Updates in Myelodysplastic Syndromes

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Disclosure of Conflicts of Interest

Francisco Socola, MD, has the following financial relationships to disclose:

Consultant – Servier

Unlabeled/investigational use of the following products will be discussed:
Magrolimab, Eprenetapopt, sabatolimab, venetoclax

Objectives

- **Updates in Low Risk MDS**
  - Luspatercept for low risk MDS that progressed on EPO

- **Updates in High Risk MDS**
  - Decitabine/cedazuridine
  - HMA + venetoclax in the newly diagnosed and relapse/refractory setting
  - Magrolimab + azacitadine
  - Sabatolimab + azacitadine
  - APR-246 + azacitadine

IPSS score

Table 5. IPSS prognostic groups and score values

All patients (n=816):

Risk group	Score	Median survival (years)	Time to AML transformation (for 25% in years)
Low risk	0	5.7	9.4
INT-1	0.5-1.0	3.5	3.3
INT-2	1.5-2.0	1.2	1.1
High risk	≥2.5	0.4	0.2

Patients below age 60 (n=205):

Risk group	Score	Median survival (years)	Time to AML transformation (for 25% in years)
Low risk	0	11.8	>9.4
INT-1	0.5-1.0	5.2	6.9
INT-2	1.5-2.0	1.8	0.7
High risk	≥2.5	0.3	0.2

Score values

Prognostic variable	Score				
	0	0.5	1	1.5	2
BM blasts (%)	<5	5-10		11-20	21-30
Karyotype°	Good	Intermediate	Poor		
Cytopenias*	0/1	2/3			

° Good: normal, -Y, del(5q), del(20q). Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities. * Hemoglobin <100 g/l, ANC <1.8 x 10^9/l, platelets <100 x 10^9/l.

Table 6. IPSS-R prognostic groups and score values

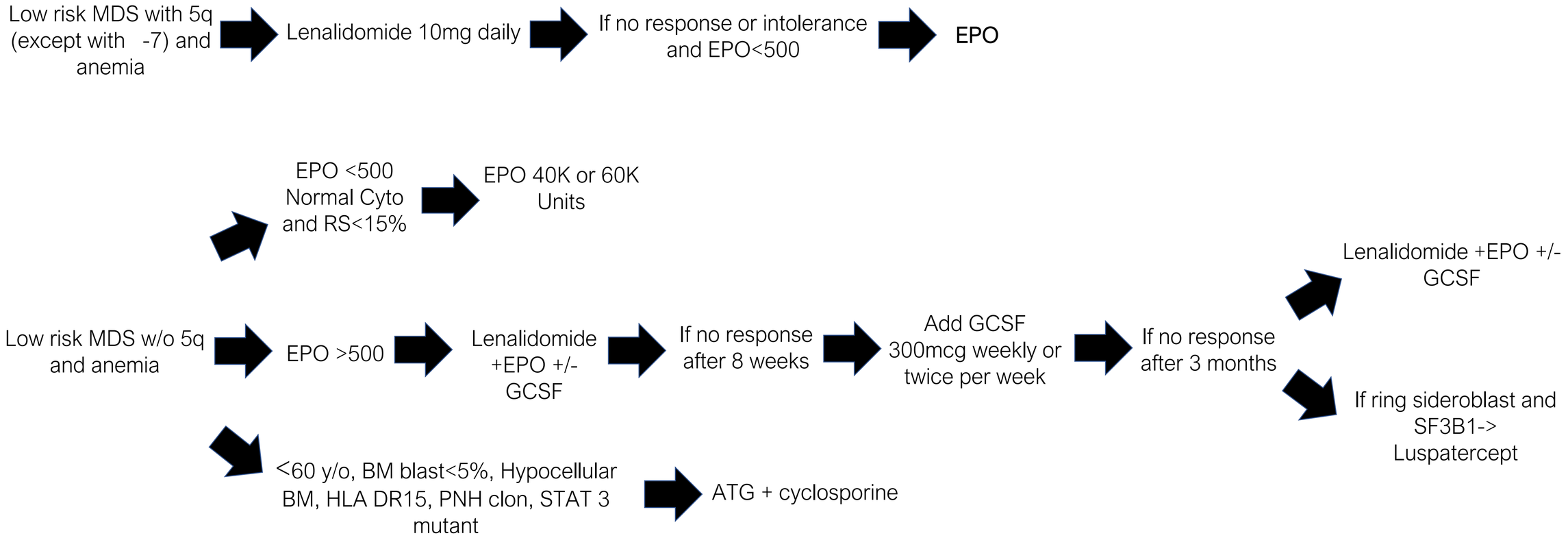
Prognostic subgroup (%)	Cytogenetic abnormalities	Median Survival (y)	Median AML evolution, 25%, y
Very good (4%)	-Y, del(11q)	5.4	NR
Good (72%)	Normal, del(5q), del(12p), del(20q), double incl. del(5q)	4.8	9.4
Intermediate (13%)	der(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor (4%)	-7, inv(3)/t(3q)/del(3q), double incl. -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very poor (7%)	Complex: > 3 abnormalities	0.7	0.7

Prognostic variable	Score						
	0	0.5	1	1.5	2	4	5
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blasts, %	≤2%	-	>2%-<5%	-	5%-10%	>10%	-
Hemoglobin	≥100	-	80-<100	<80			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Risk group	Risk score	Patients (%)	Survival (median, y)	AML transformation (25% of patients, y), 95% CI
Very low	≤1.5	19	8.8	NR (14.5-NR)
Low	>1.5-3	38	5.3	10.8 (9.2-NR)
Intermediate	>3-4.5	20	3.0	3.2 (2.8-4.4)
High	>4.5-6	13	1.6	1.4 (1.1-1.7)
Very high	>6	10	0.8	0.73 (0.7-0.9)

LOW RISK MDS

Low risk MDS treatment



Refractory to everything: Azacitadine

Lenalidomide in lower risk MDS with 5q del

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Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

Alan List et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New England Journal of Medicine, 2006 Oct 5;355(14):1456-65

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

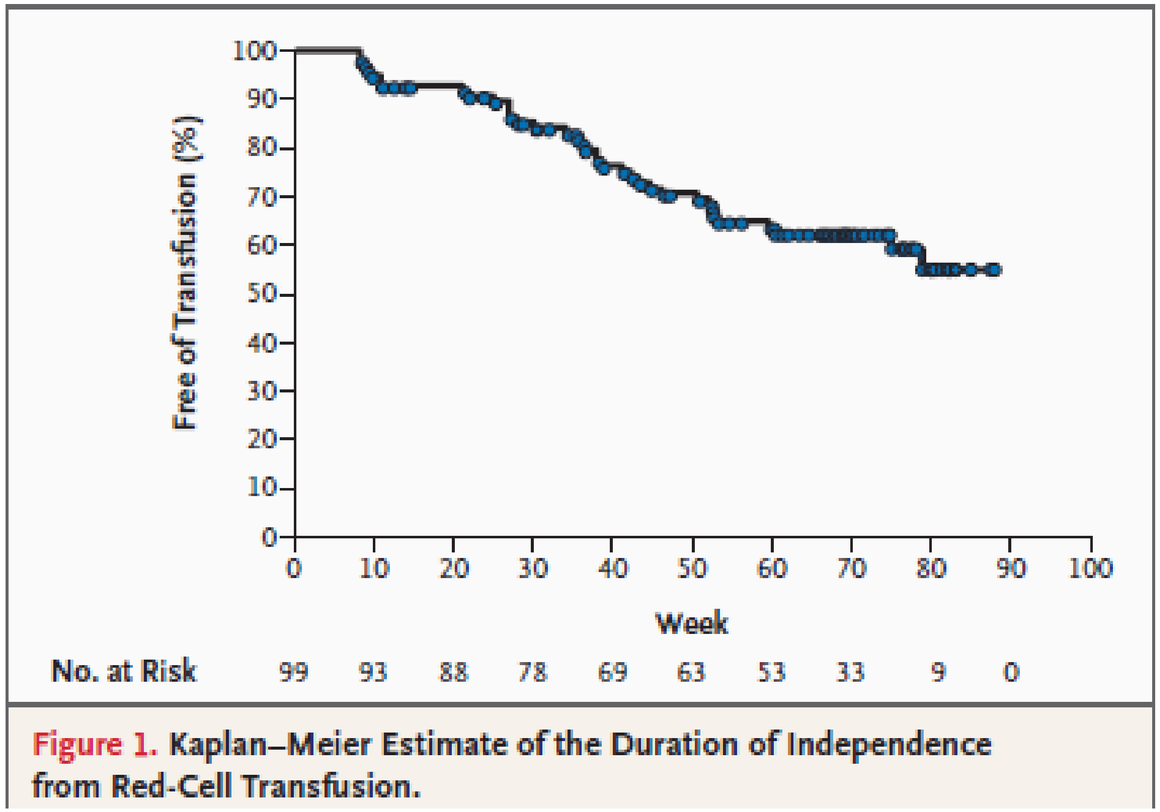

Figure 1. Kaplan–Meier Estimate of the Duration of Independence from Red-Cell Transfusion.

Table 3. Frequency of Cytogenetic Response According to Karyotype Complexity.

Complexity	Patients Who Could Be Evaluated*	Cytogenetic Response	Complete Cytogenetic Remission
Isolated 5q deletion — no. (%)	64	49 (77)	29 (45)
5q deletion + 1 additional abnormality — no. (%)	15	10 (67)	6 (40)
Complex (≥3 abnormalities) — no. (%)	6	3 (50)	3 (50)
P value		0.27	0.93

Alan List et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New England Journal of Medicine, 2006 Oct 5;355(14):1456-65

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Table 4. Grade 3 and 4 Treatment-Related Adverse Events.

Adverse Event	Grade 3		Grade 4		Grade 3 or 4
	Continuous Daily Dosing* (N=102)	21-Day Dosing* (N=46)	Continuous Daily Dosing* (N=102)	21-Day Dosing* (N=46)	Both Schedules (N=148)
	number of patients (percent)				
Neutropenia	20 (20)	8 (17)	45 (44)	8 (17)	81 (55)
Thrombocytopenia	37 (36)	14 (30)	7 (7)	7 (15)	65 (44)
Anemia (not otherwise specified)	4 (4)	2 (4)	4 (4)	0	10 (7)
Leukopenia (not otherwise specified)	3 (3)	2 (4)	4 (4)	0	9 (6)
Rash	5 (5)	4 (9)	0	0	9 (6)
Febrile neutropenia	2 (2)	1 (2)	2 (2)	1 (2)	1 (1)
Pruritus	2 (2)	2 (4)	0	0	4 (3)
Fatigue	2 (2)	2 (4)	0	0	4 (3)
Muscle cramp	3 (3)	0	0	0	3 (2)
Pneumonia	1 (1)	2 (4)	1 (1)	0	4 (3)
Nausea	3 (3)	1 (2)	0	0	4 (3)
Diarrhea	4 (4)	0	0	0	4 (3)
Deep-vein thrombosis	3 (3)	1 (2)	0	0	4 (3)
Hemorrhage	1 (1)	2 (4)	1 (1)	1 (2)	4 (3)
Hypokalemia	1 (1)	1 (2)	0	0	2 (1)
Pyrexia	1 (1)	0	0	0	1 (1)

Alan List et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New England Journal of Medicine, 2006 Oct 5;355(14):1456-65

EPO for low risk MDS without del 5q

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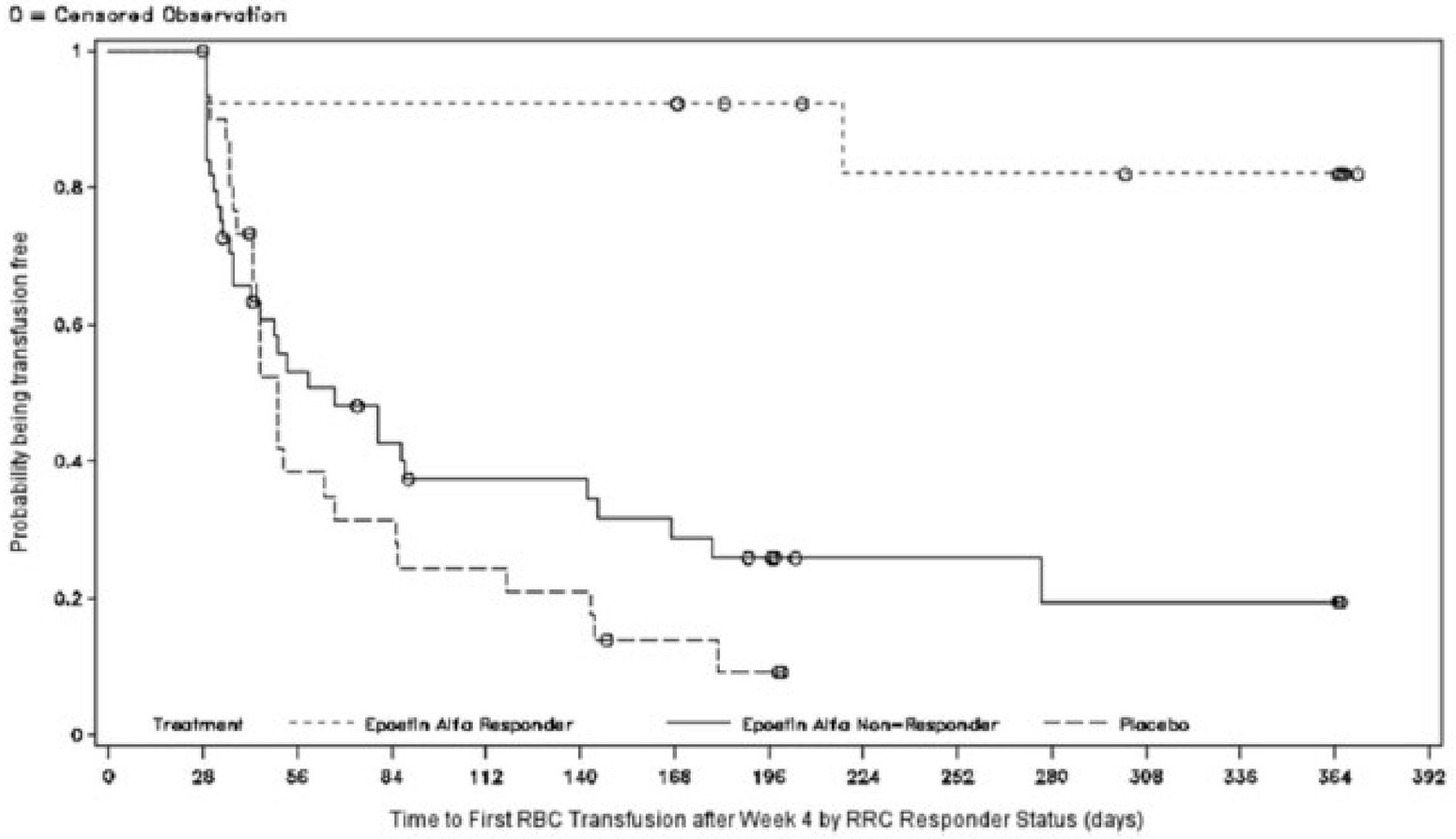
A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS

- **Methods:** double-blind, placebo-controlled study assessed the efficacy and safety of epoetin-α in IPSS low- or intermediate-1 risk MDS patients with Hb ≤ 10, with no or moderate RBC transfusion dependence (≤4 RBC units/8 weeks).
  - Patients were randomized, 2:1, to epoetin-α 450 IU/kg/week or placebo for 24 weeks, followed by treatment extension in responders.
  - The primary endpoint was erythroid response through Week 24.
- **Results:** A total of 130 patients were randomized (85 to epoetin-α and 45 to placebo). The erythroid response was 31.8% for epoetin-α vs 4.4% for placebo ($p < 0.001$)
- **Conclusion:** Epoetin-α reduced RBC transfusions and increased the time-to-first-transfusion compared with placebo

Pierre Fenaux et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. Leukemia (2018) 32:2648–2658

A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS



Time-to-first-red blood cell (RBC)-transfusions after week 4 by RRC responder status (mITT)

Pierre Fenaux et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. Leukemia (2018) 32:2648–2658

Lenalidomide monotherapy vs Len + EPO in patients with EPO refractory low risk MDS

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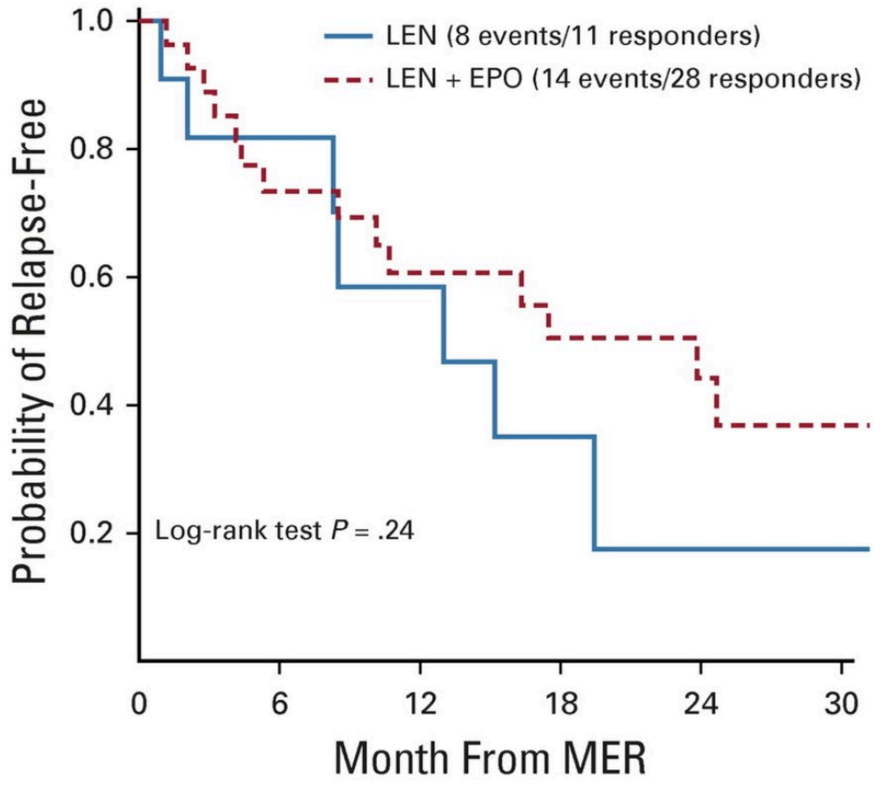
Combined Treatment with Lenalidomide (LEN) and Epoetin Alfa (EA) Is Superior to Lenalidomide Alone in Patients with Erythropoietin (Epo)-Refractory, Lower Risk (LR) Non-Deletion 5q [Del(5q)] Myelodysplastic Syndrome (MDS)

Registered to study
(N = 247)

38 del (5q) MDS registered to receive Len monotherapy directly

Randomly assigned
(n = 209)

Len monotherapy (n = 103)	Len + EPO alfa (n = 106)
7 patients excluded*	7 patients excluded*
Included in analysis (n = 96)	Included in analysis (n = 99)
Received ≥16 wk of study tx (n = 64)	Received ≥16 wk of study tx (n = 72)
Crossover to Len + EPO alfa (n = 38) →	10 achieved MER



No. at Risk						
LEN	11	8	5	2	1	1
LEN + EPO	28	18	13	10	6	5

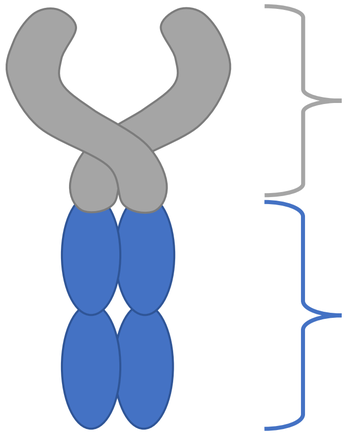
Alan F List. et al, Lenalidomide-Epoetin Alfa Versus Lenalidomide Monotherapy in Myelodysplastic Syndromes Refractory to Recombinant Erythropoietin. J Clin Oncol 2021 Mar 20;39(9):1001-1009.

Luspatercept for low risk MDS with ring sideroblast that failed to EPO

Luspatercept: Mechanism of Action

- Luspatercept is an investigational first-in-class erythroid-maturation agent
- It neutralizes the TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS model

Luspatercept
ActRIIB/IgG1 Fc recombinant fusion protein



Modified extracellular domain of ActRIIB

Human IgG1 Fc domain

1. Suragani. Nat Med. 2014;20:408. 2. Platzbecker. Lancet Oncol. 2017;18:1338.

MEDALIST: Study Design

- International, randomized, double-blind, placebo-controlled phase III trial

Randomized 2:1

Patients ≥ 18 yrs of age with non-del(5q) MDS and ring sideroblasts per WHO 2016 criteria; IPSS-R risk that is very low, low, or intermediate; refractory, intolerant, or ineligible for ESAs; RBC transfusion dependent
(N = 229)

Luspatercept
1.0 mg/kg* SC Q3W for ≥ 24 wks
(n = 153)

Placebo
SC Q3W for ≥ 24 wks
(n = 76)

Treatment continued until lack of clinical benefit or PD

*Could be titrated up to 1.75 mg/kg if needed.

- Primary endpoint: RBC-TI for ≥ 8 wks between Wk 1 and Wk 24
- Secondary endpoints: RBC-TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

MEDALIST Updated Analysis: Patient Characteristics

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

WHO classification of MDS — no. (%)†			
MDS with refractory anemia with ring sideroblasts	7 (5)	2 (3)	9 (4)
MDS with refractory cytopenia with multilineage dysplasia‡	145 (95)	74 (97)	219 (96)
IPSS-R risk category — no. (%)§			
Very low	18 (12)	6 (8)	24 (10)
Low	109 (71)	57 (75)	166 (72)
Intermediate	25 (16)	13 (17)	38 (17)
Median serum erythropoietin level (range) — U/liter¶	156.9 (12–2454)	130.8 (29–2760)	153.2 (12–2760)
Serum erythropoietin level category — no. (%)			
<100 U/liter	51 (33)	31 (41)	82 (36)
100 to <200 U/liter	37 (24)	19 (25)	56 (24)
200 to 500 U/liter	43 (28)	15 (20)	58 (25)
>500 U/liter	21 (14)	11 (14)	32 (14)
Missing data	1 (1)	0	1 (<1)
Mutated *SF3B1* — no./total no. (%)‖	138/148 (93)	64/74 (86)	202/222 (91)
Median red-cell transfusion burden (range) — no. of units/8 wk over period of 16 wk**	5 (1–15)	5 (2–20)	5 (1–20)
Red-cell transfusion-burden category — no. (%)			
≥6 units/8 wk	66 (43)	33 (43)	99 (43)
4 to <6 units/8 wk	41 (27)	23 (30)	64 (28)
<4 units/8 wk	46 (30)	20 (26)	66 (29)
Median pretransfusion hemoglobin level (range) — g/dl††	7.6 (6–10)	7.6 (5–9)	7.6 (5–10)
Received ESA previously — no. (%)	148 (97)	70 (92)	218 (95)
Disease refractory to ESA — no./total no. (%)	144/148 (97)	69/70 (99)	213/218 (98)
Discontinued previous ESA-containing regimen owing to an adverse event — no./total no. (%)	4/148 (3)	1/70 (1)	5/218 (2)

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

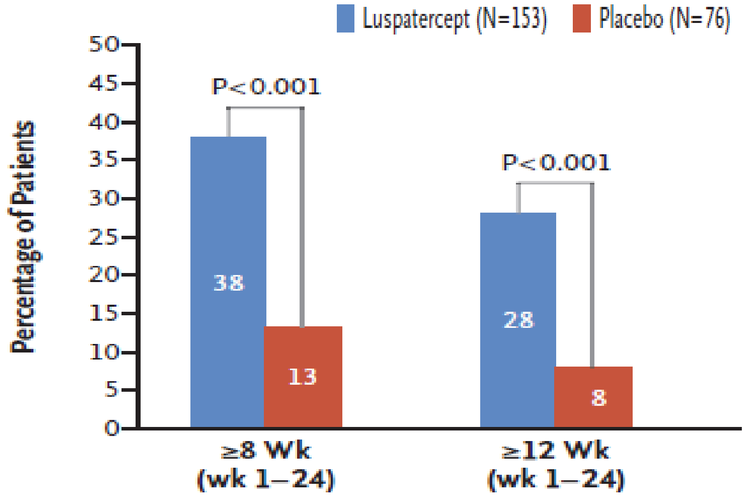
MEDALIST: Outcomes

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

MEDALIST: Outcomes, transfusion independency



No. of Patients with Response (% [95% CI])		
Luspatercept	58 (38 [30–46])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

MEDALIST: Side effects

Table 3. Adverse Events Occurring in at Least 10% of Patients.*

Event	Luspatercept (N=153)		Placebo (N=76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
General disorder or administration-site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea†	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal or connective-tissue disorder				
Back pain†	29 (19)	3 (2)	5 (7)	0
Arthralgia	8 (5)	1 (1)	9 (12)	2 (3)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea†	23 (15)	1 (1)	5 (7)	0
Cough	27 (18)	0	10 (13)	0
Infection or infestation				
Bronchitis†	17 (11)	1 (1)	1 (1)	0
Urinary tract infection†	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning, or procedural complication: fall	15 (10)	7 (5)	9 (12)	2 (3)

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

MEDALIST Updated Analysis: Disease Progression

Disease Progression, n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Progression to HR-MDS or AML	8 (5.2)	4 (5.3)
▪HR-MDS	5 (3.3)	2 (2.6)
▪AML	3 (2.0)	2 (2.6)

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Eng J Med*. 2020;382(2):140-151

Future trial

- **Trial**: Luspatercept vs EPO for newly Diagnose low risk MDS with ring sideroblast

Treatment for high risk MDS

High risk MDS treatment

Int 2 and high risk MDS transplant candidate → HMA follow by allogeneic transplant

Int 2 and high risk MDS non-transplant candidate → Azacitadine or decitabine or Decitabine/cedazuridine → HMA+ venetoclax vs clinical trial

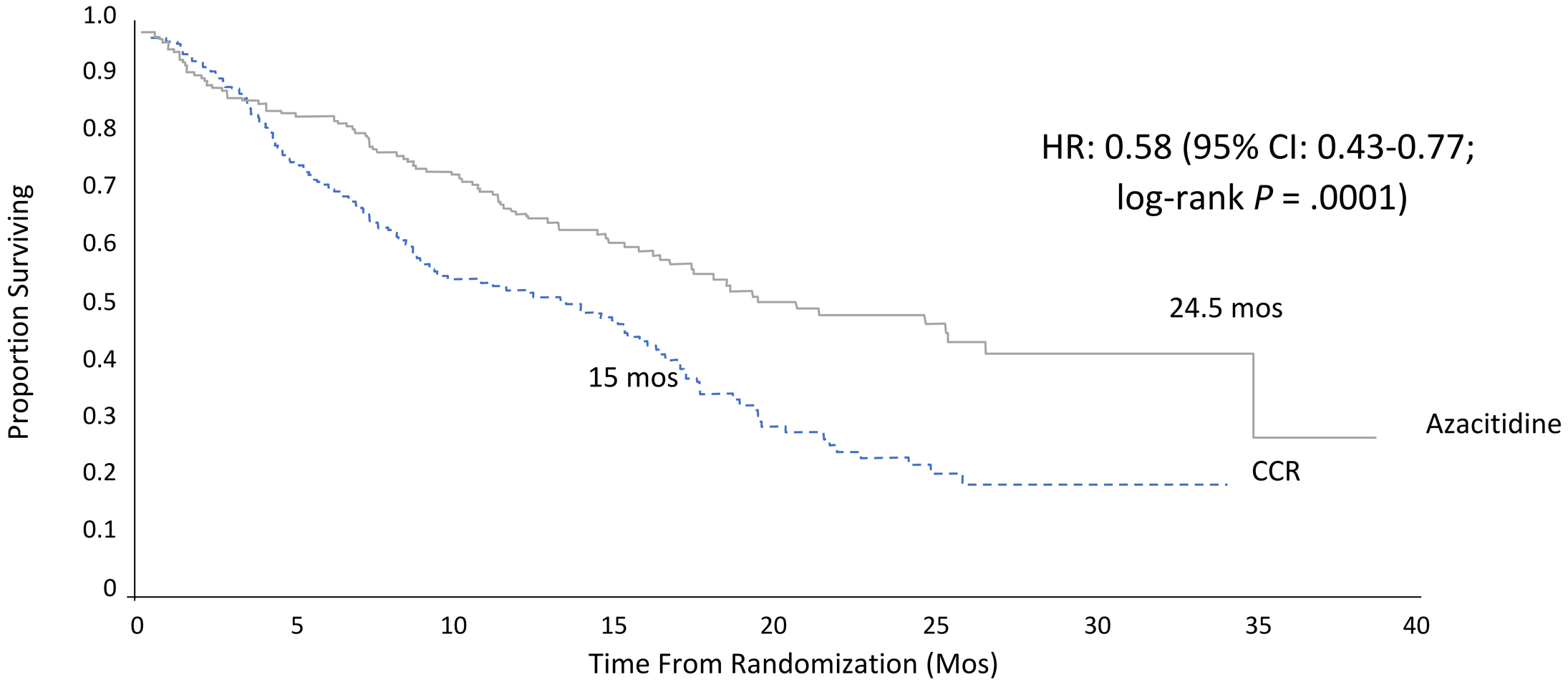
Int 2 and high risk MDS non-transplant candidate → clinical trial

Efficacy of azacitidine compared to conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study

- Randomized phase III study of pts with high risk MDS not eligible for allo, compared azacitidine to BSC (BSC alone, LDAC, or AML-like chemo)
- 179 pts were enrolled in each group
- There was a significant improvement in OS with azacitidine (24 vs 15 months, p=0.0001) and time to AML transformation (24 vs 12 months, p=0.004).
- Twenty-nine percent of azacitidine treated patients responded with CR or PR.
- A total of 50% responded (CR, PR and hematological improvement = HI), first response was seen in 91% of the responders within 6 cycles.

Fenaux et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol. 2009;10:223.

AZA-001 Trial: Azacitidine Significantly Improves OS in Higher-Risk MDS



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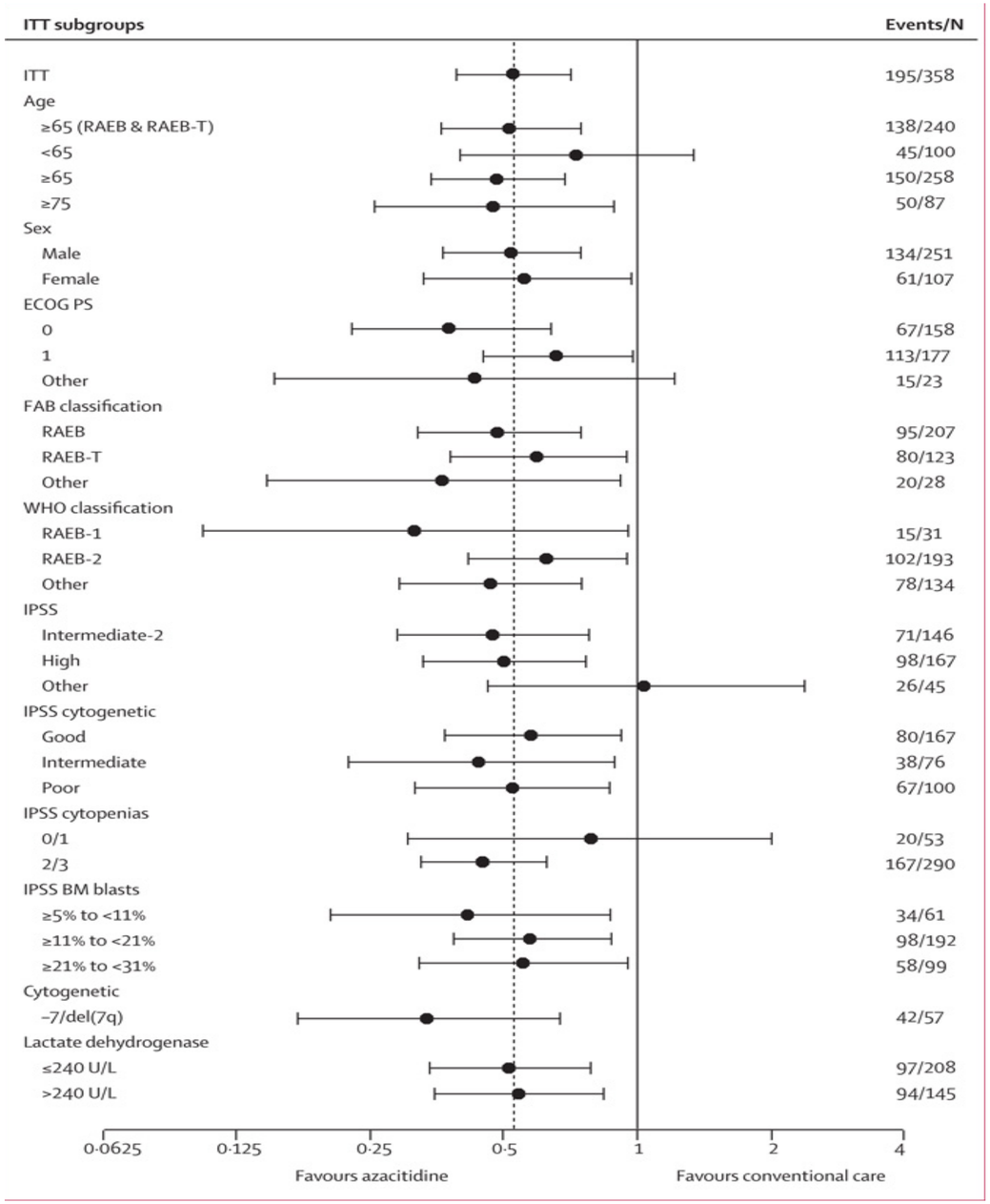
Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study

	BSC only (n=222)			
	Azacitidine (n=117)	BSC (n=105)	HR (95%CI)	p value
Overall survival (months)	21·1 (10·5-NR)	11·5 (5·7-NR)	0·58 (0·40–0·85)	0·0045
Time to transformation to AML (months)	15·0 (8·8–27·6)	10·1 (3·9–19·8)	0·41 (0·27–0·63)	<0·0001



Fenaux et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol. 2009;10:223.

Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study

	Total ITT (n=358)		
	Azacitidine (n=179)	CCR (n=179)	p value*
Haematological response			
Any remission	51 (29%)	21 (12%)	0–0001
Complete remission	30 (17%)	14 (8%)	0–015
Partial remission	21 (12%)	7 (4%)	0–0094
Stable disease	75 (42%)	65 (36%)	0–33
Haematological imarovement†			
Any improvement	87/177 (49%)	51/178 (29%)	<0–0001
Major erythroid improvement	62/157 (40%)	17/160 (11%)	<0–0001
Major platelet improvement	46/141 (33%)	18/129 (14%)	0–0003
Major neutrophil improvement	25/131 (19%)	20/111 (18%)	0–87

	Total ITT (n=358)	
	Azacitidine (n=179)	Conventional care (n=179)
Deaths	82 (46%)	113 (63%)
Deaths during first 3 months* of treatment	20 (11%)	16 (9%)
Safety population	175	165
Discontinuation before study completion due to haematological adverse events†	8 (5%)	4 (2%)
Grade 3 or 4 toxicity‡		
Neutropenia	159 (91%)	126 (76%)
Thrombocytopenia	149 (85%)	132 (80%)
Anaemia	100 (57%)	112 (68%)
Baseline grade 0–2 progressed to grade 3 or 4 during treatment†		
Neutropenia	67/80 (84%)	46/76 (61%)
Thrombocytopenia	72/97 (74%)	68/94 (72%)
Anaemia	84/156 (54%)	83/130 (64%)

Fenaux. Lancet Oncol. 2009;10:223.

Azacitadine as bridge for transplant

- Two publications suggest that azacitidine treatment as a bridging therapy to allogeneic SCT is feasible and does not seem to alter the post-transplant prognosis.

Field T, Perkins J, Huang Y, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2010;45:255-260.

Kim DY, Lee JH, Park YH, et al. Feasibility of hypomethylating agents followed by allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome. Bone Marrow Transplant. 2012;47:374-379.

TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

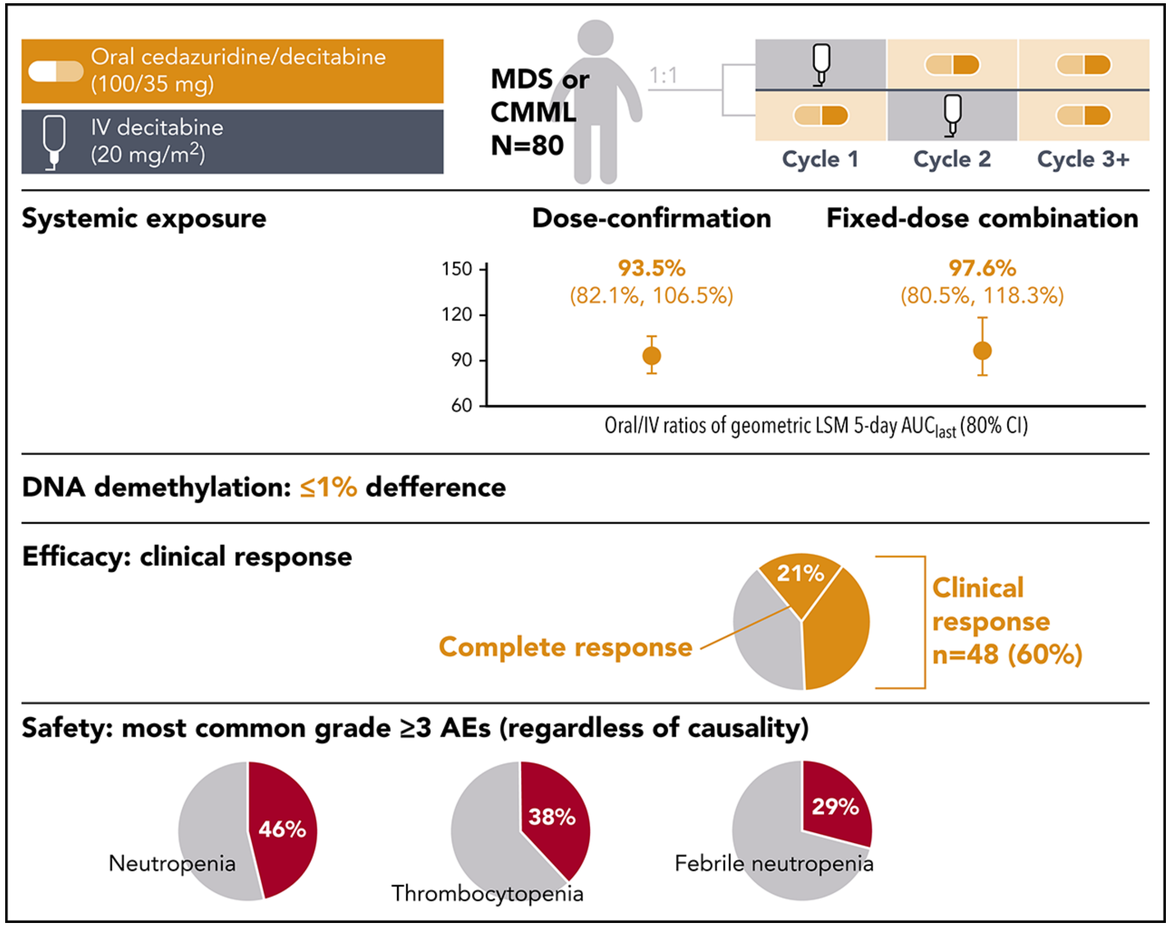
- Welch et all describe the outcomes of 10 days decitabine treatment on 116 patients with AML
- 46% of them achieved bone marrow blast clearance (<5%) in the group
- From these 116 patients 21 had P53 mutation and all of them had either marrow blast clearance (<5%) with or w/o complete hematologic response.

Welch JS et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. N Engl J Med. 2016 Nov 24;375(21):2023-2036.

Decitabine/cedazuridine for the treatment of MDS

LOUISIANA ONCOLOGY SOCIETY

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study



Garcia-Manero. ASH 2019. Abstr 846. Savona. ASH 2020. Abstr 1230. Savona. MDS 2021. Abstr P48.

Azacitadine + venetoclax for newly diagnosed high risk MDS

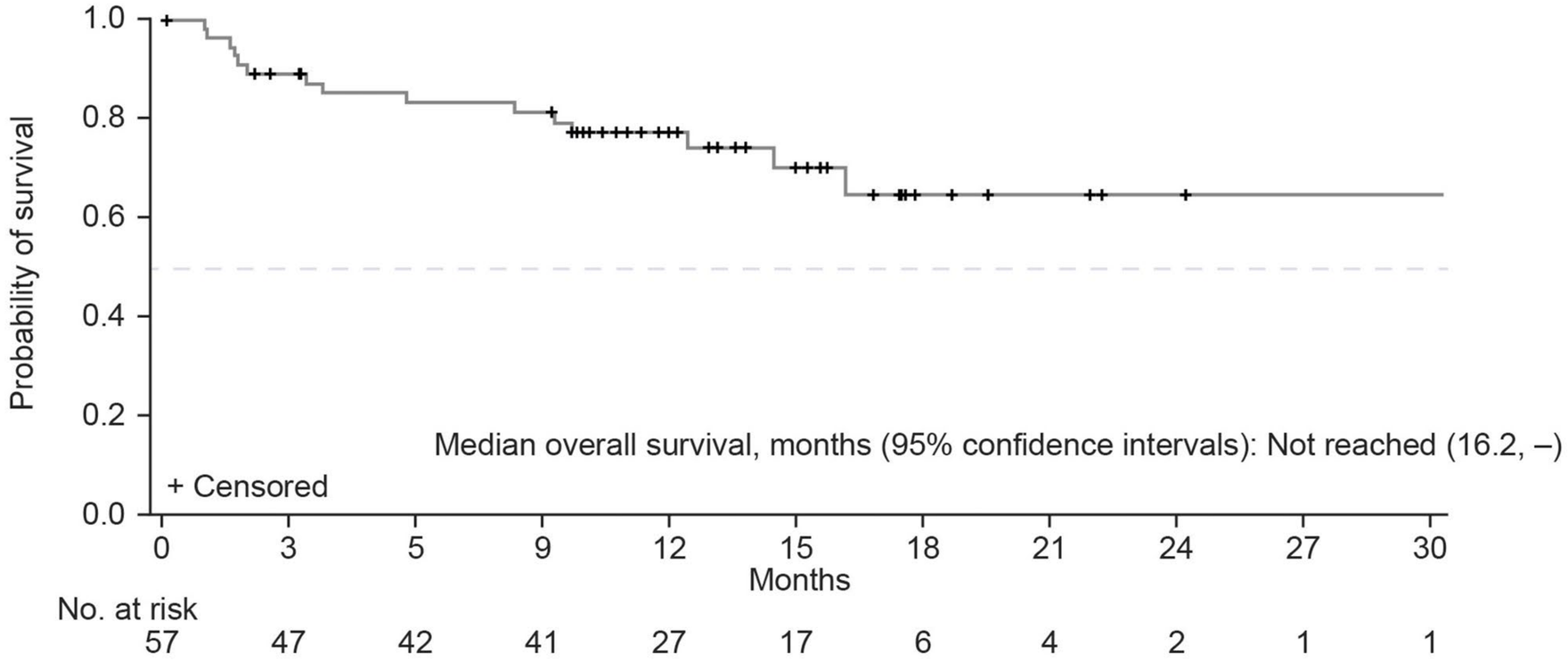
Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

- Treatment-naïve HR-MDS, IPSS intermediate risk-2 or high, bone marrow blasts <20% at baseline, and ECOG score ≤2 were enrolled. Transplant ineligible
- RP2D was (100, 200, and 400 mg) for 14 days in a 28-day cycle. Aza was administered at 75 mg/m^2 SC on Days 1-7 of each 28-day cycle.
- Results: at data cut off, December 31, 2019, 57 patients had received Ven+Aza, with a median follow-up of 13.0 months
- All patients experienced ≥1 adverse event (AE), the most common being constipation (54%), neutropenia (51%), and nausea (51%). Grade ≥3 AEs were experienced by 97% of patients, with neutropenia (51%), febrile neutropenia (46%), and thrombocytopenia (30%) the most common. Febrile neutropenia was the most common serious AE (42%). The 30-day mortality rate was 2%.
- The ORR was 77%, including complete remission (CR) and marrow CR (mCR) achieved by 42% and 35% of patients (of whom 40% achieved mCR + hematological improvement). Median OS was not reached (95% CI 16.2 months, not estimable; Figure 1).
- Median duration of response was 14.8 months (95% CI 12.9 months, not estimable). Median progression-free survival was 17.5 months (14.5, not estimable).

Jacqueline S. Garcia et al. Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study. *Blood* (2020) 136 (Supplement 1): 55–57.

Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

Figure 1. Kaplan–Meier Curve for Overall Survival of All Patients



Jacqueline S. Garcia et al. Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination with Azacitidine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study. *Blood* (2020) 136 (Supplement 1): 55–57.

Azacitadine + venetoclax for relapse/refractory high risk MDS

Venetoclax ± Azacitidine in MDS: Study Design

- Multicenter, open-label, nonrandomized phase Ib dose-finding study (data cutoff: August 30, 2019)

Patients ≥ 18 yrs of age with **relapsed/refractory** MDS following initial CR, PR, or haematologic improvement with ≥ 4 cycles of azacitidine or decitabine within last 5 yrs; BM blasts < 20%; ECOG PS ≤ 2; ineligible for HSCT; no prior therapy with BH3 mimetic or transplant; no preexisting MPN
(N = 64)

Venetoclax* QD on Days 1-14 +
Azacitidine 75 mg/m^2 QD on Days 1-7
(n = 38)

Venetoclax† QD on Days 1-14
(n = 26)

*Escalating doses of 100 mg (n = 9), 200 mg (n = 7), and 400 mg (n = 7 + 15 in safety expansion cohort at RP2D). †400 mg (n = 15) or 800 mg (n = 11) following safety review.

Primary endpoints: safety, MTD, RP2D, PK of VEN alone and in combination with AZA

Secondary endpoints: ORR (modified IWG 2006 criteria), PFS, TTR, DoR, OS, hematologic improvement, transfusion independence

Zeidan. ASH 2019. Abstr 565.

Venetoclax ± Azacitidine in MDS: Baseline Characteristics

Characteristic	Venetoclax* + Azacitidine (n = 38)	Venetoclax† (n = 26)	All Patients (N = 64)
Male, n (%)	33 (87)	21 (81)	54 (84)
Median age, yrs (range)	74 (44-91)	77 (58-88)	75 (44-91)
ECOG PS, n (%)			
▪0	9 (24)	2 (8)	11 (18)
▪1	22 (60)	22 (85)	44 (70)
▪2	6 (16)	2 (8)	8 (13)
BM blasts, n (%)			
▪< 5%	11 (31)	14 (54)	25 (40)
▪5% to 9%	19 (53)	9 (35)	28 (45)
▪10% to 19%	6 (17)	3 (12)	9 (15)
▪Missing	2	0	2

Characteristic	Venetoclax* + Azacitidine (n = 38)	Venetoclax† (n = 26)	All Patients (N = 64)
No. prior therapies			
▪1	34 (90)	18 (69)	52 (81)
▪2	3 (8)	5 (19)	8 (13)
▪3	1 (3)	2 (8)	3 (5)
▪> 3	0	1 (4)	1 (2)
No. prior HMA therapies			
▪1	36 (95)	25 (96)	61 (95)
▪2	1 (3)	1 (4)	2 (3)
Median no. prior HMA cycles	8	11	9

*Escalating doses of 100 mg (n = 9), 200 mg (n = 7), and 400 mg (n = 22, including safety expansion cohort).
†400 mg (n = 15) or 800 mg (n =11).

Zeidan. ASH 2019. Abstr 565

Venetoclax ± Azacitidine in MDS: TEAE Summary

AEs in ≥ 20% of Patients	Venetoclax* + Azacitidine (n = 38)	Venetoclax† (n = 26)	All Patients (N = 64)
Any AE	37 (97)	26 (85)	63 (98)
Neutropenia‡	19 (50)	10 (38)	29 (45)
Nausea	18 (47)	10 (38)	28 (44)
Leukopenia‡	15 (39)	9 (35)	24 (38)
Diarrhea	13 (34)	9 (35)	22 (34)
Thrombocytopenia‡	17 (45)	3 (12)	20 (31)
Constipation	15 (40)	4 (15)	19 (30)
Febrile neutropenia	11 (29)	6 (23)	17 (27)
Fatigue	10 (26)	7 (27)	17 (27)
Headache	9 (24)	4 (15)	13 (20)

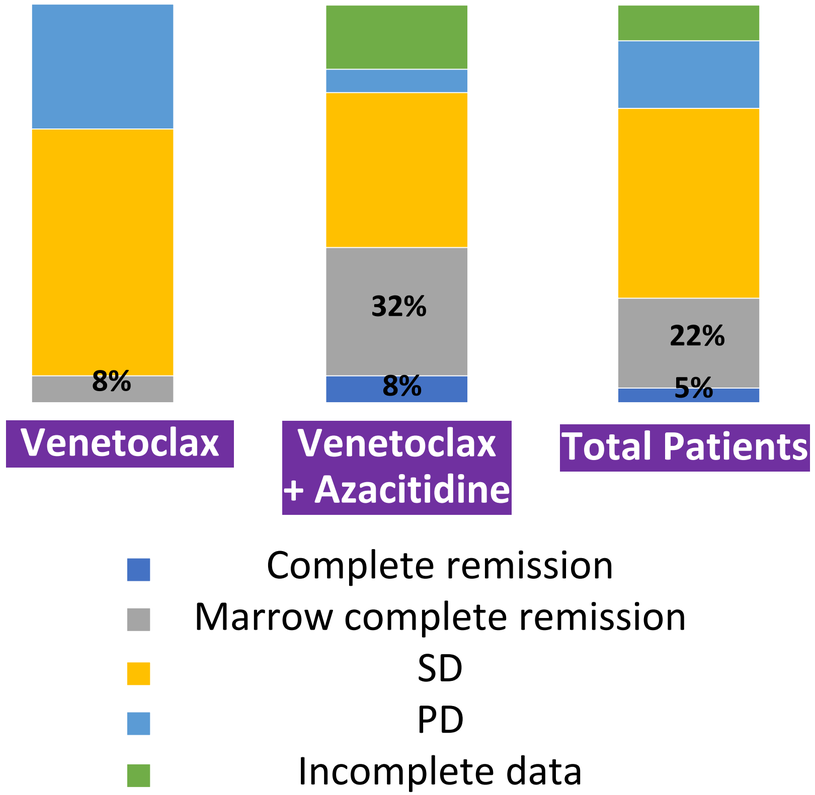
Grade ≥ 3 AEs in ≥ 10% of Patients	Venetoclax* + Azacitidine (n = 38)	Venetoclax† (n = 26)	All Patients (N = 64)
Any grade ≥ 3 AEs	37 (97)	21 (81)	56 (88)
Neutropenia	19 (50)	9 (35)	28 (44)
Leukopenia	15 (39)	9 (35)	24 (38)
Thrombocytopenia	16 (42)	3 (12)	19 (30)
Febrile neutropenia	11 (29)	6 (23)	17 (27)
Pneumonia	6 (16)	4 (15)	10 (16)
Anemia‡	6 (16)	4 (15)	10 (16)
Serious AE	37 (97)	26 (85)	63 (98)

*Escalating doses of 100 mg (n = 9), 200 mg (n = 7), and 400 mg (n = 22, including safety expansion cohort). †400 mg (n = 15) or 800 mg (n = 11).
‡Includes decreased count.

- No dose-limiting toxicities; RP2D of venetoclax established as 400 mg for combination with azacitidine

Venetoclax ± Azacitidine in MDS: Response

Best Overall Response

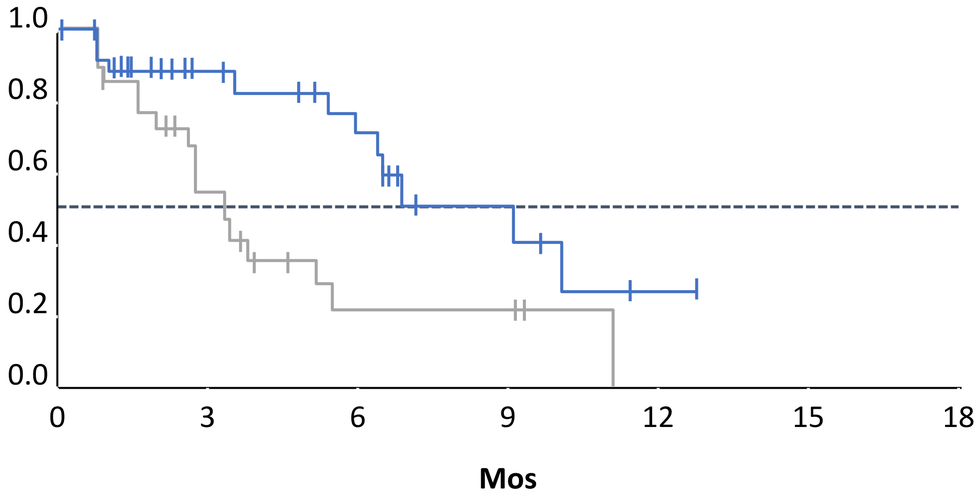


Zeidan. ASH 2019. Abstr 565.

Venetoclax ± Azacitidine in MDS: Survival

PFS

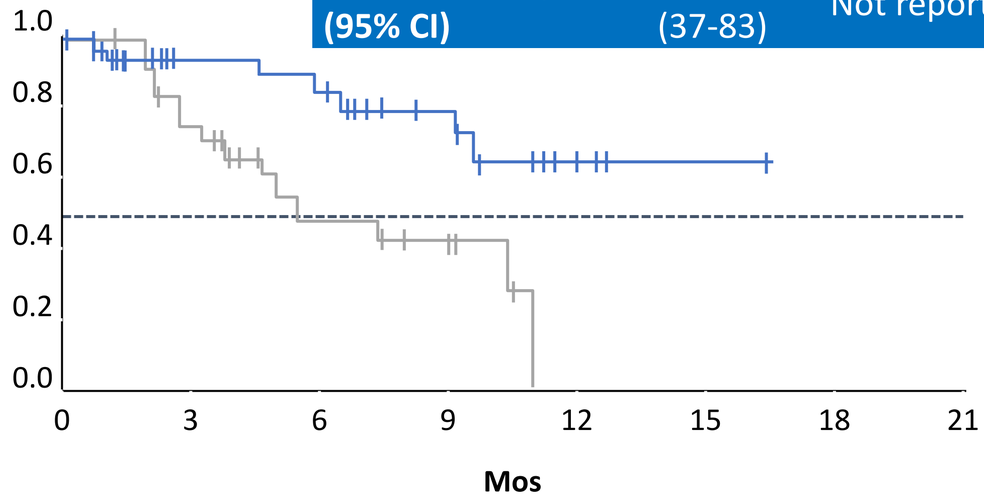
	Venetoclax + Azacitidine	Venetoclax
Median PFS, mos (95% CI)	9.1 (5.9-NE)	3.3 (2.7-5.2)



VEN	26	12	3	3	0	0
VEN + AZA	38	18	12	5	1	0

OS

	Venetoclax + Azacitidine	Venetoclax
Median OS, mos (95% CI)	NR	5.5 (3.3-11.1)
Est. 12-Mo OS, % (95% CI)	65 (37-83)	Not reported



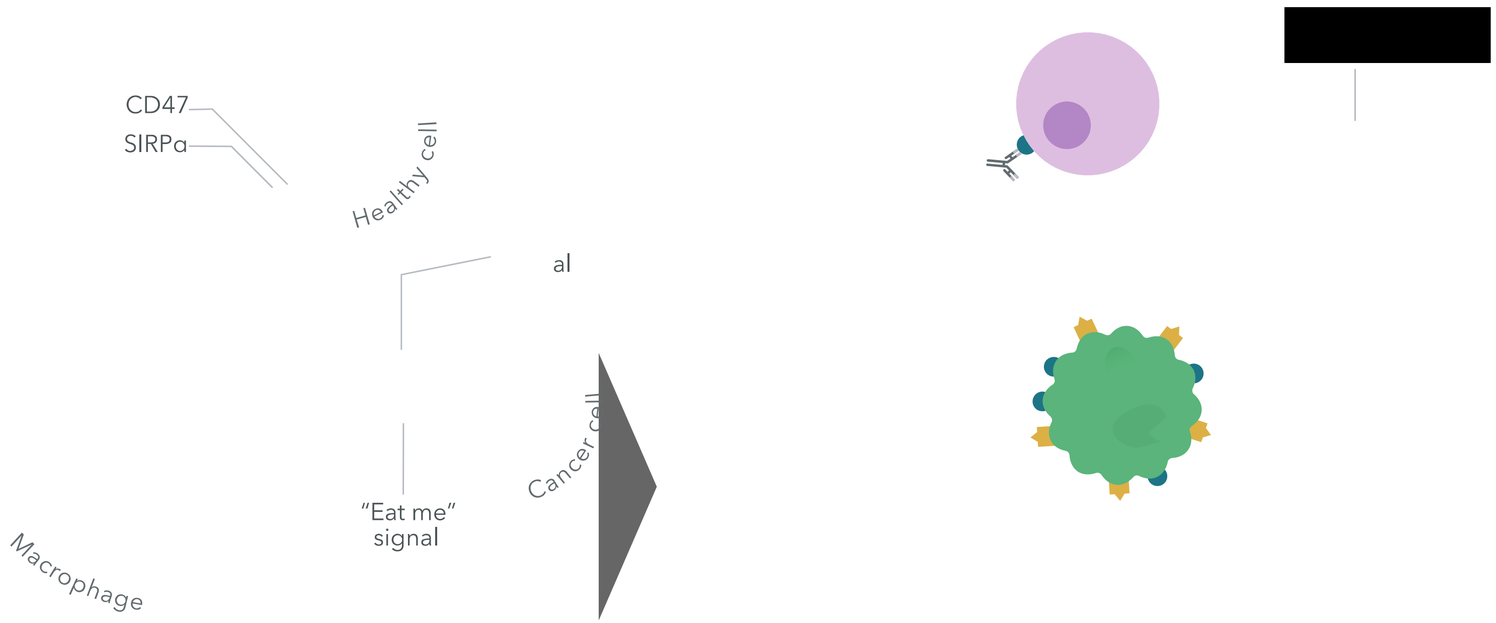
VEN	26	18	8	5	0	0	0
VEN + AZA	38	21	19	11	4	1	0

Zeidan. ASH 2019. Abstr 565.

Magrolimab + azacitadine for high risk MDS

LOUISIANA ONCOLOGY SOCIETY

Magrolimab is a Macrophage Checkpoint Inhibitor



Control mAb: No Phagocytosis

Anti-CD47 mAb: Phagocytosis

Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Daver. EHA 2020. Abstr S144.

Magrolimab + Aza in Patients With MDS and AML: Study Design

- Multicenter, single-arm phase Ib study
  - Current analysis reports data from expansion phase

Patients with untreated AML ineligible for induction CT or untreated MDS classed intermediate to very high risk by IPSS-R
(N = 68)

→

Magrolimab 1, 30 mg/kg QW* +
Aza 75 mg/m^2 Days 1-7
(n = 6)

→

Magrolimab 1, 30 mg/kg QW or Q2W* +
Aza 75 mg/m^2 Days 1-7
(n = 68)

- Primary endpoints: safety, efficacy
- Secondary endpoints: magrolimab PK, PD, immunogenicity
- Exploratory endpoints: CD47 receptor occupancy, immune activity markers, molecular profiling

Sallman DA, Al Malki M, Asch AS, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. Oral abstract #7507. ASCO Annual Meeting 2020; May 29–31, 2020

Magrolimab + Aza in Patients With MDS and AML: Baseline Characteristics

Characteristic	MDS (n = 39)	AML (n = 29)
Median age, yrs (range)	70 (47-80)	74 (60-89)
ECOG PS, n (%)		
▪0	11 (81)	7 (24)
▪1	26 (67)	20 (69)
▪2	2 (5)	2 (7)
Cytogenetic risk, n (%)		
▪Favorable	0	0
▪Intermediate	11 (28)	2 (7)
▪Poor	25 (64)	21 (72)
▪Unknown/missing	3 (8)	6 (21)
WHO AML classification, n (%)		
▪MRC		19 (66)
▪Recurrent genetic abnormalities	NA	2 (7)
▪Therapy related		3 (10)
▪NOS		5 (17)

Characteristic	MDS (n = 39)	AML (n = 29)
WHO MDS classification, n (%)		
▪RS and single/multilineage dysplasia	1 (3)	NA
▪Multilineage dysplasia	7 (18)	
▪RS with multilineage dysplasia	3 (8)	
▪Excess blasts	22 (56)	
▪Unclassifiable/unknown/missing	6 (15)	
IPSS-R (MDS), n (%)		
▪Intermediate	13 (33)	NA
▪High	19 (49)	
▪Very high	6 (15)	
▪Unknown/missing	1 (3)	
Therapy-related MDS, n (%)	12 (31)	NA
▪Unknown/missing	1 (3)	
TP53 mutation, n (%)	5 (13)	13 (45)

Sallman DA, Al Malki M, Asch AS, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. Oral abstract #7507. ASCO Annual Meeting 2020; May 29–31, 2020

Magrolimab + Aza in Patients With MDS and AML: Response

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

Outcome, n (%)	MDS (n = 33)	AML (n = 25)
RBC transfusion independence	11/19 (58)	9/14 (64)
Complete cytogenetic response	9/26 (35)	6/12 (50)
MRD negativity in responders	6/30 (20)	8/16 (50)
Median DoR, mos	NR (0.03+ to 10.4+)	NR (0.03+ to 15.1+)
Median follow-up, mos (range)	5.8 (2.0 to 15.0)	9.4 (1.9 to 16.9)

- Median TTR: 1.9 mos; median OS: NR (either arm)
- 6-mo CR rate, MDS patients: 56%
- 9 of 58 (16%) patients received alloSCT

Sallman, ASCO 2020, Abstr 7507

Sallman DA, Al Malki M, Asch AS, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. Oral abstract #7507. ASCO Annual Meeting 2020; May 29–31, 2020

Magrolimab + Aza in Patients With MDS and AML: Response in Patients With *TP53* Mutation

Outcome	MDS *TP53* Mutant (n = 12)	AML *TP53* Mutant (n = 4)
ORR, n (%)	9 (75)	3 (75)
CR, n (%)	5 (42)	2 (50)
CRi/marrow CR, n (%)	4 (33)	1 (25)
Complete cytogenetic response, n/N (%)*	4/8 (50)	3/3 (100)
MRD negativity in responders, n/N (%)	4/9 (44)	0
Median DoR, mos	NR (0.03+ to 15.1)	NR (0.03+ to 5.2+)
6-mo survival probability, %	91	100
Median follow-up, mos (range)	8.8 (1.9 to 16.9)	7 (4.2 to 12.2)

Sallman DA, Al Malki M, Asch AS, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: Phase Ib results. Oral abstract #7507. ASCO Annual Meeting 2020; May 29–31, 2020

Other trials

- **Sabatolimab + azacitadine**
  - Preliminary data presented at ASH in 2021, indicated an ORR of 57% with a complete remission duration of 19 months and an excellent toxicity profile.
- **APR-246 + azacitadine vs aza(Phase III)**
  - The trial failed to meet its primary endpoint of complete remission (CR) rate.
- **Pevodinostat + azacitadine vs aza (Phase III)**
  - The trial failed to meet its primary endpoint of event free survival.

Sekeres M, Girshova L, Doronin V, et al: Pevonedistat + azacitidine versus azacytidine alone as first-line treatment for patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or acute myeloid leukemia with 20-30% marrow blasts: The randomized phase 3 PANTHER trial (NCT03268954). 2021 ASH Meeting & Exposition. Abstract 242. Presented December 11, 2021.

Brunner AM, Esteve J, Porkka K, et al. Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients with Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS): Updated Results from a Phase 1b Study. Presented at: 2020 ASH Annual Meeting & Exposition; December 5-8, 2020; Virtual. Abstract 657.