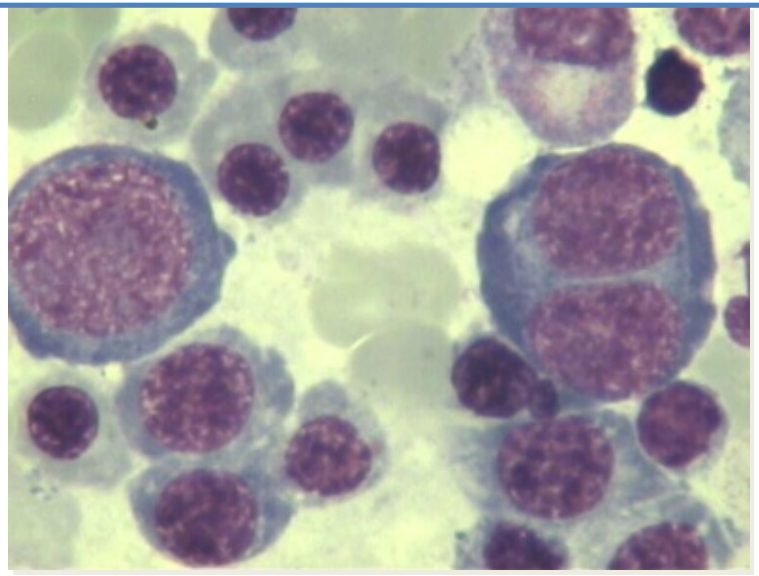
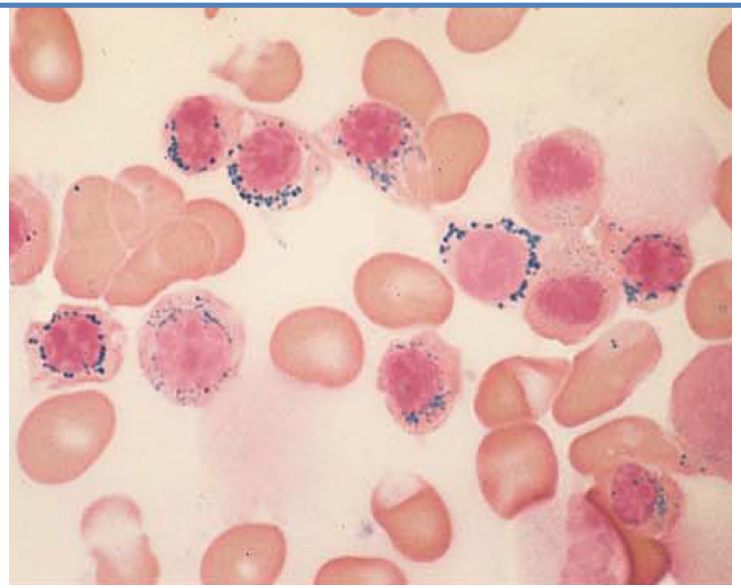
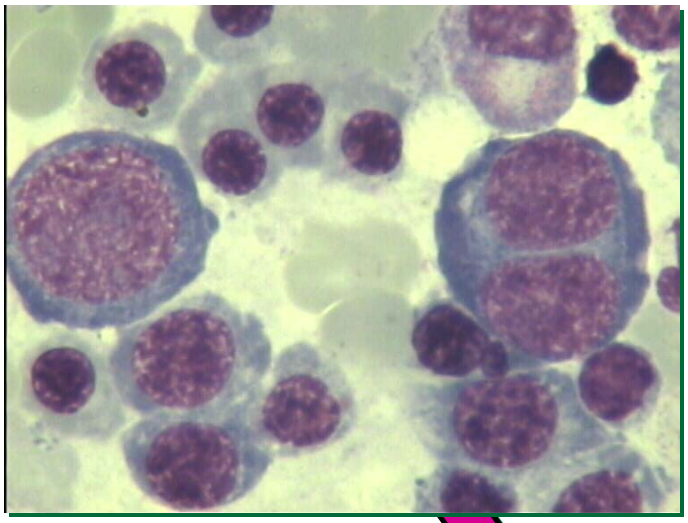
How I treat myelodysplastic syndromes

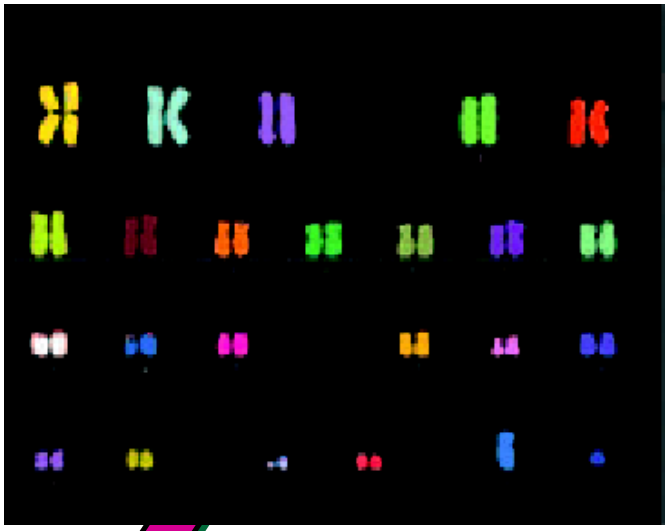




Valeria Santini
MDS Unit
University of Florence, Italy

Myelodysplastic syndromes are a constellation of diseases with difficult diagnosis



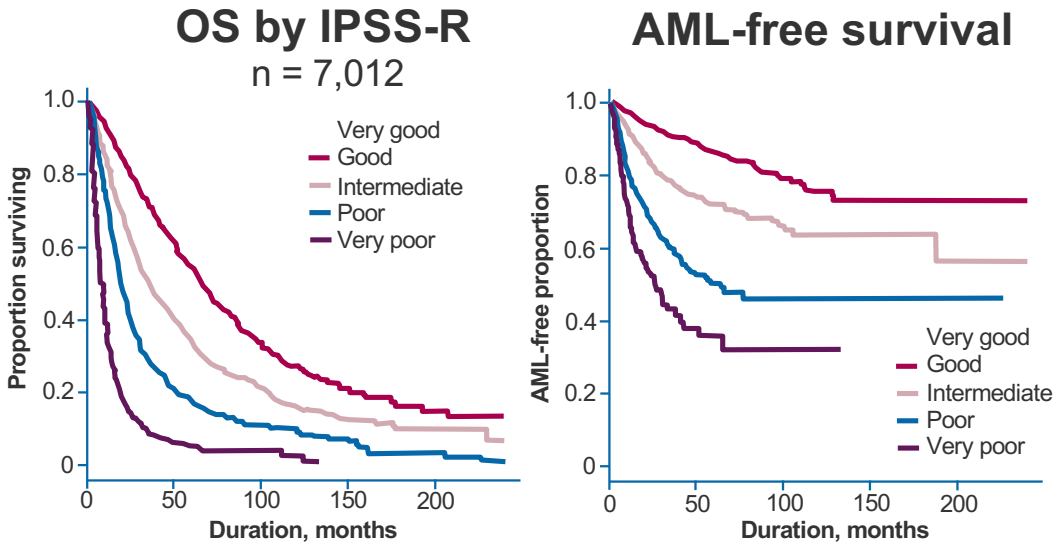


An accurate diagnosis is the basis for successful prognostic stratification (and treatment) of MDS

Criteria: presence and number of dysplastic lineages, mithocondrial iron, percentage of bone marrow blasts, cytogenetic abnormalities

IPSS-R: prognostic scores and risk groups

Risk category	Score
Very low	≤ 1.5
Low	> 1.5–3
Intermediate	> 3–4.5
High	> 4.5–6
Very high	> 6



	Very low	Low	Intermediate	High	Very high
Median OS, years	8.8	5.3	3.0	1.6	0.8
AML 25%, years	NR	10.8	3.2	1.4	0.73

* Values for 70-year-old patient (for consideration of age: [age in years − 70] x 0.04, add result to sum of other variables). Age, PS, ferritin, and LDH were significant additive features for OS but not for AML transformation.

NR, not reached.

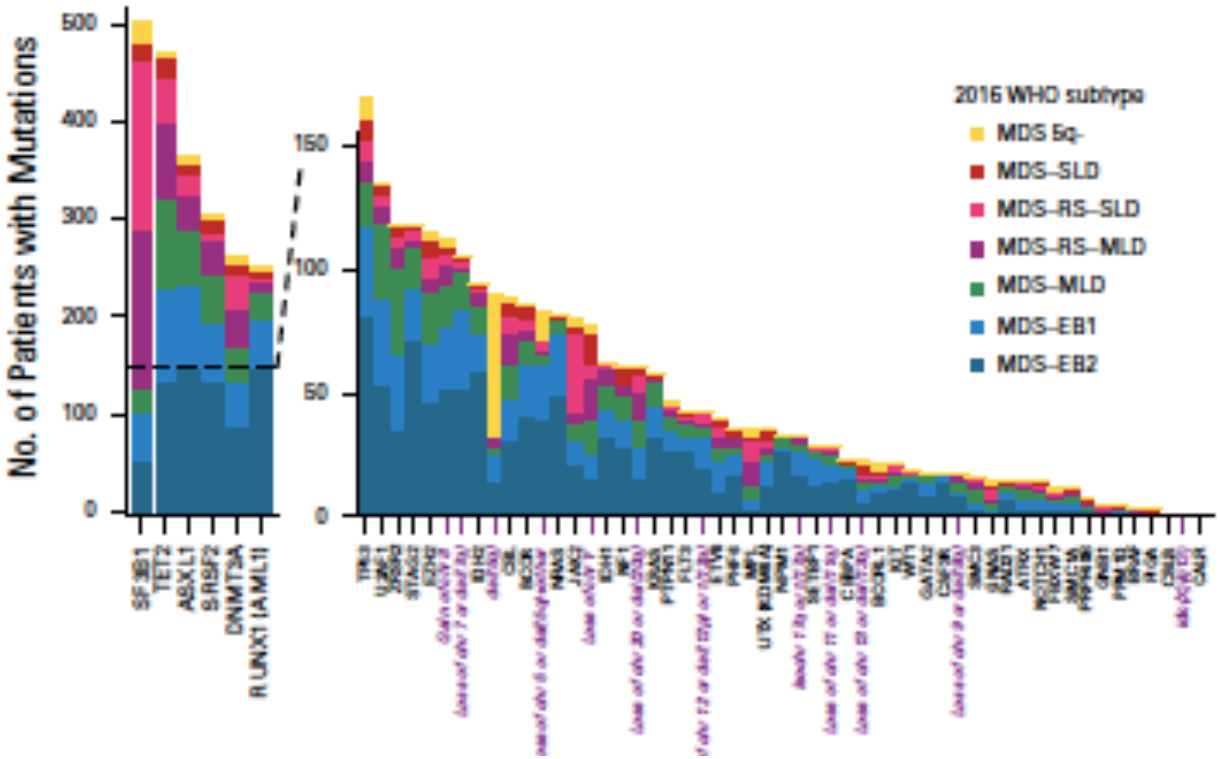
Greenberg PL, et al. Blood. 2012;120:2454-65 and updated data.

Somatic mutation evaluation in MDS

1. Help refining diagnosis (according to WHO for MDS with RS).
2. Prompt to earlier intervention in presence of multiple mutations
3. Prognostic established value in MDS of TP53 biallelic mutation
4. Prognostic value in HSCT
5. Identify inherited predisposition
6. Clonal hemopoiesis /Prediction of AML progression
7. Indicate possibility of targeted therapy

Frequency of recurrently mutated genes and chromosomal abnormalities in the EuroMDS cohort, broken down by MDS subtype according to 2016 WHO criteria.

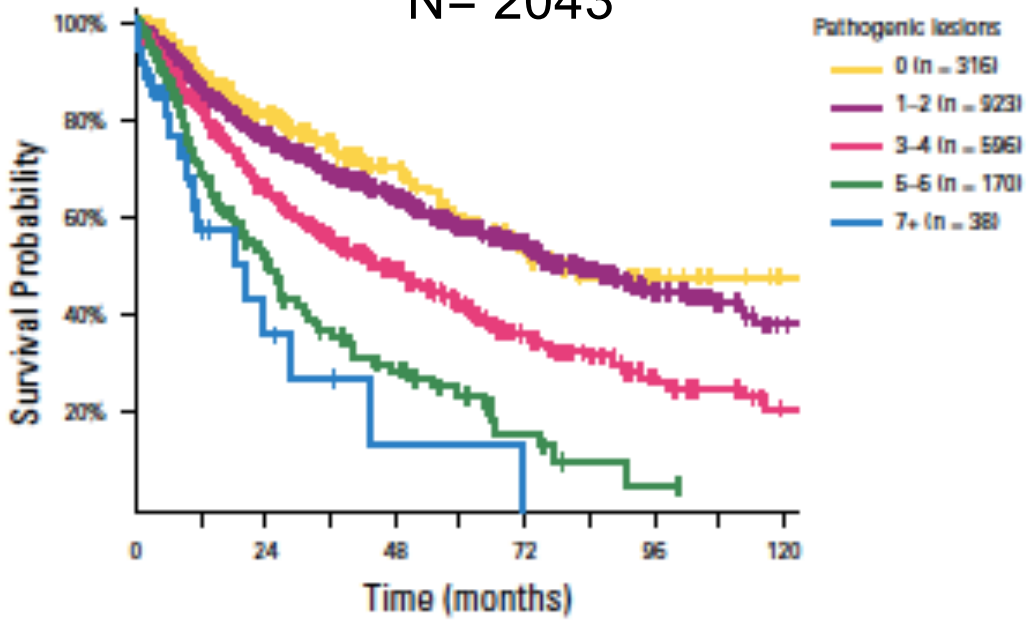
N= 2043



J Clin Oncol 39:1223-1233. © 2021 by American Society of Clinical Oncology

Correlation between number of genomic alterations (chromosomal and molecular) and Overall Survival

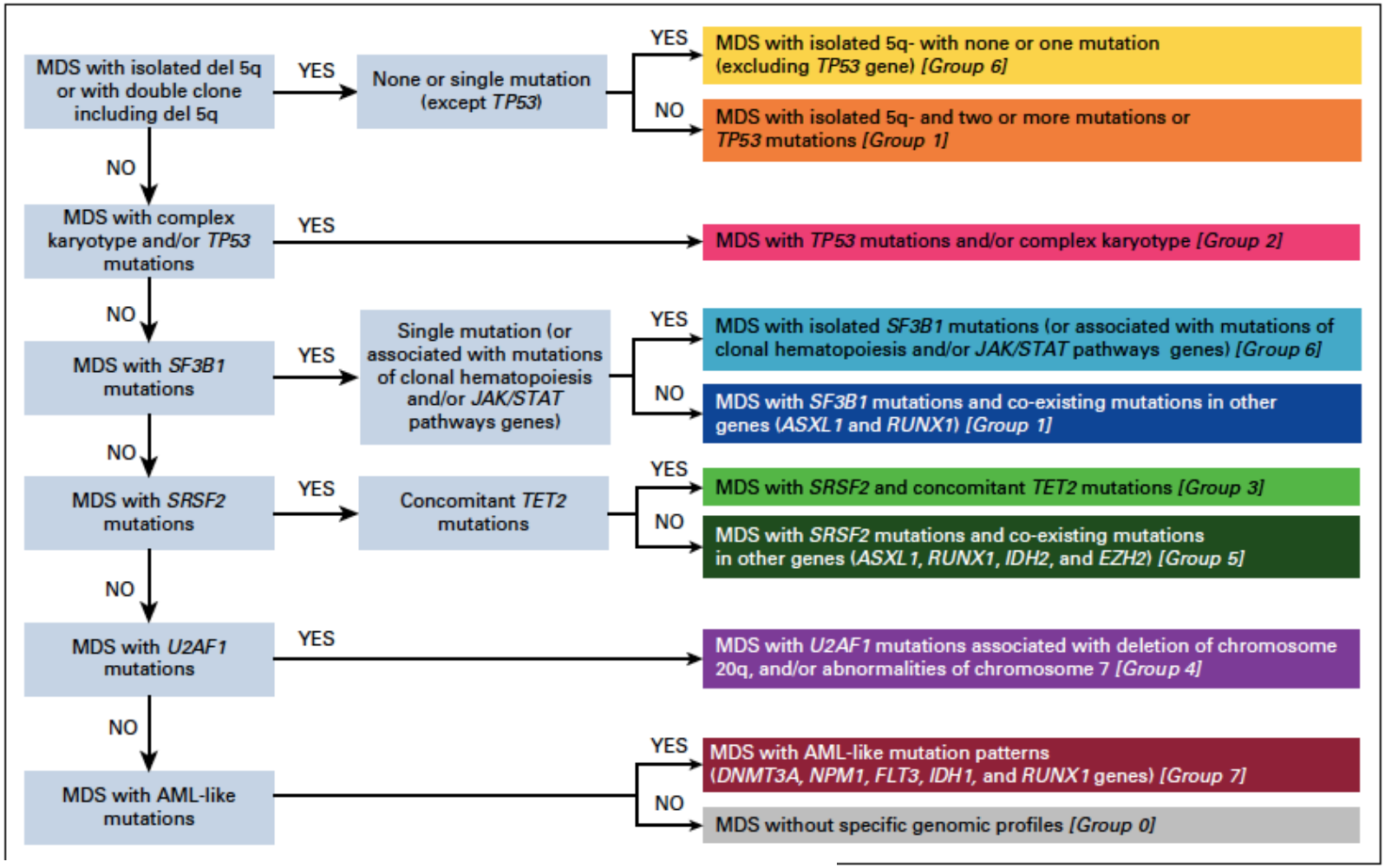
N= 2043



No. at risk

0	192	58	30	18	11	7
1–2	508	157	116	85	37	20
3–4	356	107	70	39	16	8
5–6	125	25	14	5	1	0
7+	33	4	1	0	0	0

Diagram for correct classification of MDS



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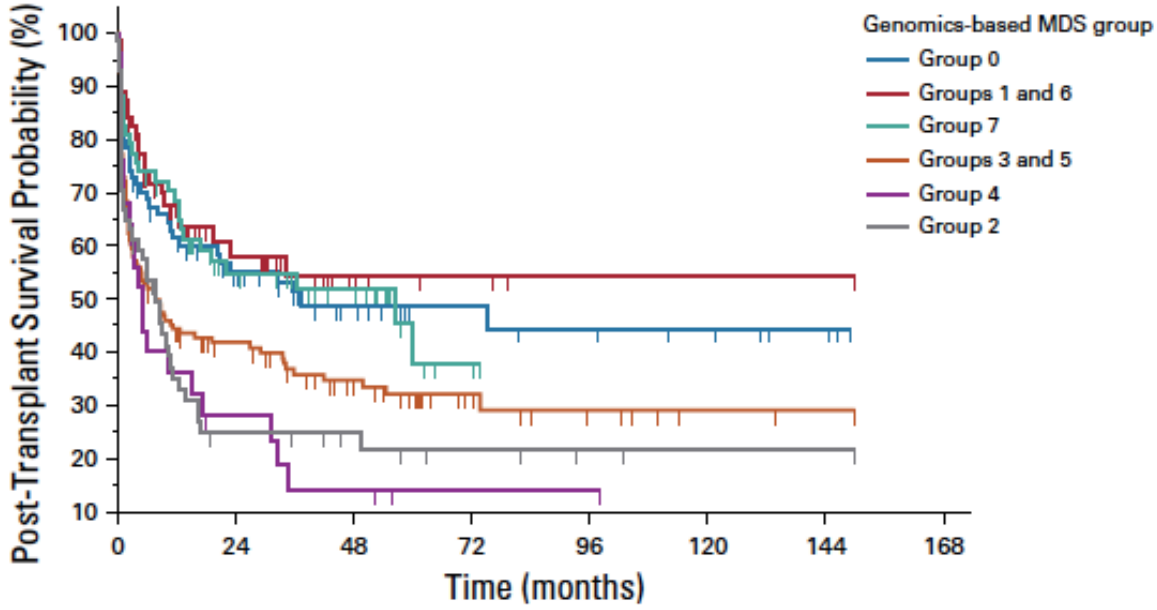
Probability of overall survival after allogeneic transplantation in the EuroMDS cohort.

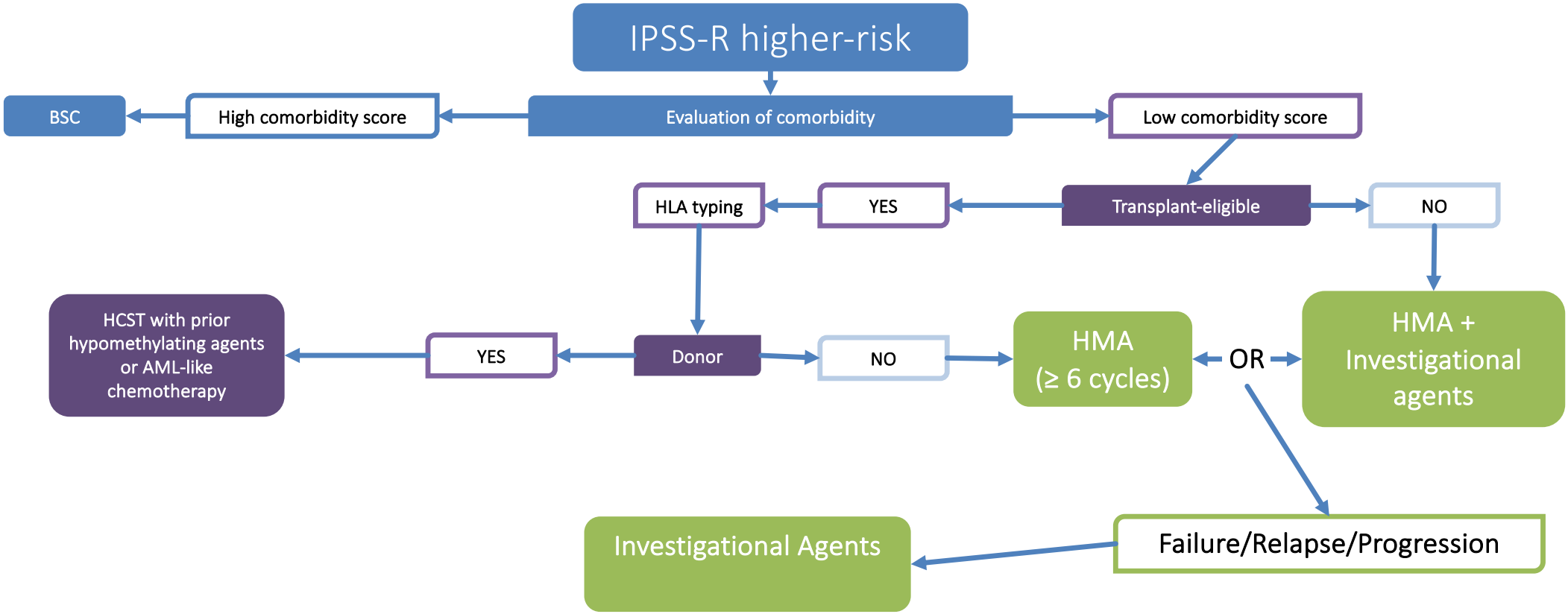


No. at risk

Group: Group 0	94	32	17	11	9	7	3	0
Group: Groups 1 and 6	75	21	8	3	1	1	1	0
Group: Group 7	65	24	16	3	0	0	0	0
Group: Groups 3 and 5	163	45	27	12	7	3	2	0
Group: Group 4	31	6	3	1	1	0	0	0
Group: Group 2	62	11	8	5	2	1	1	0

J Clin Oncol 39:1223-1233.

Therapeutic Options for Higher-Risk MDS

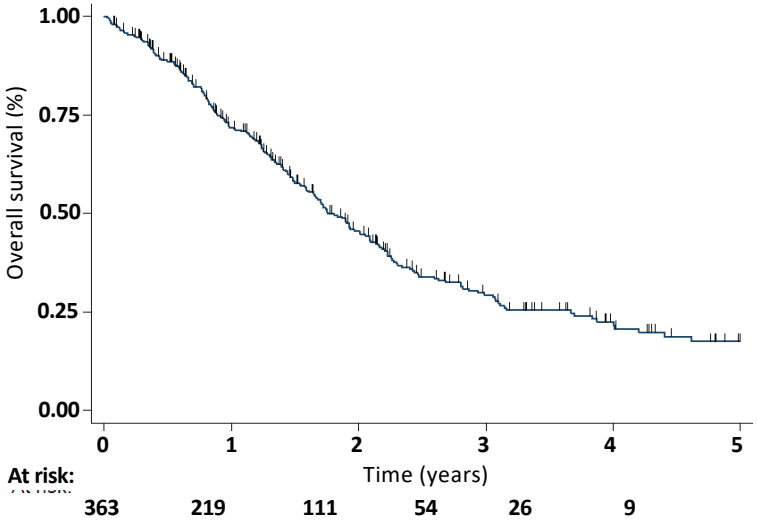


AML, acute myeloid leukemia; BSC, best supportive care; HLA, human leukocyte antigen; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IPSS-R, Revised International Prognostic Scoring System.

Santini V. Hematology Am Soc Hematol Educ Program. 2012;2012:65-73.

Survival of patients with higher-risk MDS after azacitidine treatment in real-world studies

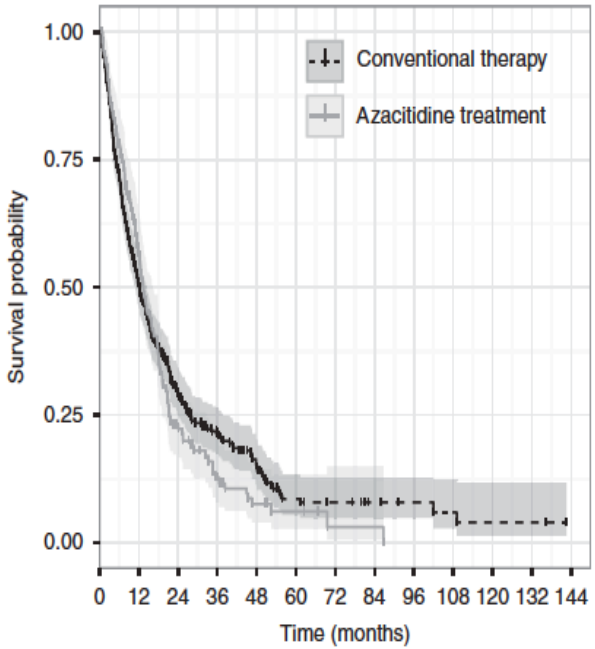
Italian registry[1]



Median AZA cycles 7

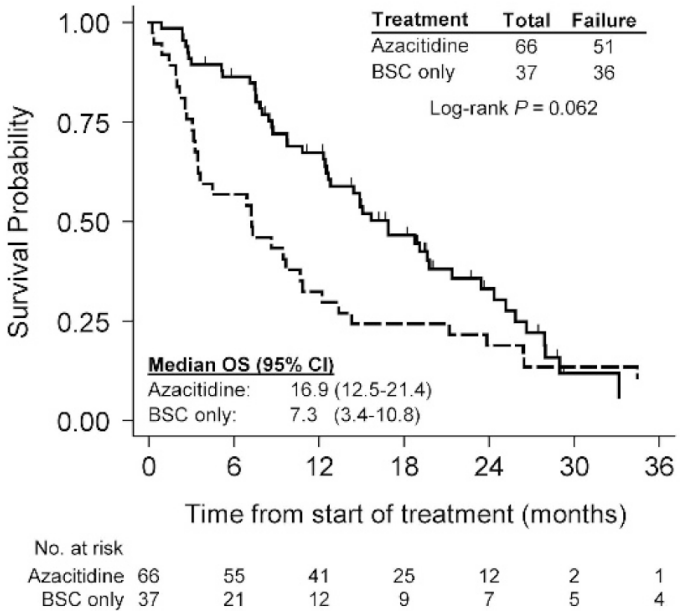
Median OS from start AZA: 16 mo

Spanish registry[2]



Median OS 13.4 vs 12.2 mo

Dutch registry[3]



Median OS 16.9 vs 7.3 mo

AZA, azacitidine; BSC, best supportive care; CI, confidence interval; mo, months; OS, overall survival.

1. Data from MDS Italian National Registry, 2016; 2. Bernal T, et al. *Leukemia*. 2015;29(9):1875-1881; 3. Dinmohamed AG, et al. *Leukemia*. 2015;29(12):2449-2451.

Hypomethylating Agents

- Beneficial effects of hypomethylating agents are noted generally after 2 to 4 cycles of therapy[1,2]
- Achievement of sole hematological improvement may assure prolonged survival[3]
- Interruption of treatment provokes loss of response[3]
- Patients with complex karyotype may achieve response although not durable[2,4]
- Only 60% of patients respond

AND…

- Patients resistant or relapsed have an extremely short survival irrespective of further treatment[5,6]

1. Lübbert M, et al. J Clin Oncol. 2011;29(15):1987-1996; 2. Fenaux P, et al. Lancet Oncol. 2009;10(3):223-232. 3. Garcia-Manero et al. J Clin Oncol. 2011;29(5):516-523; 4. Kuendgen A, et al. Oncotarget. 2018;9(45):27882-27894; 5. Prébet T, et al. J Clin Oncol. 2011;29(24):3322-3327; 6. Jabbour E, et al. Cancer. 2010;116(16):3830-3834.

Resistance to HMAs

Primary resistance

- No HI/CR/PR at any time, with/without progression to AML or HR-MDS, or severly hypoplastic BM

Secondary resistance or adaptive resistance

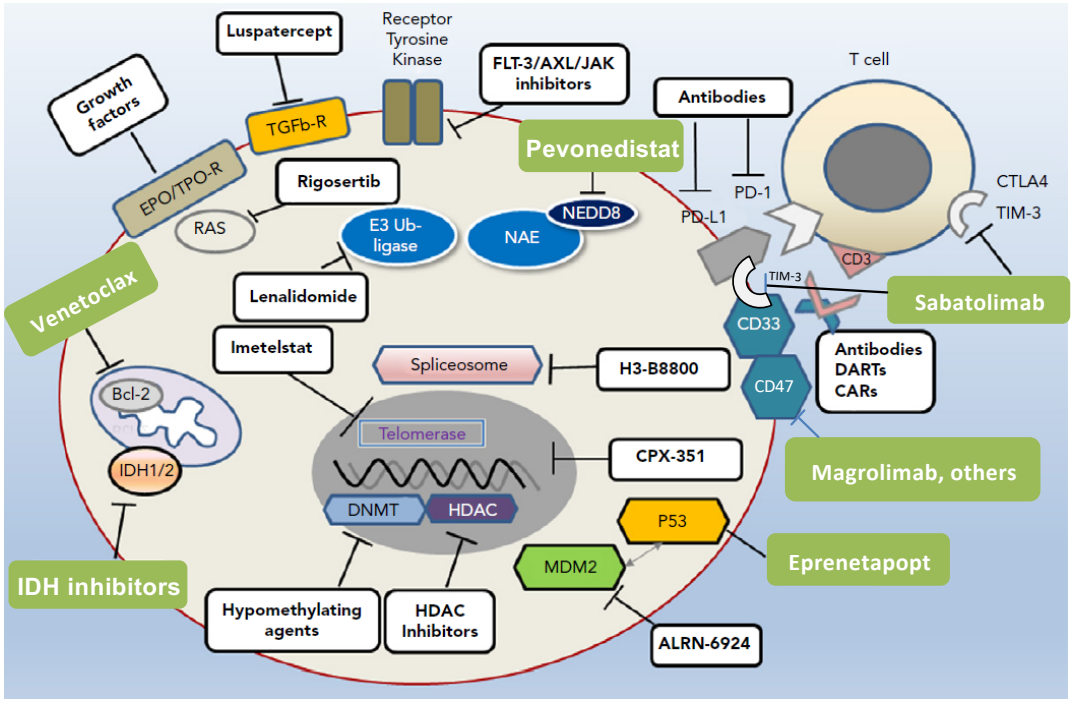
- After any response (CR, mCR, PR, HI) maintained for any number of cycles and without therapy interruption or delays exceeding 5 weeks between cycles, the response is lost
- These situations may be encountered in both higher-risk and lower-risk MDS patients receiving azacitidine or decitabine

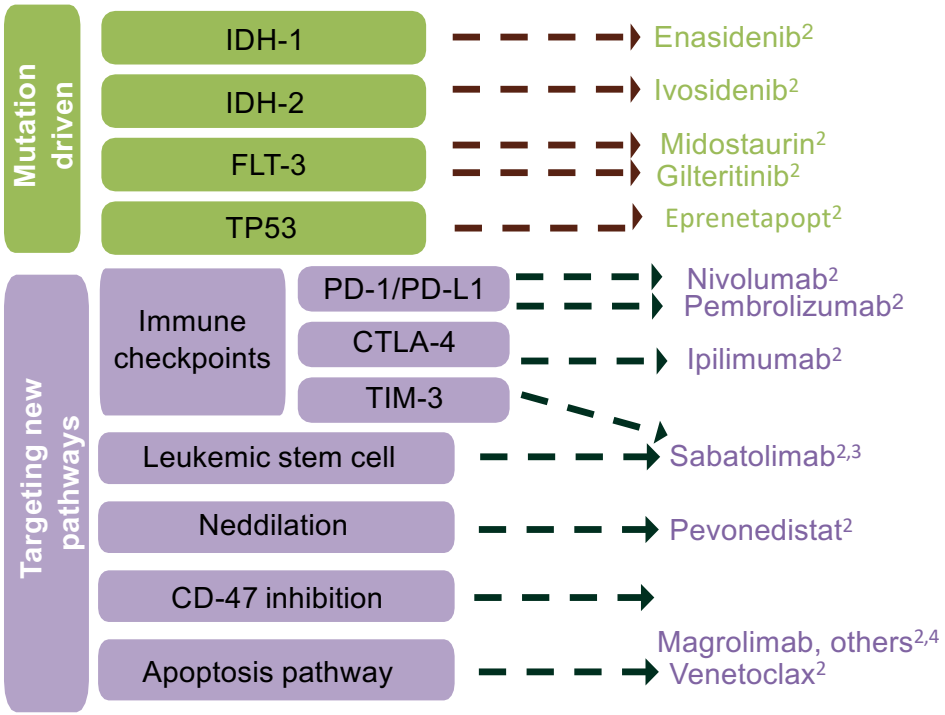
The mechanisms of primary and secondary resistance are unknown

AML, acute myeloid leukemia; CR, complete remission; HI, hematological improvement; HMAs, hypomethylating agents; HR-MDS, higher-risk myelodysplastic syndrome; mCR, bone marrow CR; PR, partial remission.

Santini V. Blood. 2019;133(6):521-529.

Possible new approaches aiming to optimize treatment of patients with higher-risk MDS [1-4]

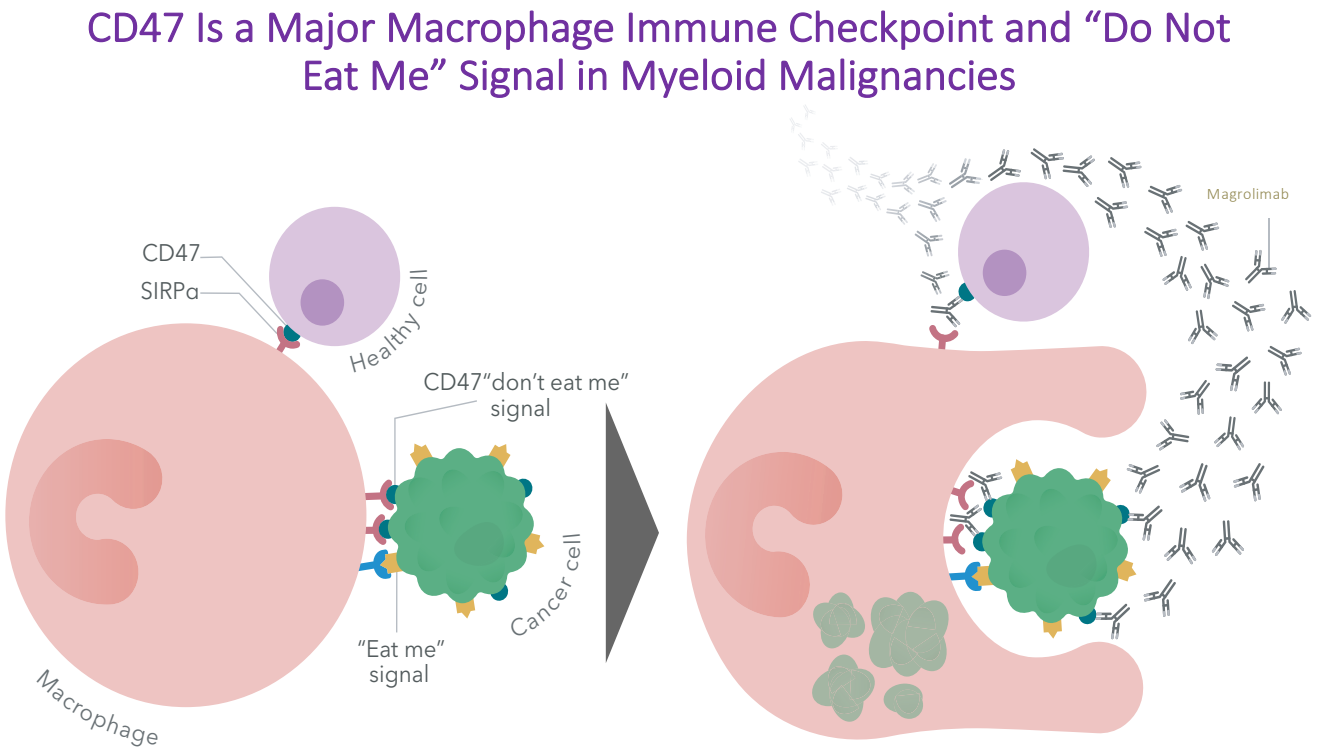




AXL, anexelekto; Bcl-2, B-cell lymphoma-2; CAR, chimeric antigen receptor; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DART, dual affinity retargeting protein; DNMT, DNA methyltransferase; EPO, erythropoietin; FLT-3, fms-like tyrosine kinase 3; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; JAK, janus kinase; MDS, myelodysplastic syndrome; NAE, NEDD88 activating enzyme; NEDD8, neural precursor cell expressed developmentally downregulated protein 8; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TGFb-R, transforming growth factor beta receptor; TIM-3, T-cell immunoglobulin domain and mucin domain-3; TPO-R, thrombopoietin receptor.

1. Platzbecker. Blood. 2019;133(10):1096-1107; 2. Pagliuca S, et al. Cancers. 2021;13:784; 3. Brunner A, et al. ASH 2020. Oral 657; 4. Puro R, et al. Mol Cancer Ther. 2020;19:835-846.

Magrolimab is a macrophage immune checkpoint inhibitor targeting CD47



- IgG4 monoclonal antibody that targets CD47, which plays an important role in self-recognition
- Blockade of CD47 allows for macrophage recognition and phagocytosis

CD, cluster of differentiation; Ig, immunoglobulin; SIRPα, signal regulatory protein alpha.

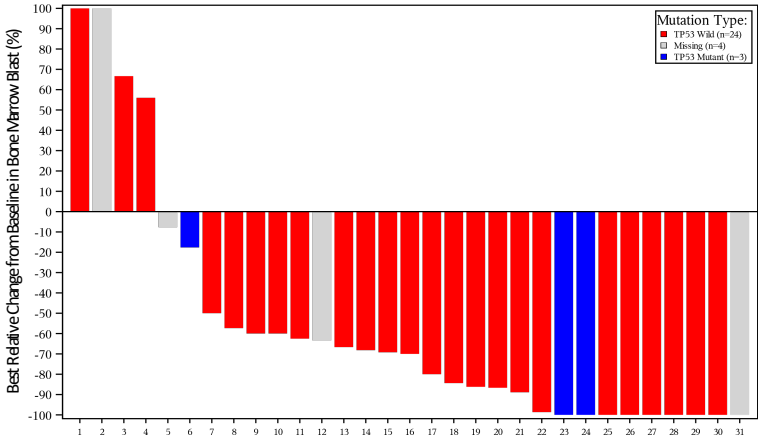
Daver N, et al. EHA 2020. Abstract S144 (oral).

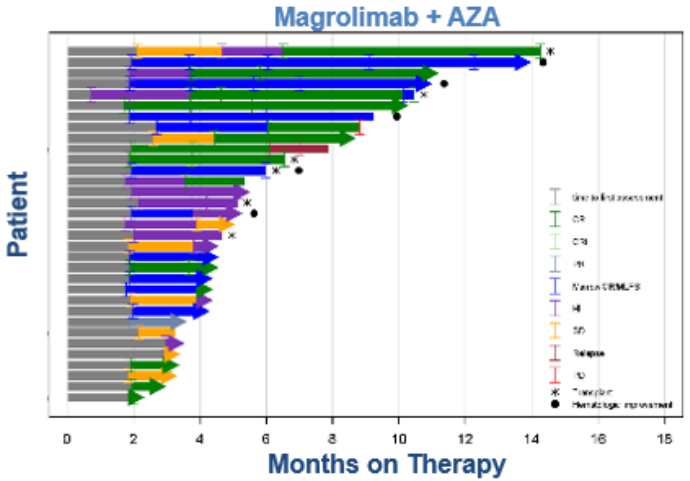
Magrolimab + AZA achieved promising ORR and durable response in patients with higher-risk MDS in a Phase Ib trial

Safety[1]

- Treatment was well tolerated with no exacerbation of cytotoxicities vs AZA monotherapy, and no patient discontinued due to a drug-related AE

Best Overall Response	1L MDS, N=33
ORR	30 (91%)
CR	14 (42%)
PR	1 (3%)
Marrow CR	8 (24%) 4 with marrow CR + HI
HI	7 (21%)
SD	3 (9%)
PD	0





Efficacy[1]

- **Magrolimab + AZA induces a 91% ORR (42% CR)**
- Responses deepened over time, with a 56% 6-month CR rate (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6%-17%[2,3])

1L, first-line; AE, adverse event; AZA. Azacitidine, CR, complete remission; HI, hematologic improvement; MDS, myelodysplastic syndrome; ORR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.

1. Sallman D, et al. EHA 2020. Abstract S187 (oral); 2. Vidaza (azacitidine) [package insert]. Summit, NJ: Celgene Corporation;2020; 3. Fenaux P, et al. Lancet Oncol. 2009;10(3):223-232.

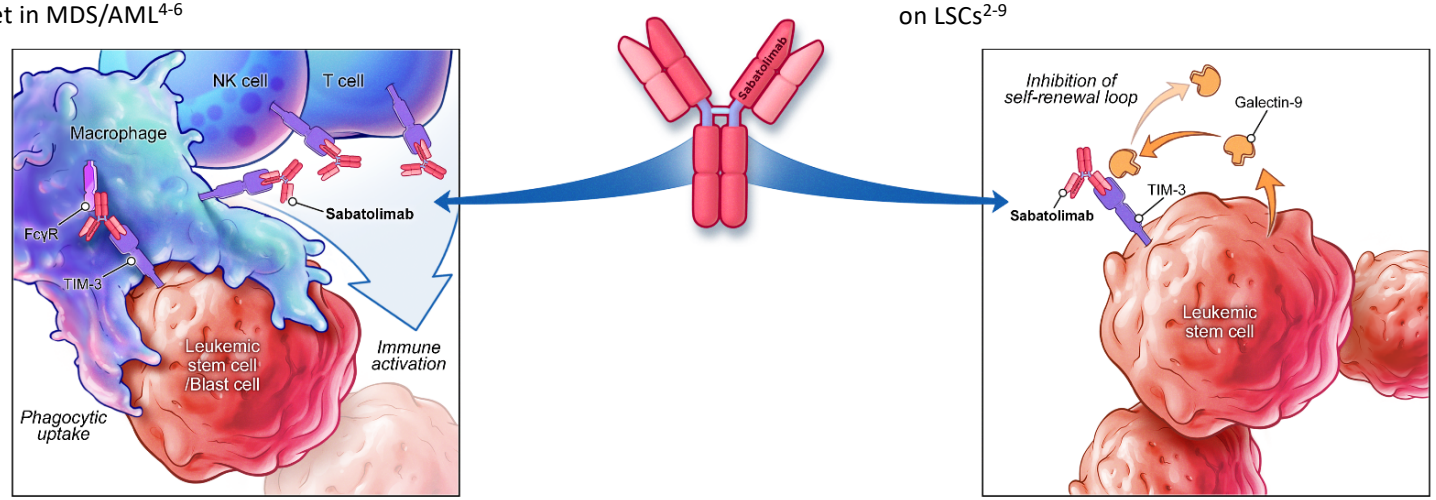
Sabatolimab is an immuno-myeloid therapy that targets TIM-3 on immune cells and leukemic stem cells and blasts

TIM-3

- Inhibitory receptor expressed on macrophages, monocytes, NK cells, dendritic cells, and T cells[1,2]
- Involved in regulating innate and adaptive immune responses[1,2]
- Expressed on LSCs/blasts but not normal HSCs,[3,4] making it a promising target in MDS/AML[4-6]

Targeting LSCs and blasts

- High-affinity, humanized, IgG4 anti–TIM-3 monoclonal antibody[6,7]
- Enhances antileukemia immune activation and phagocytic uptake, facilitating immune cell-mediated killing of LSCs/blasts[2,7-9]
- May inhibit TIM-3/galectin-9–driven LSC self-renewal via blockade of TIM-3 on LSCs[2-9]

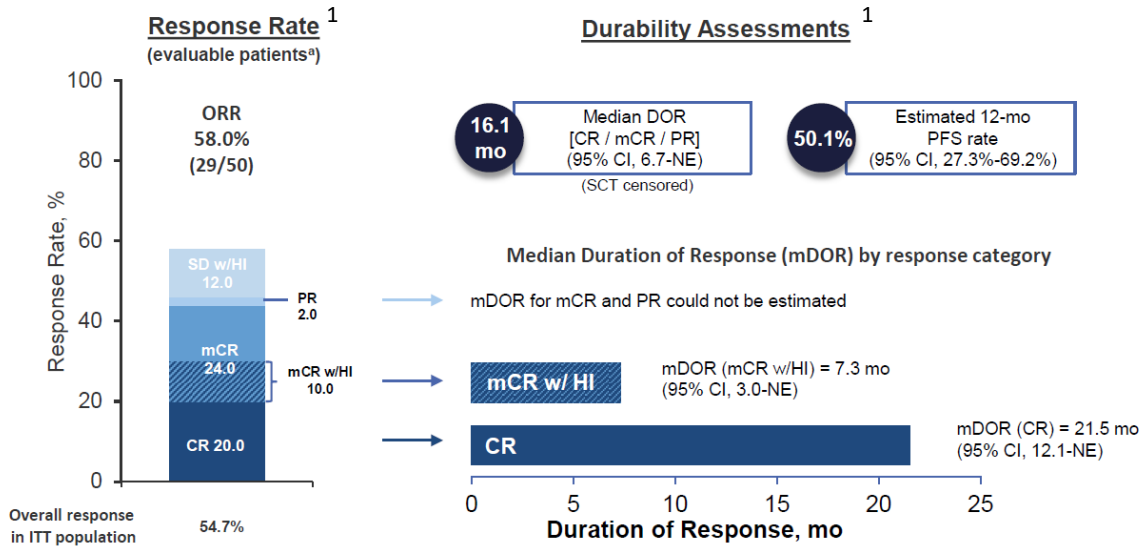


Sabatolimab aims to reawaken the immune system to enable selective attack of LSCs and blasts, enhance antibody-dependent cellular phagocytosis, and inhibit LSC self-renewal[2]

AML, acute myeloid leukemia; FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; IgG4, immunoglobulin G4; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Wolf Y, et al. Nat Rev Immunol. 2020;20(3):173-185; 2. Acharya N, et al. J Immunother Cancer. 2020;8(1):e000911; 3. Haubner S, et al. Leukemia. 2019;33(1):64-74; 4. Asayama T, et al. Oncotarget. 2017;8(51):88904-88917; 5. Kikushige Y, et al. Cell Stem Cell. 2015;17(3):341-352; 6. Mach N, et al. Ann Oncol. 2019;30(suppl 5):Abstract 1202P; 7. Borate U, et al. HemaSphere. 2020;4(suppl 1):Abstract S185; 8. Borate U, et al. EHA 2020. Oral presentation; 9. Sabatos-Peyton C, et al. SITC 2020. Abstract 439.

Sabatolimab + HMA demonstrates promising durable clinical benefit in patients with vHR/HR-MDS in a Phase Ib study [1]



Safety[1]

- Sabatolimab + HMA is well tolerated. Most commonly reported TEAEs were consistent with those for HMA alone
- No vHR/HR-MDS patients discontinued therapy due to AE
- No grade 3/4/5 treatment related possible immune-mediated AEs from sabatolimab + HMA therapy, in MDS

- **Sabatolimab + HMA demonstrated promising durable clinical benefit in vHR/HR-MDS[1,2]**
- **Encouraging durability was also observed in vHR/HR-MDS patients with adverse risk characteristics [1]**
  - **Patients with *TP53* mutation: remission rate[c] was 55% (6/11; 4/6 in remission >200 days)**
  - **Patients with ≥ 1 of *TP53, RUNX1, or ASXL1* mutations: remission rate was 59% (13/22; 8/13 in remission >200 days)**
  - **Remission rates were similar in patients ≥75 years old (50%; 6/12) and 65-74 years old (65%; 11/17); an estimated 83% and 86%, respectively, remained in remission after 6 months**

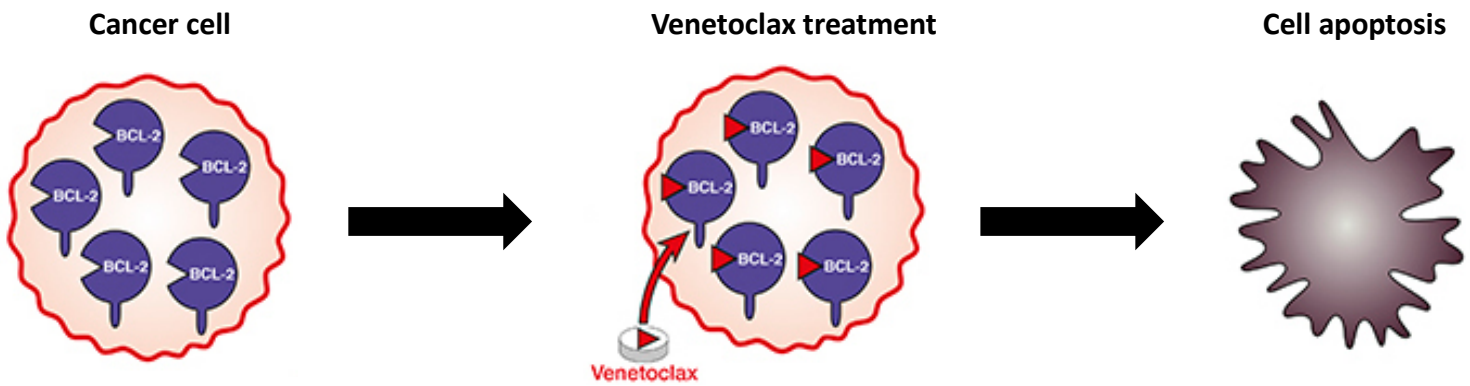
AEs, adverse events; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; EOT, end of treatment; HI, hematological improvement; HMA, hypomethylating agent; HR, high-risk; IPSS-R, Revised International Prognostic Scoring System; ITT, intent-to-treat; mCR, bone marrow CR; MDS, myelodysplastic syndrome; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease; TEAE, treatment-emergent adverse event; vHR, very high-risk.

aEvaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment;
bORR for patients with MDS or CMML was defined as CR + mCR + PR + SD with HI; cRemission rates were defined as CR+mCR+PR.
1. Wei A, et al. EHA 2021. Abstract S168.; 2. Brunner A, et al. ASH 2020. Oral Presentation 656

Venetoclax is an orally bioavailable, small-molecule inhibitor that selectively targets Bcl-2 [1-3]

- **Bcl-2** is a regulatory protein that **prevents programmed cell death**
- Bcl-2 overexpression occurs in **cancer cells**, where it mediates cell survival and chemoresistance
- Venetoclax is a small-molecule inhibitor that selectively targets Bcl-2
- This leads to **apoptosis of cancer cells** either through direct response or response to other anticancer treatment

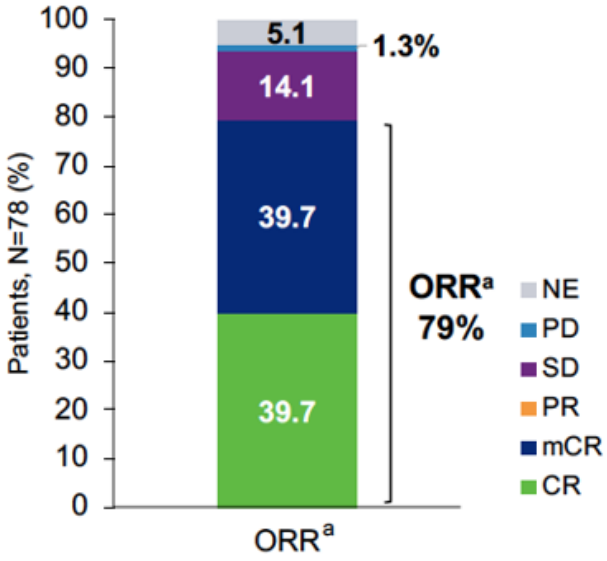
Venetoclax MoA



MoA, mechanism of action.

1. Juárez-Salcedo LM, et al. Drugs Context. 2019;8:212574; 2. Delbridge ARD, Strasser A. Cell Death Differ. 2015;22(7):1071-1080. 3. Janssens J. Berg J Hematol. 2017;8(7):265-271.

Venetoclax + azacitidine shows promising and durable efficacy, with improved QoL, in higher-risk MDS in a Phase Ib study



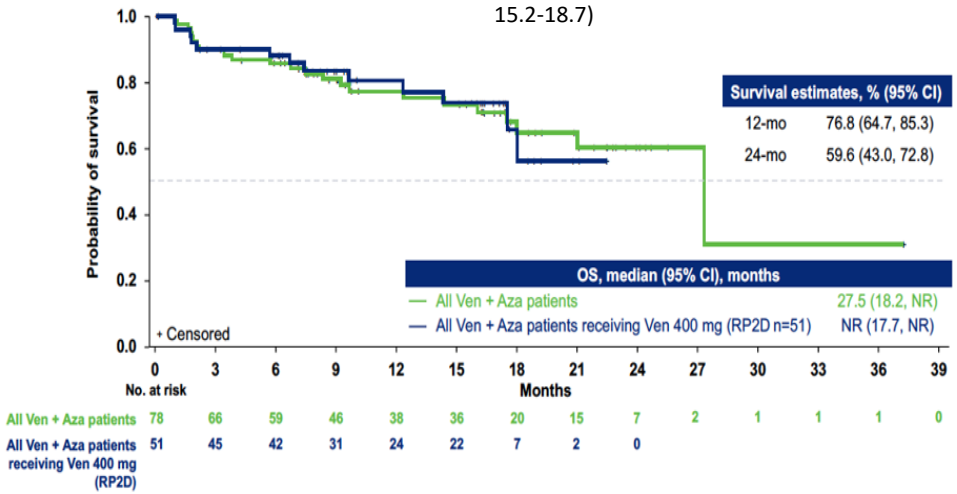
Transfusion independence rate	n (% of N=78)
RBC and platelet	51 (65%)
RBC	52 (67%)
Platelet	60 (77%)

- Median DOR: 12.9 months (min-max, 12.1-16.8)
- Median DOR after CR: 13.8 months (min-max, 6.5-20.9)
- Median time to CR: 2.6 months (min-max, 1.2-19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)[b]
- 84% achieved ORR[a]
  - 47% achieved ORR by cycle 2
  - 78% achieved ORR by cycle 3
- 35% achieved CR

- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant and 9 received stem cell transplant

OS for all patients

Median time on the study: 16.4 months (95% CI, 15.2-18.7)



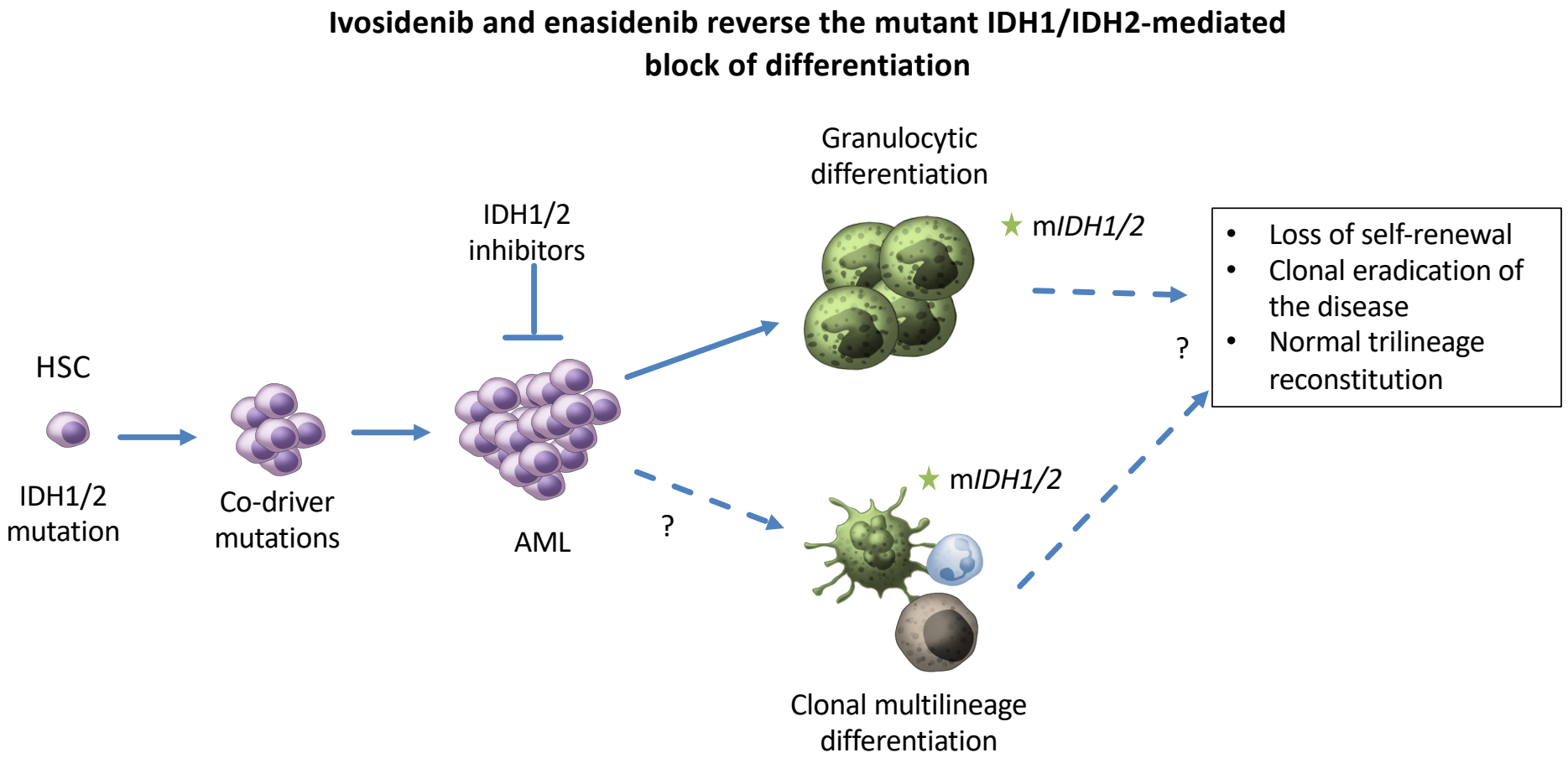
Data cutoff: June 30, 2020

Aza, azacitidine; CR, complete remission; DOR, duration of response; IWG 2006, International Working Group 2006; mCR, marrow CR; MDS, myelodysplastic syndrome; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; QoL, quality of life; RBC, red blood cell; RP2D, recommended Phase II dose; SD, stable disease; Ven, venetoclax

aExcludes patients of Arm C (Aza only); ORR includes CR+mCR+PR; PR n=0; per IWG 2006 (Cheson BD, et al. Blood. 2006;108(2):419-425); bExcludes 5 patients from the randomization phase who received 28-day Ven.

Garcia J, et al. ASH 2020. Abstract 656 (oral).

IDH1/2 mutants as therapeutic targets



AML, acute myeloid leukemia; HSC, hematopoietic stem cell; IDH, isocitrate dehydrogenase; m, mutant.

Martelli MP, et al. Minerva Med. 2020;11(5):411-426.

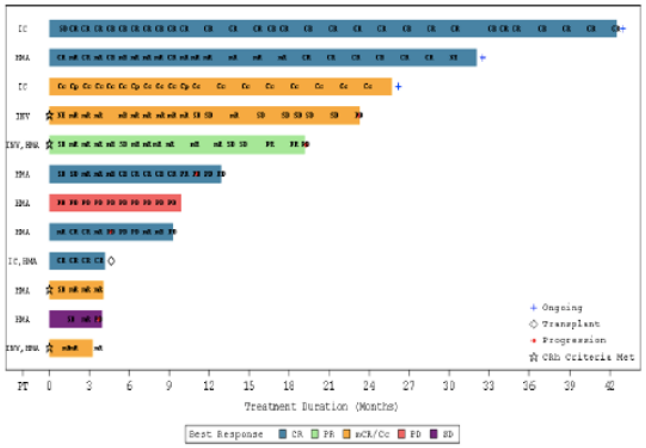
IDH1/2 mutant inhibitors alone and in combination with HMA in patients with MDS

mIDH1 inhibitor

Ivosidenib[1]

- 12 patients with MDS were treated on the Phase I (AG120-001 study at 500mg daily)
- Median age 72.5 years; 9 of 12 patients have received prior HMA therapy
- 9 of 12 responders including CR

	R/R MDS 500 mg (n=12)
ORR, n (%) [95% CI]	**9 (75.0) [42.8, 94.5]**
Time to first response, months, median (range)	1.9 (1.0-2.8)
Duration of response, months, median [95% CI]	21.4 [2.3-NE]
Best response, n (%)	
CR	**5 (41.7)**
PR	**1 (8.3)**
mCR	**3 (25.0)**
SD	1 (8.3)
PD	1 (8.3)



mIDH2 inhibitor

Enasidenib[2]

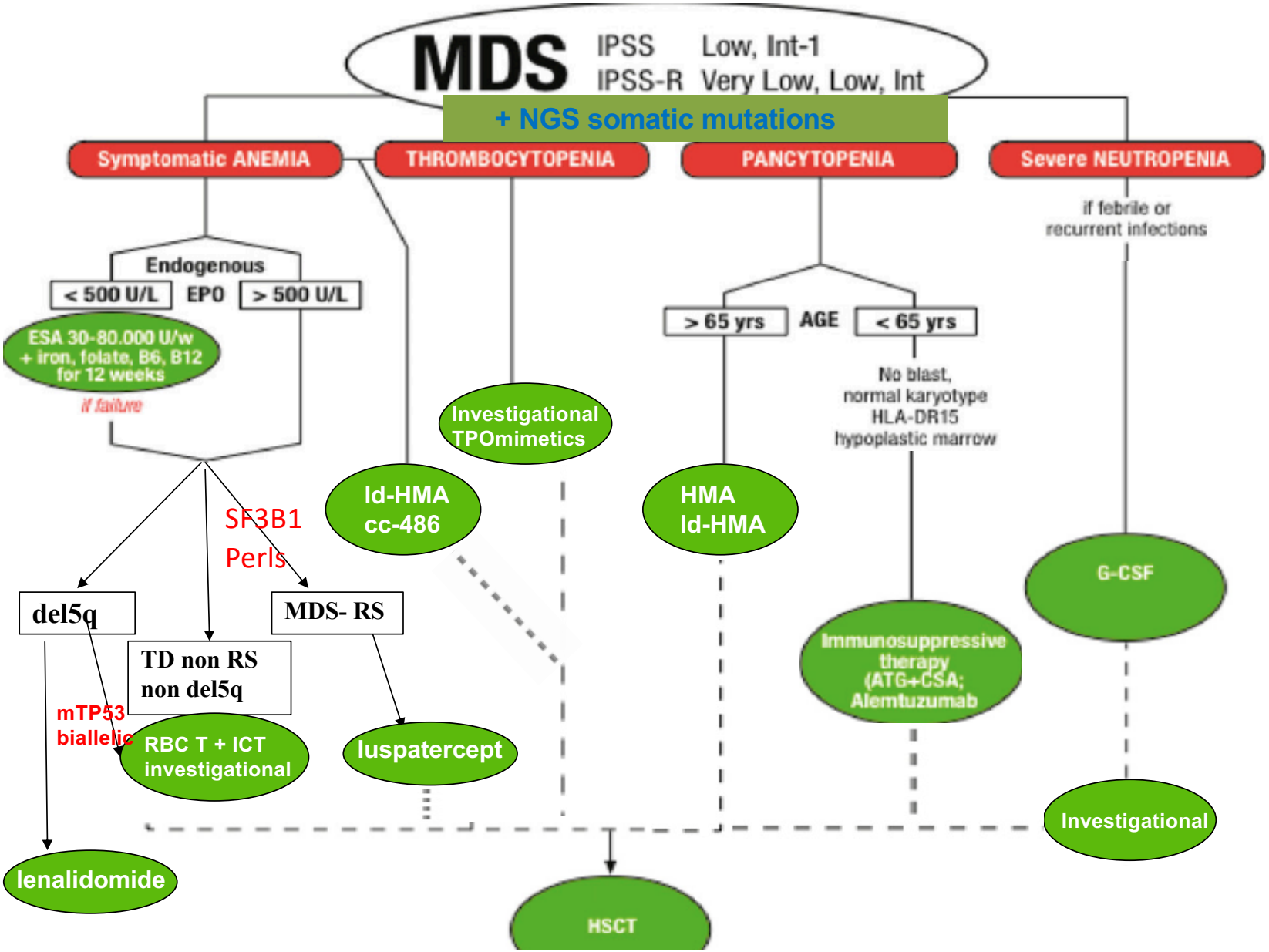
- Phase II, multi-center, open label clinical trial of enasidenib in patients with high-risk IDH2-mutated MDS

Response rate

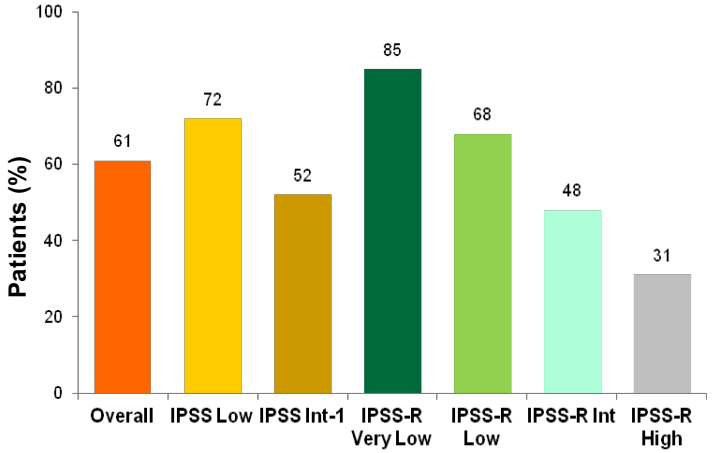
	Total (N=31)	Arm A (untreated) AZA + ENA (N=13)	Arm B (HMA failure) ENA (N=18)
ORR, n (%)	**21 (68)**	**11 (85)**	**10 (56)**
CR	8 (26)	3 (23)	5 (28)
PR	1 (3)	0 (0)	1 (6)
mCR	9 (29)	7 (54)	2 (11)
HI only	3 (10)	1 (8)	2 (11)
No response, n (%)	**10 (32)**	**2 (15)**	**8 (44)**
SD	9 (29)	2 (15)	7 (39)
PD	1 (3)	0 (0)	1 (6)

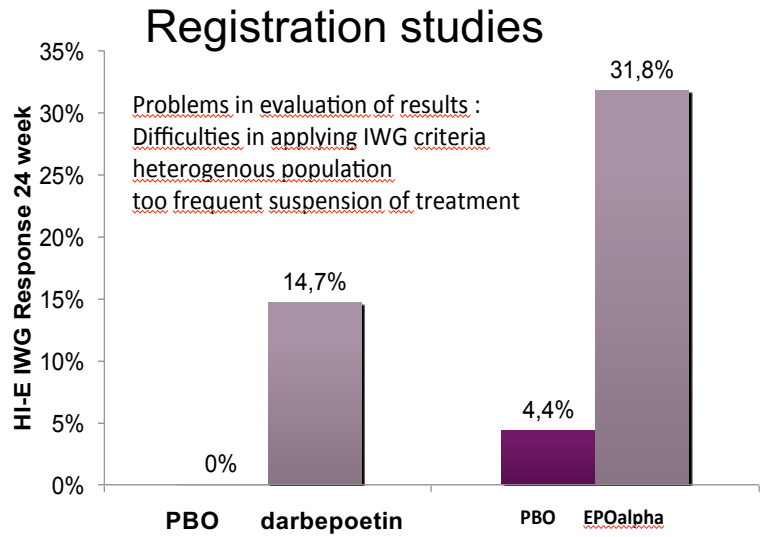
AZA, azacitidine; CR, complete remission; ENA, enasidenib; HI, hematological improvement; HMA, hypomethylating agent; mCR, marrow CR; MDS, myelodysplastic syndrome; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial remission; R/R, relapsed or refractory; SD, stable disease.

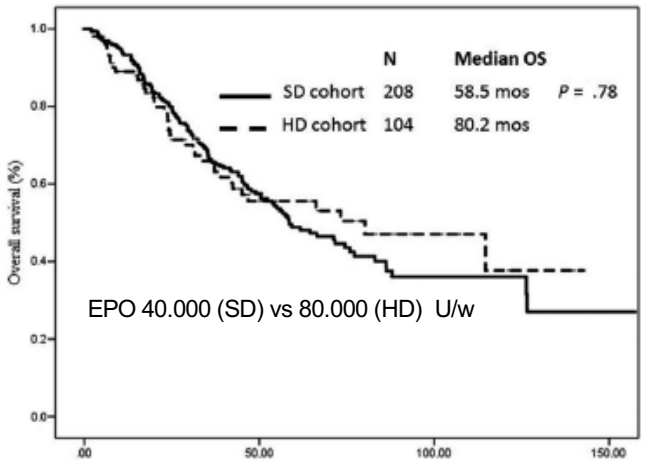
1. DiNardo CD, et al. IACH 2020; 2. Richard-Carpentier G, et al. ASH 2019


MDS
IPSS Low, Int-1
IPSS-R Very Low, Low, Int
+ NGS somatic mutations
Symptomatic ANEMIA
THROMBOCYTOPENIA
PANCYTOPENIA
Severe NEUTROPENIA
if febrile or recurrent infections
Endogenous
< 500 U/L
EPO
> 500 U/L
ESA 30-80.000 U/w + iron, folate, B6, B12 for 12 weeks
if failure
Investigational TPOmimetics
> 65 yrs
AGE
< 65 yrs
No blast, normal karyotype HLA-DR15 hypoplastic marrow
Id-HMA cc-486
HMA Id-HMA
SF3B1
Perls
del5q
MDS- RS
TD non RS non del5q
mTP53 biallelic
RBC T + ICT investigational
luspatercept
Immunosuppressive therapy (ATG+CSA; Alemtuzumab
G-CSF
Investigational
lenalidomide
HSCT

Erythropoietic stimulating agents (ESAs) in MDS







Santini V, et al. Blood. 2013;122:2286-8.

Fenaux et al. Leukemia. 2018 Dec;32(12):2648-2658.

Platzbecker et al. Leukemia 2017 Sep;31(9):1944-1950

Balleari e et al, Cancer Med. 2019 Dec;8(18):7567-7576

What we know about erythropoietic stimulating agents (ESAs)

ESAs are effective in MDS at high doses, better fixed than weight-adjusted (darbopoetin 300-500µg/ 3w; erythropoietin 30.000-80.000U/w)

Hematological improvement is predictable by serum EPO <500U/L, transfusion independence, lower IPSS-R risk, absence of blasts in BM, normal karyotype, isolated erythroid dysplasia, recent diagnosis

Interruption of treatment almost constantly provokes loss of response

Patients responding to ESAs may have prolonged OS

Thrombotic events are rare provided Hb levels are controlled

Duration of response is shorter in MDS with del5q

Latagliata R et al. Acta Haematol. 2008; 120:104-7
Moyo V et al *Ann Hematol* 2008 87:527–536
Mundle S, et al. *Cancer* 2009;115:706-715
Hellström-Lindberg E et al. Br J Haematol. 1997;99(2):344-51
Santini V, et al. Blood. 2013;122:2286-8
Park S et al Leuk Res. 2010; 34:1430-6

Park S, et al. Blood. 2008;111:574-82
Jädersten M, et al. J Clin Oncol. 2008;26:3607-13
Smith SW Haematologica. 2012 ; 97:15-20
Keiladi K et al. Leuk Res. 2008 Jul;32(7):1049-53

Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes

N= 212/ 5673

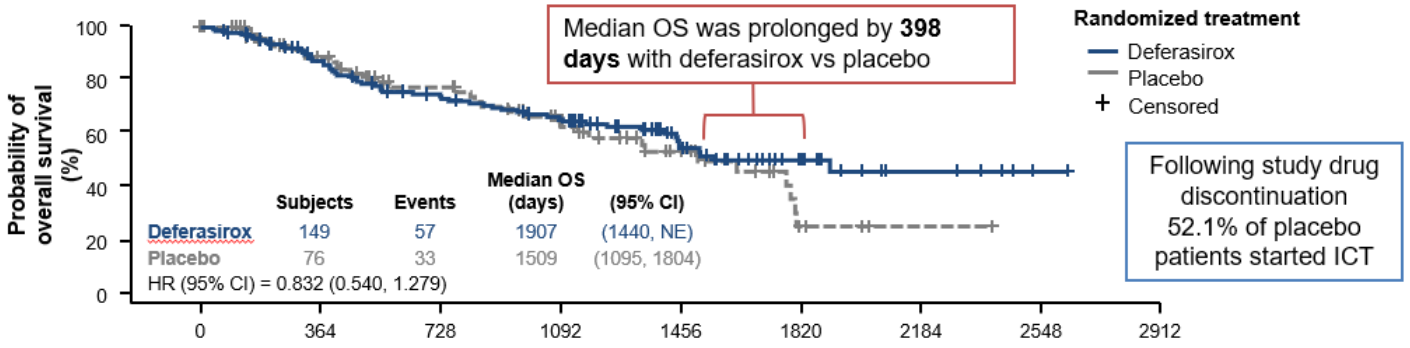
(OR=1.21, 95% CI: 0.60, 2.43).
Central venous catheter (OR=6.47, 95% CI: 2.37, 17.62)
and RBC ransfusion(OR=4.60, 95% CI: 2.29, 9.23)
were associated with deep vein thrombosis.

Weiss Smith et al, Haematologica, 97: 15-20, 2012

Iron chelation delays fatal events in TD LR-MDS (Telesto trial)

All patients*		Log-rank test		Cox model
	Event/N (%)	Median time to event (95% CI), days†	*P* value‡	HR (95% CI)§
Deferasirox	62/149 (41.6)	1440 (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	37/76 (48.7)	1091 (820, 1348)		

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)



Angelucci et al, 2019

Lenalidomide in RBC transfusion-dependent patients with IPSS Lower risk MDS with del(5q)

MDS-001 (PI–II; 2005)[1]

- Patients with all FAB subtypes (n=43)
- Erythroid response del(5q) = **83%**

MDS-003 (PII; 2006)[2]

- Patients with RBC-TD lower-risk MDS (n=148)
- Erythroid response = **76%**

MDS-004 (PIII; 2011)[3]

- Patients with RBC-TD lower-risk MDS (n=205)
- Placebo-controlled
- RBC-TI ≥26 weeks = **43–56%**

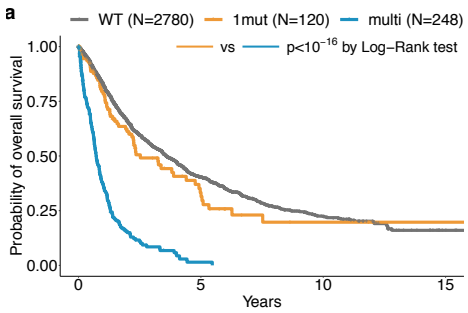
Lenalidomide-CCyR is lower in TP53 mutated patients (zero of seven mutated, 12 of 24 nonmutated; χ^2 P = .024)

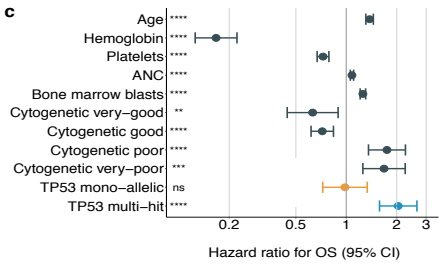
mutTP53 predicts poor outcome and progression

1.List A, et al. N Engl J Med 2005;352:549–57;
2. List A, et al. N Engl J Med 2006;355:1456–65;
3. Fenaux P, et al. Blood 2011 6;118(14):3765-76].
4. Jädersten M et al. JCO 2011;29:1971-1979

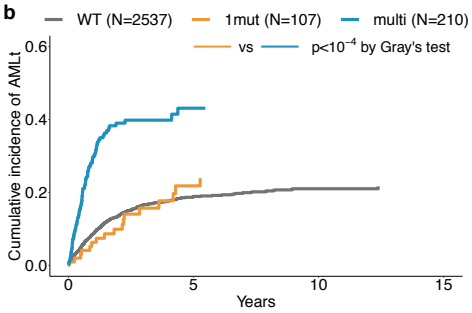
TP53 allelic state shapes clinical outcomes

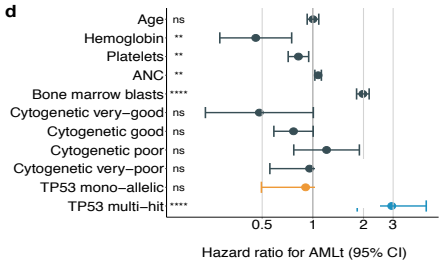
Overall Survival



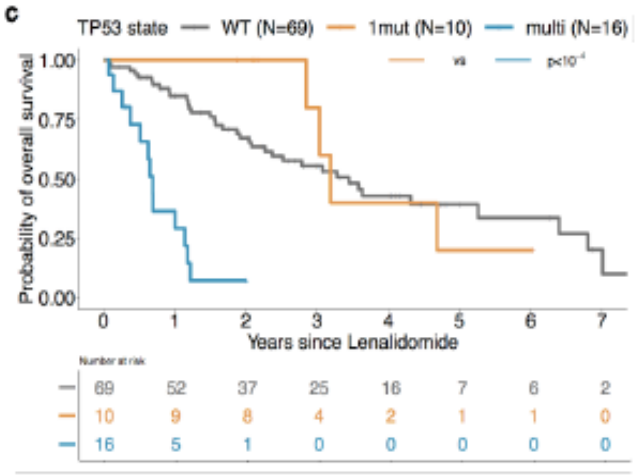


AML Transformation



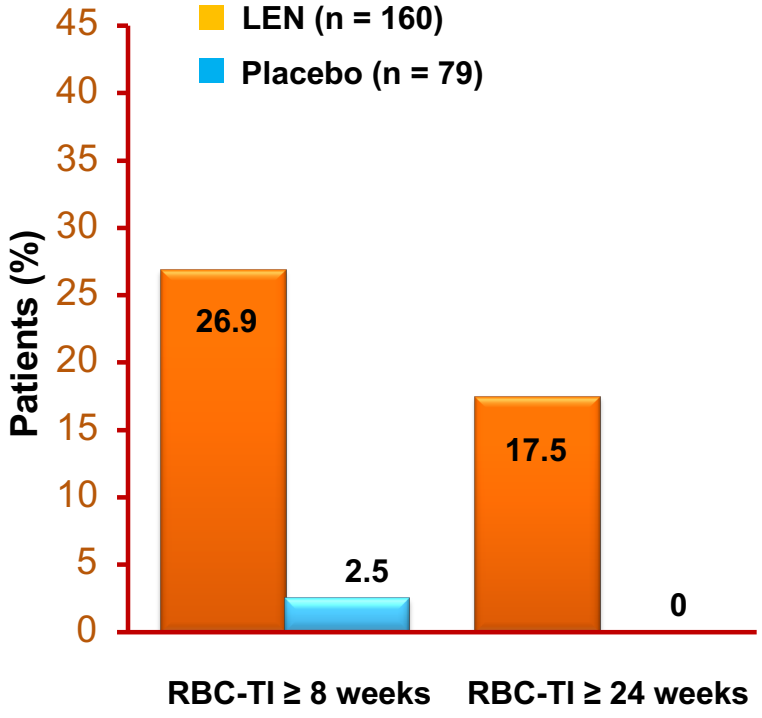


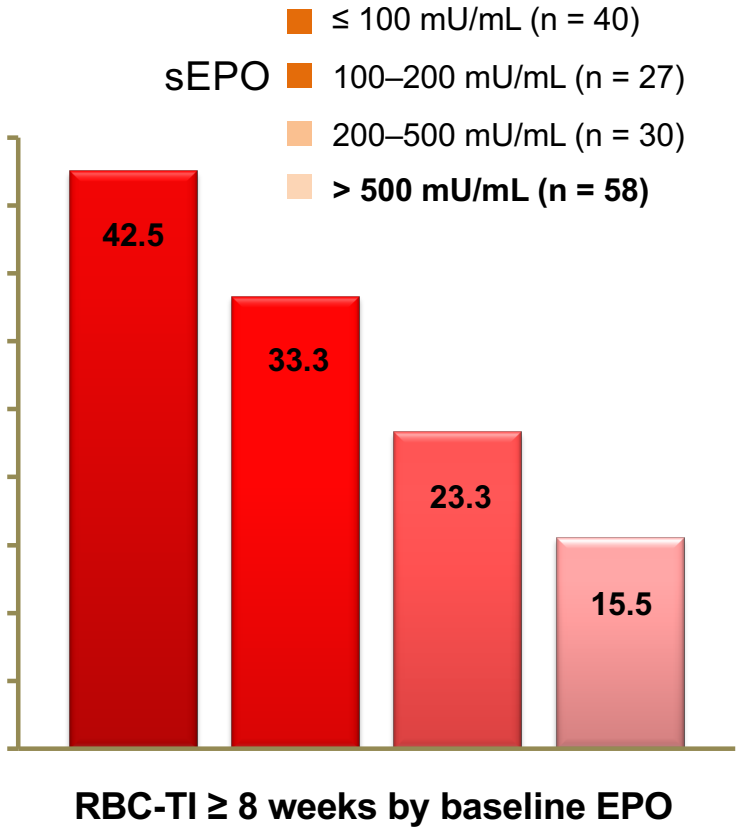
Overall Survival after LEN



Bernard E, et al. Nat communications 2020

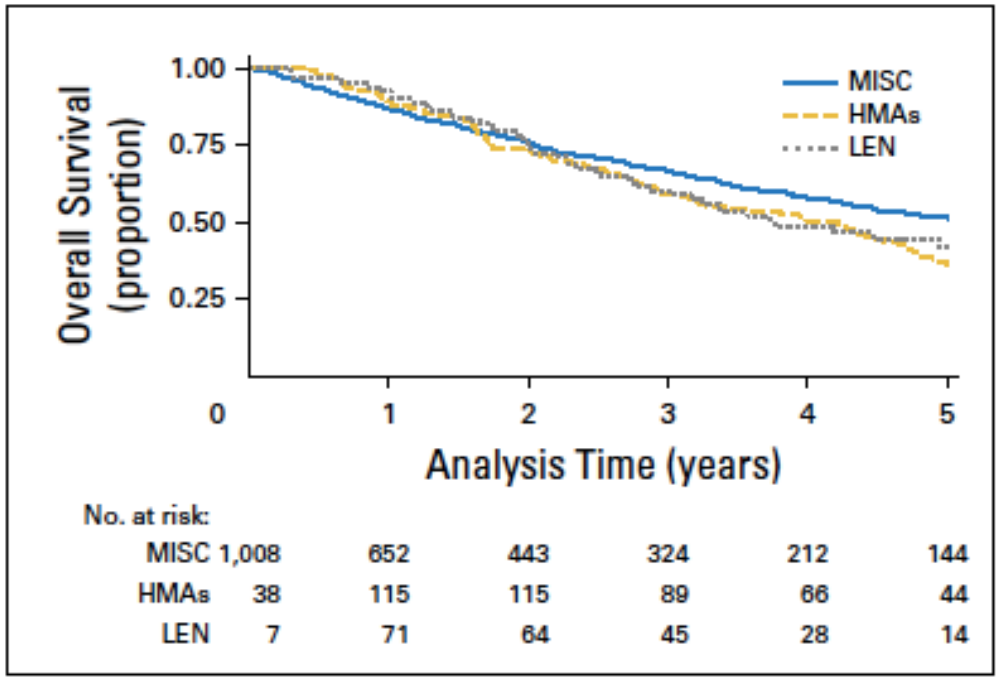
Lenalidomide in non-del5q MDS induces RBC-TI

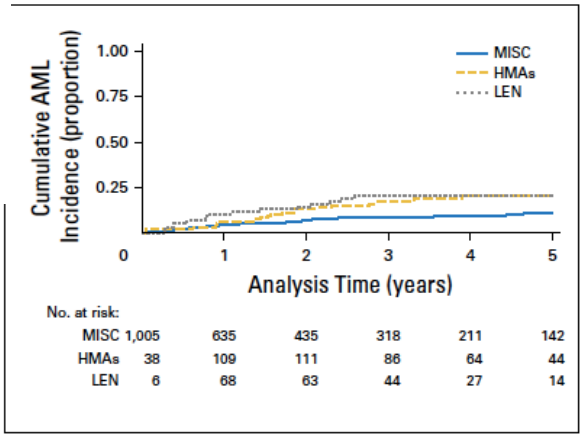




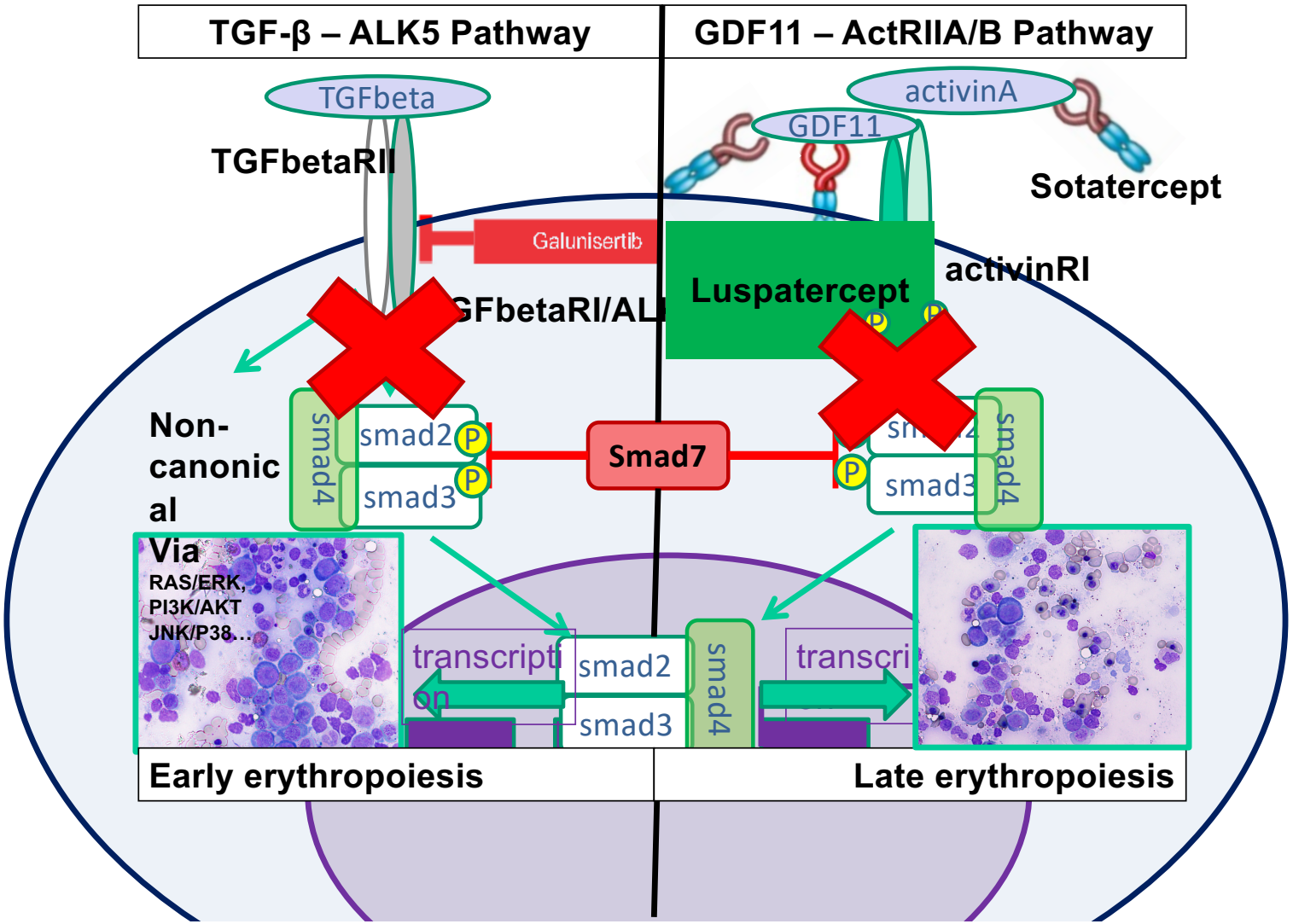
Santini V J Clin Oncol. 2016 Sep 1;34(25):2988-96.

Treatment with LEN of LR non-del5q MDS patients resistant to ESA does not prolong survival





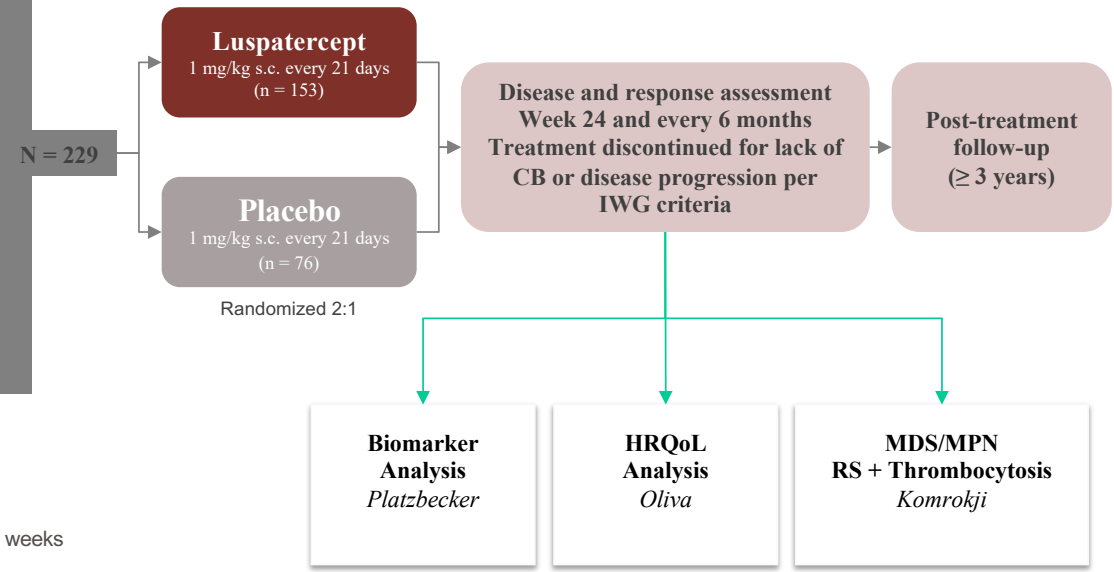
Park S et al; J Clin Oncol 35:1591-1597. 2017


TGF-β – ALK5 Pathway
GDF11 – ActRIIA/B Pathway
TGFbeta
TGFbetaRII
activinA
GDF11
Sotatercept
Galunisertib
activinRI
Luspatercept
Non-canonical
Via
RAS/ERK,
PI3K/AKT
JNK/P38…
smad2
smad3
smad4
Smad7
transcription
Early erythropoiesis
Late erythropoiesis

Luspatercept in MDS-RS

Eligibility Criteria

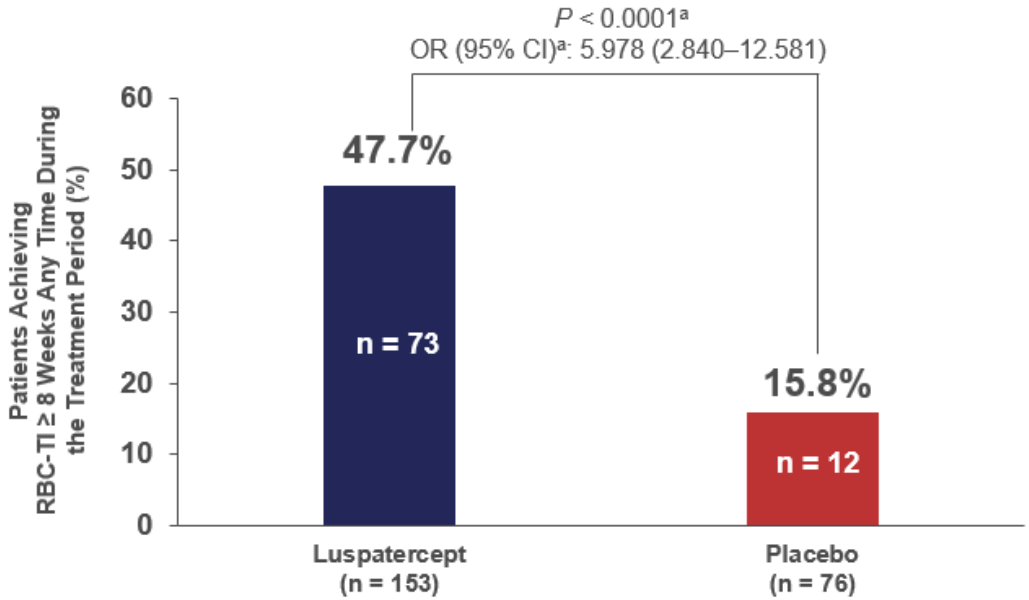
- MDS with RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- Non-del(5q) MDS
- IPSS-R-defined very low-, low-, or intermediate-risk MDS
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
  - No prior treatment with disease-modifying agents



Key Endpoints

- **Primary**: Transfusion independence of at least 8 weeks between Week 1 and 24
- **Key Secondary**: Transfusion independence of at least 8 weeks between Week 1 and 48, erythroid response, Hb increase, HR QoL, neutrophil response, platelet response, serum ferritin, iron chelation therapy, safety

Luspatercept induces Transfusion independence in *RS(+)* LR-MDS



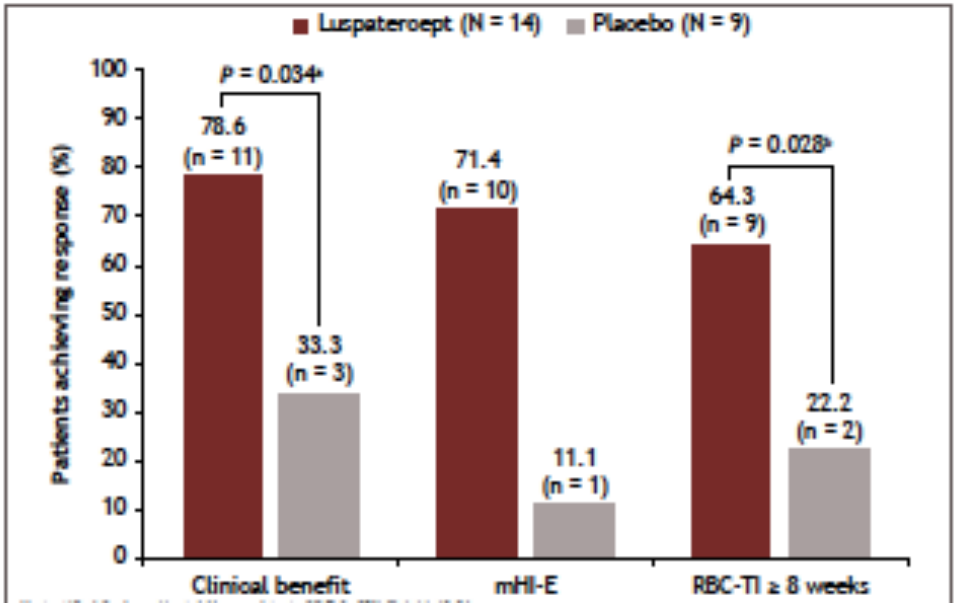
When assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥ 8 weeks compared with placebo than previously reported (37.9% of patients receiving luspatercept achieved RBC-TI ≥ 8 weeks during Weeks 1–24 of treatment vs 13.2% of placebo-treated patients; $P < 0.0001$)[1]

Platzbecker et al, N Engl J Med. 2020 Jan 9;382(2):140-151.

Luspatercept has been approved by FDA and EMA in 2020 for TD MDS-RS

Luspatercept is very active in MDS/MPN RS-T

Figure 2. Rates of clinical benefit, mHI-E, and RBC-TI ≥ 8 weeks in patients with MDS/MPN-RS-T during Weeks 1-24



Fenaux et al, N Engl J Med. 2020 Jan 9;382(2):140-151.

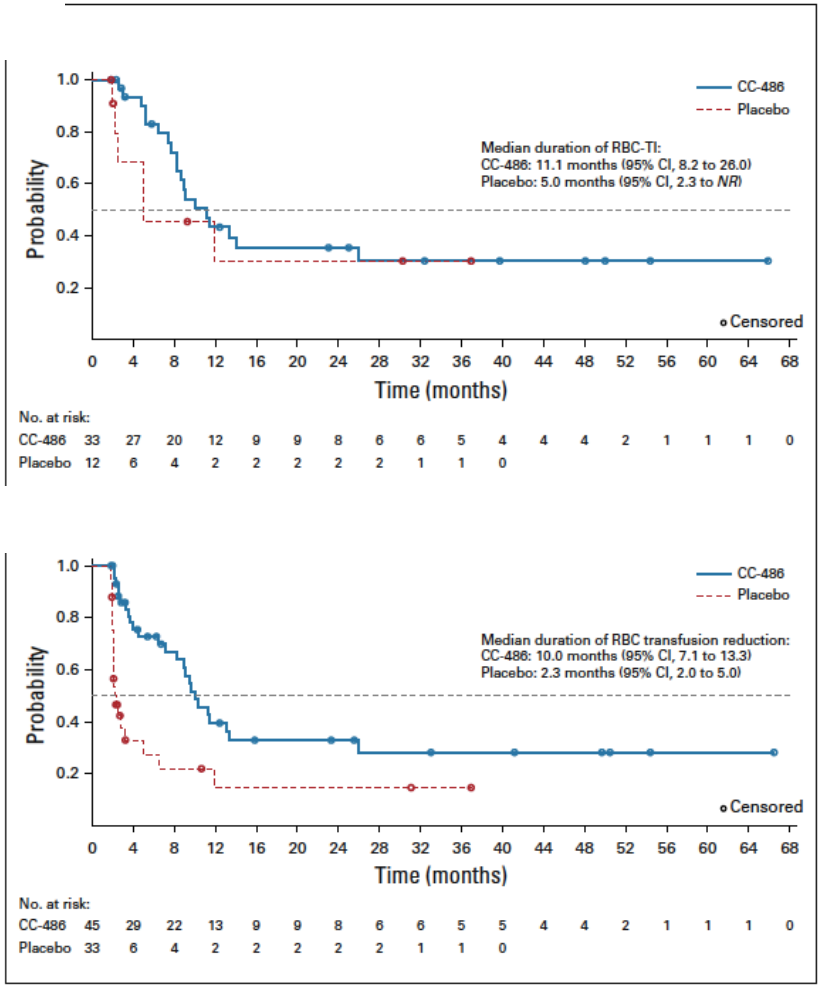
Luspatercept has been approved by FDA and EMA in 2020 for TD MDS-RS

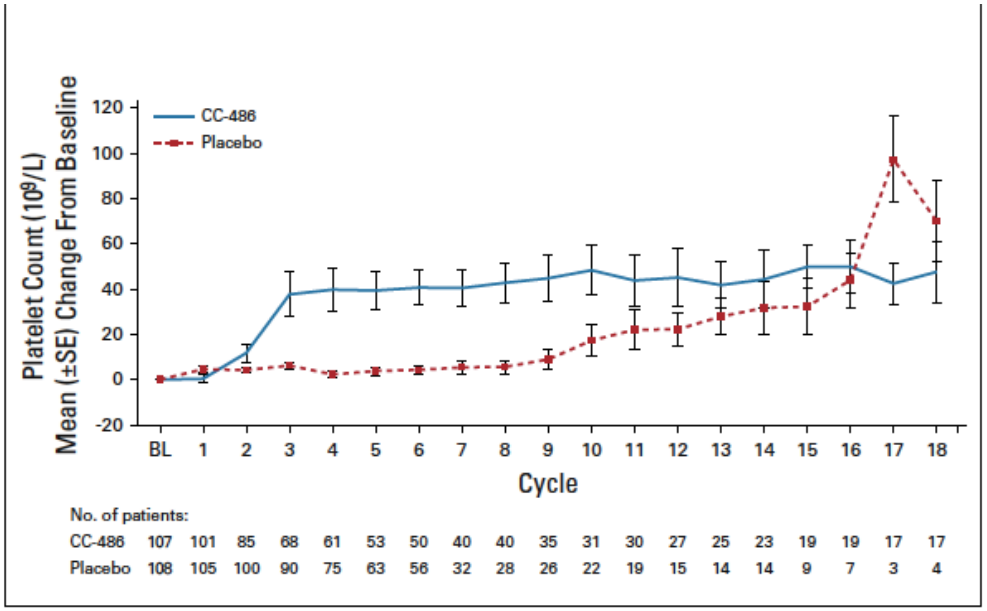
Results from three randomized trials of attenuated HMA dosing in lower-risk MDS

Study	N	ORR%	CR%	TI%	OS
Low dose DAC[41]					
DAC daily x3	43	23	16	67	Not reached
DAC weekly ×3	22	23	0	59	Not reached
DAC vs AZA[39]					
DAC daily ×3	73	70	37	32	Not reached
AZA daily ×3	40	49	36	16	Not reached
CC-486 vs placebo					
CC-486	107	NA	NA	30.8	17.3 mo
placebo	109	NA	NA	11.1	16.2 mo

https://library.ehaweb.org/eha/2020/eha25th/295000/guillermo.garcia-manero.a.phase.iii.placebo-controlled.trial.of.cc-486.in.html

CC-486 is active in LR MDS with thrombocytopenia





J Clin Oncol. 2021 May 1;39(13):1426-1436.

Imetelstat, sc telomerase inhibitor induces durable RBC-TI in non-del5q LR-MDS

Parameters	N = 38
8-week TI, n (%) Time to onset of 8-week TI, weeks, median (range) Duration of TI, weeks, median (95% CI)[a] Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a] Hb rise ≥ 3.0 g/dL during TI[c], n (%)	**16 (42)** 8.3 (0.1-40.7) **88.0 (23.1 – 140.9*)** 92.3 (42.9, 140.9) 12 (32)
24-week TI, n (%) Hb rise ≥ 3.0 g/dL during TI[c], n (%)	**12 (32)** 11 (29)
1-year TI, n (%)	**11 (29)**

[a] Kaplan Meier method; [b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; [c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
CI, confidence interval; Hb, hemoglobin

***Longest TI > 2.7 years**

Platzbecker et al, abs EHA 2020

Potential Disease-Modifying Activity with Imetelstat Treatment: Reduction of Malignant Clones Associated with Treatment Response

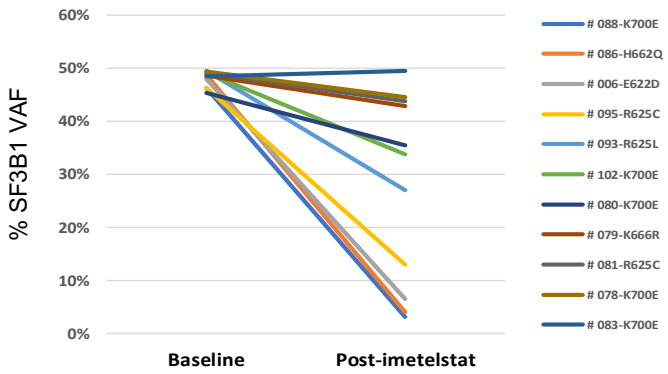
11 patients had SF3B1 mutations detected at baseline and had paired post-treatment mutation data available:

A. **10/11 had reduction** (ranging 10-93%) in SF3B1 variant allele frequency (VAF)

B. The greater reduction of SF3B1 VAF, **the longer TI duration** patients maintained

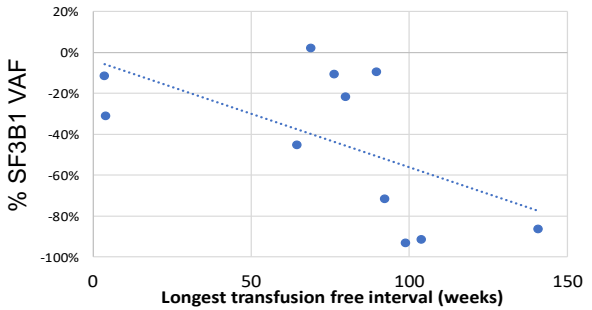
C. Significant correlation between greater reduction of SF3B1 VAF and **shorter onset time** to achieve the longest TI interval (Pearson correlation coefficient r=0.646, p=0.032)

A. Reduction of SF3B1 VAF with Imetelstat treatment



Steensma DP, JCO 2021 Jan 1;39(1):48-56 .

B. Reduction of SF3B1 VAF vs the longest TI duration



C. Reduction of SF3B1 VAF vs time to the longest TI

Patient ID	The longest TI interval (weeks)	Time to the longest TI interval start (weeks)	% SF3B1 VAF reduction
200088*	98.9	6.6	-93.3%
200086*	104	4.3	-91.8%
200006	140.9	9.9	-86.4%
200095	92.4	5.4	-71.9%
200093*	64.6	40.7	-45.5%
200102*	4	32.9	-31.2%
200080	79.9	44.1	-21.9%
200079	3.6	20.7	-11.6%
200081*	76.3	12.1	-10.9%
200078*	89.7	23.1	-9.8%
200083*	68.9	37.1	2.0%

*Remain on treatment as of 4 Feb 2020

Roxadustat , Oral HIF hydroxylase inhibitor Results in low burden TD LR-MDS

Efficacy Endpoints	Weeks 1-28 (Primary)	Weeks 1-52
Transfusion Independence ≥8 Weeks, n (%)	9 (38%)	10 (42%)

	Weeks 1-28	Weeks 1-52
≥50% Reduction in pRBC Over Any 8 Weeks, n (%)	13 (54%)	14 (58%)

- Median (range) number of days without transfusion: 79 (56-361) days
- No patient required IV iron
- 78% (7 of 9) patients were on 2.5 mg/kg dose at the time of transfusion independence

Henry et al, submitted 2021

Boulevard of broken dreams???

Pevonedistat inhibitor of the NEDD8-activating enzyme[1-3] Phase II trial -higher-risk MDS

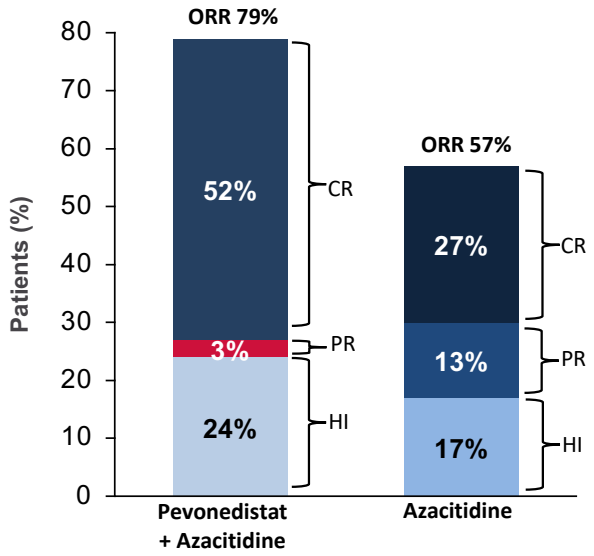
Safety

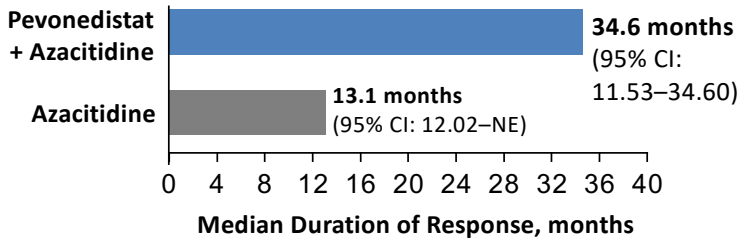
- Pevonedistat + azacitidine had comparable safety profile to azacitidine alone
- AEs, SAEs, and grade ≥3 AEs per A cycle dosed appeared lower with P+A vs A

Efficacy

- EFS and OS favored pevonedistat + azacitidine among patients with higher-risk MDS (IPSS-R very high-, high-, or intermediate-risk with ≥5% BM myeloblasts)
- CR rate was nearly doubled and median duration of response was almost tripled with pevonedistat + azacitidine
- Median time to AML transformation[a] was delayed in patients with higher-risk MDS

Response-evaluable patients with higher-risk MDS (n=59):





	Pevonedistat + Azacitidine n=32	Azacitidine n=35
Median EFS, months	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	
Median OS, months	23.9	19.1
Hazard ratio (95% CI)	0.701 (0.386–1.273) P=0.240	

A, azacitidine; AE, adverse event; AML, acute myeloid leukemia; BM, bone marrow; CI, confidence interval; CR, complete response; EFS, event-free survival; HI, hematologic improvement; IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndrome; NE, not evaluable; ORR, overall response rate; OS, overall survival; P, pevonedistat; PR, partial response; SAE, serious AE.

aTransformation to AML defined according to WHO classification as >20% blasts in blood or marrow and 50% increase in blast count from baseline

Sekeres MA, et al. Blood. 2020;136(suppl 1):Abstract 653.

1. Pan Y, et al. Int J Biochem Mol Biol. 2012;3(3):273-281; 2. Zhou L, et al. Mol Cancer. 2019;18(1):77; 3. Moyo TK, et al. Blood. 2019;134(suppl 1):Abstract 4236.

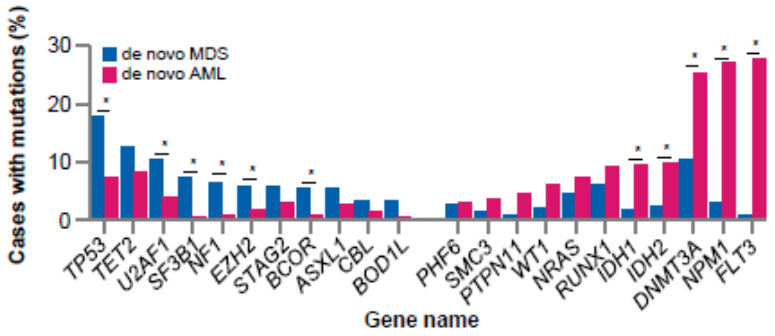
Conclusions

- Encouraging efficacy was observed with pevonedistat + AZA in patients with higher-risk MDS in the P-2001 study
- Longer EFS and favorable OS with pevonedistat + AZA versus AZA were associated with:
  - Double the CR rate
  - Nearly triple the median DOR
  - Delayed transformation to AML
  - Increased rate of transfusion independence
  - Lower transfusion rates
- EFS and OS favored pevonedistat + AZA among patients with MDS assessed as high-risk by the combined Cleveland Clinic model formula
- Clinical activity was observed in patients with adverse-risk mutations, including *TP53*
- Exposure-adjusted AE rates were lower with pevonedistat + AZA, without added myelosuppression
- Despite these encouraging results, the phase 3 PANTHER trial (NCT03268954) of pevonedistat + AZA did not achieve pre-defined statistical significance for the primary endpoint of EFS. Full data results will be submitted for presentation at an upcoming medical congress

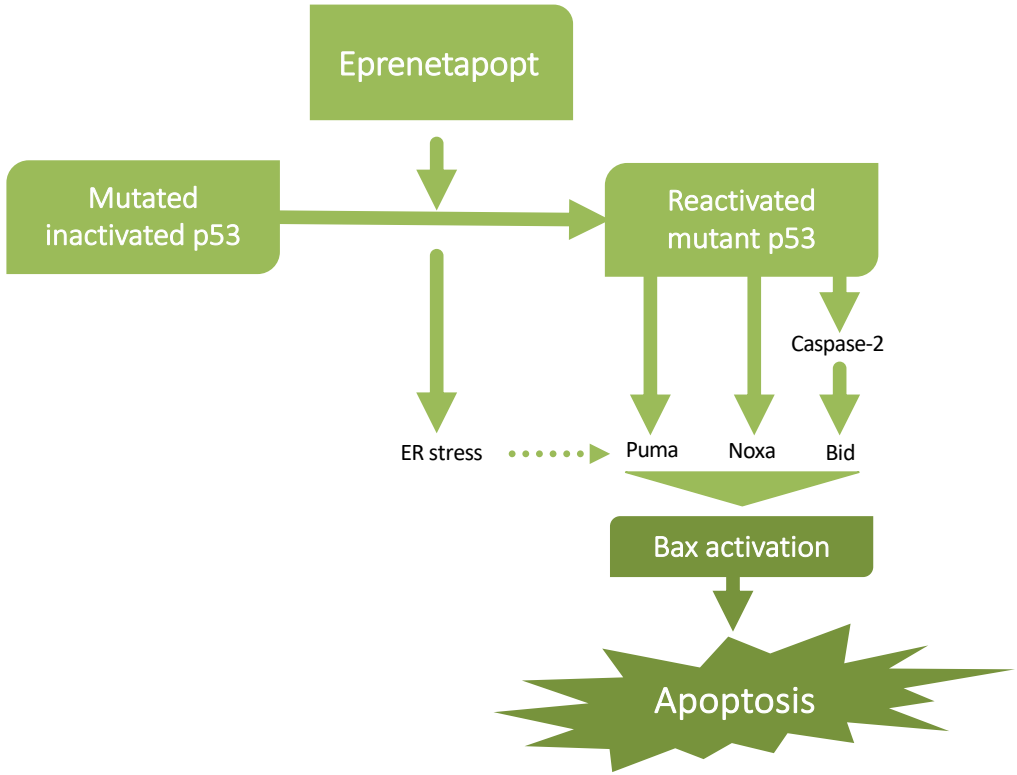
AE, adverse event; AML, acute myelogenous leukemia; AZA, azacitidine; CR, complete response; DOR, duration of response; EFS, event-free survival; MDS, myelodysplastic syndromes; OS, overall survival.

Eprenetapopt (APR-246), a p53 reactivator in development for TP53m MDS and AML

TP53 mutations are present in ≈ **20% of MDS**[1]



TP53 mutation is commonly associated with other **HR features and with worse outcome**[2,3]



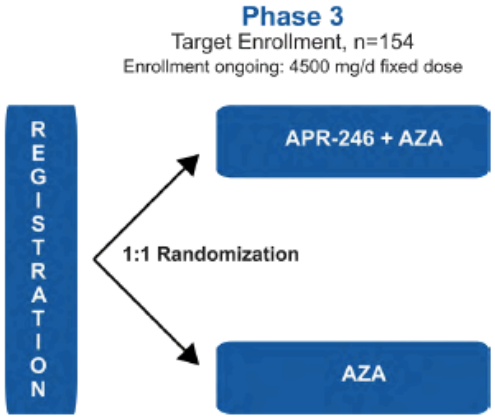
Eprenetapopt is a PRIMA-1 analogue that restores mutant TP53 to its WT conformation, thereby **reactivating TP53** within tumor cells

AML, acute myeloid leukemia; Bax, Bcl-2-associated X protein; Bid, Bcl-2 homology 3 interacting-domain death agonist; ER, endoplasmic reticulum; HR, high-risk; MDS, myelodysplastic syndrome; PRIMA-1, p53 reactivation and induction of massive apoptosis 1; Puma, p53 upregulated modulator of apoptosis; TP53, tumor protein 53; TP53m, TP53 mutant; WT, wild-type.

1. Reproduced from Walter MJ, et al. Leukemia. 2013;27(6):1275-1282. © 2013, Macmillan Publishers Limited. 2. Reproduced from Bernard E, et al. Nat Med. 2020;26(10):1549-1556. © 2020, The Authors.
3. Haase D, et al. Leukemia. 2019;33(7):1747-1758. http://creativecommons.org/licenses/by/4.0/.

Pivotal Phase 3 MDS Trial in *TP53* Mutant MDS

- Randomized study of frontline azacitidine ± APR-246 in *TP53* mutant MDS



- Intermediate/High/Very High Risk *TP53* mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

- Status
  - Enrollment commenced in January 2019 and has completed 6/2020
  - Fast Track Designation for MDS: granted by FDA in April 2019,
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019
  - Breakthrough Designation for MDS granted in 2020

ClinicalTrials.gov NCT03745716

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Sallman D , presentation SOHO 2020

Eprenetapopt Phase III study did not meet its primary endpoint of CR rate

In ITT population (N=154), **CR rate**:
Eprenetapopt + azacitidine: 33.3% (95% CI, 23.1% - 44.9%) ***P* = 0.13**
Azacitidine alone: 22.4% (95% CI, 13.6% - 33.4%)

Analysis of secondary endpoints ORR and duration of response favor the eprenetapopt + azacitidine arm but not significantly different

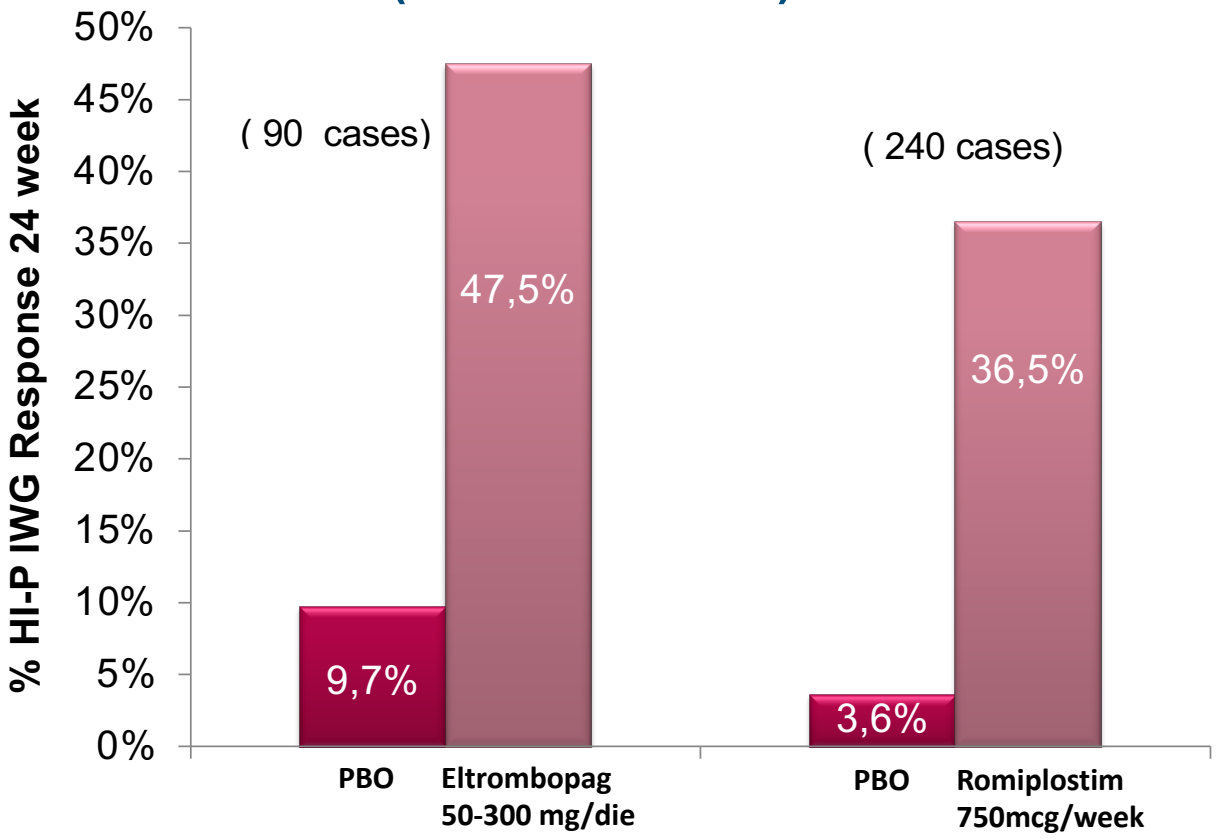
The median OS was similar between the arms

CI, confidence interval CR, complete remission; ITT, intent-to-treat; ORR, overall response rate; OS, overall survival

https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3. Accessed 6 May 2021

Thrombomimetic agents induce platelet increase in LR-MDS patients

(IWG 2006 HI-P)



Oliva et al ; Lancet Hematology 2017

Giagounidis et al, Cancer 2014;120:1838–46

Allogeneic HSCT is potentially the only curative treatment for MDS[1-3]

Despite improved understanding of the molecular pathogenesis of MDS, **currently available therapeutic agents** may lead to prolongation of life, but **do not cure MDS**

Allogeneic HSCT is used increasingly **as a curative option for patients with MDS; however, less than 15% of patients with MDS are eligible for HSCT**

1. Fenaux P, et al. *Ann. Oncol.* 2014;25(suppl3):iii57-69; 2. Passweg JR, et al. *Biol. Blood Marrow Transplant.* 2011;17(12):1869-1873; 3. Uy N, et al. *Expert Opin Pharmacother.* 2017;18(12):1212-1224; 4. Shlomchik WD. Nat Rev Immunol. 2007;7(5):340-52; 5. Bartenstein M and Deeg HJ. *Hematol. Oncol. Clin. North Am.* 2010;24(2):407-422.

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