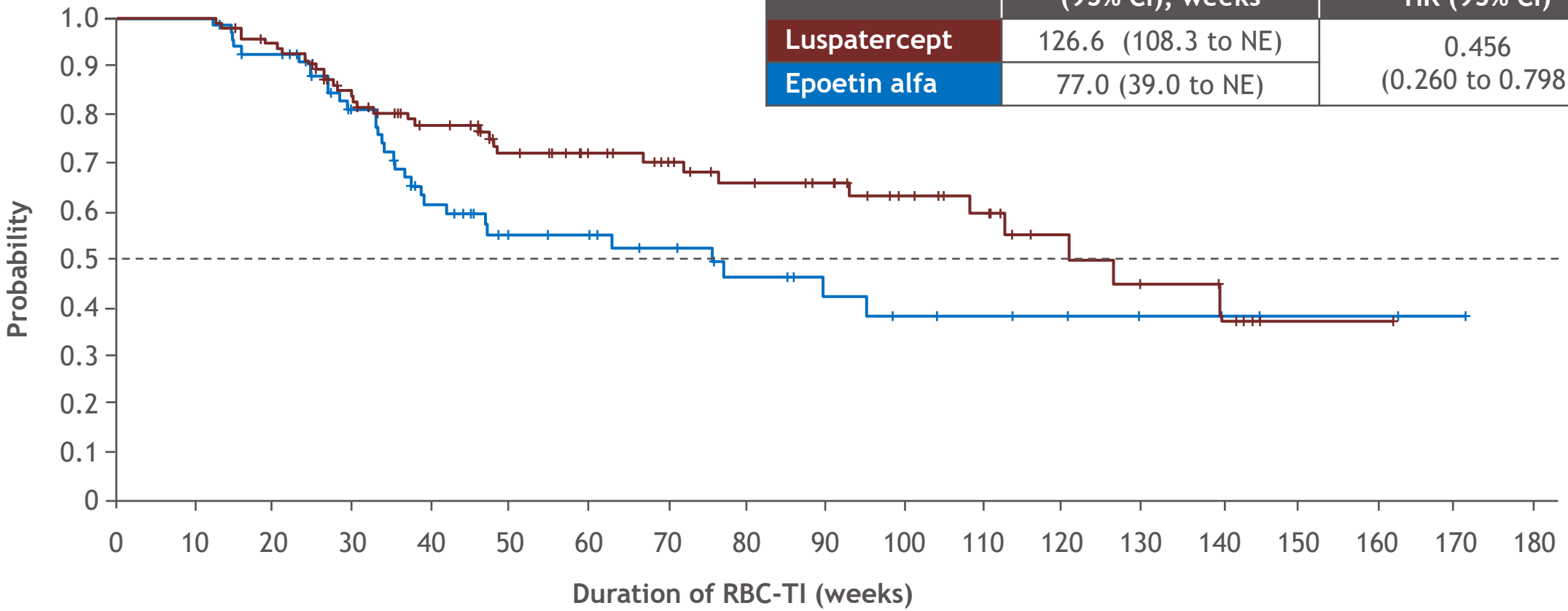


This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment.

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]

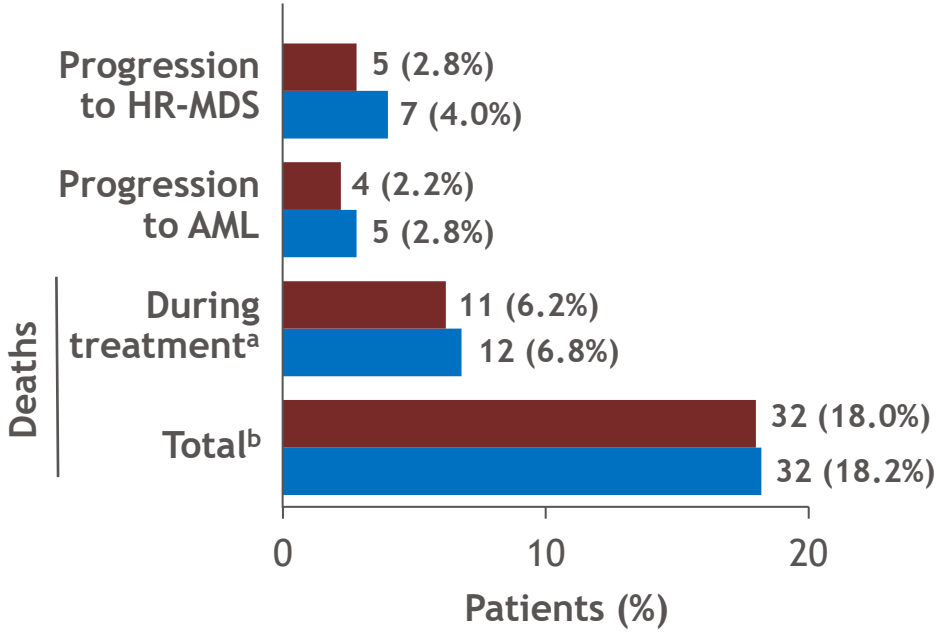
Safety profile of luspatercept manageable and comparable to previous studies

- Exposure to luspatercept was ~2 times longer compared with epoetin alfa, providing a longer reporting period for AEs

Patients, n (%)	Luspatercept (N = 178)		Epoetin alfa (N = 176)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

TEAEs of any grade
164 (92.1%) luspatercept
150 (85.2%) epoetin alfa

Treatment duration, median (range), weeks
41.6 (0–165) luspatercept
27.0 (0–171) epoetin alfa



Safety data are not exposure-adjusted.
[a]11 deaths in each arm led to treatment discontinuation. One additional death occurred in the epoetin alfa arm after treatment discontinuation due to an AE; the death occurred during the 42-day safety follow up, which was considered a death during treatment but not counted as a death leading to treatment discontinuation. [b]Deaths during treatment period and post-treatment period. TEE, thromboembolic event.

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

Summary

- COMMANDS study achieved its primary endpoint, demonstrating that luspatercept is superior to ESA in ESA-naive transfusion-dependent LR-MDS
  - The primary endpoint was achieved in 59% of patients treated with luspatercept vs 31% with ESA
  - Median duration of response was 127 weeks vs 77 in favor of luspatercept, which is ~1 year longer than ESAs
- Luspatercept provides clinical benefit regardless of subgroups and baseline mutational burden
- Luspatercept has a manageable and predictable safety profile, consistent with previous clinical experience and convenient (Q3W) administration

Luspatercept is the first and only therapy to demonstrate superiority in a head-to-head study against ESAs and brings a paradigm shift in the treatment of LR-MDS-associated anemia

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

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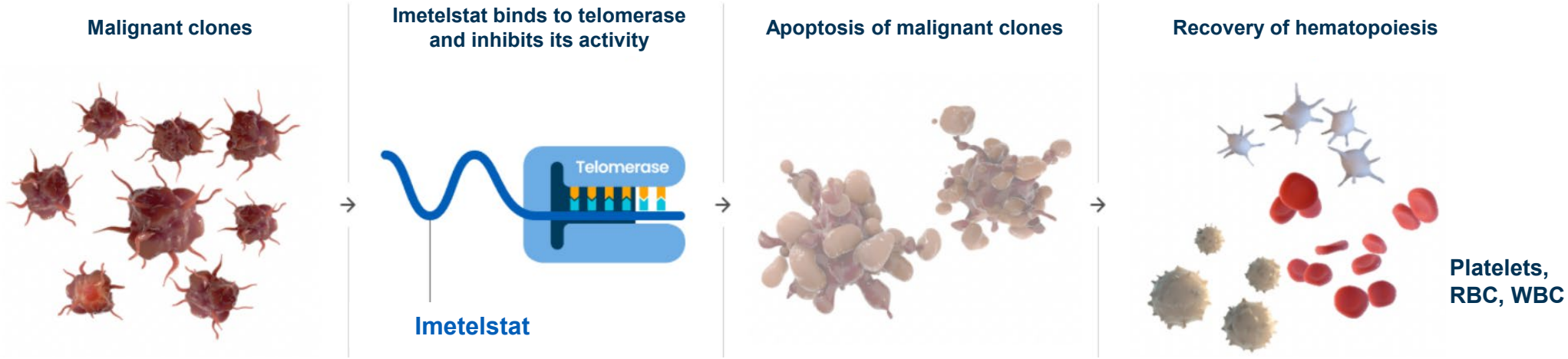
09/06/2023

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

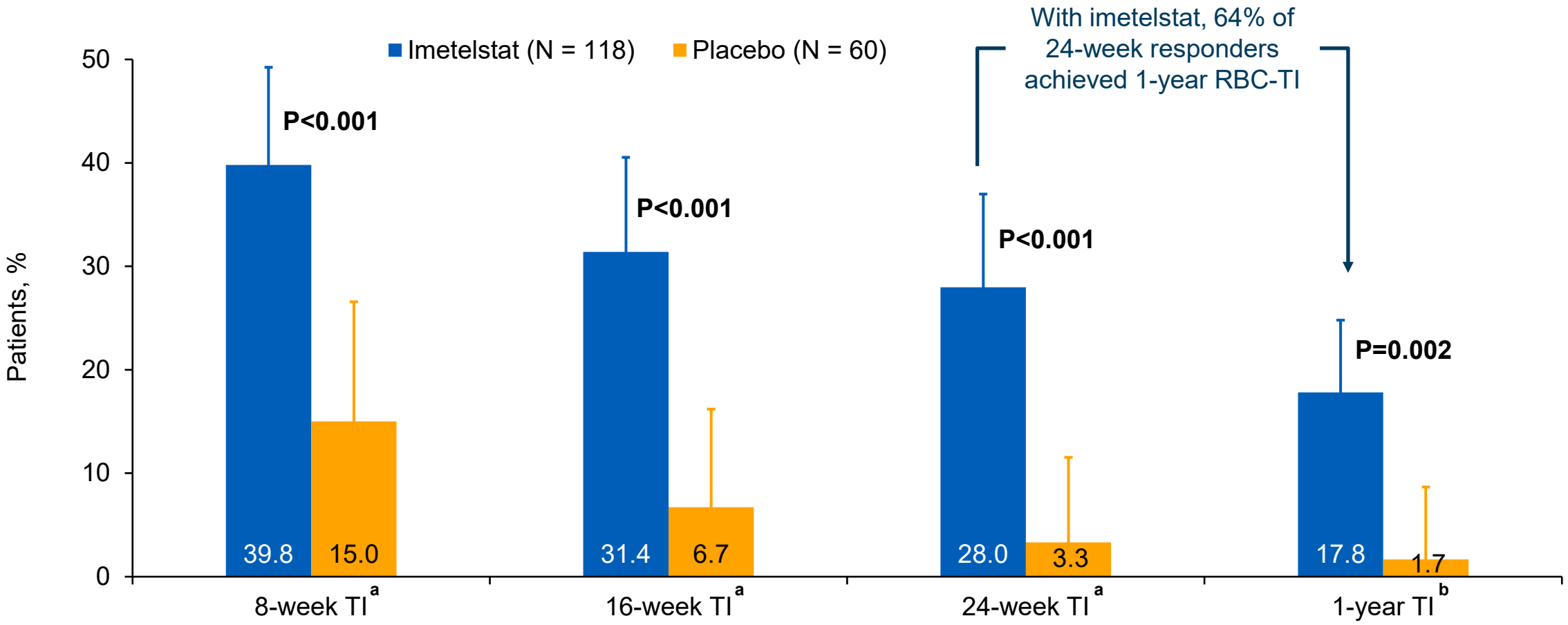
[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 units, epoetin beta ≥30,000 units or darbepoetin alfa 150 µg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 units/8 weeks or transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic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

Baseline Patient and Disease Characteristics

Characteristic	Imetelstat (N = 118)	Placebo (N = 60)
Median age, years (range)	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Median time since diagnosis, years (range)	3.5 (0.1-26.7)	2.8 (0.2-25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS-	44 (37)	23 (38)
IPSS risk category n (%)		
Low	80 (68)	39 (65)
Intermediate-1	38 (32)	21 (35)
Median pretreatment Hgb, g/dL (range)[a]	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Median prior RBC transfusion burden, RBC units/8 weeks (range)	6 (4-33)	6 (4-13)
Prior RBC transfusion burden, n (%)		
≥4 to ≤6 units/8 weeks	62 (53)	33 (55)
>6 units/8 weeks	56 (48)	27 (45)
Median sEPO, mU/mL (range)	174.9 (6.0-4460.0)	277.0 (16.9-5514.0)
sEPO level, n (%)		
≤500 mU/mL	87 (74)	36 (60)
>500 mU/mL	26 (22)	22 (37)
Prior ESA, n (%)	108 (92)	52 (87)
Prior luspatercept, n (%)[b]	7 (6)	4 (7)

[a]Average of all Hgb values in the 8 weeks prior to the first dose date, excluding values within 14 days after a transfusion; thus, considered to be influenced by transfusion. [b]Insufficient number of patients previously treated with luspatercept to draw conclusions about the effect of imetelstat treatment in such patients.
ESA, erythropoiesis stimulating agent; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization.

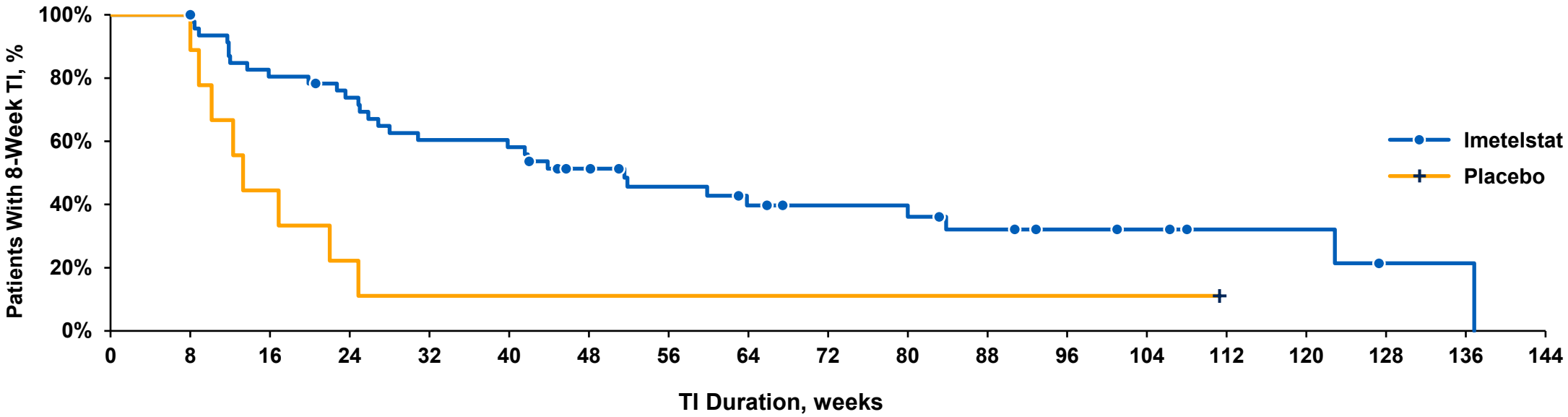
Higher Rates of Longer-Term Duration of RBC TI Observed With Imetelstat vs Placebo, Including 1-year RBC TI With Additional 3 Month Follow-up



[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.

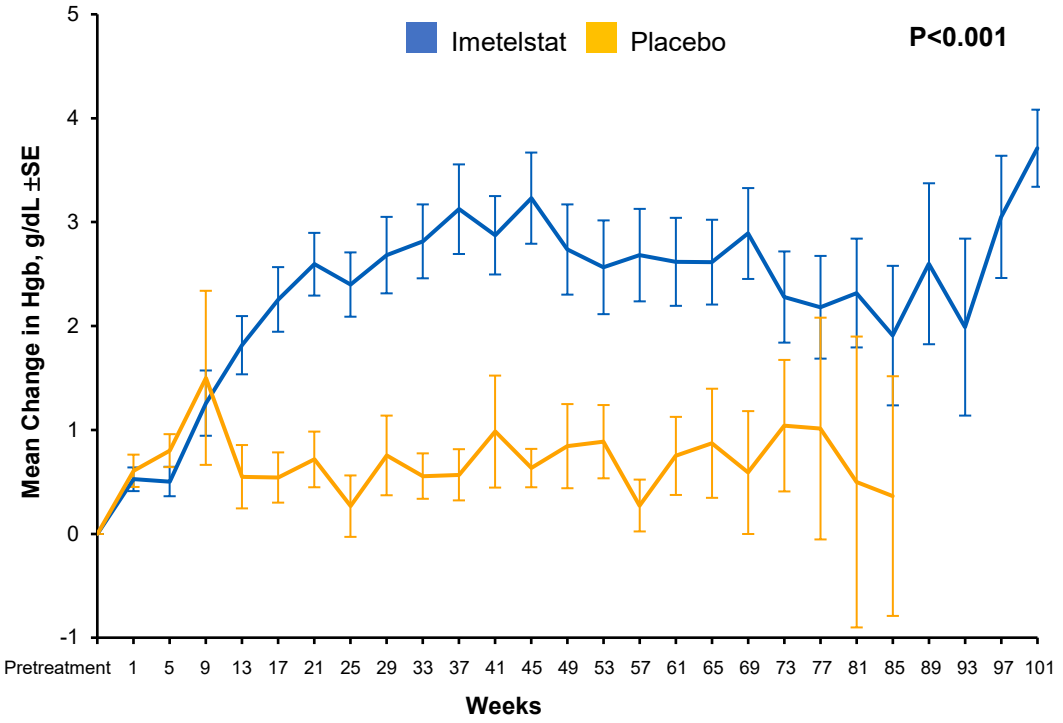
[a]HR (95% CI) from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC units/8-weeks during a 16-week period prior to randomization) and baseline IPSS risk category (low vs intermediate-1), with treatment as the only covariate. [b]P value (2-sided) for superiority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

Grade 3–4 Cytopenias Were of Short Duration and Manageable

- Median duration of grade 3–4 thrombocytopenia and neutropenia was <2 weeks and >80% of events were reversible to grade ≤2 within 4 weeks
- 41 patients (34.7%) in the imetelstat group and 2 patients (3.4%) in the placebo group had ≥1 dose of a myeloid growth factor mostly within Cycles 2–4
- **Clinical consequences of grade 3–4 infection and bleeding were low and similar for imetelstat and placebo**

Grade 3–4 Cytopenias per lab value	Imetelstat (N = 118)	Placebo (N = 59)
Thrombocytopenia		
Median duration, weeks (range)	1.4 (0.1–12.6)	2.0 (0.3–11.6)
Resolved within 4 weeks, %	86.3	44.4
Neutropenia		
Median duration, weeks (range)	1.9 (0–15.9)	2.2 (1.0–4.6)
Resolved within 4 weeks, %	81.0	50.0

Event, n (%)	Imetelstat (N = 118)	Placebo (N = 59)
Grade ≥3 bleeding events	3 (2.5)	1 (1.7)
Grade ≥3 infections	13 (11.0)	8 (13.6)
Grade 3 febrile neutropenia	1 (0.8)	0

Data cutoff: October 13, 2022.

Imetelstat AEs Were Manageable With Dose Modifications

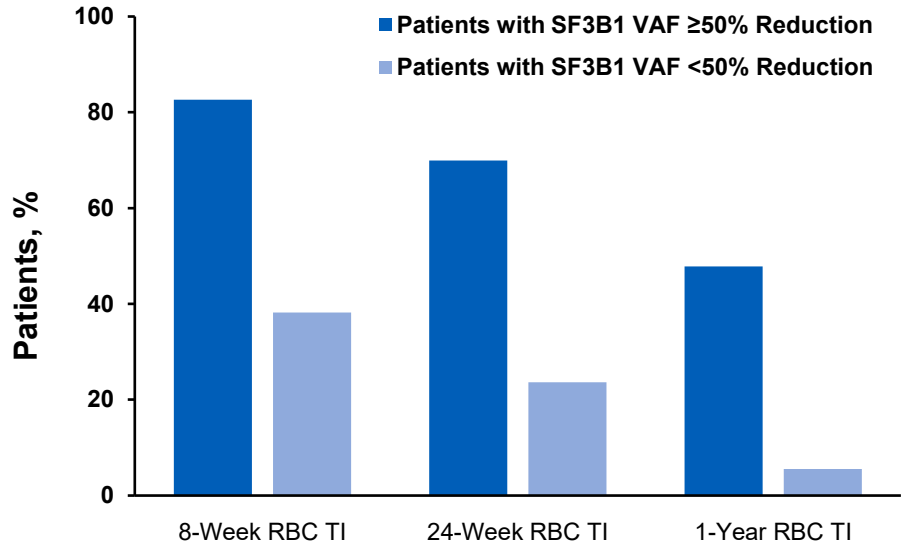
- Most AEs leading to dose modifications were grade 3–4 neutropenia and thrombocytopenia
- Although 74% of patients treated with imetelstat had dose modifications due to AEs, <15% of patients discontinued treatment due to TEAEs
- Discontinuation of imetelstat due to a TEAE generally occurred late in treatment, with a median time to treatment discontinuation of 21.1 weeks (range, 2.3 to 44.0 weeks)

Dose Modifications, n (%)	Imetelstat (N = 118)	Placebo (N = 59)
Patients with any dose delay due to TEAE	81 (68.6)	14 (23.7)
Patients with dose reduction due to TEAE	58 (49.2)	4 (6.8)
Patients with treatment discontinuation due to TEAE	17 (14.4)	0

Data cutoff: October 13, 2022.
AE, adverse event; TEAE, treatment-emergent adverse event.

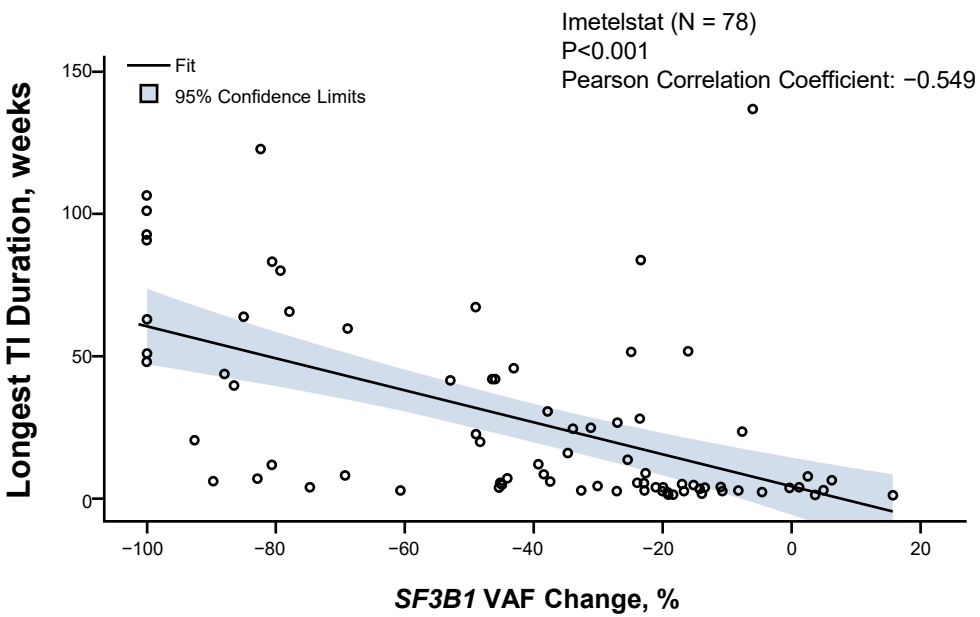
Among Patients Treated With Imetelstat, *SF3B1* ≥ 50% Reductions Associated With Durable RBC-TI Rates and Longer RBC-TI Duration

RBC-TI Rate by *SF3B1* VAF Reduction



Patients With RBC-TI, n/N (%)			
In ≥50% VAF Reduction Pts	19/23 (82.6)	16/23 (69.6)	11/23 (47.8)
In <50% VAF Reduction Pts	21/55 (38.2)	13/55 (23.6)	3/55 (5.5)
P-value	<0.001	<0.001	<0.001

Longest RBC-TI Duration vs Maximum Reduction in *SF3B1* VAF



- With imetelstat, a greater reduction in SF3B1 VAF correlated with longer RBC-TI duration, validating the result from the phase 2 study

Data cutoff: October 13, 2022.
P-values based on Fisher's exact test. Analyses include patients in the imetelstat ITT population with detectable mutant allele for the indicated gene (≥5%) pretreatment and any postbaseline mutation assessment.
ITT, intent-to-treat; RBC TI, red blood cell transfusion independence; VAF, variant allele frequency.

Higher Cytogenetic Response Rate Per IWG 2006 Criteria With Imetelstat vs Placebo

Cytogenetic Response[a]	Imetelstat (N = 118)	Placebo (N = 60)
Patients with baseline cytogenetic abnormality based on central laboratory review, n (%)[b]	26 (22)	13 (22)
Cytogenetic best response, n (%)[c,d]		
Cytogenetic CR	5 (19)	1 (8)
Cytogenetic PR	4 (15)	1 (8)
Cytogenetic CR or PR criteria not met	5 (19)	5 (39)
Not evaluable	12 (46)	6 (46)
Cytogenetic CR or PR, n (%)[d]	9 (35)	2 (15)
95% CI[e]	17-56	2-45
% Difference (95% CI)[f]	19 (-16 to 44)	
P value[g]	0.216	

- Complete or partial cytogenetic responses were observed in 9 patients (35%) in the imetelstat group and 2 patients (15%) in the placebo group
- Among cytogenetic responders, 6/9 patients (67%) in the imetelstat group also achieved 24-week RBC-TI, none in the placebo group

[a]Cytogenetic testing was done centrally, and the cytogenetic response was assessed by IRC. [b]Percentages calculated using the number of patients in each treatment group as the denominator. [c]Only patients considered for IRC adjudication are those assessed as having baseline cytogenetic abnormality by the IRC based on central laboratory data. [d]Percentages calculated using the number of patients with a baseline cytogenetic abnormality per central laboratory review within each treatment group as the denominator. [e]Exact Clopper-Pearson confidence interval. [f]Wilson score confidence interval. [g]P-value derived from the Cochran-Mantel-Haenszel test controlling for prior RBC transfusion burden (≤6 vs >6 units RBC) and IPSS risk group (low vs intermediate-1) applied to randomization.
CR, complete response; IPSS, International Prognostic Scoring System; IRC, independent review committee; PR, partial response; RBC, red blood cell; TI, transfusion independence.

DISEASE-MODIFYING ACTIVITY OF IMETELSTAT IN PATIENTS WITH HEAVILY TRANSFUSED NON-DEL(5Q) LOWER-RISK MYELODYSPLASTIC SYNDROMES RELAPSED/REFRACTORY TO ERYTHROPOIESIS-STIMULATING AGENTS IN IMERGE PHASE 3

Valeria Santini,[1] Uwe Platzbecker,[2] Pierre Fenaux,[3] Mikkael A. Sekeres,[4] Michael Robert Savona,[5] Yazan F. Madanat,[6] Maria Díez-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] Faye Feller,[12] Amer M. Zeidan,[13]* Rami S. Komrokji[14]*

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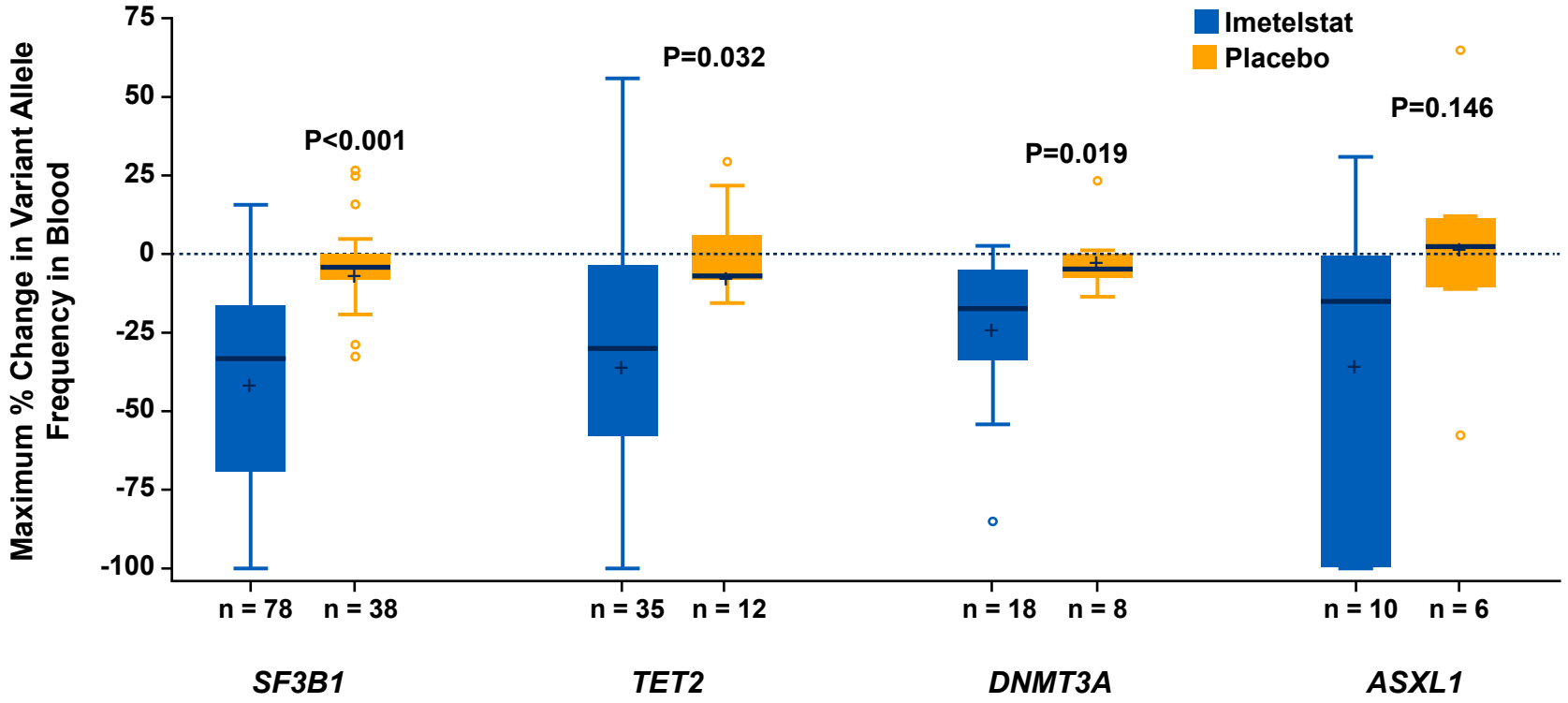
11-06-2023

Session: s448 MDS biology and translational updates

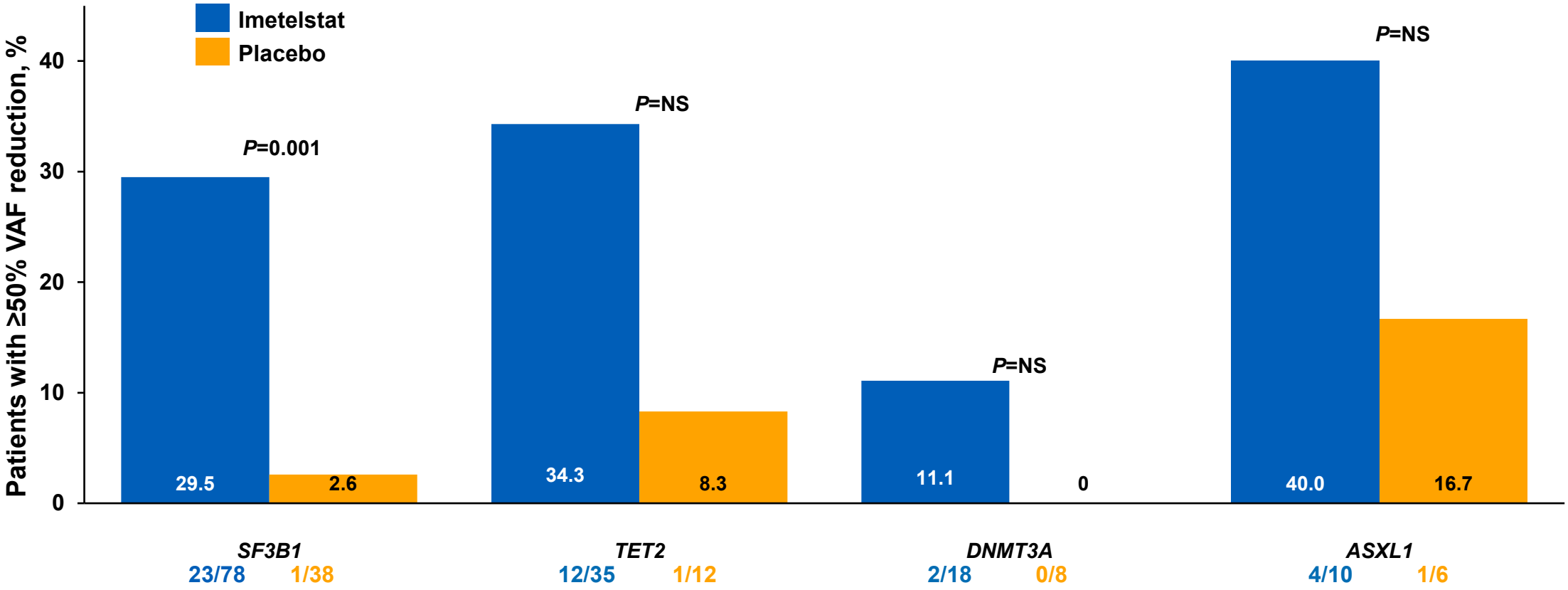
Reductions in VAF of Genes Frequently Mutated in MDS Were Greater With Imetelstat vs Placebo

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



Note: Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of the indicated gene. P-values based on the two-sample *t*-test. Analyses included patients in the intent-to-treat population with a detectable mutant allele for the indicated gene (≥5%) prior to treatment and ≥1 postbaseline mutation assessment.
ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyl**Note:** Figure shows the comparison between each treatment group in the maximum percentage change from baseline in mutant VAF of the indicated gene. P-values based on the two-sample *t*-test. Analyses included patients in the intent-to-treat population with a detectable mutant allele for the indicated gene (≥5%) prior to treatment and ≥1 postbaseline mutation assessment.
ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; MDS, myelodysplastic syndromes; NGS, next generation sequencing; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.
transferase 3A; MDS, myelodysplastic syndromes; NGS, next generation sequencing; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

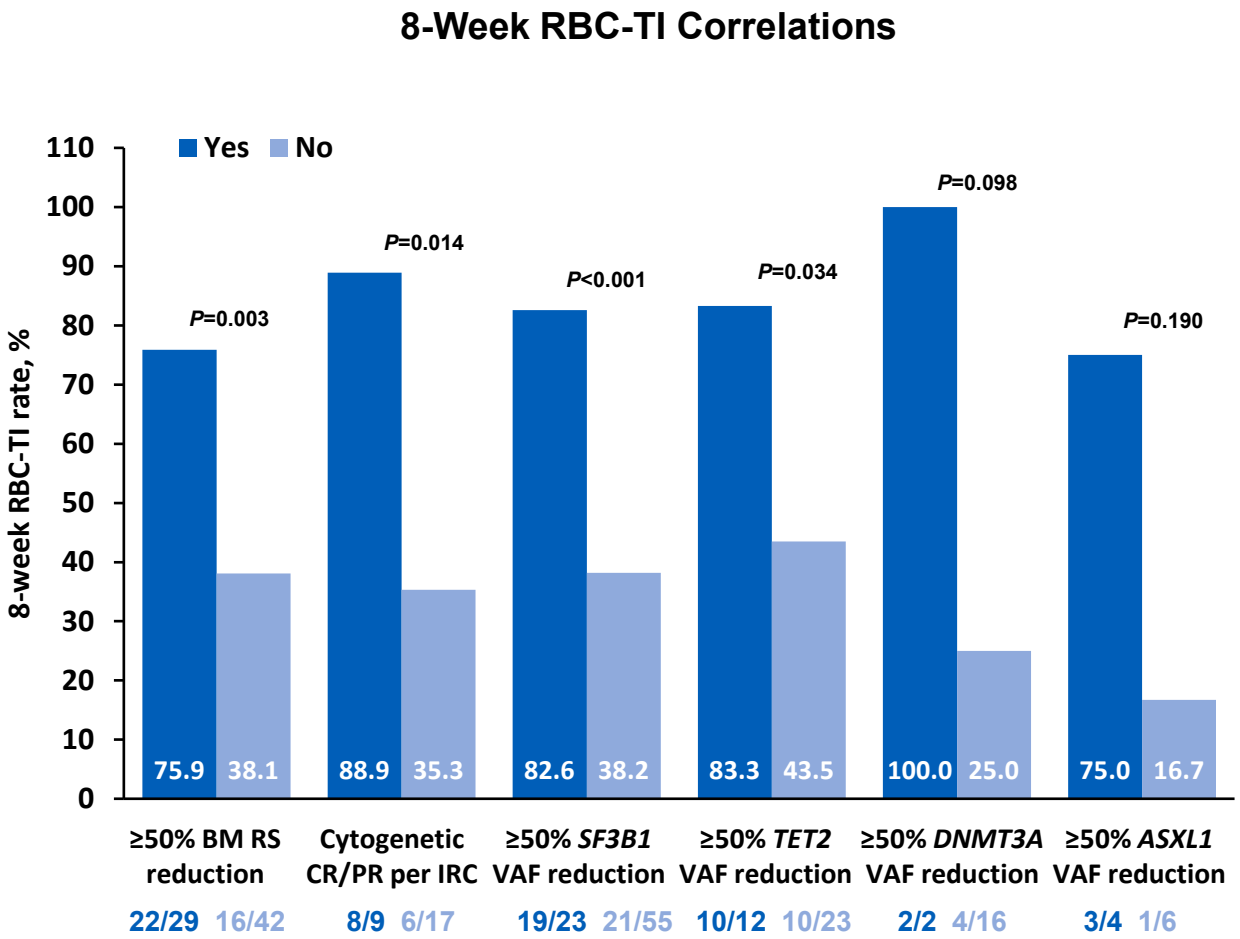
More Patients Treated With Imetelstat vs Placebo Had ≥50% VAF Reduction in *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* Mutations

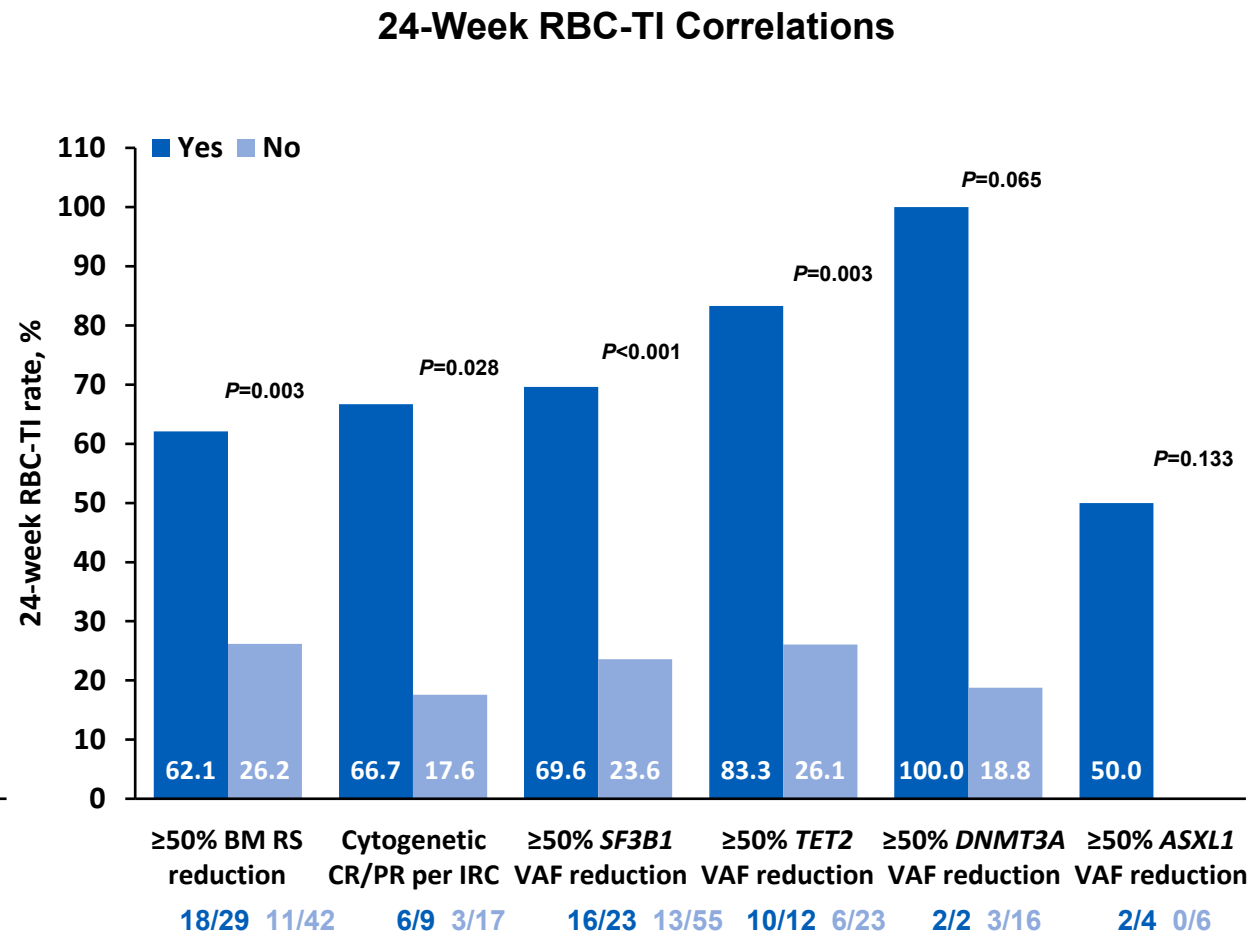


Note: Analyses included patients in the intent-to-treat population with a detectable mutant allele for the indicated gene (≥5%) prior to treatment and ≥1 postbaseline mutation assessment**.** Ratios underneath the bars represent the number of patients with ≥50% VAF reduction as numerator and the total number of patients with detectable assessment (≥5% VAF) in specified mutation at baseline and any postbaseline mutation assessment as denominator. *P* value based on Cochran-Mantel-Haenszel test stratified for prior RBC transfusion burden (≤6 units or >6 units of RBC/8 weeks) and baseline IPSS risk score (low or intermediate-1).

ASXL1, additional sex combs like-1; DNMT3A, DNA (cytosine-5)-methyltransferase 3A; IPSS, International Prognostic Scoring System; NS, not significant; RBC, red blood cell; SF3B1, splicing factor 3b subunit 1; TET2, Tet methylcytosine dioxygenase 2; VAF, variant allele frequency.

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.

S172 PHASE 1/2 STUDY OF ORAL DECITABINE/CEDAZURIDINE IN COMBINATION WITH VENETOCLAX IN TREATMENT-NAÏVE HIGHER-RISK MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Alex Bataller*1, Alexandre Bazinet1, Sangeetha Venugopal2, Guillermo Montalban-Bravo1, Yesid Alvarado1, Kelly Chien1, Ghayas Issa1, Nicholas Short1, Danielle Hammond1, Lucia Masarova1, Tapan Kadia1, Rashmi Kanagal-Shamanna1, Stephany Hendrickson1, Farhad Ravandi1, Elias Jabbour1, Hagop Kantarjian1, Guillermo Garcia-Manero1 1Leukemia, The University Of Texas Md Anderson Cancer Center, Houston, United States; 2Sylvester Comprehensive Cancer Center, Miami, United States

Aims: Determine safety, tolerability and overall response rate (ORR) of ASTX727 in combination with venetoclax in patients with treatment-naïve higher-risk MDS or chronic myelomonocytic leukemia (CMML).

Methods: a phase 1/2 open-label, single center clinical trial (NCT04655755). Eligibility criteria included a confirmed diagnosis of treatment-naïve MDS or CMML (IPSS intermediate-2 or high) and bone marrow blasts > 5%. The phase 1 portion (dose escalation) used the standard 3+3 study design to identify the recommended phase 2 dose. In the phase 2 dose expansion.

Results: 37 patients were enrolled. The median age was 71 years old (27-94), with 26 (70%) male patients. The WHO 2016 diagnoses were MDS with excess-blasts 1 (n=6, 16%), MDS with excess-blasts 2 (n=24, 65%), CMML-2 (n=6, 16%) and atypical chronic myeloid leukemia (n=1, 3%). The most common mutations were ASXL1 (n=18, 49%), RUNX1 (n=14, 38%), SRSF2 (n=11, 30%), TET2 (n=8, 22), and TP53 (n=7, 19%).

The **phase 2 dose was established as ASTX727 100/35mg on days 1-5 plus venetoclax 400mg on days 1-14**. The most common grade 3-4 TEAEs were decreased platelet count (n=30, 81%), decreased neutrophil count (n=26, 70%), febrile neutropenia (n=7, 19%), and anemia (n=6, 16%). Grade 3-4 infectious complications included lung infection (n= 4, 11%), skin infection (n=3, 8%), sepsis (n=2, 5%), and SARS-Cov-2 infection (n=2, 5%). 3 deaths occurred on study (2 from sepsis and 1 from pneumonia). **The 4-week and 8-week mortality were 0% and 3%, respectively.**

The ORR was 94.5%: 13 (35.1%) complete remission (CR), 11 (29.7%) marrow CR (mCR) with hematological improvement (mCR-HI), and 11 (29.7%) mCR alone. The median number of cycles to achieve first response and best response was 1 (1-2) and 1 (1-6), respectively. In patients with cytogenetic abnormalities at diagnosis, 53% achieved cytogenetic response. The median duration of response was 23 months. After a median follow-up 9.6 months, the median OS was not reached and the median progression-free survival (PFS) was 23 months.

Summary/Conclusion: The combination of ASTX727 plus venetoclax is a promising, fully oral combination that is well-tolerated and demonstrates a high response rate in higher-risk MDS

FLAG-Ida combined with Gemtuzumab Ozogamicin (GO) reduced MRD levels and improved overall survival in *NPM1*^{mut} AML independent of *FLT3* and MRD status. Results from a randomised comparison with Daunorubicin, AraC + GO in the AML19 Trial

NH. Russell, J. Othman, R. Dillon, N. Potter, C. Wilhelm-Benartzi, S. Knapper, L M. Batten, J Canham, E L, U. Malthe Overgaard, A. Gilkes P. Mehta, P. Kottaridis, J. Cavenagh, C. Hemmaway, C. Arnold, SD. Freeman, M. Dennis on behalf of the NCRI AML WG

NCRI National Cancer Research Institute

EHA

CANCER RESEARCH UK

EHA2023

Summary *NPM1*^{mut} AML

FLAG-Ida-GO improved the OS of *NPM1*^{mut} AML by 18% at 5yrs (82% vs 64%, HR 0.5, CI 0.31-0.81, p=0.005) and reduced the proportion who were PB PC2 MRD+ve compared to DA-GO (12% vs 24%)

The FLAG-IDA-GO survival benefit was independent of *FLT3* mutation status and was seen in both PB PC2 MRD+ve and MRD-ve patients

PC2 BM MRD levels in were lower with FLAG-Ida-GO including those testing PB MRD-ve

.

For those patients who were PB MRD-ve after 2 cycles of FLAG-Ida-GO (88%), this treatment appears sufficient

In a randomised comparison, outcomes in *NPM1*^{mut} are improved by sequential MRD monitoring (Poster 503)

Title: PRELIMINARY RESULTS OF QUIWI: A DOUBLE BLINDED, RANDOMIZED CLINICAL TRIAL COMPARING STANDARD CHEMOTHERAPY PLUS QUIZARTINIB VERSUS PLACEBO IN ADULT PATIENTS WITH NEWLY DIAGNOSED FLT3-ITD WILD-TYPE AML

Montesinos P, et al. S130

Results:

From September 2019 to November 2021, 284 Pts were enrolled in 45 Spanish PETHEMA centers, 11 of them were included in the safety run-in phase establishing 60 mg/day of Quiz or PBO for the randomized phase. 273 Pts were randomized to Quiz (n=180) or PBO (n=93). The median age was 57 y [IQR, 48 – 64 y]. Baseline pts and disease characteristics were balanced between the 2 arms. At data cutoff (February 2023), the median follow-up was 17 months. Median EFS was 16.6 mo with Quiz vs 10.6 mo with PBO (hazard ratio [HR], 0.729; 95% CI, 0.522-1.018; 2-sided P=0.062) (Figure 1A). Regarding OS, 50 out of 180 patients died in the Quiz arm, and 45 out of 93 in the PBO. Median OS was not reached with Quiz vs 15 mo with PBO (HR, 0.558; 95% CI, 0.373-0.834; P=0.004), and the 2-years OS was 63.5% with Quiz vs 47% with PBO. (Figure1B). Disease-free survival was not reached with Quiz vs 15.4 mo with PBO (HR 0.643; 95% CI 0.411-1.005; P=0.050). CR/CRi rate after 2 cycles was 76.7% in the Quiz arm and 76.4% in the PBO. CR/CRi with MRD negativity after 2 cycles was achieved in 41.5% in the Quiz arm and 41.6% in the PBO. No new safety signals were observed among Quiz arm.

Figure 1A.- Event free survival

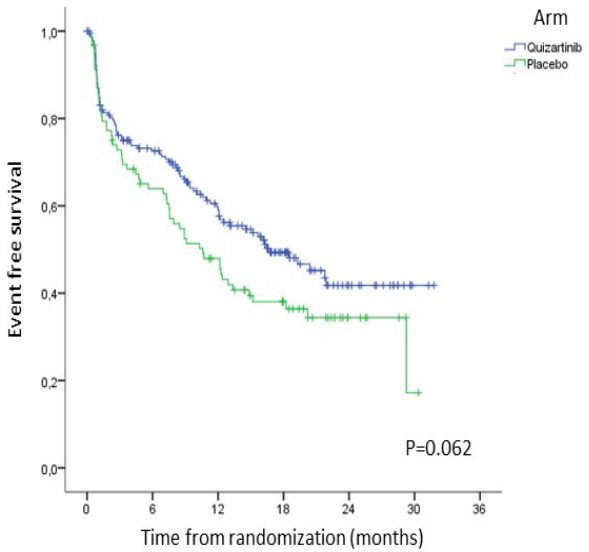
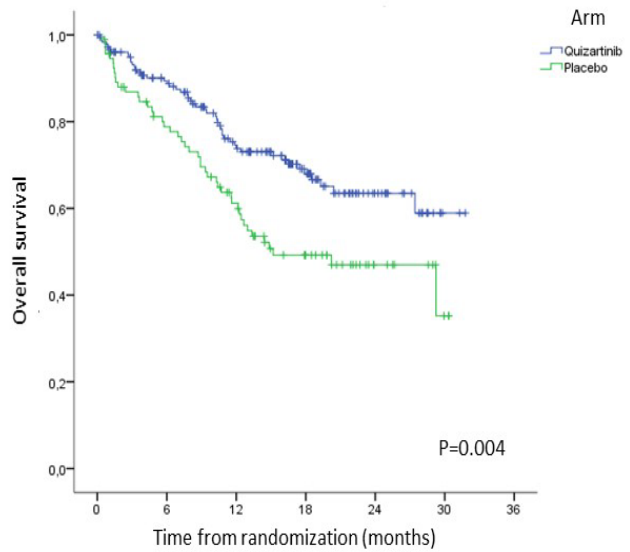


Figure 1B.- Overall survival



LB2711 BMT-CTN 1506 (MORPHO): A RANDOMIZED TRIAL OF THE FLT3 INHIBITOR GILTERITINIB AS POST-TRANSPLANT MAINTENANCE FOR FLT3-ITD AML

Topic: Late-Breaking Oral Session

Mark J Levis*[1], Mehdi Hamadani[2], Brent Logan[2], Rick Jones[1], Anurag K. Singh[3], Mark Litzow[4], John R. Wingard[5], Esperanza B. Papadopoulos[6], Alexander E. Perl[7], Robert Soiffer[8], Celalettin Ustun[9], Masumi Ueda Oshima[10], Geoffrey Uy[11], Edmund K. Waller[12], Sumithira Vasu[13], Melhem Solh[14], Asmita Mishra[15], Lori Muffly[16], Hj Kim[17], Matthias Stelljes[18], Yuho Najima[19], Masahiro Onozawa[20], Kirsty Thomson[21], Arnon Nagler[22], Andrew Wei[23], Guido Marcucci[24], Nancy L. Geller[25], Nahla Hasabou[26], David Delgado[26], Matt Rosales[26], Jason Hill[26], Stanley Gill[26], Rishita Nuthethi[26], Denise King[27], Heather Wittsack[27], Adam Mendizabal[27], Steven Devine[28], Mary Horowitz[2], Yi-Bin Chen[29]

Background: Patients with acute myeloid leukemia with an internal tandem duplication mutation of FLT3 (FLT3-ITD AML) have a high risk of relapse and routinely undergo allogeneic hematopoietic cell transplantation (HCT). FLT3 inhibitors are often administered as post-HCT maintenance therapy to decrease relapse risk, but this practice is based on randomized studies of sorafenib that included patients salvaged with FLT3 inhibitors pre-transplant. Aims: BMT-CTN1506 (“MORPHO”) was an international phase 3 randomized placebo-controlled, double blinded study of post-HCT maintenance with the FLT3 inhibitor gilteritinib. The primary objective was to determine if post-HCT maintenance with gilteritinib improved relapse-free survival (RFS) compared with placebo for participants (pts) with FLT3-ITD AML transplanted in first remission. Overall survival (OS) was a key secondary objective. Additional secondary objectives included examining the effect of measurable residual disease (MRD) pre- and posttransplant on RFS and OS, rates of non-relapse mortality, event-free survival, and acute and chronic graft-versushost disease (GVHD) in participants treated with gilteritinib versus plac

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Methods: Adults with FLT3-ITD AML in first remission after receiving no more than two cycles of induction therapy with HCT planned within 12 months of achieving remission were screened for eligibility. After induction and consolidation therapy, pts were registered and underwent HCT. After engraftment, between 30-90 days after HCT, they were randomized to placebo or 120 mg/day gilteritinib for 24 months. Marrow aspirates for MRD were collected pre-transplant, pre-randomization, and at 3, 6, 12, 18, and 24 months post-randomization. MRD was analyzed using a PCR-NGS assay that could detect a FLT3-ITD mutation at a level of 1 x 10 -6 . Randomization was stratified by pre-HCT MRD of 10 -4 or greater, conditioning regimen intensity, and time from HCT to randomization of -/+ 60 days.

LB2711 BMT-CTN 1506 (MORPHO): A RANDOMIZED TRIAL OF THE FLT3 INHIBITOR GILTERITINIB AS POST-TRANSPLANT MAINTENANCE FOR FLT3-ITD AML

Topic: Late-Breaking Oral Session

Results: We screened 620, registered 488, and randomized 356 pts. By intention-to-treat analysis, RFS (Figure 1A) was higher for pts randomized to gilteritinib, but the difference was not statistically significant **(HR: 0.679; 95% CI: 0.459, 1.005; 2-sided p-value: 0.0518).** OS was similar in both groups (HR: 0.846; 95% CI: 0.554, 1.293; 2-sided pvalue: 0.4394 (Figure 1B). Two-year RFS was 77.2% (95% CI 70.1%, 82.8%) for gilteritinib and 69.9% (95% CI: 62.4%, 76.2%) for placebo. 50.6% of pts had MRD (10 -6 or greater) pre-HCT or pre-randomization. **In prespecified subgroup analysis, the effect of gilteritinib was more pronounced in pts with detectable MRD (HR=0.515, 95% CI: 0.316, 0.838, p = 0.0065) than in pts without detectable MRD (HR=1.213, 95% CI: 0.616, 2.387, p = 0.575) (Figure 2).** 143 (80.3%) in gilteritinib arm and 129 (72.9%) in placebo arm experienced dose interruptions and 97 (54.5%) in gilteritinib arm and 45 (25.4%) in placebo arm required dose reductions. Treatment-emergent adverse events (TEAE), including neutrophil decrease (42.1 versus 15.8%) and chronic GVHD (52.2 versus 42.1%), were more common in the gilteritinib arm, as were TEAEs leading to withdrawal of treatment.

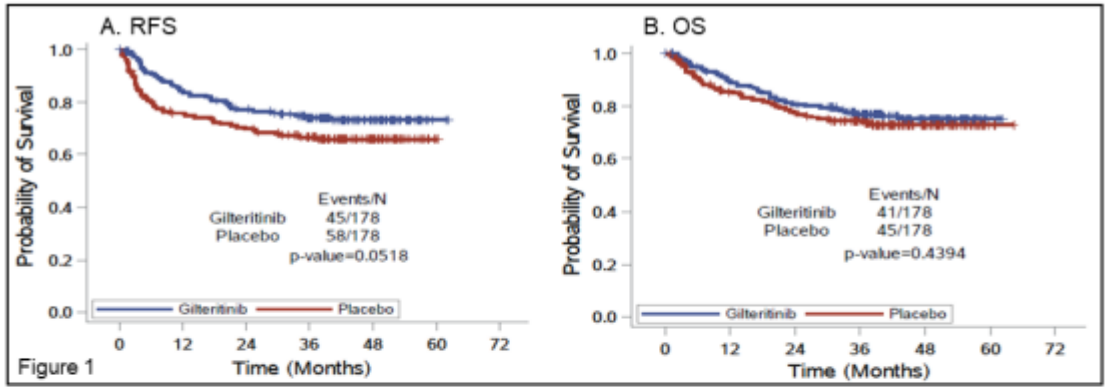

Figure 1

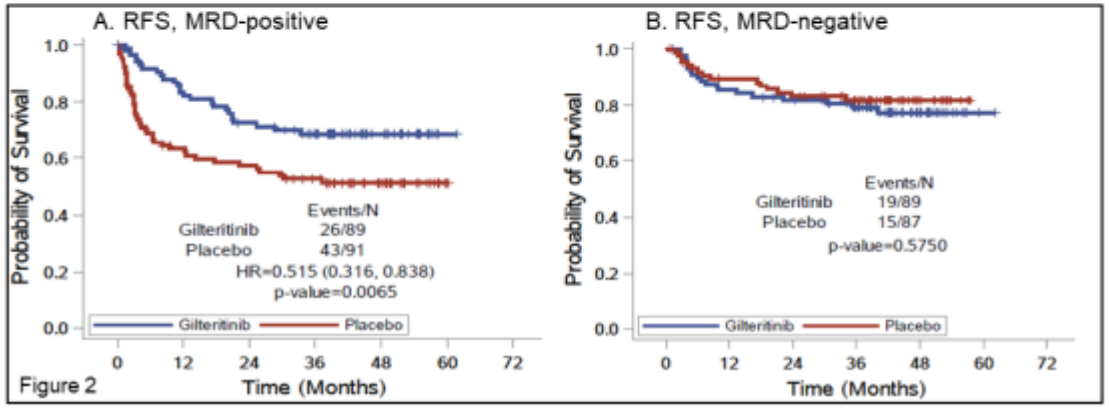

Figure 2

LB2711 BMT-CTN 1506 (MORPHO): A RANDOMIZED TRIAL OF THE FLT3 INHIBITOR GILTERITINIB AS POST-TRANSPLANT MAINTENANCE FOR FLT3-ITD AML

Topic: Late-Breaking Oral Session

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Summary/Conclusion: **Gilteritinib appears to have a clear benefit for the 50% of pts with detectable MRD pre- or post-HCT, compared to those without detectable MRD. TEAEs associated with gilteritinib were primarily myelosuppression and increased incidence of chronic GVHD. These data are among the first to support the effectiveness of MRD-based post-HCT maintenance therapy.**

P502 PHASE II STUDY ON VENETOCLAX PLUS DECITABINE FOR ELDERLY (≥60 <75YEARS) PATIENTS WITH NEWLY DIAGNOSED HIGH-INTERMEDIATE RISK AML ELEGIBLE FOR ALLO-SCT : MIDTERM UPDATE OF VEN-DEC GITMO STUDY

Topic: 4. Acute myeloid leukemia - Clinical

Domenico Russo*[1,2], Nicola Polverelli[1,2], Marika Vezzoli[2], Stella Santarone[3], Luca Castagna[4], Francesco Onida[5], Stefania Bramanti[6], Roberto Sorasio[7], Angelo Michele Carella[8], Attilio Olivieri[9], Calogero Vetro[10], Germana Beltrami[11], Antonio Curti[12], Massimo Bernardi[13], Valentina Mancini[14], Pellegrino Musto[15], Elisabetta Terruzzi[16], Piero Galieni[17], Cristina Skert[18], Luisa Giaccone[19], Raffaella Cerretti[20], Erika Borlenghi[21], Mirko Farina[1,2], Alessandro Leoni[2], Simona Bernardi[2], Stefano Calza[2], Angela Gheorghiu[13], Michele Malagola[1,2], Massimo Martino[22], Fabio Ciceri[13]

Rationale:

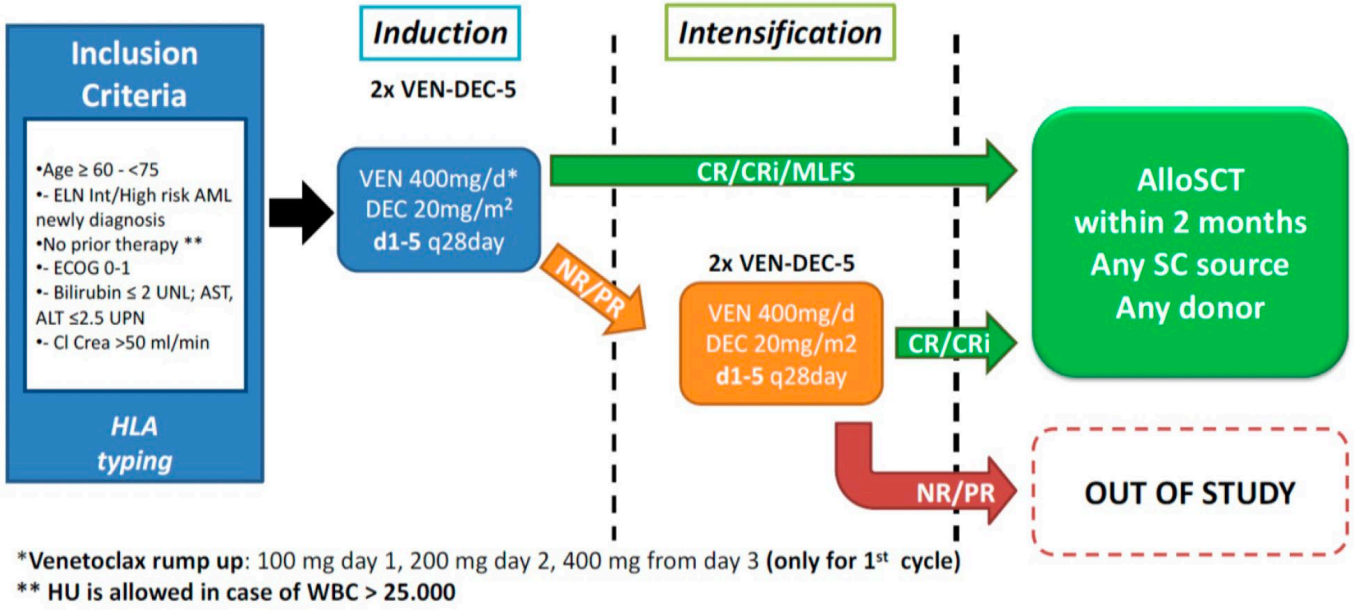
- To identify transplantation rate for older (age 60-75) patients induced with ven-decitabine (?expected to be fit for transplant from AML dx)

Patient population:

- as listed, age 60-75, fit, no ELN favorable, no prior MDS or AML therapy

Design:

- Simon 2-stage design in up to 100 patients to determine response rate and transplant rate.
- Primary endpoint: proportion of elderly AML patients who receive allo-SCT in CR with VEN-DEC.
- According to the statistical plan, primary endpoint was met in case of > 15% of patients in CR submitted to allo-SCT.



Results:

- Enrolled 94 pts (6 screen fails)
- 75 completed at least 2 cycles and are evaluable for response
- 49/75 (65%) had CR after 2 cycles (?did not say CR/CRi/MLFS though….)
- After 4 cycles an additional 4 (15% of the patients with PR or NR after 2 cycles) also responded (ORR= 71%)
- Primary endpoint was met, as 41/94 (43.6%) patients proceeded to alloHSCT
- 8/94 (9%) died prior to transplant, mostly of toxicity, n=3 from relapse, 12 patients have responded but are not yet transplanted
- survival analysis ongoing

What do these data mean?

- We need more demographic and genomic data on who these patients are
- What happened to the 19 patients that did not receive 2 cycles—was this mortality/toxicity?
- These numbers are encouraging but also are not very surprising
- still, the majority of responding older patients *are* proceeding to transplant, which is potentially higher than recorded for 7&3 or CPX large/cooperative group trials (30% of entire cohort in CPX-351 pivotal trial).
- A randomized comparison of IC vs. Ven/HMA is currently enrolling in US, which will collect similar results but with a control arm.

S132 UPDATED RESULTS OF VEN-A-QUI STUDY: A PHASE 1-2 TRIAL TO ASSESS THE SAFETY AND EFFICACY OF TRIPLETS FOR NEWLY DIAGNOSED UNFIT AML PATIENTS: AZACITIDINE OR LOW-DOSE CYTARABINE WITH VENETOCLAX AND QUIZARTINIB

Topic: 4. Acute myeloid leukemia - Clinical

Juan Miguel Bergua Burgues*[1], Rebeca Rodríguez-Veiga[2], Isabel Cano Ferri[2], Ferran Vall-Llovera Calmet[3], Antonio Garcia-Guiñon[4], Joaquin Gomez Espuch[5], Mercedes Colorado[6], Ignacio Casas-Avilés[1], Jordi Esteve[7], Antonia Sampol[8], Maria Victoria Verdugo[9], Fernando Ramos[10], Marta Valero, Evelyn Gloria Acuña Cruz[2], Blanca Boluda[2], Laura Torres Miñana[2], Joaquín Martinez-Lopez[11], Eva Barragan[2], Rosa Ayala Diaz[11], David Martínez Cuadrón[2], Pau Montesinos[2]

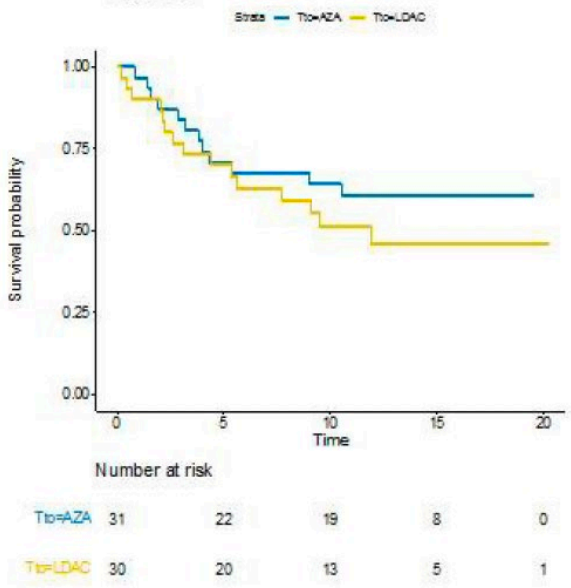
Background

- studied whether adding quizartinib, a potent, selective type II inhibitor of FLT3 would improve response and survival to ven/aza backbone in patients older patients with ND AML
- primary endpoints: establish RP2D and describe efficacy/safety in expansion cohort of each triplet

Design:

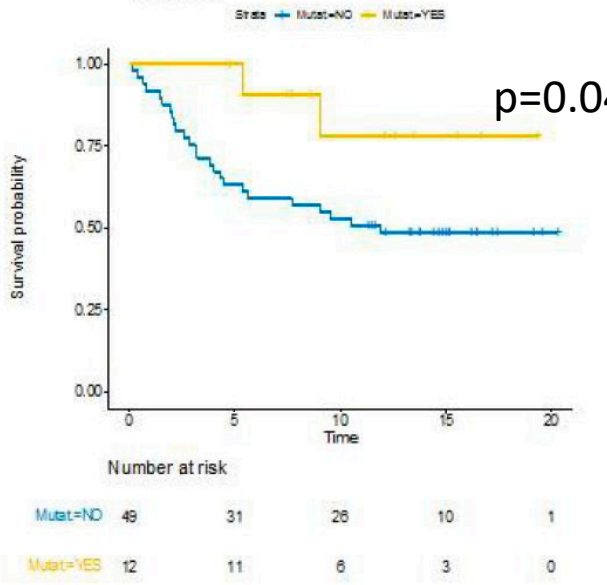
- newly diagnosed AML, age >70 or >65 with comorbidity
- FLT3-ITD+ and (-) allowed, prior HMA allowed as MDS therapy
- enrolled 3+3 for safety initially then moved to phase 2 expansion
- randomization of 1:1 to triplet with quiz + ven/aza or ven/LDAC
- Goal of >12 FLT3-ITD+ patients enrolled

Figure 1a



VEN-LDAC + QUIZ
VEN-AZA + QUIZ

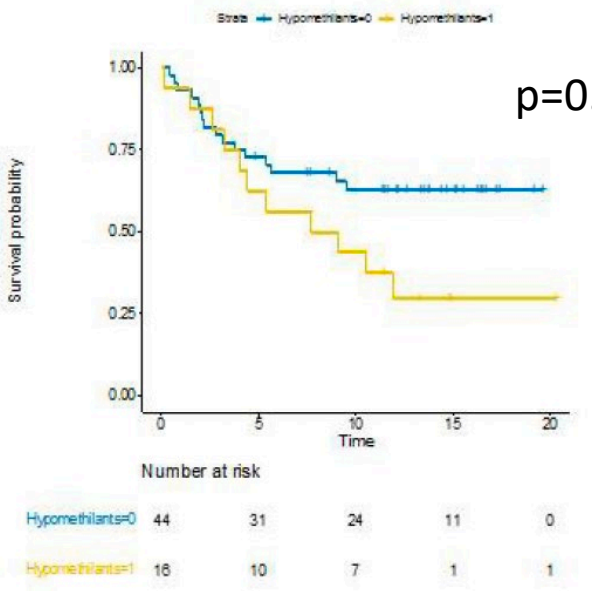
Figure 1b



p=0.04

FLT3-ITD+
FLT3-ITD (-)

Figure 1c



p=0.06

prior HMA: YES
NO

- **Results/Conclusions:**
- Interim analysis presented of ph2, median follow up 14.4 months at cutoff
- 77 patients from 11 Spanish centers (16 in ph1, 61 in phase 2)
- median age 74 (70-88)
- DLTs prolonged thrombocytopenia with CNS bleeding at 60 mg of quiz + ven/LDAC
- no DLTs in VEN/AZA (Quiz RP2D: 40 mg with LDAC or 60 mg with AZA)
- protocol amended to include day 14-21 marrow bx and withholding chemo until count recovery
- Data look overall promising, particularly in FLT3-ITD+ group, ongoing study and will also be gilt triplets in trials soon—is this low intensity?

EHA 2023:P555: Olutasidenib in Post-Venetoclax Patients with Mutant IDH1 AML Cortes J

- Background: Olutasidenib is approved for R/R AML based on the registrational cohort (n=153) of Phase 2 trial: CR or CRh of 35%, DOR of 25.9 mo
- 17 patients from Phase 2 trial previously treated with VEN combination regimens
- Of 17 patients with prior VEN treatment, 5 are ongoing and 12 discontinued due to progressive disease (6), adverse events (4), or withdrawal by subject (2)
- Best response to olu was CR/CRh in 5/17 (29.4%), 4 (23.5%) were CR
  - In the 8 pts who previously received VEN-AZA, 3 (37.5%) patients achieved a CR/CRh
- Time to CR/CRh was med 2.1 months; duration of CR/CRh was med 18.5+ months
- Considerations: able to achieve durable response even after prior ven; option for sequencing therapy

EHA:2023 P504: Updated Data for Ziftomenib in Patients with NPM1-Mutated Relapsed or Refractory AML and LBA
Fathi A

- Menin-KMT2A protein complex is regulator of genes critical in maintenance of leukemia
- KOMET-001: global, open-label Ph 1/2 study of ziftomenib in adults with R/R AML
- 20 pts treated at 600 mg po daily: median age 70.5 years (22 to 86y);
  - 35% FLT3, 30% IDH1/2
  - Median number of prior therapies was 2.5 with 60% with prior venetoclax
- 85% had at least one ≥Gr 3 TEAE, with 30% of TEAEs potentially treatment-related
- Gr 3 AEs anemia - 25%; PNA - 20%; thrombocytopenia, neutropenia and hyperglycemia – 15% Any grade DS: 20%; 5% (n=1) Gr 3
- CR 30%, CRc 35%; median DoR 8.2 months (still maturing); median time to CR 70 days
- Median OS 5.1m; At the cutoff, 57.1% of pts achieving CRc remain on txt or in post-SCT follow- up
- MEN1-M327I in 1 of 29 pts (3.4%) detected at C4D28; pt had stable disease through cycle 7
- Considerations: longer follow-up desired, optimizing use, combination studies. Which menin inhibitor will be front runner and in which population?

ASCO & EHA to clinical practice summary

- Current MDS and AML classifications integrate molecular data.
- Luspatercept moving upfront in management of lower risk MDS.
- Imetelstat active drug in lower risk MDS.
- Oral decitabine/venetoclax feasible combination in higher risk MDS.
- AML-NPM-1 mutant better results with FLAG-IDA-GO.
- Gilteritinib maintenance post allo-SCT for MRD+
- HMA/venetoclax combination maybe alternative for IC as bridge to allo-SCT.
- Triplet HMA/Ven/FLt-3 inhibitor treatment for non-IC eligible FLT-3 AML patients.
- Olutasidenib active in IDH-1 MT AML post ven failure.
- Menin inhibitors showing promising activity in AML

Thank You

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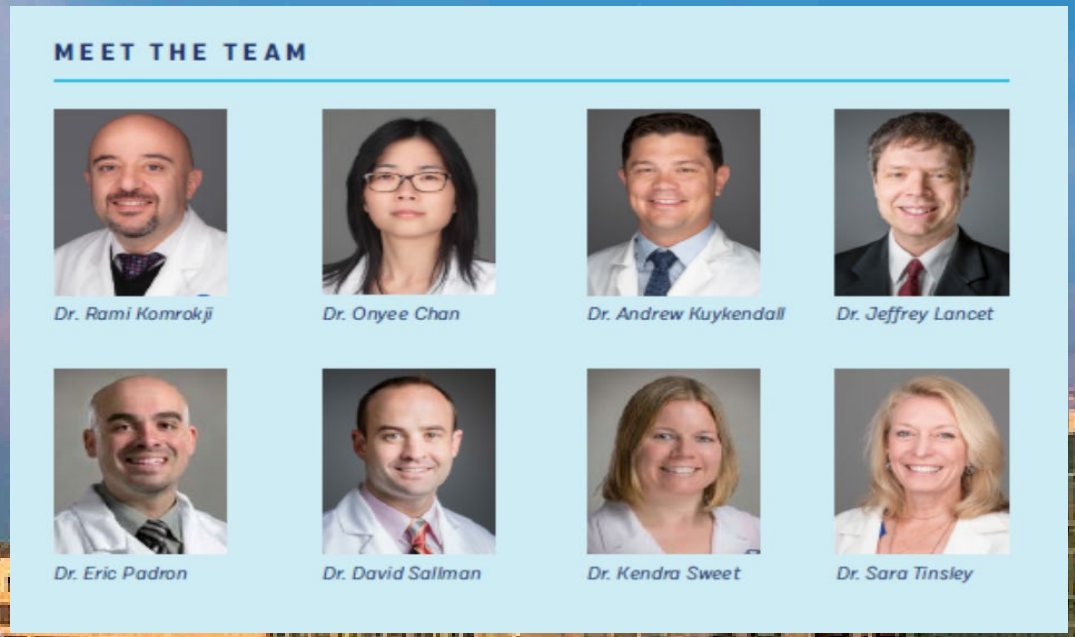

Moffitt Myeloid team: Only perfect counts !!!

Acknowledgements:

- Our patients and their caregivers
- Moffitt Myeloid team

AmerisourceBergen