How do I manage Myelodysplastic Syndromes/Neoplasms in 2023 (with selected ASH 2022 updates) ?

Amer Zeidan, MBBS, MHS

Associate Professor of Medicine
Leader, Myeloid diseases and Leukemia Disease Aligned Research Team
Director, Hematology Early Therapeutics Research
Department of Internal Medicine
Section of Hematology
Yale University School of Medicine
Yale Cancer Center

Amer.Zeidan@yale.edu
Dr_AmerZeidan

Disclosures

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

Outline

- Updates in MDS classification
- Updates in MDS prognostication
- Updates in clinical management of lower risk MDS
- Updates in clinical management of higher risk MDS

MDS Minimal Diagnostic Criteria

Prerequisite criteria: *both 1 and 2 must be fulfilled*

1. Persistent cytopenia(s)

- Hb <12 (women) or 13 (men) g/dL, *or*
- ANC <1800/µL, *or*
- Platelets <150 x 10^9/L

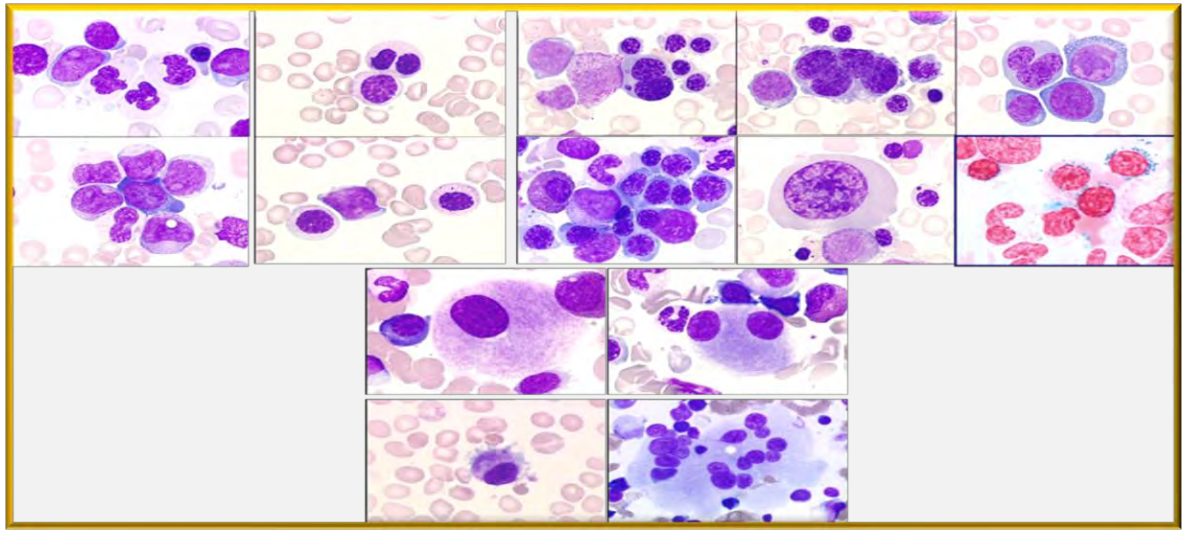
2. EXCLUDE other causes of cytopenias and morphological changes:

- Vitamin B12/folate/copper deficiency
- HIV or other infections
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (RA, SLE, etc.)
- Hereditary BMF syndromes (Fanconi anemia, etc)
- Other hematological disorders (aplastic anemia, LGL MPN, etc)

MDS major criteria

i. Dysplasia of ≥10% of cells in 1 or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in RS of ≥15% (or ≥5% in the presence of a *SF3B1* mutation)
ii. An increase in myeloblasts of 5%-19% in dysplastic BM smears or 2%-19% myeloblasts in peripheral blood smears
iii. An MDS-related (5q-, -7, complex…) karyotype

At least 1 of these major MDS criteria has to be met (together with prerequisite criteria) to diagnose MDS



Valent. Oncotarget. 2017;8:73483. NCCN Guidelines in Oncology: Myelodysplastic Syndromes. V3.2022.

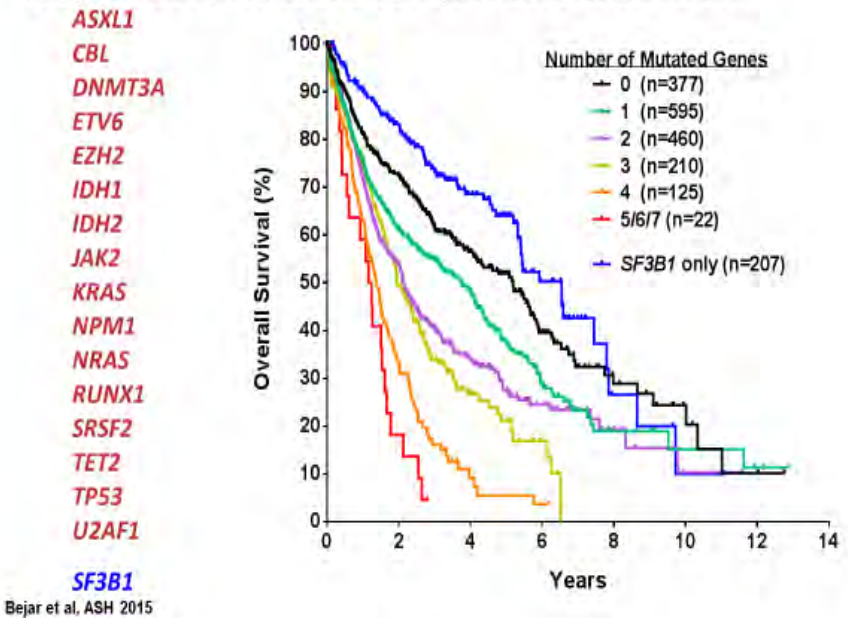
Oncogenic Gene Mutations in MDS

Mutations with potential prognostic and therapeutic significance in MDS

Gene	Frequency	Prognosis	Features	Therapeutic consideration
SF3B1	20-30%	Good	Ring sideroblasts	Luspatercept
ASXL1	10-20%	Poor	Association with U2AF1	Lower response to HMA
TET2	20-25%	Unknown	Monocytic differentiation	Higher response to HMA
DNMT3A	8%	Poor	Association with *IDH2*	Lower response to HMA (R882) and poor outcomes after HCT
IDH1/2	5-8%	Poor	Differentiation block	Ivosidenib/Enasidenib
TP53	7-10%	Poor	Genomic instability and high-risk features	APR-246 Magrolimab
RUNX1, SETBP1	4-9%	Poor	Chr. 7 abnormalities	Poor outcomes after HSCT
RAS pathway genes	5-10%	Poor	Chr. 7 abnormalities	Rigosertib
DDX41	1-3%	Unknown	Familiar predisposition	HMA, Chemotherapy, HSCT (unrelated donors)
UBA1	Unknown, rare	Poor	Autoimmunity, BM vacuoles, thrombosis	Ruxolitinib, HMA, HSCT

Overall Survival by Mutation Number

17 genes sequenced in 1996 patients with OS data

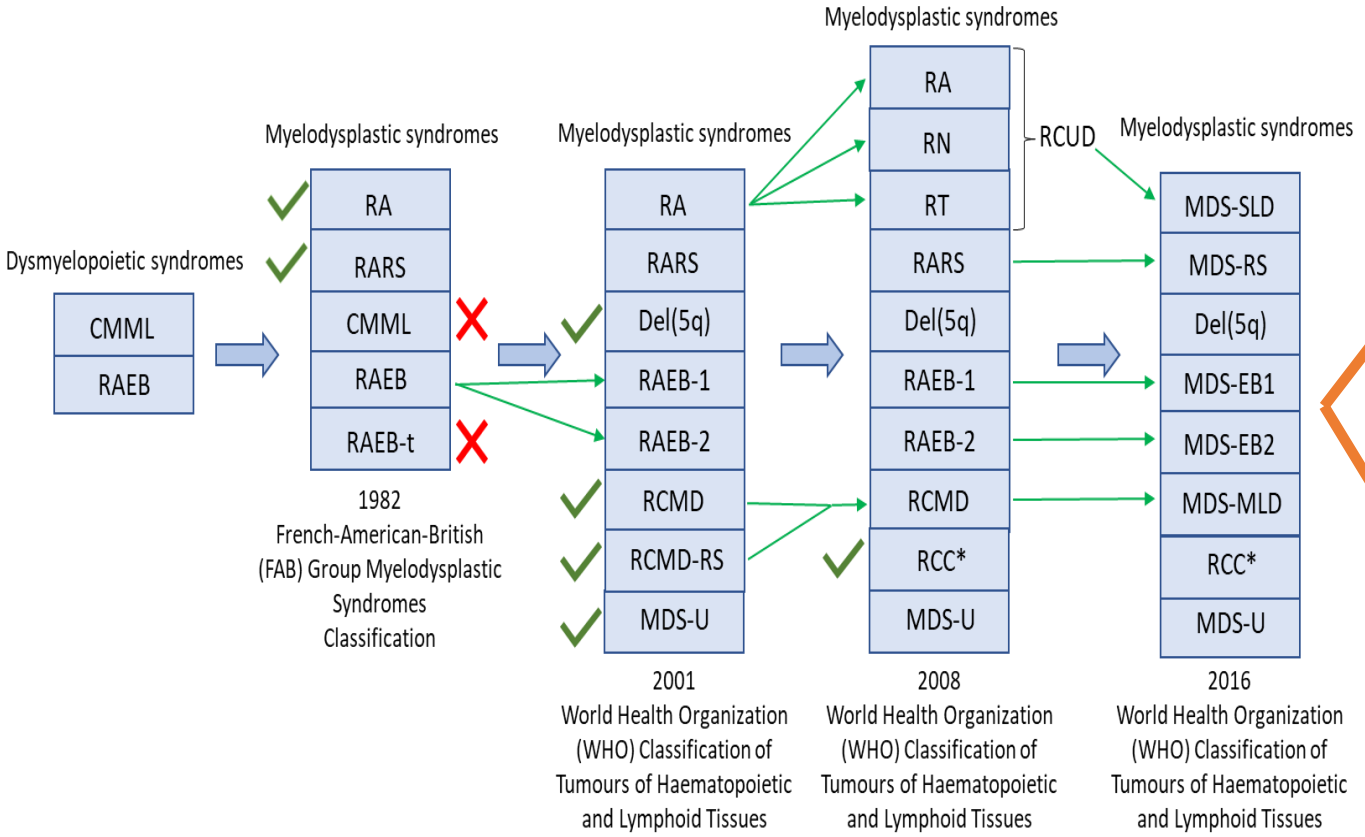


Bejar et al, ASH 2015

- >85-90% of pts have ≥ 1 mutation
- More than 45 mutations, none specific to MDS
- Only 5-6 mutations seen >10% cases
- Average number of mutations per patient is 3-4

Chokr,,,,and Zeidan A. Expert Review of Hematology. 2019
Papaemmanueil et al blood 2013; Bejar et al, ASH 2015

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, Eric Solary, Oussama Abla, Yassmine Akkari, Rita Alaggio, Jane F. Apperley, Rafael Bejar, Emilio Berti, Lambert Busque, John K. C. Chan, Weina Chen, Xueyan Chen, Wee-Joo Chng, John K. Choi, Isabel Colmenero, Sarah E. Coupland, Nicholas C. P. Cross, Daphne De Jong, M. Tarek Elghetany, Emiko Takahashi, Jean-Francois Emile, Judith Ferry, Linda Fogelstrand, Michaela Fontenay, Ulrich Germing, Sumeet Gujral, Torsten Haferlach, Claire Harrison, Jennelle C. Hodge, Shimin Hu, Joop H. Jansen, Rashmi Kanagal-Shamanna, Hagop M. Kantarjian, Christian P. Kratz, Xiao-Qiu Li, Megan S. Lim, Keith Loeb, Sanam Loghavi, Andrea Marcogliese, Soheil Meshinchi, Phillip Michaels, Kikkeri N. Naresh, Yasodha Natkunam, Reza Nejati, German Ott, Eric Padron, Keyur P. Patel, Nikhil Patkar, Jennifer Picarsic, Uwe Platzbecker, Irene Roberts, Anna Schuh, William Sewell, Reiner Siebert, Prashant Tembhare, Jeffrey Tyner, Srdan Verstovsek, Wei Wang, Brent Wood, Wenbin Xiao, Cecilia Yeung and Andreas Hochhaus

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

Zeidan A et al, Blood Reviews, 2019; Khoury J et al, Leukemia; Arber D et al, Blood 2022

WHO vs ICC 2022 classifications of MDS

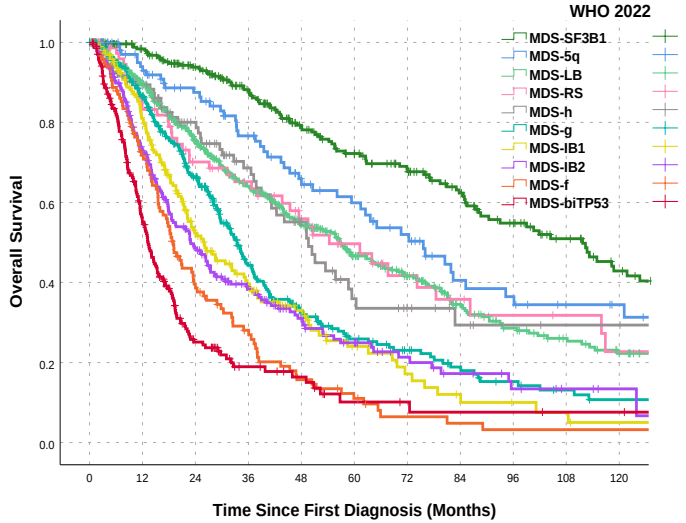
		WHO 2016	WHO 2022	ICC
Nomenclature		Myelodysplastic syndrome	Myelodysplastic neoplasms	Myelodysplastic syndrome
Lineage		MDS with single lineage dysplasia (MDS-SLD)	Dysplastic lineages are removed MDS with low blasts (MDS-LB) <5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
		MDS with multi-lineage dysplasia (MDS-MLD)		MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
Genetic defined:	*SF3B1*	MDS with ring sideroblasts • Single lineage dysplasia (MDS-RS-SLD) • Multi-lineage dysplasia (MDS-RS-MLD)	• MDS-*SF3B1:* MDS with low blasts and *SF3B1*^{MT}; • or MDS with RS (if *SF3B1* wild-type)	• MDS-*SF3B1* • Or MDS, NOS (with RS but *SF3B1* wild type)
	5q	MDS with isolated del(5q)	MDS-5q: MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q): Must be isolated or with other CG aberration except -7/del(7)
	TP53 mutation	Not included	MDS-bi*TP53:* MDS with biallelic *TP53* inactivation (supersedes MDS-5q and MDS-*SF3B1*)	Myeloid neoplasms with mutated *TP53* (including MDS, MDS/AML, AML) For MDS, it must be multi-hit *TP53* mutation

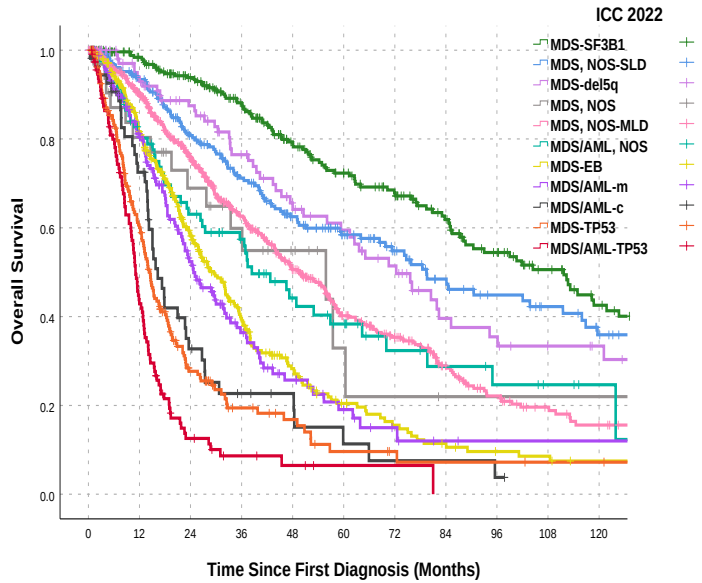
		WHO 2016	WHO 2022	ICC
Nomenclature		Myelodysplastic syndrome	Myelodysplastic neoplasms	Myelodysplastic syndrome
Blasts	5-9%	MDS excess blasts-1 (MDS-EB1; 5-9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1): 5-9% BM and/or 2-4% PB blasts	MDS excess blasts (5-9% BM and/or 2-9% PB blasts)
	10-19%	MDS excess blasts-2 (MDS-EB2; 10-19% BM or PB blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2): 10-19% BM or 5-19% PB blasts or Auer rods)	MDS/AML (10-19% BM or PB blasts)
Added subgroup	In ICC	Not included	Not included	MDS, NOS (cytopenia, but lack of dysplasia (e.g., monosomy 7/del(7q) or complex karyotype); in another word, -7/del(7q), complex karyotype are MDS defining
	In WHO	Not included	MDS, hypoplastic (MDS-h)	Not included
		Not included	MDS with fibrosis (MDS-f)	Not included
Deleted subgroup:		MDS unclassifiable	Not included	Not included
CH/CHIP/CCUS		Not included	Clonal hematopoiesis (CHIP, CCUS)	CCUS and other pre-malignant clonal cytopenias, e.g., CMUS
AML		AML-defining genetics	AML-defining genetics independent of BM and PB blast	AML-defining genetics with ≥10% BM and PB blasts
		AML (≥20% BM and PB blasts)	AML (≥20% BM and PB blasts)	AML (≥20% BM and PB blasts)

Modified from Khoury J et al, Leukemia; Arber D et al, Blood 2022

Validation and comparison of 2022 WHO and ICC Classifications in MDS
An Analysis on Behalf of the International Consortium for MDS (icMDS)

- WHO and ICC classifications validated but have room for improvement
- Molecularly defined entities (*SF3B1*, 5q-, & "multi-hit" *TP53*) are unique
- "Multi-hit *TP53* state" remained independent predictor of survival
- Survival of MDS-RS (*SF3B1*-WT) is similar to MDS-LB
- MDS-MLD had worse outcomes than MDS-SLD
- Blast ≥5% correlated better with OS than ≥10%
- Grade 2/3 fibrosis was associated with worse OS in MDS-IB group
- Future validation in multicenter datasets within icMDS is planned





What is lower vs higher risk MDS?

IPSS

Metric		Score
Blasts		
	<5%	0
	5-10%	0.5
	11-20%	1.5
	21-30%	2
Cytogenetics±		
	Good	0
	Intermediate	0.5
	Poor	2
Cytopenias	Hgb <10 g/dL, PLT <100/µL, ANC <1.5/µL	
	0-1	0
	2-3	0.5
Risk Group		
	Low	0
	INT-1	0.5-1
	INT-2	1.5-2
	High	≥2.5

IPSS-R

Metric		Score
Blasts		
	≤2%	0
	>2-<5%	0.5
	5-10%	1.5
	>10%	2
Cytogenetics¥		
	Very good	0
	Good	0.5
	Intermediate	2
	Poor	3
	Very poor	4
Cytopenias		
	Hgb 8-<10 g/dL	1
	Hgb <8 g/dL	1.5
	ANC <0.8/µL	0.5
	PLT 50-100/µL	0.5
	PLT <50/µL	1
Risk Group		
	Very low	≤1.5
	Low	1.5-3
	Intermediate	3.5-4.5
	High	5-6
	Very high	>6

WPSS

Metric		Score
WHO classification		
	RA, RARS, del(5q)	0
	RCMD, RCUD-RS	1
	RAEB-1	2
	RAEB-2	3
Cytogenetics±		
	Good	0
	Intermediate	1
	Poor	2
Transfusion requirement		
	Yes	1
Risk Group		
	Very low	0
	Low	1
	Intermediate	2
	High	3-4
	Very high	5-6

MDAPSS

Metric		Score
Blasts		
	5-10%	1
	11-29%	2
Cytogenetics		
	Chromosome 7 abnormality	3
	Complex karyotype¶	3
Cytopenias		
	PLT <30/µL	3
	PLT 30-49/µL	2
	PLT 50-199/µL	1
	WBC >20/µL	2
	Hgb <12 g/dL	2
Prior transfusion		
	Yes	1
Age (years)		
	≥65	2
	60-64	1
Risk Group		
	Low	0-4
	INT-1	5-6
	INT-2	7-8
	High	>9

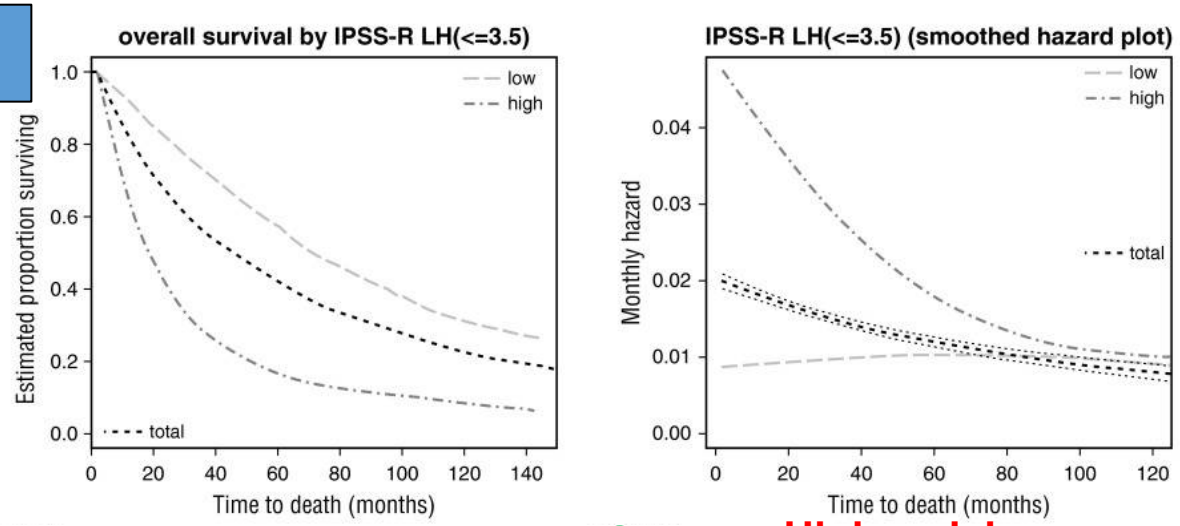
- **Only WPSS was designed as a time-dependent model.**
- **Prognostication for any individual is less certain.**
- **None incorporated relevant single gene mutations.**
- **None accounted for comorbidities.**
- **None intended to predict benefit from any particular therapy.**

IPSS: Greenberg P, et al. Blood,1997
IPSS-R:Greenberg P, et al. Blood,2012
WPSS: Malcovati L, et al. JCO, 2007
MDAPP: Kantarjian H, et al. Cancer, 2008

Zeidan et al. Current Hematologic Malignancy Reports 2013;
Zeidan, Shallis et al. Blood Reviews, 2019

Where does IPSS-R intermediate risk fall?

1

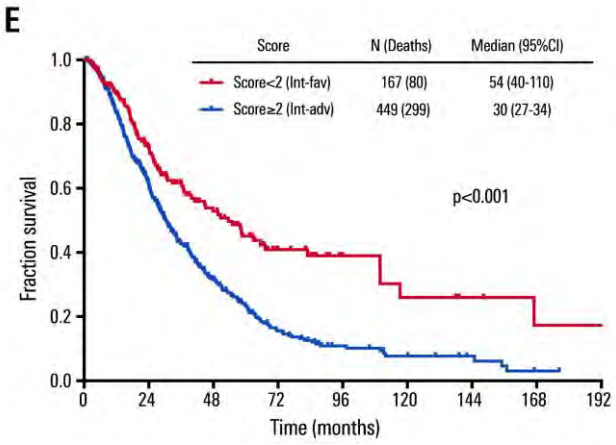


2

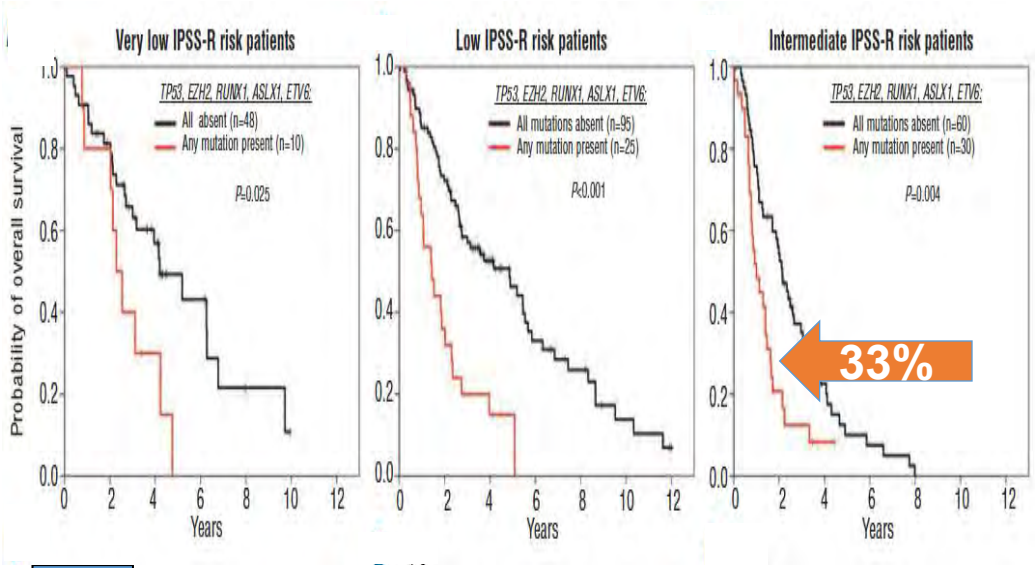
Lower-risk =<3.5 Higher-risk

Table 3. Prognostic score for patients with intermediate risk myelodysplas

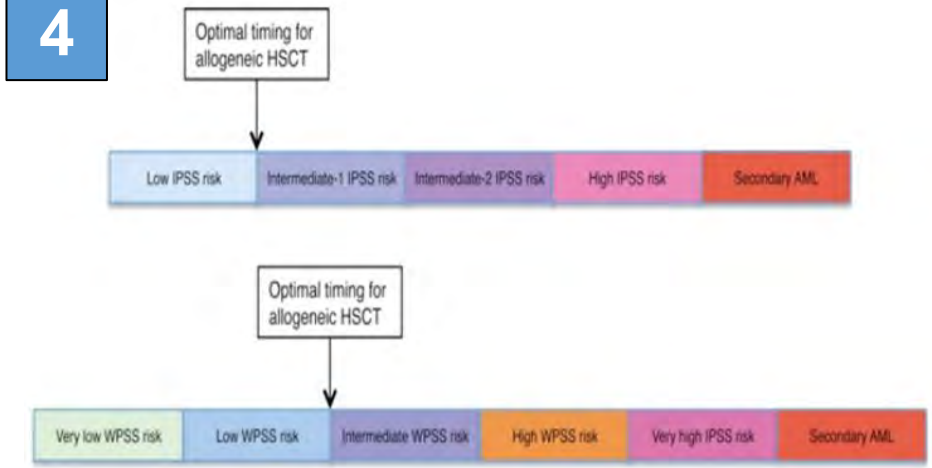
Variable	Coefficient	Score	No. Patients
* Age ≥ 66 years			
No		0	143
Yes	0.87	2	152
* Peripheral blood blasts ≥ 2%			
No		0	247
Yes	0.52	1	48
Red blood cell transfusion			
No		0	199
Yes	0.51	1	96



3



4

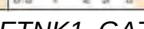


Pfeilstöcker M, et al. Blood, 2016; Benton et al, AJH, 2018, Bejar R, et al. Haematologica 2014, Della Porta Am J Hematol. 2013

The IPSS-M model

Model fit with a robust Cox multivariable regression adjusted for confounder variables

Category	Variable	Multivariable model: hazard ratio[#] (95% CI)	Weight w	Scaling x^{mean}
confounder	Age, in years	1.23 (1.05 - 1.43)	N/A	N/A
	Sex:Male	1.22 (1.06 - 1.41)	N/A	N/A
	Type:Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A	N/A
clinical	% Bone Marrow Blasts, in %	1.42 (1.30 - 1.55)	0.352	0.922
	min(Platelets,250), in x10⁹/L	0.80 (0.72 - 0.89)	-0.222	1.41
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171	9.87
cytogenetics	IPSS-R category vector[&]	1.33 (1.21 - 1.47)	0.287	1.390
gene main effects	*TP53*[multi]	3.27 (2.38 - 4.48)	1.18	0.0710
17 variables, 16 genes	*MLL*[PTD]	2.22 (1.49 - 3.32)	0.798	0.0247
	FLT3[ITD+TKD]	2.22 (1.11 - 4.45)	0.798	0.0108
	SF3B1[Sq]	1.66 (1.03 - 2.66)	0.504	0.0166
	NPM1	1.54 (0.78 - 3.02)	0.430	0.0112
	RUNX1	1.53 (1.23 - 1.89)	0.423	0.126
	NRAS	1.52 (1.05 - 2.20)	0.417	0.0362
	ETV6	1.48 (0.98 - 2.23)	0.391	0.0216
	IDH2	1.46 (1.05 - 2.02)	0.379	0.0429
	CBL	1.34 (0.99 - 1.82)	0.295	0.0473
	EZH2	1.31 (0.98 - 1.75)	0.270	0.0588
	U2AF1	1.28 (1.01 - 1.61)	0.247	0.0866
	SRSF2	1.27 (1.03 - 1.56)	0.239	0.158
	DNMT3A	1.25 (1.02 - 1.53)	0.221	0.161
	ASXL1	1.24 (1.02 - 1.51)	0.213	0.252
	KRAS	1.22 (0.84 - 1.77)	0.202	0.0271
	SF3B1[α]	0.92 (0.74 - 1.16)	-0.0794	0.186
gene residuals[§]	min(Nres,2)	1.26 (1.12 - 1.42)	0.231	0.388
1 variable, 15 genes	Possible values are 0,1 or 2			



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

Continuous clinical parameters
Marrow blasts, platelets, hemoglobin (**NO ANC**)

IPSS-R cytogenetic categories

17 genetic variables from 16 main effect genes
Individual weights attributed to each variable

1 genetic variable from 15 residual genes^
Number of mutated genes (0, 1 or 2)

The IPSS-M risk categories

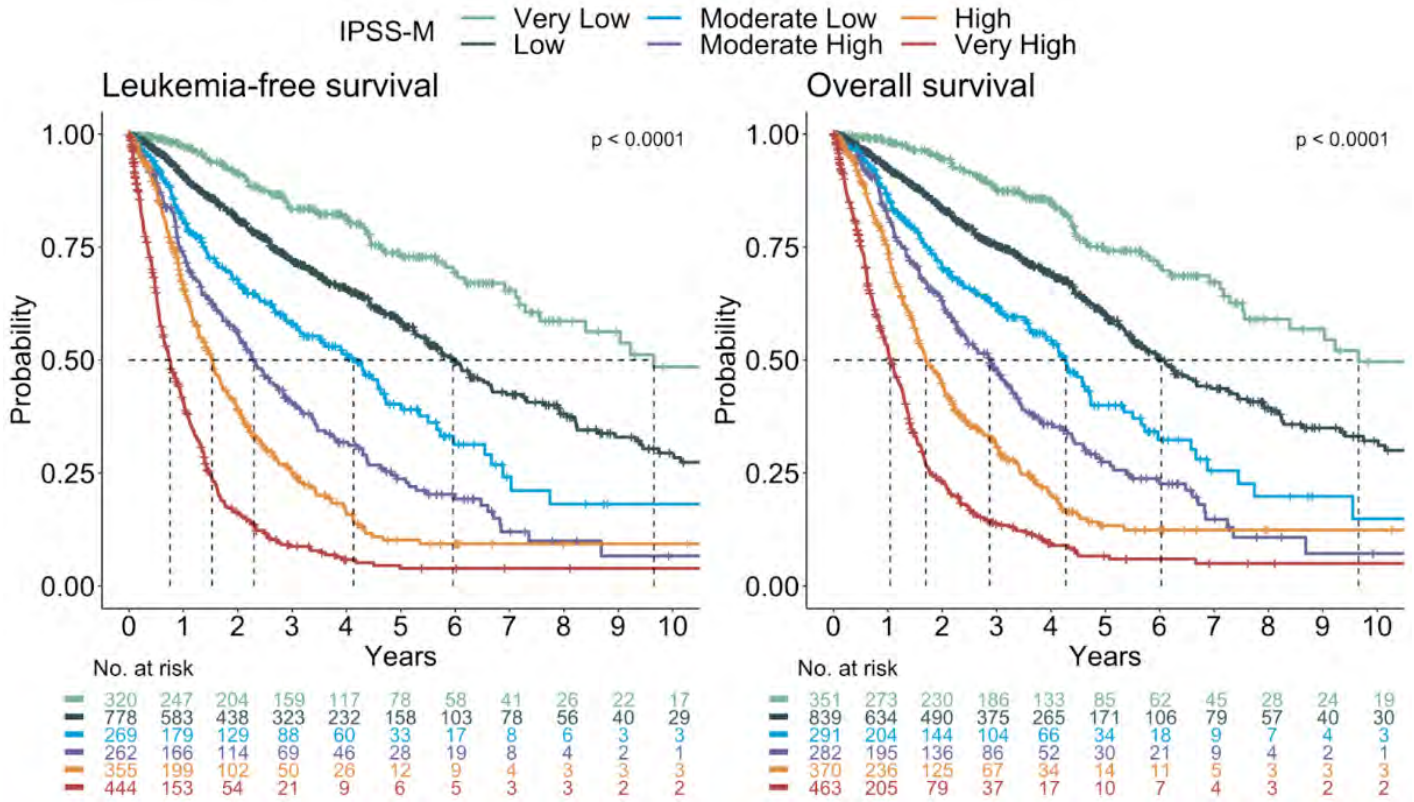
- **IPSS-M risk categories:**

Very Low (VL)
Low (L)
Moderate Low (ML)
Moderate High (MH)
High (H)
Very High (VH)

- **Lower-risk MDS (VL,L and ML) median OS 6.3 yr (95% CI 5.8-7.2 yr)**
- **Higher-risk MDS (VH, H, and MH) median OS 1.5 yr (95% CI 1.4-1.6 yr)**
- **Compared with IPSS-R, IPSS-M re-stratified 46% of patients**

www.MDS-risk-model.com

A six-category risk schema

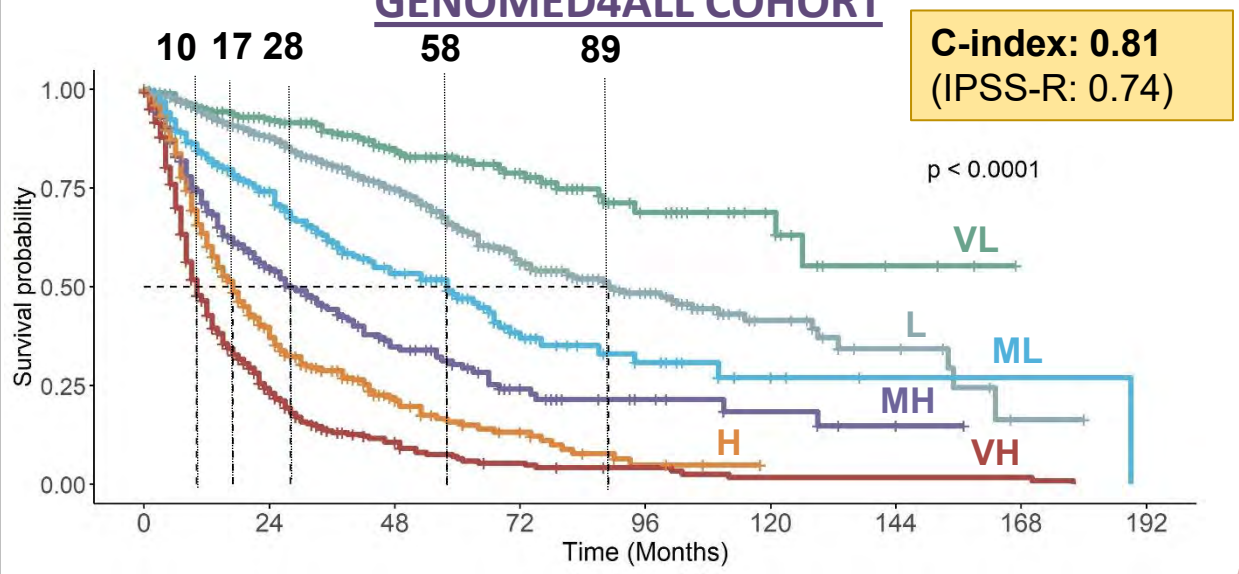


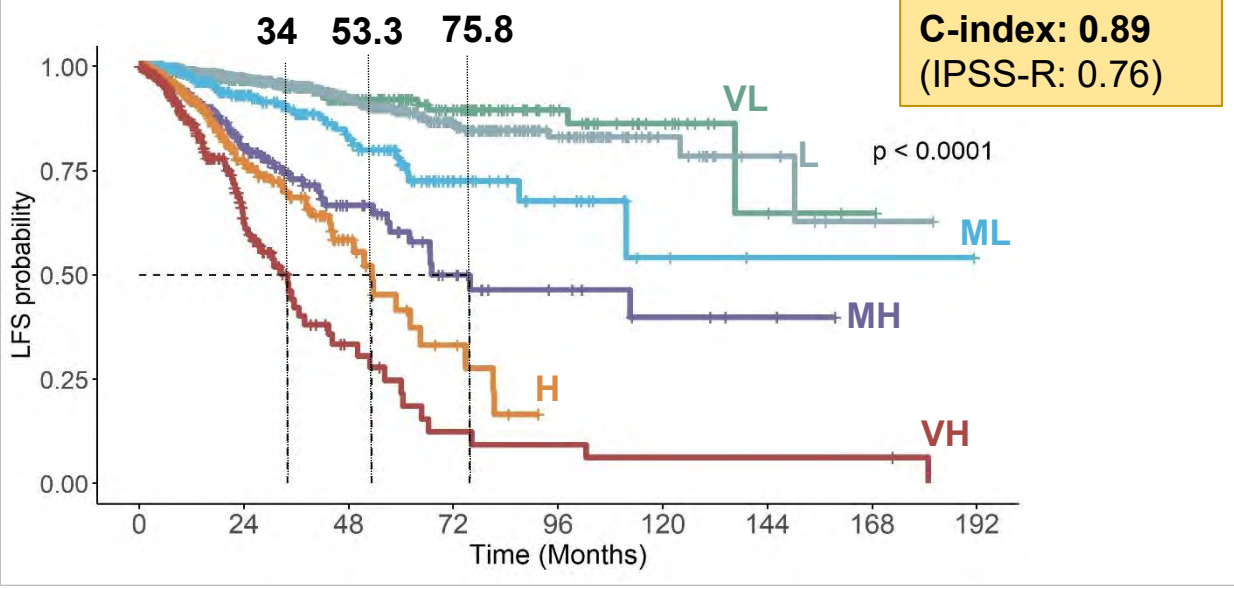
Very Low | Low | Moderate Low | Moderate High | High | Very High

Prognostic separation of the IPSS-M risk categories

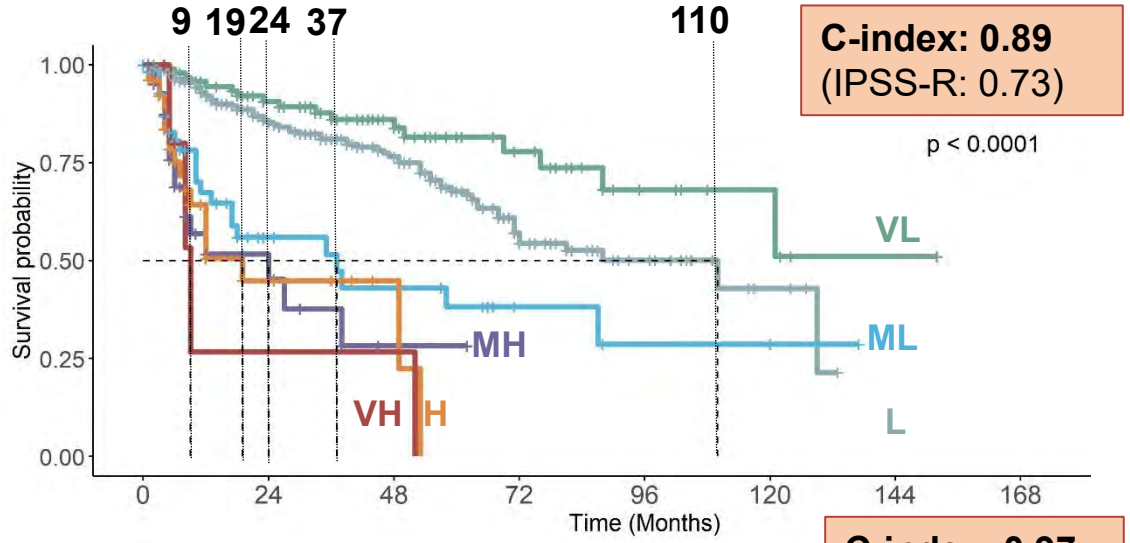
Real-life Validation of IPSS-M in GenoMed4ALL database

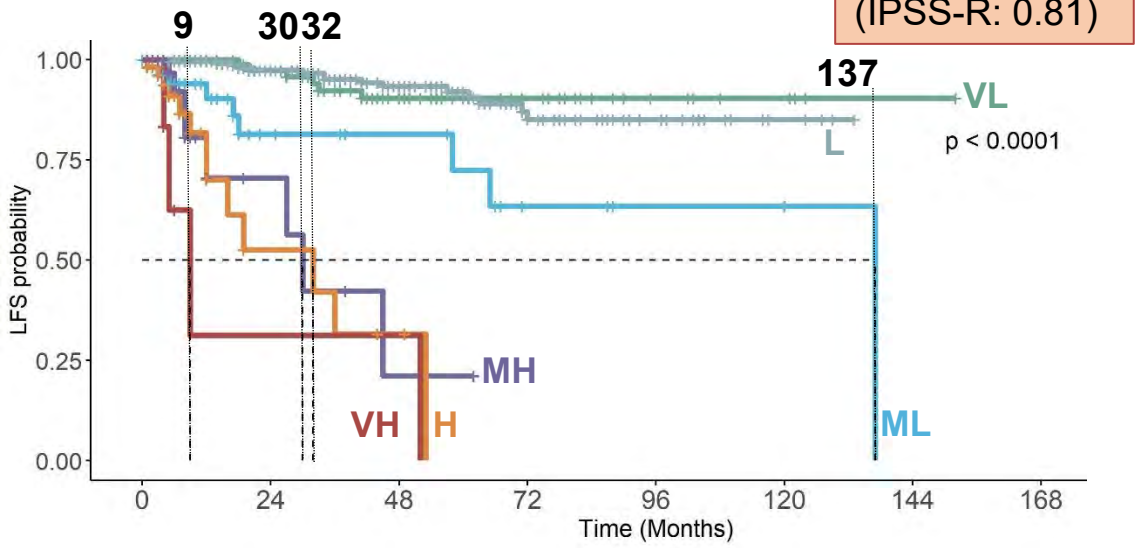
GENOMED4ALL COHORT





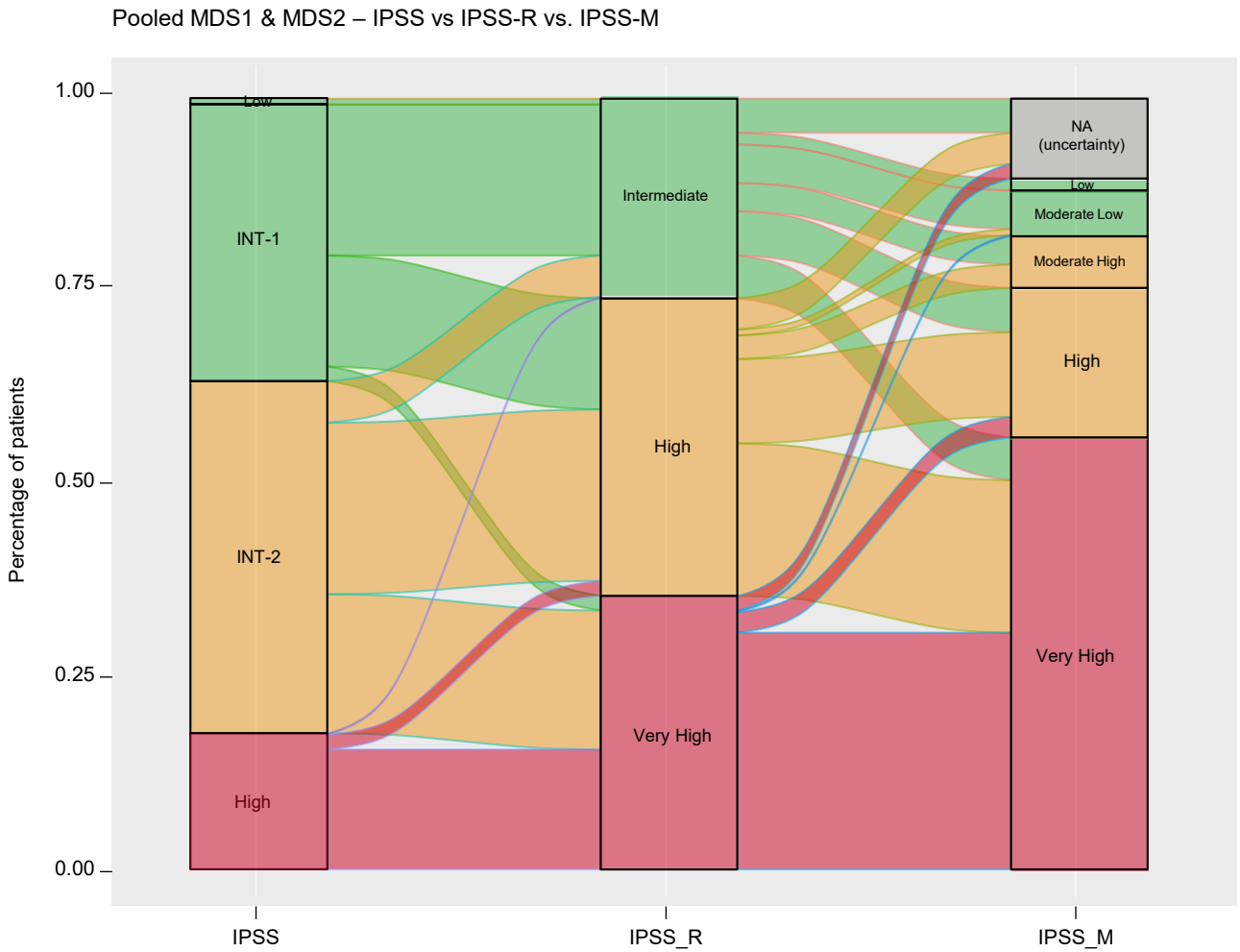
PATIENTS WITHOUT DETECTABLE IPSS-M MUTATIONS





Sauta E, et al. ASH 2022

Risk Re-stratification of HR-MDS patients in STIMULUS MDS 1 and 2 trials

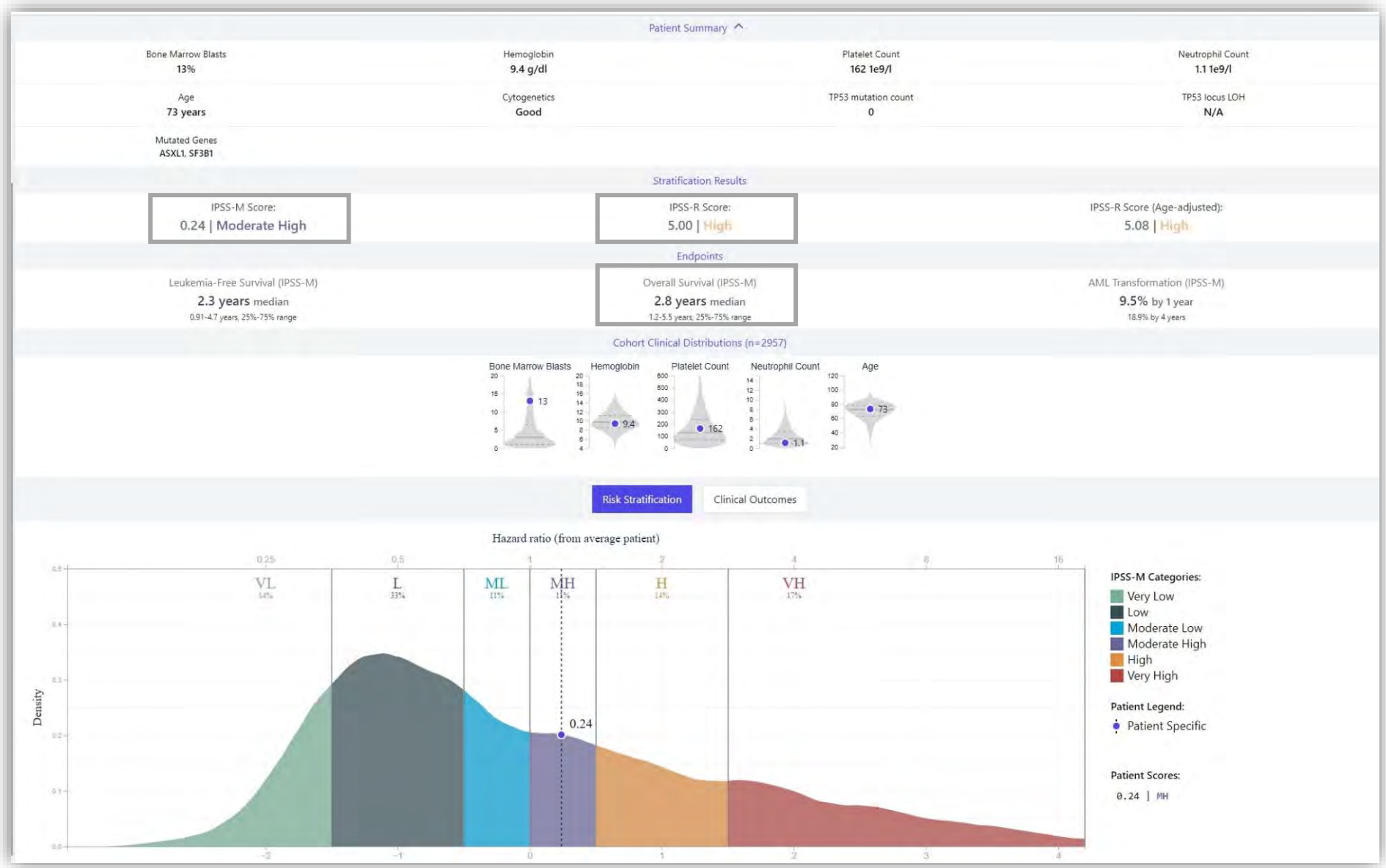


- Upstaging was observed from derived former IPSS criteria to IPSS-R
- Comparing IPSS-R and IPSS-M
  - Of patients with IR IPSS-R, 22.2% and 21.5% were upstaged to HR and vHR IPSS-M, respectively
  - 51.2% of patients with HR IPSS-R were upstaged to vHR IPSS-M
  - 86.5% of patients with vHR IPSS-R remained vHR and 7.6% were downstaged to HR IPSS-M

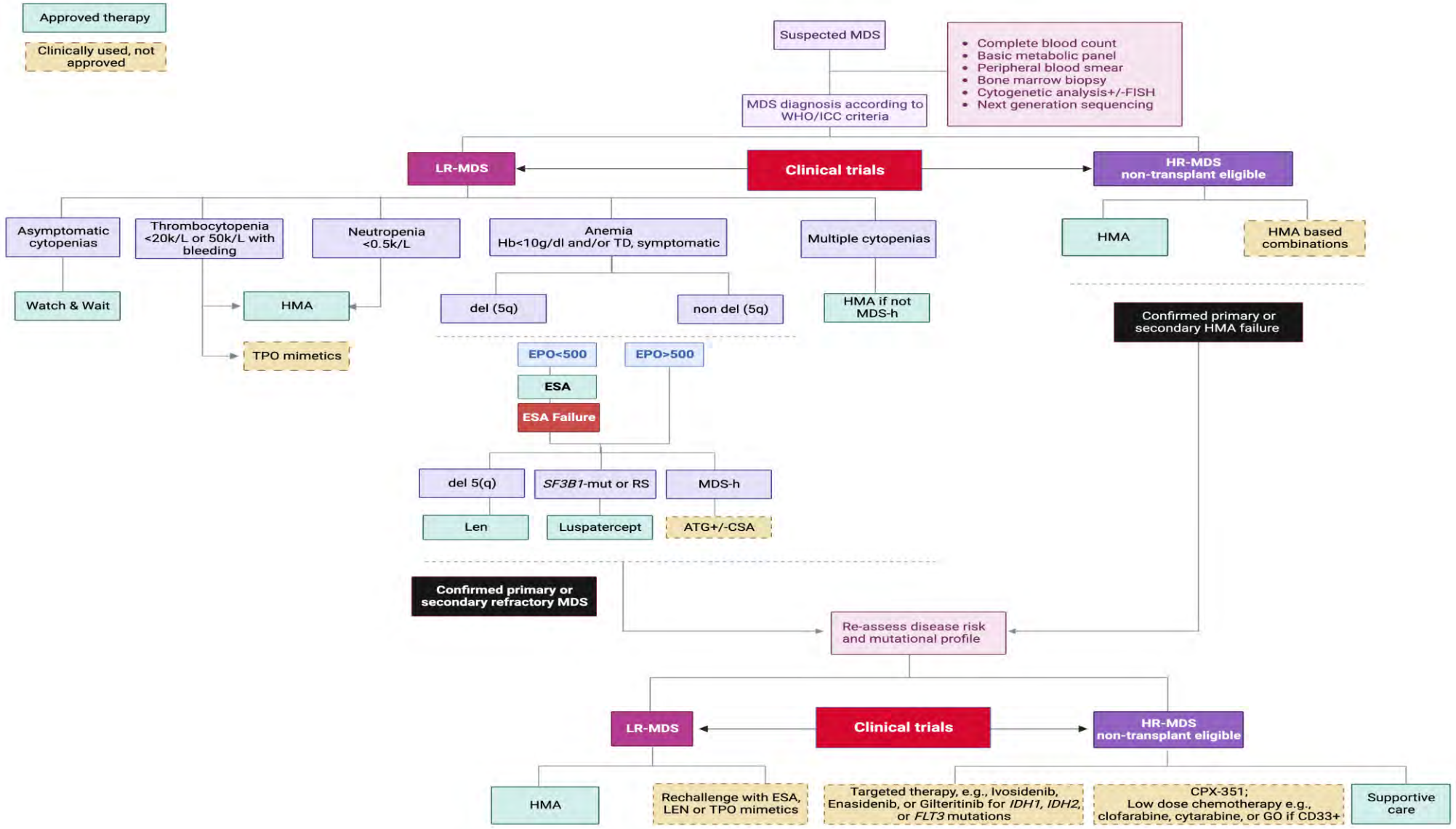
HR, high risk; INT, intermediate; IPSS, International Prognostic Scoring System, IPSS-R, revised IPSS; IPSS-M, molecular IPSS; IR, intermediate risk; MDS, myelodysplastic syndromes; MDS1, STIMULUS-MDS1; MDS2, STIMULUS-MDS2; NA, not available; vHR, very high risk.
[a]Based on N=512 MDS patients with mutation data available from pooled studies (N=118 from MDS1; N=403 from MDS2).

Example of the output for IPSS-M score and risk groups

mds-risk-model.com



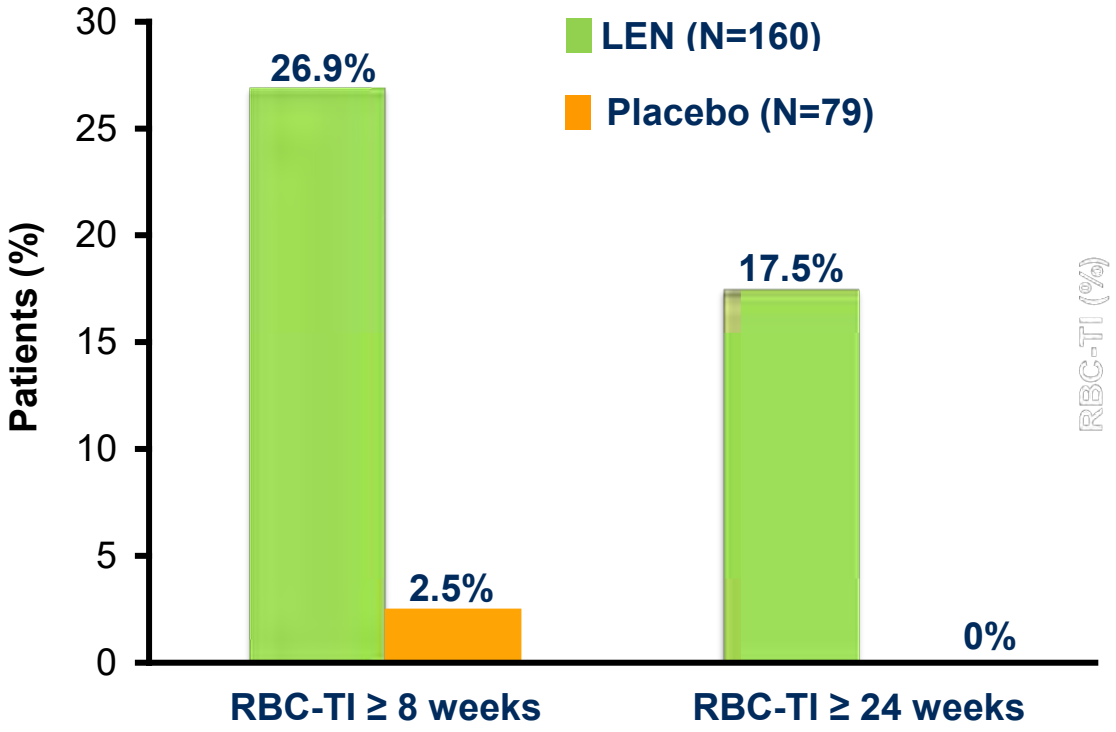
A suggested Paradigm for treatment of MDS patients



Gurnari C, Xie Z, Zeidan AM. Clin Hematol Int. 2022

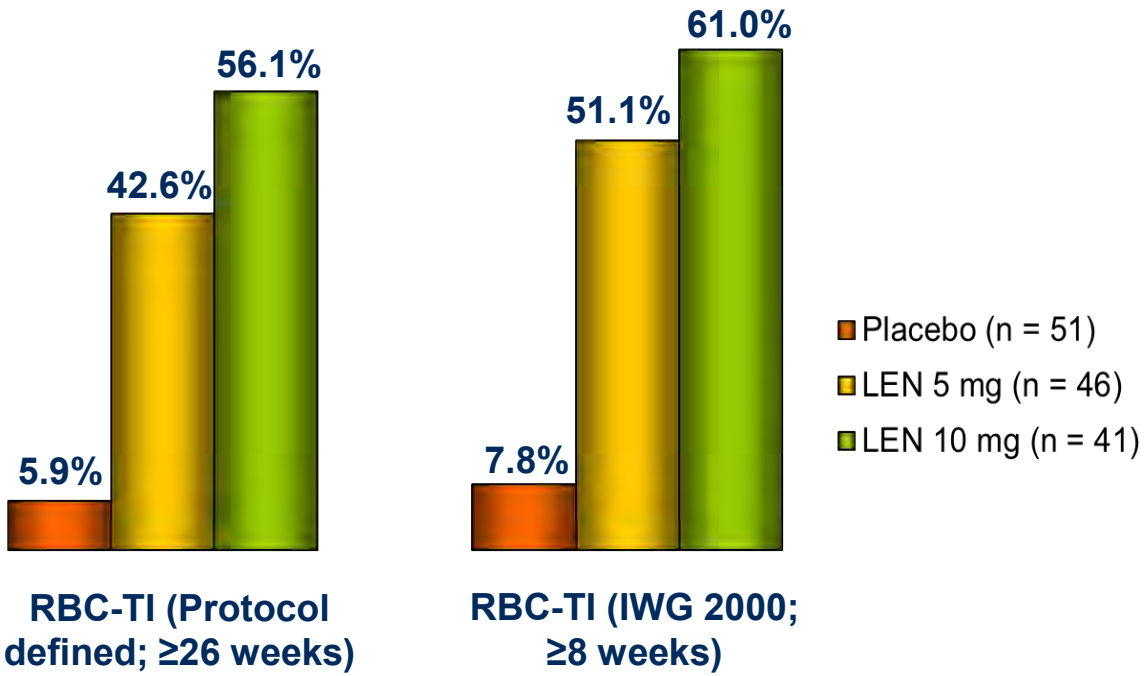
Lenalidomide in LR-MDS

Len vs. placebo in non-del5q LR-MDS MDS-005 (N=229)



- Median duration of TI: 30.9 weeks (95% CI: 20.7, 59.1) among TI ≥8 weeks LEN responders
- The most common Grade 3/4 TEAEs were neutropenia (61.9% with LEN vs. 12.7% with PBO) and thrombocytopenia (35.6% vs. 3.8%)

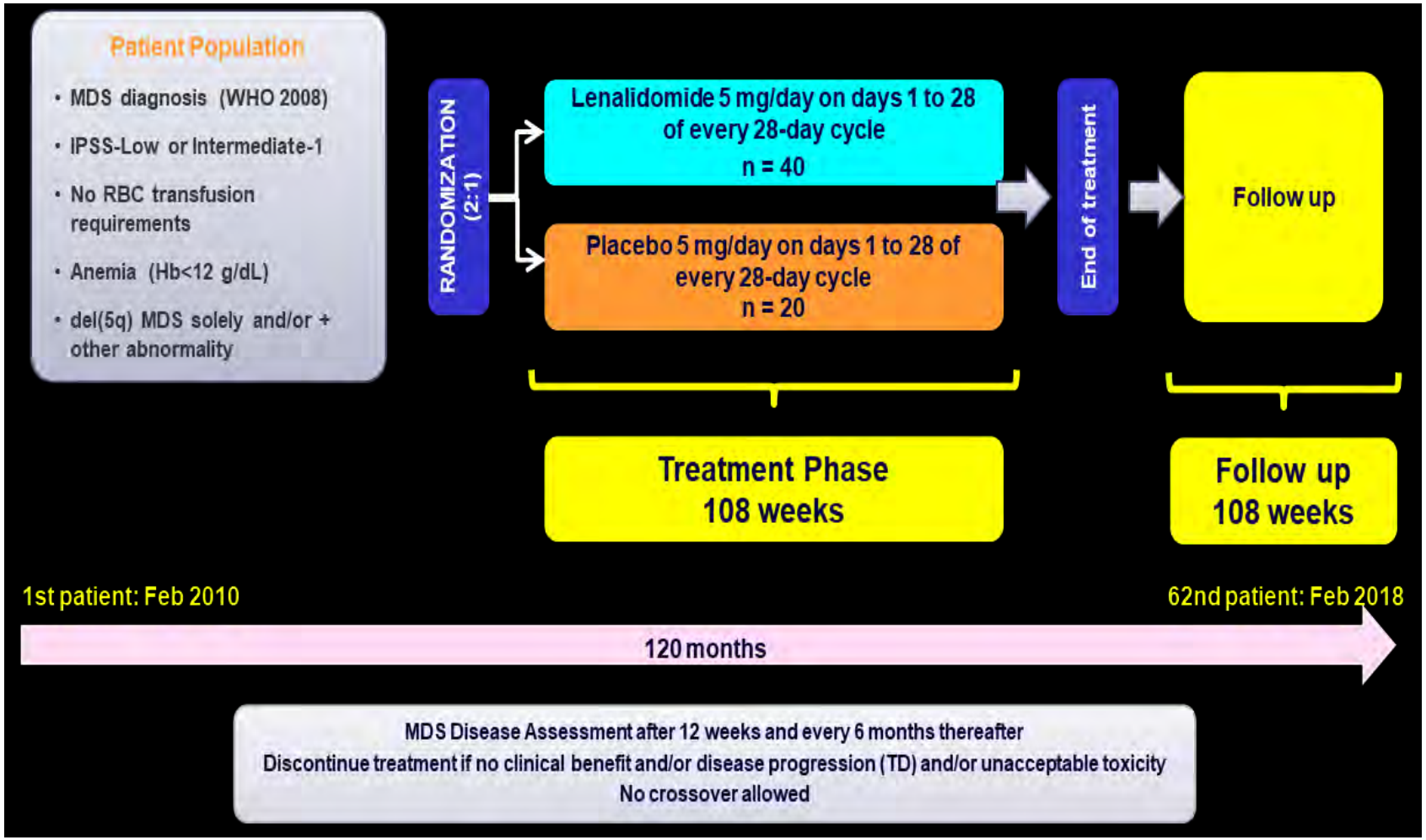
Len vs. placebo in del5q LR-MDS MDS-004[2]



- The most common Grade 3/4 TEAEs were neutropenia (73.9% with LEN 5 mg, 75.5% with LEN 10 mg and 14.9% with PBO) and thrombocytopenia (33.3%, 40.6% and 1.5%, respectively)

1. Santini V, et al. *J Clin Oncol* 2016;34(25):2988–96;
2. Fenaux P, et al. *Blood* 2011;118(14):3765–76.

The Sintra-Rev trial: A randomized Ph3 trial of early lenalidomide treatment in anemic non-TD del5q LR-MDS patients



	Len (%) N=40	Placebo (%) N=21
Gender (female)	32 (80)	18 (85.7)
Age (median)	72.2	71.9
WHO 2008		
RARS	0	1 (4.8)
RCUD	2 (5)	0
RCMD	10 (25)	5 (23.8)
RAEB-1	2 (5)	1 (4.8)
MDS with del(5q)	26 (65)	14 (66.7)
WHO 2017		
MDS-EB-1	2 (4.9%)	1 (4.8%)
MDS-del(5q)	38 (95.1%)	20 (95.2%)
IPSS		
Low	29 (72.5%)	14 (66.7%)
Int-1	11 (27.5%)	7 (33.3%)
Del(5q) abnormality		
Isolated	35 (85.5%)	19 (90.4%)
+ other abn*	5 (12.5%)	2 (9.6%)

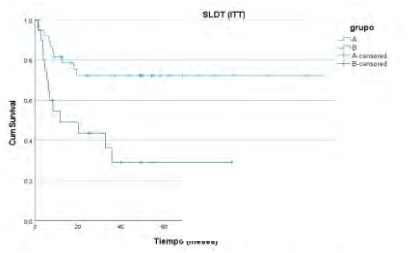
Time-limited low doses of Lenalidomide delayed and decreased transfusion dependency

Time to Transfusion Dependency

LEN median NR

p=0.003

PLACEBO median 11.6 months



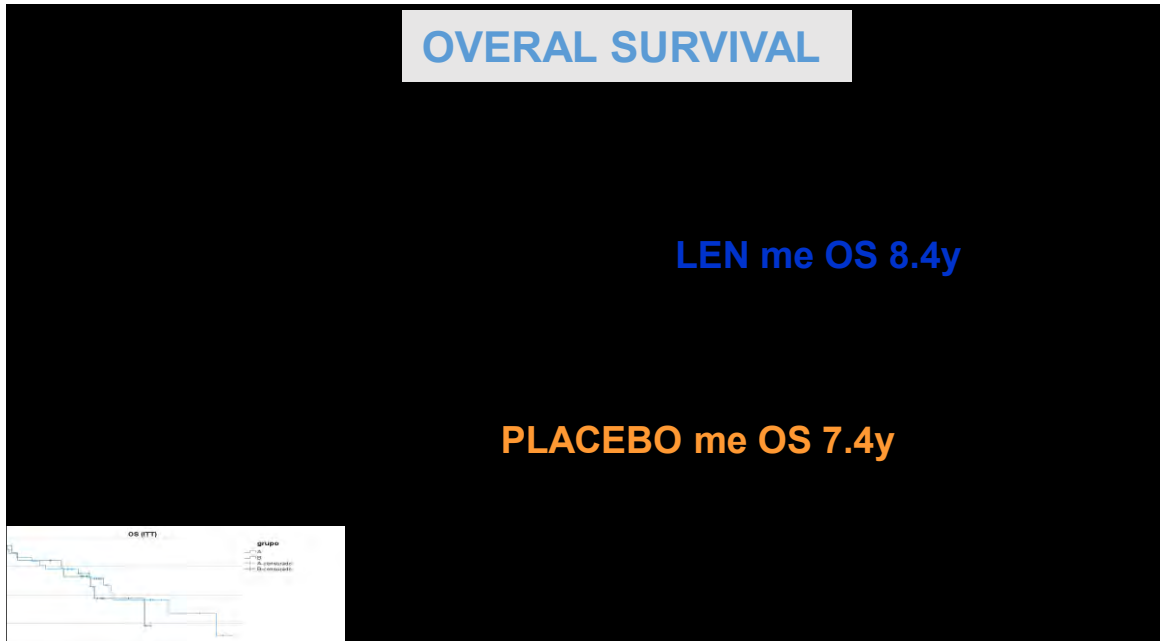
months

- TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)
- Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692), p=0.005
- Reached erythroid responses in 77.8% of patients
- Achieved cytogenetic responses in 94.1% of patients (87.5% completed)
- Acceptable safety profile, hematological toxicities not clinically relevant
- Did not promote clonal evolution, even in *TP53* mut patients

Time-limited low doses of Lenalidomide was generally well-tolerated and did NOT increase risk of progression to AML or worsen survival

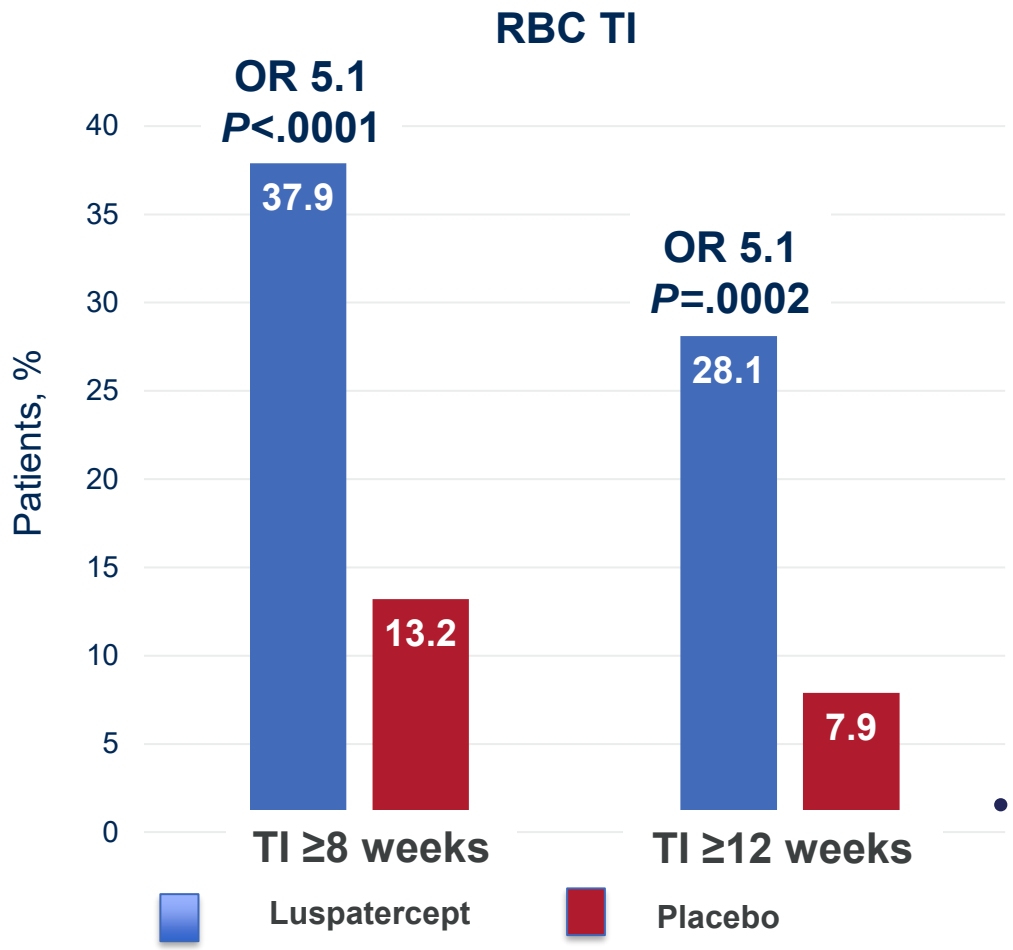
Non-Hematological	G1-2 Len	G1-2 Placebo	G3-4 Len	G3-4 Placebo
Gastrointestinal	18 (46.8%)	1 (4.8%)		
Vascular (PE/DVT)		2 (9.6%)	1 (2.6%)	
Asthenia	4 (10.5%)	2 (9.6%)		
Appetite	2 (5.3%)	1 (4.8%)		
Somnolence		1 (4.8%)		
Pruritus	4 (10.6%)	1 (4.8%)		
Rash	11 (28.6%)	3 (14.3%)	1 (2.6%)	
Hypothyroidism	1 (2.6%)			
2nd solid tumor			4 (10%)	1 (4.7%)

- **Low doses of Len did not induce clinically relevant Neutropenia or thrombocytopenia**

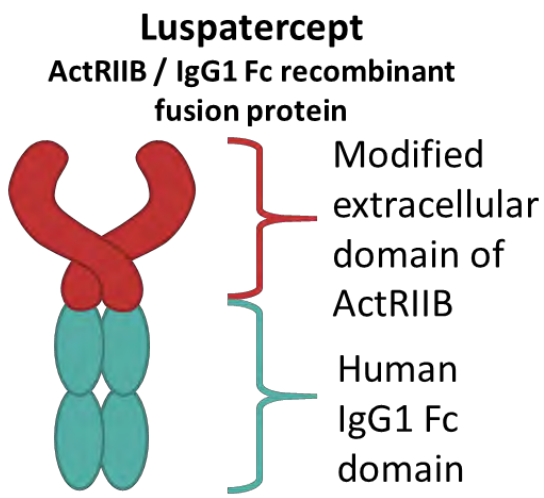


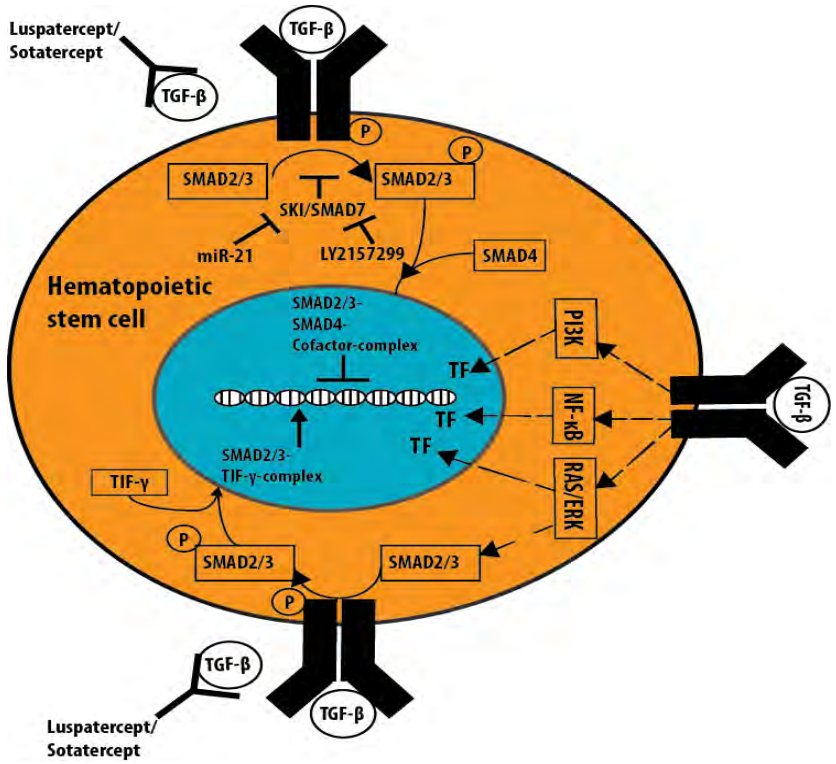
- ✓ **AML** in 11 patients (p=ns)
  - **Len 6 pts (15%)**
    - median 52 mo
    - **2/6 (33.3%) *TP53* mut**
  - **Placebo 5 pts (23.8%)**
    - median 55 mo
    - **1/5 (20%) *TP53* mut**

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



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

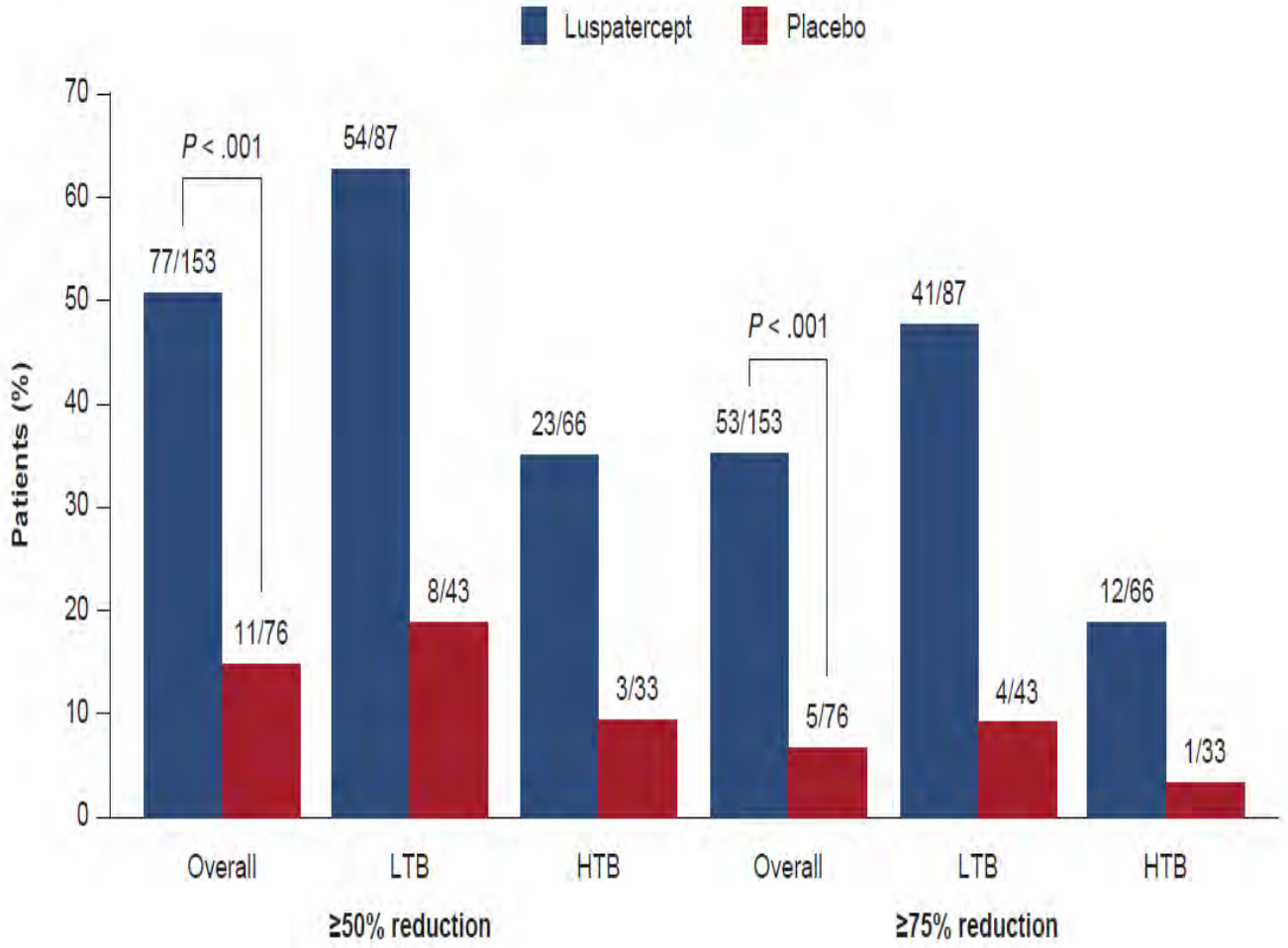




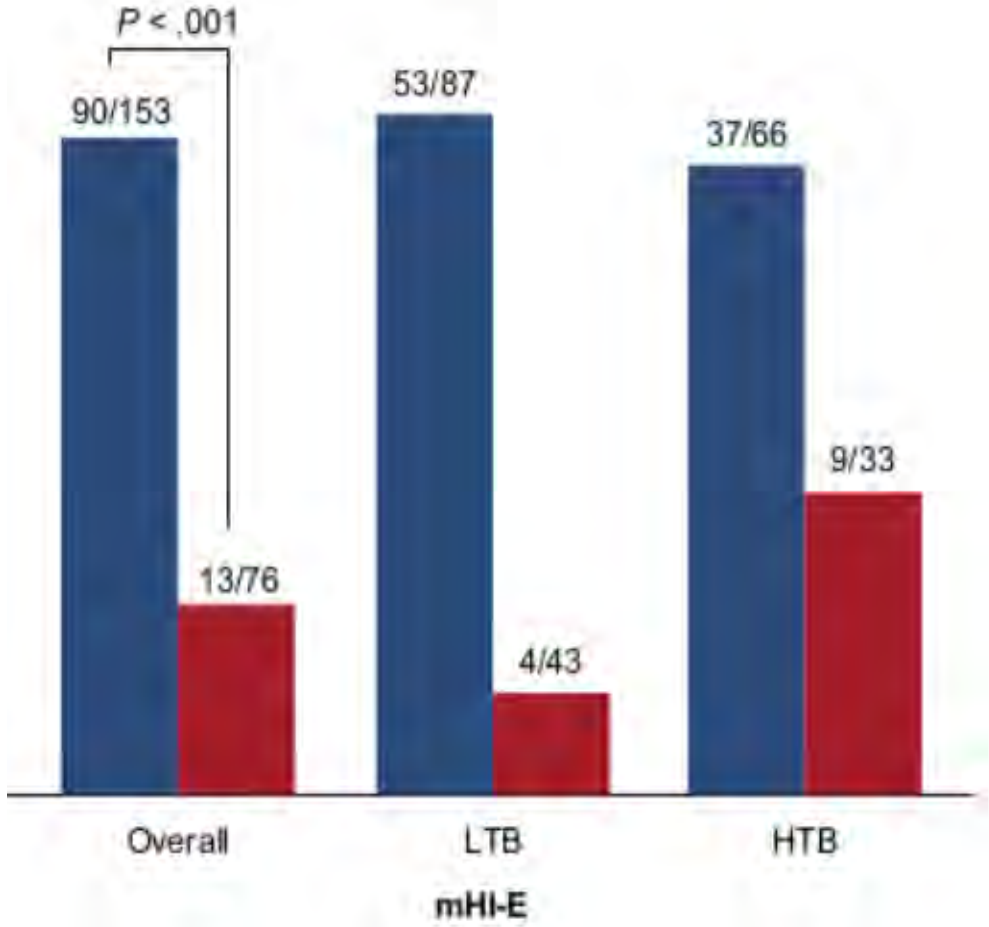
- Luspatercept is a first-in-class erythroid maturation agent (EMA) that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis

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

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



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



Change in erythroid hematologic improvement (HI-E)

Zeidan A et al, Blood 2022

COMMANDS Trial: A phase 3 trial of Frontline Luspatercept vs. ESA in RBC transfusion-dependent LR-MDS patients with and without ring sideroblasts

- **Study design**: open-label, randomized, Phase III trial
- **Inclusion criteria**: IPSS-R LR-MDS (with or without ≥15% RS) who have NOT received ESA, and who require regular RBC transfusions (defined as an average transfusion requirement of 2–6 RBC units/8 weeks for ≥8 weeks immediately prior to randomization)
- **Primary endpoint:** RBC-TI for 12 weeks (Week 1 through Week 24), with a concurrent mean Hb increase of ≥1.5 g/dL compared with baseline

Bristol Myers Squibb Announces Positive Topline Results of Phase 3 COMMANDS Trial

10/31/2022

CATEGORY: Corporate/Financial News

Reblozyl, the first erythroid maturation agent, met primary and key secondary endpoints in the first-line treatment of patients with very low/low/intermediate-risk myelodysplastic syndromes

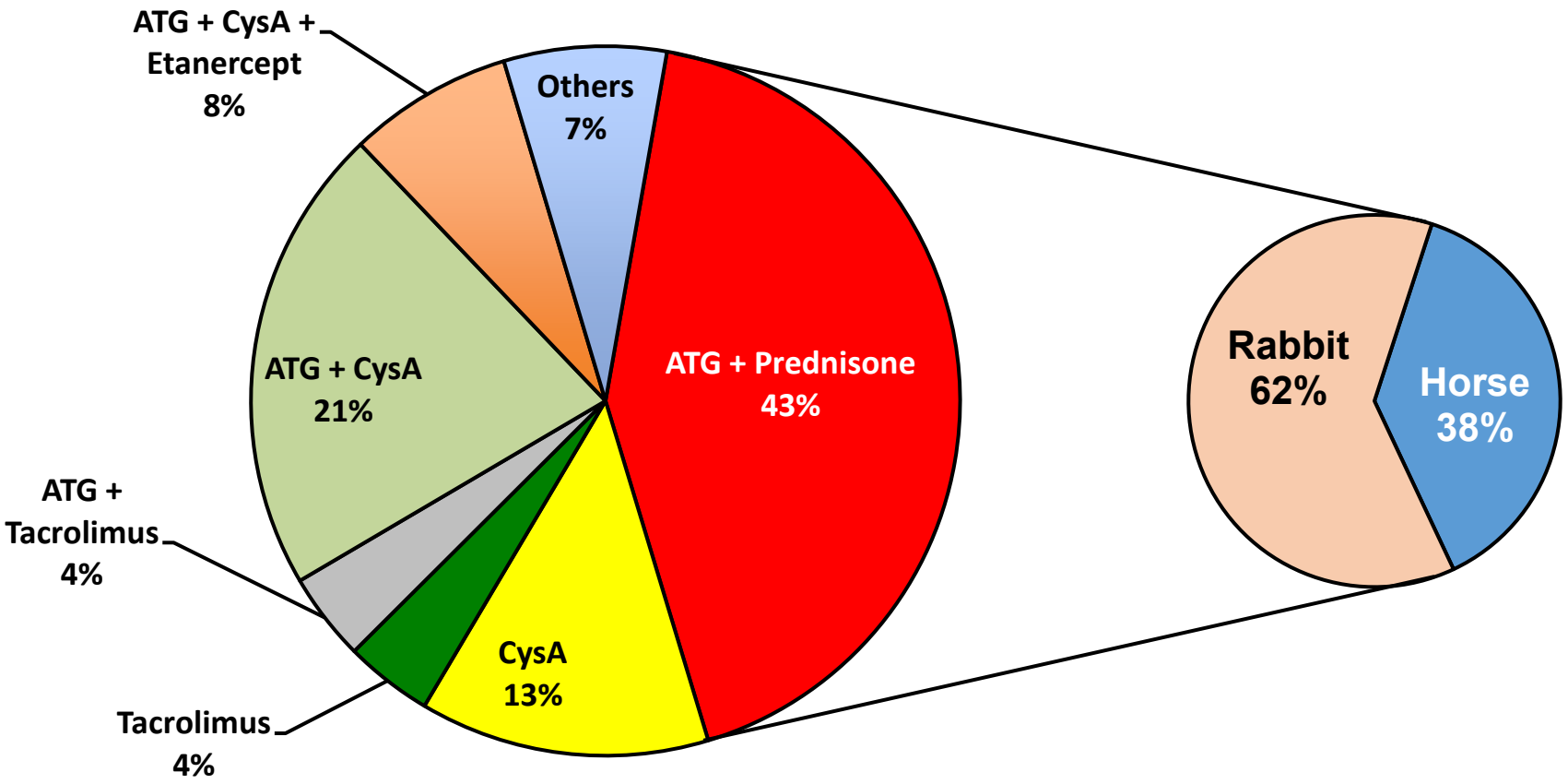
PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the COMMANDS study, a Phase 3, open-label, randomized trial evaluating *Reblozyl*® (luspatercept-aamt), met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in red blood cell transfusion independence (RBC-TI) with concurrent hemoglobin (Hb) increase in the first-line treatment of adult patients with very low-, low- or intermediate-risk myelodysplastic syndromes (MDS) who require RBC transfusions. This result was based on a pre-specified interim analysis conducted through an independent review committee. Safety results in the trial were consistent with the safety profile of *Reblozyl* previously demonstrated in the MEDALIST study (NCT02631070), and no new safety signals were reported.

†Continue treatment unless discontinued early for evidence of progression, death, unacceptable toxicity, patient/physician decision or withdrawal of consent.
‡for 5 years from the date of the last dose of IP, or 3 years from the last dose (whichever occurs later), unless the patient withdraws consent from the study, dies or is lost to follow-up.

Della Porta M, et al. *Blood* 2020;136 Suppl:1–2.

Immunosuppressive therapy for management of lower-risk MDS

Steroid only: 160 (44%) patients → excluded from analysis

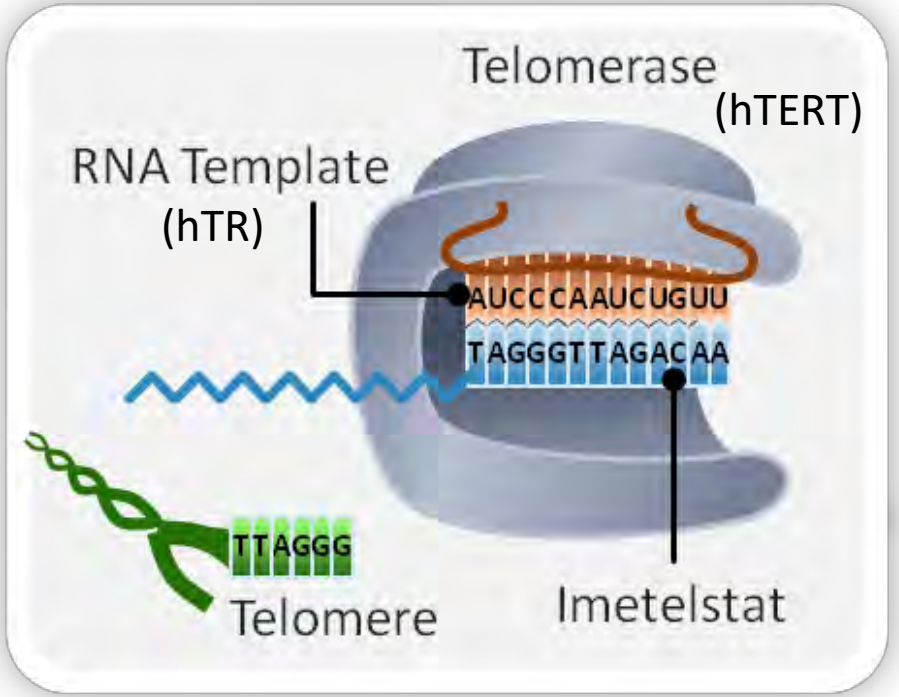


Response	%	95% CI
CR	11.2	6.5–18.4
PR	5.6	2.5–11.6
HI	32.0	24.1–41.0
SD	39.2	30.7–48.4
PD	12.0	7.1–19.3
ORR	48.8	39.8–57.9

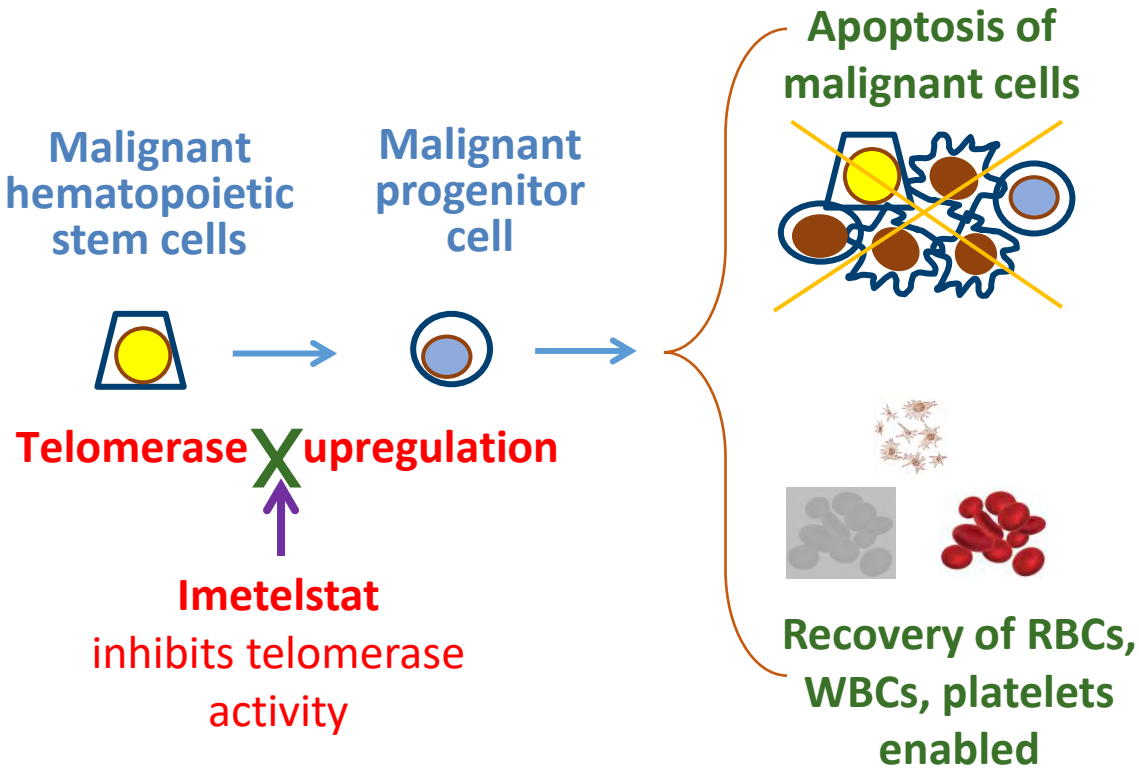
Stahl M,,,,Zeidan A. *Blood Adv* 2018;2(14):1765–72.

Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity[1,2]



- Imetelstat has disease-modifying potential to selectively kill malignant stem and progenitor cells, enabling recovery of blood cell production[3,4]



hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; 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.

Treatment with imetelstat provides durable transfusion independence (TI) in heavily transfused non-del5q LR-MDS relapsed/refractory to ESAs- results from Phase 2 IMerge study

- Global, two-part, Phase II/III study of imetelstat in patients with TD LR-MDS, with a primary endpoint of 8-week RBC TI. Patients in Phase II received open-label treatment with imetelstat 7.5 mg/kg IV Q4W

Results

Parameters	N=38
8-week TI*, n (%) Time to onset of 8-week TI, weeks, median (range) Duration of TI†, weeks, median (95% CI) Hb rise ≥ 3.0 g/dL during TI, %	**16 (42)** 8.3 (0.1–40.7) **85.9 (8.0–140.9)** 75
24-week TI*, n (%)	**11 (29)**
HI-E per IWG 2006[2], n (%) ≥1.5 g/dL increase in Hb lasting ≥ 8 weeks, n (%) Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68) 12 (32) 26 (68)

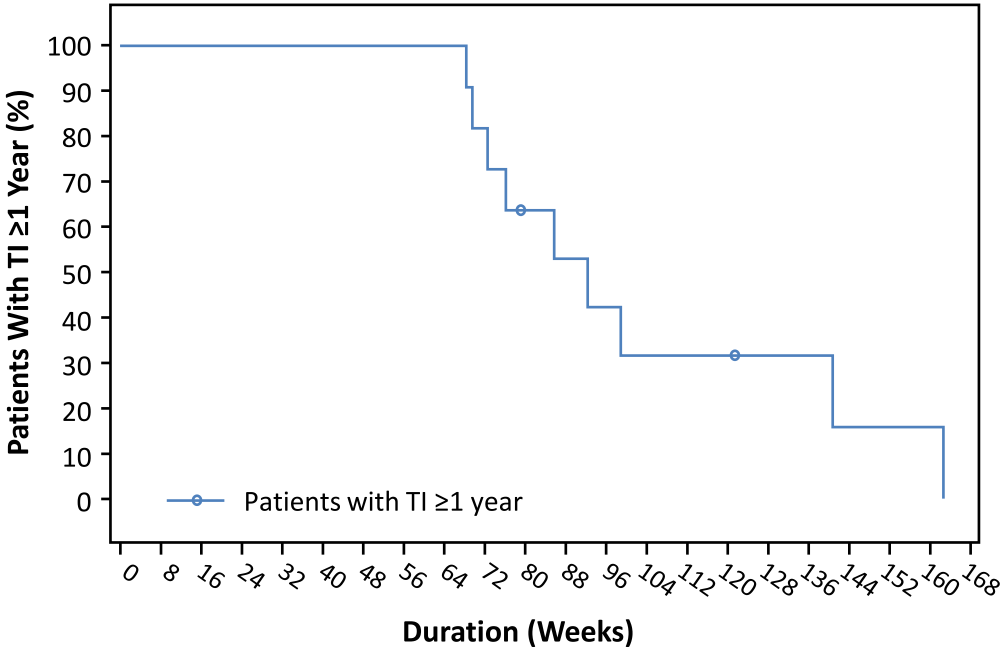
*TI rates were assessed for all treated patients
†Per Kaplan-Meier method

1. Steensma DP, et al. JCO 2020;39(1):48-56; Cheson BD, *Blood* 2006;15;108(2):419-25.

Durable TI Accompanied by Substantial Increase in Hgb in TI ≥1-Year Responders (N=11)

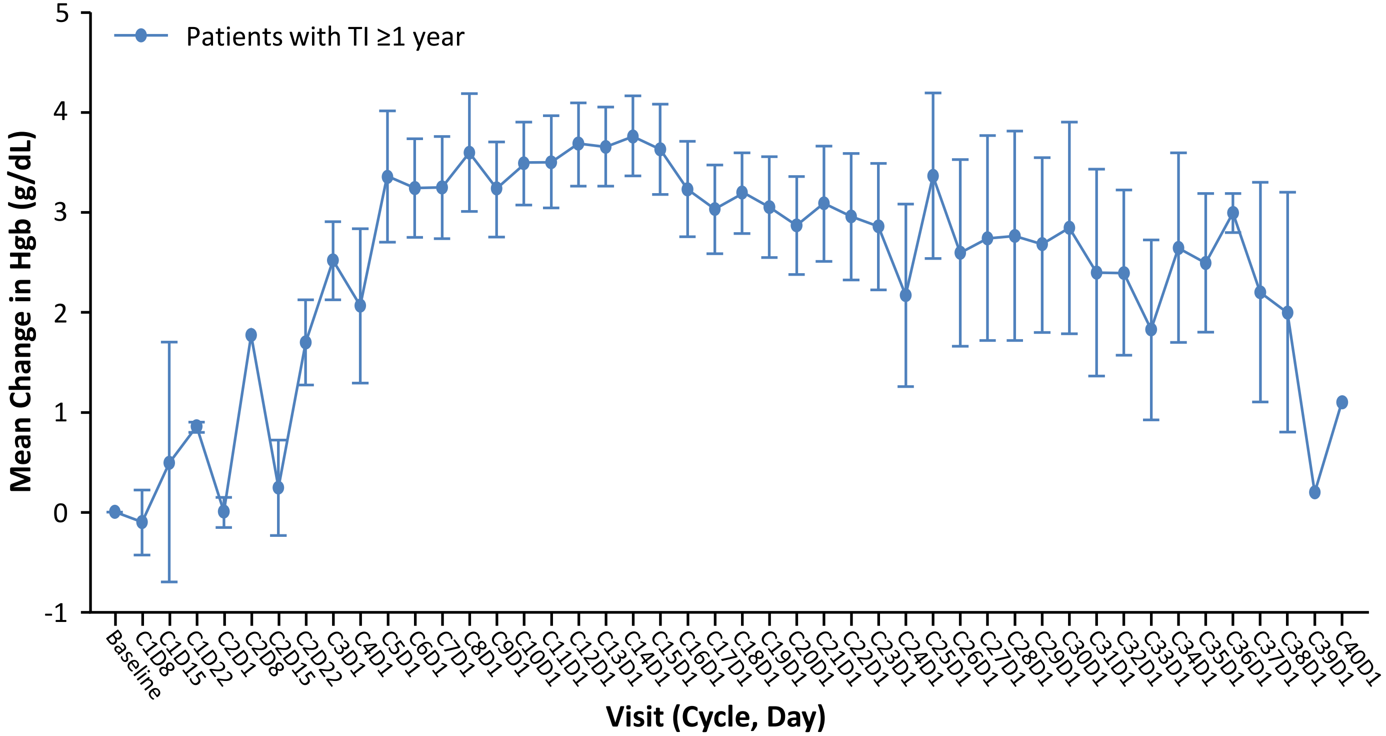
Median TI duration: 92.4 weeks[a]
(95% CI, 69.57-140.86)

Duration of TI[a]



Patients at Risk
n 11 11 11 11 11 11 11 11 11 9 6 5 4 3 3 3 2 2 1 1 1 0

Mean Change in Hgb[b]



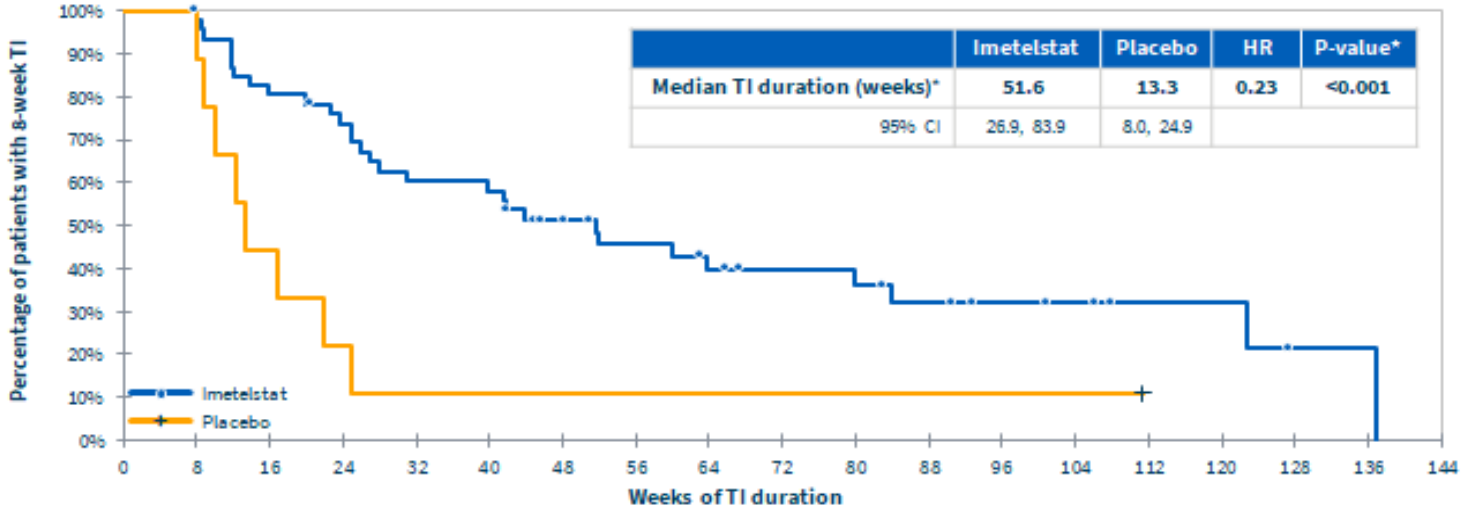
Patients at Risk
n 11 4 2 2 3 1 3 4 6 9 9 10 10 10 11 10 10 11 11 11 11 11 11 11 9 10 9 9 9 8 6 6 5 5 4 4 4 4 4 2 2 2 2 2 1 1

Data cutoff: October 13, 2022.
[a]Based on the Kaplan Meier method. [b]The mean changes from the minimum hgb of the values in the 8 weeks prior to the first dose date are shown and values that within 14 days of RBC transfusions were excluded. This plot does not include the values from unscheduled visits.
Hgb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Press release of IMerge randomized Phase 3 Topline results

Primary end point met with statistically significant and clinically meaningful improvement in 8-week TI

	Imetelstat (n=118)	Placebo (n=60)	P-value*
8-week TI, n (%)	**47 (39.8)**	**9 (15.0)**	**<0.001**
95% CI	(30.9, 49.3)	(7.1, 26.6)	



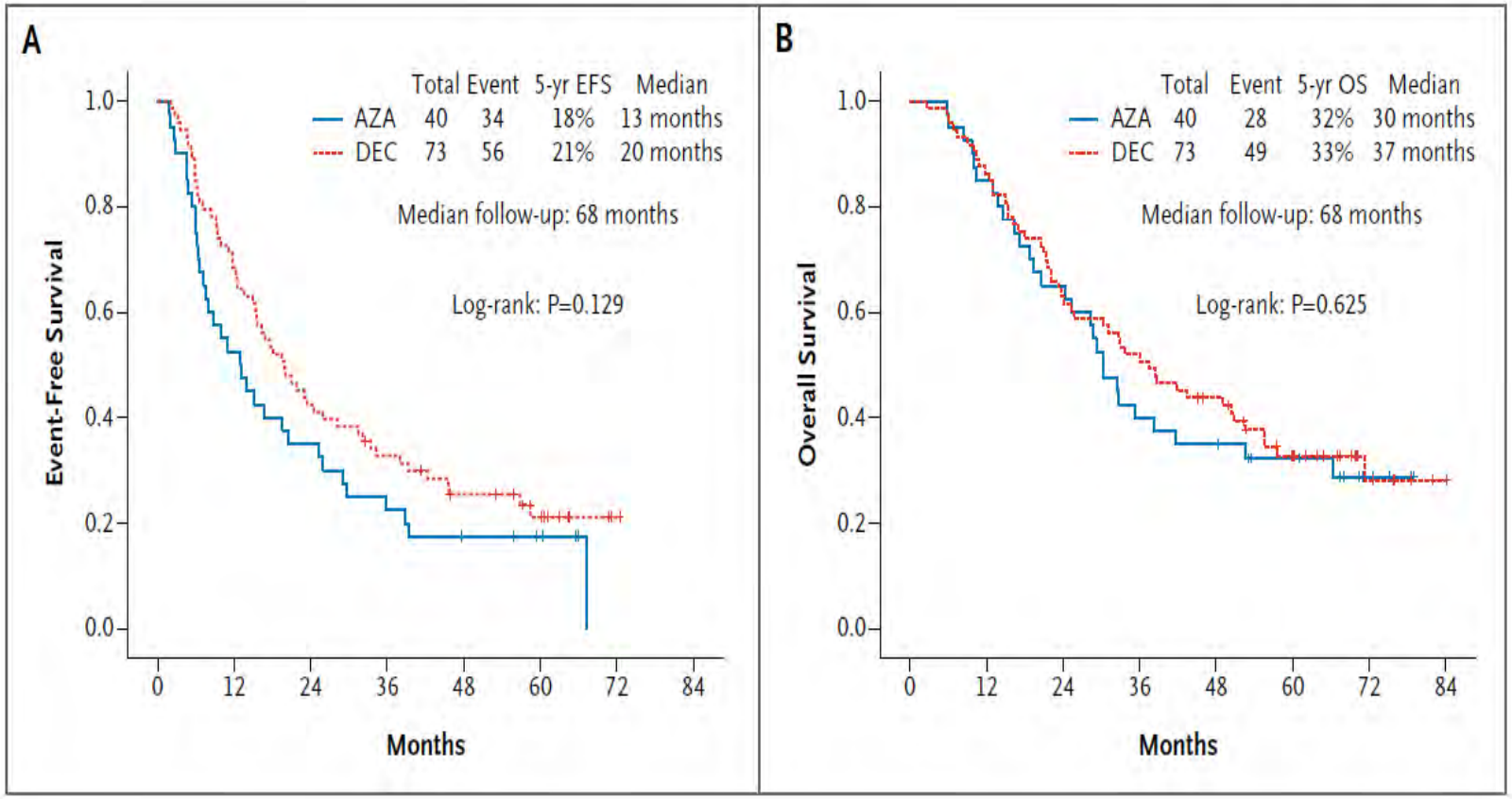
8-week TI responders*	Imetelstat n=47	Placebo n=9
Median Hgb rise (g/dL)	**3.6**	**0.8**
Median Hgb peak (g/dL)	11.3	8.9

Statistically significant and clinically meaningful durability of TI

https://ir.geron.com/investors/press-releases/press-release-details/2023/Geron-Announces-Positive-Top-Line-Results-from-IMerge-Phase-3-Trial-of-Imetelstat-in-Lower-Risk-MDS/default.aspx

Randomized trial of low dose Azacitidine vs Decitabine in LR-MDS

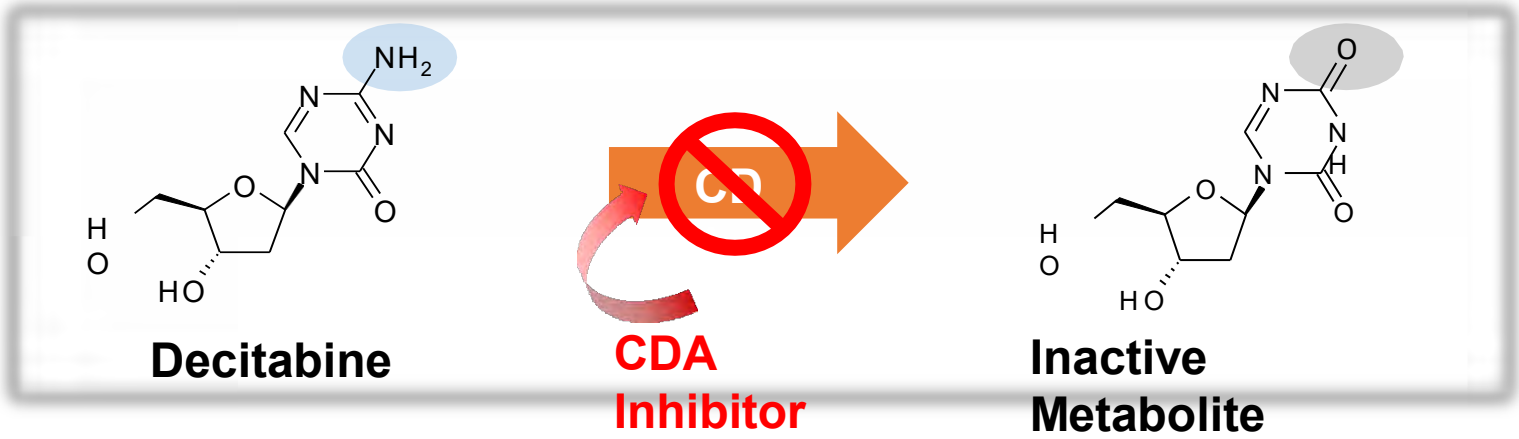
- **113 patients Randomized to:**
  - 20 mg/m² decitabine (N= 73) D1-3 q28 days
  or
  - 75 mg/m² azacitidine (N=40) D1-3 q28 days
- **ORR 67% and 48% in the decitabine and azacitidine groups, respectively (P=0.04)**
- **Among 59 pts with baseline TD, 19 (32%) reached RBC TI.**
- **RBC TI with DEC vs AZA was 41% vs 15%; P=0.04)**
- **Median duration of RBC TI: 22 months.**
- **No early death was observed.**
- **With median follow-up of 68 months, median EFS and OS were 17 months** and 33 months, respectively.



Sasaki K et al, NEM Evidence, 2022

ASCERTAIN: Phase III Study of Oral HMA ASTX727 (Cedazuridine/Decitabine) vs IV Decitabine

- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver
- Cedazuridine is a CDA inhibitor



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

*Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

Phase 1b Study of lower doses of oral Decitabine in LR-MDS

Design

Lower-Risk MDS (IPSS Low/Int-1 risk)

Cytopenia Requiring Treatment

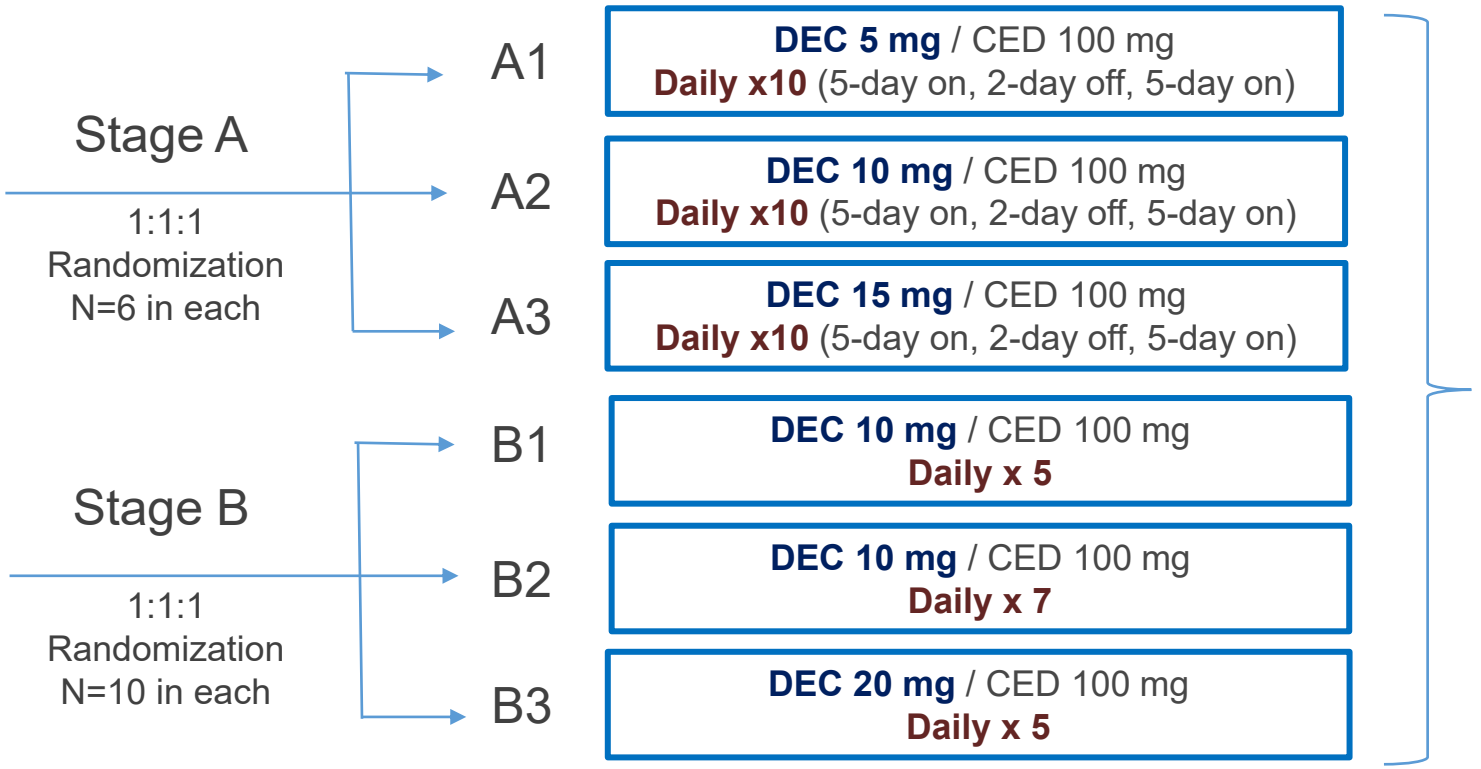
- RBC transfusion dependence of >= 2 U or Hgb of < 8.5 g/dL, in 2 timepoints

  or

- ANC of 0.5 x 10^9/L in 2 timepoints,

  or

- Platelet count of < 50 x10^9/L in 2 timepoint



Major Entry Criteria:

- Cytopenia requiring treatment
- ECOG PS 0-2
- Adequate organ function
- Prior treatment with HMA is allowed
- Exclude CMML

Primary Endpoint

- Safety as determined by incidence of drug-related Grade ≥3 AEs or DLTs

Secondary Endpoint

- Hematologic Improvement (HI) based on modified 2016 IWG criteria
- Transfusion Independence
- Overall Survival (OS), Leukemia Free Survival (LFS)

IPSS – International Prognostic Scoring System; RBC – red blood cell; ANC – absolute neutrophil count; RP2D – recommended phase 2 dose; ECOG – Eastern Cooperative Oncology Group; PS – performance status; CMML – chronic myelomonocytic leukemia; AEs – adverse events; DLTs – dose-limiting toxicities; IWG – International Working Group

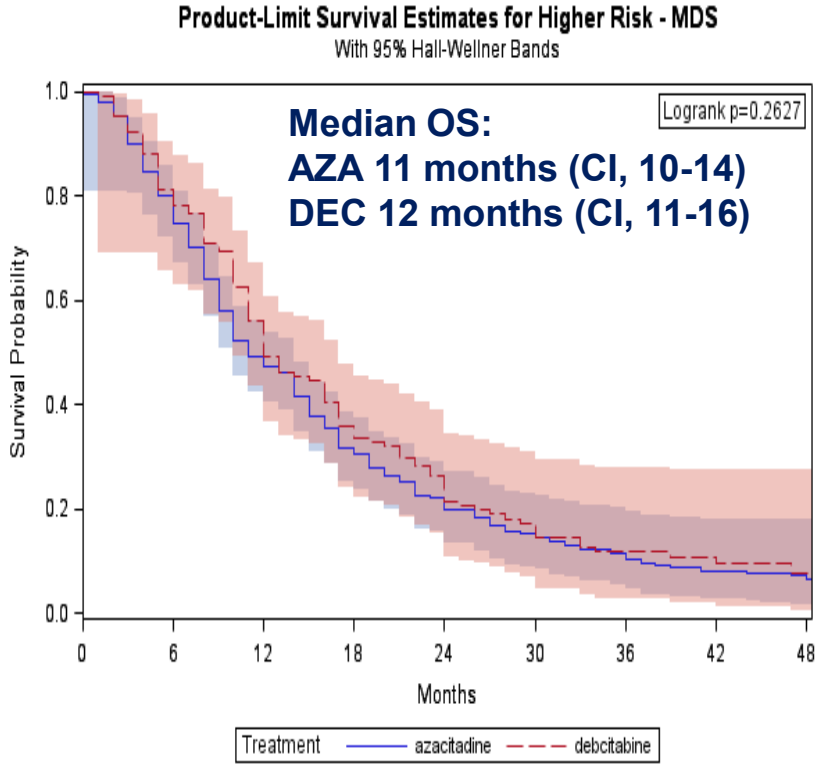
Phase 1b Study of lower doses of oral Decitabine in LR-MDS: Hematologic Improvement (HI) and Transfusion Independence (TI)

	Phase 1 Stage A		Phase 1 Stage B			
	Cohort A1 5mg 10-day N=10	Cohort A2 10mg 10-day N=4	Cohort B1 10mg 5-day N=11	Cohort B2 10mg 7-day N=11	Cohort B3 20mg 5-Day N=11	Total
Total HI endpoint evaluable subjects	10	4	11	11	11	47
HI, n (%)	2 (20.0)	2 (50.0)	4 (36.4)	3 (27.3)	3 (27.3)	14 (29.8)
HI-E endpoint evaluable subjects, n	9	3	11	10	9	42
HI-E, n (%)	1 (11.1)	1 (33.3)	4 (36.4)	2 (20.0)	2 (22.2)	10 (23.8)
HI-P endpoint evaluable subjects, n	5	3	4	4	6	22
HI-P, n (%)	1 (20.0)	1 (33.3)	2 (50.0)	2 (50.0)	2 (33.3)	8 (36.4)
HI-N endpoint evaluable subjects, n	3	2	2	1	4	12
HI-N, n (%)	1 (33.3)	1 (50.0)	0	0	0	2 (16.7)
RBC TD at baseline, n	4	1	7	5	4	21
Post treatment RBC TI, n (%)	1 (25.0)	0	4 (57.1)	1 (20.0)	1 (25.0)	7 (33.3)
Platelet TD at baseline, n	0	1	1	0	1	3
Post-Treatment Platelet TI, n (%)	0	0	0	0	1 (100.0)	1 (33.3)

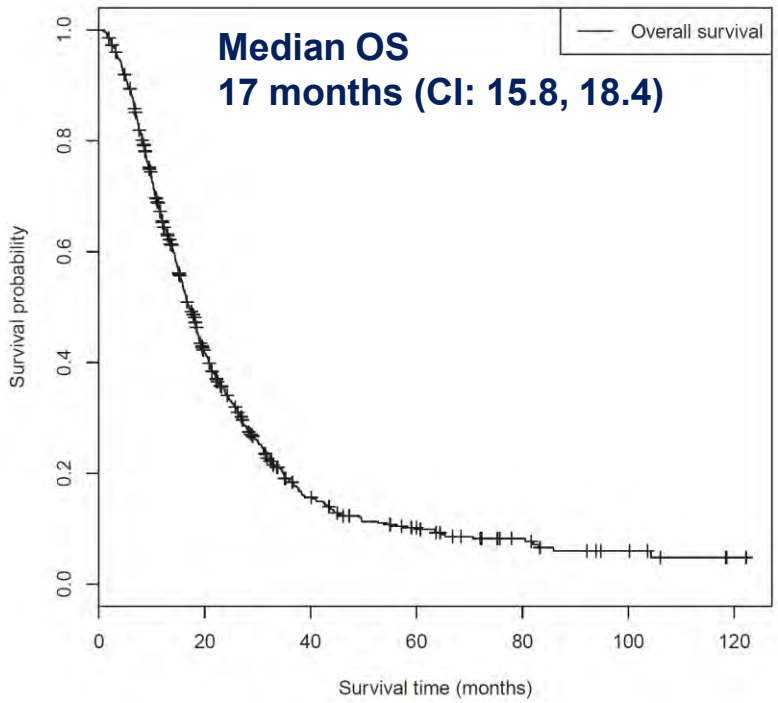
- All cohorts showed early emerging evidence of clinical activity (achieving HI and transfusion independence)

HI: Hematological Improvement based on IWG 2006 MDS response criteria
HI-E=erythroid response;
HI-N=neutrophil response;
HI-P=platelet response,
TD: Transfusion Dependence

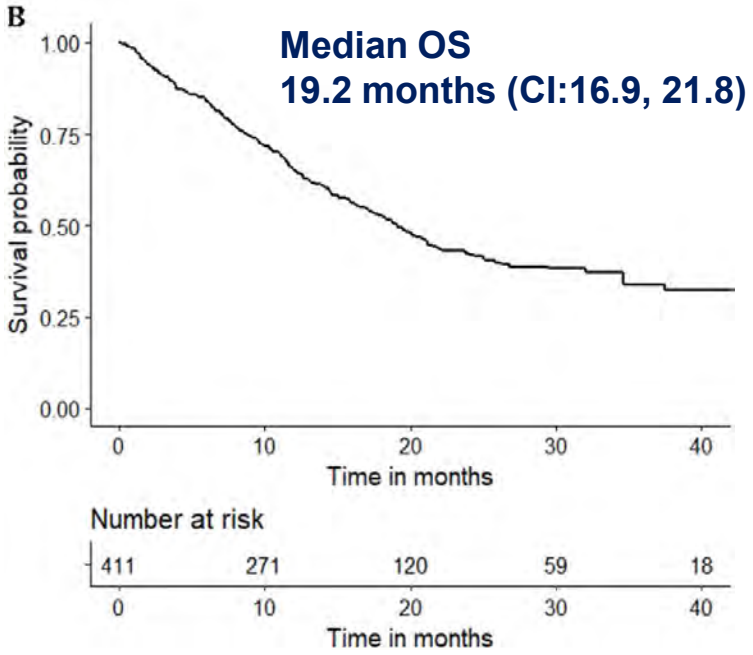
Survival of patients with HR-MDS remains poor despite use of HMAs



- 532 patients ≥ 66 years at RAEB diagnosis
- All received ≥ 10 days of HMA (76% AZA).
- In multivariate analysis of OS, hazard ratio: 0.98 (95% CI: 0.78-1.23)



- 636 HR-MDS patients of all ages in the MDS CRC who received HMA
- Median 5 cycles
- 72% received ≥ 4 cycles
- 68% received AZA.



- Pooled OS estimates using individual patient-level data for patients after AZA monotherapy in Clinical trials
- OS at: 1 year 65.4% (CI: 60.8%, 70.3%), 2 years 42% (CI: 37% ,48%), and 3 years 34% (CI: 28%, 41%)

Zeidan et al, Leukemia, 2015; Zeidan et al, BJH, 2016 , Zeidan et al. Blood Cancer Journal 2018

The Graveyard for HMA-based combinations for frontline treatment of HR-MDS keeps expanding

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

IWG 2006 Response Criteria – Several shortcomings

Respo
Comp
(CR)
Hema
impro
Stable
Partia
Marro
Cytog

blood®

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS AUTHOI

ses
ase

ot

nt
tes

y in

y
nase

REVIEW ARTICLE | FEBRUARY 1, 2023

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

Amer M. Zeidan ✉, Uwe Platzbecker, Jan Philipp Bewersdorf, Maximilian Stahl, Lionel Adès, Uma Borate, David T Bowen, Rena J. Buckstein, Andrew M. Brunner, Hetty E Carraway, Naval G. Daver, Maria Díez-Campelo, Theo M de Witte, Amy E. DeZern, Fabio Efficace, Guillermo Garcia-Manero, Jacqueline S. Garcia, Ulrich Germing, Aristoteles Giagounidis, Elizabeth A Griffiths, Robert P Hasserjian, Eva Hellström-Lindberg, Marcelo C Iastrebner, Rami S. Komrokji, Austin G Kulasekararaj, Luca Malcovati, Yasushi Miyazaki, Olatoyosi Odenike, Valeria Santini, Guillermo F. Sanz, Phillip Scheinberg, Reinhard Stauder, Arjan A Van de Loosdrecht, Andrew H Wei, Mikkael A. Sekeres, Pierre Fenaux

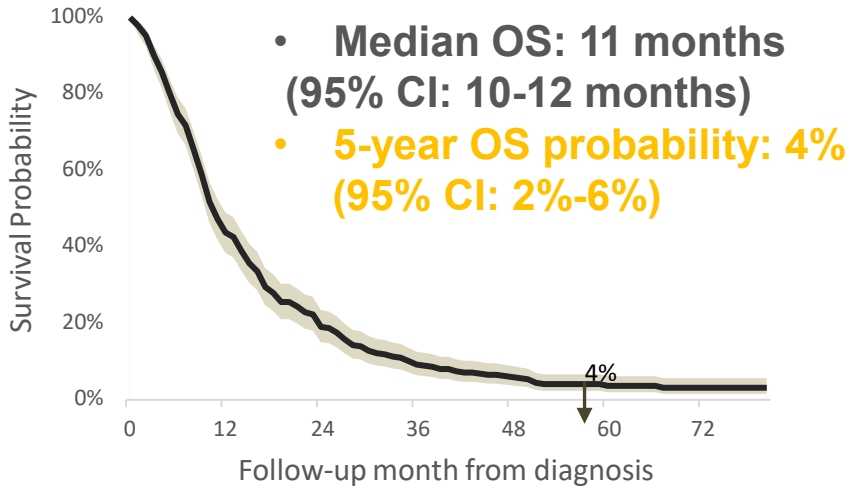
Blood blood.2022018604.

https://doi.org/10.1182/blood.2022018604 Article history

Cheson et al, 2006

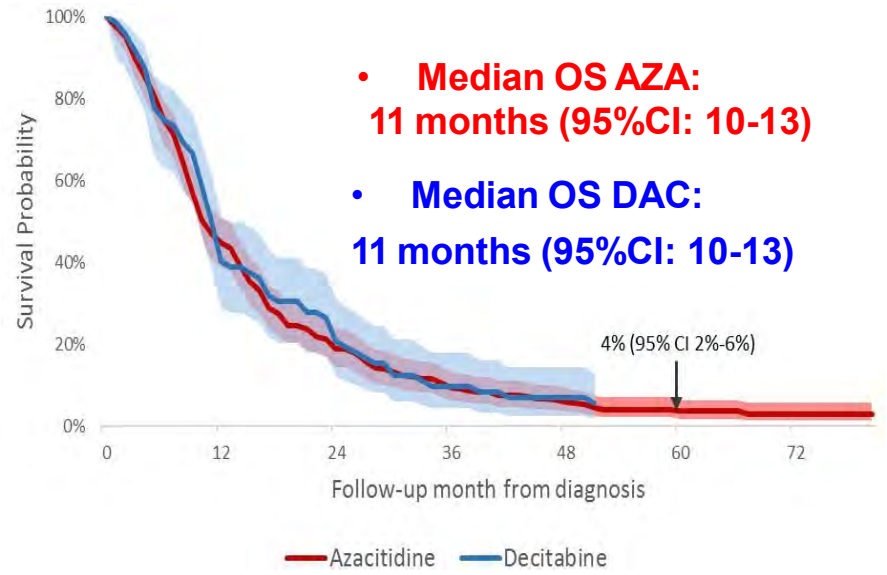
Long-term survival of MDS patients treated with HMAs who do not undergo transplantation

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



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

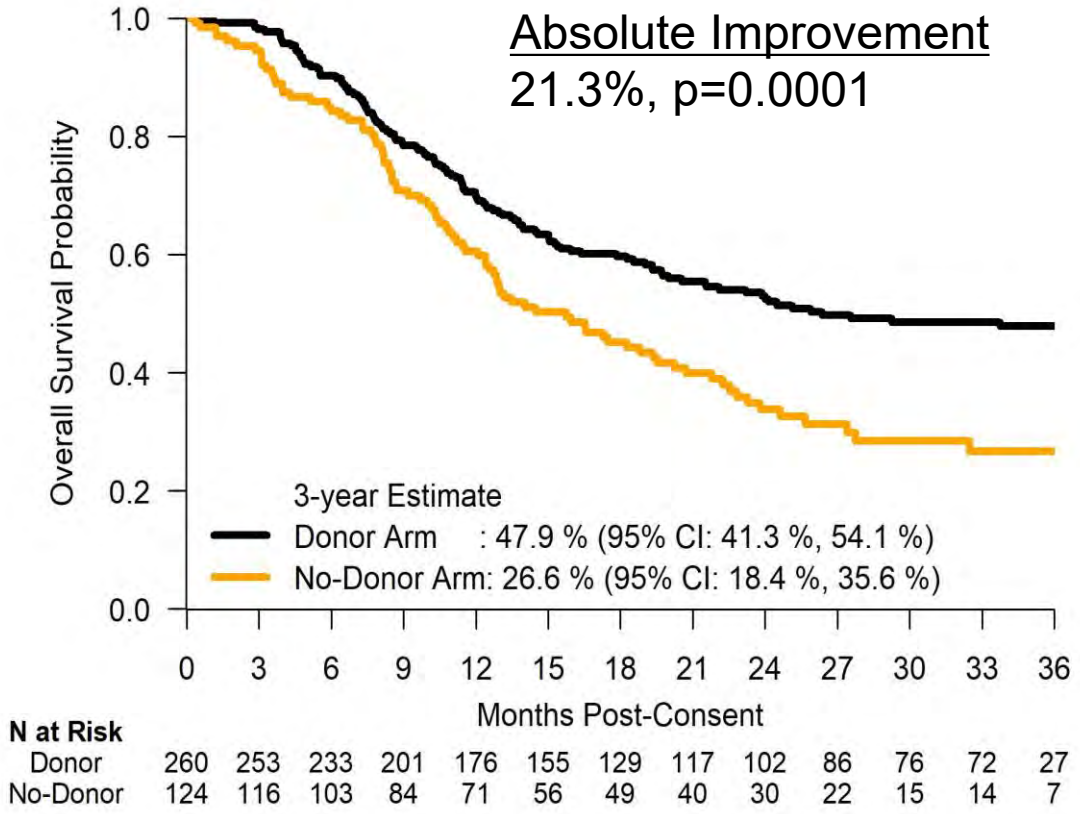
Even among patients who received at least 6 cycles of HMA therapy:
Five-year OS probability 6%
(95% CI: 3 -11%)



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

Zeidan et al, Blood, 2018

A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity AlloHSCT to HMA in Patients Aged 50-75 with Advanced MDS: Blood and Marrow Transplant Clinical Trials Network Study 1102



Among higher-risk MDS patient aged 50-75, having a suitable donor leads to improved outcomes:

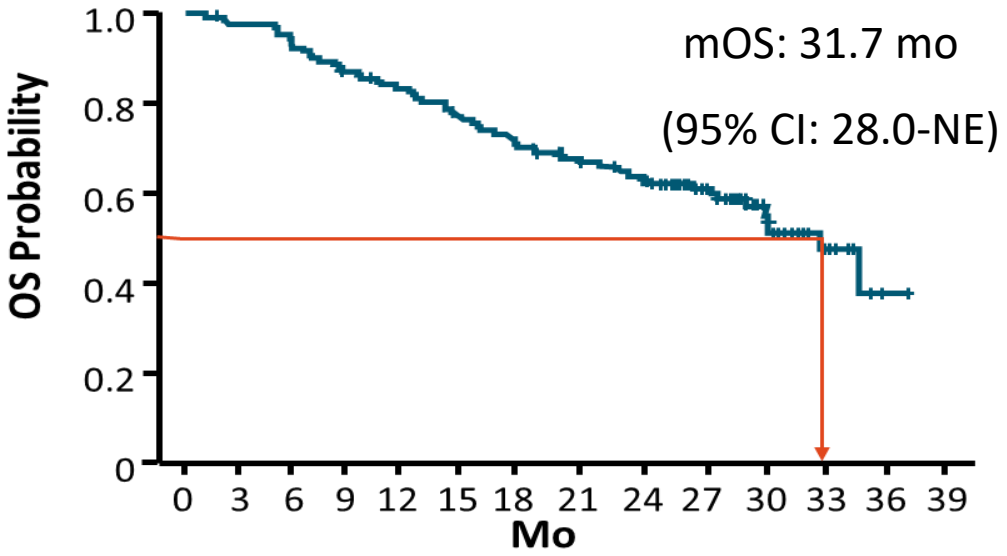
- Overall survival improved by 21% (47.9% vs. 26.6%, p = 0.0001)
- Leukemia-free survival improved by 15% (35.8% vs 20.6%, p=0.003)
- Subjects > 65 (Medicare aged) had similar results to those < 65
- No decrease in Quality of Life compared to No Donor controls
- **As-treated analyses suggest strong advantage for HCT vs. non-HCT therapy (47.4% vs 16% 3 yr OS, p < 0.0001)**

Nakamura et al, ASH 2020, JCO 2021

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

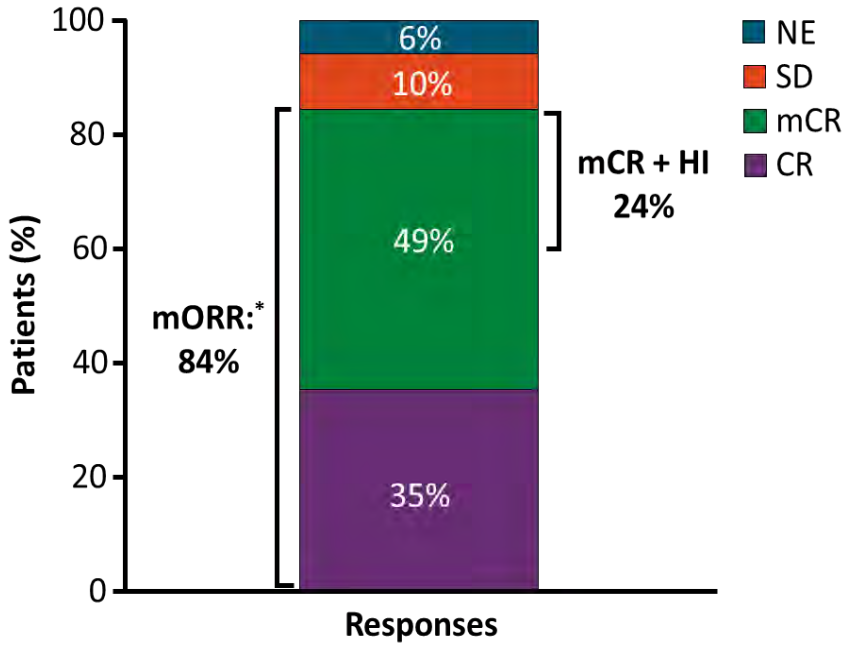
Response Category	Treated Patients (N = 133)
CR, n (%)	29 (22)
PR, n (%)	0
mCR, n (%)	43 (32.3)
▪ mCR with HI	22 (16.5)
HI, n (%)	10 (7.5)
▪ HI-erythroid	2 (1.5)
▪ HI-neutrophils	1 (0.8)
▪ HI-platelet	7 (5.3)
Overall response (CR + PR + mCR + HI), n (%)	82 (61.7)
RBC transfusion independence, n/N (%)*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

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

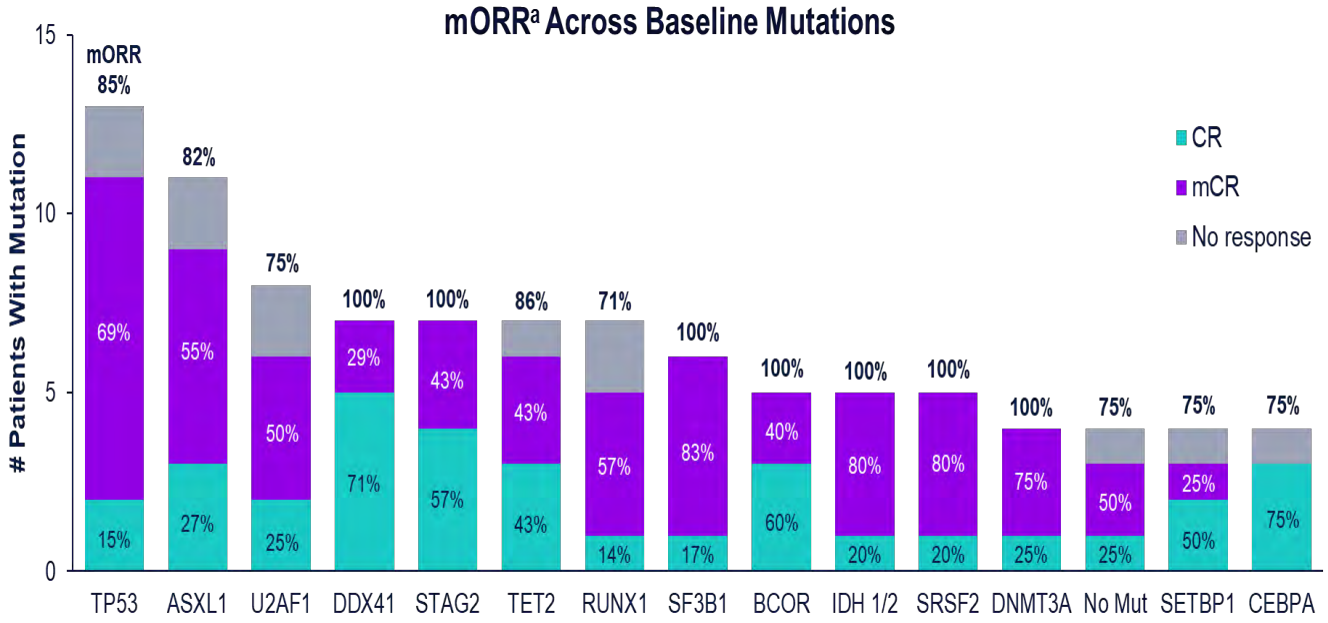


Savona. ASH 2020. Abstr 1230. 2. Savona. MDS 2021. Abstr P48

Phase 1b study of Venetoclax in Combination With Azacitidine for frontline Treatment of Patients With HR-MDS



- 51 patients received the RP2D Ven 400 mg D1–14
- Median follow-up: 23 months (range 0.1–44.2)
- ORR: 84% at RP2D
- Median TTR: 0.9 months (95% CI, 0.7-5.8)
- Median DOR: 12.4 months (95% CI, 9.9-NR)



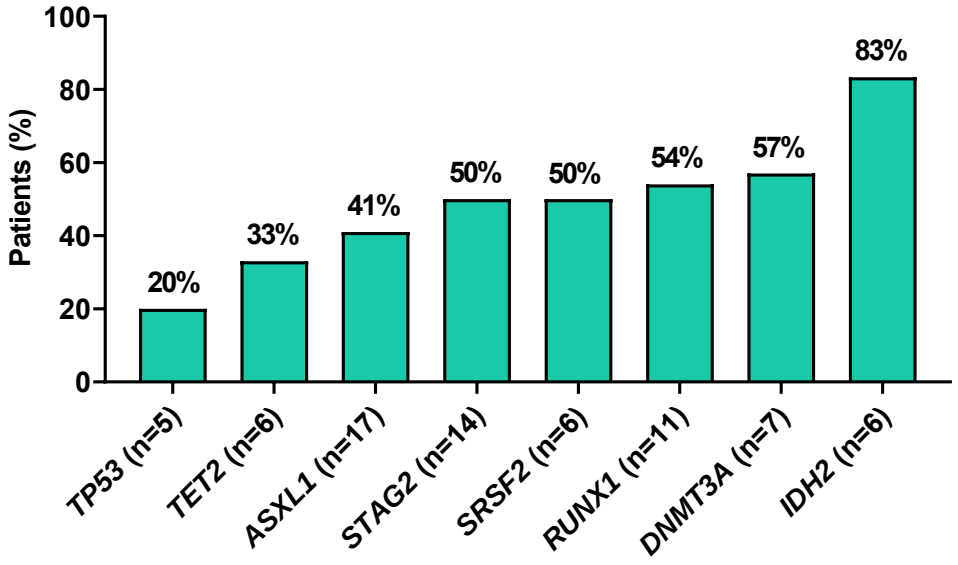
- 7 of 13 *TP53* mutations pts had multi-hit/bi-allelic *TP53* mutations
- Responses in multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation: CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff Dec 15, 2020

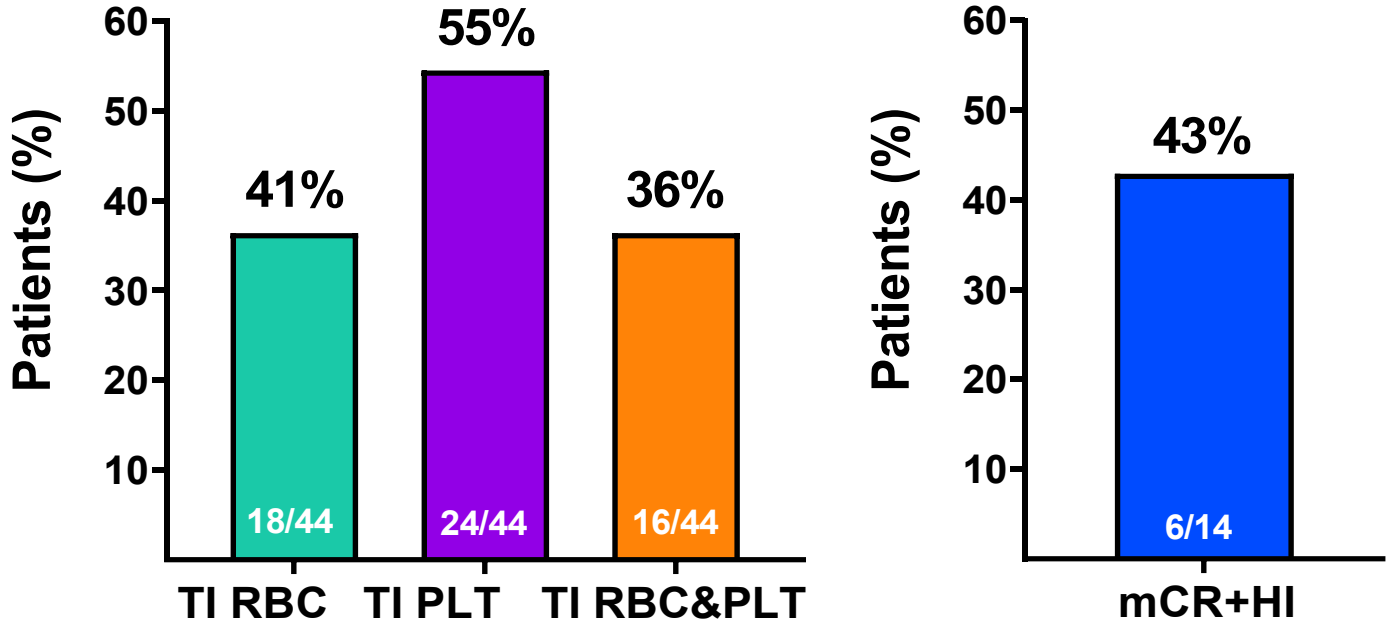
Garcia JS, et al. ASH 2021

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

CR+mCR by baseline mutations



Transfusion independence and Hematological Improvement



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

Zeidan A et al, ASH 2021, AJH 2023

Trial In Progress: VERONA
Design

P3
Phase 3

Double-blind Placebo-controlled

Randomized

International ~210 sites 23 countries

Multicenter

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

NCT04401748

First Subject Dosed October 4, 2020

~500 patients newly diagnosed with higher–risk MDS

1:1 Randomization

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

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

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

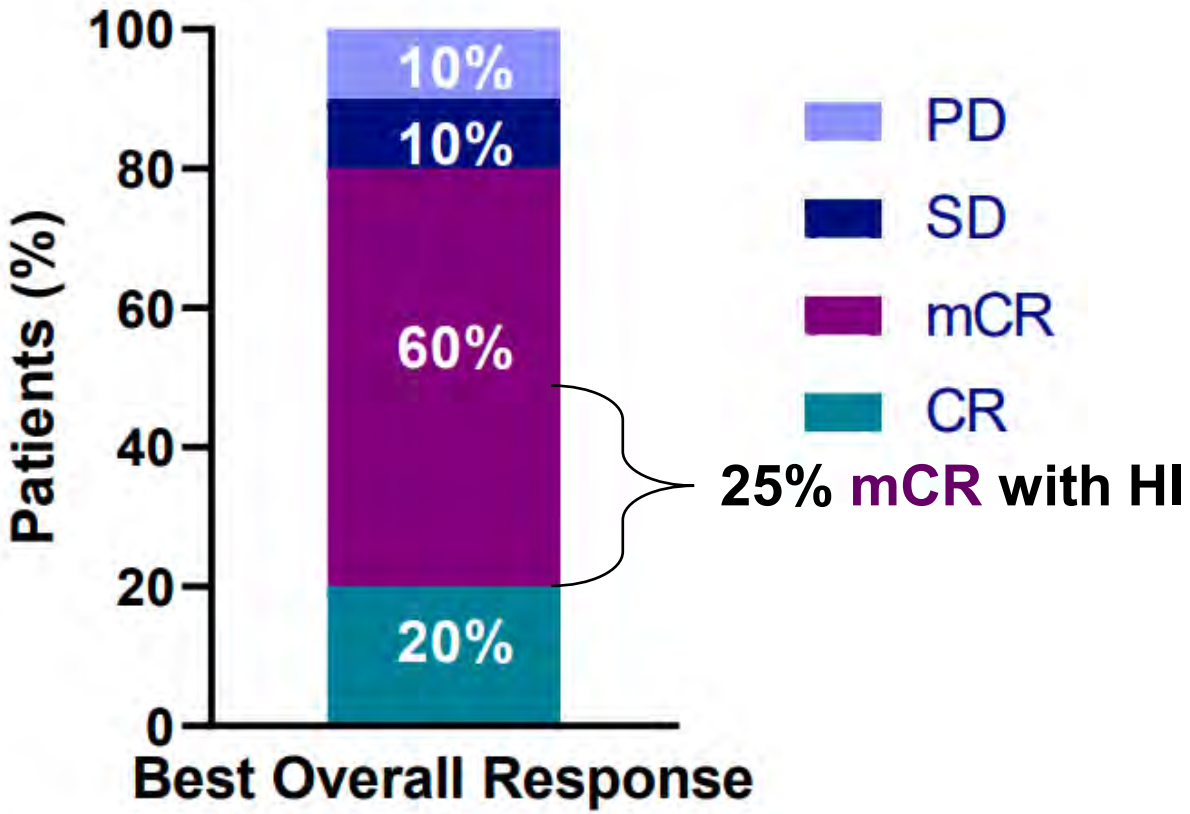
Primary endpoints (PE):
- Dual PE are CR and OS

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

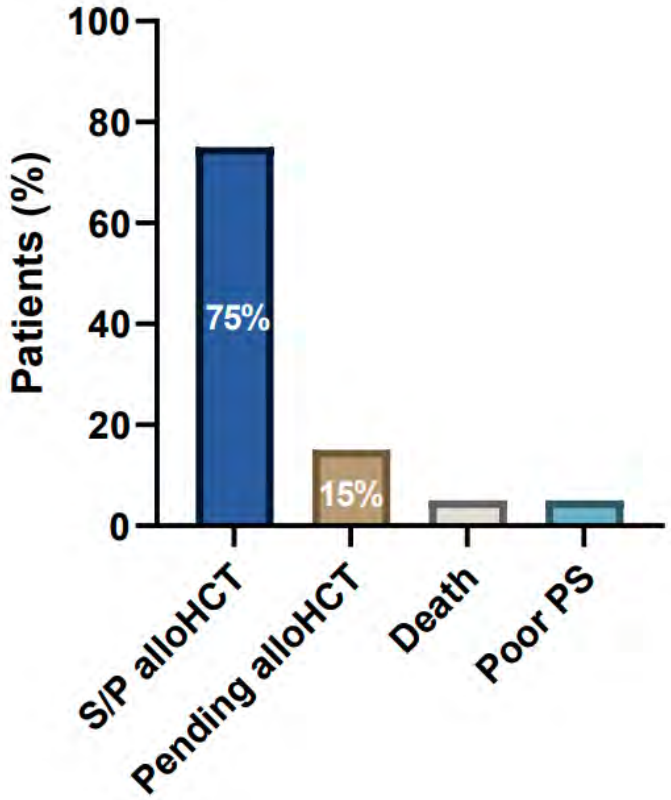
Considerations in use of venetoclax in Refractory/relapsed MDS

- Off-label use and risks/benefits should be thoroughly discussed with patient
- MDS patients are older and frailer than AML patients and usually have less reserve hematopoiesis
- AML experience can not be always extrapolated to HR-MDS (as evidenced by the 2-week dosing schedule of MDS vs. AML)
- Growing experience of how to manage cytopenias, dose reduction, interruption/delays of aza/Ven
- Early bone marrow sampling after first to second cycle is likely needed compared to standard HMA use
- Early data suggests minimal TLS risk, no need for hospitalization or ramp-up in majority of patients.
- Attention to drug-drug interactions is vital

Pilot Study of liposomal daunorubicin/cytarabine (CPX-351) in Transplant-Eligible Patients With Previously Untreated HR-MDS



Patients Proceeding to alloHCT



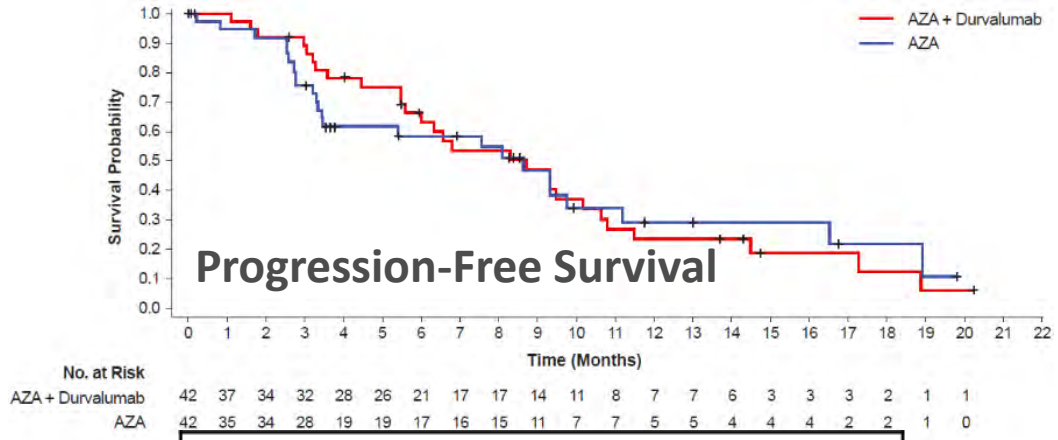
- 0/20 patients died within 30 days of induction
- 1/20 patients died within 60 days of induction, from PD to sAML

Database cutoff 10/1/2021

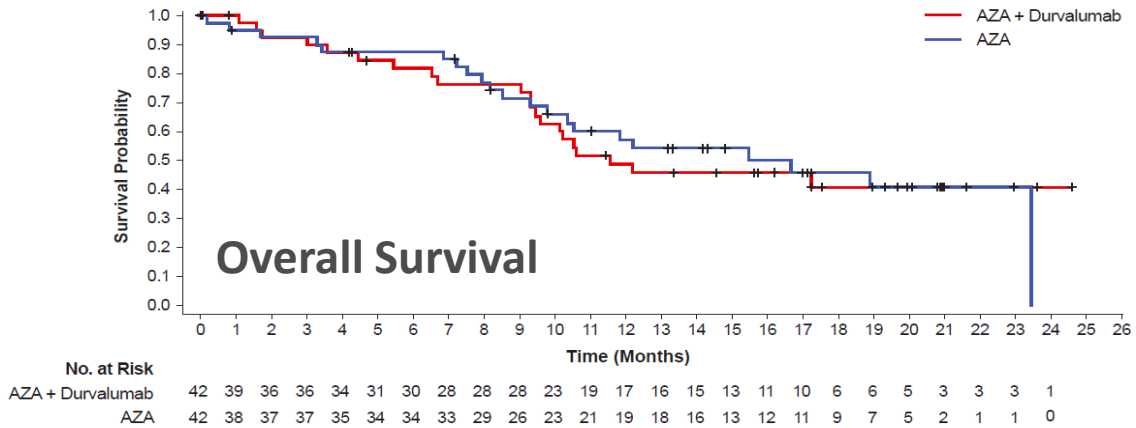
Reponses assessed by IWG 2006 criteria

Fusion 001 Trial: First randomized trial of Immune checkpoint blockade in MDS-azacitidine vs. azacitidine+anti-PDL1 durvalumab in frontline HR-MDS

Response, n (%) [95% CI]	AZA + Durvalumab	AZA
	n=42	n=42
ORR (CR + PR + mCR + HI)	26 (61.9) [47.2, 76.6]	20 (47.6) [32.5, 62.7]
	P=0.1838	
CR	3 (7.1) [0.0, 14.9]	4 (9.5) [0.7, 18.4]
PR	0	0
mCR	15 (35.7) [21.2, 50.2]	8 (19.0) [7.2, 30.9]
HI only	8 (19.0) [7.2, 30.9]	8 (19.0) [7.2, 30.9]
SD, n (%)	6 (14.3)	3 (7.1)
PD, n (%)	1 (2.4)	8 (19.0)
NE/Missing,† n (%)	6 (14.3)	7 (16.7)



Treatment	Events, n (%)	Median PFS, mo (95% CI)
AZA + durvalumab (n=42)	28 (67)	8.7 (5.6–10.2)
AZA (n=42)	24 (57)	8.6 (3.4–11.2)



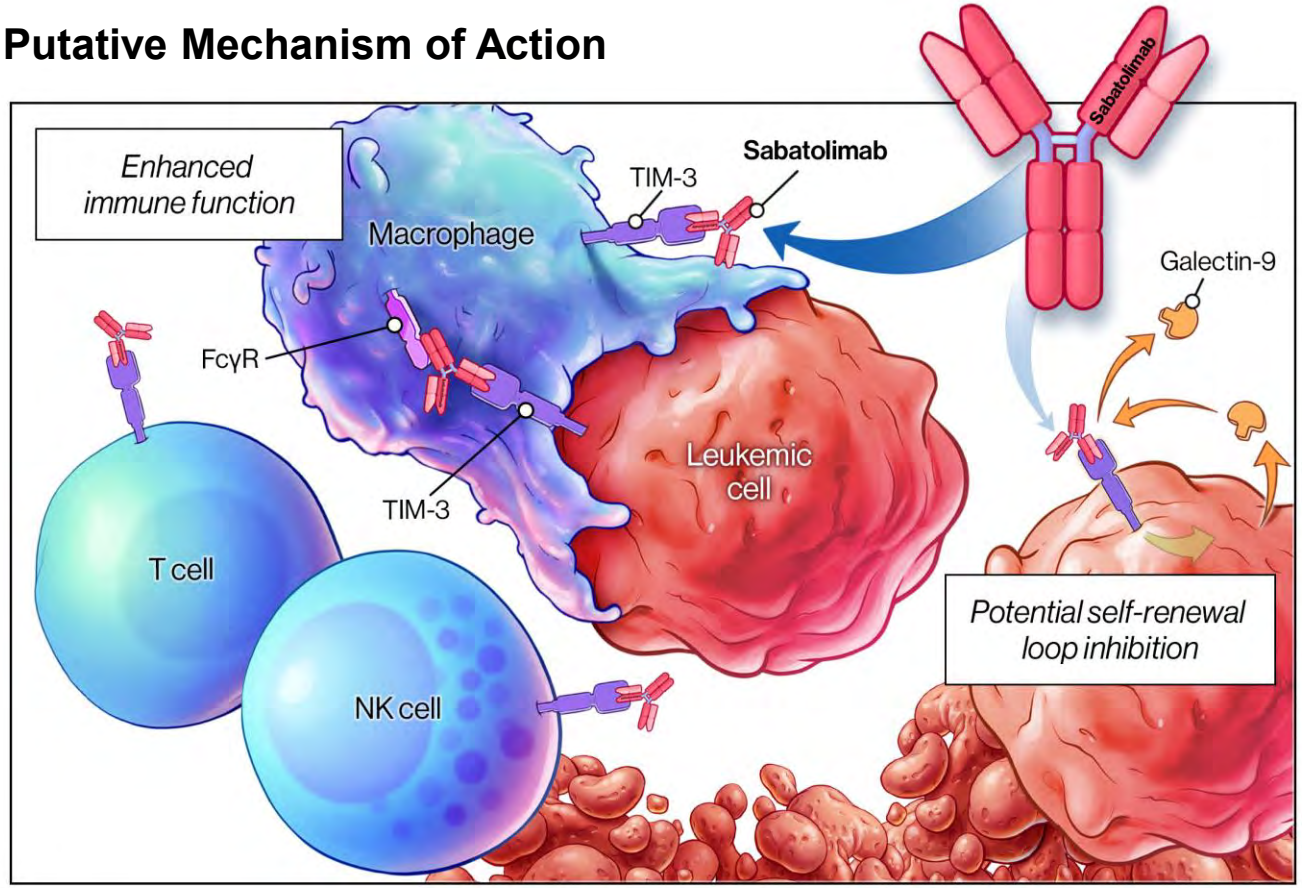
Treatment	Events, n (%)	Median OS, mo (95% CI)
AZA + durvalumab (n=42)	21 (50)	11.6 (9.5–NE)
AZA (n=42)	21 (50)	16.7 (9.8–23.5)

Zeidan AM et al; Blood Advances 2021

Sabatolimab: A novel immunotherapy targeting immuno-myeloid regulator TIM-3

- TIM-3 is expressed on LSCs and blasts, but not on normal HSCs[1-5]
- As an inhibitory receptor, TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- Preclinical studies show that sabatolimab has a potential dual mechanism to combat myeloid malignancies by reactivating the immune system[6]
- Sabatolimab + HMAs demonstrated clinical benefit with favorable tolerability in a Phase Ib study in patients with HR/vHR-MDS[7]

Putative Mechanism of Action



FcγR, Fc gamma receptor; HMA, hypomethylating agent; HR/vHR, high risk/very high risk; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; MDS, myelodysplastic syndromes; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

References: 1. Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev.* 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol.* 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell.* 2010;7(6):708-717; 5. Ngiow SF. *Cancer Res.* 2011;71(10):3540-3551; 6. Schwartz S, et al. *Immunother Adv.* 2022;2(1):ltac019; 7. Brunner AM, et al. ASH 2021. Abstract 244. Oral presentation.

STIMULUS-MDS 1 design: Phase II, randomized, double-blind, placebo-controlled

Patients

- Age ≥18 years
- Morphologically confirmed MDS
- IPSS-R risk: **Very high**, **high**, or **intermediate with ≥5% bone marrow blasts** at baseline
- Not suitable for intensive chemotherapy
- No planned HSCT
- ECOG PS 0-2

ClinicalTrials.gov identifier: **NCT03946670**

1:1 Randomization

Stratified by HMA[a] and IPSS-R[b]

Sabatolimab IV Q2W
(400 mg Day 8 and Day 22)
+
Decitabine IV (20 mg/m^2/day, Day 1-5) **or**
Azacitidine SC or IV (75 mg/m^2/day, Day 1-7 or Day 1-5+Day 8-9)

Placebo IV Q2W
(Day 8 and Day 22)
+
Decitabine IV (20 mg/m^2/day, Day 1-5) **or**
Azacitidine SC or IV (75 mg/m^2/day, Day 1-7 or Day 1-5+Day 8-9)

28-day cycles until disease progression

The study was unblinded following the final PFS analysis.
Follow-up will continue up to 4 years after the last patient was randomized.

Primary Endpoints:
Complete remission (CR)[c]
Progression-free survival (PFS)[d]

Secondary Endpoints:
Overall survival (OS)
Duration of CR
Response rates
Event-free survival
Leukemia-free survival
Transfusion independence
Safety
Pharmacokinetics
Immunogenicity

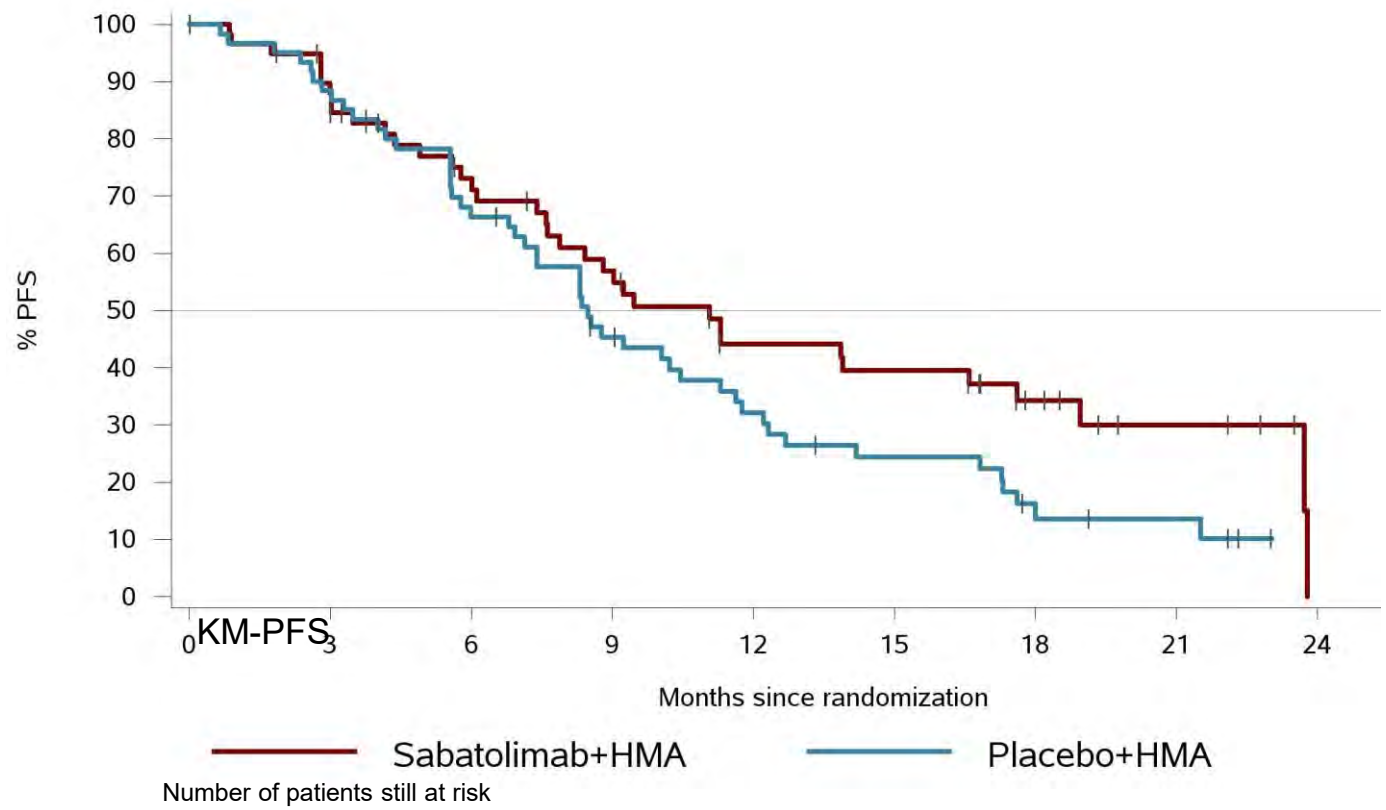
17 countries

47 study centers

Final PFS analysis data cutoff: March 1, 2022
Median duration of follow-up (randomization to cutoff): 24 months

CR, complete remission; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; SC, subcutaneous. [a]Decitabine or azacitidine per investigator discretion based on local standard of care. [b]IPSS-R prognostic risk categories (intermediate, high, very high) per investigator assessment. [c]Per modified International Working Group-MDS criteria. [d]Time from randomization to progression (including acute myeloid leukemia), relapse from CR, or death.

Sabatolimab + HMA did not result in a statistically significant improvement in CR or PFS



Number of patients still at risk

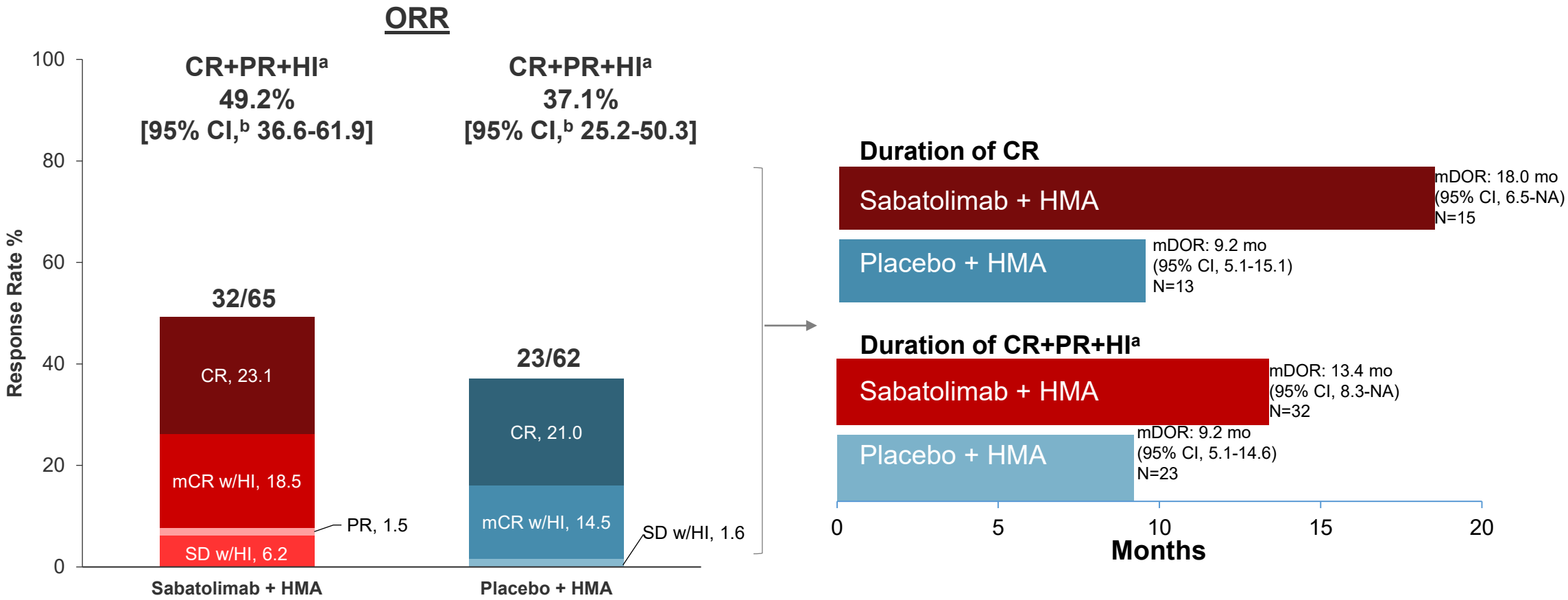
Time (Months)	0	3	6	9	12	15	18	21	24
Sabatolimab+HMA	65	51	37	28	19	17	10	5	0
Placebo+HMA	62	53	39	25	17	12	6	4	0

	Sabatolimab + HMA n=65	Placebo + HMA n=62
Primary CR rate (95% CI), %	**21.5 (12.3-33.5)**	**17.7 (9.2-29.5)**
P value[a]	0.769, ns	
PFS, median[b] (95% CI), mo	11.1 (7.6-17.6)	8.5 (6.9-11.3)
P value[c]	0.102, ns	
Hazard ratio[d]	0.749 (0.479, 1.173)	

- CR was evaluated earlier (March 10, 2021) by an independent data monitoring committee based on data up to 7 months after the last patient was randomized
- **Sabatolimab + HMA may have a delayed-onset benefit in terms of PFS**

KM, Kaplan-Meier; ns, not significant; PFS, progression-free survival.
[a]The critical value threshold for CR was 0.007. [b]The median follow-up time for PFS (time from the date of randomization to the date of PFS event or the date of censoring for PFS [i.e., the last adequate response assessment date]) was 7.89 months. [c]The critical value threshold for PFS was 0.0179. [d]Calculated via Cox model stratified by IPSS-R.

Sabatolimab + HMA demonstrated a potential benefit in duration of response



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

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

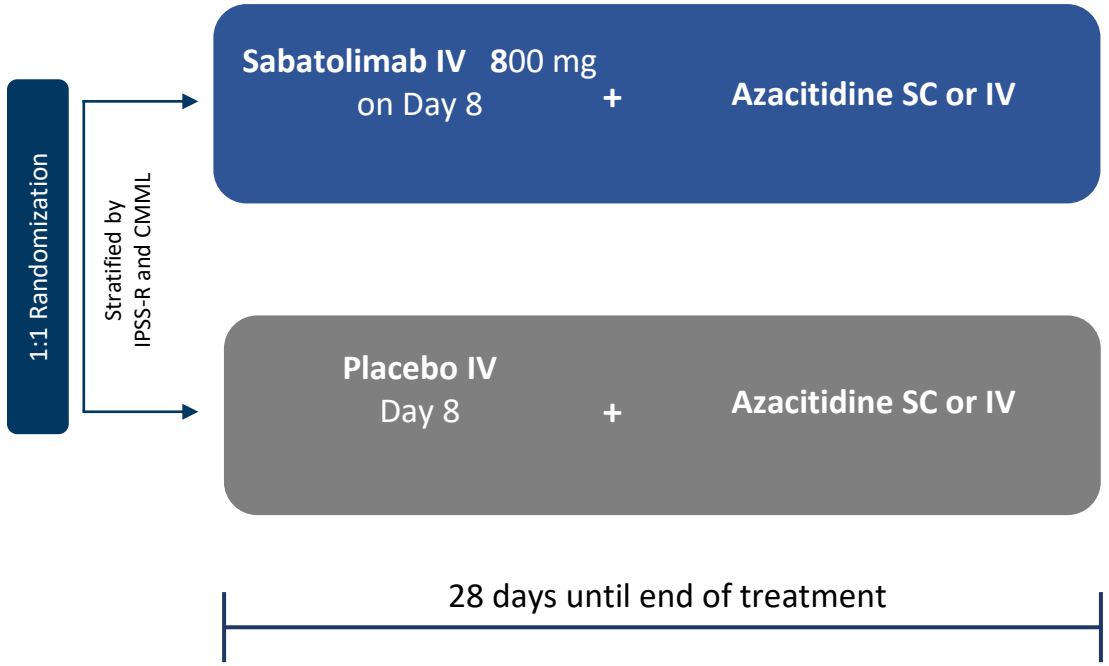
STIMULUS-MDS2: A Randomized Phase 3 trial of Sabatolimab+AZA vs. PBO+AZA in Patients With Higher Risk MDS

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

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

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

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



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

Magrolimab + AZA Induces promising clinical benefits in HR-MDS

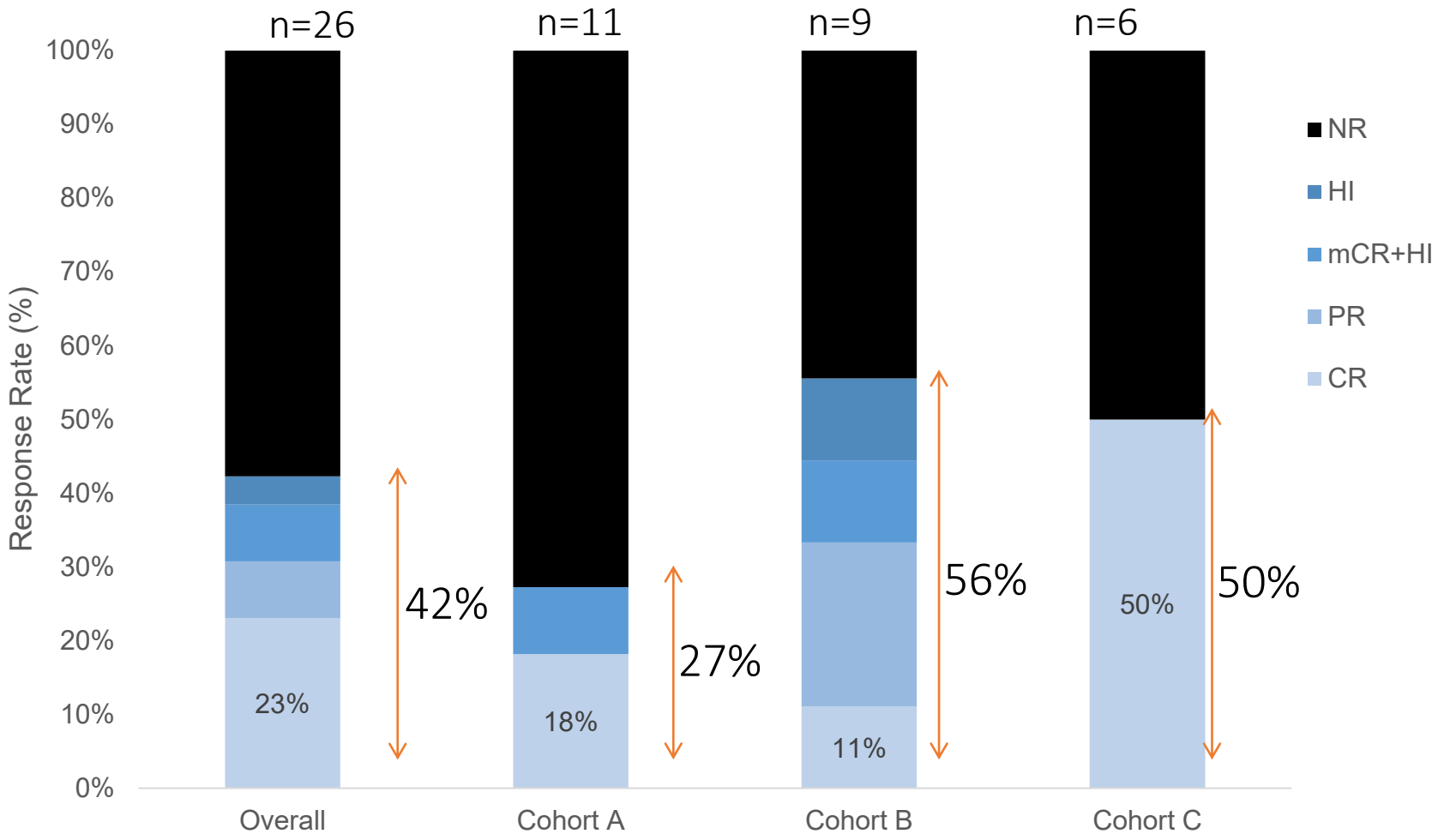
Outcome	All (N = 95)*	*TP53*-wt (N = 61)	*TP53*-mut (N = 25)
ORR, %*	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4, 43.0)	31.1 (19.9, 44.3)	40.0 (21.1, 61.3)
DCR, median (95% CI), mo	11.1 (7.6, 13.4)	12.9 (8.0, NR)	7.6 (3.1, 13.4)
DOR, median (95% CI), mo	9.8 (8.8, 12.9)	9.8 (8.5, 18.5)	9.2 (5.0, 12.2)
CCyR, n/N† (%)	19/65 (29.2)	13/41 (31.7)	6/20 (30)

- With a median follow-up of 17.1 months, median OS was not reached and was 16.3 months in *TP53*-mut MDS.

– CR rate was 32.6% and ORR was 74.6%, with response rates similar in *TP53*-mut and *TP53*-wt.

*Defined as CR + PR + marrow CR + HI without PD in all patients who received ≥ 1 magrolimab dose. †N = number with abnormal cytogenetics at baseline.
CR = complete remission; CCyR = complete cytogenetic remission; DCR = duration of CR; DOR = duration of response; mut = mutant; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; wt = wild type.

Enasidenib Is Effective in Patients with IDH2 Mutated MDS: The IDEAL Phase 2 Study by the GFM Group

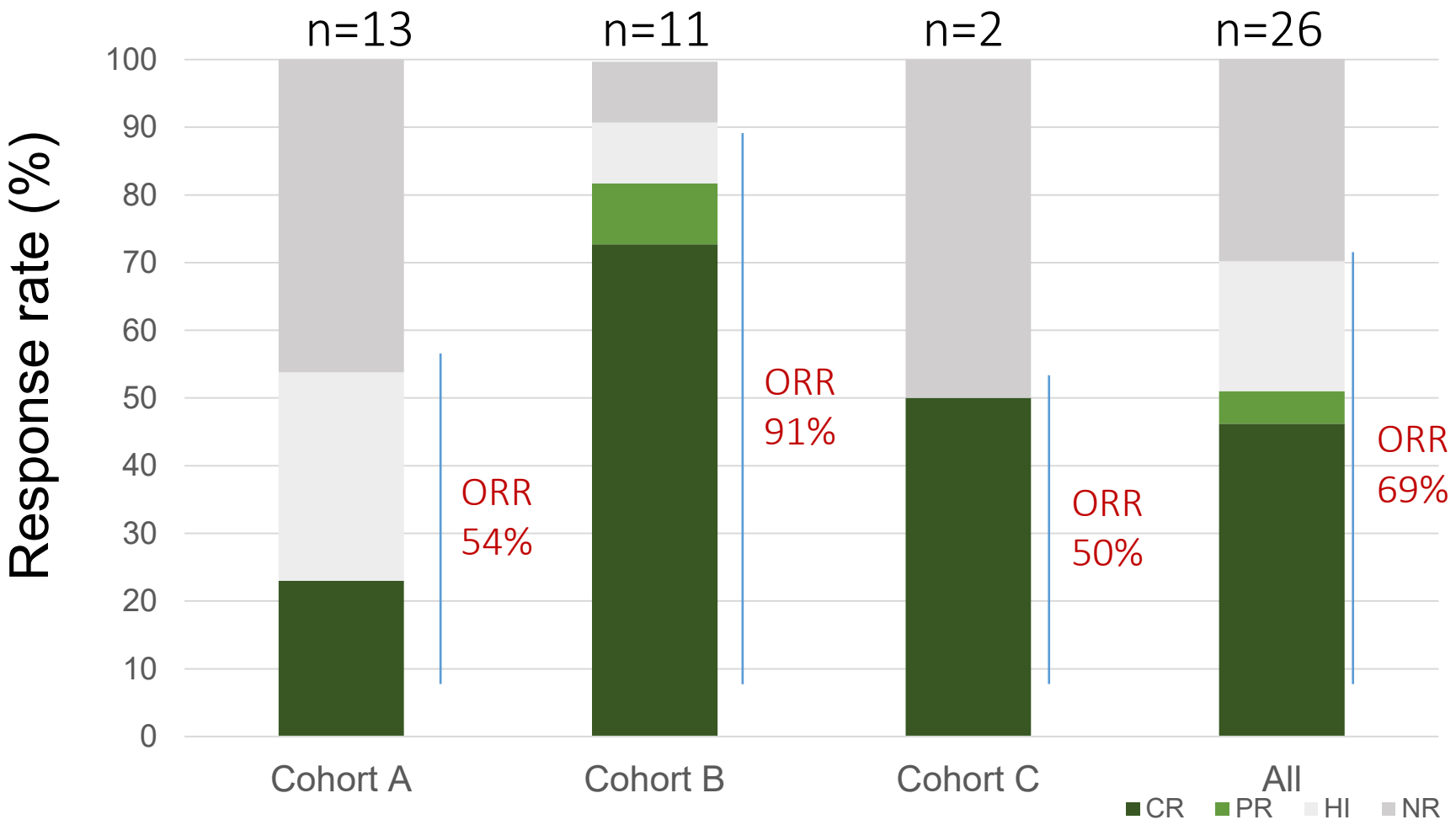


Cohort A –HR-MDS after HMA failure
Cohort B –HR-MDS Untreated
Cohort C –LR-MDS after ESA failure

In cohort B, AZA wad added to Ena in 3 patients who were primary resistant to ENA. Among them, 2/3 patients subsequently achieved a response

Ades L, et al. Blood. 2021;138: Abstract 63

Ivosidenib is Effective in Patients with IDH1 Mutated MDS
The IDIOME Phase 2 Study By the GFM Group



Cohort A –HR-MDS after HMA failure
Cohort B –HR-MDS Untreated
Cohort C –LR-MDS after ESA failure

- 46% of CR (including 73% in cohort B)
- 94,4% of the responders achieved response at 3 cycles
- Only one patient received azacitidine in association with Ivo after three cycles of Ivo in cohort B, without additional response

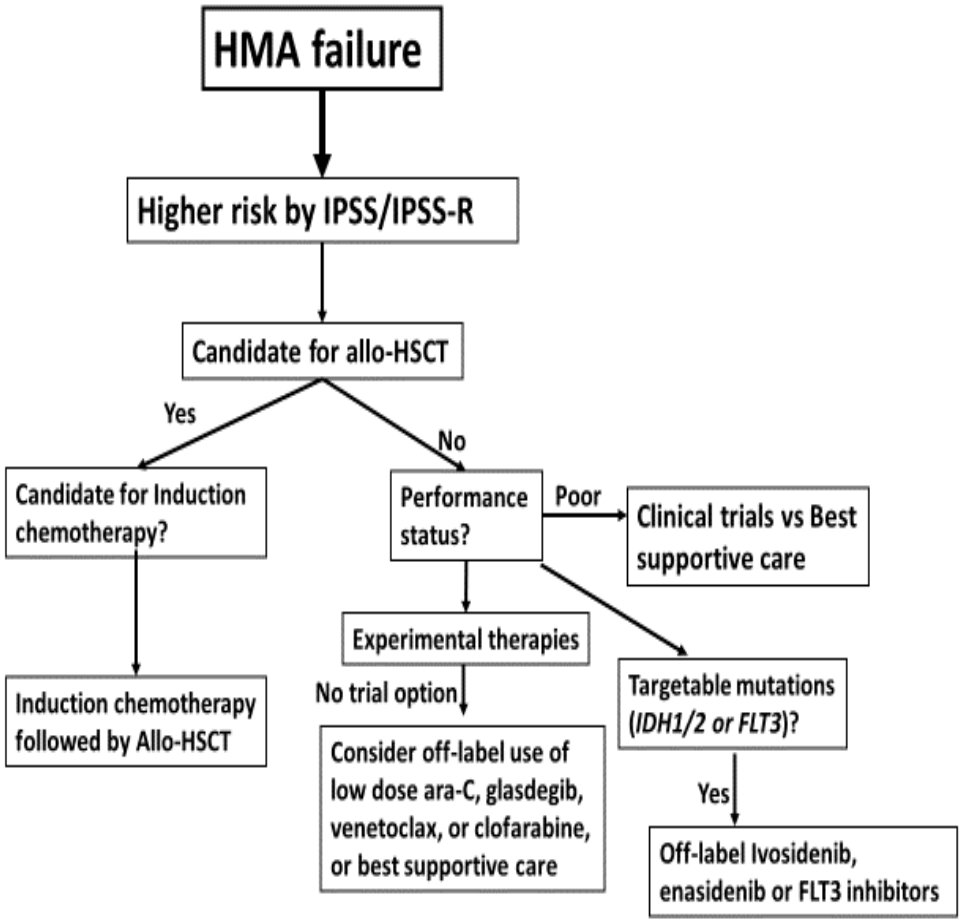
Sebert M, et al. Blood. 2021;138: Abstract 62

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

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

Source: Clinicaltrials.gov

How do I manage patients with HR-MDS after HMA failure?



Novel therapies for HMA-resistant/refractory MDS

Molecularly targeted agents:
- IDH1/2 inhibitors (ivosidenib, enasidenib, FT-2102)
- APR-246
- H3B-8800
- FLT3 inhibitors (e.g. gilteritinib)

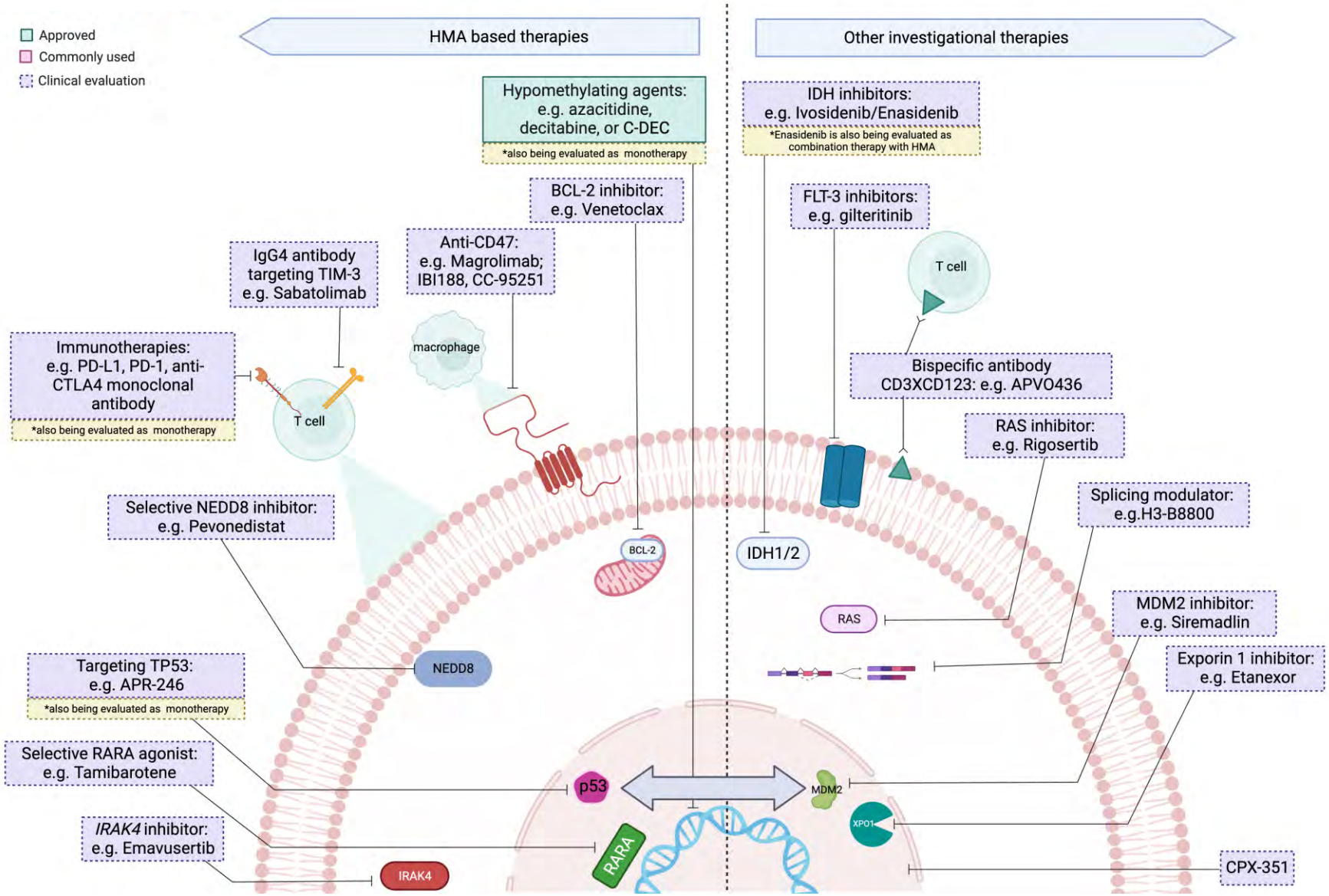
Genetically agnostic small molecule inhibitors:
- Pevonedistat
- Venetoclax
- Glasdegib
- Rigosertib

Immunotherapies:
- Anti-PD1/PD-L1 antibodies
- Anti-CTLA4
- Anti-TIM3
- Anti-CD47 antibodies

Chemotherapy/epigenetic agents:
- CPX-351
- Novel HMA (ASTX727, CC-486, guadecitabine)
- HDAC inhibitors

Bewersdorf J and Zeidan A, Expert Review of Hematology 2020;
Bewersdorf J and Zeidan A, Leukemia and Lymphoma 2020

Active clinical drug development in HR-MDS

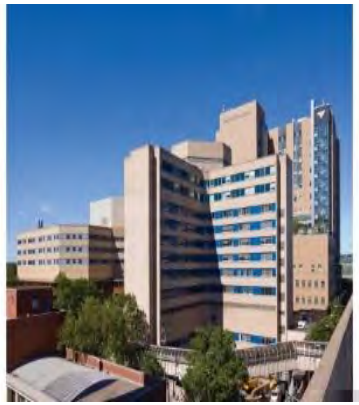


Madanat F, Xie Z, Zeidan AM, Expert Review of Hematology, In Press

Acknowledgements

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

someday is today®



Yale NewHaven Health
Smilow Cancer Hospital
Yale CANCER CENTER

The Ed Evans FOUNDATION
Registered Charity No. 1126226

Aplastic Anemia & MDS INTERNATIONAL FOUNDATION

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

MDS Clinical Research Consortium

Dennis Cooper Award

COPPER MDS

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

The Deluca Fund
Judge Schaller Fund

Questions?
Amer.Zeidan@yale.edu
Dr_AmerZeidan