ASH Updates

MDS

Elie Traer, MD PhD

Associate Professor

Outline

- Review of MDS and genetic prognostication
- Low risk MDS
  - Not just ESAs anymore!
- High risk MDS
  - Update on aza+ven
- Targeted therapy

Prognostication in MDS

IPSS-R: Cytogenetics, blasts, CBC predict risk

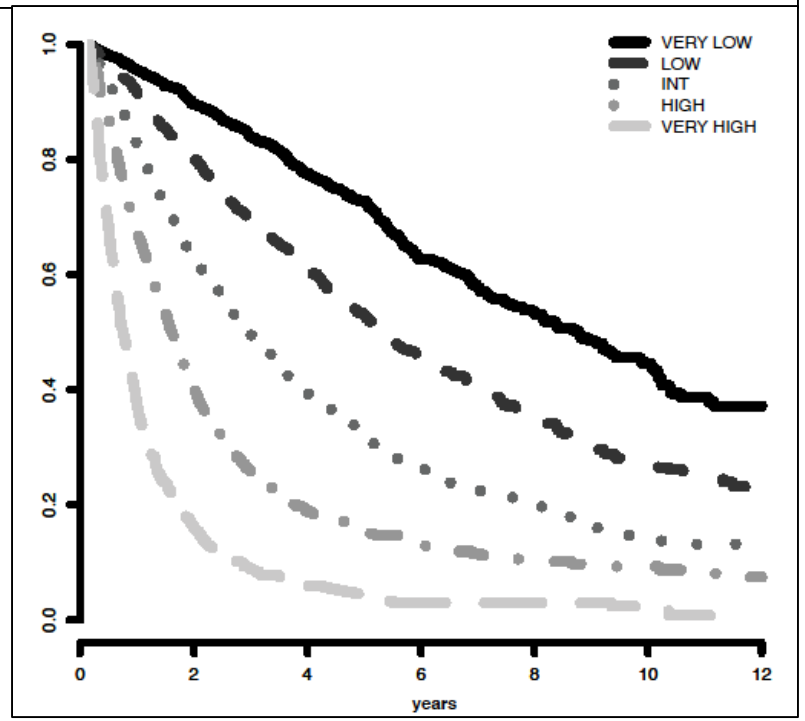
Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

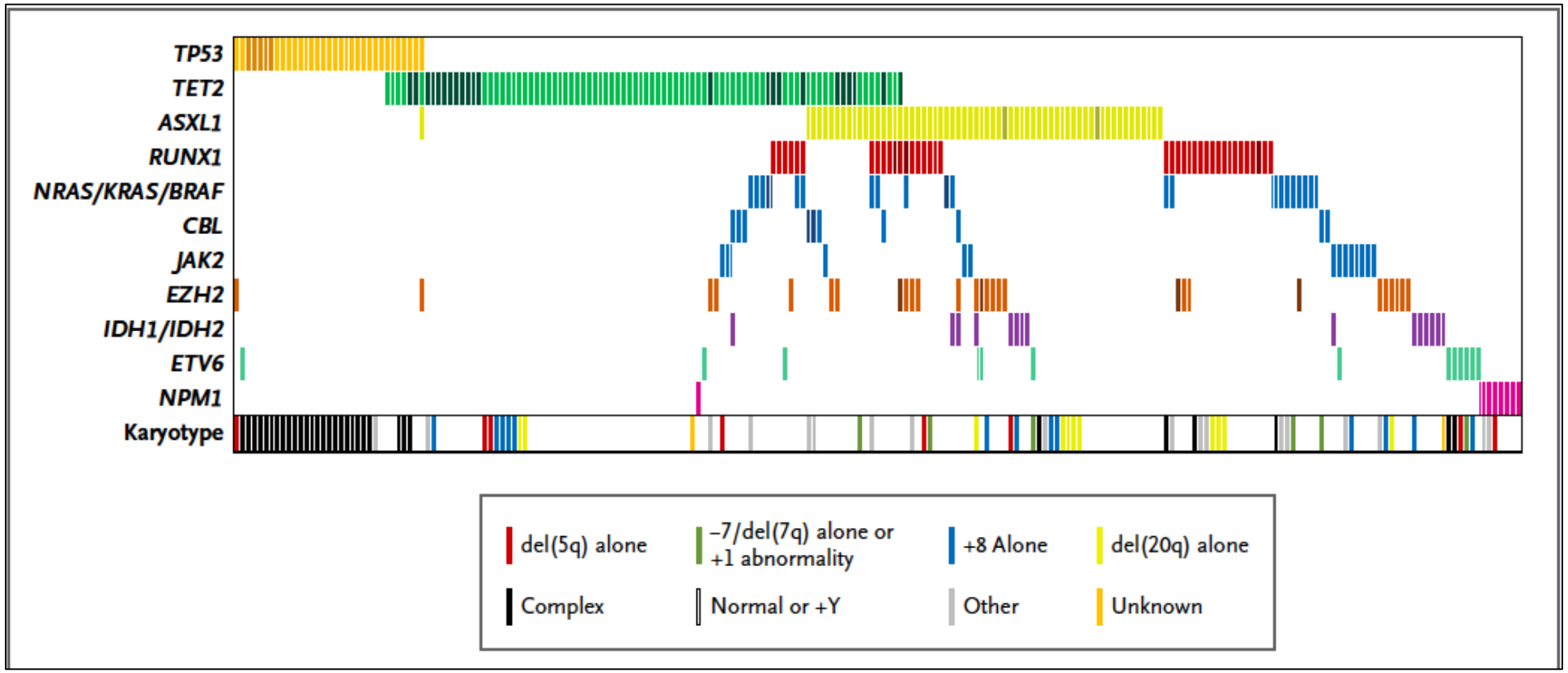
Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6



Blood. 2012;120(12):2454

MDS point mutations



N Engl J Med. 2011 364(26):2496-506

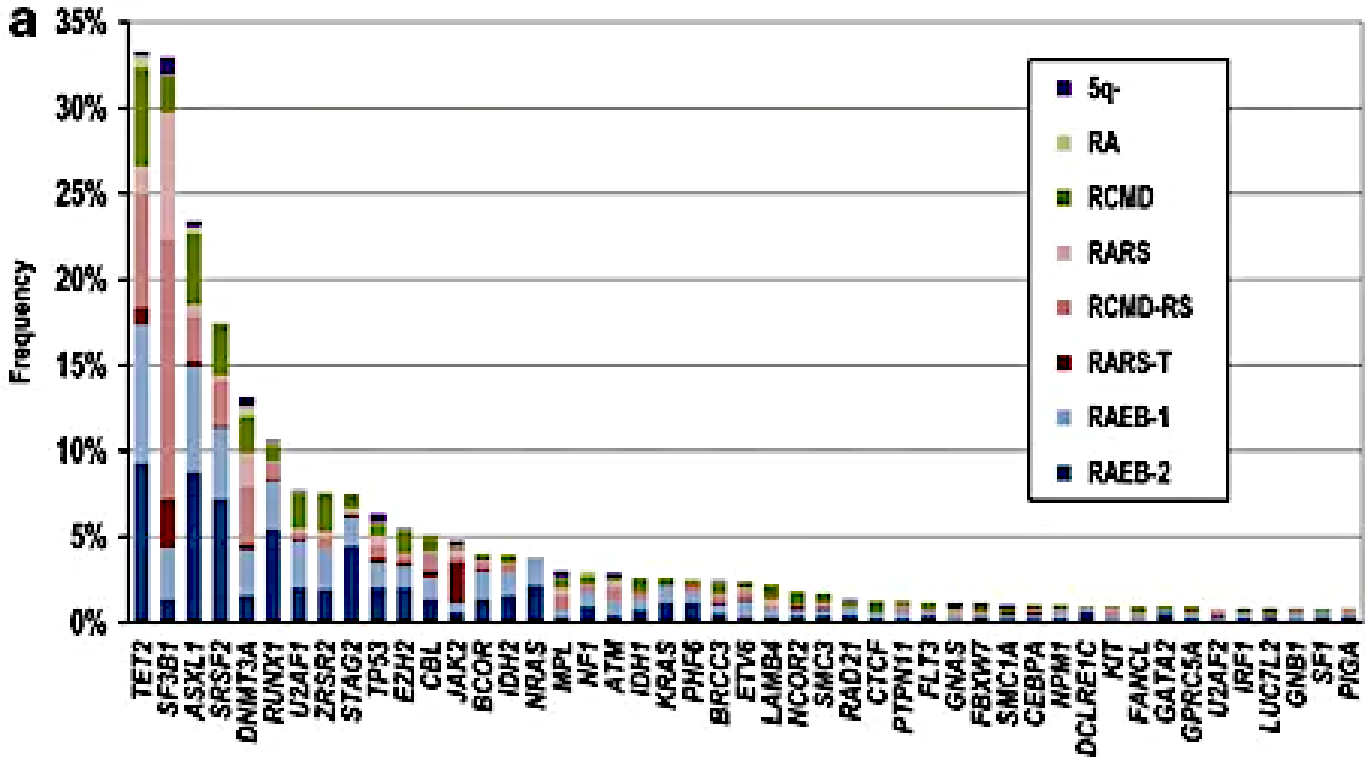
Mutations also affect risk

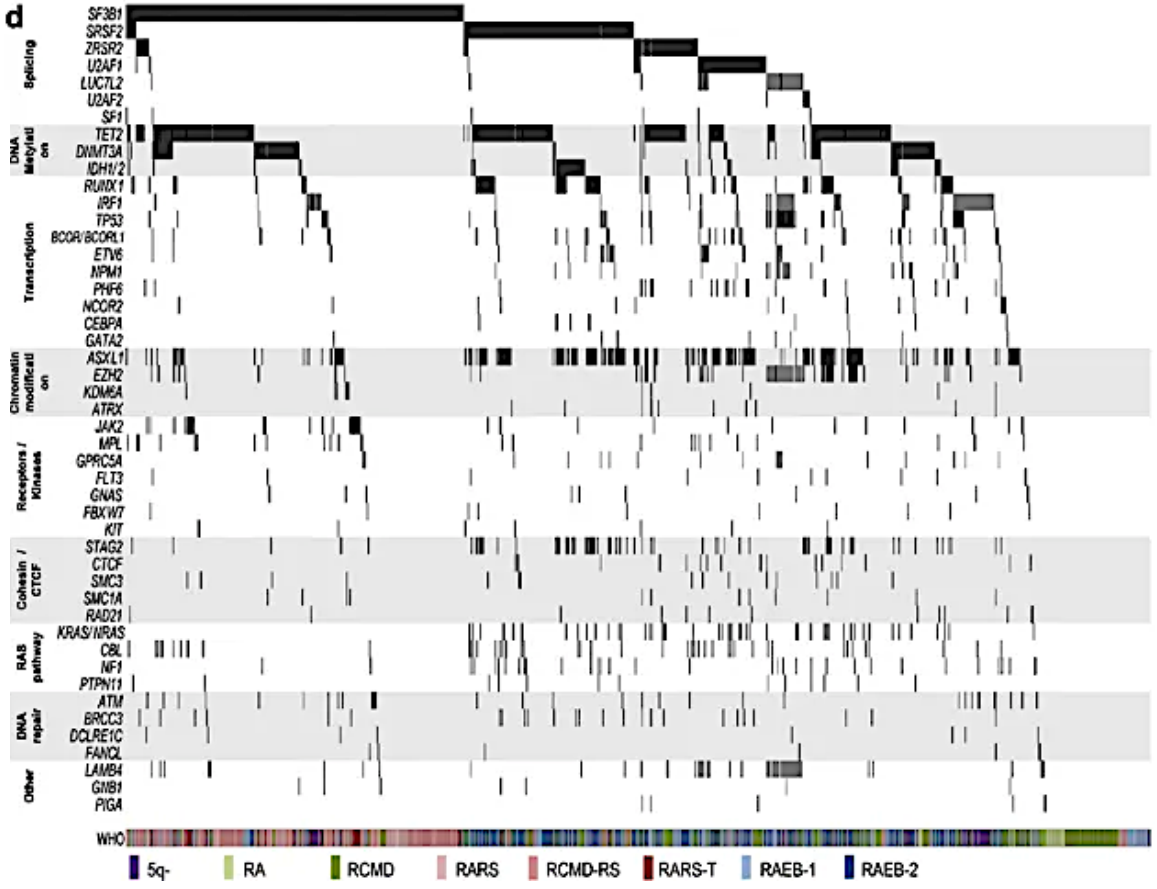
Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049

N Engl J Med. 2011 364(26):2496-506

More MDS mutations

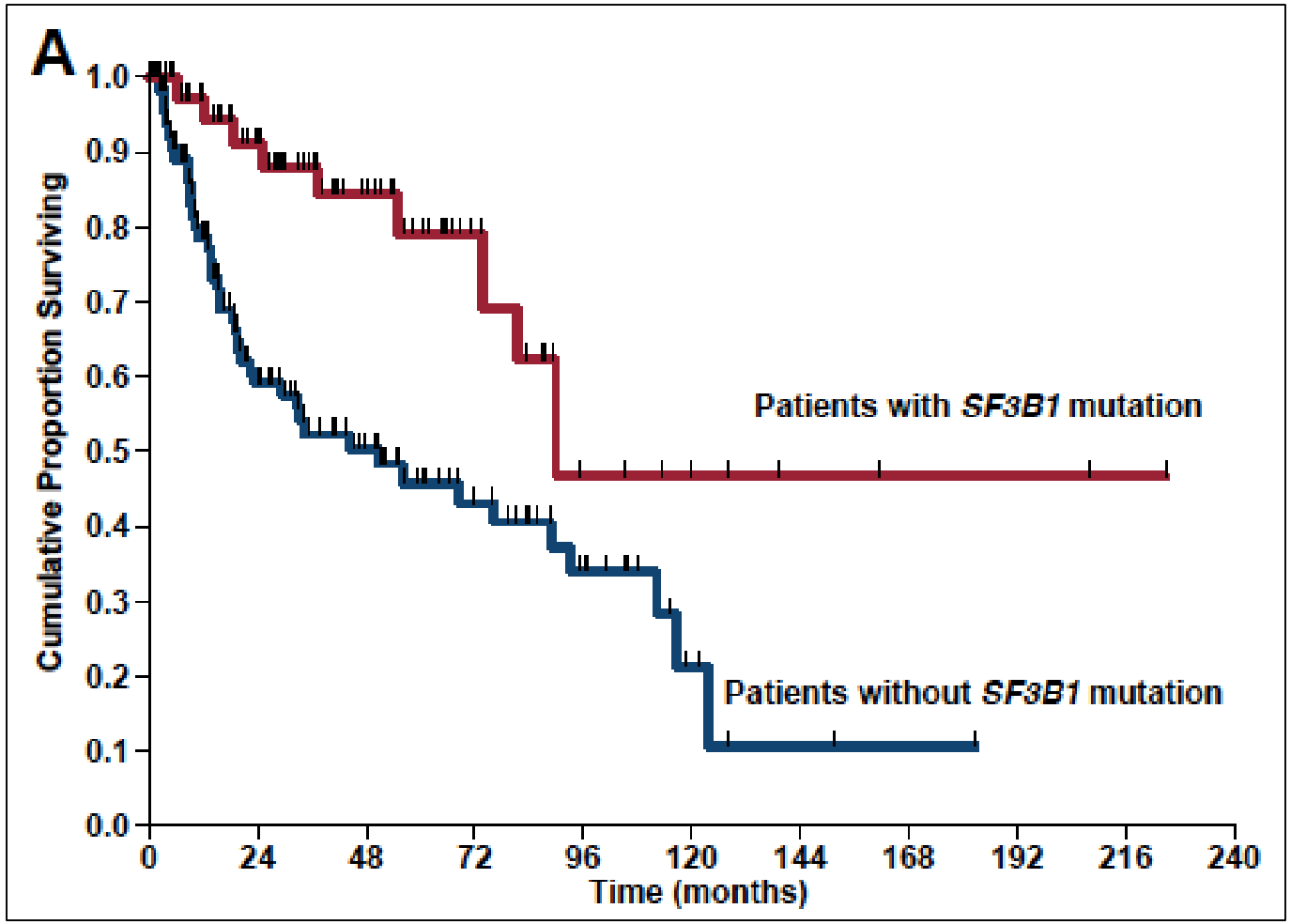




Haferlach T et al. Leukemia 2014

Spliceosome, epigenetic, transcription, chromatin mutations very common

SF3B1 mutations – improved OS!



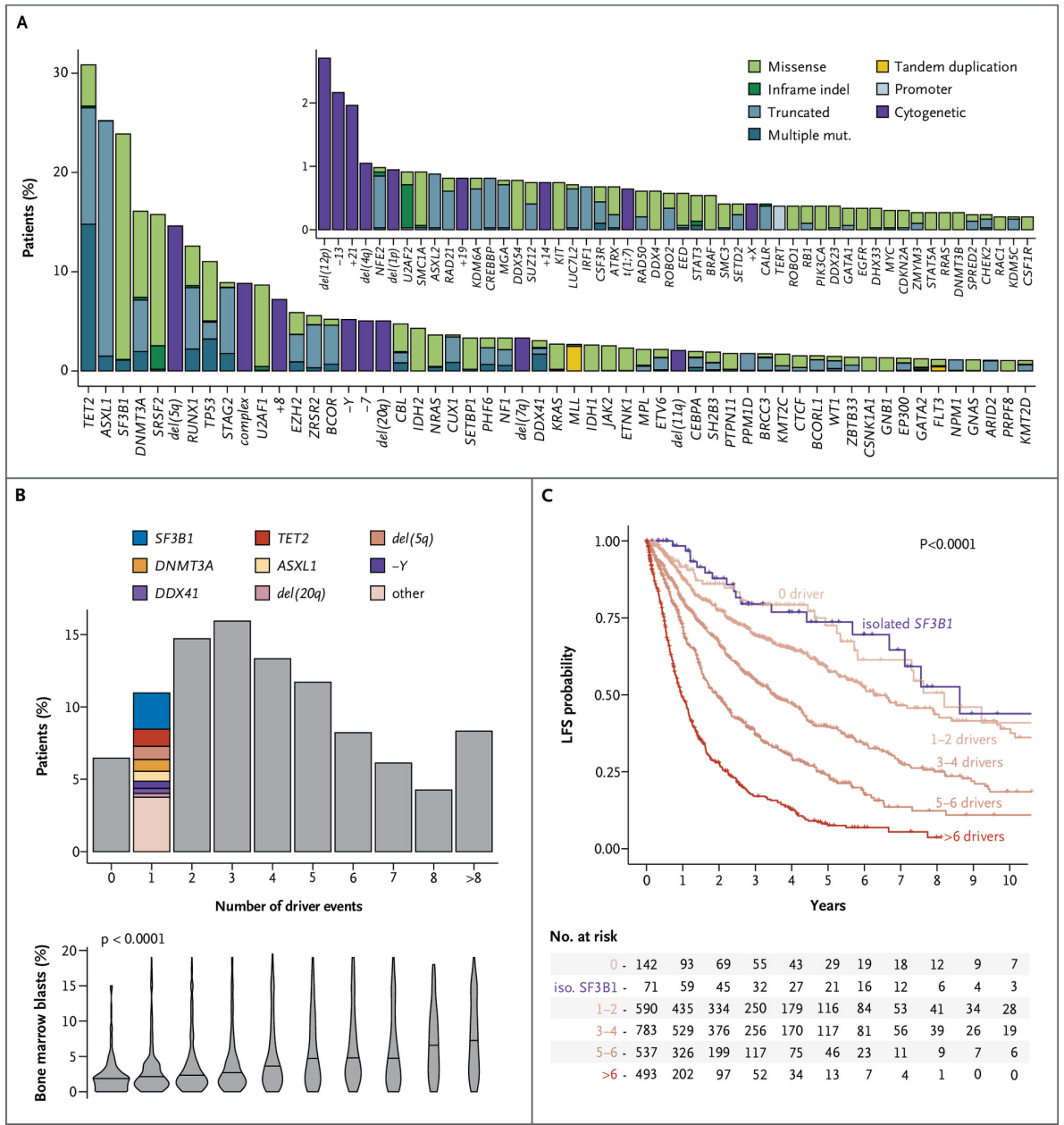
Blood 2011 118(24):6239-46

* co-mutations important

Incorporation of all types of mutations into prognostic score – IPSS-M

- 2957 MDS samples
- Cytogenetic and point mutations analyzed
- Usually multiple drivers per patient
- Increasing driver mutations associated with decreased survival
  - SF3B1 exception BUT, this is strongly affected by co-mutations
- DDX41 associated with higher blasts and chance of transformation to AML but also longer survival
  - Less intensive approach better

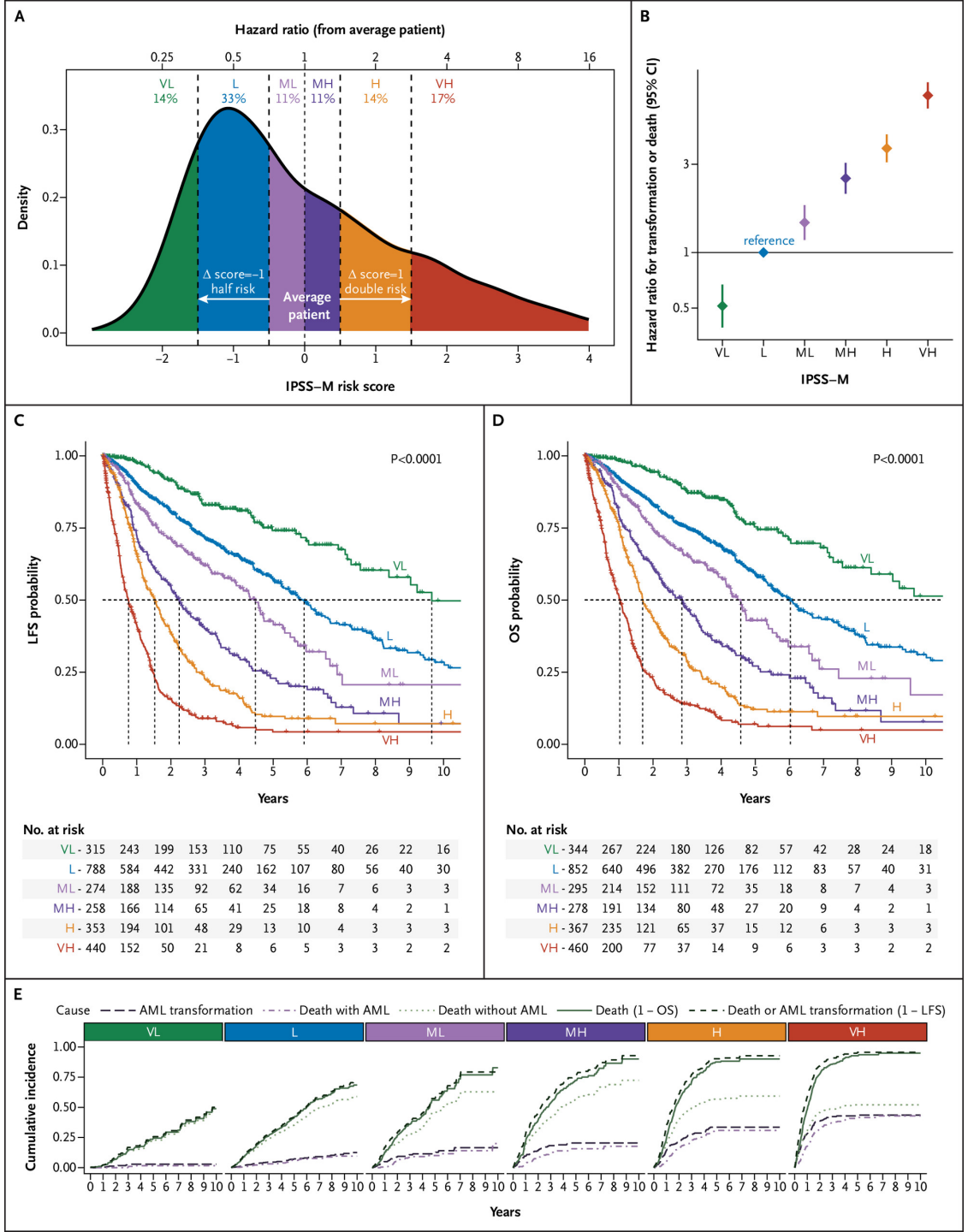
Bernard et al. NEJM Evid 2022;1(7)



IPSS-M

- Creation of risk score based on drivers and survival

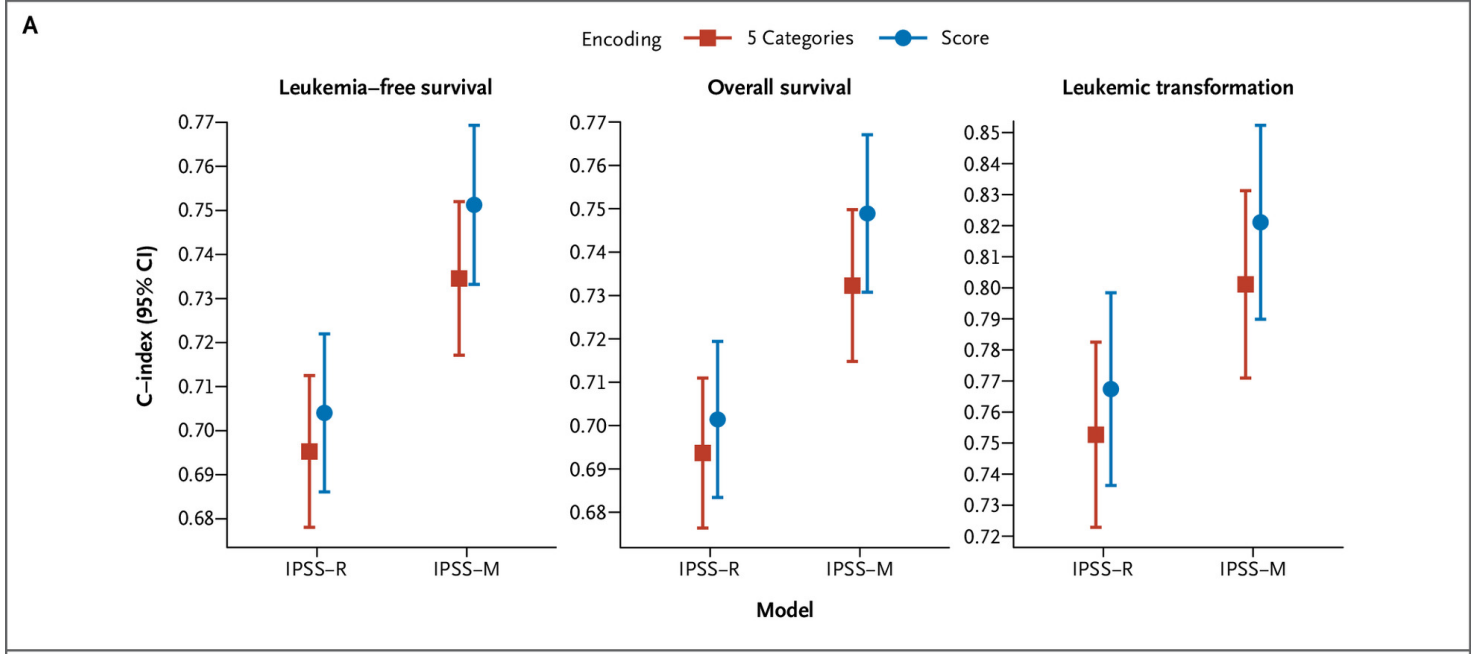
- Risk groups
  - Very low risk
  - Low risk
  - Medium low/high
  - High risk
  - Very high risk

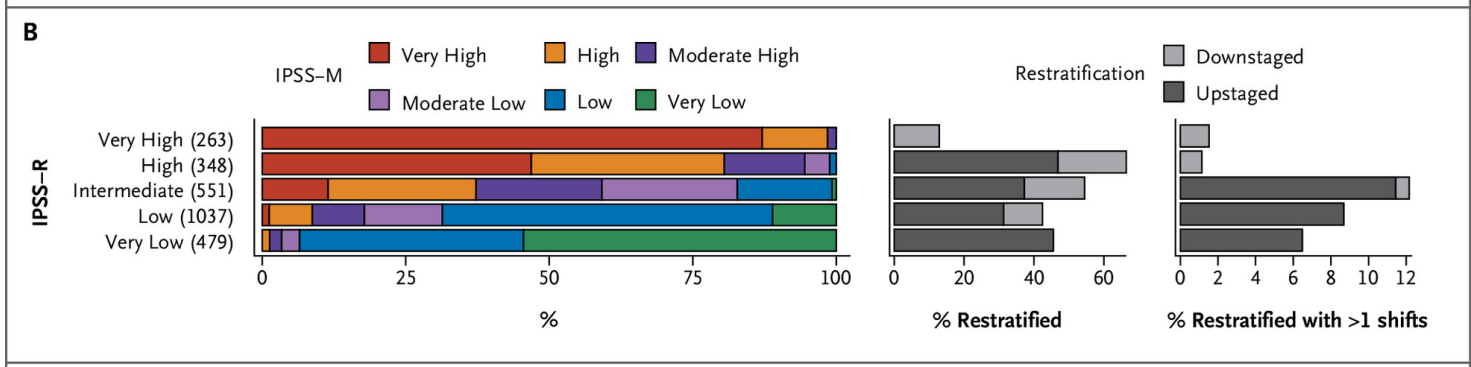


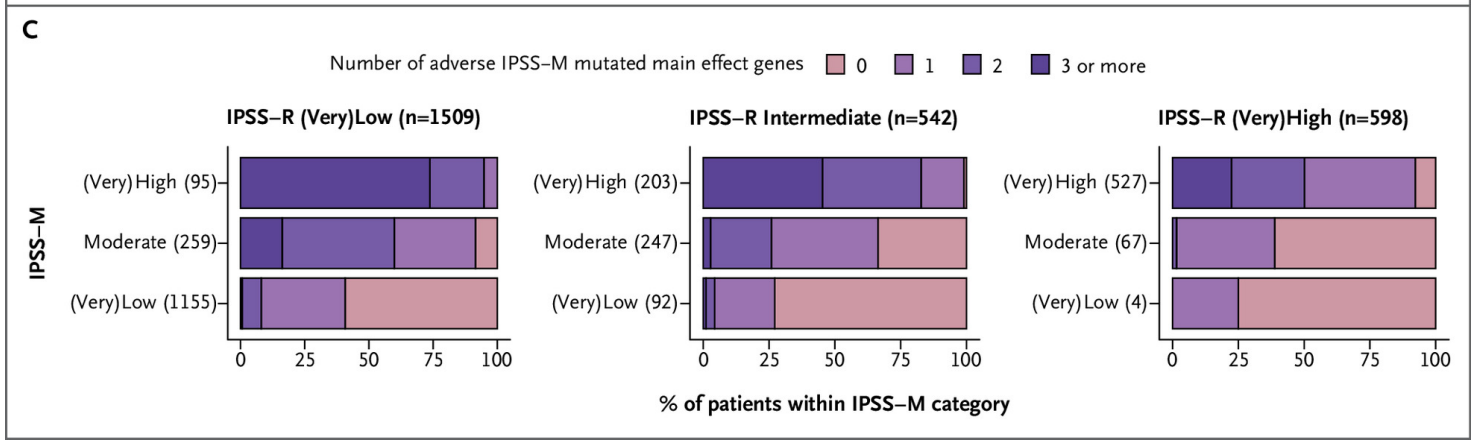
Bernard et al. NEJM Evid 2022;1(7)

Comparison to IPSS-R

- Guess what?!
- It's better…
- But also mostly overlaps







Bernard et al. NEJM Evid 2022;1(7)

Website calculators - multiple

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

- Further analysis of this dataset presented at ASH

997 Molecular Taxonomy of Myelodysplastic Syndromes and Its Clinical Implications

Elsa Bernard, PhD[1*], *Robert Hasserjian*[2], *Peter L. Greenberg, MD*[3], *Juan E Arango Ossa*[1*], *Maria Creignou, MD*[4*], *Yasuhito Nannya, MD, PhD*[5], *Heinz Tuechler*[6*], *Juan S Medina-Martínez*[7*], *Max F Levine*[7*], *Martin Jädersten, MD, PhD*[8*], *Ulrich Germing*[9*], *Guillermo Sanz, MD, PhD*[10*], *Arjan A. van de Loosdrecht, MD, PhD*[11], *Olivier Kosmider, PharmD, PhD*[12*], *Matilde Yung Follo, PhD*[13*], *Felicitas Thol*[14], *Lurdes Zamora, PhD*[15*], *Ronald Feitosa Pinheiro, MD, PhD*[16*], *Andrea Pellagatti*[17*], *Harold K Elias, MD*[18], *Detlef Haase, MD, PhD*[19*], *Maria Sirenko, PhD*[1], *Christina Ganster, PhD*[20], *Lionel Ades, MD, PhD*[21], *Magnus Tobiasson, MD*[22*], *Laura Palomo, PhD*[23*], *Matteo Giovanni Della Porta, MD*[24*], *Pierre Fenaux, MD, PhD*[25], *Monika Belickova, PhD*[26*], *Michael R. Savona, MD*[27], *Virginia M. Klimek, MD*[28*], *Fabio P. S. Santos, MD*[29], *Jacqueline Boultwood, PhD*[30*], *Ioannis Kotsianidis, MD, PhD*[31], *Valeria Santini, MD*[32], *Francesc Sole, PhD*[33], *Uwe Platzbecker, MD*[34], *Michael Heuser, MD*[14], *Peter Valent, MD*[35], *Carlo Finelli, MD*[36*], *Maria Teresa Voso, MD*[37], *Lee-Yung Shih, MD*[38], *Michaela Fontenay, MD, PhD*[39*], *Joop H. Jansen, PhD*[40*], *Jose Cervera, MD, PhD*[41*], *Norbert Gattermann, MD*[42], *Benjamin L. Ebert, MD, PhD*[43], *Rafael Bejar, MD, PhD*[44], *Luca Malcovati, MD*[45], *Mario Cazzola, MD*[46], *Seishi Ogawa*[47], *Eva Hellstrom Lindberg, MD, PhD*[48*] *and Elli Papaemmanuil, PhD*[1]

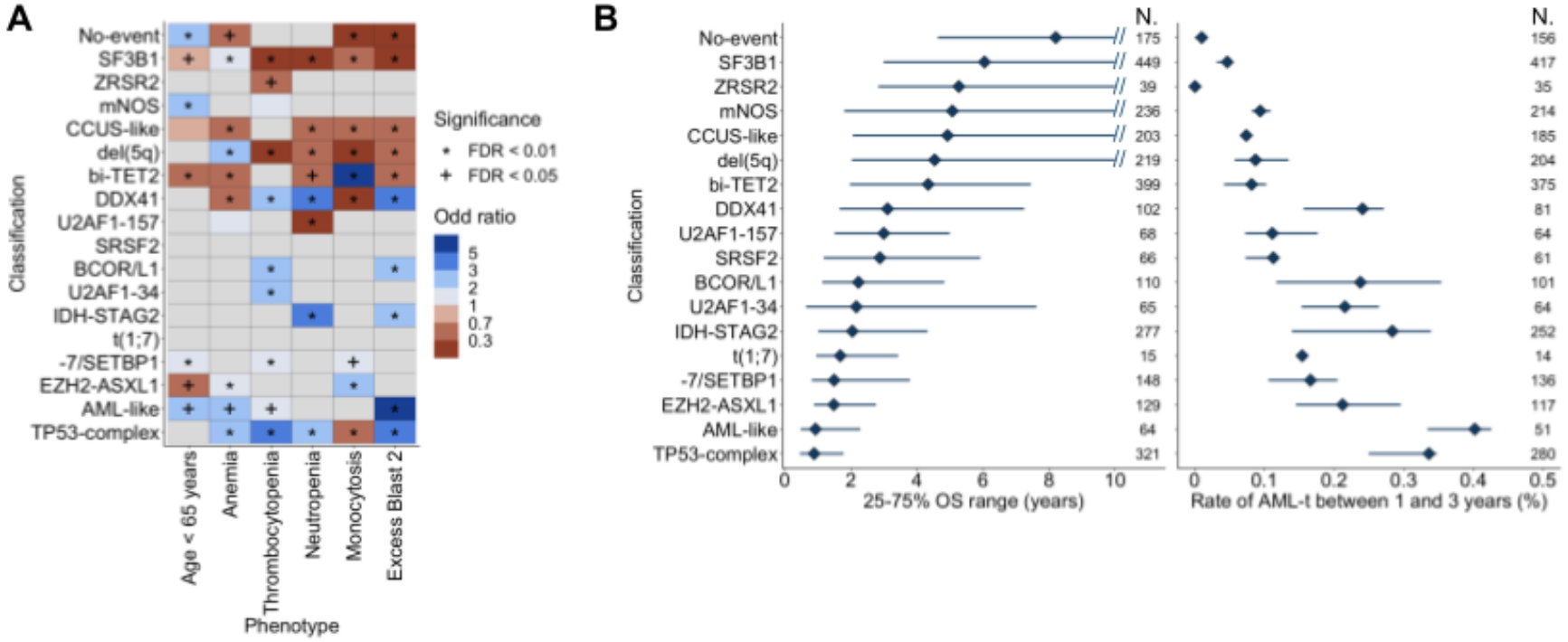


Figure 1. Associations between MDS molecular groups, clinical phenotypes, and outcomes. A. Association between molecular groups and clinical phenotypes. **B.** Association between molecular groups and outcomes, for overall survival (OS, left) and acute myeloid leukemia transformation (AML-t, right). Left: dots indicate median survival and lines extend to the interquartile (IQR) range. Right: dots indicate the 2-year incidence of AML-t and lines extend to the 1 year and 3rd years incidences. **C.** Cumulative incidence curves of AML transformation stratified with the range of blast percentages within the *DDX41* and *AML-like* subgroups (0-5, 5-10, and 10-20% in shades of green). P-values are from the Gray's test. **D.** Kaplan-Meier probability estimates of OS stratified with the range of blast percentages within the *EZH2-ASXL1* and *-7/SETBP1* subgroups. P-values are from the log rank test.

Conclusions

- Clinical impact of blasts depends upon genetic subtype
  - (increase in blasts should be considered in genetic context)

- Working to improve future classification schemes

Summary

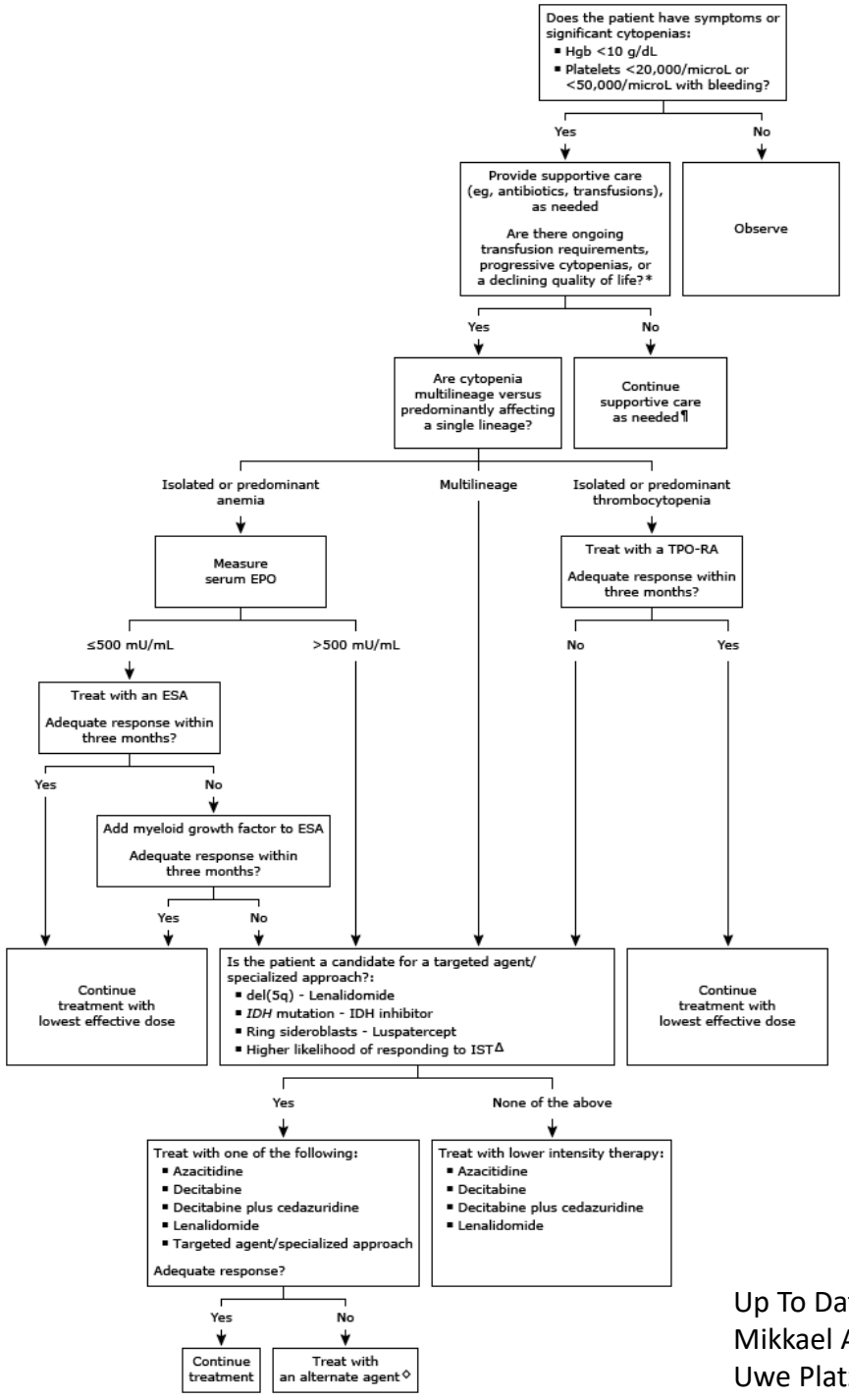
- IPSS-R is still useful, and frequently used in clinical trials
- However, mutation analysis can improve risk stratification and “highly recommended” in NCCN guidelines
- Way to identify targeted therapies
  - Ivosidenib (IDH1 inhibitor) approved for R/R MDS Oct 2023
- **Next-gen panel should be done routinely on all new MDS pts**

Lower risk MDS

Moving beyond ESAs

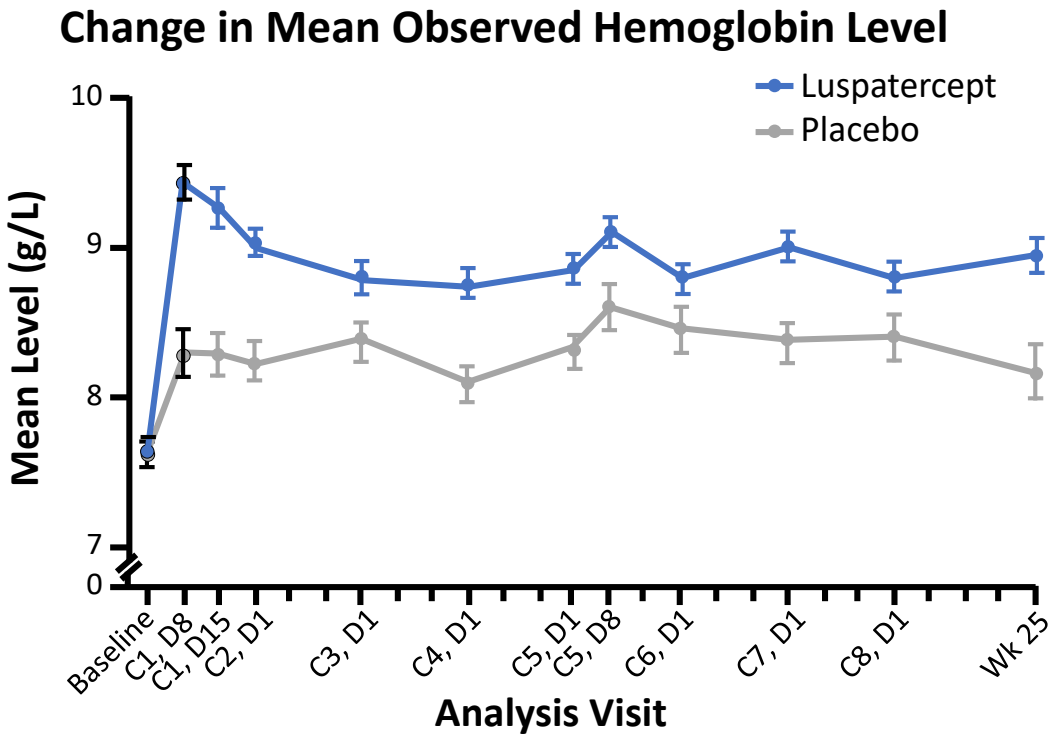
MDS low risk treatment

- Low risk MDS patients often don't need immediate treatment
- 5q del - lenalidomide
- Multilineage cytopenias - HMA
- Anemia is frequent and ESAs recommended
- Luspatercept now approved for all low risk MDS (not just RARS)



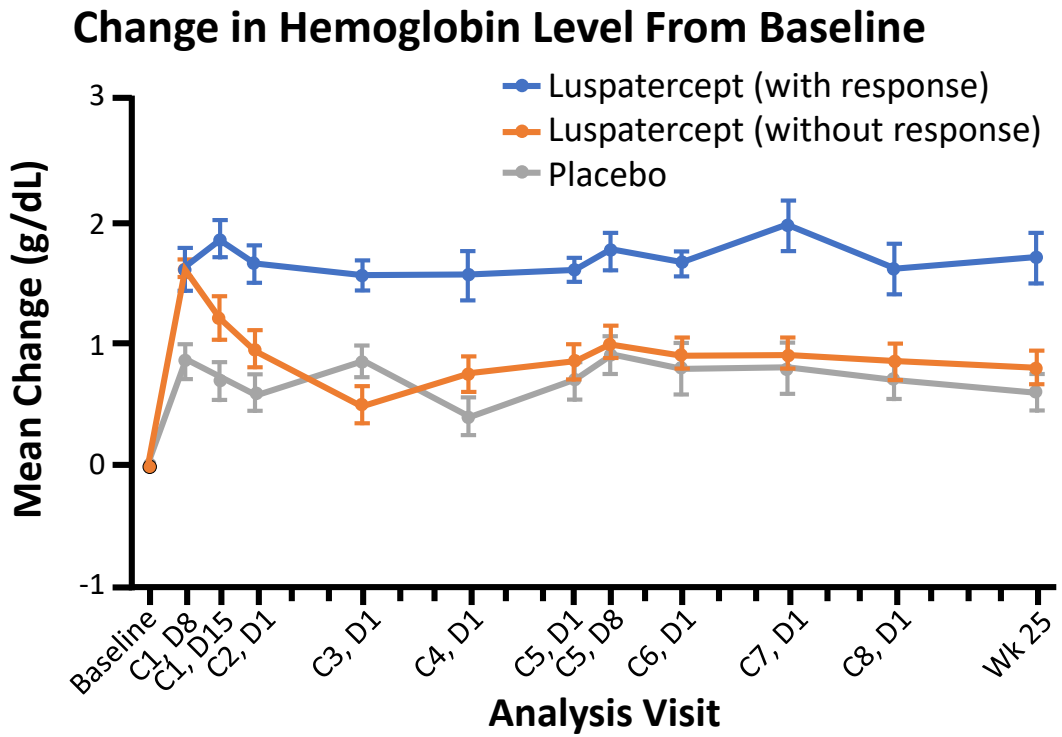
Up To Date
Mikkael A Sekeres, MD, MS
Uwe Platzbecker, MD

MEDALIST: Change in Hemoglobin Levels



Patients at Risk, n

Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32



Patients at Risk n

Luspatercept (with response)	–	24	36	55	53	52	50	42	47	50	42	45
Luspatercept (without response)	–	33	51	61	52	60	53	34	45	56	48	35
Placebo	–	32	36	41	47	44	52	29	44	47	44	32

Fenaux. NEJM. 2020;382:140.

MEDALIST: Adverse Events

AE in ≥10% of patients*	Luspatercept (n = 153)		Placebo (n = 76)	
	Any Grade	Grade 3	Any Grade	Grade 3
General or administration-site condition				
▪ Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
▪ Asthenia	31 (20)	4 (3)	9 (12)	0
▪ Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
▪ Diarrhea	34 (22)	0	7 (9)	0
▪ Nausea†	31 (20)	1 (1)	6 (8)	0
▪ Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
▪ Dizziness	30 (20)	0	4 (5)	0
▪ Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal/connective tissue disorder	29 (19)	3 (2)	5 (7)	0
▪ Back pain†	8 (5)	1 (1)	9 (12)	2 (3)
▪ Arthralgia				

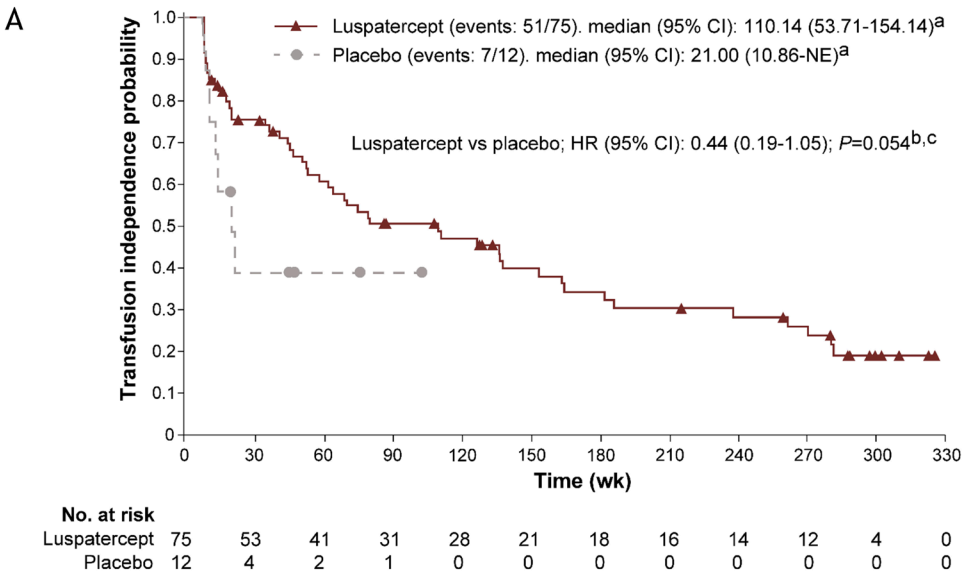
AE in ≥10% of patients*	Luspatercept (n = 153)		Placebo (n = 76)	
	Any Grade	Grade 3	Any Grade	Grade 3
Respiratory, thoracic, or mediastinal disorder				
▪ Dyspnea	23 (15)	1 (1)	5 (7)	0
▪ Cough	27 (18)	0	10 (13)	0
Infection or infestation				
▪ Bronchitis†	17 (11)	1 (1)	1 (1)	0
▪ UTI†	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning or fall	15 (10)	7 (5)	9 (12)	2 (3)

Fenaux. NEJM. 2020;382:140.

915 Long-Term Evaluation of Luspatercept in Erythropoiesis-Stimulating Agent (ESA)-Intolerant/Refractory Patients (pts) with Lower-Risk Myelodysplastic Syndromes (LR-MDS) in the Phase 3 MEDALIST Study

Valeria Santini[1], *Rami S. Komrokji, MD*[2], *Guillermo Garcia-Manero, MD*[3], *Rena Buckstein, MD, FRCPC*[4], *Esther Natalie Oliva, MD*[5], *Karen L. Keeperman*[6*], *Shelonitda Rose*[6*], *Ana Carolina Giuseppi*[6*], *Valerie Vilmont*[7*], *Yinzhi Lai*[6*], *Dimana Miteva*[7*], *Barkha Aggarwal*[6*], *Uwe Platzbecker, MD*[8], *Pierre Fenaux, MD, PhD*[9] *and Amer M. Zeidan, MBBS, MHS*[10]

A



B

	Luspatercept (N = 153)		Placebo (N = 76)	
TEAE	n (%)	EAIR per 100 pt y	n (%)	EAIR per 100 pt y
Treatment-related grade 3/4	14 (9.2)	5.3	3 (3.9)	6.6
Treatment-related grade 5	0	0	0	0
TEAE leading to permanent treatment discontinuation	24 (15.7)	8.6	6 (7.9)	13
TEAE				
Preferred Term	n (%)	EAIR per 100 PY	n (%)	EAIR per 100 PY
Fatigue	47 (30.7)	22.1	11 (14.5)	27.1
Diarrhea	47 (30.7)	23.5	8 (10.5)	18.4
Asthenia	41 (26.8)	18.8	9 (11.8)	21.5
Peripheral edema	40 (26.1)	17.6	13 (17.1)	32.0
Back pain	38 (24.8)	16.8	5 (6.6)	11.7
AESI				
Preferred Term	n (%)	EAIR per 100 PY	n (%)	EAIR per 100 PY
Cardiac-related events	54 (35.3)	26.9	11 (14.5)	25.7
Tachycardia	11 (7.2)	4.1	0	0
Hypertension	20 (13.1)	8.0	7 (9.2)	16.9
Thromboembolic events	7 (4.6)	2.6	3 (3.9)	6.6
Malignancies	19 (12.4)	6.8	6 (7.9)	10.4
Basal cell carcinoma	5 (3.3)	1.8	0	0

Cumulative duration of RBC-TI is defined as the sum of all respective durations for responders over the entire treatment period. [a]Medians and associated two-sided 95% CIs were calculated using the KM method. [b]*P*-values were calculated using the log-rank test to compare luspatercept and placebo, stratified by average baseline RBC transfusion requirement (≥ 6 units vs. < 6 units of RBC per 8 wks) and baseline IPSS-R score (Very low or Low vs. Intermediate). [c]HRs were calculated using the Cox proportional hazards model with RBC transfusion requirement (≥ 6 units vs. < 6 units of RBC per 8 weeks) and baseline IPSS-R score (Very low or Low vs. Intermediate) as covariates. CI, confidence interval; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; KM, Kaplan–Meier; NE, not estimable; RBC, red blood cell; RBC-TI, RBC transfusion independence; wk, week.

- Additional 26 months of follow up original MEDALIST study
- sustained periods of RBC-TI – >50% with RBC-TI for ≥ 1 year
- safety profile of luspatercept largely unchanged
- AEs were mostly lower grade with rates of fatigue decreasing with increasing luspatercept dose

193 Efficacy and Safety of Luspatercept Versus Epoetin Alfa in Erythropoiesis-Stimulating Agent (ESA)-Naive Patients (Pts) with Transfusion-Dependent (TD) Lower-Risk Myelodysplastic Syndromes (LR-MDS): Full Analysis of the COMMANDS Trial

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

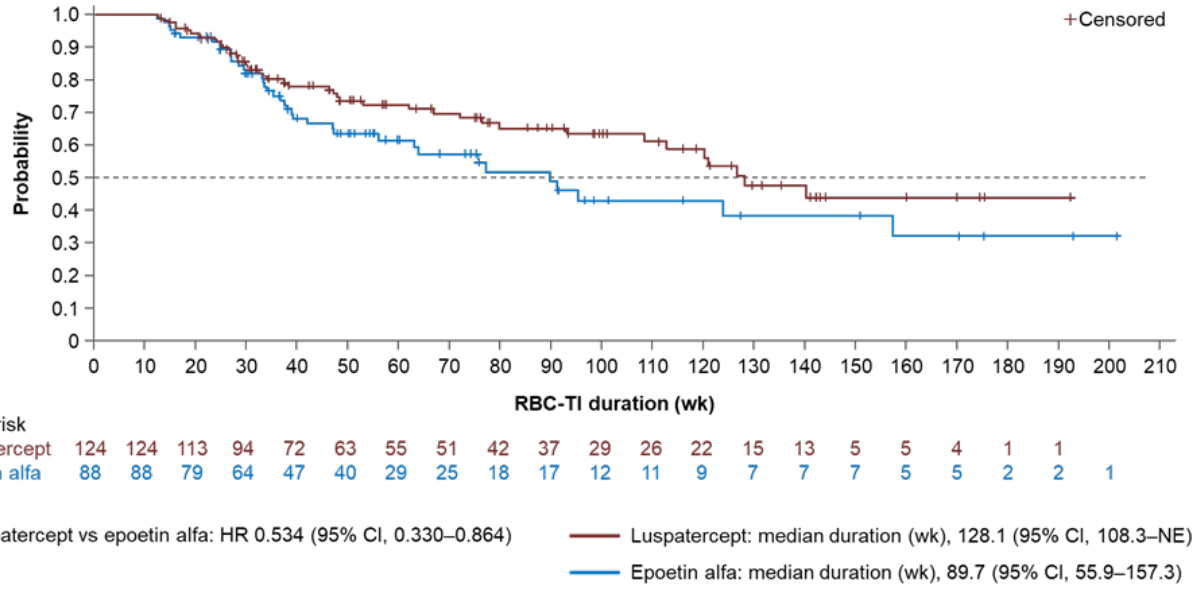
- Randomized 1:1 to luspatercept (1.0–1.75 mg/kg) SC Q3W, or epoetin alfa (450–1050 IU/kg) SC Q1W for ≥ 24 wk

- stratified by baseline RBC transfusion burden (< 4 vs ≥ 4 RBC U/8 wk)

- primary endpoint was the achievement of RBC-TI ≥ 12 wk and concurrent mean Hgb increase ≥ 1.5 g/dL

Figure. Duration of RBC-TI ≥ 12 wk for the ITT population (A) and subgroup analysis of the primary endpoint (B)

A



B

	Luspatercept	Epoetin Alfa
Overall, n/N (%)	110/182 (60.4%)	63/181 34.8%
***SF3B1* mutated, n/N (%)**	80/114 (70.2%)	33/101 (32.7%)
***SF3B1* non-mutated, n/N (%)**	29/65 (44.6%)	26/72 (36.1%)
sEPO ≤ 200 U/L, n/N (%)	96/145 (66.2%)	59/144 (41.0%)
sEPO > 200 U/L, n/N (%)	14/37 (37.8%)	4/37 (10.8%)
RS+, n/N (%)	87/133 (65.4%)	38/130 (29.2%)
RS−, n/N (%)	23/49 (46.9%)	25/50 (50.0%)

CI, confidence interval; ITT, intent to treat; NE, not estimable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblast; sEPO, serum erythropoietin; wk, week.

More drugs targeting anemia

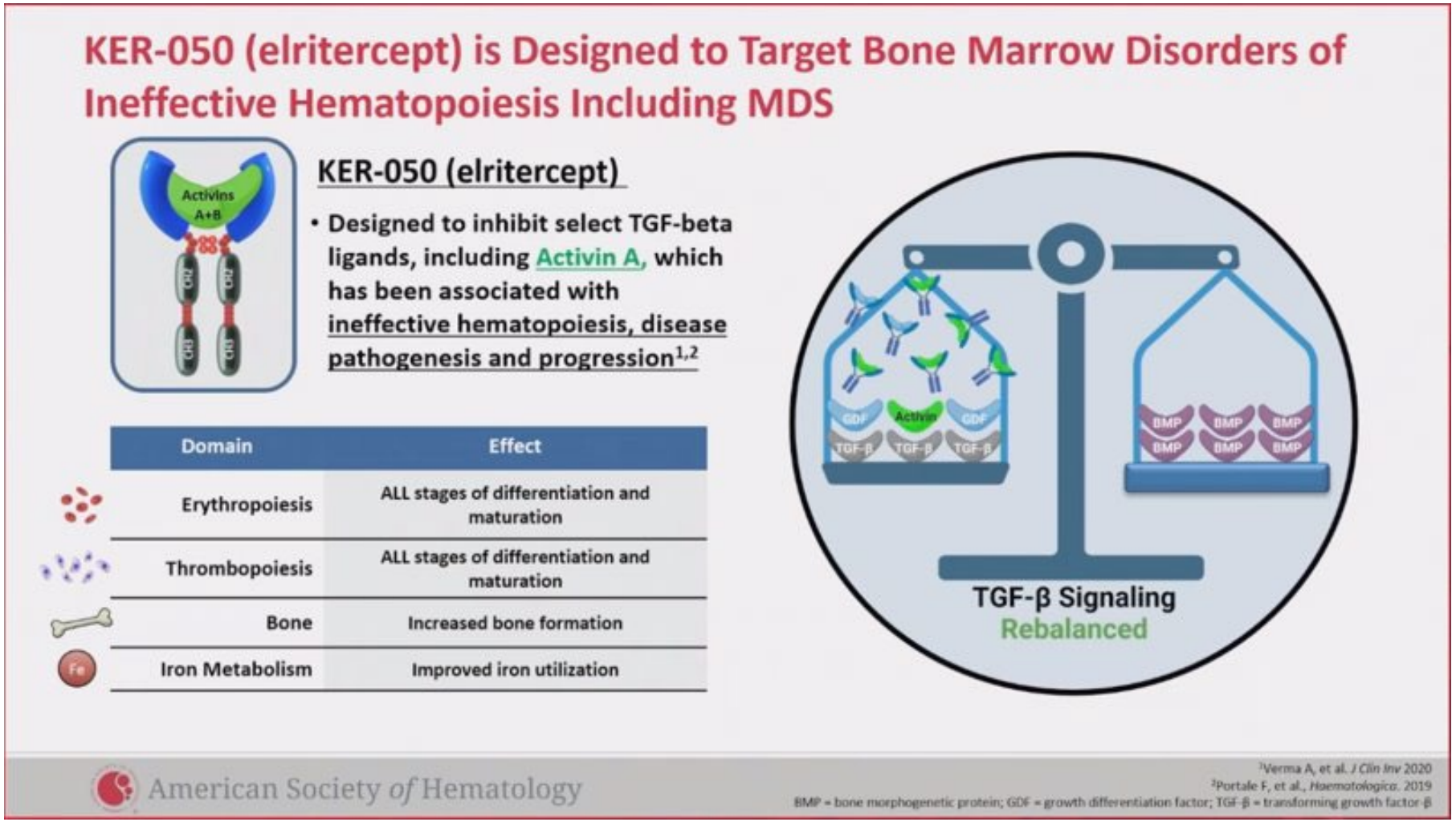
196 Durable Clinical Benefit with Ker-050 Treatment: Findings from an Ongoing Phase 2 Study in Participants with Lower-Risk MDS

Maria Diez-Campelo, MD, PhD[1*], *David M. Ross, MBBS, PhD, FRACP, FRCPA*[2*], *Aristoteles Giagounidis*[3], *Shuhying Tan, FRACP, FRCPA, MBBS*[4*], *Thomas Cluzeau, MD, PhD*[5], *Lynette C.Y. Chee, MBBS, PhD, FRACP, FRCPA*[6], *David Valcarcel, MD, PhD*[7], *Montserrat Arnan, MD, PhD*[8*], *Christine Graham, PhD*[9*], *Allie McGinty*[9*], *Miranda Ross, BS*[9*], *Wei Feng*[9*], *Ying Jiang*[9*], *Suresh Bobba*[9*], *Montagu Hankin, MSc*[9*], *Christopher Rovaldi*[9*], *Dena Grayson, MD, PhD*[9*], *Simon Cooper, MBBS*[9] *and Jen L. Salstrom, MD, PhD*[9]

Ligand trap designed to inhibit select TGF-β superfamily ligands (activins A, B, GDFs 8, 11) that bind ACRV type IIA

Similar pathway to luspatercept

Same target of momelotinib and pacritinib



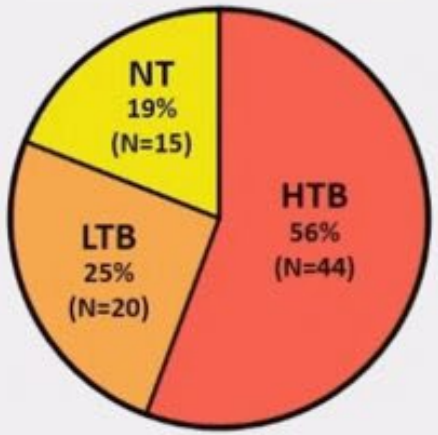
Study Enrolled Hard-to-Treat Patients With High Disease Burden

Majority had high transfusion burden or multi-lineage dysplasia at baseline

Baseline Characteristic	RP2D (N=79)
Median age, years (range)	75 (53, 89)
Sex, male, n (%)	50 (63.3)
Hemoglobin, g/dL, median (range)	8.37 (3.7, 10.5)
RS+, n (%)	57 (72.2)
Non-RS, n (%)	22 (27.8)
Prior ESA, n (%)	21 (26.6)
Median baseline EPO level, U/L (range)*	127.8 (1, 4000)
Thrombocytopenia, n (%) (platelets < 150 x 10^9/L)	20 (25)

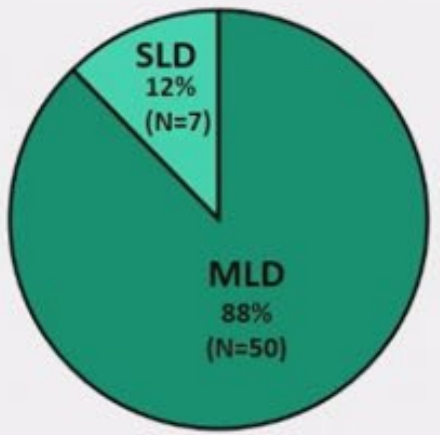
*9 RP2D participants had missing baseline EPO

Baseline Transfusion Burden



- 44 (56%) had high transfusion burden (HTB, ≥4 RBC units/8 weeks)
- 25 (32%) heavily transfused (≥ 6 RBC units/8 weeks)

Baseline Dysplasia Category**



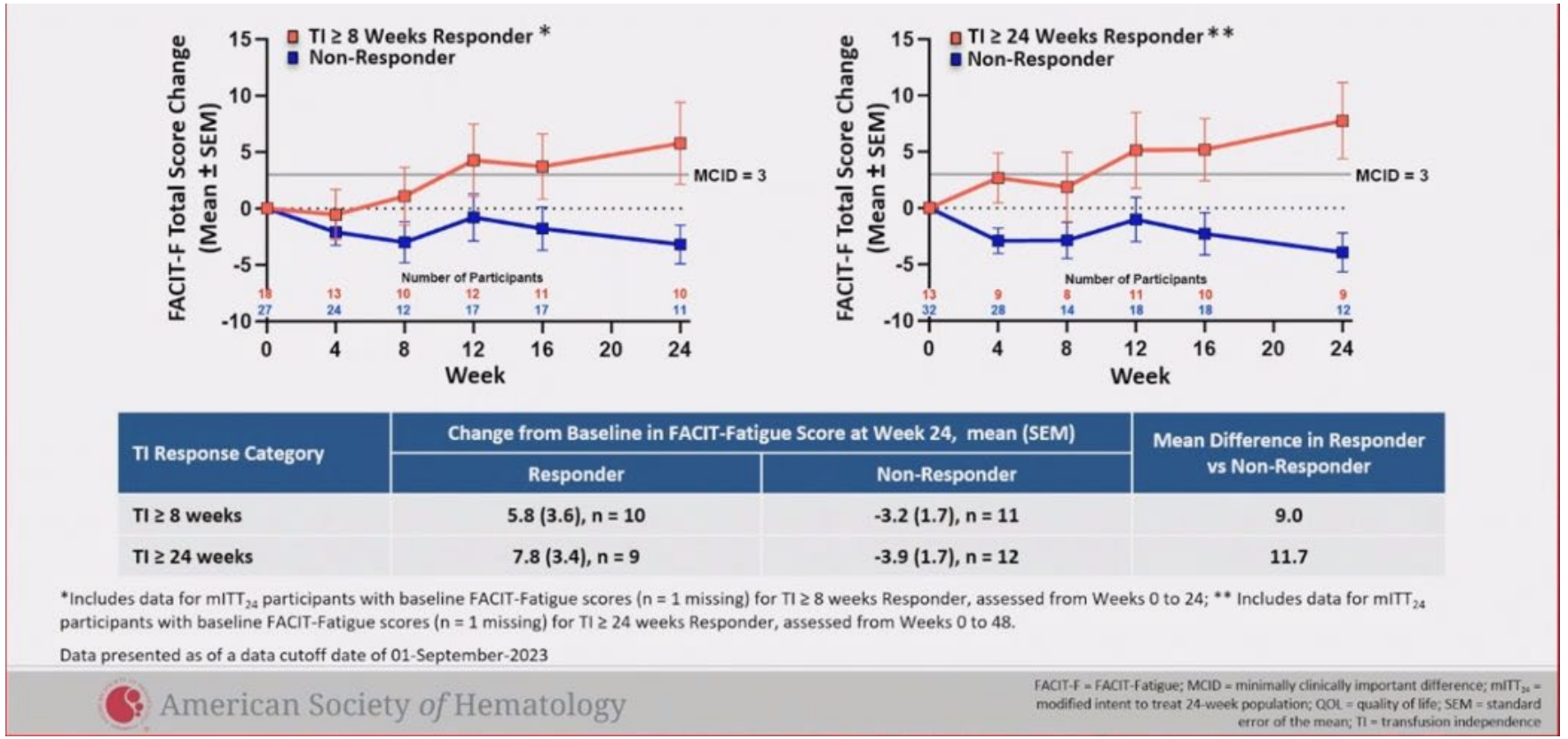
- 50 (88%) had multi-lineage dysplasia (MLD)

**Excludes 22 RP2D participants with unknown dysplasia category

Data presented as of a data cutoff date of 01-September-2023

EPO = erythropoietin; HTB = high transfusion burden; LTB = low transfusion burden; MDS = myelodysplastic syndrome; MLD = multi-lineage dysplasia; NT = non-transfused; Q4W = every 4 weeks; RP2D = recommended Part 2 dose; RS = ring sideroblasts; SLD = single lineage dysplasia.

Patients who achieved TI also showed improvement in FACIT-Fatigue scores



TI Response Category	Change from Baseline in FACIT-Fatigue Score at Week 24, mean (SEM)		Mean Difference in Responder vs Non-Responder
	Responder	Non-Responder	
TI ≥ 8 weeks	5.8 (3.6), n = 10	-3.2 (1.7), n = 11	9.0
TI ≥ 24 weeks	7.8 (3.4), n = 9	-3.9 (1.7), n = 12	11.7

*Includes data for $mITT_{24}$ participants with baseline FACIT-Fatigue scores (n = 1 missing) for TI ≥ 8 weeks Responder, assessed from Weeks 0 to 24; ** Includes data for $mITT_{24}$ participants with baseline FACIT-Fatigue scores (n = 1 missing) for TI ≥ 24 weeks Responder, assessed from Weeks 0 to 48.

Data presented as of a data cutoff date of 01-September-2023

American Society *of* Hematology

FACIT-F = FACIT-Fatigue; MCID = minimally clinically important difference; $mITT_{24}$ = modified intent to treat 24-week population; QOL = quality of life; SEM = standard error of the mean; TI = transfusion independence

KER-050 achieved erythroid response in 51.4% and transfusion independence in 42.3% of subjects

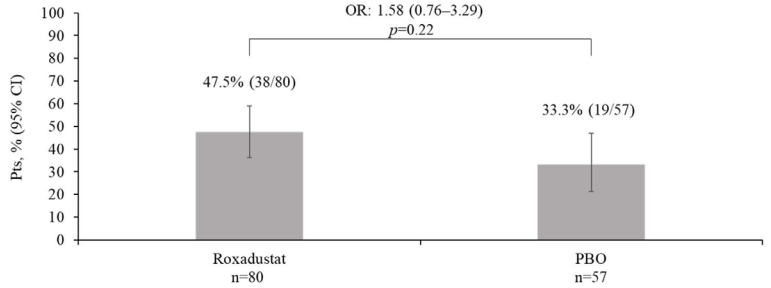
Alternative therapies to improving anemia

195 Efficacy and Safety of Roxadustat for Treatment of Anemia in Patients with Lower-Risk Myelodysplastic Syndrome (LR-MDS) with Low Red Blood Cell (RBC) Transfusion Burden: Results of Phase III Matterhorn Study

Moshe Mittelman, MD[1], *David H. Henry*[2], *John Glaspy*[3*], *Anil Tombak*[4*], *Rosemary Anne Harrup*[5*], *Krzysztof Madry, MD, PhD*[6*], *Barbara Grabowska*[7*], *Uwe Platzbecker, MD*[8], *Tyson Lee*[9*] *and Katharina Modelska*[9*]

- Roxadustat is a first-in-class, hypoxia-inducible factor prolyl hydroxylase inhibitor for treatment of anemia with chronic kidney disease
- Phase 3 double blind study in LR-MDS (Matterhorn study)
- No significant improvement in transfusion independence (TI)
- Well tolerated
- too many patients enrolled with low transfusion needs?

Figure. TI responders[a]



CI, confidence interval; OR, odds ratio; PBO, placebo; pts, patients; TI, transfusion independence.
Full analysis population (all pts who were randomized and received ≥1 dose of treatment).
[a]TI responders defined as pts with TI ≥56 consecutive days during the first 28 treatment weeks.

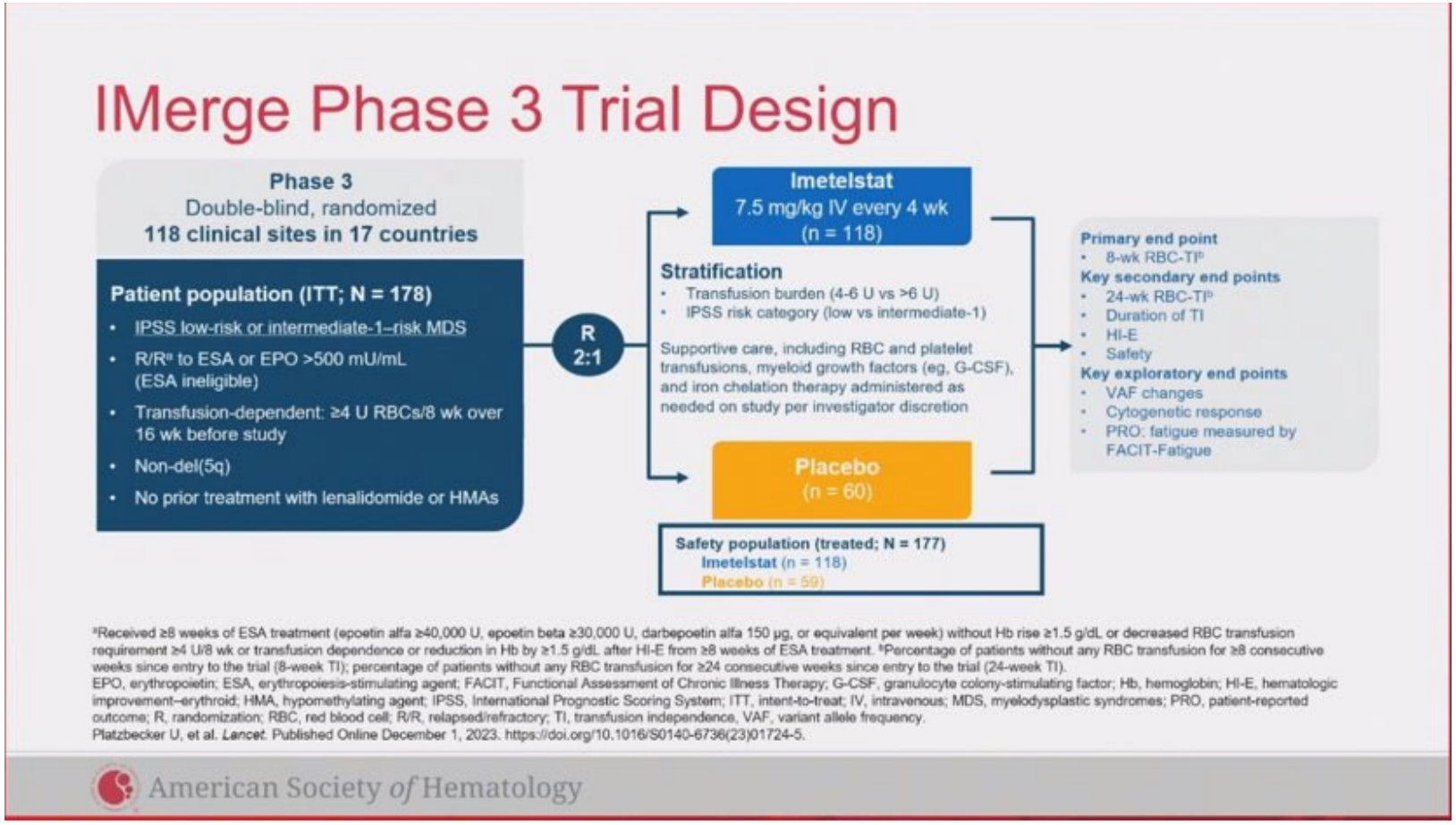
Table. Safety summary

TEAEs, n (%)	Roxadustat (n=82)	Placebo (n=58)
TEAEs, any grade	73 (89.0)	52 (89.7)
TEAEs, grade ≥3	31 (37.8)	12 (20.7)
Serious TEAEs	22 (26.8)	9 (15.5)
TEAEs leading to treatment discontinuation	12 (14.6)	5 (8.6)
TEAEs leading to death	4 (4.9)	2 (3.4)
Most common TEAEs[a], any grade		
Nausea	19 (23.2)	7 (12.1)
Fatigue	15 (18.3)	6 (10.3)
Constipation	11 (13.4)	1 (1.7)
Dizziness	10 (12.2)	9 (15.5)
Asthenia	10 (12.2)	7 (12.1)
ALT increased	10 (12.2)	6 (10.3)
Peripheral edema	9 (11.0)	4 (6.9)
Diarrhea	6 (7.3)	8 (13.8)
COVID-19	5 (6.1)	7 (12.1)

ALT, alanine aminotransferase; COVID-19, coronavirus disease of 2019; pts, patients; TEAE, treatment-emergent adverse event.
Safety population (all pts who received ≥1 dose of treatment).
[a]TEAEs occurring in ≥10% of pts in either treatment arm and listed in descending order of frequency in the roxadustat arm.

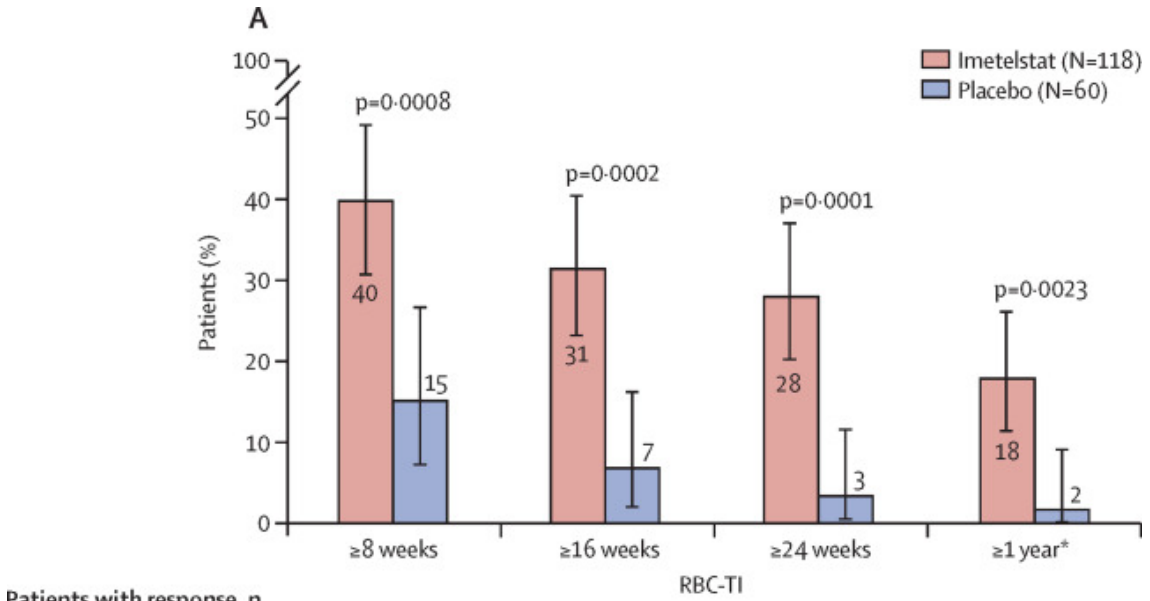
194 Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence (RBC-TI) across Different Risk Subgroups in Patients with Lower-Risk Myelodysplastic Syndromes (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis-Stimulating Agents (ESAs) in IMerge Phase 3 Study

Rami S. Komrokji, MD[1], *Valeria Santini, MD*[2*], *Pierre Fenaux, MD, PhD*[3], *Michael R. Savona, MD*[4*], *Yazan F. Madanat, MD*[5], *Tymara Berry, MD*[6*], *Laurie Sherman, BSN*[6], *Shyamala Navada, MD*[6*], *Faye M. Feller, MD*[6], *Libo Sun, PhD*[6*], *Qi Xia, PhD*[6*], *Ying Wan, MD, PhD*[6*], *Fei Huang, PhD*[6], *Amer M. Zeidan, MBBS, MHS*[7] *and Uwe Platzbecker, MD*[8]

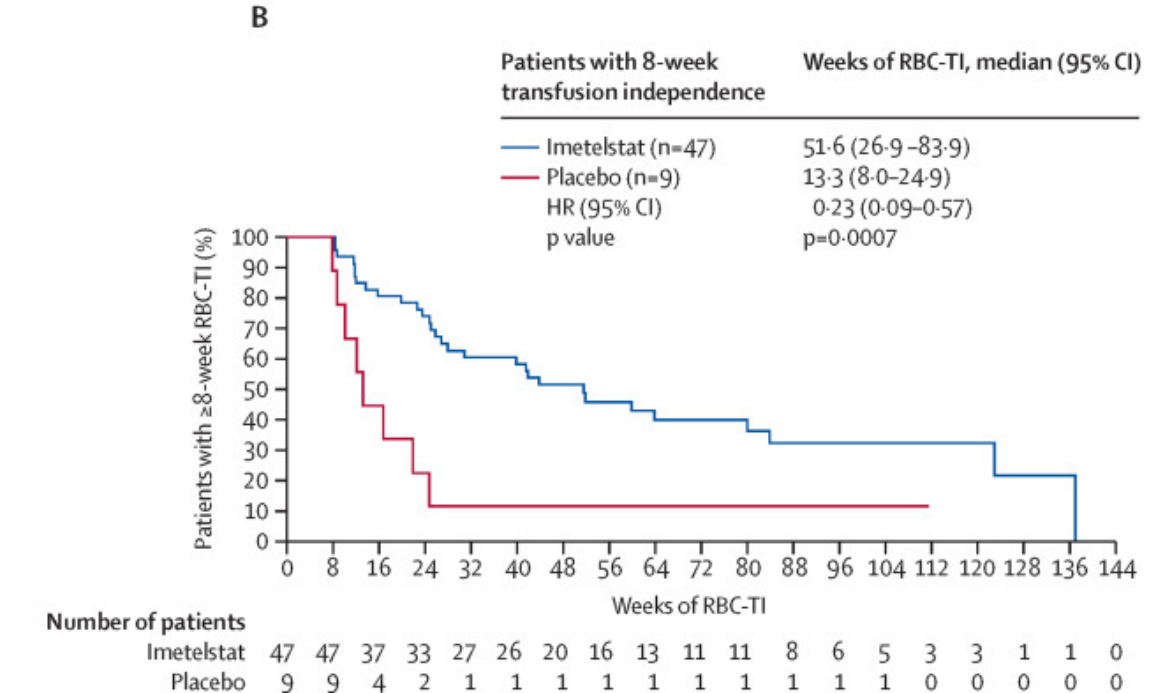


Published Jan 2024 in The Lancet

- Durable improvement in RBC-TI with imetelstat compared to placebo

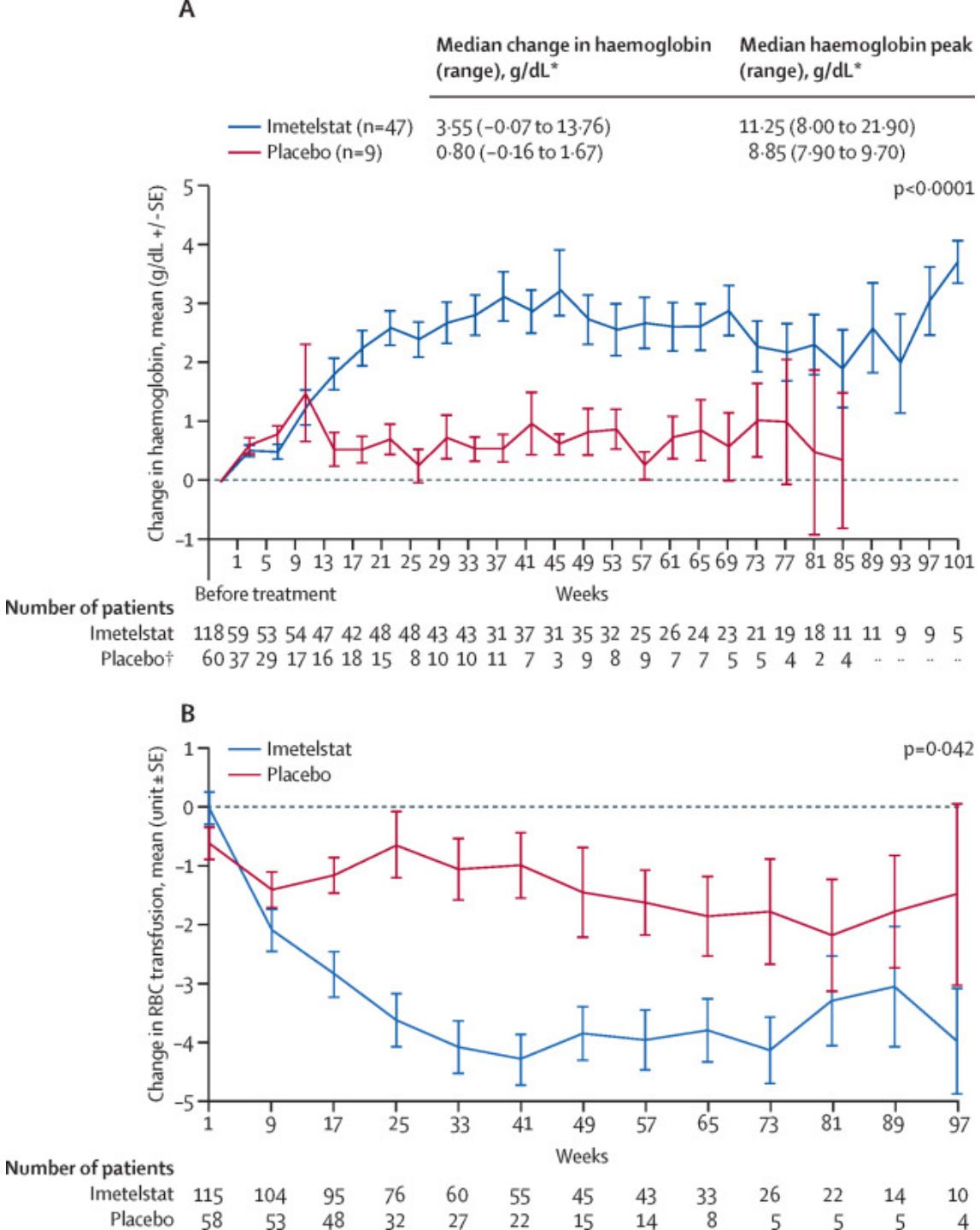


Patients with response, n (% [95% CI])				
Imetelstat	47 (40% [31–50])	37 (31% [23–41])	33 (28% [20–37])	21 (18% [11–26])
Placebo	9 (15% [7–27])	4 (7% [2–16])	2 (3% [0·4–12])	1 (2% [0·04–9])



Platzbecker U et al. The Lancet 2024

- Improvement in Hgb
- Fewer transfusions



Platzbecker U et al. The Lancet 2024

194 Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence (RBC-TI) across Different Risk Subgroups in Patients with Lower-Risk Myelodysplastic Syndromes (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis-Stimulating Agents (ESAs) in IMerge Phase 3 Study

- Heme toxicities
- Headaches and LFT abnormalities
- Otherwise well tolerated
- Will be submitted to FDA this year

	Imetelstat (N=118)		Placebo (N=59)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Haematological				
Thrombocytopenia	89 (75%)	73 (62%)	6 (10%)	5 (8%)
Neutropenia	87 (74%)	80 (68%)	4 (7%)	2 (3%)
Anaemia	24 (20%)	23 (19%)	6 (10%)	4 (7%)
Leukopenia	12 (10%)	9 (8%)	1 (2%)	0
General disorders and administration site conditions				
Asthenia	22 (19%)	0	8 (14%)	0
Oedema peripheral	13 (11%)	0	8 (14%)	0
Pyrexia	9 (8%)	2 (2%)	7 (12%)	0
COVID-19	22 (19%) †	3 (3%)‡	8 (14%) †	3 (5%)‡
Gastrointestinal disorders				
Diarrhoea	14 (12%)	1 (1%)	7 (12%)	1 (2%)
Constipation	9 (8%)	0	7 (12%)	0
Headache	15 (13%)	1 (1%)	3 (5%)	0
Alanine aminotransferase increased	14 (12%)	3 (3%)	4 (7%)	2 (3%)
Hyperbilirubinaemia	11 (9%)	1 (1%)	6 (10%)	1 (2%)

*Includes all patients who received at least one dose of study drug. †Includes COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. ‡Only COVID-19 pneumonia events were classified as grade 3–4 events for COVID-19.

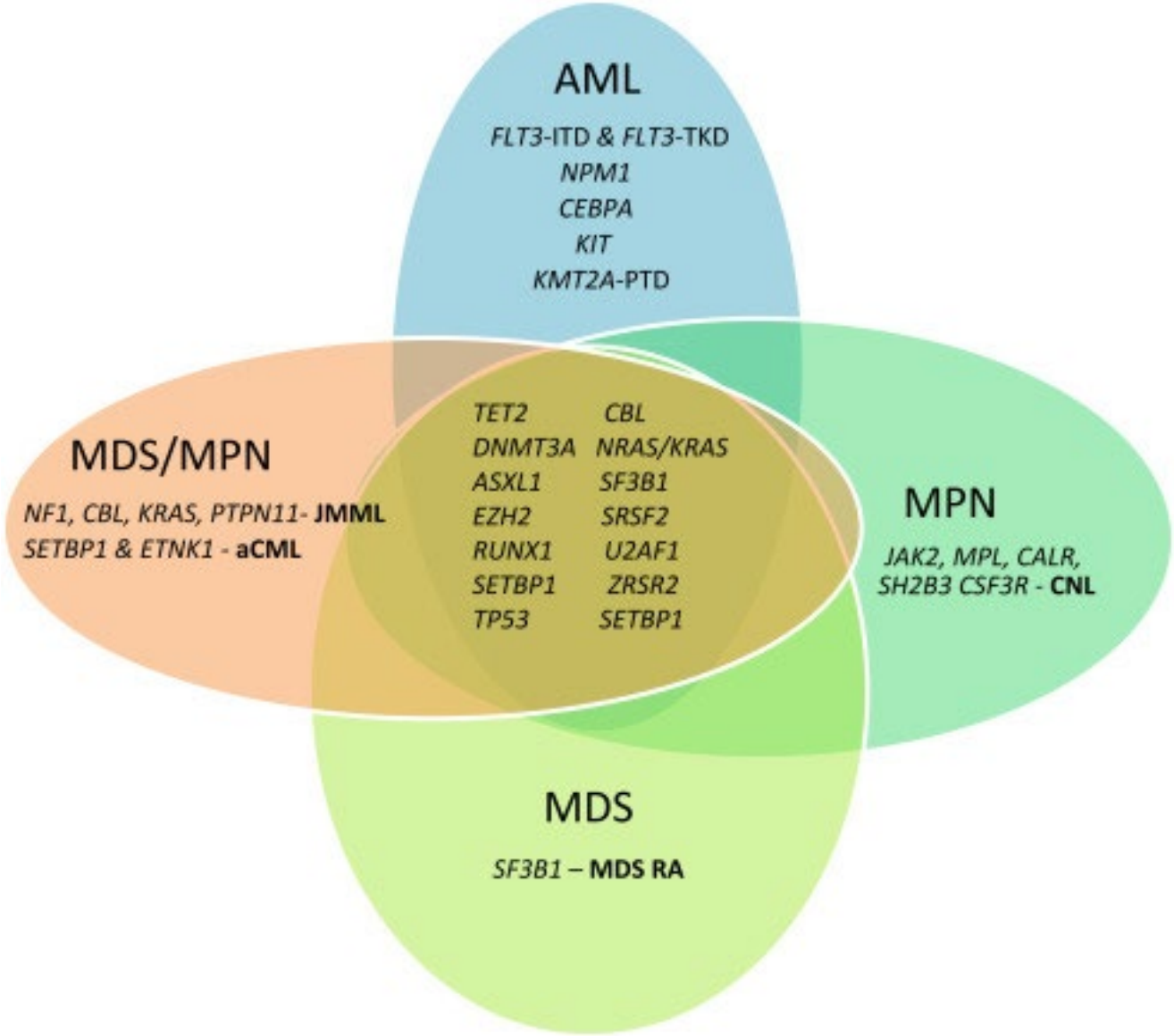
Table 3:* Number of patients with treatment-emergent adverse events occurring in at least 10% of patients in the safety population

Platzbecker U et al. The Lancet 2024

High risk MDS – treating more like AML

But still awaiting confirmation this is the best approach…

Myeloid neoplasms – genetic overlap



Patel et al. Clin Lymph Myeloma and Leuk. July 2017, Pages S62-S74

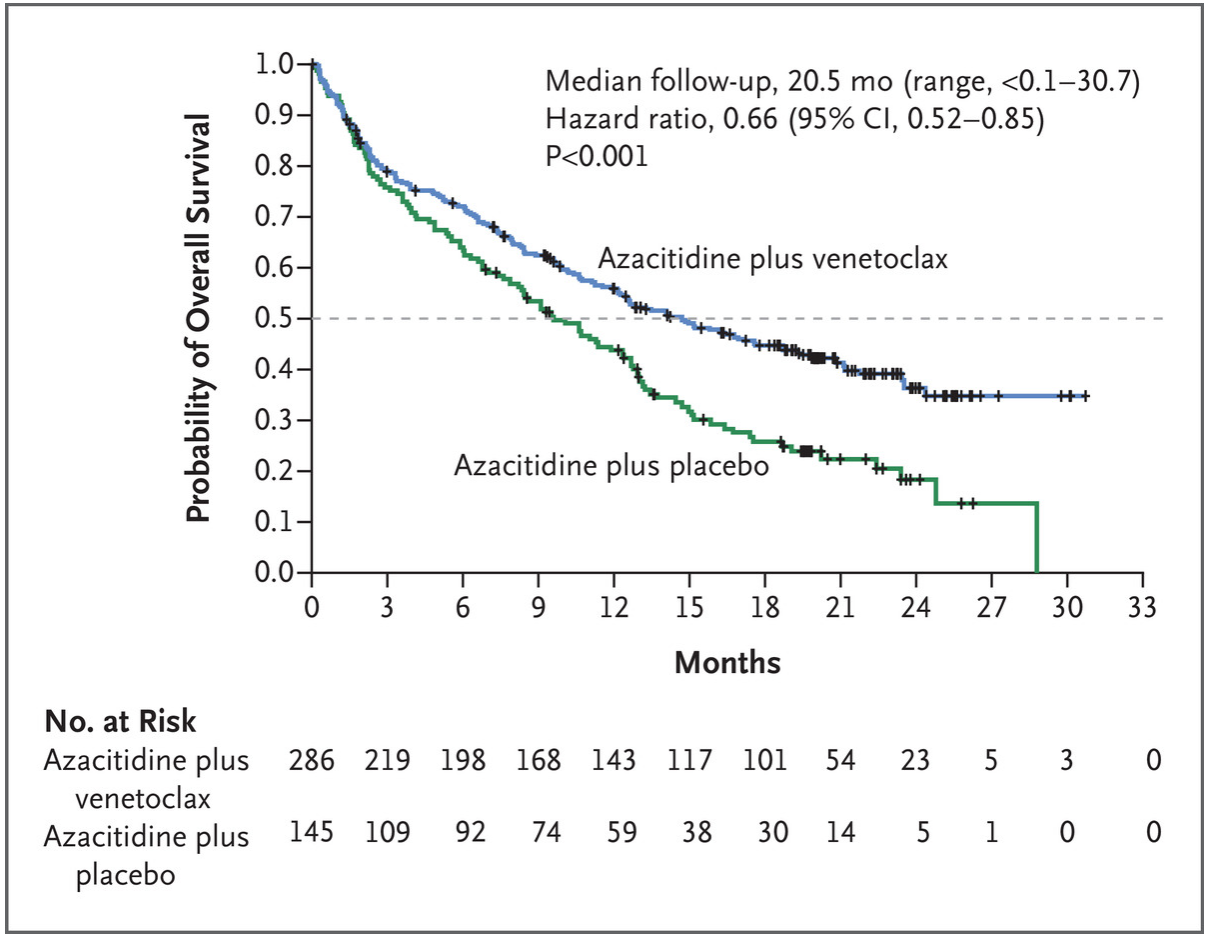
MDS classification: WHO vs ICC

4th edition WHO	5th edition WHO	ICC
MDS with single lineage dysplasia MDS-SLD	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)*
MDS with multilineage dysplasia MDS-MLD	MDS with low blasts and SF3B1 mutation*(MDS-SF3B1)	MDS with mutated SF3B1*
MDS with ring sideroblasts (≥ 15% RS or ≥ 5% if +SF3B1) • MDS-RS-SLD • MDS-RS-MLD	MDS with biallelic TP53 inactivation (MDS-biTP53)	MDS with mutated TP53
MDS with excess blasts • MDS-EB1 • MDS-EB2	MDS with low blasts (MDS-LB)	MDS, NOS with single lineage dysplasia MDS, NOS with multi-lineage dysplasia
MDS associated with isolated del (5q)	MDS with increased blasts (MDS-IB) • MDS-IB1 (5–9% BM or 2–4% PB) • MDS-IB2 (10-19% BM, 5-19% PB)	MDS with excess blasts (5-9% BM, 2-9% PB) MDS/AML (10-19% BM/PB blasts)
Myelodysplastic syndrome – unclassified (MDS-U)	MDS, hypoplastic (MDS-h)	MDS, NOS without dysplasia

Same

different

VIALE-A trial results
One combo for all elderly AML?



CD DiNardo et al. N Engl J Med 2020;383:617-629.

High risk MDS too?

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Male sex — no. (%)	172 (60)	87 (60)
AML type — no (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML — no./total no. (%)		
History of myelodysplastic syndrome or CMML	46/72 (64)	26/35 (74)
Therapy-related AML	26/72 (36)	9/35 (26)
ECOG performance-status score — no. (%)†		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
Bone marrow blast count — no. (%)		
<30%‡	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)
≥50%	140 (49)	71 (49)
AML with myelodysplasia-related changes — no. (%)	92 (32)	49 (34)
Cytogenetic risk category — no. (%)§		
Intermediate	182 (64)	89 (61)
Normal karyotype — no.	128	62
Trisomy 8; +8 alone — no.	13	10
Poor	104 (36)	56 (39)
7 or 7q deletion — no.	20	11
5 or 5q deletion — no.	46	22
Complex, ≥3 clonal abnormalities — no.	75	36
Somatic mutations — no./total no. (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
FLT3 ITD or TKD	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline cytopenia grade ≥3¶		
Anemia — no. (%)	88 (31)	52 (36)
Neutropenia — no./total no. (%)	206/286 (72)	90/144 (62)
Thrombocytopenia — no. (%)	145 (51)	73(50)
Baseline transfusion dependence — no. (%)‖		
Red cells	144 (50)	76 (52)
Platelets	68 (24)	32 (22)
≥2 Reasons for ineligibility to receive intensive therapy — no. (%)	141 (49)	65 (45)

* AML denotes acute myeloid leukemia, CMML chronic myelomonocytic leukemia, ITD internal tandem duplications, and TKD tyrosine kinase domain.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
‡ These bone marrow blast counts were between 20 and 29%.
§ Only cytogenetic risks of interest are shown.
¶ Cytopenia was graded according to the Common Terminology Criteria for Adverse Events.
‖ Baseline transfusion dependence was transfusion within 8 weeks before the first dose of azacitidine–venetoclax or azacitidine–placebo or randomization.

319 Efficacy and Safety of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Treatment-Naive, Higher-Risk Myelodysplastic Syndromes

Jacqueline S. Garcia, MD[1], *Uwe Platzbecker, MD*[2], *Olatoyosi Odenike*[3], *Shaun Fleming*[4*], *Chun Yew Fong*[5*], *Rachel J. Cook, MD*[6], *Meagan Jacoby*[7*], *Daniel Nowak*[8*], *Brenda Chyla*[9], *Ying Zhou*[9*], *Grace Ku*[10*], *Jalaja Potluri*[9] *and Guillermo Garcia-Manero, MD*[11]

Patients with treatment-naive MDS with IPSS ≥1.5 (amended to include IPSS-revised int, high, very high, and planning to undergo ASCT); BM blasts <20%; ECOG PS 0-2
(n = 78)

Randomization Phase (28 Days Venetoclax)

- Azacitidine* + Venetoclax 400 mg D1-28 (n = 5)
- Azacitidine* + Venetoclax 800 mg D1-28 (n = 5)
- Azacitidine* (n = 2)

Dose-Escalation Phase (14 Days Venetoclax)

- Azacitidine* + Venetoclax 100 mg D1-14 (n = 8)
- Azacitidine* + Venetoclax 200 mg D1-14 (n = 59)
- Azacitidine* + Venetoclax 400 mg D1-14 (n = 8)

- No DLTs in cycle 1
- 2 deaths in cycle 2
- Protocol amended to assess 14-d venetoclax

Cohort 3: Safety Expansion After Preliminary Safety and Efficacy Analysis

Safety Expansion 1 (14 Days Venetoclax)
Azacitidine* + Venetoclax 400 mg D1-14 (n = 22)

Safety Expansion 2 (14 Days Venetoclax)
Azacitidine* + Venetoclax 400 mg D1-14 (n = 21)

Primary endpoints
- Safety, establish RP2D

Secondary endpoints
- ORR, OS

Study Design for M15-531

Phase 1b Study of Venetoclax Plus Azacitidine in Patients With Treatment-Naive Higher-Risk Myelodysplastic Syndromes[1]

Patients (N=107)

- Adult patients with de novo treatment-naive HR MDS defined by IPSS/IPSS-R risk categories (IPSS score ≥1.5 or IPSS-R score >3)
- BM blasts <20% at baseline
- ECOG PS ≤2
- No prior therapy for MDS or with a BH3 mimetic
- No prior SCT or solid organ transplantation
- No history of an active malignancy within the past 2 years prior to study entry[a]

Primary End Point

- CR per IWG 2006

Venetoclax 400 mg orally daily on Days 1–14 of each 28-day cycle[b]
+
Azacitidine 75 mg/m^2 IV or SC on Days 1–7 or Days 1-5, 8, 9

Treatment until progression

Key Secondary End Points

- mCR, ORR, DOR, DoCR: per IWG 2006
- TTNT, overall survival
- Safety
- Hematologic improvement
- Postbaseline RBC and platelet TI
- Rate, time to AML transformation

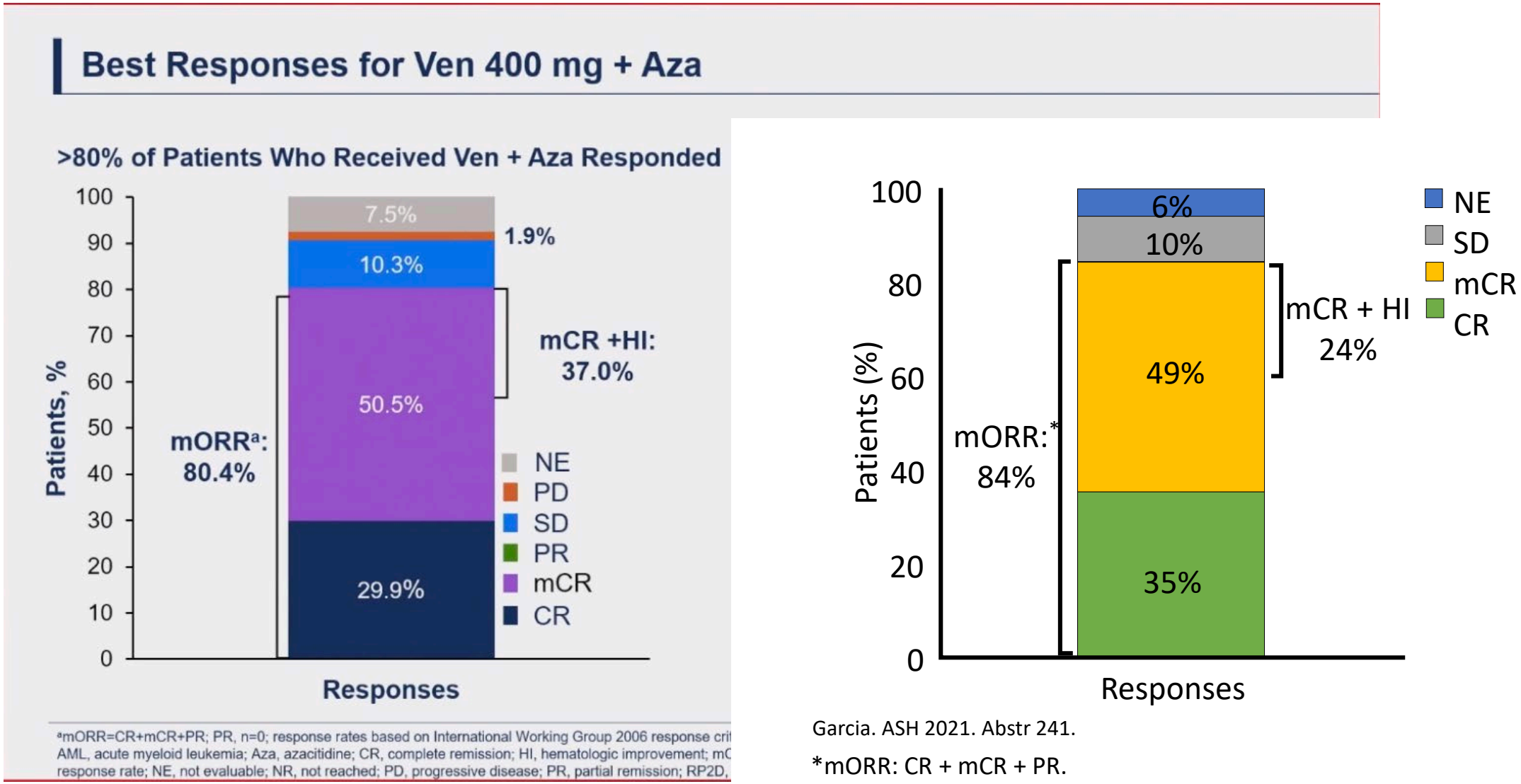
Population

- 107 patients
- Median age 68
- >75% high or very high risk

Table 1. (A) Baseline Characteristics and (B) Efficacy

(A) Baseline Characteristics	N=107
Median age (range), years	68 (26–87)
Male sex, n (%)	74 (69.2)
ECOG PS, n (%)[a]	
0	56 (52.8)
1	43 (40.6)
2	7 (6.6)
Baseline BM blast category, n (%)	
<5%	11 (10.3)
5–10%	32 (29.9)
>10%	64 (59.8)
Median baseline BM blast count, median % (SD)	11.0 (1.0–19.5)
IPSS-R prognostic score, n (%)	
Low	1 (0.9)
Intermediate	14 (13.1)
High	40 (37.4)
Very high	52 (48.6)
Baseline mutations, n/N (%)	
ASXL1	29/84 (34.5)
TP53	20/84 (23.8)

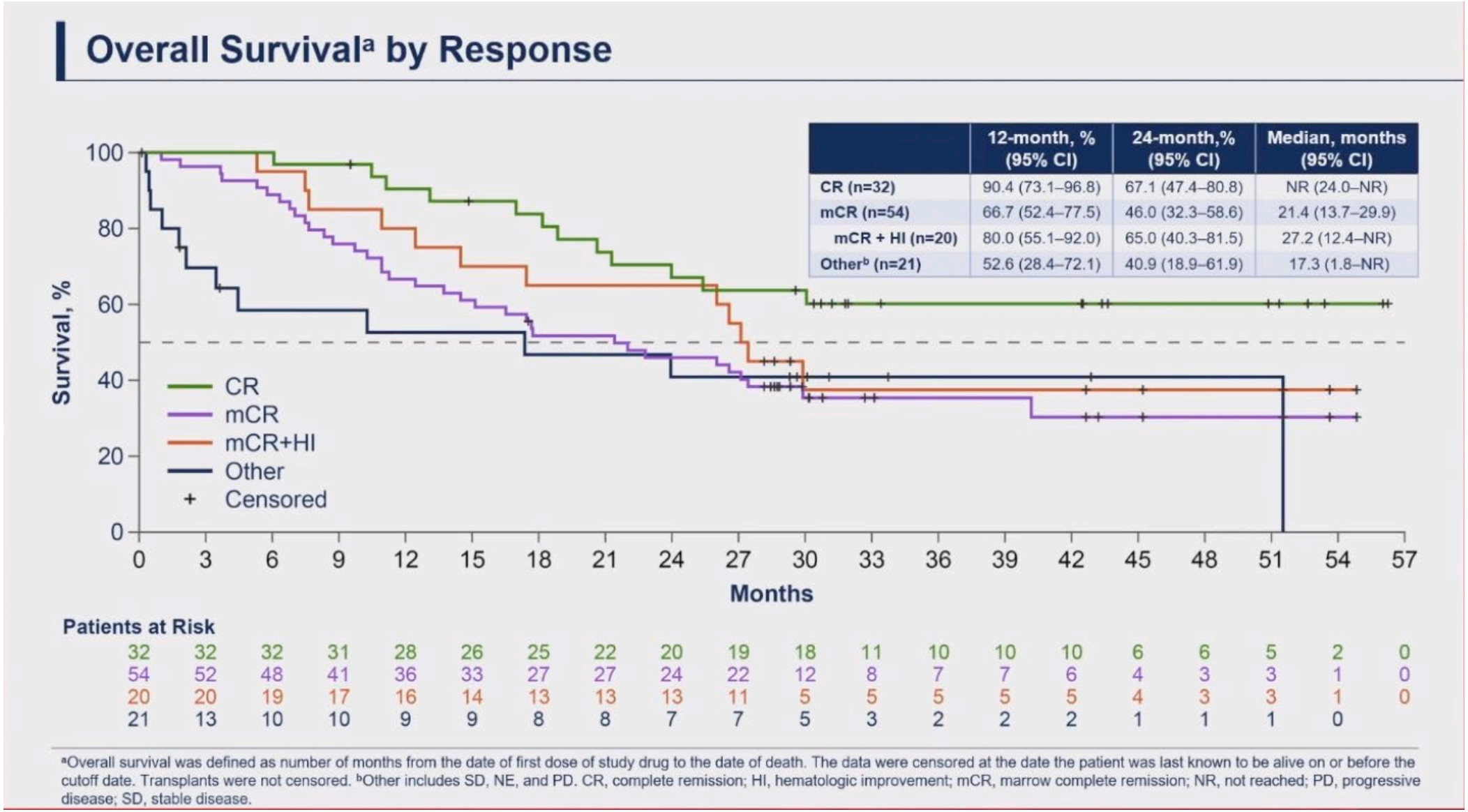
Response rates



Garcia. ASH 2021. Abstr 241.

*mORR: CR + mCR + PR.

Survival based on response



[a]Overall survival was defined as number of months from the date of first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date. Transplants were not censored. [b]Other includes SD, NE, and PD. CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; NR, not reached; PD, progressive disease; SD, stable disease.

Conclusions

- Still promising results
- Testing aza+ven vs aza+placebo in Phase 3 trial

VERONA: Venetoclax + Azacitidine in Treatment-Naive Patients With Higher-Risk MDS

- Randomized phase III trial

Patients with newly diagnosed MDS, IPSS-R >3 (intermediate, higher, very high risk); HSCT eligible; no previous HMA or venetoclax therapy; ECOG PS ≤2 (planned N = 500)

Stratified by IPSS-R, HSCT eligible vs ineligible, geography

Venetoclax 400 mg QD (Days 1-14) +
+ Azacitidine 75 mg/m^2
(7 days within 9 calendar days/28-day cycle)

Placebo + Azacitidine 75 mg/m^2
(7 days within 9 calendar days/28-day cycle)

Until relapse, disease progression, unacceptable toxicity, or HSCT

- Primary endpoints: CR, OS
- Secondary endpoints: transfusion independence, ORR, modified ORR, QoL, PRO
- **STILL WAITING FOR RESULTS**

Zeidan. ASCO 2021. Abstr TPS7054. NCT04401748.

Aza + ven in HR-MDS summary

- Good activity and higher response rates
  - Similar to AML
- Toxicity and neutropenia still an issue
  - Similar to AML
  - **Only use 14 days VEN**
- Unclear how durable these responses are… Wait for phase III results
- I use in younger patients with high/very high risk MDS that I am trying to get to transplant (faster CR)
- MDS/AML overlap classification (10-20%) blasts can make this easier to acquire venetoclax

321 Venetoclax (VEN) Improves Response Rates but Not Survival in Patients with Chronic Myelomonocytic Leukemia (CMML) Treated with Hypomethylating Agents (HMA): A Multicenter, Propensity Score Analysis

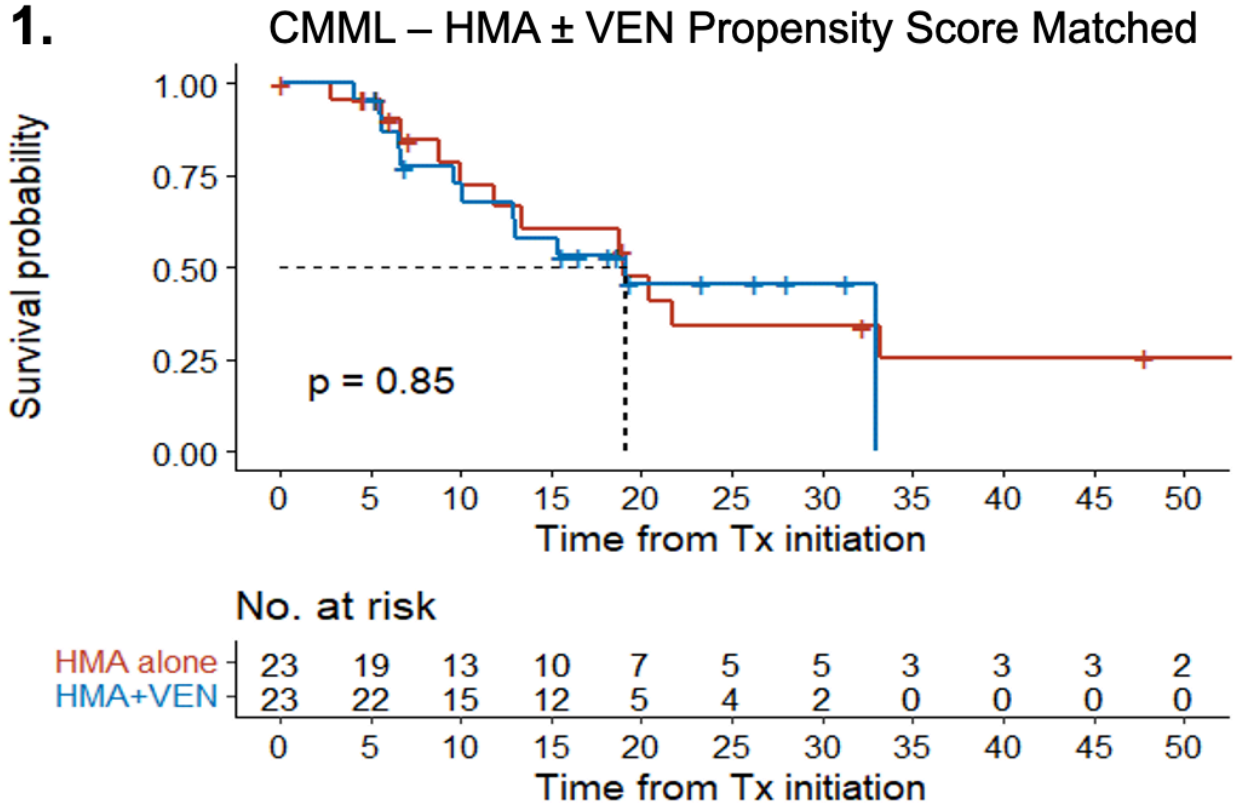
Douglas Tremblay, MD[1], *Clifford M Csizmar, MD, PhD*[2], *Courtney D. DiNardo, MD, MSc*[3], *Somedeb Ball, MD*[4], *Noa Rippel, MD*[1], *Danielle E. Hammond, MD*[3], *Tapan M. Kadia, MD*[3], *Farhad Ravandi, MD, MBBS*[3], *Kelly S. Chien, MD*[3], *Grace Van Hyfte*[5*], *Antoine Saliba, MD*[6], *Abhishek A Mangaonkar, MBBS*[6], *Terra L. Lasho, PhD*[2], *Aref Al-Kali, MD*[6], *Marina Kremyanskaya, MD, PhD*[1], *Jonathan Feld, MD*[1], *Lewis R Silverman, MD*[1], *Rami S. Komrokji, MD*[7], *John Mascarenhas, MD*[1*], *Eric Padron, MD*[7], *Guillermo Garcia-Manero, MD*[8], *David A Sallman, MD*[9], *Mrinal M. Patnaik, MD, MBBS*[2] *and Guillermo Montalban-Bravo, MD*[3]

- retrospective study using propensity-matched scores

- 89 CMML patients

- ORR significantly higher with HMA+VEN (95%) compared to HMA alone (46%), p < 0.001

- no significant OS difference (19.1 mos vs 19.1 mos, p = 0.85)



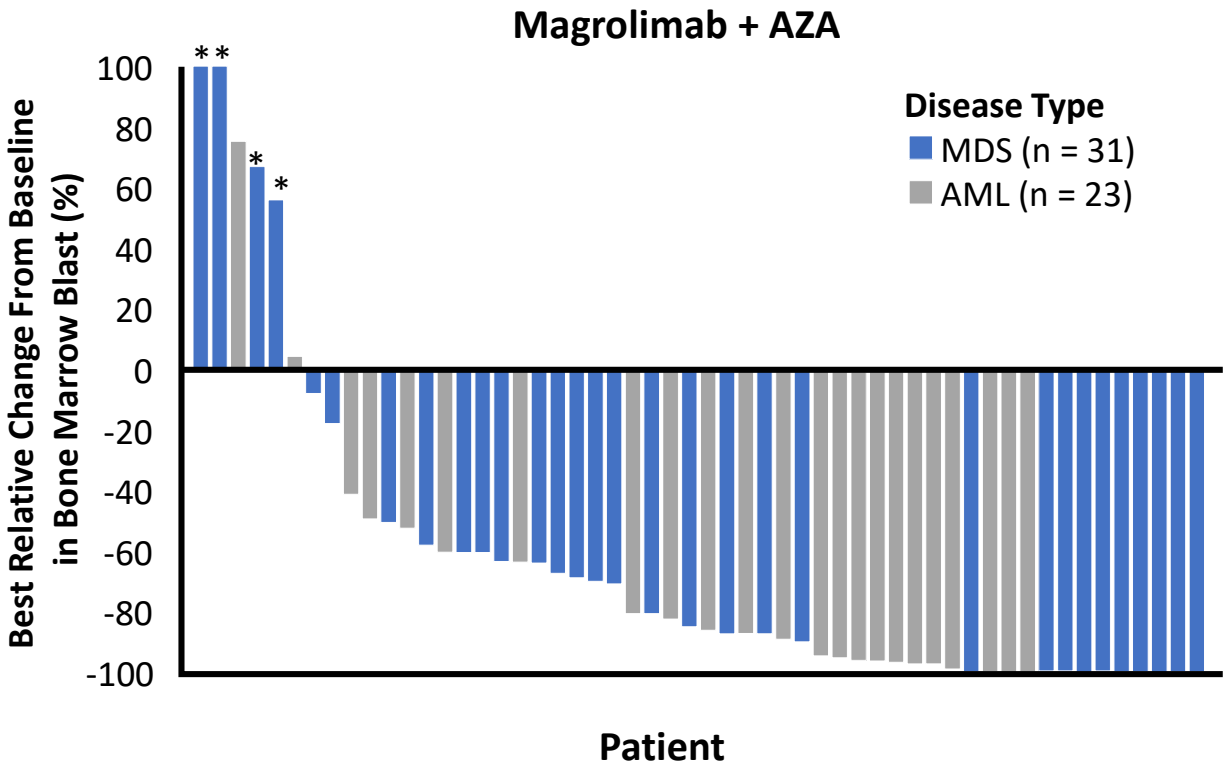
Whatever happened to CD47 antibodies…

Activity of Magrolimab + AZA in MDS and AML

Best Overall Response*	1L MDS N = 33	1L AML N = 25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	-	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	-
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

*Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with ≥1 post-treatment response assessment are shown. Patients not evaluable: 2 MDS patients (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal).

- Magrolimab + AZA ORR
  - MDS: 91% ORR (50% CR)
  - AML: 64% ORR (56% CR/CRi)
- Median time to response: 1.9 mo, more rapid than AZA alone
- Magrolimab + AZA response higher than AZA monotherapy



4 patients not shown due to missing values.
<5% blasts imputed as 2.5%.
*Baseline bone marrow blasts ≤5%.

Sallman. ASCO 2020. Abstr 7507.

ENHANCE: Magrolimab + Azacitidine vs Placebo + Azacitidine in Treatment Naive Higher-risk MDS

- Randomized, double-blind, phase III trial

Patients with untreated intermediate to very high risk MDS by IPSS-R, adequate PS
(Planned N = 520)

Magrolimab* +
+ Azacitidine 75 mg/m^2 days 1-7

Placebo +
Azacitidine 75 mg/m^2 days 1-7

Until disease progression, loss of benefit, unacceptable toxicity, or 5 yr

*Cycle 1: 1mg/kg priming dose on D1, D4; 15 mg/kg on D8; 30 mg/kg on D11, 15, 22.
Cycle 2: 30 mg/kg once weekly (D1, 8, 15, 22). Cycle ≥3: 30 mg/kg Q2W on D1, D15.

- Primary endpoints: CR, OS
- Secondary endpoints: Duration of CR, ORR, DoR, RBC TI, PFS, EFS, MRD negative RR, time to transformation to AML, safety, PK

Phase 3 trial ended early

- Interim analysis determined futility July 2023
- Patients on magrolimab arm did worse
- Enhance-2 comparing aza+magro vs aza+ven discontinued Sept 2023
- Enhance-3 with aza+ven + magro/placebo ongoing

320 Preliminary Results of a Phase 2 Study of IMM01 Combined with Azacitidine (AZA) As the First-Line Treatment in Adult Patients with Higher Risk Myelodysplastic Syndromes (MDS)

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No priming dose needed

No grade ≥3 hemolysis

INTRODUCTION

- CD47 is an innate immune checkpoint that binds signal regulatory protein alpha (SIRPα) , and serves as a mechanism of immune surveillance evasion and suppress macrophage phagocytosis[1,2]. (Fig.1)

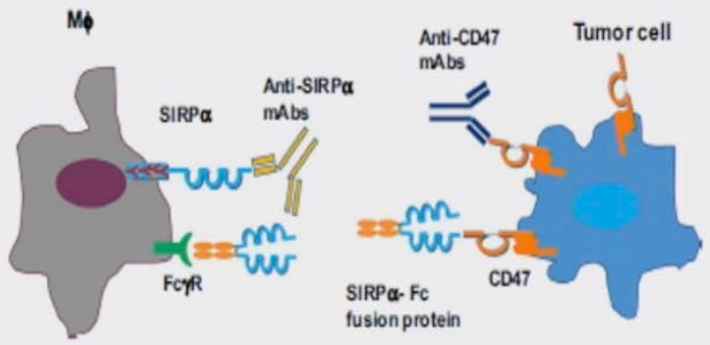


Fig.1 The mechanism of CD47-SIRP α

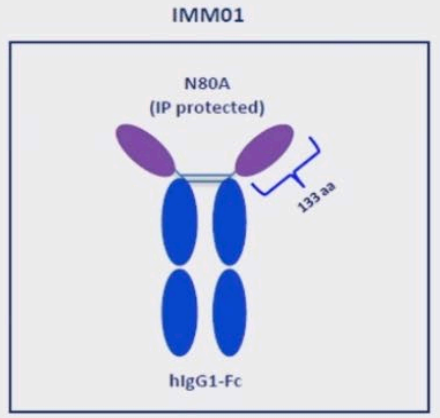


Fig.2 The Structure of IMM01（Timdarpacept）

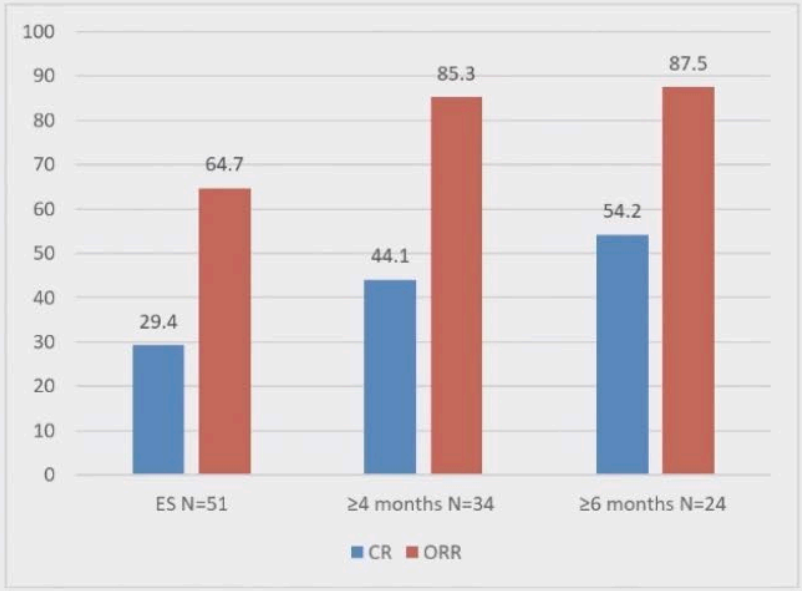
1. Jaiswal S, et al. Cell 2009;138:271–85.
2. Majeti R, et al. Cell 2009;138:286–99.
3. Jifeng Yu, et al. J Hematol Oncol . 2022;15:167.

Response rates

- Response rates reasonable
- Seem to increase with time?
- Need more data
- Unclear how well this approach will work

Table 2. Best Overall Response

Best response rate, n (%)	ES N=51	≥4 months N=34	≥6 months N=24
CR	15 (29.4)	15 (44.1)	13 (54.2)
PR	0	0	0
mCR+HI	7 (13.7)	6 (17.6)	4 (16.7)
mCR	8 (15.7)	5 (14.7)	3 (12.5)
HI	3 (5.9)	3 (8.8)	1 (4.2)
SD	12 (23.5)	5 (14.7)	3 (12.5)
NE(SD*)	4 (7.9)	0	0
PD	2 (3.9)	0	0
ORR (CR+PR+mCR+HI)	33 (64.7)	29 (85.3)	21 (87.5)
DCR (CR+PR+mCR+HI+SD)	45(88.2)	34 (100)	24 (100)



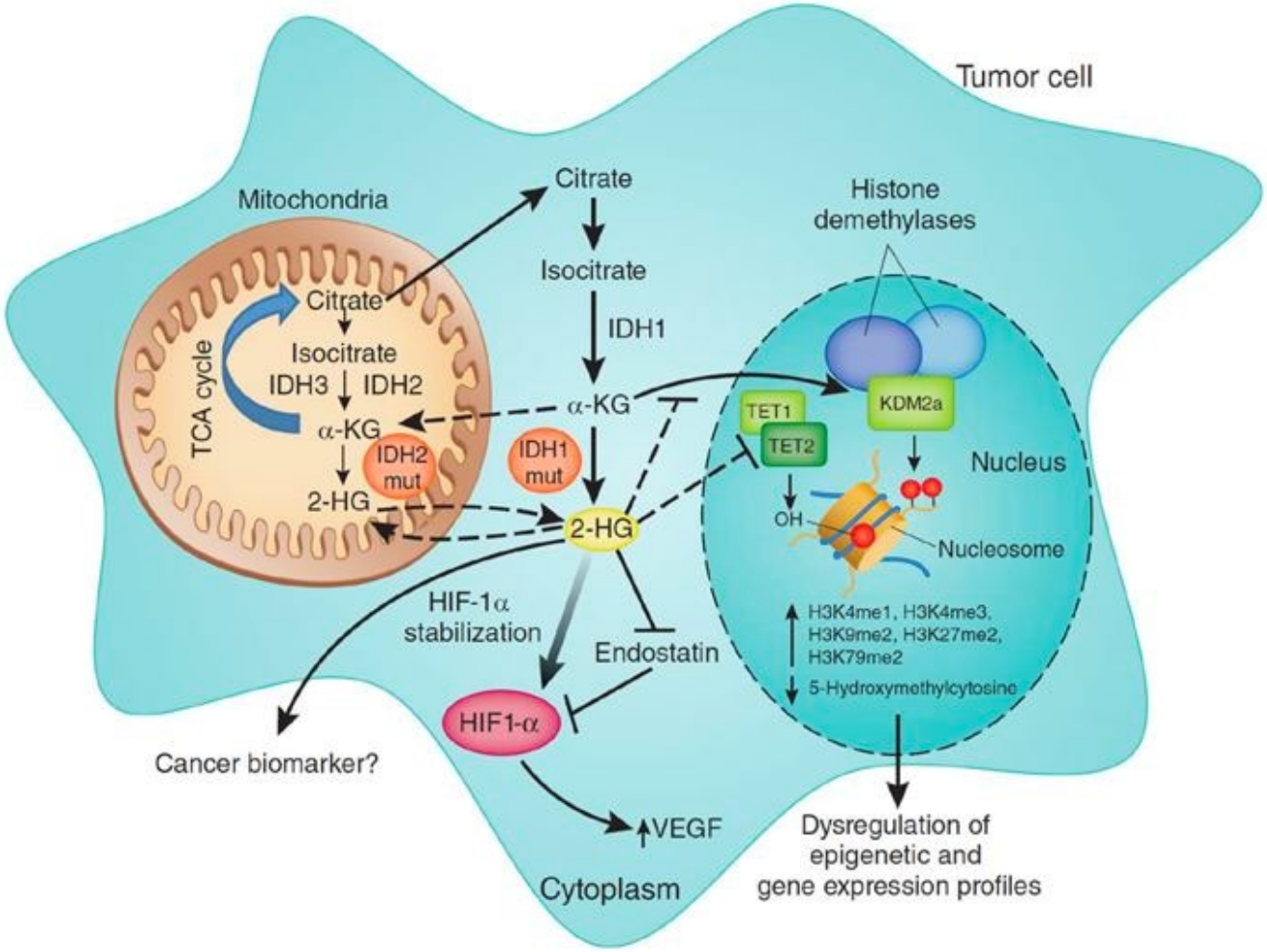
CR: complete response; PR: partial remission; mCR: marrow complete response; HI: Hematologic improvement; SD: stable disease; SD*:The SD not met for >8 weeks; PD: progressive disease; NE: not evaluable; ORR: overall response rate; DCR:disease control rate; ES (Evaluable analysis set): Defined as subjects with at least one post-baseline tumor assessment.

American Society of Hematology

Targeted therapies

IDH1/2 inhibitors in myeloid malignancies

- IDH mutations cause production of 2-HG instead of α-KG
- 2-HG inhibits TET2 and methylation of DNA
- This blocks normal maturation of white blood cells
- Drugs developed to block the mutated IDH1 or IDH2 proteins



Prensner JR and Chinnaiyan AM
Nature Medicine 2011

Ivosidenib approved for R/R MDS

- Approved October 2023
- 18 adult patients with relapsed or refractory MDS harboring an *IDH1* mutation
- CR rate was 38.9% (95% CI, 17.3%-64.3
- median time to CR 1.9 months (range, 1.0-5.6)
- median duration of CR not reached

1872 Olutasidenib Alone or in Combination with Azacitidine Induces Durable Complete Remissions in Patients with *mIDH1* Myelodysplastic Syndromes/Neoplasms (MDS)

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- 22 MDS patients evaluated
- Good activity as single agent and with aza
- Similar results to ivosidenib

Table 2: Response to Olutasidenib Monotherapy and Combination Therapy

Parameter	Monotherapy[c] (N=6)	Combination Therapy (N=16)	Pooled (N=22)
Best response, n (%)			
ORR[a]	2 (33)	11 (69)	13 (59)
CR	1 (17)	5 (31)	6 (27)
Marrow CR	1 (17)	6 (38)	7 (32)
Partial remission (PR)	0	0	0
Stable disease (SD)	1 (17)	3 (19)	4 (18)
Clinical Benefit (CB)	1 (17)	0	1 (5)
Disease Progression (PD)	1 (17)	0	1 (5)
Not Evaluated[b]	1 (17)	2 (13)	3 (14)
Overall Response (CR, marrow CR)			
Time to first response in months, median (range)	4.7 (1.0, 8.3)	2.0 (1.0, 13.0)	2.0 (1.0, 13.0)
Duration of response in months, median (range)	NR (6.7, NR at 29.7+)	NR (0, NR at 30.1+)	NR (0, NR at 30.1+)

[a] ORR, overall response (CR, marrow CR, and PR); NR, not reached

[b] 3 patients were not evaluated due to short duration of treatment (1-2.5 months).

[c] 3 patients received monotherapy at full dose; 1 had a CR, 1 had a marrow CR, and 1 was not evaluated. The other 3 patients received a lower than approved dose; 1 had SD, 1 had CB, and 1 had PD.

Trials for MDS at OHSU

Study	Target/Regimen
Syros MDS: 23643	**untreated MDS IPSS-R>3, RARA+;** aza+tamibarotene/placebo. Tamibarotene (SY-1425) is a selective agonist of retinoic acid receptor alpha (RARα)
OSU tMDS: 24341	**untreated tMDS, IPSS-R>3.5;** aza+ven. Venetoclax is a selective inhibitor of BCL-2
MDACC: 26278	**HR MDS, MDS/MPN, MPN, IDH1-R132 (2HG);** aza + ven + ivosidenib; Ivosidenib (AG120) is an IDH1 inhibitor
ABNL-MARRO: 25941	**CMML, aCML, MDS/MPN-RS-T, MDS/MPN-U, de novo and R/R**; itacitinib+ DNMTi. Itacitinib is a JAK1 inhibitor
Schrödinger: 26088	**R/R MDS & AML;** SGR-2921 monotherapy; SGR-2921 is a cycle 7-related protein kinase inhibitor (CDC7)

Thank you!

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