LEUKEMIA2020-2021

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ASSOCIAZIONE ITALIANA CONTRO LE LEUCEMIE-LINFOMI E MIELOMA ONLUS

Novel Therapies in High-Risk MDS

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GITMO

SIES Società Italiana Ematologia Sperimentale

SIE - Società Italiana di Ematologia

Conflict of Interests Disclosures

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Celgene/ BMS	x				x	x	
Astellas					x		
Jazz					x	x	
Abbvie					x		

Themes in HR-MDS

Combination therapies

- Usually a HMA (AZA >>DAC) alone compared to HMA plus new agent
- Venetoclax

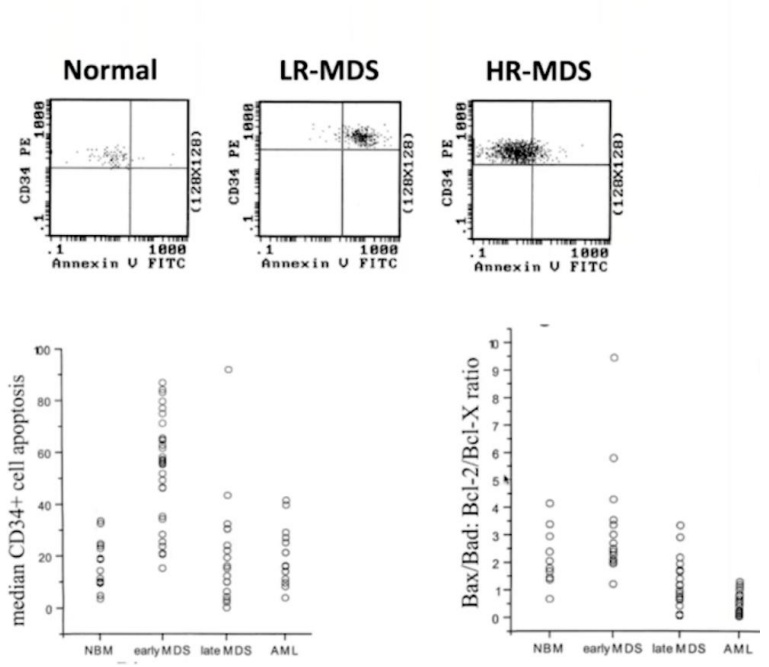
Novel drugs

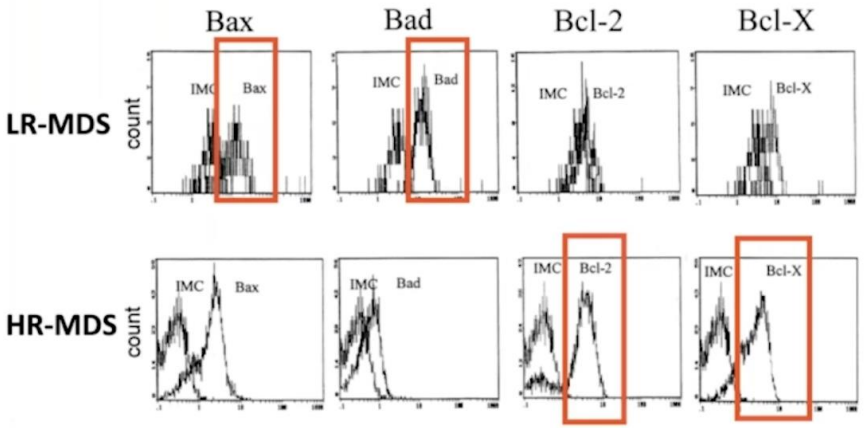
- Magrolimab
- TIM3 inhibitors

Targeted drugs

- TP53: APR-246
- IDH inhibitors

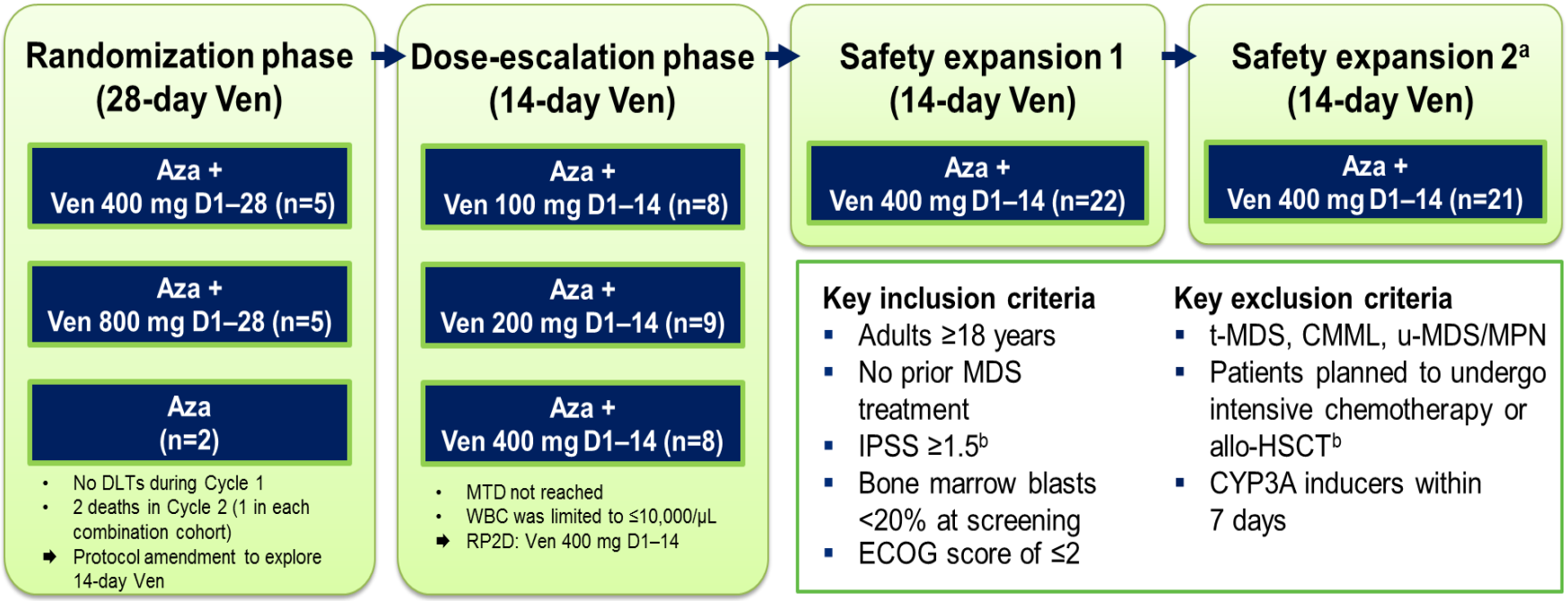
Apoptosis and BCL2-expression in MDS





Parker et al, BJH 2018

Venetoclax /Azacitidine in Patients With Higher-Risk MDS: A Phase 1b Study

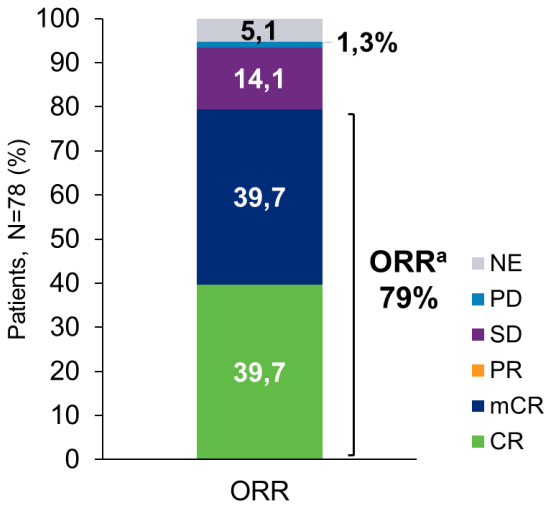


n=51 pts RP2D

Garcia J et al, ASH 2020

Patient Characteristics and Response

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 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)

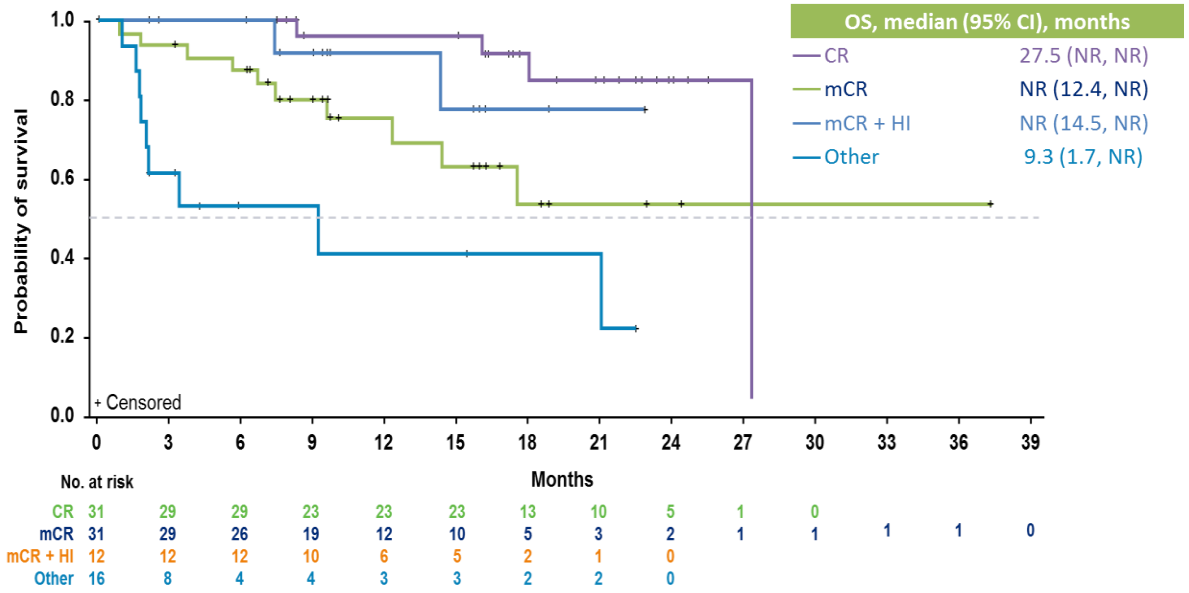


- Median DoR: 12.9 months (12.1–16.8)
- Median DoR after CR: 13.8 months (6.5–20.9)
- Median time to CR: 2.6 months (1.2–19.6)
- 16 patients (21%) went on to receive HSCT
- For patients receiving Ven 400 mg (RP2D; n=51)
  - 84% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved 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)

Garcia J et al, ASH 2020

Survival and Safety



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

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

✓ The recommended dose of Ven is 400 mg for Days 1–14 of a 28-day cycle when combined with Aza (75 mg/m2, Days 1–7)

A further phase 3 study (VERONA1) is currently recruiting

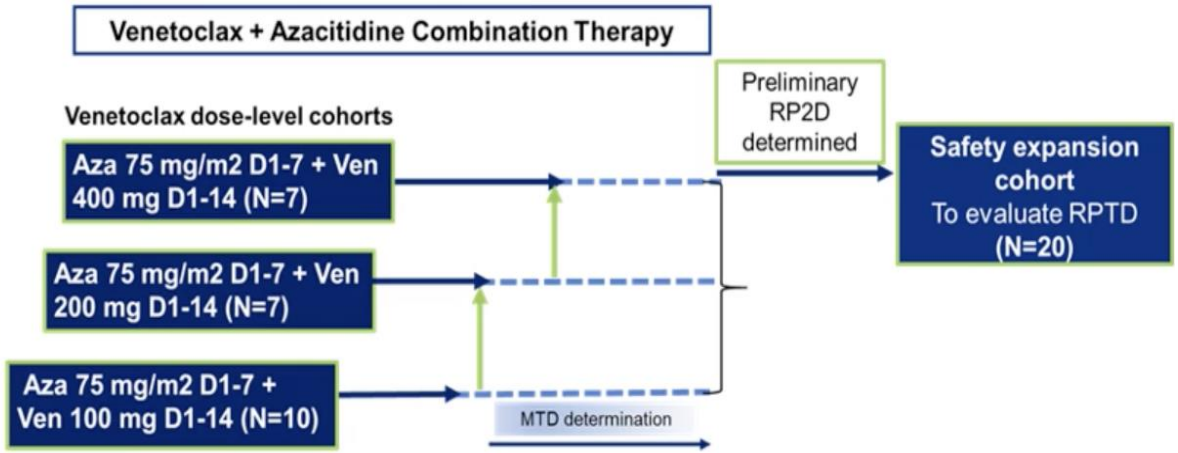
Garcia J et al, ASH 2020

M15-522 Trial: Venetoclax/AZA in R/R MDS

NCT02966782

Key inclusion criteria:

- ≥18 years with RR-MDS
- ECOG scores ≤2
- Bone marrow blasts <20% at screening
- Not candidates for hematopoietic stem cell transplantation



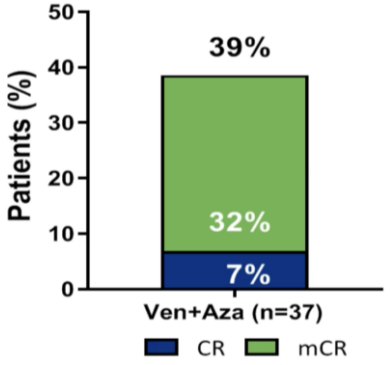
Key endpoints:
ORR, DOR, HI, TI, Exploratory biomarkers

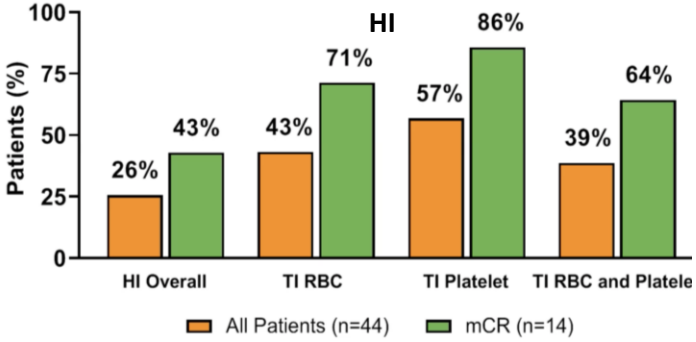
Zeidan et al, ASH 2020

Ven/AZA: patient characteristics and response

Characteristic		Ven+Aza n=44
Median age, years (range)		74 (44 – 91)
ECOG performance score, n (%)	0	11 (25)
	1	26 (59)
	2	7 (16)
Bone marrow blasts, n (%)	≤5%	14 (32)
	>5% – 20%	30 (68)
Number of prior HMA therapies†, n (%)	1	41 (93)
	2	2 (5)
Median (range) number of cycles of prior HMAs		9 (2 – 72)
Baseline IPSS-R risk categories, n (%)	Low	4 (9)
	Intermediate	8 (18)
	High	16 (36)
	Very high	16 (36)
Received RBC or platelet transfusion ≤8 weeks of first dose of venetoclax and azacitidine		31 (70)

Objective Response rate

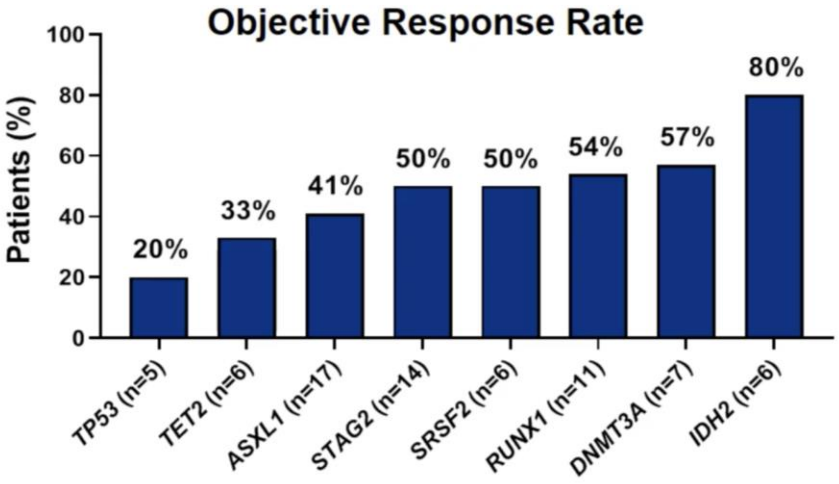


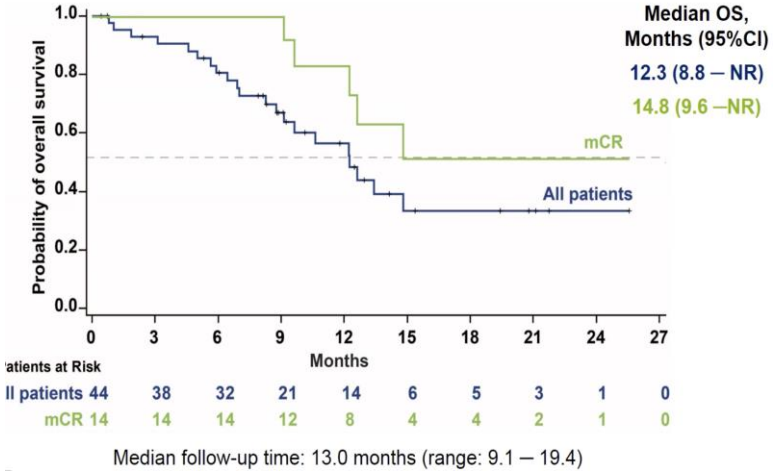


Median duration of response for ORR: 8.6 months (95% CI: 6.2-13.2), for CR: 9.1 mos (95% CI: 6.3-11.8)

Zeidan et al, ASH 2020

VEN/AZA: mutation status and survival





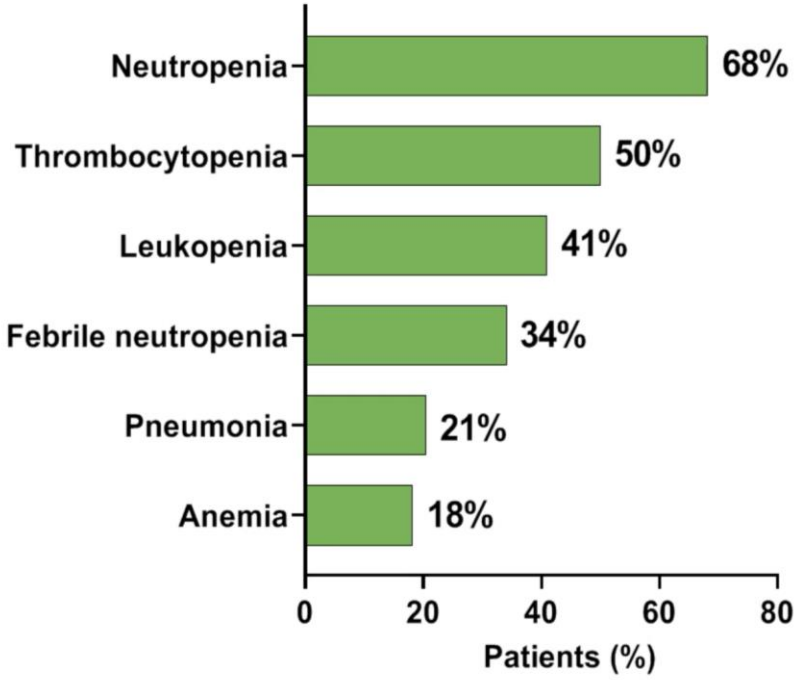
Median follow-up time: 13.0 months (range: 9.1 – 19.4)

Mutations	Median PFS, months	Median OS, months
TP53 (n=5)	5.1	5.9
TET2 (n=6)	8.3	12.3
ASXL1 (n=17)	8.1	12.6
STAG2 (n=14)	9.2	14.8
SRSF2 (n=6)	NR	NR
RUNX1 (n=11)	6.9	NR
DNMT3A (n=7)	6.5	13.4
IDH2 (n=6)	13.4	13.4

Response and survival were independent of blasts % and BCL2/BCL-xL ratio

Zeidan et al, ASH 2020

VEN/AZA: treatment-emergent adverse events ≥ grade 3

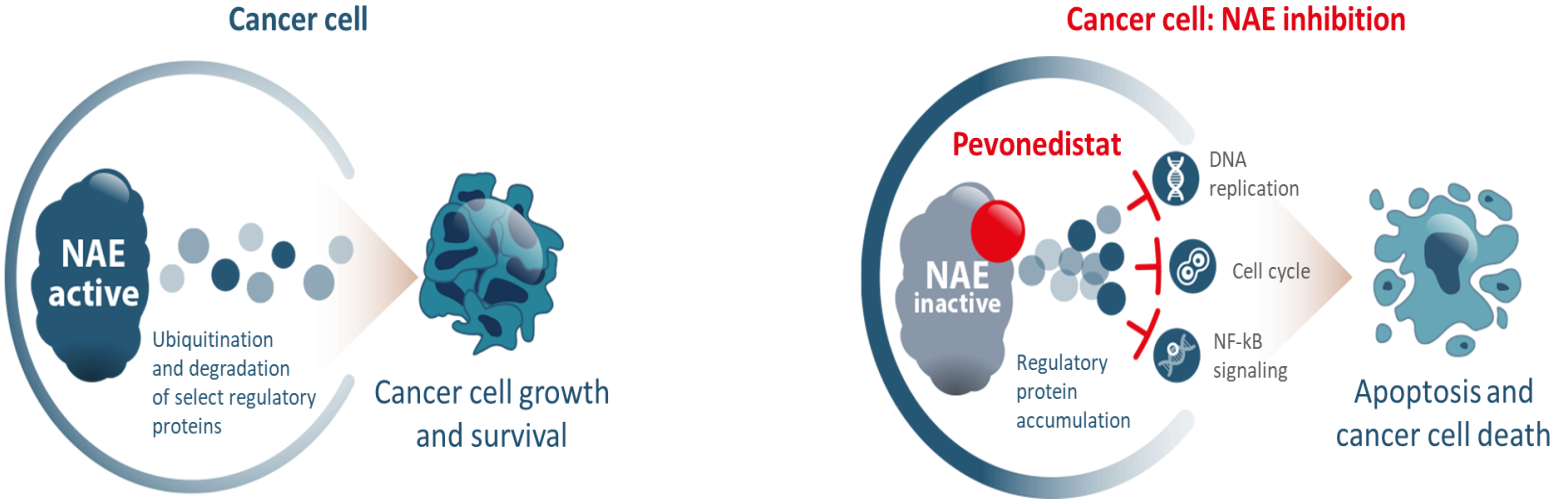


- All 44 patients (100%) had at least one treatment-emergent adverse event (AE) of any grade and 42 (96%) had at least one ≥ grade 3 AE
- Predominant ≥ grade 3 AEs were hematological AEs and infections
- One (2%) death occurred ≤ 30 days after first dose of treatment
- No additional toxicities were identified

Zeidan et al, ASH 2020

Pevonedistat: first-in-class inhibitor of the NEDD8-activating enzyme

- Inhibiting the NEDD8-activating enzyme blocks ubiquitination of select proteins upstream of the proteasome.[1,2]
- Treatment with pevonedistat disrupts cell cycle progression and cell survival, leading to cell death in cancers.[2,3]
- Pevonedistat exhibits synergistic activity in combination with azacitidine in cellular and mouse xenograft models of AML.[4]

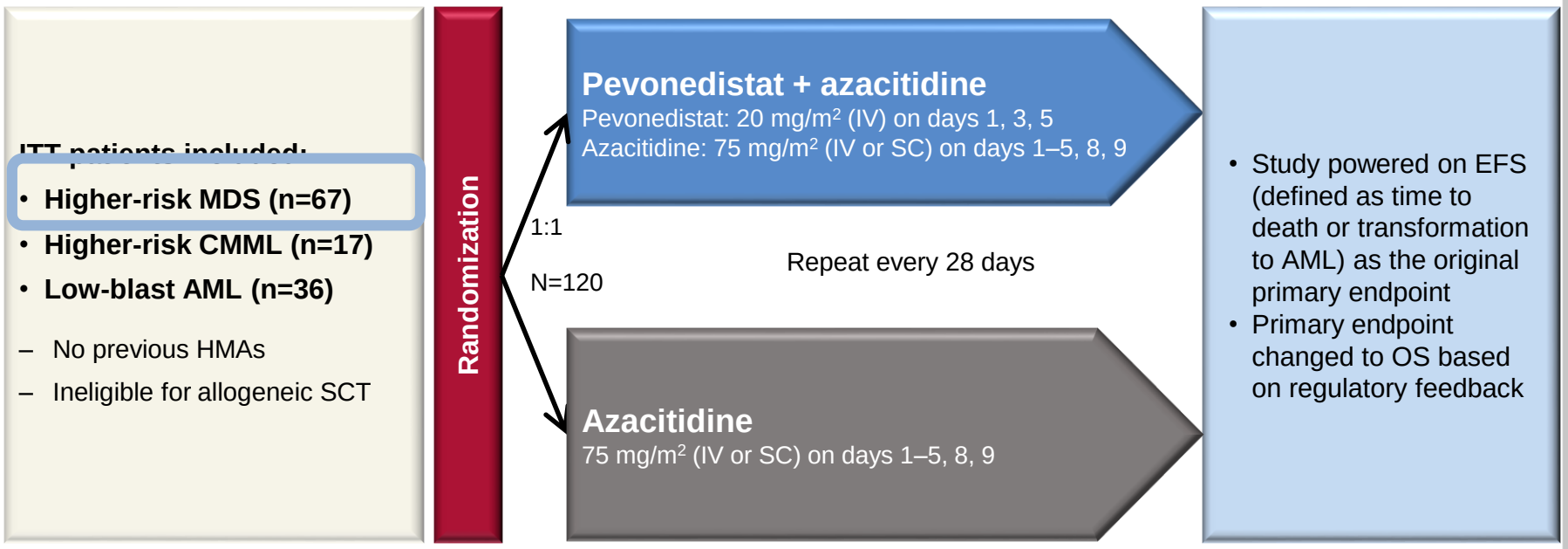


AML, acute myeloid leukemia; NAE, NEDD8-activating enzyme;
NEDD8, neural precursor cell expressed, developmentally downregulated 8;
NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells.

1. Brownell JE, et al. Mol Cell 2010;37:102–11; 2. Soucy TA, et al. Nature 2009;458:732–6; 3. Soucy TA, et al. Clin Cancer Res 2009;15:3912–16. 4. Smith PG, et al. Blood 2011;118:abstract 578.

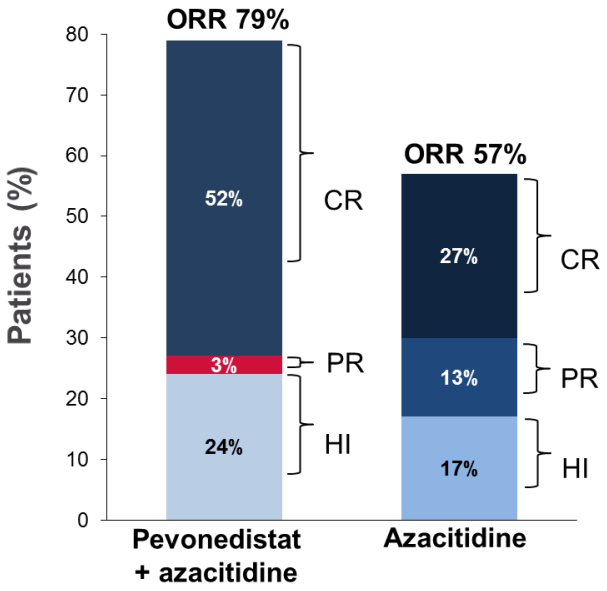
Sekeres MA, et al. Blood 2020

NCT02610777: phase 2, randomized, open-label study



Sekeres MA, et al. ASH 2020

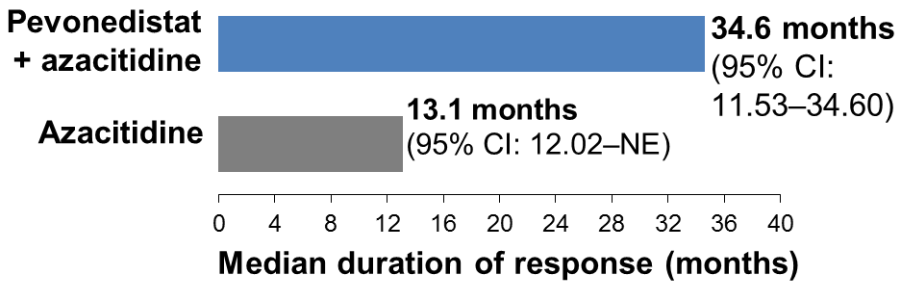
Response-evaluable patients with higher-risk MDS (n=59)



	P-value (pevonedistat + azacitidine vs azacitidine)
ORR	0.065
CR rate	0.050

	Pevonedistat + azacitidine n=16	Azacitidine n=12
Median time to first CR or PR among responders, months (range)	3.83 (1.8–25.8)	4.29 (2.0–13.2)

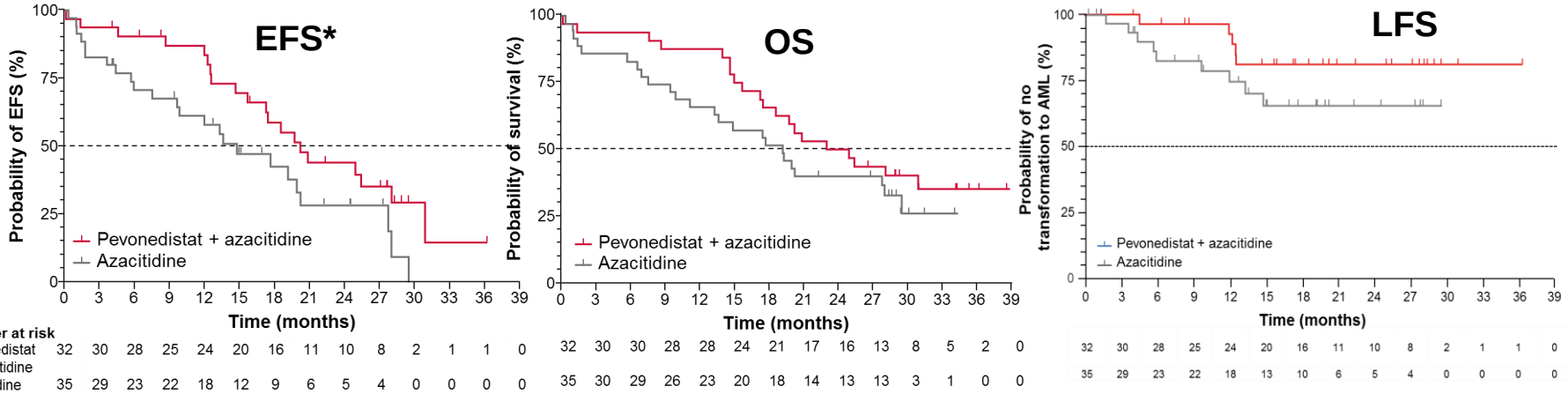
- ✓ Rate of RBC and platelet transfusion independence was increased in the PEV/AZA group
- ✓ Median duration of transfusion independence was also significantly longer (23.3 vs 11.6 months)



Sekeres MA, et al. Blood 2020

Survival in patients with higher-risk MDS according to IPSS-R

Longer EFS was particularly evident in patients with IPSS-R-defined very-high-risk MDS (n=26; HR: 0.47; 95% CI: 0.19–1.18) and high-risk MDS (n=21; HR: 0.53; 95% CI: 0.17–1.72)



	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	

	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median OS, months	23.9	19.1
Hazard ratio (95% CI)	0.701 (0.386–1.273) P=0.240	

	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median time to AML transformation, months	NE	NE
Hazard ratio (95% CI)	0.465 (0.156–1.388) P=0.159	

- *EFS defined as time to death or transformation to AML in higher-risk MDS.

Sekeres MA, et al., ASH 2020

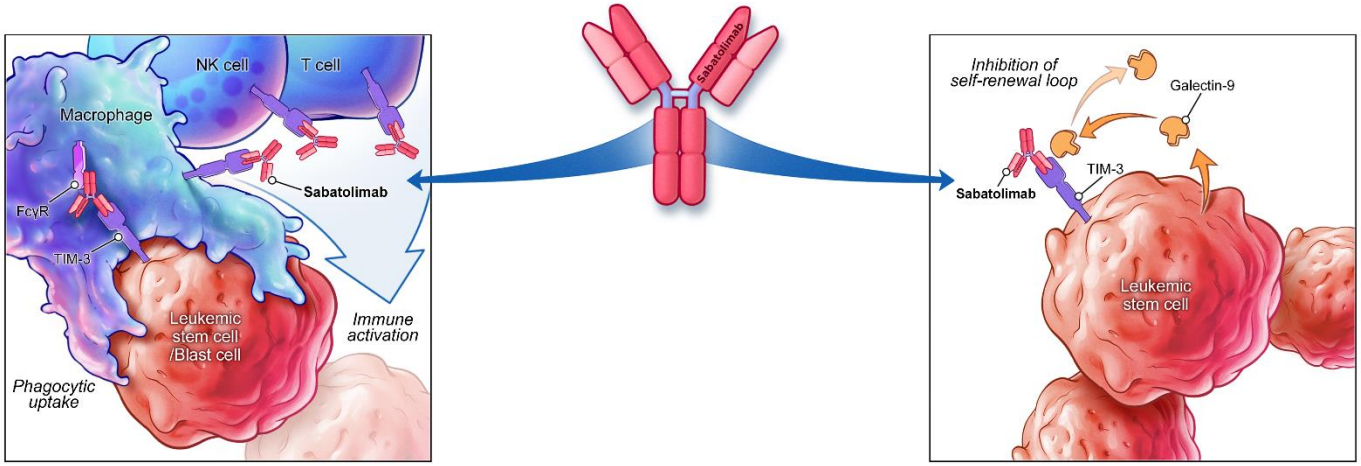
Dual targeting of TIM-3 on immune and leukemic cells by sabatolimab

Targeting Immune Effectors

- Binds TIM-3 on immune cells, enhancing anti-leukemia immune activation[1,2]
- Enhances phagocytic uptake, facilitating cell-mediated killing of LSCs and blasts[1-4]

Targeting Leukemic Cells

- Directly Targets LSCs through high-affinity binding of TIM-3[2]
- Blockade of TIM-3 on LSCs may inhibit TIM-3/Galectin 9 driven self-renewal[1,2]



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. 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 (MBG453) in Combination With Hypomethylating Agents in Patients With AML and High-Risk MDS: Phase Ib Study

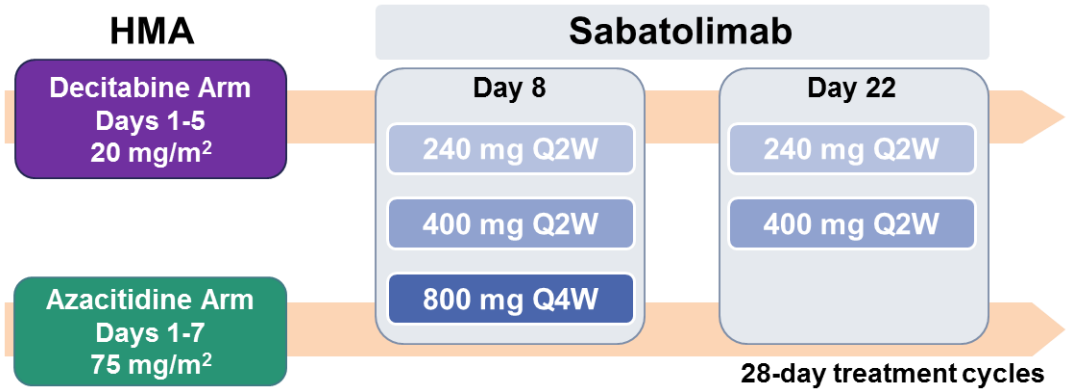
vHR/HR-MDS: IPSS-R high- or very high-risk MDS

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

CMML: Patients with CMML ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648**



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

Brunner et al, ASH 2020

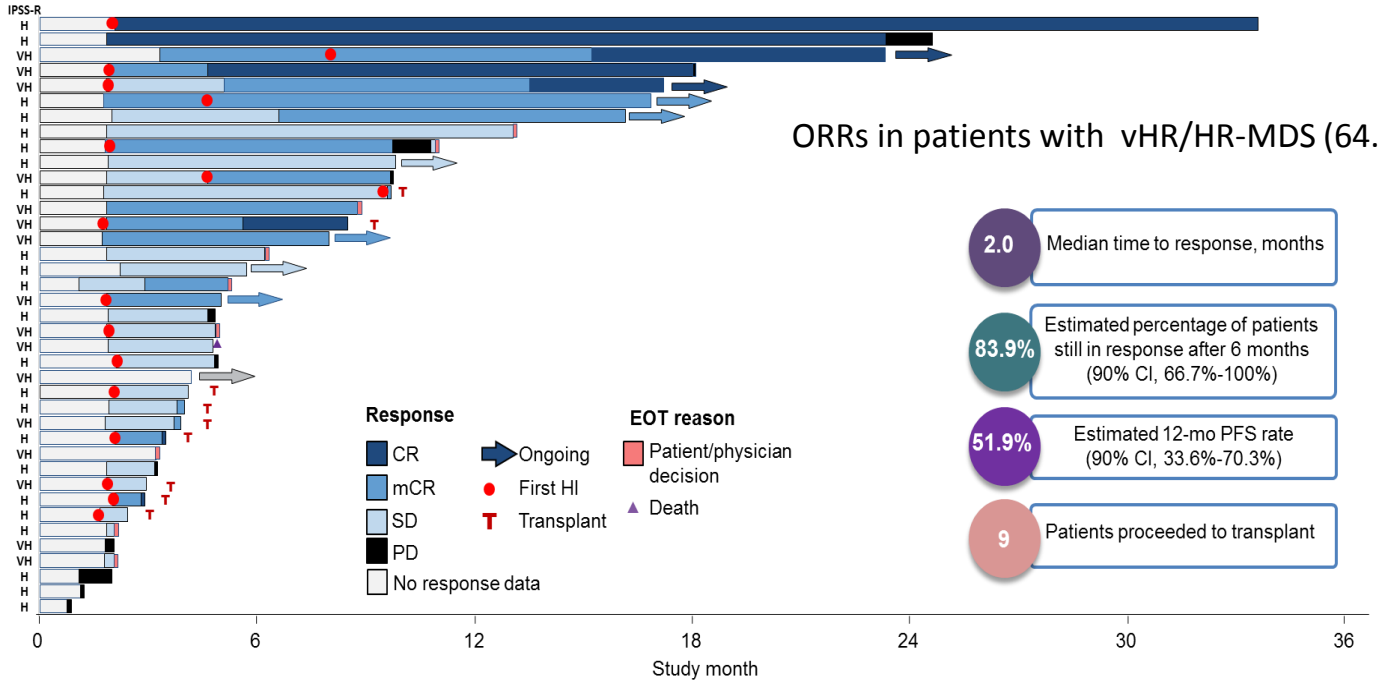
Patient characteristics

Parameter	vHR/HR-MDS n=41	ND-A ML n=48	CMML n=12
Sabatolimab + decitabine, n	**19**	**22**	**5**
Sabatolimab + azacitidine, n	**22**	**26**	**7**
Median age (range), y	70.0 (23-90)	75.0 (59-89)	68.5 (53-79)
Male, n (%)	23 (56.1)	26 (54.2)	9 (75.0)
ECOG performance status, n (%)			
0	13 (31.7)	15 (31.3)	6 (50.0)
1	24 (58.5)	28 (58.3)	4 (33.3)
2	4 (9.8)	5 (10.4)	2 (16.7)
IPSS-R category (MDS), n (%)			
High	25 (61.0)	–	9 (75.0)
Very high	16 (39.0)	–	2 (16.7)
2017 ELN risk classification[1] (AML), n (%)			
Favorable	–	0	–
Intermediate	–	21 (44)	–
Adverse	–	27 (56)	–

available mutation data:	TP53	ASXL1	RUNX1	SRSF2	U2AF1
vHR/HR-MDS (n=31)	12/31	7/31	3/31	4/31	4/31
ND-AML (n=31)	5/31	5/31	6/31	6/31	1/31

Brunner et al, ASH 2020

Response in vHR/HR-MDS



ORRs in patients with vHR/HR-MDS (64.1%)

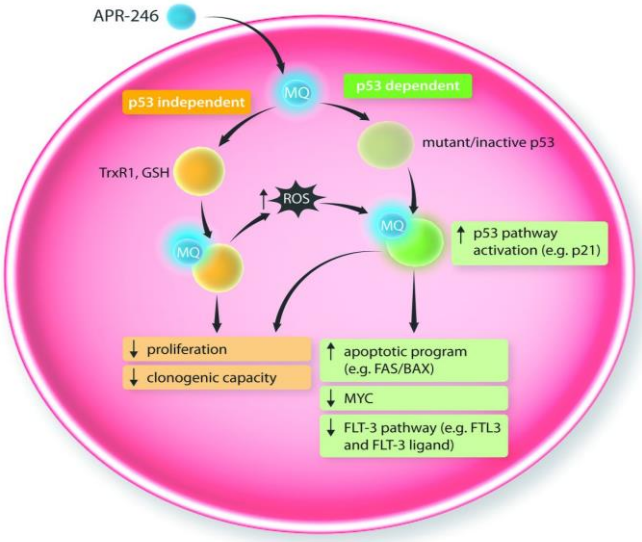
- **2.0** Median time to response, months
- **83.9%** Estimated percentage of patients still in response after 6 months (90% CI, 66.7%-100%)
- **51.9%** Estimated 12-mo PFS rate (90% CI, 33.6%-70.3%)
- **9** Patients proceeded to transplant

STIMULUS Clinical Trial Program		
STIMULUS-MDS1	Phase II study of MBG453 + HMA in higher-risk MDS	NCT03946670
STIMULUS-MDS2	Phase III study of MBG453 + azacitidine in higher-risk MDS	NCT04266301
STIMULUS-AML1	Phase II study of MBG453 + azacitidine ± venetoclax in unfit AML	NCT04150029

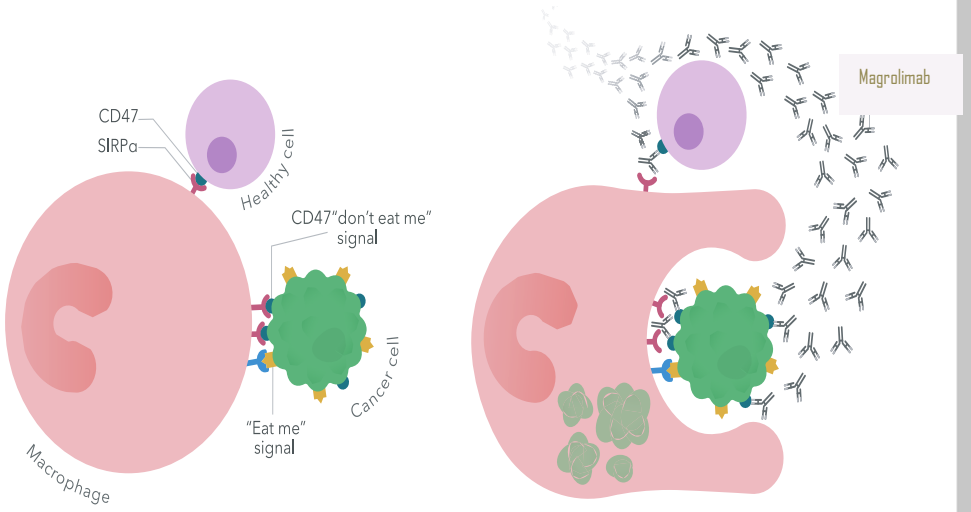
Brunner et al, ASH 2020

Targeting TP53 mutations in MDS

APR-246



Magrolimab



Sallman DA, Haematologica 2020

APR-246 / Azacitidine

Phase 2

✓ **Phase 2:** Primary: CR rate

Secondary: Safety, ORR, DoR, OS, Tp53 IHC and serial NGS (sensitivity 0.1% VAF)

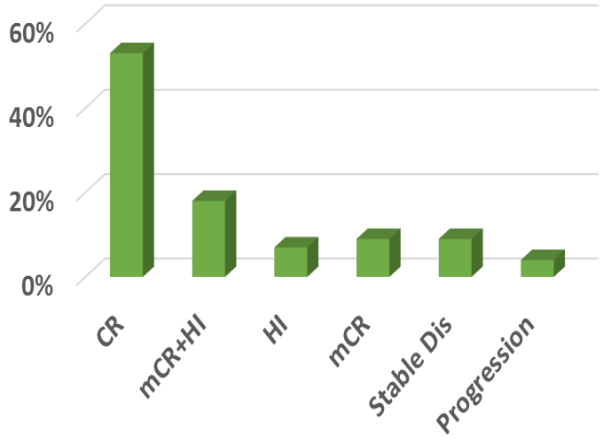
APR-246 400 mg fixed dose, i.v. days 1-4
AZA (sc or iv) days 4-10 or 4-5 and 8-12
28-day cycle

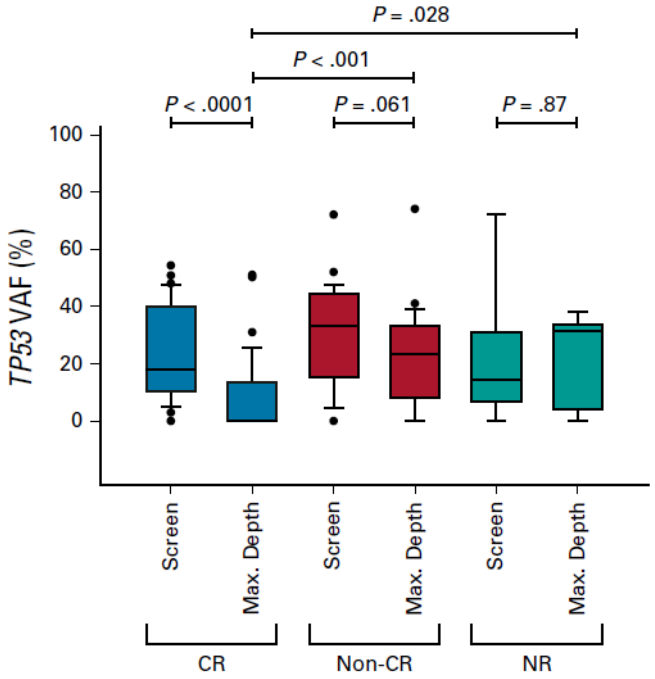
- By **WHO**: 40 MDS, 11 AML-MRC and 4 CMML/MDS-MPN; 85% had **complex cytogenetics** and 33% **tMDS/AML**.
- All pts had **higher IPSS-R** (7% Intermediate, 24% High, 69% Very High).
- 50 pts (91%) had a ***TP53* missense** mutation in the DNA binding domain, multiple mutations in 18 (33%), and median variant allele frequency (VAF) of 25%.
- 30- and 60-day mortality: 2% (n=1) and 6% (n=3), respectively.
- Median **time to response**: 2.1 months (0.1-5.4), median duration of response: 6.5 months.

Sallman et al., J Clin Oncol 2021

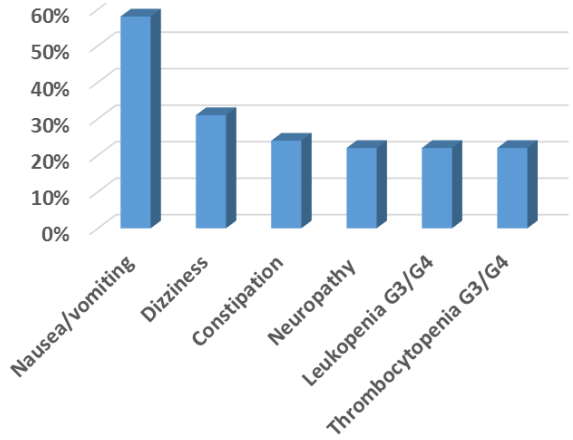
Response to APR-246/AZA

ORR (n= 45 pts, median follow-up: 10.5 months)





Tx-related adverse events (G1/G2)



Sallman et al., J Clin Oncol 2021

NCCN Guidelines Version 3.2021
Myelodysplastic Syndromes

NCCN Guidelines Index
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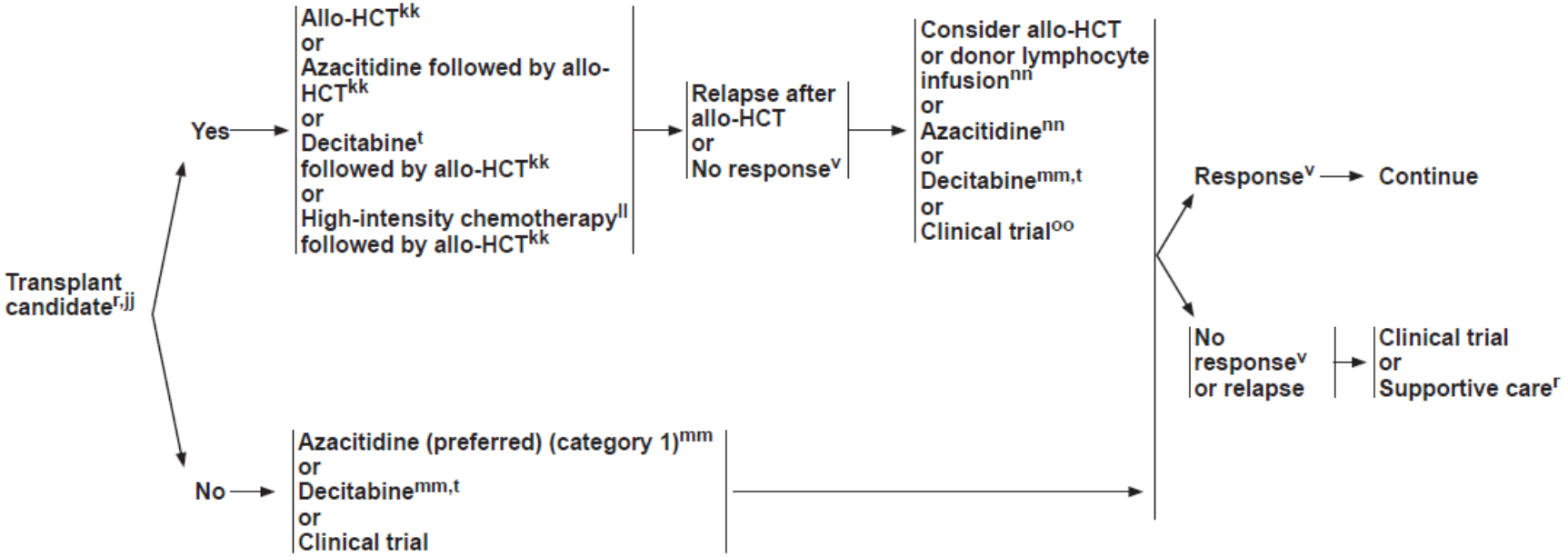
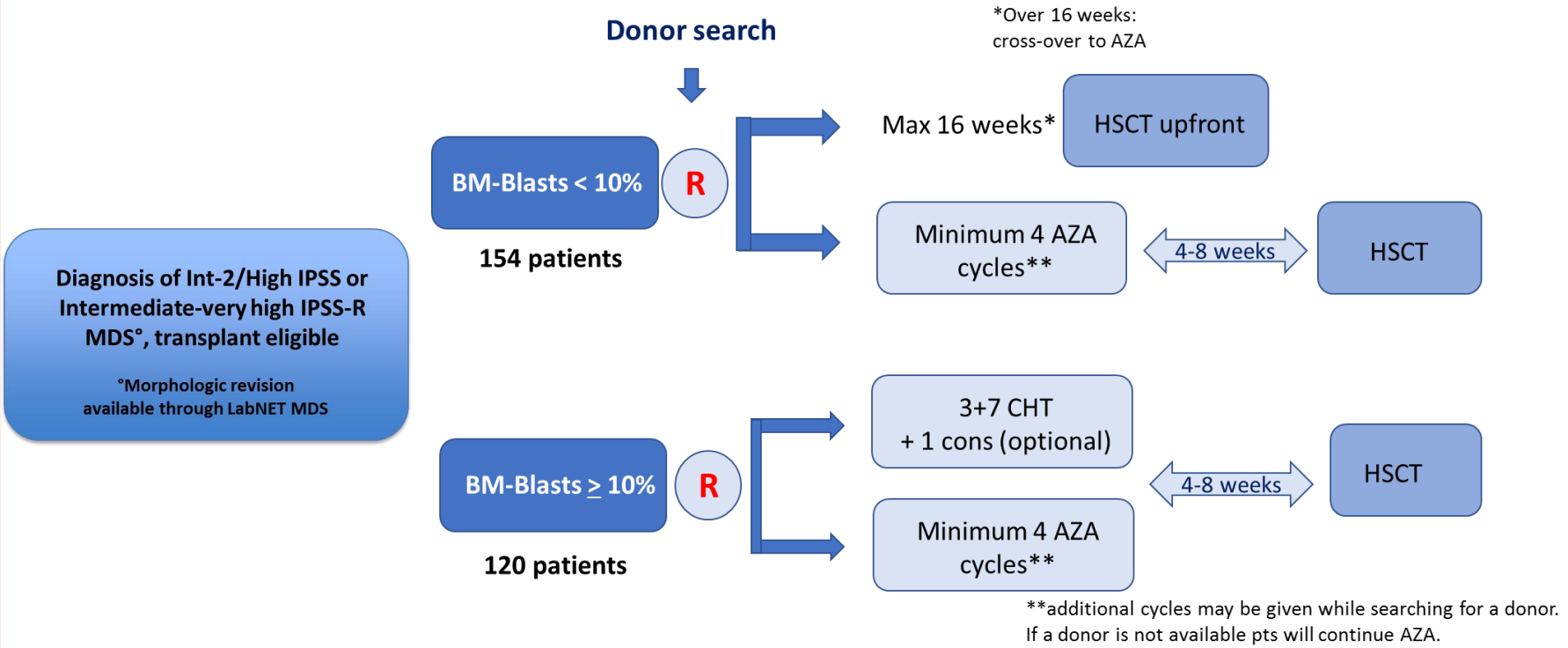
PROGNOSTIC CATEGORY[o]

IPSS-R: Intermediate,[p] High, Very High
IPSS: Intermediate-2, High
WPSS: High, Very High

TREATMENT



ACROBAT Protocol (MDS0519)



**additional cycles may be given while searching for a donor. If a donor is not available pts will continue AZA.