Manejo clínico y terapéutico del paciente con SMD de Alto Riesgo

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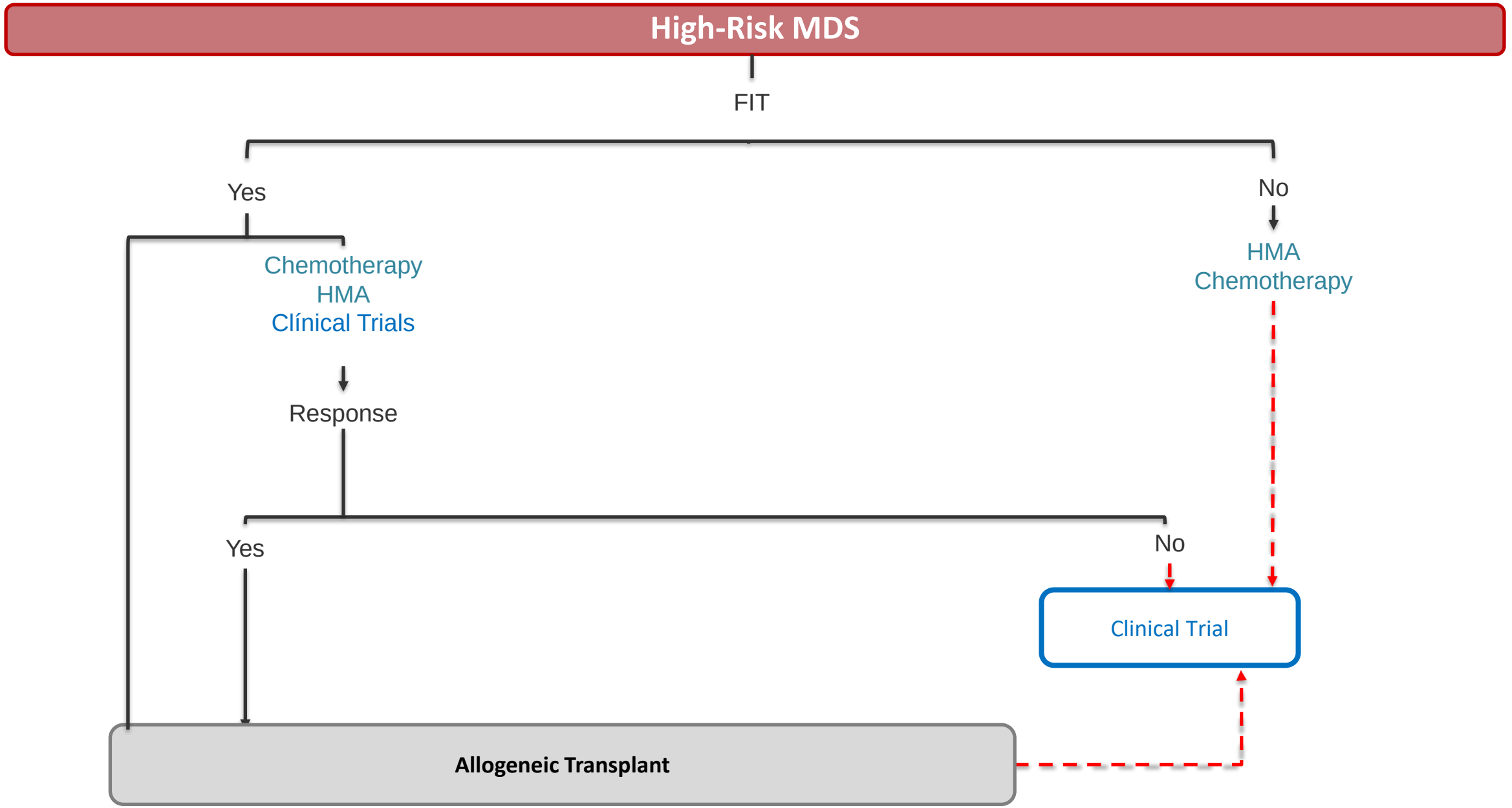
Current MDS treatment

MDS

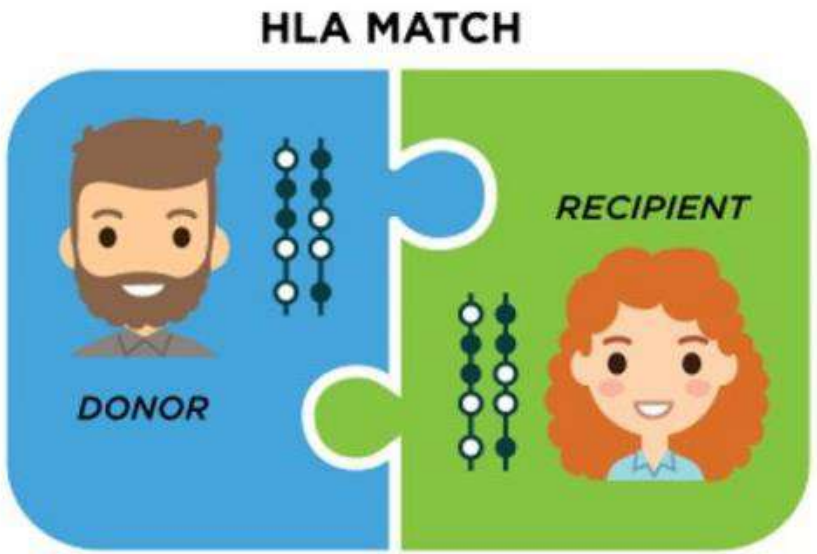
- **Low Risk (IPSS low or int-1)**
  - *OS > 30 months*
  - **Objective: Improve Quality of Life**
- **High Risk (IPSS int-2 or high)**
  - *OS < 30 months*
  - **Objective: Modify Overall Survival**

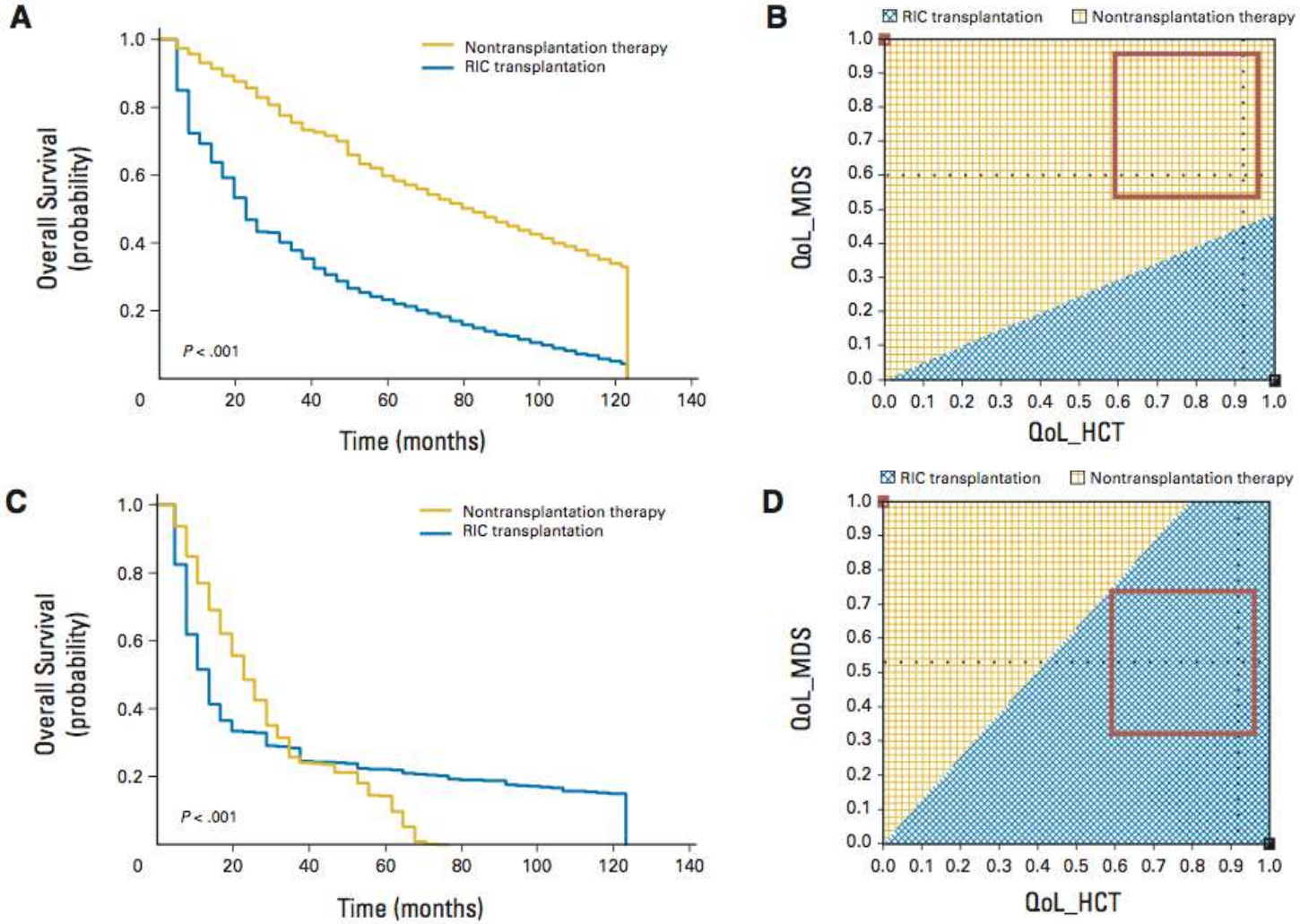
Current MDS treatment



Curative Treatment: Allogeneic Stem-Cell Transplantation

Role of **Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem-Cell Transplantation** in Older Patients With De Novo Myelodysplastic Syndromes: An International Collaborative Decision Analysis





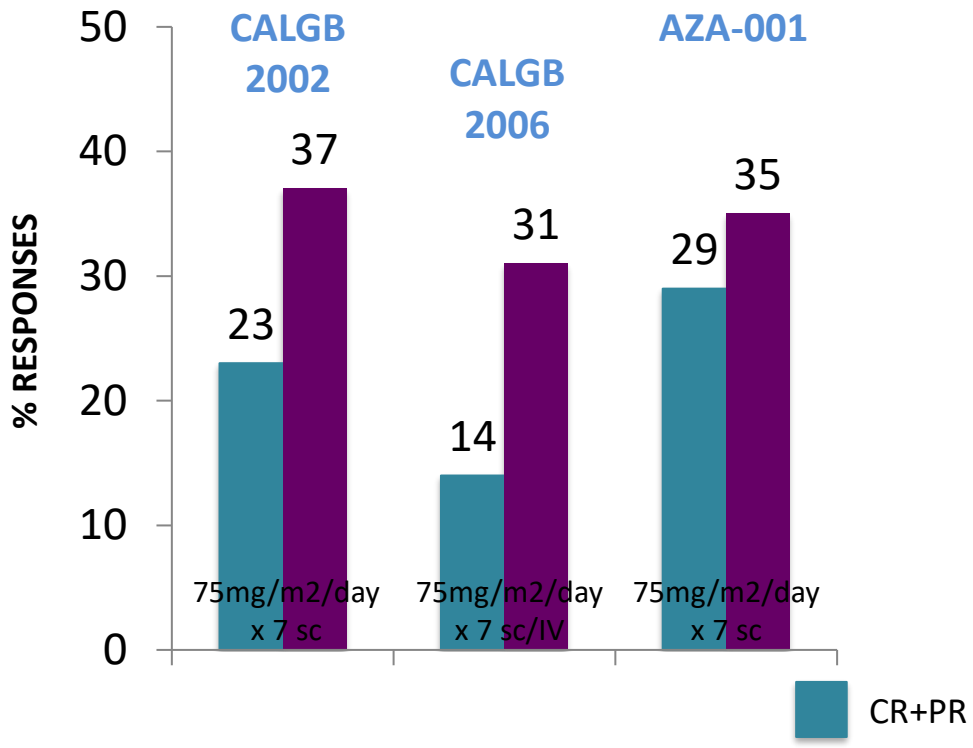
Koreth J et al. J Clin Oncol. 2013;31(21):2662-70.

Current treatment - High Risk MDS

Hypomethylating Agents

ORR

AZACITIDINA



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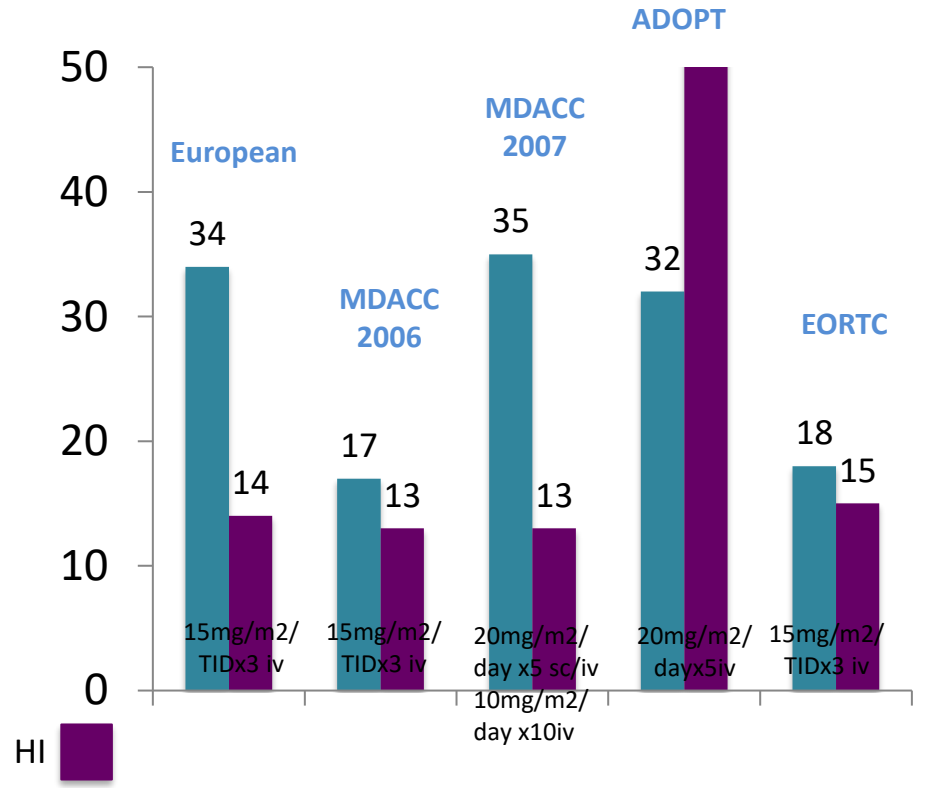


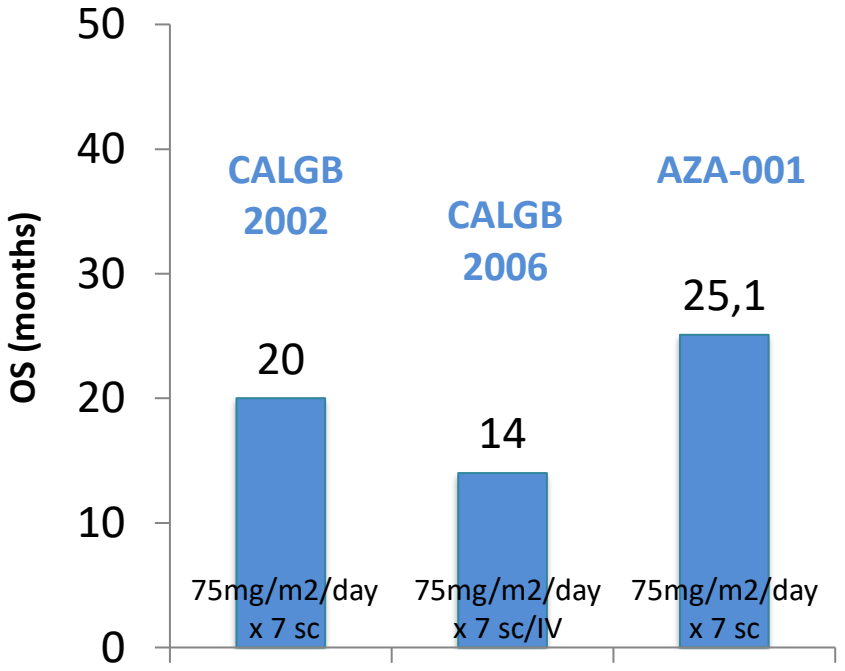
Silverman LR. J Clin Oncol. 2002;20(10):2429-40
Silverman LR. J Clin Oncol. 2006 ;24(24):3895-903.
Fenaux P et al. Lancet Oncol. 2009 Mar;10(3):223-32

Wjiermans Ann Hematol 2005;84:9-17
Kantarjian H et al. Cancer 2006;106:1794-803
Kantarjian H et al. Blood 2007;109:52-7
Steensma DP et al. JCO 2009;24:3842-8
Lubberrt M et al. JCO. 2011;29(15):1987-96.

Hypomethylating Agents

OS

AZACITIDINA



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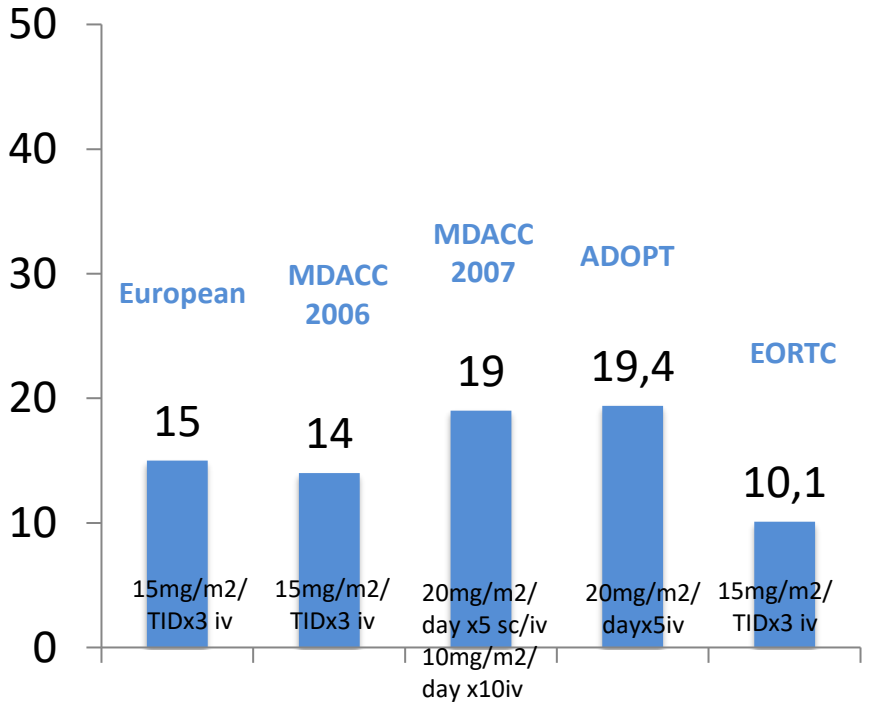

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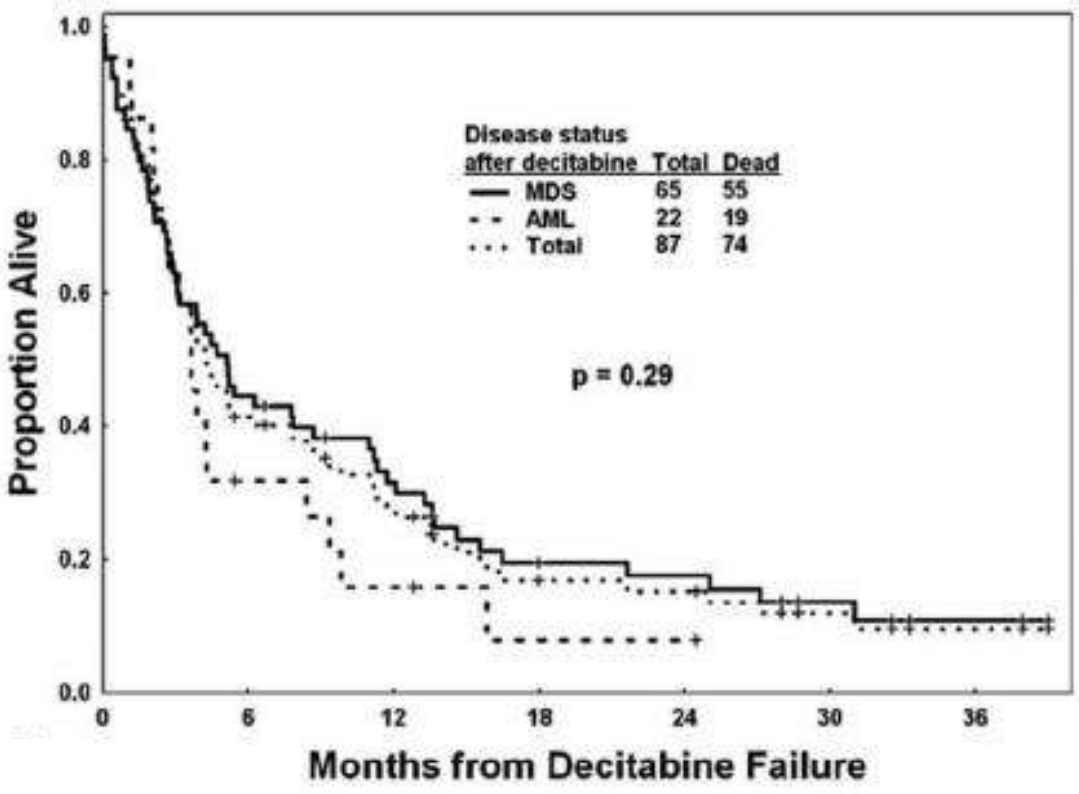
Kantarjian H et al. Blood 2007;109:52-7
Steensma DP et al. JCO 2009;24:3842-8
Lubberrt M et al. JCO. 2011;29(15):1987-96.

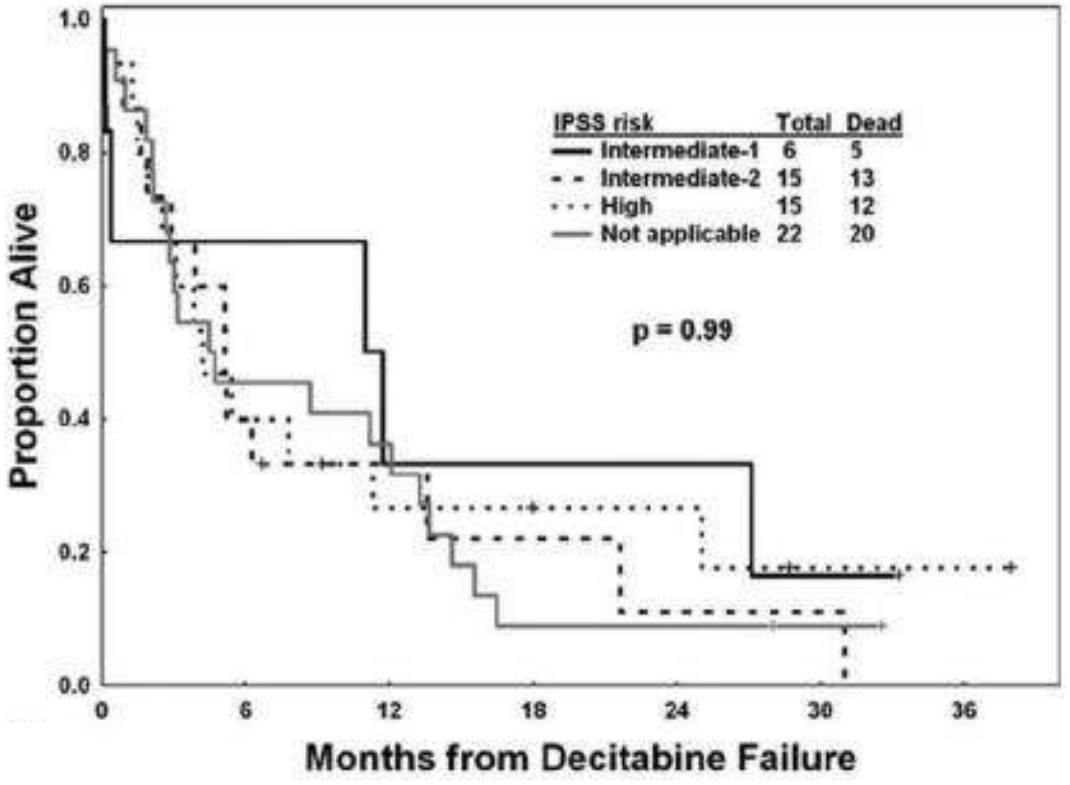
EMA (2009): adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with INT-2 and HR MDS according to the IPSS

HMA failure

Failure to HMA

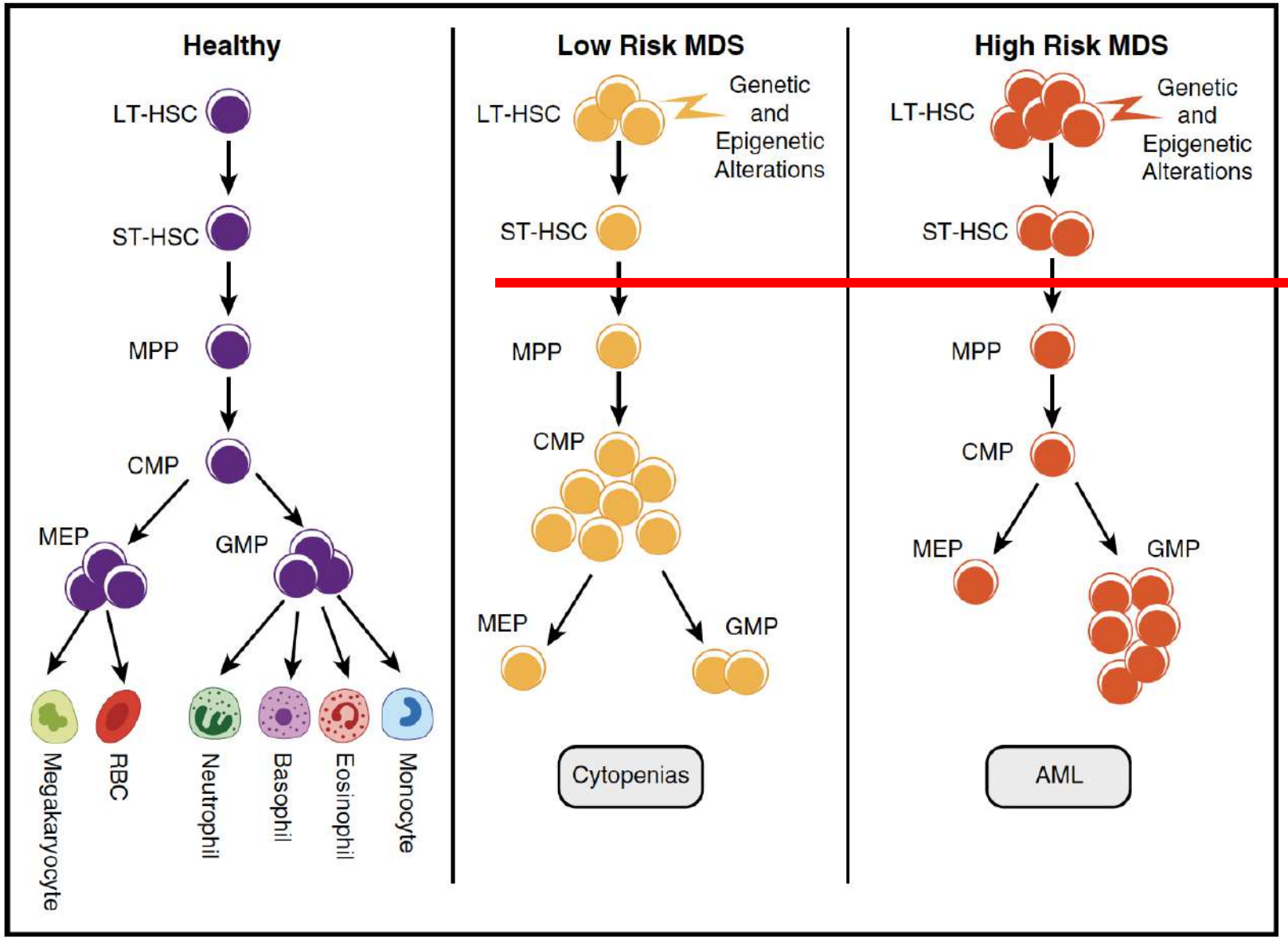
- Failure to hypomethylating agents (HMA) associated to disease progression and dismal prognosis
- Poorly understood, unpredictable, unpreventable
- Independent of genetic alterations





Jabbour, E. J. et al. Cancer 121, 876–882 (2015)

HSC and HSPC in MDS



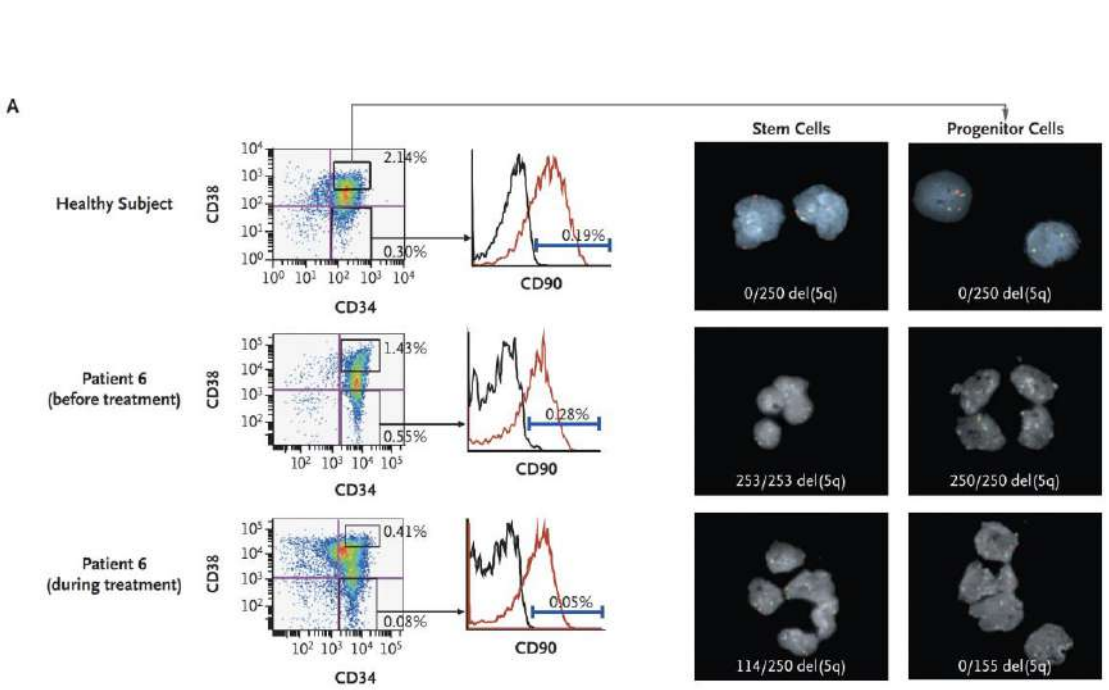
Allogeneic Stem- Cell Transplant

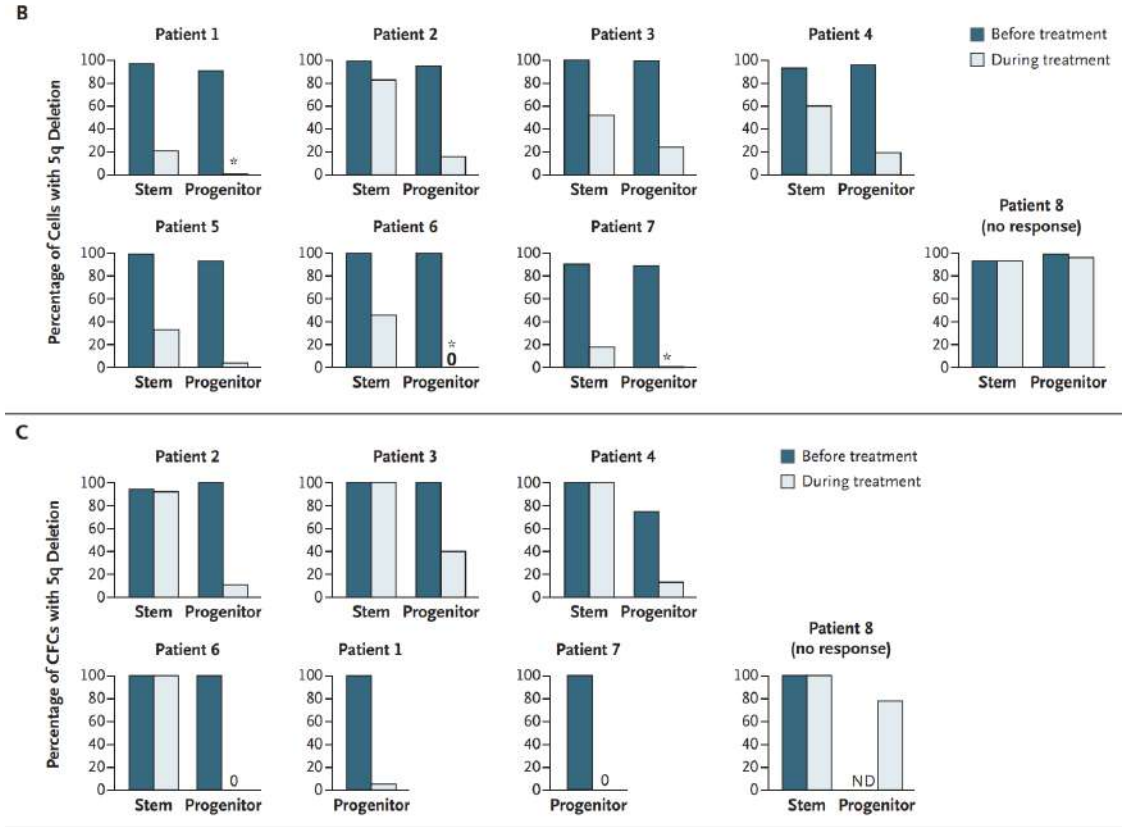
Lenalidomide

Hypomethilating Agents

Shastri A et al. Blood. 2017 Mar 23;129(12):1586-1594.

Role of HSPCs in disease relapse





Persistence of lenalidomide-resistant MDS stem cells provides a reasonable explanation for relapses and clinical and cytogenetic progression during lenalidomide treatment and may facilitate delineation of specific cellular targets apart from those in the bulk of the clone.

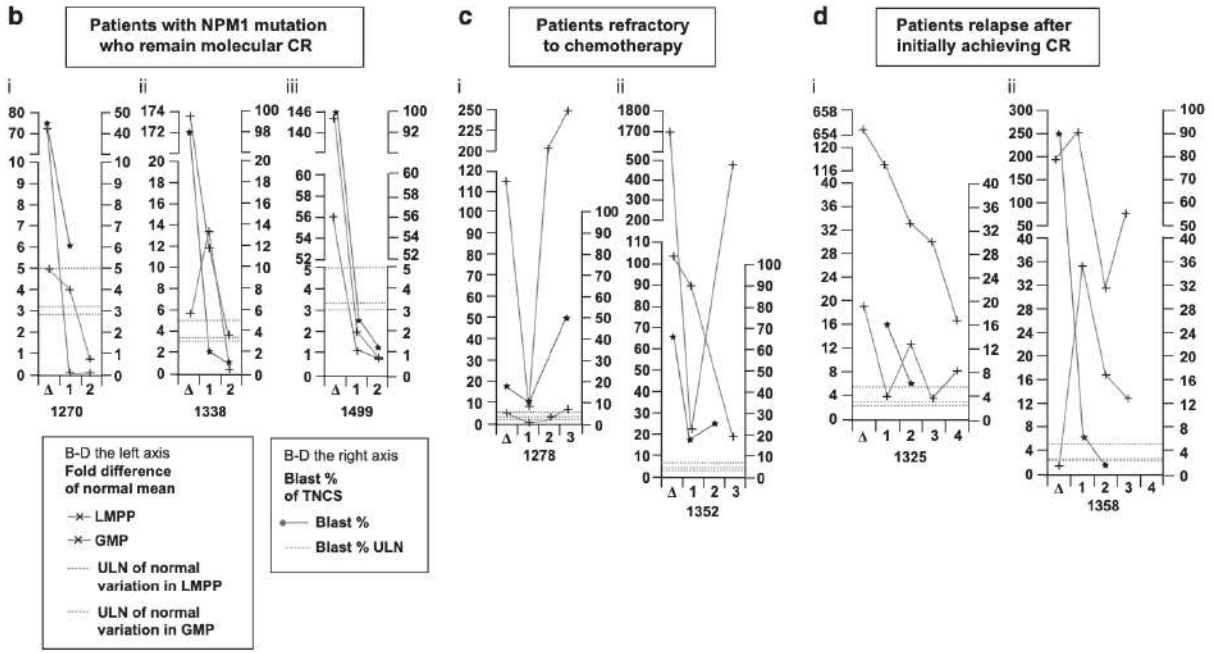
Tehranchi MD et al. N Engl J Med 2010;363:1025-37.

Role of HSPCs in disease relapse

ORIGINAL ARTICLE

Azacitidine fails to eradicate leukemic stem/progenitor cell populations in patients with acute myeloid leukemia and myelodysplasia

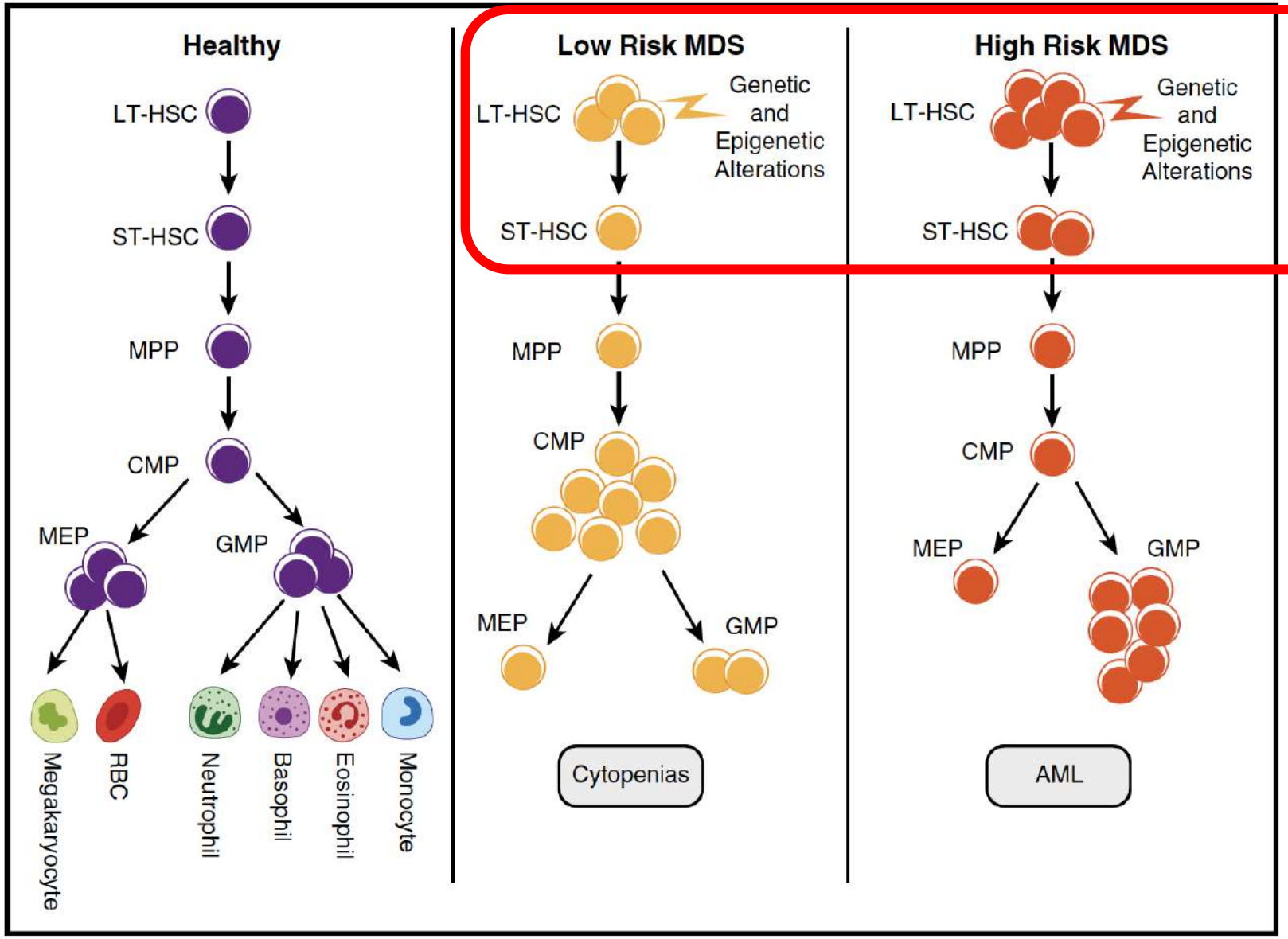
C Craddock[1,2], L Quek[3,4,14], N Goardon[3,14], S Freeman[1,5], S Siddique[1,2], M Raghavan[1,2], A Aztberger[3], A Schuh[4], D Grimwade[6,7], A Ivey[6,7], P Virgo[8], R Hills[9], T McSkeane[1,2], J Arrazi[1], S Knapper[9], C Brookes[2], B Davies[10], A Price[10], K Wall[11], M Griffiths[11], J Cavenagh[12], R Majeti[13], I Weissman[13], A Burnett[9] and P Vyas[3,4]



Persistence of leukemic stem/progenitor cells in patients treated with epigenetic therapies responsible of clinical relapse in AML/MDS patients treated with Azacitidine + Sodium Valproate

Craddock C et al. Leukemia. 2013;27(5):1028-1036.

HSC and HSPC in MDS



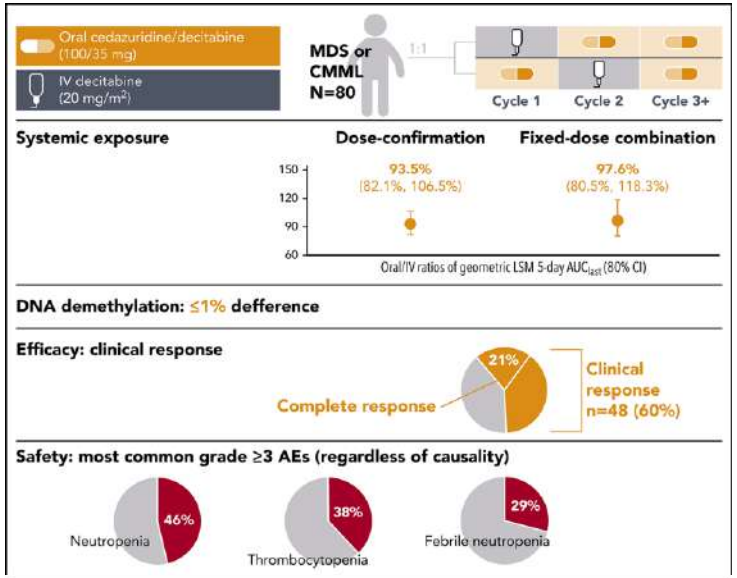
- Understand altered pathways in HSC
- Design treatments aimed at reversing these HSC alterations → Improve the outcomes of MDS patients

Shastri A et al. Blood. 2017 Mar 23;129(12):1586-1594.

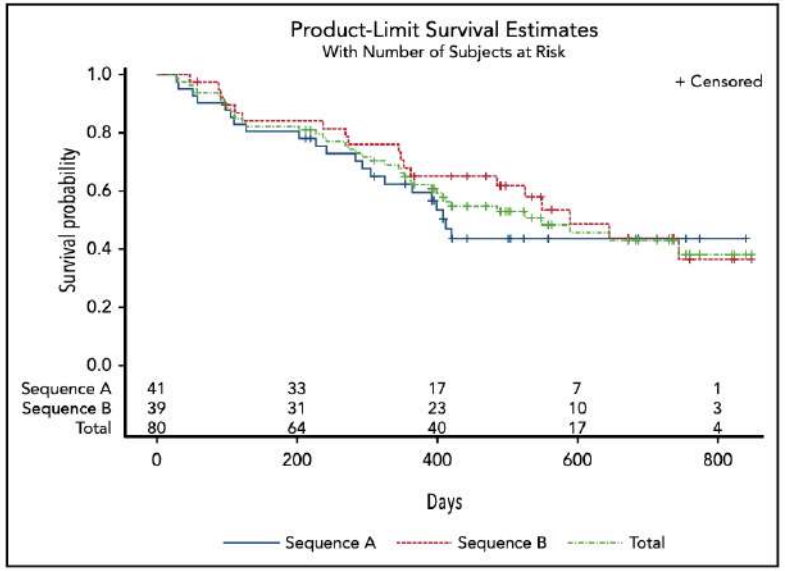
Future treament – HR MDS

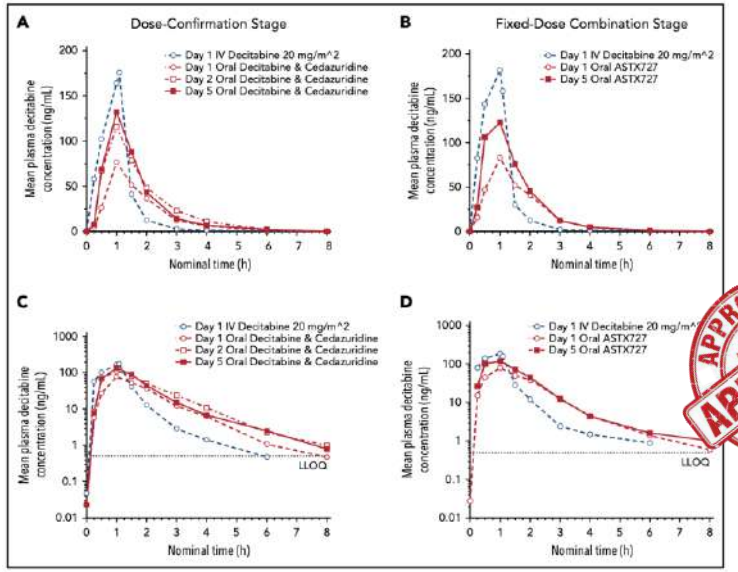
Hypomethylating Agents

Oral cedazuridine/decitabine



Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52





- **Similar PK**
- **Similar ORR**
- **Median FUP: 24.3 months (range, 12.0-29.2 months)**
- **Median overall survival for all patients treated was 18.3 months (95% CI, 9.1-not estimable).**

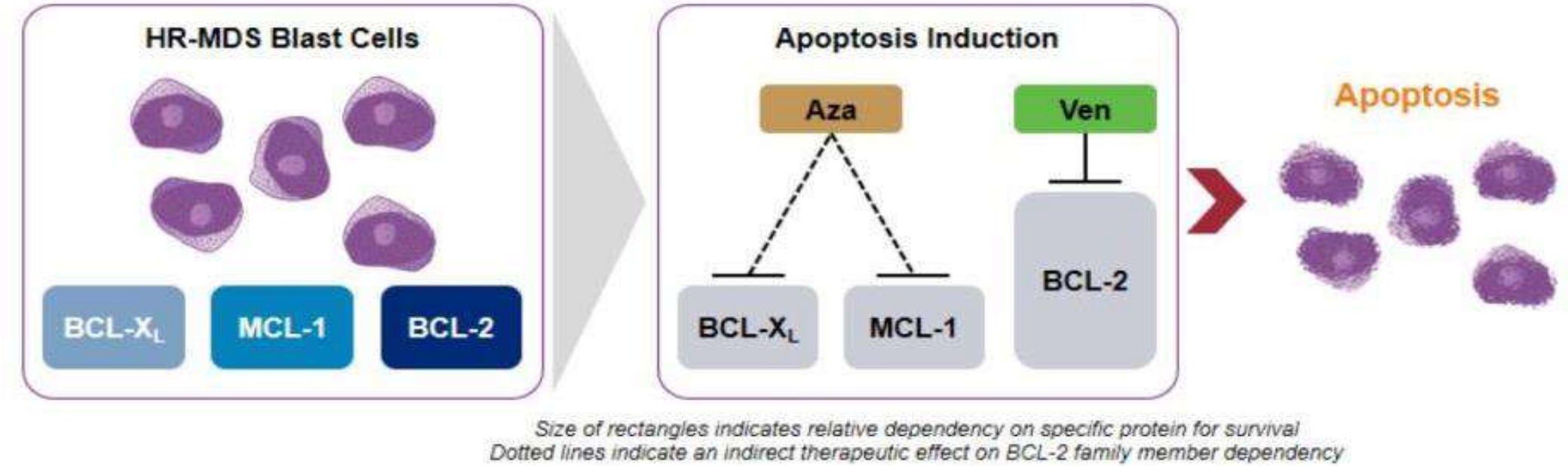
FDA approved: previously untreated MDS patient with IPSS int-1, int-2 and HR

ASCERTAIN Ph III trial: currently enrolling patients (in EU, MDS patients not included)

Garcia-Manero G. Blood. 2020 Aug 6;136(6):674-683.

Venetoclax + HMA

Venetoclax



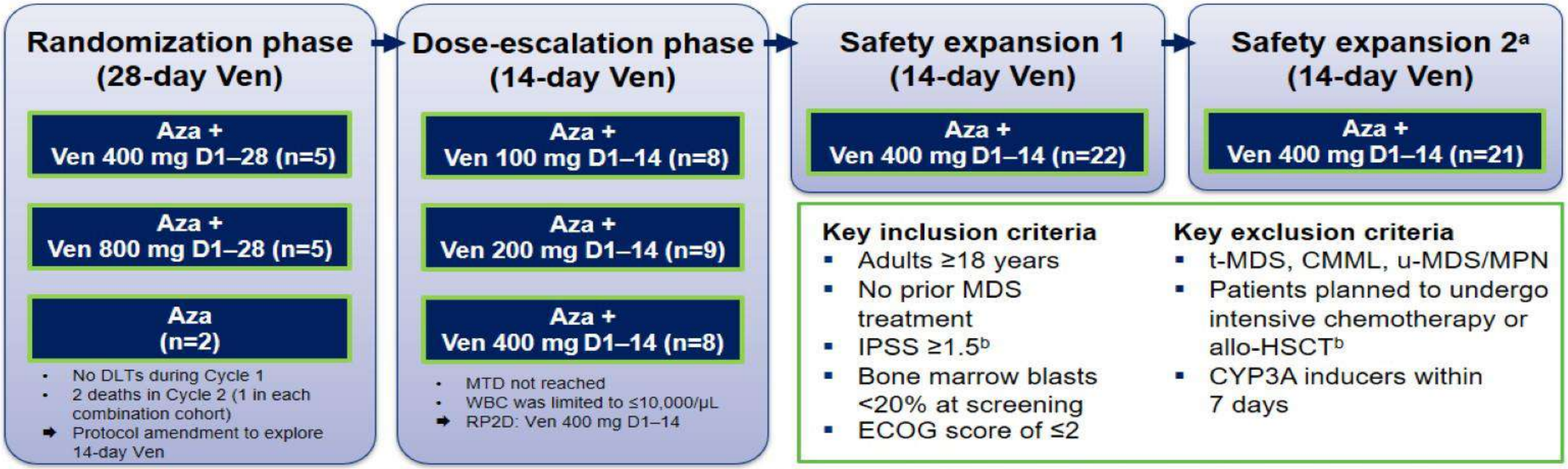
- Venetoclas (VEN) is a selective potent, orally bioavailable BCL-2 inhibitor, approved for use in combination with AZA, DEC or low-dose cytarabine to treat patient with newly diagnosed AML
- VEN has been shown to synergize with HMA agents In preclinical and clinical studies of myeloid malignancies
  - AZA increases sensitivity to VEN-mediated BCL-2 inhibition through modulation of BCL-2 family members in myeloid malignant cells

Garcia J, EHA 2020

Venetoclax

M15-531: Ph 1b VEN+AZA in untreated HR-MDS

Treatment cohorts (28-day cycles); Aza 75 mg/m² D1–7



Primary objectives

1. Safety
2. Establish the RP2D

Secondary objectives

1. ORR
2. OS

Garcia J, EHA 2020

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M15-531: Ph 1b VEN+AZA in untreated HR-MDS: **Baseline demographics and disease characteristics**

Characteristic	n (% of N=78)
Male	56 (72)
Median age, years [range]	70 [26–87]
ECOG performance score	
0	33 (42)
1	38 (49)
2	7 (9)
Bone marrow blasts	
≤5%	7 (9)
>5% to ≤10%	21 (27)
>10% to ≤20%	49 (63)
>20%	1 (1)[a]
IPSS karyotype risk	
Good	31 (40)
Intermediate	17 (22)
Poor	30 (39)

Characteristic	n (% of N=78)
IPSS risk classification	
Intermediate-2	57 (73)
High	21 (27)
IPSS-R risk classification[b]	
Intermediate	14 (18)
High	20 (26)
Very high	44 (56)
Baseline cytopenias (Grade ≥3)	
Neutropenia[c]	46 (59)
Thrombocytopenia[d]	26 (33)
Leukopenia[e]	33 (42)
Anemia[f]	10 (13)

Garcia J, EHA 2020

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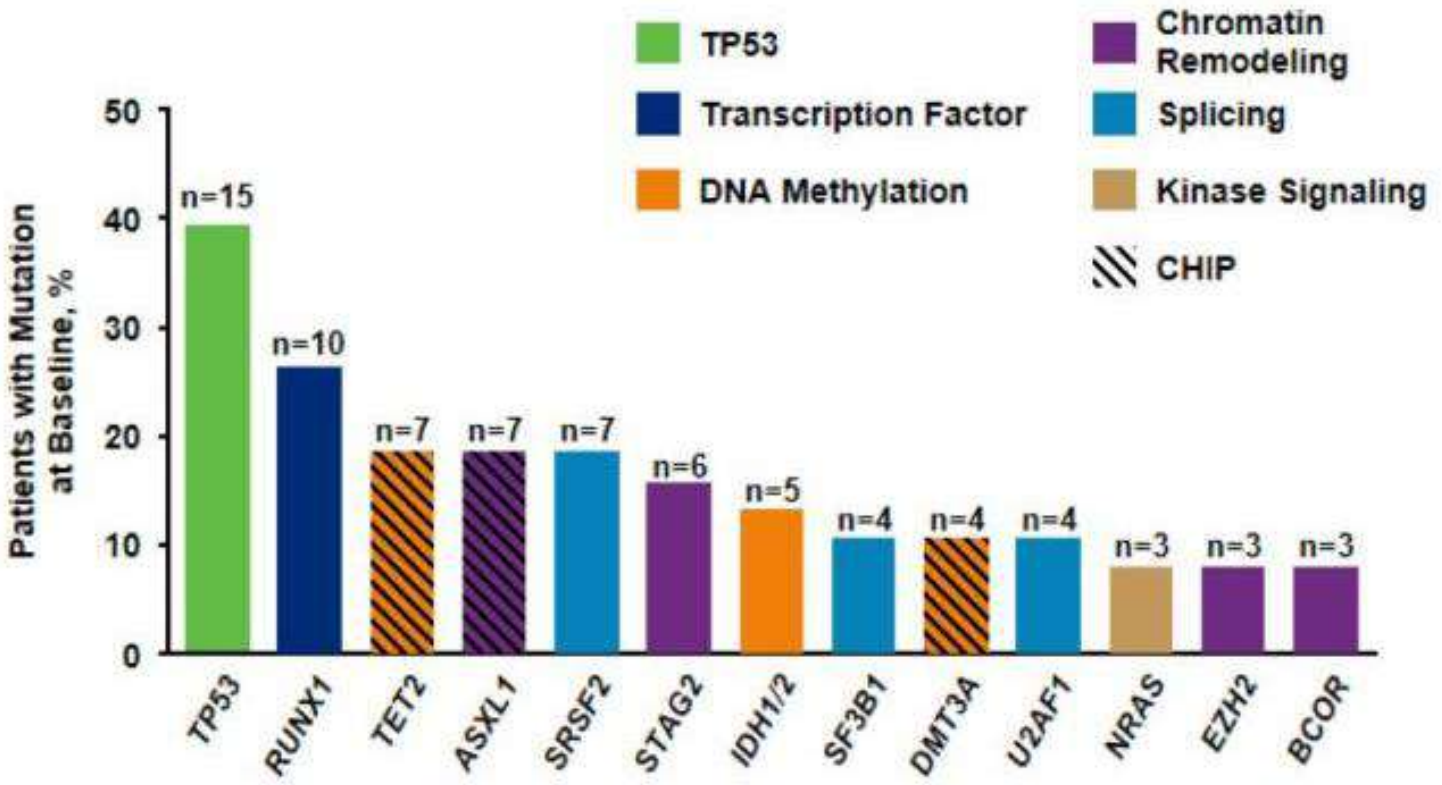
M15-531: Ph 1b VEN+AZA in untreated HR-MDS - **Baseline demographics and disease characteristics**

- Mutational analysis was available for 38 patients, of whom 15 had a *TP53* mutation
- The spectrum of mutations observed were consistent with other higher-risk MDS study populations



MDS, myelodysplastic syndrome
38 patients assessed; genes illustrated limited to those observed in ≥5% of patients

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M15-531: Ph 1b VEN+AZA in untreated HR-MDS: **Safety**

Any AEs, n (%)	78 (100)
Neutropenia[a]	65 (83)
Febrile neutropenia	38 (49)
Nausea	43 (55)
Constipation	42 (54)
Diarrhea	38 (49)
Thrombocytopenia[b]	38 (49)
Vomiting	32 (41)
Leukopenia[c]	30 (38)
Anemia[d]	23 (29)
Fatigue	20 (26)
Hypokalemia	16 (21)

Grade 3/4 AEs, n (%)	75 (96)
Neutropenia[a]	64 (82)
Febrile neutropenia	38 (49)
Thrombocytopenia[b]	33 (42)
Leukopenia[c]	30 (38)
Anemia[d]	18 (23)

Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

- Overall, 74 patients (95%) required a cycle delay; median time to delay 15.0 days (range 3–99)
- 43 patients (55%) had ≥2 Ven dose interruptions
  - AEs 59 (80%); hematologic toxicity 27 (37%); logistics/scheduling 19 (26%), other 41 (55%)
- A total of 35% of patients required ≥1 Ven dose reduction[e]
  - AEs 6 (21%); starting CYP3A inhibitor 20 (71%); other 7 (25%)
- A total of 33% of patients required ≥1 Aza dose reduction[e]
- 30-day mortality after first dose was 1%

Garcia J, EHA 2020

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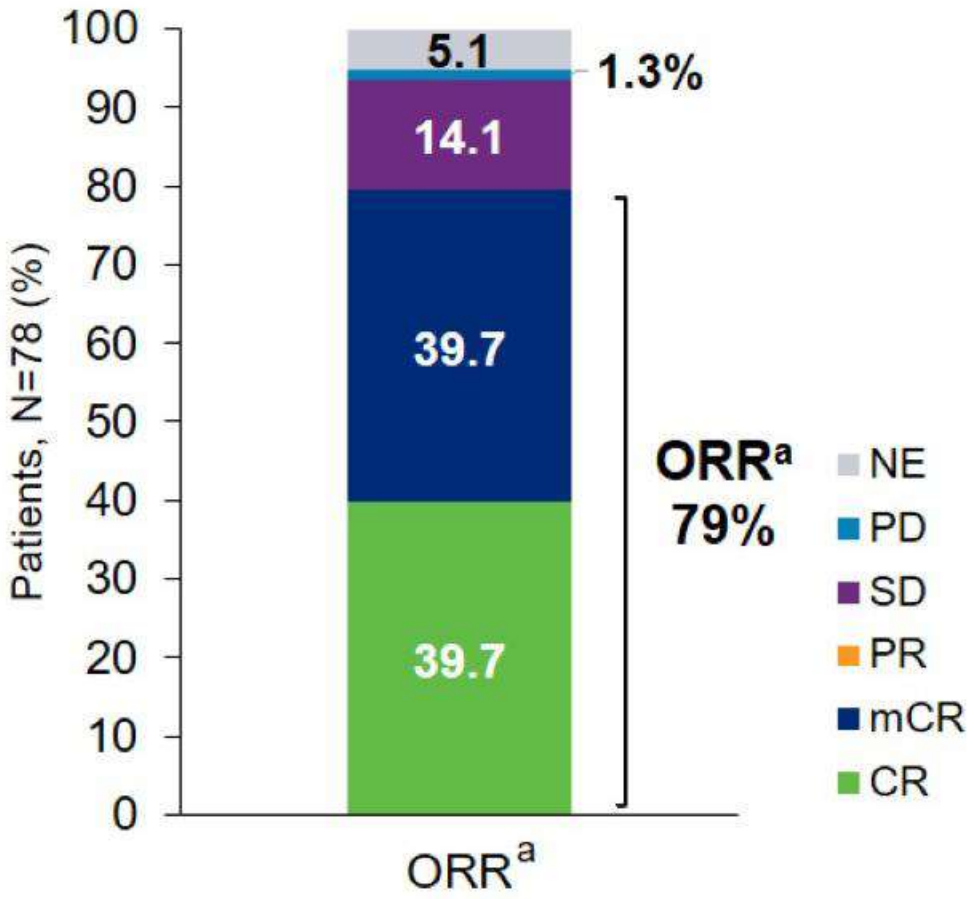
M15-531: Ph 1b VEN+AZA in untreated HR-MDS - **Responses**



- 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% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

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

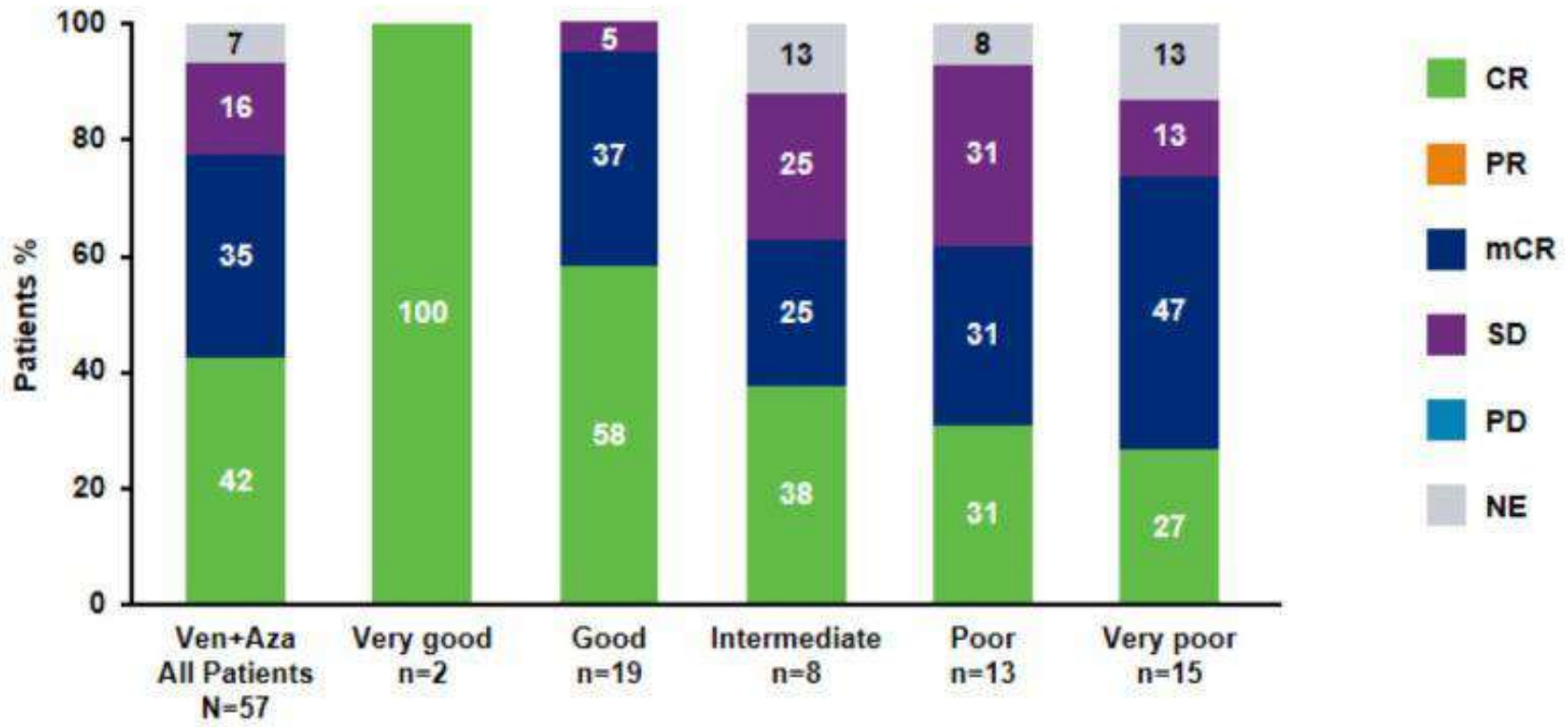
- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

[a]Excludes 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):419–25);
[b]Excludes 5 patients from the randomization phase who received 28-day Ven
Aza, azacitidine; CR, complete remission; DoR, duration of response; IWG 2006, International Working Group 2006; mCR, marrow CR; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, disease progression; PR, partial response; RBC, red blood cell; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax

Data cutoff: June 30, 2020

Venetoclax

M15-531: Ph 1b VEN+AZA in untreated HR-MDS: **Responses (by cytogenetic category)**



CR, complete remission; IPSS-R, Revised International Prognostic Scoring System; mCR, marrow CR; NE, not evaluable; PD, disease progression; PR, partial response; SD, stable disease

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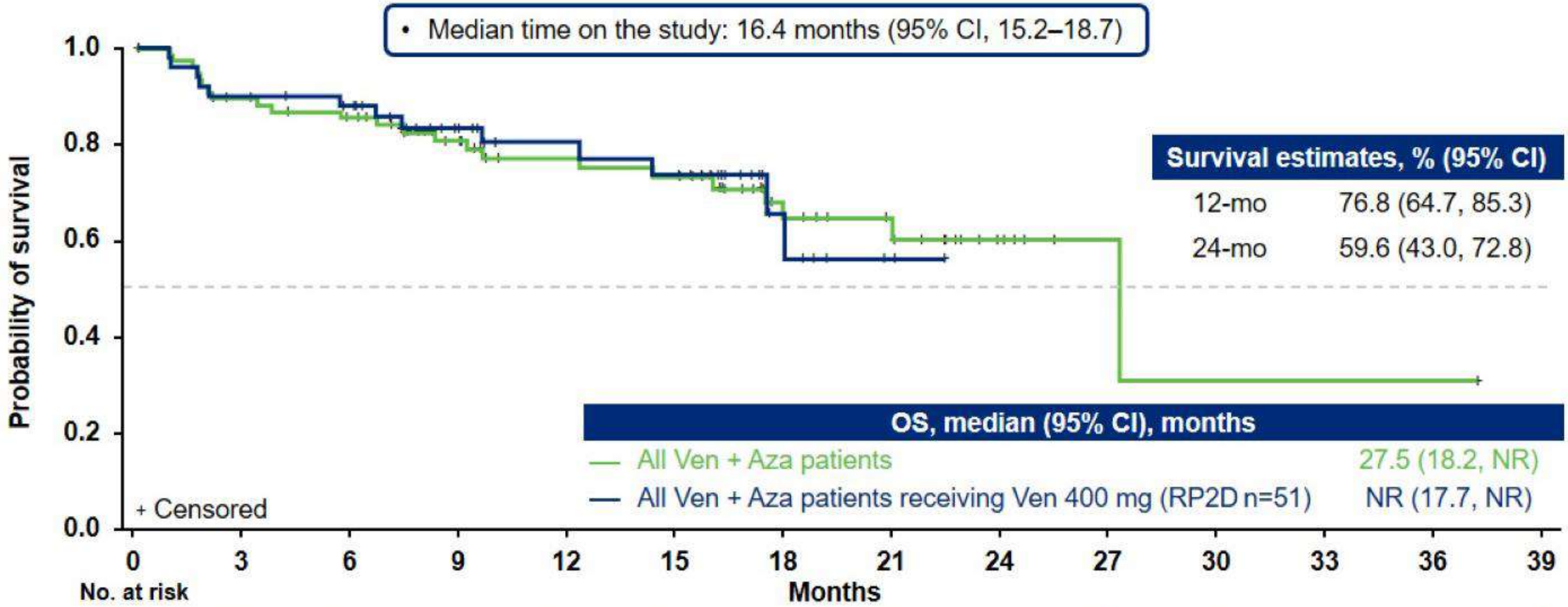
M15-531: Ph 1b VEN+AZA in untreated HR-MDS: **OS**



No. at risk														
All Ven + Aza patients	78	66	59	46	38	36	20	15	7	2	1	1	1	0
All Ven + Aza patients receiving Ven 400 mg (RP2D)	51	45	42	31	24	22	7	2	0					

Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax

Data cutoff: June 30, 2020

Garcia J, EHA 2020

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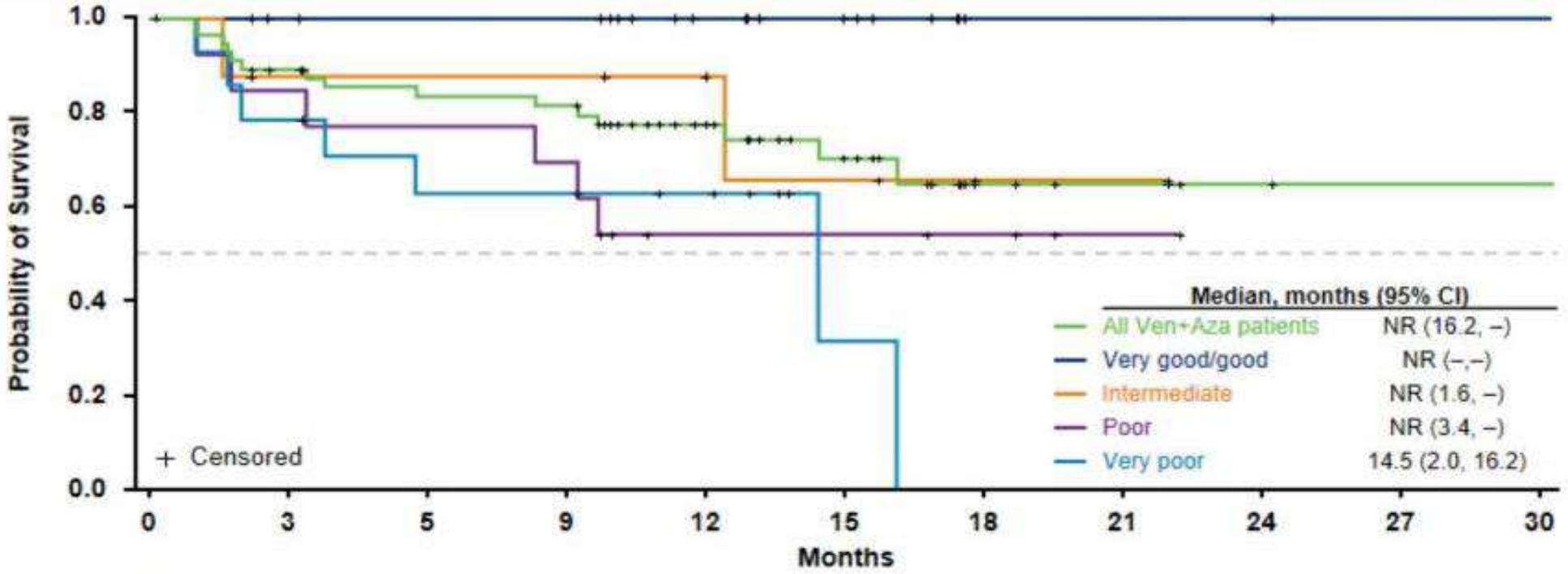
M15-531: Ph 1b VEN+AZA in untreated HR-MDS: **OS (by cytogenetic category)**



No. at risk											
All Ven+Aza patients	57	47	42	41	27	17	6	4	2	1	1
Very good/good	21	19	18	18	12	9	2	2	2	1	1
Intermediate	8	6	6	6	5	3	1	1	0		
Poor	13	11	10	9	4	4	3	1	0		
Very poor	15	11	8	8	6	1	0				

CI, confidence interval; IPSS-R, Revised International Prognostic Scoring System; NR, not reached

Adapted from the Garcia presentation at EHA on June 12, 2020

Garcia J, EHA 2020

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RWD (Moffit): VEN+HMA vs HMA

		HMA 1L	HMA/Ven 1L	P value
n		1127	35	
Age	mean	68.4	67.8	.76
Gender	Male	66%	71%	.5
Race	White	90%	97%	.66
t-MDS		24%	23%	.86
WHO 2016	MDS-SLD/MLD	18%	4%	.04
	MDS-RS	6%	4%	
	MDS-EB1	33%	9%	
	MDS-EB2	39%	78%	
R-IPSS	Intermediate	31%	17%	.22
	High	31%	37%	
	Very High	38%	46%	
Myeloblasts	Mean (%)	8	13	< .005
Hgb	Mean (g/dl)	9	9	1.0
WBC	Mean	4	10.6	< .005
ANC	Mean	1.8	4.1	<.005
platelets	platelets	96	100	.8
Somatic Mutations (n= 546 sequenced)	SF3B1	5%	0	.3
	TET-2	16%	23%	.3
	IDH-1	3%	3%	.7
	IDH-2	5%	14%	.056
	ASXL-1	21%	46%	.002
	TP53	27%	34%	.6
	NRAS	4%	11%	.07

Komrokji R, ASH 2021

Venetoclax

RWD (Moffit): VEN+HMA vs HMA

	1L HMA VEN	1L HMA	
All cohort	n=35	n=1127	
ORR	77%	40%	<.005
CR	34%	13%	
mCR	37% (62% + HI)	11%	
PR	3%	1%	
HI	3%	15%	
***ASXL-1* MT**	n=16	n=106	
ORR	87%	32%	<.005
CR	44%	8%	
TP53 MT	n=12	n=137	
ORR	75%	44%	.038
CR	25%	17%	.47

* Among evaluable pts for response

Komrokji R, ASH 2021

Venetoclax

RWD (Moffit): VEN+HMA vs HMA

	1L HMA VEN	1L HMA	
All cohort	n=35	n=1127	
ORR	77%	40%	<.005
CR	34%	13%	
mCR	37% (62% + HI)	11%	
PR	3%	1%	
HI	3%	15%	
***ASXL-1* MT**	n=16	n=106	
ORR	87%	32%	<.005
CR	44%	8%	
TP53 MT	n=12	n=137	
ORR	75%	44%	.038
CR	25%	17%	.47

* Among evaluable pts for response

Median FUP:
HMA: 96 months
HMA+VEN: 15 months

Komrokji R, ASH 2021

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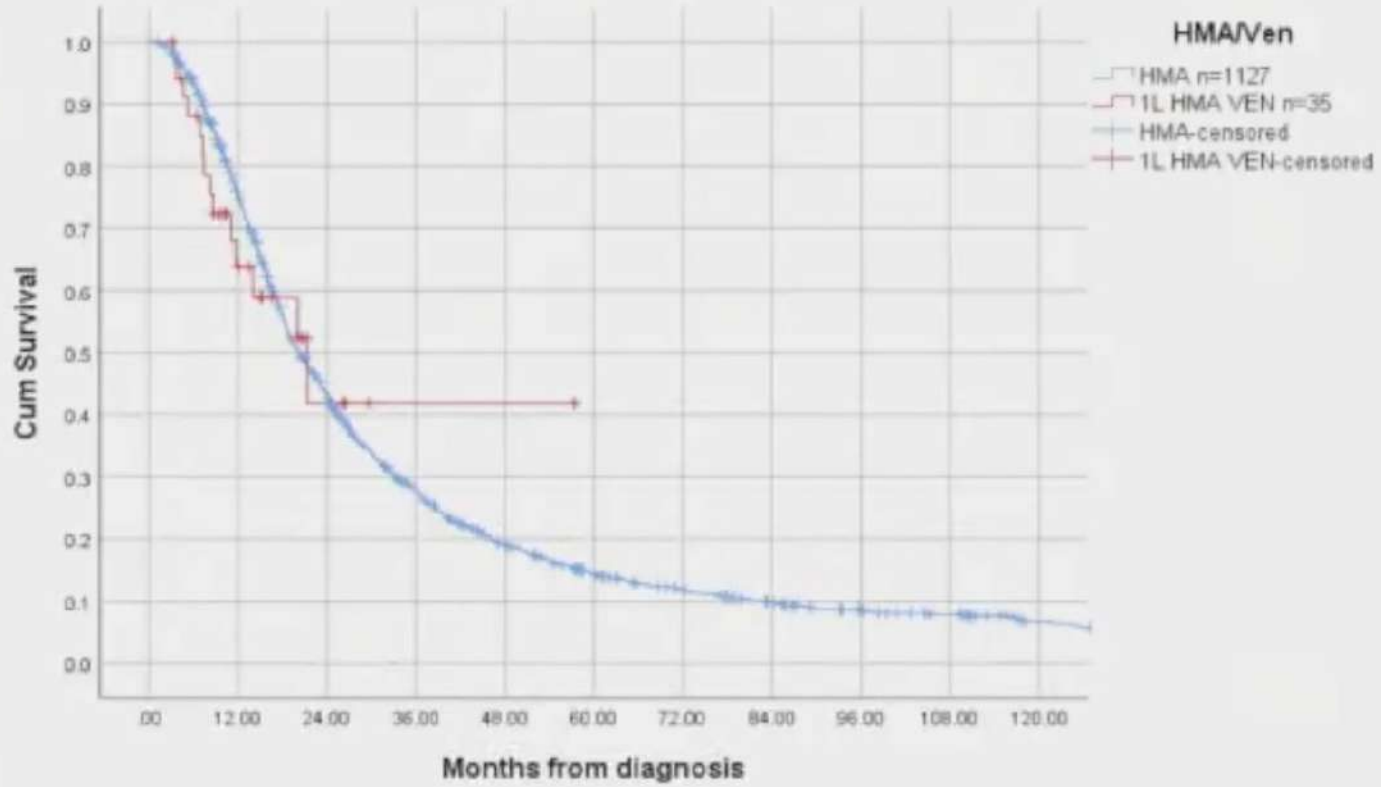
RWD (Moffit): VEN+HMA vs HMA

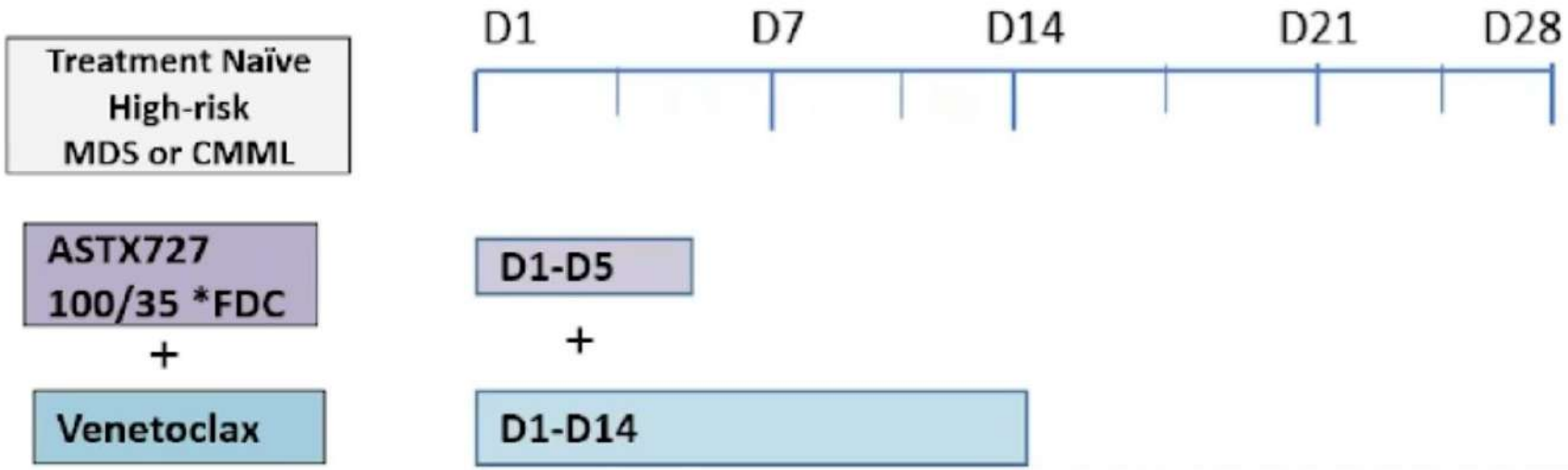


- The median overall survival from diagnosis was 21 mo (95% CI 11-32) and 20 mo (95%CI 19-22) for 1L HMA/Ven and 1L HMA alone respectively, p= .86.
  - The median OS from start of therapy was 19.4 vs 17.2 (p=.88)
- The rate of AML transformation was 23% and 37% for 1L HMA/Ven and 1L HMA alone respectively, p = .08.

Komrokji R, ASH 2021

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML



Dose level	Venetoclax	VEN dose reduction with concomitant posaconazole	With other strong CYP3A4 i
+1	400 mg	70mg	100 mg
0	200 mg	Not permitted	50 mg
-1	100 mg	Not permitted	20 mg

* FDC-Fixed dose combination, i-Inhibitor

NCT04655755

Venogupal S. ASH 2021. Abstract 245

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Demographics**

Demographics	N=9	Dose level 0 N=3	Dose level 1 N=6
Age (years), median [range]	72 (54-84)	71 (54-77)	73 (59-84)
Age ≥ 65 years, n(%)	6 (67)	2 (67)	4 (67)
Disease subtype			
Higher risk MDS	6 (67)	2(67)	4 (67)
CMML-2	3 (33)	1(33)	2 (33)
Hematological parameters, median [range]			
Absolute Neutrophil Count (x 10^9/L)	1.5 (0.1-7.8)	1.4 (0.9-1.9)	1.6 (0.1-7.8)
Hemoglobin (g/dL)	9.2 (7.5-12.4)	8.4 (8.3-9.2)	9.9 (7.5-12.4)
Platelets (x 10^9/L)	43 (19-140)	33 (25-76)	52 (19-140)

Demographics	N=9	Dose level 0 N=3	Dose level 1 N=6
Bone marrow blasts (%), median [range]	13 (6-15)	9 (7-13)	15 (6-15)
Cytogenetics, n (%)			
Good	4 (44)	0	4 (67)
Intermediate	4 (44)	2 (67)	2 (33)
Poor	1 (12)	1 (33)	0
Key Mutations, n(%)			
ASXL1	6 (67)	2 (67)	4 (67)
RUNX1	4 (44)	0	4 (67)
SRSF2	4 (44)	0	4 (67)
TP53	1 (12)	1 (33)	0
No. of mutations, median, (range)	4 (1-9)	7 (1-7)	4 (2-9)

Venogupal S. ASH 2021. Abstract 245

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Safety**

TEAE:Grade ≥ 3	Total N=9 (%)	Dose level 0 N=3	Dose level 1 N=6
Anemia	7 (78)	3 (100)	4 (67)
Thrombocytopenia	9 (100)	3 (100)	6 (100)
Neutropenia	9 (100)	3 (100)	6 (100)
Febrile Neutropenia	0	0	0
Constipation	1 (11)	-	0
30- day mortality	0	0	0
60-day mortality	0	0	0

Nausea/ vomiting of any grade was not observed

Venogupal S. ASH 2021. Abstract 245

Venetoclax

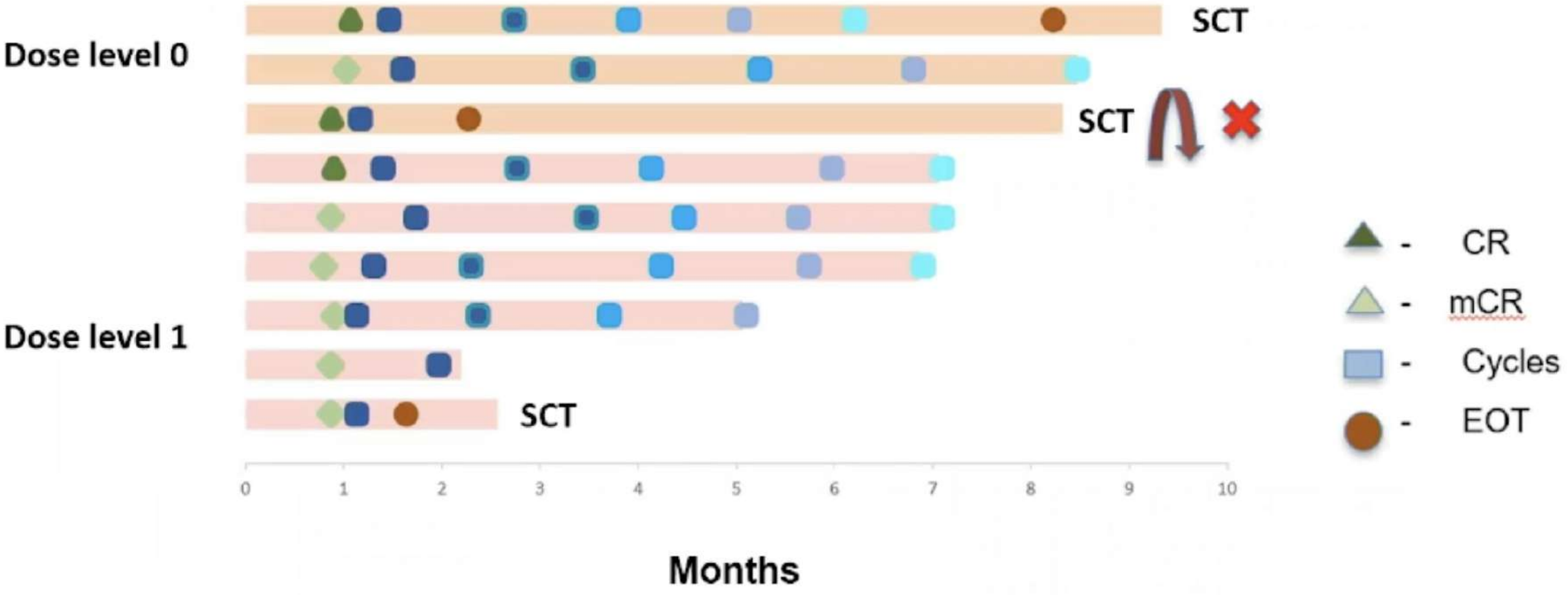
A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Efficacy**

Response	N=9
Overall Response Rate , n (%)	9 (100)
CR	3 (33)
mCR	6 (67)
Median number of cycles given n, (range)	6 (2-6)
Median time to initial response, days (range)	27(24-33)
Median time to best response, days (range)	28 (24-43)

Venogupal S. ASH 2021. Abstract 245

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Efficacy**

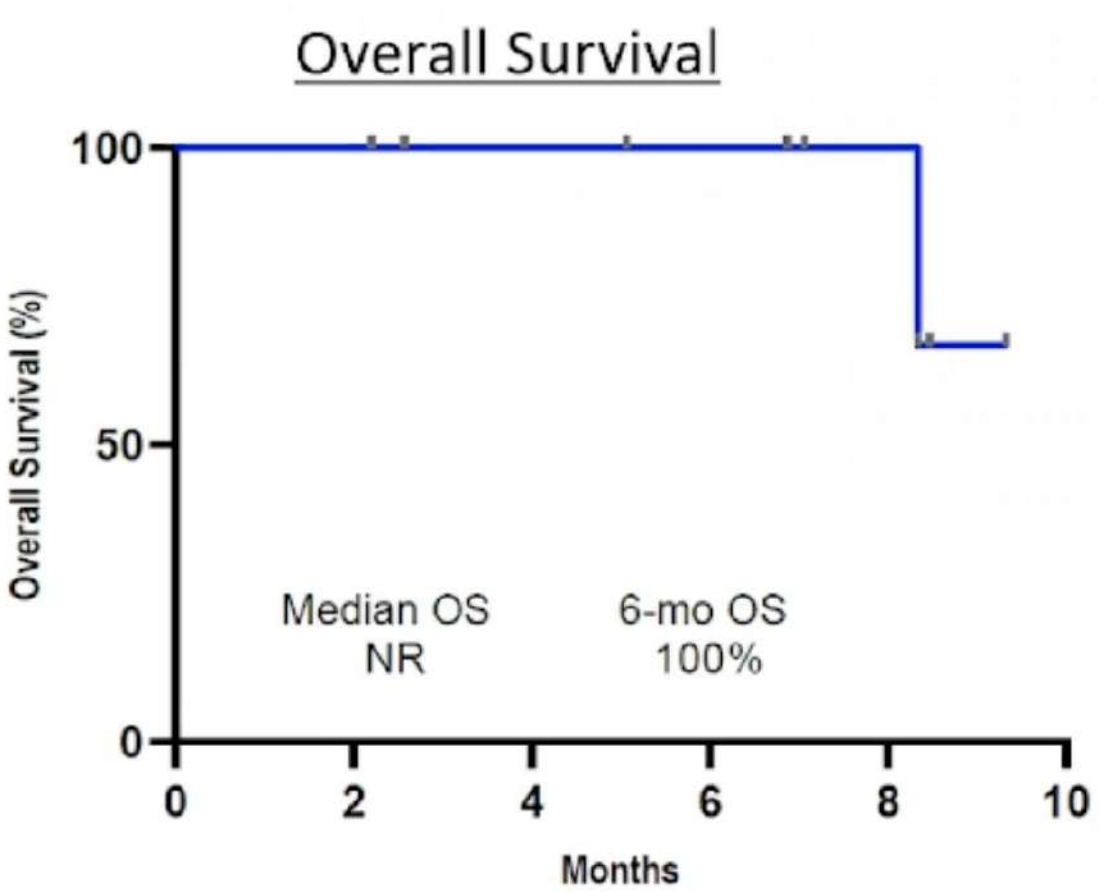


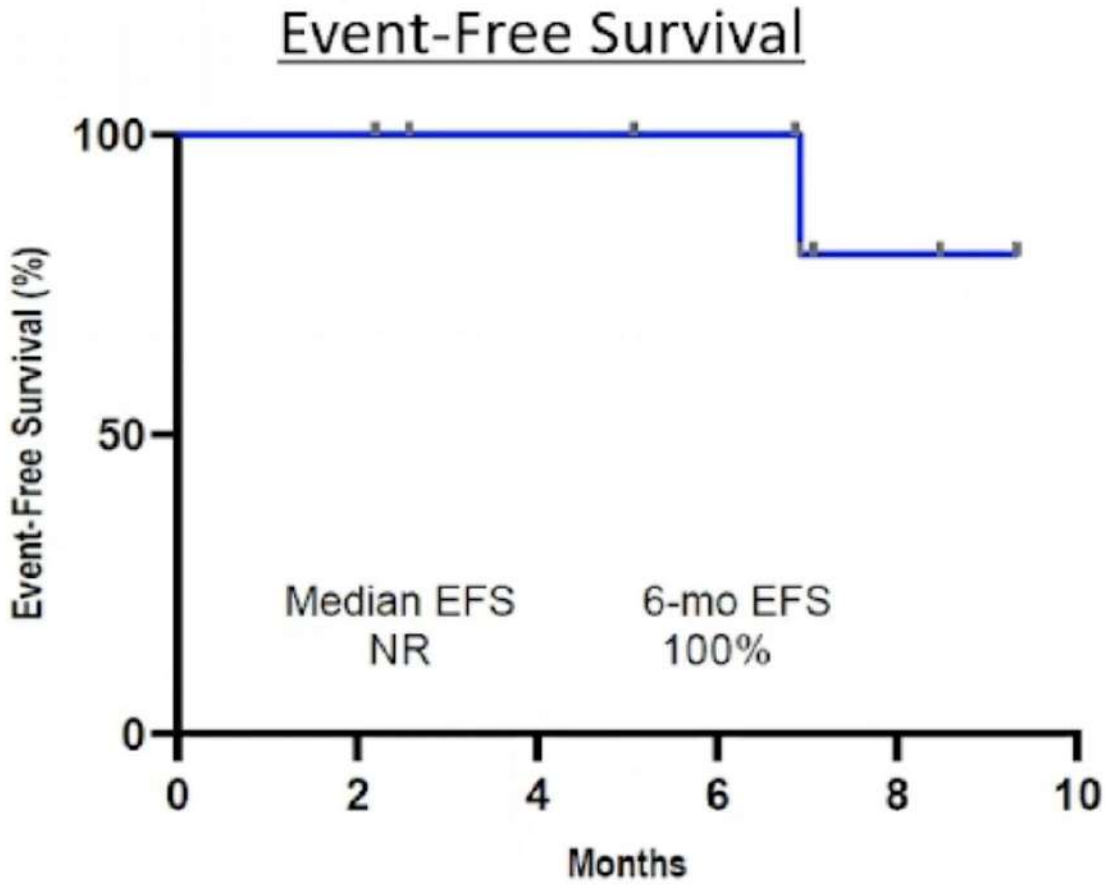
Venogupal S. ASH 2021. Abstract 245

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Efficacy**

Median duration of follow up -7.1 months





Venogupal S. ASH 2021. Abstract 245

Venetoclax

A Phase I/I Study of Venetoclax ASTX727 (cedazuridine/decitabine) in ND High-risk MDS or CMML: **Efficacy**

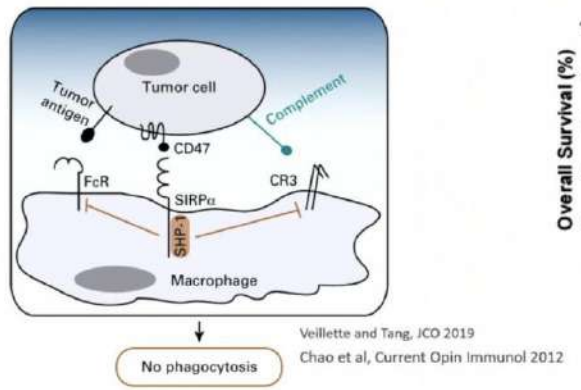
- Total oral therapy with VEN+ASTX727 appears safe and well tolerated
- The ORR is 100% with encouraging OS with short follow up
- Decreased duration of VEN may facilitate faster count recovery
- Phase II dose expansion is underway and currently enrolling (NCT04655755)

Venogupal S. ASH 2021. Abstract 245

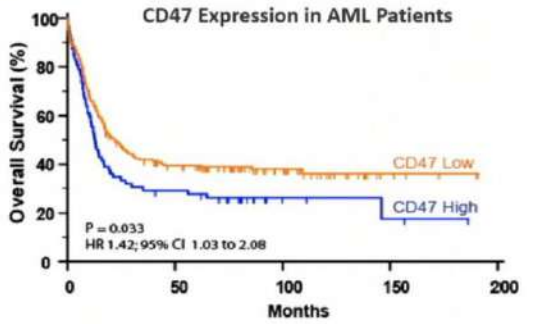
Magrolimab + AZA

Magrolimab

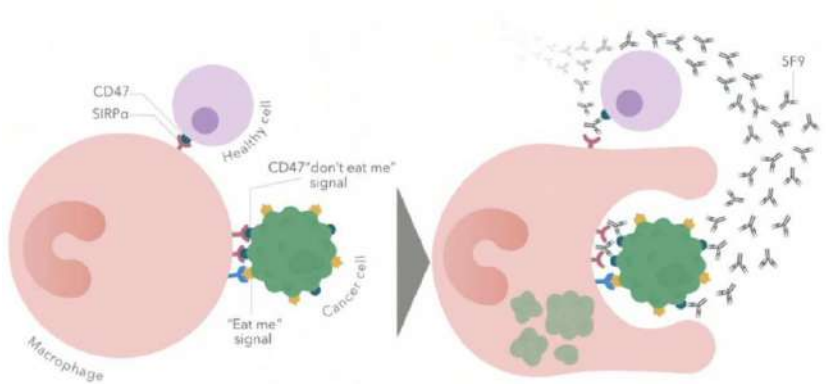
- CD47 is a major macrophage immune checkpoint and “Do Not Eat Me” signal in myeloid malignancies including AML and MDS
- Increased CD47 expression predicts worse prognosis in AML patients



Veillette and Tang, JCO 2019
Chao et al, Current Opin Immunol 2012



Majeti, Chao et al., Cell 2009

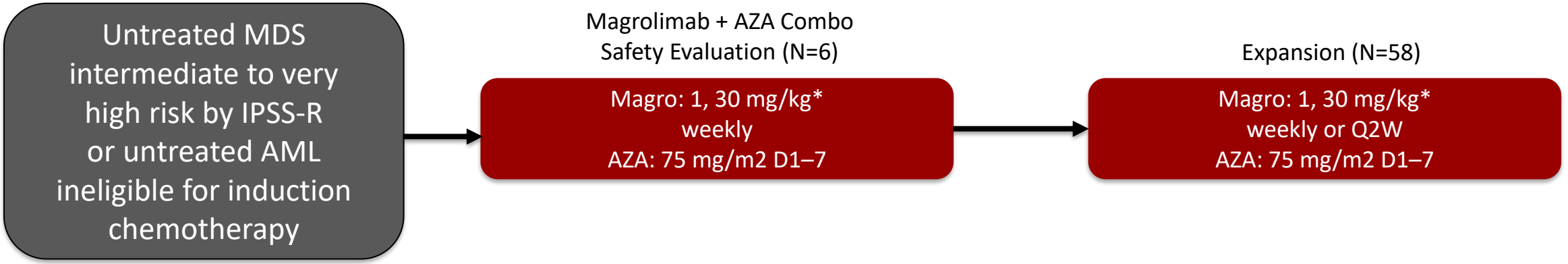


- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Salmann DA, EHA June 14, 2020; Figure at left adapted from Veillette A, Tang Z. J Clin Onc. 2019;37(12)1012-1014, and Chao MP, et al. Current Opin Immunol. 2012; 24(2):225-232. Figure at right adapted from Majeti R, et al. Cell. 2009;138(2):286-299.

Magrolimab

5F9005: Phase 1b, Magrolimab + AZA in untreated HR-MDS and AML



- A magrolimab priming dose (1 mg/kg) and dose ramp-up were utilized to mitigate on-target anemia
- Data from the MDS expansion cohort are presented

Primary objectives	1. Safety of magrolimab alone or with AZA 2. Efficacy of magrolimab + AZA in untreated AML/MDS
Secondary objectives	1. Pharmacokinetics, pharmacodynamics, andimmunogenicity of 5F9 2. Additional measures of efficacy (DOR, PFS, OS)
Exploratory objective	To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

Salmann DA, EHA June 14, 2020;.

Magrolimab

Baseline demographics and disease characteristics

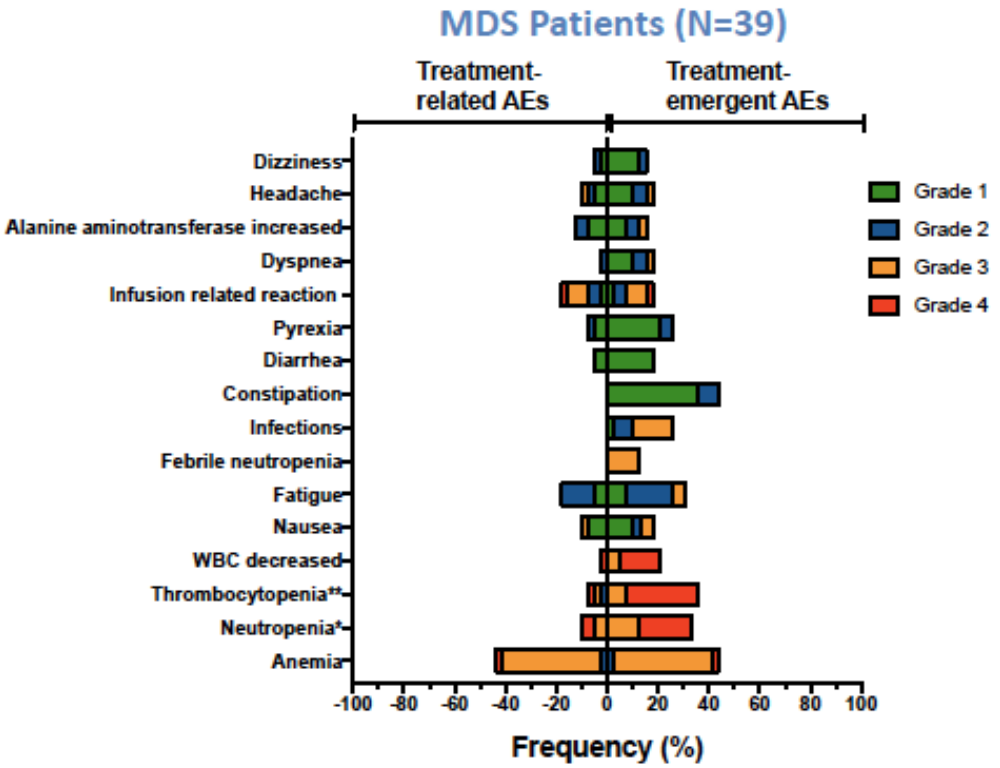
	Magrolimab +azacitidine n=39
Median age in years (range)	70 (47–80)
ECOG Performance Status:	
0	11 (28%)
1	26 (67%)
2	2 (5%)
Cytogenetic Risk:	
Favorable	0
Intermediate	11 (28%)
Poor	25 (64%)
Unknown/missing	3 (8%)
WHO MDS classification:	
RS and single/multilineage dysplasia	1 (3%)
Multilineage dysplasia	7 (18%)
RS with multilineage dysplasia	3 (8%)
Excess blasts	22 (56%)
Unclassifiable/unknown/missing	6 (15%)
IPSS-R (MDS):	
Intermediate	13 (33%)
High	19 (49%)
Very High	6 (15%)
Unknown/missing	1 (3%)
Therapy related MDS	12 (31%)
Unknown/missing	1 (3%)
Harboring a TP53 mutation	5 (13%)

- 64% of patients are poor cytogenetic risk
- The majority of patients were high or very high risk by IPSS-R
- 31% of patients are therapy related
- 13% of patients are TP53 mutant

Salmann DA, EHA June 14, 2020;.

Magrolimab

Safety



- No maximum tolerated dose was reached; magrolimab + AZA profile consistent with AZA monotherapy
- No significant worsening of cytopenias, infections, or autoimmune AEs were observed (most patients were cytopenic at baseline)
- No deaths were observed in the first 60 days on therapy
- No treatment discontinuations due to drug-related AEs

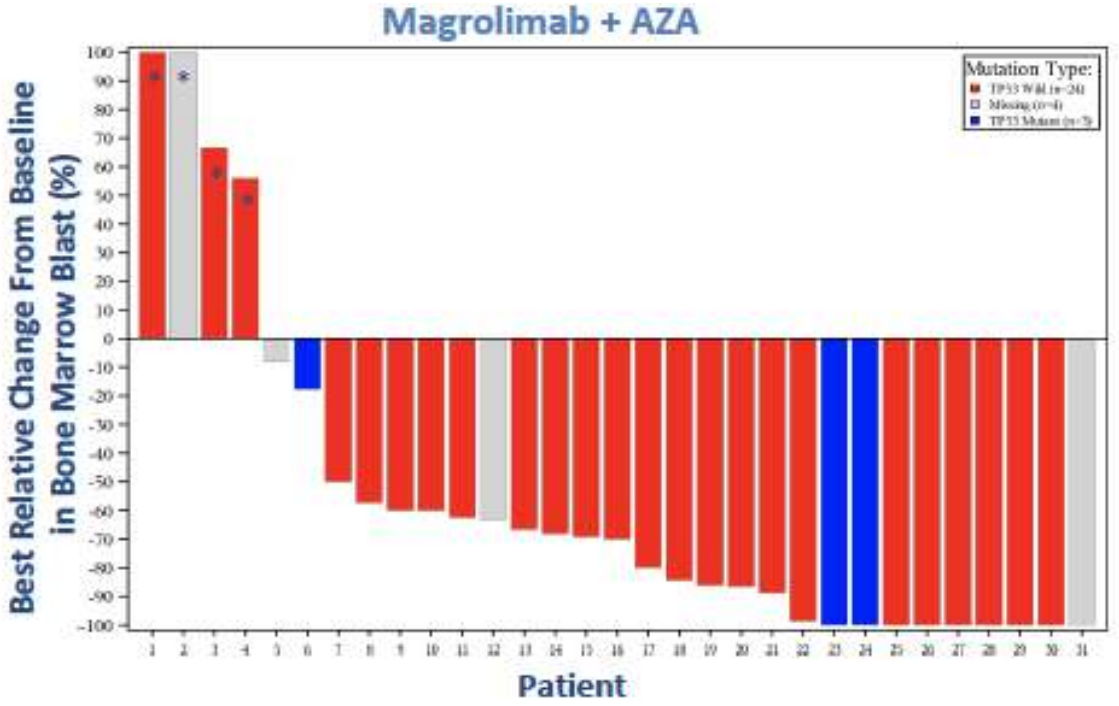
Salmann DA, EHA June 14, 2020;.

Magrolimab

Responses

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
Hematologic improvement (HI)	7 (21%)
SD	3 (9%)
PD	0

Response assessments per 2006 IWG MDS criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent).



- 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%)

Salmann DA, EHA June 14, 2020;.

Magrolimab

Responses

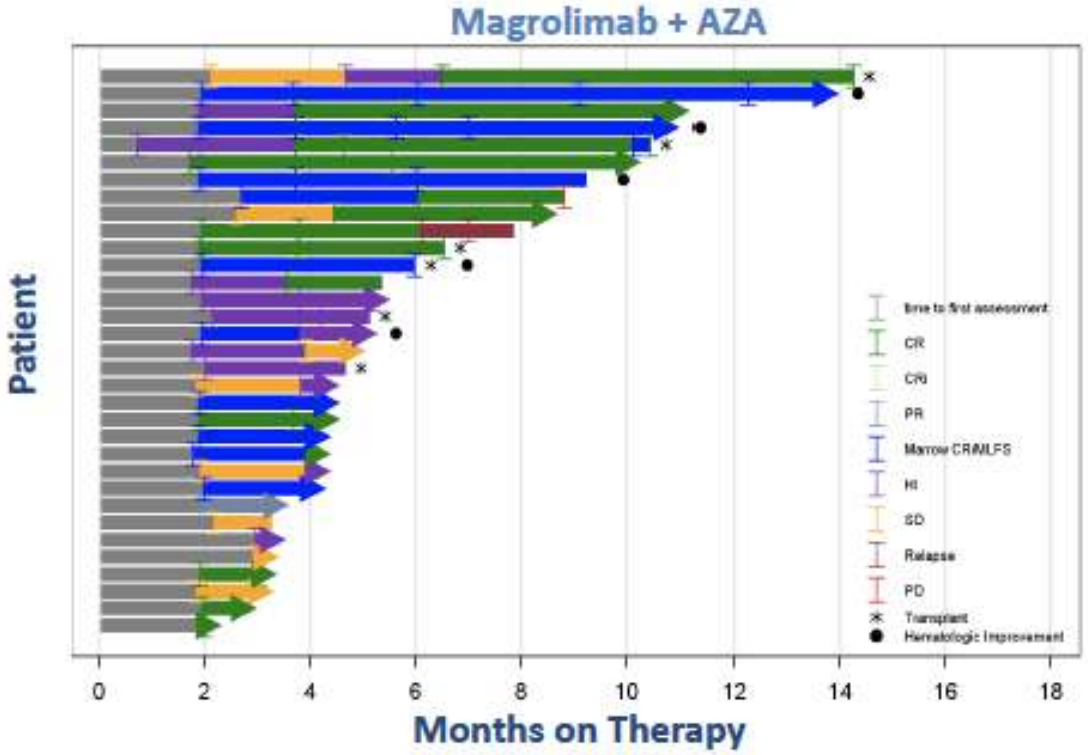
Parameter	1L MDS N=33
RBC transfusion independence[1]	11/19 (58%)
Complete cytogenetic response[2]	9/26 (35%)
MRD negativity in responders	6/30 (20%)
Median duration of response in months (range)	Not reached (0.03+ – 10.4+)
Median follow-up in months[3] (range)	5.8 (2.0–15.0)

MRD was evaluated by multiparameter flow cytometry; cytogenetic response defined per 2003 and 2006 IWG criteria.

[1]Patients shown for those who were RBC transfusion dependent at baseline and achieved RBC transfusion independence at any time on study.

[2]Responses shown for all responding patients with abnormal cytogenetics at baseline.

[3]Follow-up in responders



- High rates of RBC transfusion independence, complete cytogenetic responses, and MRD negativity is observed
- No median duration of response has been reached
- Many patients deepen their response to CR over time on therapy

Salmann DA, EHA June 14, 2020;.

Magrolimab

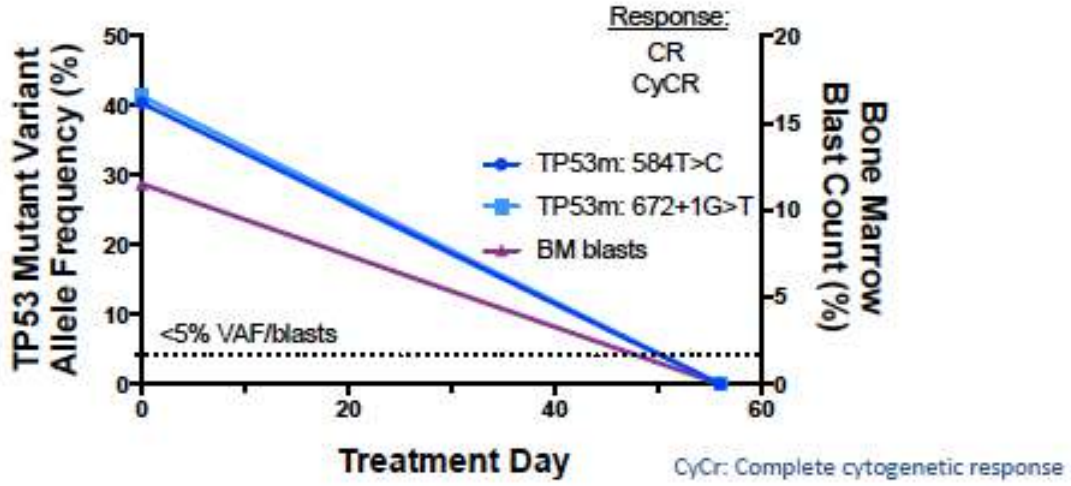
Responses

Efficacy in *TP53*-Mutant MDS Patients

Best Overall Response	MDS *TP53* Mutant (N=4)
ORR	3 (75%)
CR	2 (50%)
Marrow CR	1 (25%)
Complete cytogenetic response in responders*	3/3 (100%)
MRD negative of responders	0
Median duration of response (months)	Not reached (0.03+ – 5.2+)
Median overall survival (months)	100%
Median follow-up (range) (months)	7 (4.2 – 12.2)

*For patients with abnormal cytogenetics at baseline.

77M very high risk, complex karyotype, and double *TP53*-mutant MDS: Achieved a CR, CyCr, and clearance of both *TP53* mutations at Cycle 3



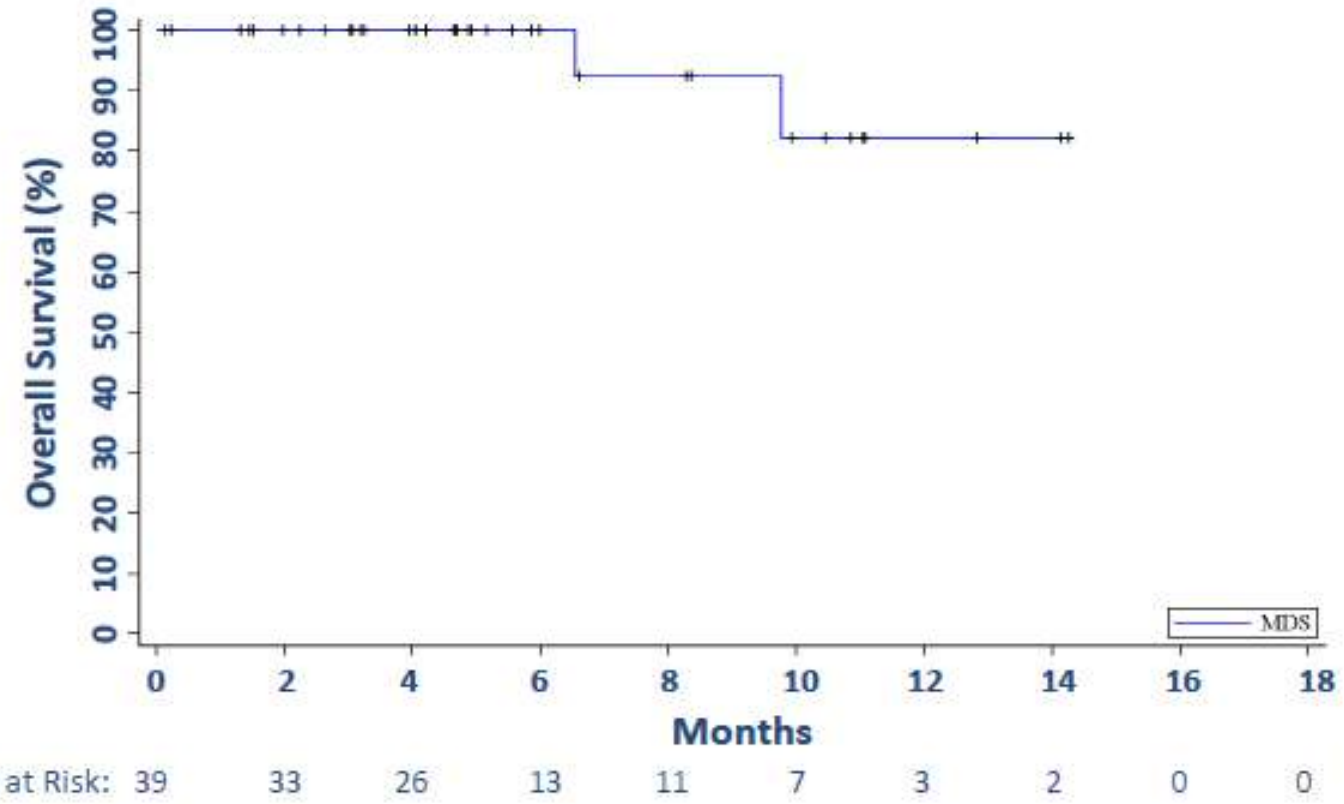
CyCr: Complete cytogenetic response

- In small patient numbers, magrolimab + AZA has a high response rate and encouraging durability
- Magrolimab + AZA has also shown a 75% CR/CRi rate with no median duration reached in 12 untreated TP53-mutant AML patients who are unfit for intensive chemo (Daver N, et al., EHA 2020)

Salmann DA, EHA June 14, 2020;.

Magrolimab

OS



Parameter	N=39
Median OS in months (range)	Not reached (0.1+ – 14.3+)
6-month estimated OS	100%
Median follow-up in months (range)	4.7 (0.1 – 14.3)

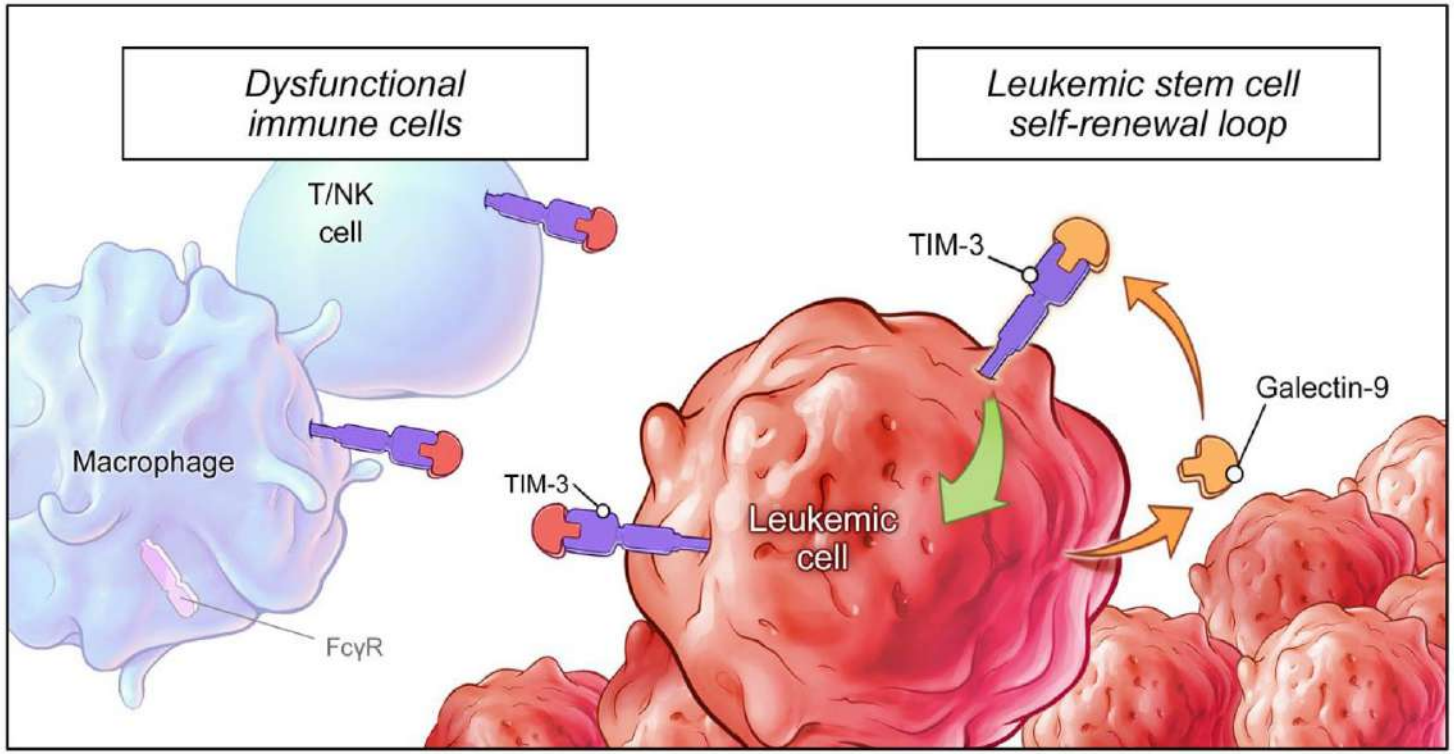
- Median overall survival has not been reached with a 6-month estimated survival of 100%

Salmann DA, EHA June 14, 2020;.

Sabatolimab + HMA

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS



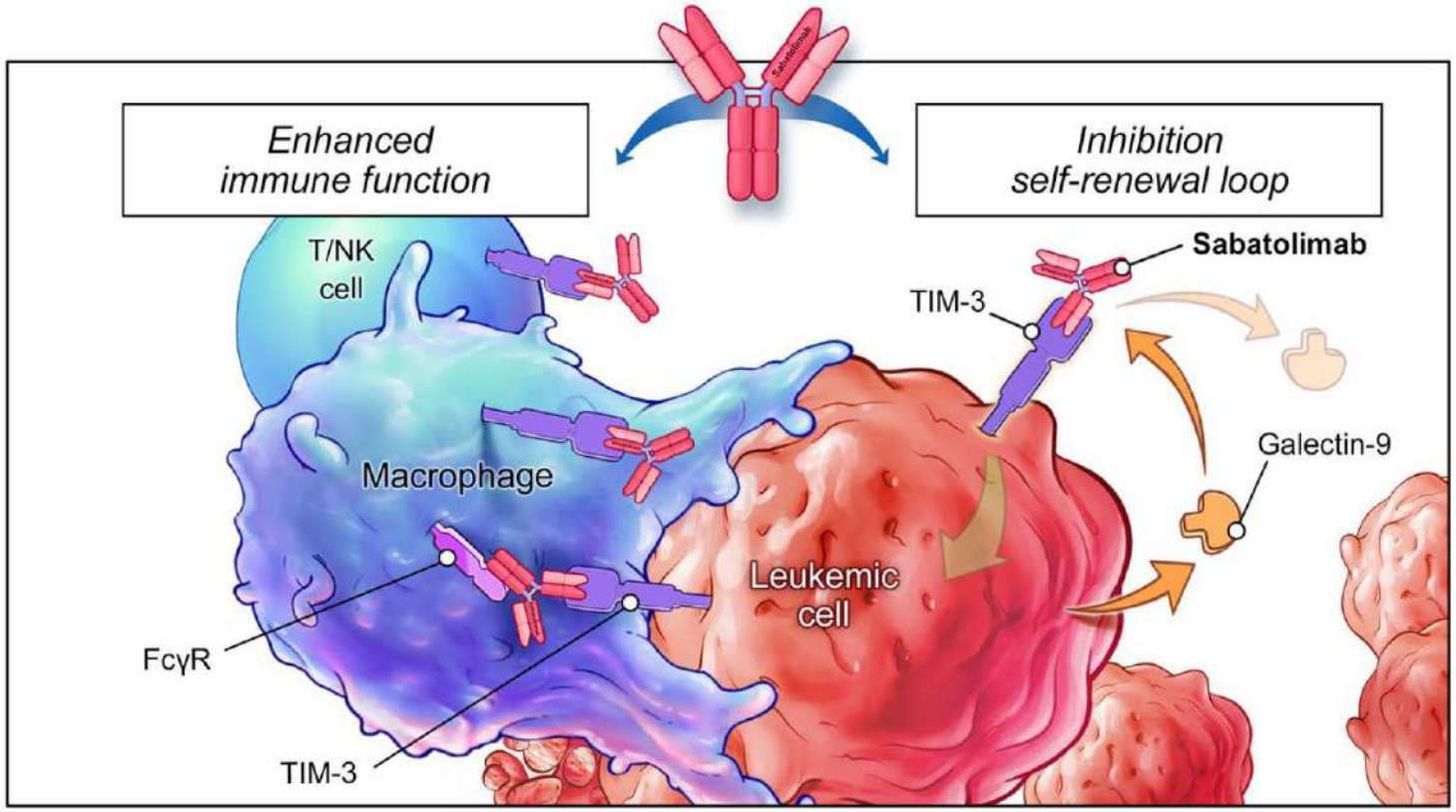
- TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7,8]

FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

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. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS



- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

Sabatolimab

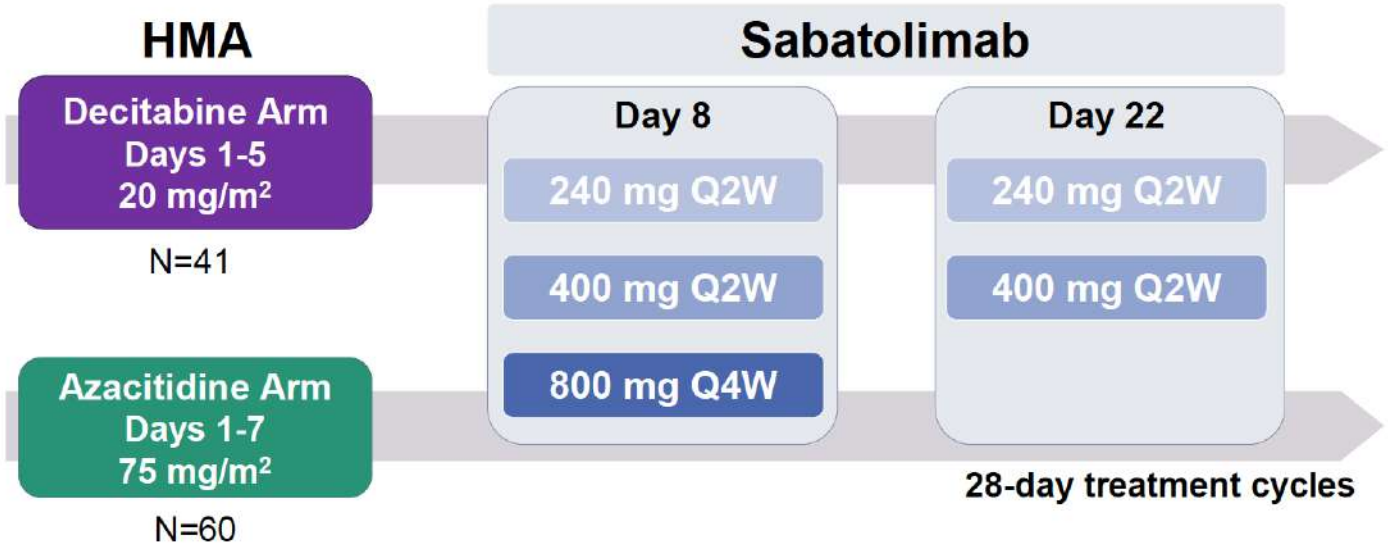
Phase Ib: HMA + Sabatolimab in HR MDS

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648**[a]



8 countries

11 trial centers

Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability
Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

[a]Multi-arm, open-label, Phase Ib dose-escalation and -expansion study of sabatolimab as a single agent or in combination with HMAs or spartalizumab.
AML, acute myeloid leukemia; HMA, hypomethylating agent; HR, high-risk; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; ND, newly diagnosed; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Patient characteristics**

Parameter	vHR/HR-MDS n=53	ND-AML n=48
Sabatolimab + decitabine, n	19	22
Sabatolimab + azacitidine, n	34	26
Median age (range), years	70 (23-90)	75 (59-89)
Male, n (%)	29 (54.7)	26 (54.2)
ECOG performance status, n (%)		
0	18 (34.0)	14 (29.2)
1	30 (56.6)	29 (60.4)
2	5 (9.4)	5 (10.4)
Risk Category n (%)	IPSS-R[1]	2017 ELN risk[2]
	High: 32 (60.4)	Intermediate: 18 (37.5)
	Very high: 21 (39.6)	Adverse: 30 (62.5)

Select available mutation data:	TP53 (n)	≥1 ELN adverse risk mutation (n)[a]
vHR/HR-MDS (n=42[b])	15	33
ND-AML (n=33[b])	6	14

[a]ELN adverse risk mutations: TP53, ASXL1, and RUNX1; [b]Patients with any reported mutation
ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; IPSS-R, Revised International Prognostic Scoring System.
1. Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465; 2. Döhner H, et al. *Blood*. 2017;129(4):424-447.

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Patient characteristics**

		vHR/HR-MDS n=53	ND-AML n=48
Median exposure (range), mo	Sabatolimab + decitabine[a]	8.02 (0.9-33.5)	6.8 (0.8-33.9)
	Sabatolimab + azacitidine[b]	4.45 (0.8-18.1)	5.98 (1.1-21.6)
Ongoing,[c] n (%)		**9 (17)**	**2 (4.2)**
Discontinued, n (%)		**44 (83)**	**46 (95.8)**
Reason for discontinuation			
SCT		13 (24.5)	0
Disease progression		16 (30.2)	29 (60.4)
AE:	Unrelated to study treatment	0	2 (4.2)
	Related to study treatment	0	1 (2.1)
Death:	Unrelated to study treatment	2 (3.8)	4 (8.3)
	Related to study treatment	1[d] (1.9)	0
Patient decision		5 (9.4)	2 (4.2)
Physician decision		8 (15)	8 (16.7)
DLT		0	1 (2.1)[e]

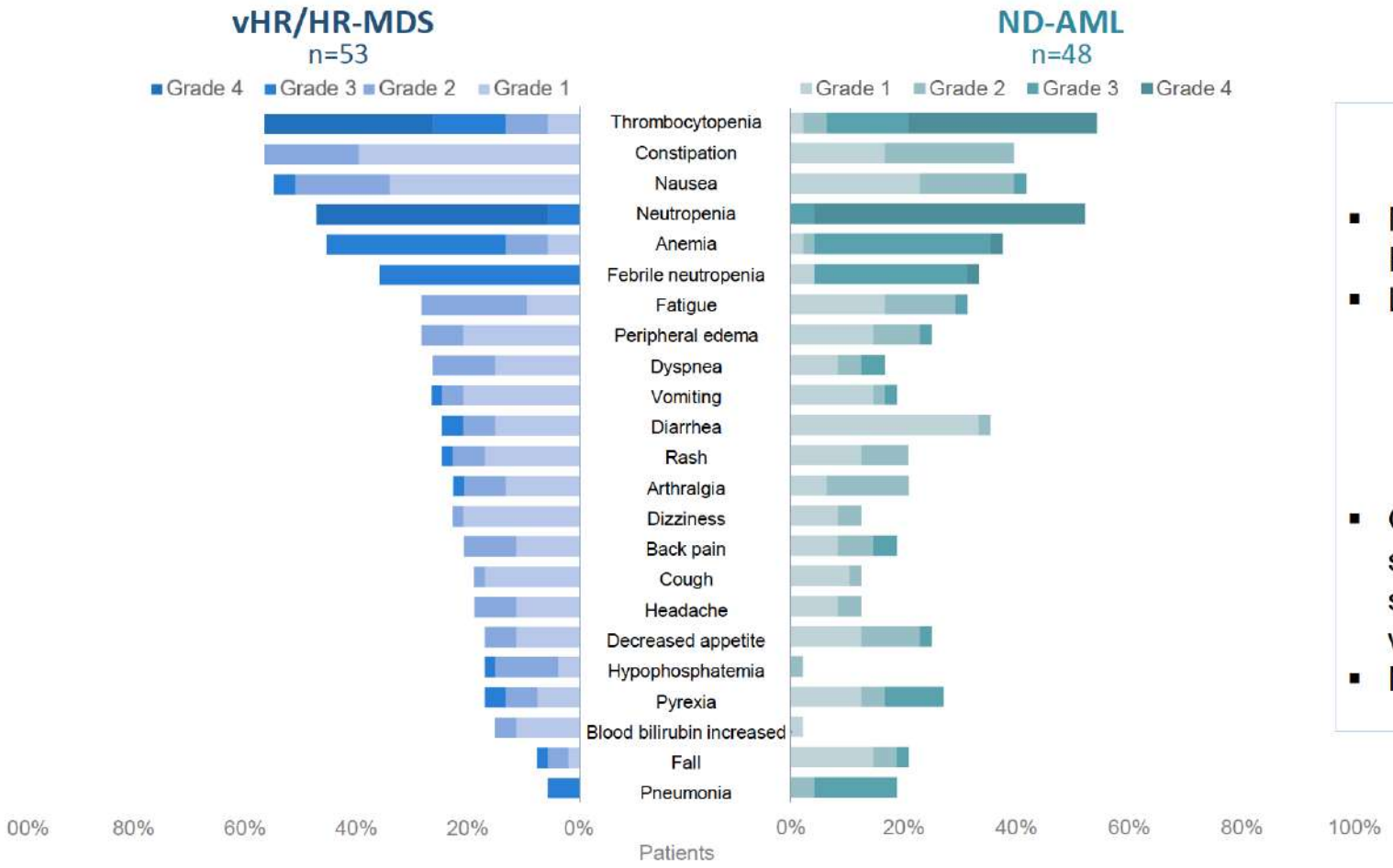
[a]Enrollment started August 2017; [b]Enrollment started February 2019; [c]As of the cutoff date of September 6, 2021;
[d]1 patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock; [e]Single DLT was a grade 3 event of elevated ALT/hepatitis.
AE, adverse event; ALT, alanine aminotransferase; DLT, dose-limiting toxicity; SCT, stem cell transplant.

Brunner A, ASH 2021

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Safety**

Most commonly occurring AEs ***(≥15% in either population, regardless of relationship to treatment)***



vHR/HR-MDS and ND-AML AEs

- Most common reported AEs were consistent with HMA alone
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
  - 38/101 (38%) patients had dose interruption[a] due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- One patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

[a]Dose interruption: Cycle delay >7 days.

Brunner A, ASH 2021

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Safety**

	vHR/HR-MDS n=53	ND-AML n=48	
	Gr 1/2	Gr 1/2	Gr 3
Patients with possible imAEs regardless of relationship to study treatment[a]	7 (13.2)	5 (10.4)	5 (10.4)
Peripheral neuropathy	2 (3.8)	1 (2.1)	1 (2.1)
Acute febrile neutrophilic dermatosis	1 (1.9)	0	0
Autoimmune hepatitis	1 (1.9)	0	0
Dermatitis	1 (1.9)	1 (2.1)	0
Pericarditis	1 (1.9)	0	0
Pneumonitis	1 (1.9)	0	0
Arthritis	0	3 (6.3)	0
Colitis	0	1 (2.1)	1 (2.1)
Cutaneous vasculitis	0	0	0
Encephalopathy	0	0	1 (2.1)
Hemophagocytic lymphohistiocytosis	0	0	1 (2.1)
Hepatitis	0	0	1 (2.1)
Hypothyroidism	0	0	1 (2.1)
Immune-mediated lung disease	0	0	1 (2.1)

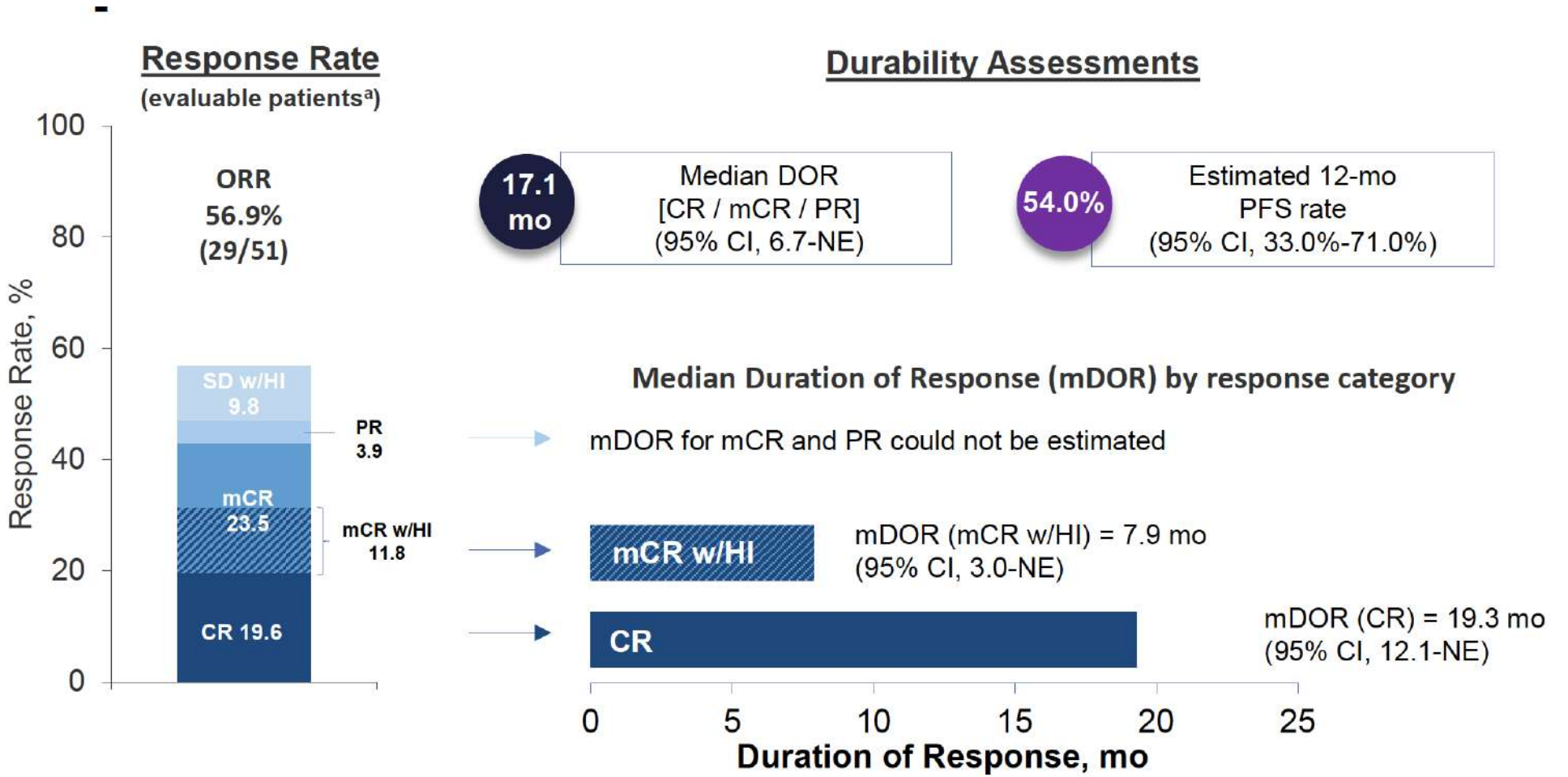
- 7/53 (13%) patients with vHR/HR-MDS and 10/48 (21%) patients with ND-AML experienced ≥1 possible imAEs
- No grade ≥3 possible imAEs were observed in patients with vHR/HR-MDS; no grade 4/5 possible imAEs were observed in patients with AML
- No patient with vHR/HR-MDS and 1 patient with ND-AML discontinued treatment due to a possible imAE suspected to be related to sabatolimab
- No serious late-onset sabatolimab-related imAEs were identified[b]
- Of the 7 patients with vHR/HR-MDS who had an imAE, all achieved remission
- Among patients with ND-AML, the frequency of possible imAEs was similar regardless of remission status

[a]Based on maximum grade. Events retrieved based on pre-defined case retrieval strategy including MedDRA SMQ immune-mediated disorder terms.
[b]Events 150 days after last dose of sabatolimab

Brunner A, ASH 2021

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Efficacy**

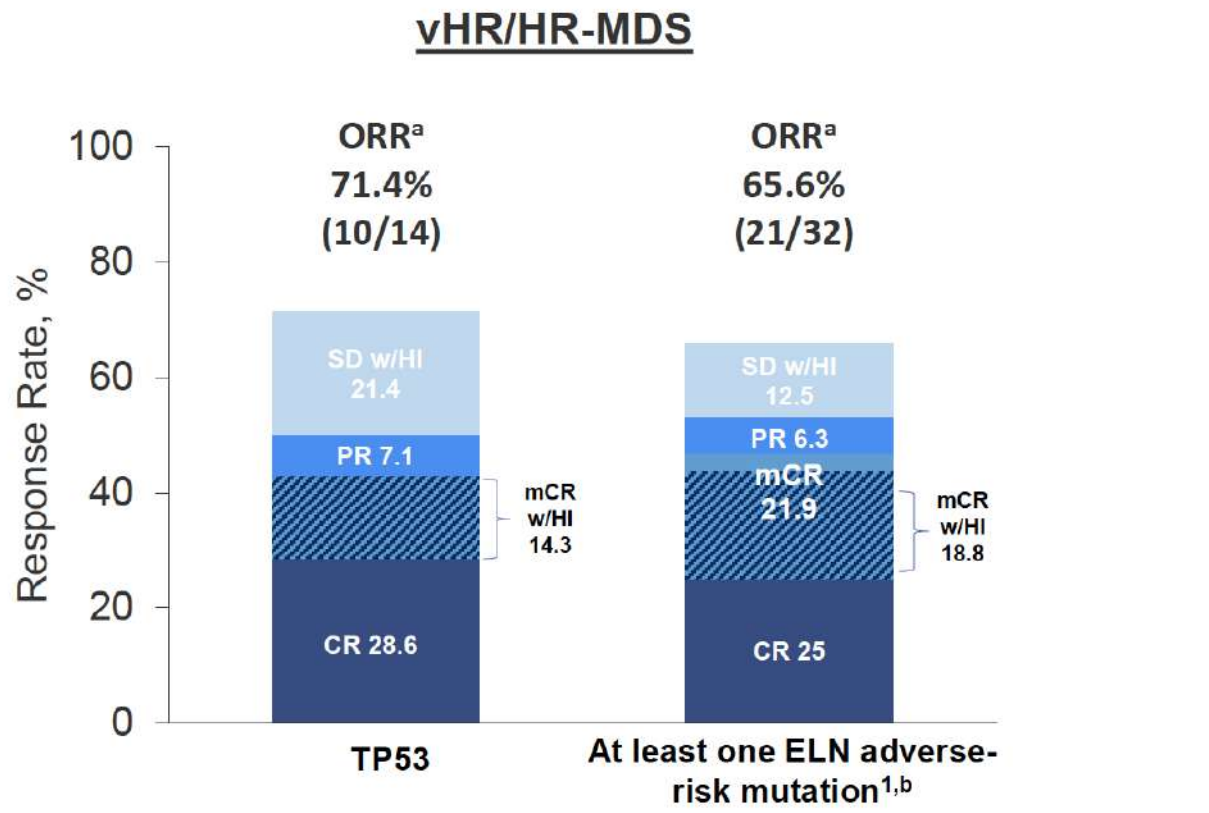


[a]Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.
CR, complete remission; DOR, duration of response; HI, hematologic improvement; mCR, bone marrow CR; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Brunner A, ASH 2021

Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Efficacy**



Median duration of response	21.5 mo 95% CI, 6.7-NE Events, 3/7[c]	16.1 mo 95% CI, 6.7-NE Events, 7/17[c]

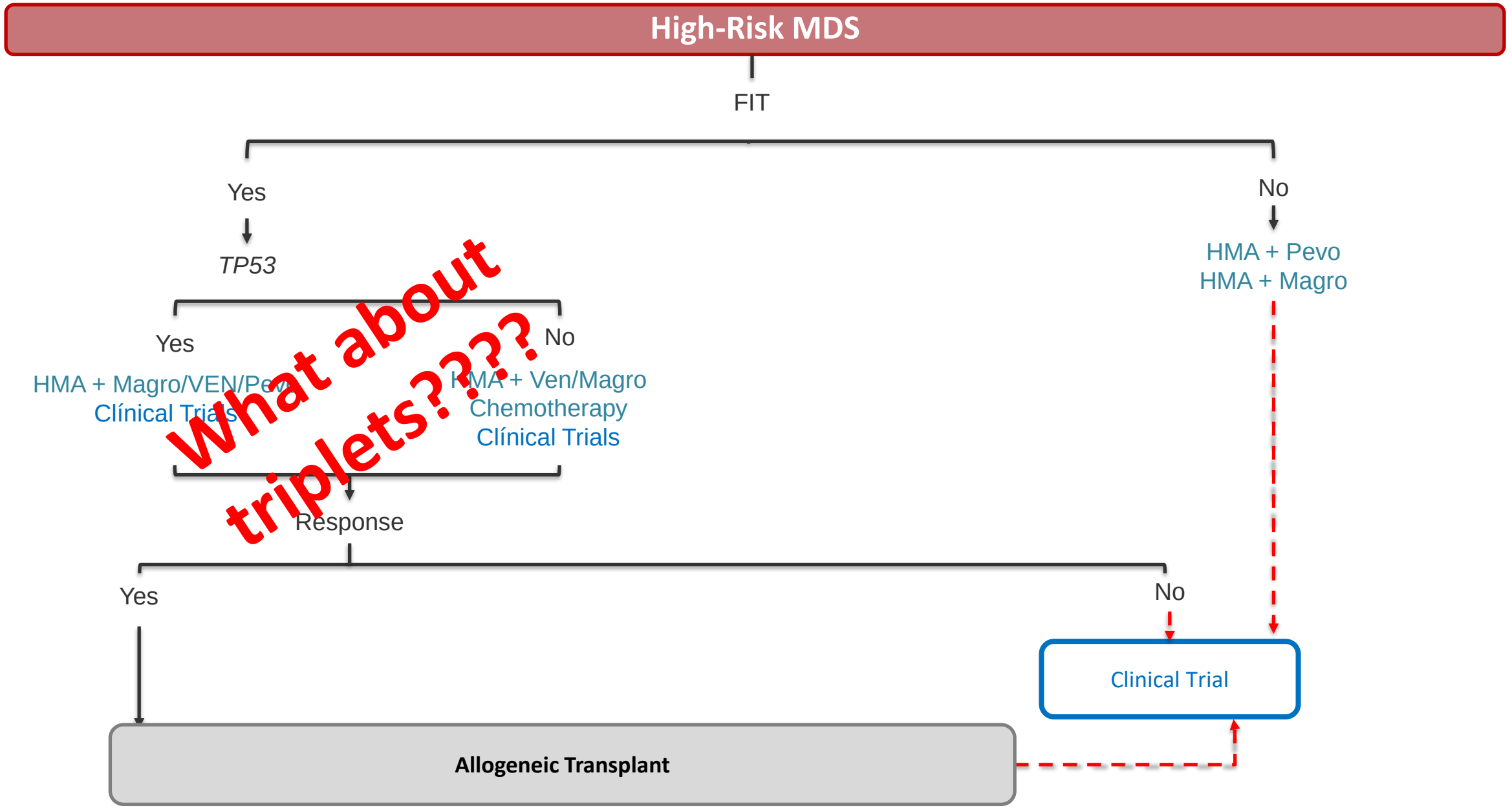
Sabatolimab

Phase Ib: HMA + Sabatolimab in HR MDS: **Conclusions**

- Sabatolimab + HMA is well tolerated in MDS/AML
  - The most commonly observed AEs were similar to HMA alone
  - Very few patients had clinically significant treatment-related possible imAEs
- Sabatolimab + HMA demonstrated durable clinical benefits in patients with vHR/HR-MDS and ND-AML
  - vHR/HR-MDS, ORR: 56.9%; Median DOR: 17.1 months (95% CI, 6.7-NE)
  - ND-AML, ORR: 42.5%; Median DOR: 12.6 months (95% CI, 5.2-18.0)
- Durable responses were seen in patients with mutations conferring adverse risk
- The STIMULUS clinical trial program is evaluating sabatolimab-based combination therapy in multiple Phase II and III studies in MDS and AML

Brunner A, ASH 2021

Conclusions



Las nuevas combinaciones en el tratamiento de los pacientes con SMD de alto riesgo

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