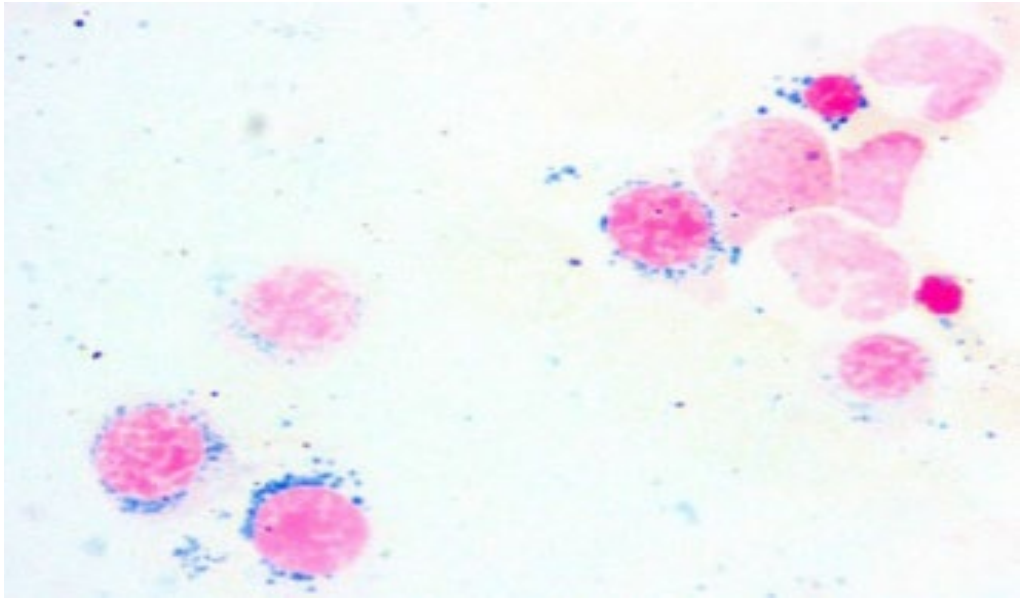
Myelodysplastic Syndromes (MDS) : Emerging and Targeted Therapies



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Disclosures- Richard M. Stone, MD

- **Consulting relationships past three years:**
  - **AbbVie*; Actinium, Agios*; Amgen; Argenix Data Safety and Monitoring Board (DSMB); Arog*; Astellas; AztraZenaca; Biolinerx, BMS/Celgene (includes DSMB and steering committee); Elevate Bio, Fujifilm, Janssen; Jazz, Juno; Macrogenics; Novartis*; Ono; Orsenix; Pfizer; Roche; Stemline, Sumitomo; Syndax*; Syntrix (DSMB only); Syros; Takeda (DSMB), Trovagene**
  - *** denotes support to my institution for clinical trials on which I was local PI**
- **Securities, employment, promotional activities, intellectual property, gifts, grants**
  - **None**

Objectives

- **Understand the role of newly drugs in MDS**
  - **Clinical trials that lead to the approval**
- **Be familiar with key agents in development for MDS**
- **Review the current algorithm for treating patients with MDS**

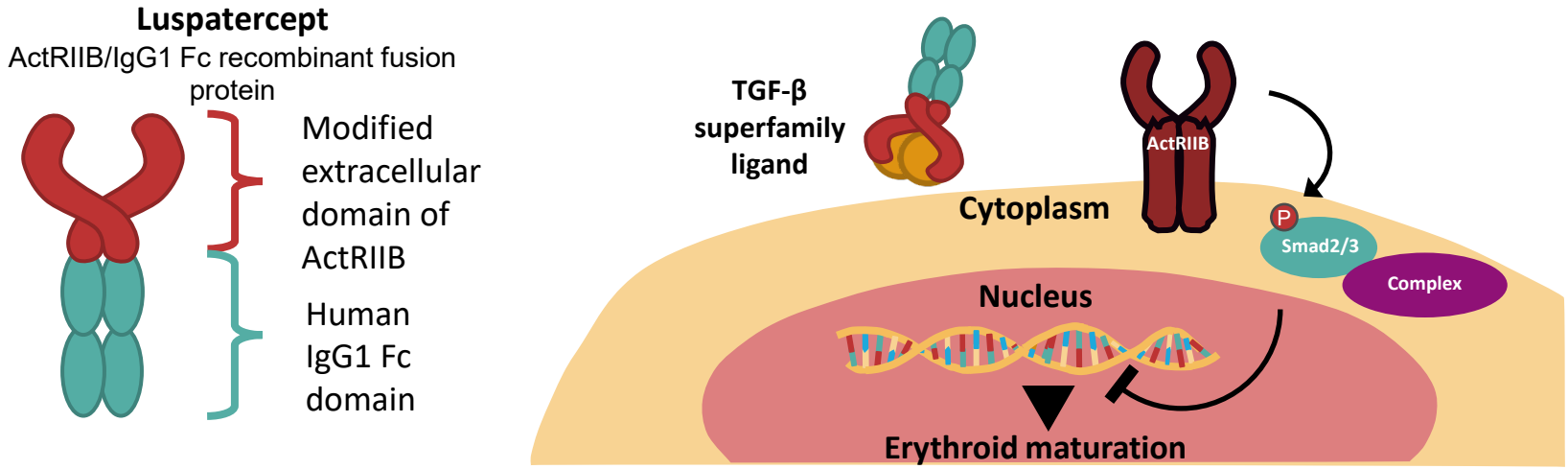
New Drugs in MDS: Outline

- Therapy of lower risk disease
  - Lenalidomide in 5q-
  - Erythropoietin (EPO) +/- G-CSF; Lenalidomide +EPO
  - Luspatercept
    - Maybe
      - » Low dose Hypomethylating agent (HMA), Iron chelation
    - Horizon
      - » Roxudostat, telomerase inhibition, spliceosome targeted
- Therapy of Higher risk disease
  - Hypmethylating agent (HMA) (including now: Oral decitabine/cytidine deaminase inhibitor=ASTX727), allogeneic stem cell transplant (alloSCT) if possible, remains the standard
    - Maybe
      - » add venetoclax, (isocitrate dehydrogenase)IDH inhibitor
    - Horizon
      - » aCD47, checkpoint inhibitor (CPI), TP53 refolding, NEDD8 converting enzyme inhibitor (NAEi)

Recently Approved

MEDALIST Luspatercept Trial

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion-reduction or RBC-TI in patients with MDS-RS (52%) vs. other subtypes (30%)[2]



1. Suragani RN, et al. *Nat Med*. 2014;20:408.;
2. Platzbecker U, et. A. Lancet Oncol 2017; 18:1338.

ActB, activin B; ActRIIB, human activin receptor type IIB; BMP, bone morphogenetic protein; GDF, growth differentiation factor; IgG1 Fc, immunoglobulin G1 fragment crystallizable; LR, lower-risk; MDS, myelodysplastic syndromes; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor-beta.

MEDALIST Trial

Study Design - A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- MDS-RS (WHO 2008): ≥ 15% ring sideroblasts or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Int-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naïve: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease modifying agents (e.g., iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (subcut) every 21 d
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

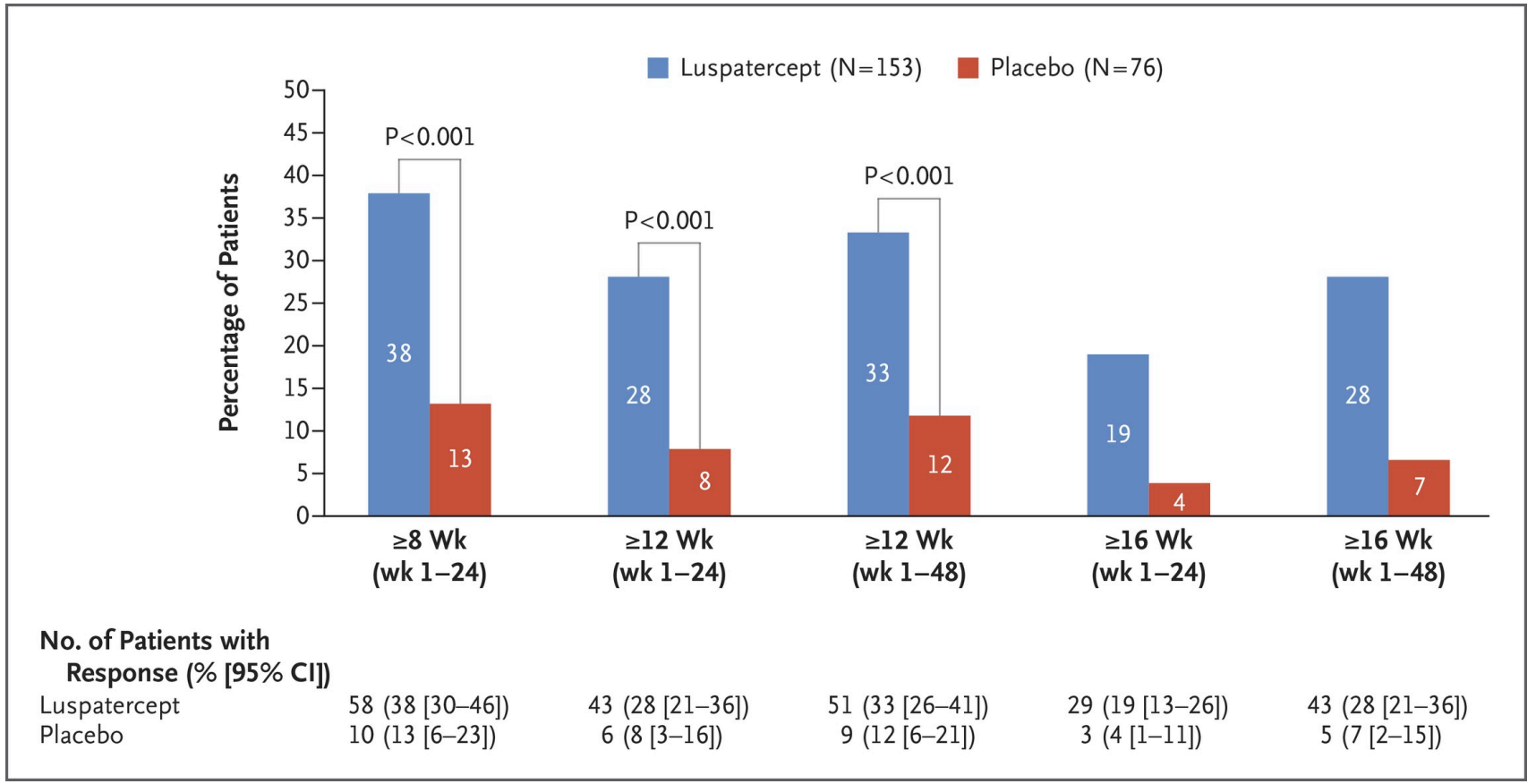
Disease & Response Assessment week 24 & q 6 months Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; No crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Fenaux, P et al, NEJM 302: 140-151, 2020

MEDALIST Trial

Primary Endpoint Achieved: Red Blood Cell – Transfusion Independence) ≥ 8 Weeks



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

AE: No excess Gr ¾ but about Gr 1/2 fatigue, GI, dizzy/HA 20 % w Luspatercept (<10% in placebo); clinical benefit extends to 92 weeks (Fenaux ASH 2019)

Fenaux, P et al, NEJM 302: 140-151, 2020

MDS: New Approaches for Lower Risk

- **Reset Oxygen sensing: roxudostat**
  - **Prevents HIF1α degradation**
  - **Based on work done by Wm Kaelin DFCI, Semenza, JHU and Ratcliffe, Crick**

  - Some responses in MDS: Henry et al, ASH 2019

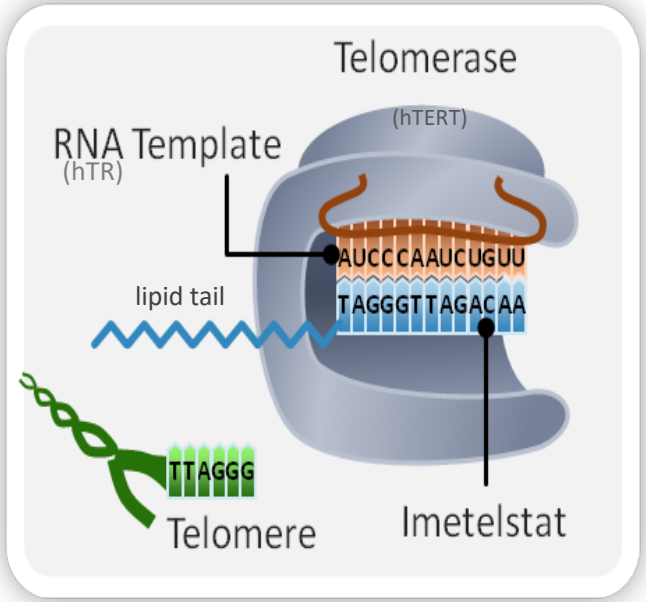
- **Short course hypomethylating agents for lower risk pts**
  - 3d decitabine higher ORR (70)% than 3d azacytidine (33%)
  - Jabbour et al., Blood. 2017 130(13):1514-1522
  - Ongoing MDS consortium rand trial of 3 low dose HMA arms
- **Telomerase Inhibition**

Imetelstat: First-in-Class Telomerase Inhibitor

Imetelstat

- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability.
- **Potent, first in class competitive inhibitor of telomerase**: IC50 = 0.5-10 nM
- **Target:** selectively targets heme (MF) malignant stem and progenitor cell proliferation.[1, 2]

Imetelstat binds to RNA template preventing maintenance of telomeres



- Short telomere length (TL), high levels of telomerase activity (TA) and high expression of human telomerase reverse transcriptase (hTERT) correlated with higher risk, disease progression and shorter OS in patients with myeloid malignancies.[3-5]
- Nonclinical studies demonstrated that imetelstat reduces TA, hTERT expression level, and JAK2V617F^{+} hematopoietic progenitor cells in MF patient samples, indicative of mechanism based on-target activity.[1,2]
- **Cells with high levels of TA and hTERT and short TL, represent best target for treatment with telomerase inhibitor.**

[1]Wang, et al. *Blood Adv* 2018;2:2378-88.
[2]Mosoyan, et al. *Leukemia* 2017;31:2458-67.
[3]Briatore, et al. *Cancer Biol Ther* 2009;8:883-9.
[4]Kishtagari and Watts. *Ther Adv Hematol* 2017;8:317-26.
[5]Wang, et al. *Int J Lab Hematol* 2010;32:230-8.

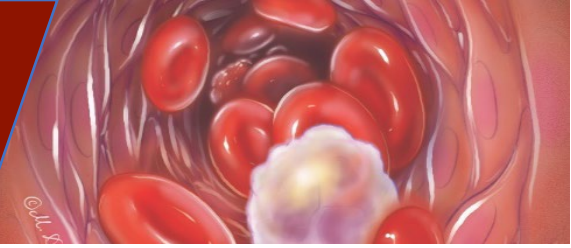
57 Lower Risk MDS pts (38 were HMA naïve, non 5q-)

8 and 24 week TI rate 37%, 23%

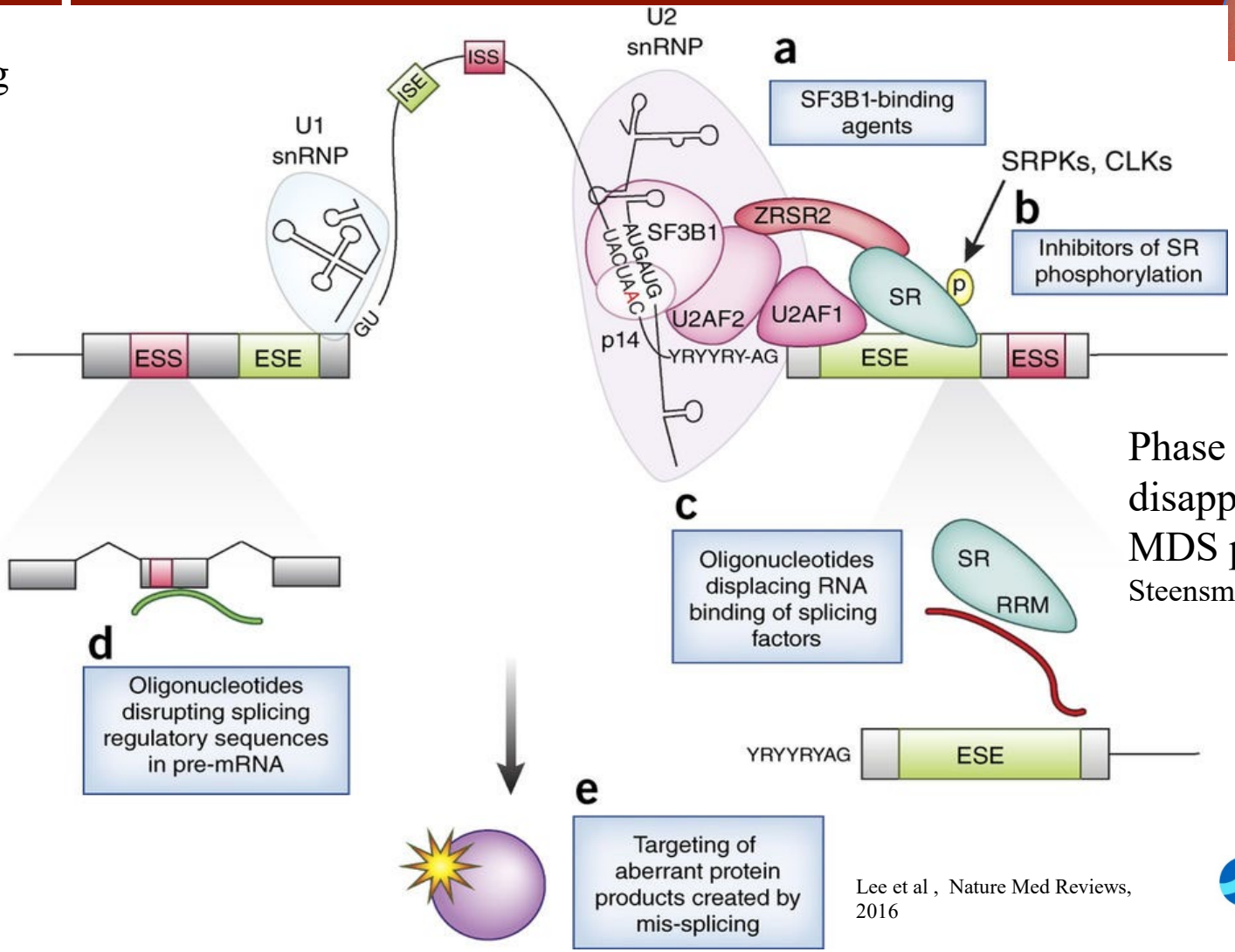
Med response duration=65 weeks

Steensma D, et al. ICO 2020

Targeting MDS with splicing Complex mutations*



The splicing complex can be disrupted leading to synthetic lethality



Phase I trial of H3B-8800 was disappointing (though 5/15 MDS pt w SF2B1 muts exp TI)
Steensma, D et al. Leukemia 2021

Lee et al , Nature Med Reviews, 2016

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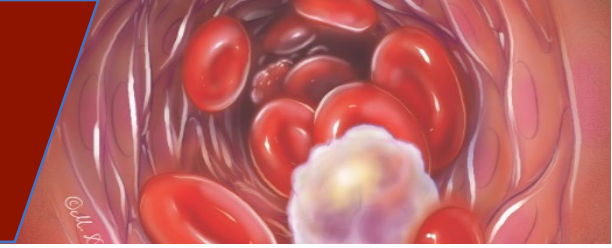
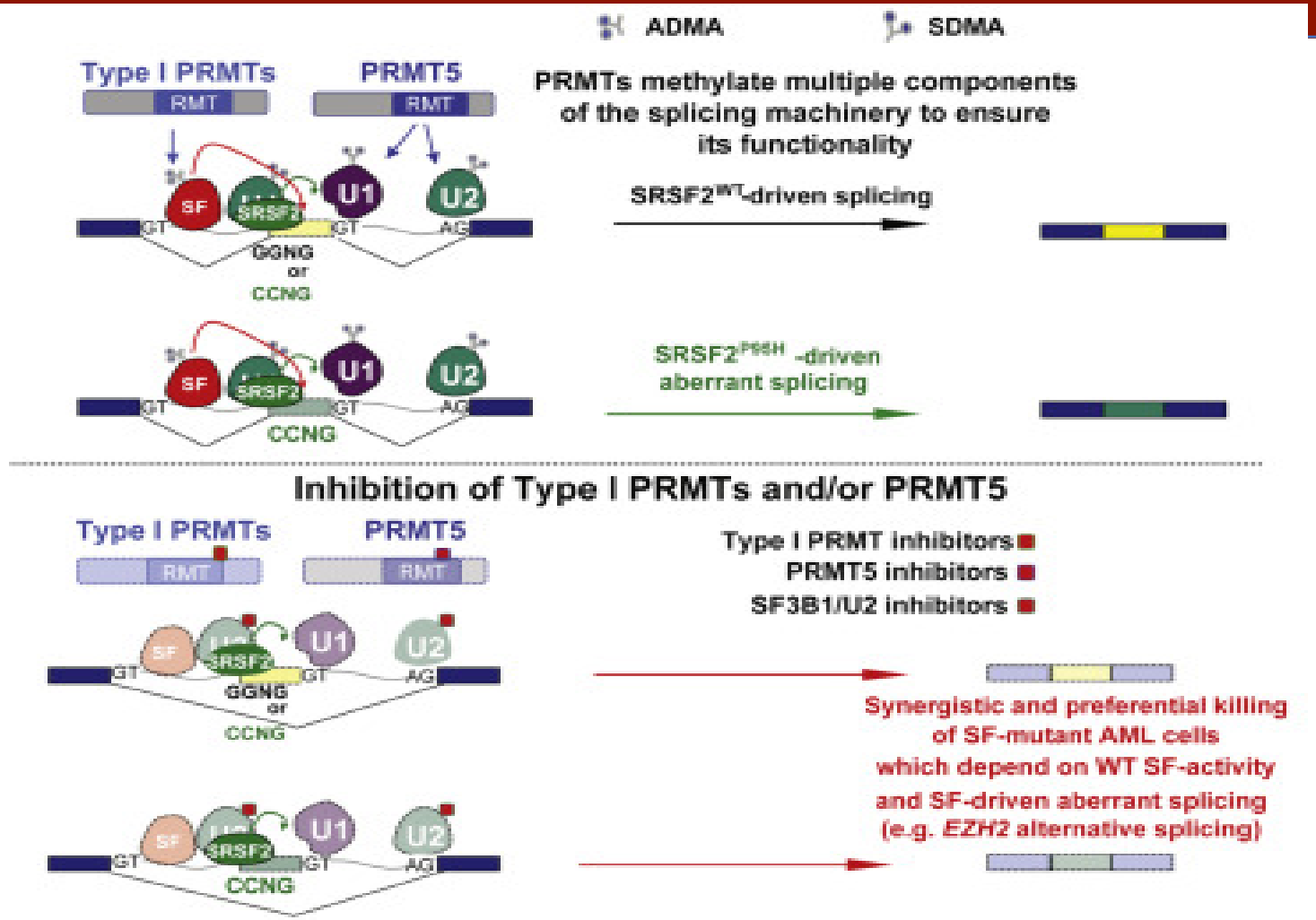
*SF3B1, U2AF1, SRSF2, ZRSR2





Inhibit Protein Arginine Methylation (PRMTs)

Fong et al, Cancer Cell 36:194, 2019…..

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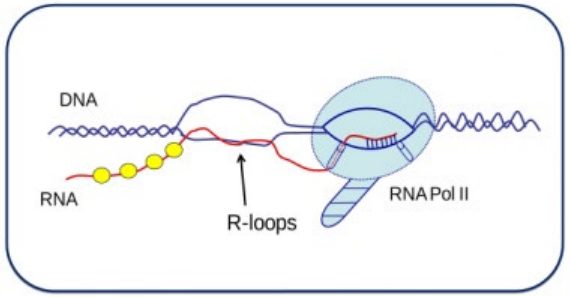
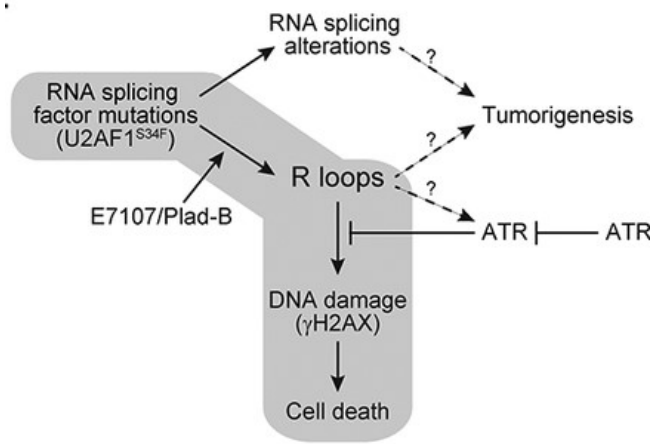


Spliceosome mutations cause R-loops

Nguyen H et al, Can Res 78: 5464, 2018



ATR inhibition may fail to resolve R-loops leading to synthetic lethality

Nguyen H, Zou Z, Graubert T. Oncotarget 10: 2381, 2019…..

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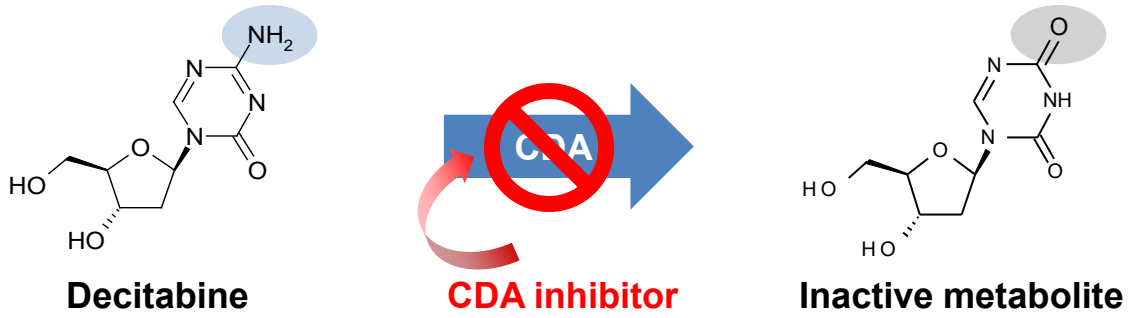
ORAL HMA in MDS?
1) oral Aza- useful in AML maintenance (Wei A, et al < LBA ASH 2019) and b) ASTX727 (Cedazuridine/Decitabine)

- Current HMA treatment poses significant patient burden due to 5 to 7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver



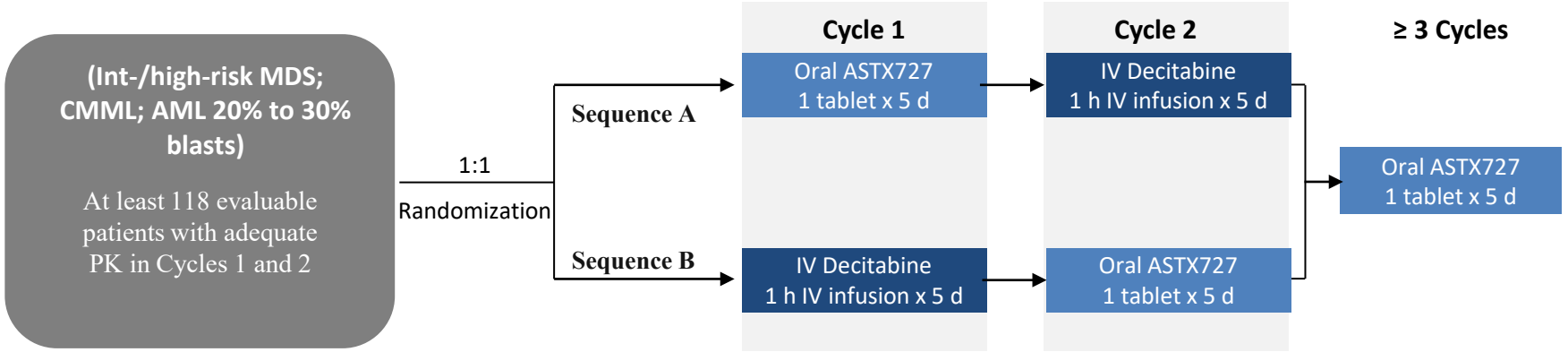
Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel CDA inhibitor

Garcia-Manero G, et al. Blood 2020.

ASCERTAIN Trial: Oral ASTX727 (Cedazuridine/Decitabine) vs IV Decitabine, Phase 3 Study in MDS/CMML

– ASTX727 is an oral, fixed-dose combination of cedazuridine and decitabine



Major entry criteria

- Candidates for IV decitabine
- ECOG PS 0 to 1
- Life expectancy of ≥ 3 months
- Adequate organ function
- 1 prior cycle of HMA is allowed

Primary endpoint

- Total 5-d decitabine AUC equivalence (oral/IV 90% CI between 80% and 125%)

Secondary endpoints

- Efficacy: response rate; TI; duration of response; leukemia-free and OS
- Safety of ASTX727
- Max LINE-1 demethylation

Garcia-Manero G, et al. Blood 2020.

ASCERTAIN Trial: 5-Day Decitabine AUC Equivalence

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

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

- Study met its primary endpoint with high confidence: oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93% to 106%
- All sensitivity and secondary PK AUC analyses confirmed findings from primary analysis
- Demethylation similar to IV decitabine
- AEs similar to 5 d decitabine
- Efficacy data similar to that reported in phase II data: CR-12%, marrow CR-46%

Garcia-Manero G, et al. Blood 2020.

Enasidenib in Higher-Risk *IDH2*-Mutated MDS: Response Rates

	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)**
Complete remission	8 (26)	3 (23)	5 (28)
Partial remission	1 (3)	0 (0)	1 (6)
Marrow complete remission	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)

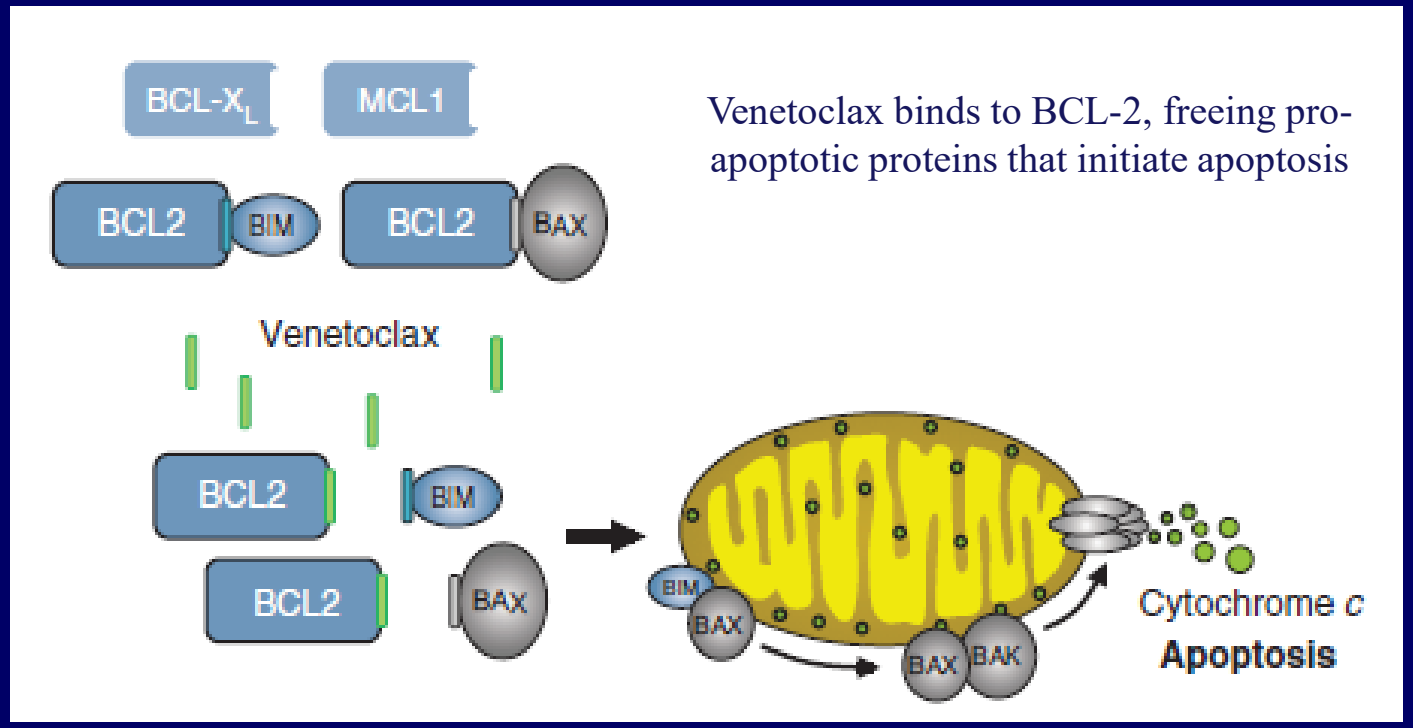
Richard-Carpentier G, et al. ASH 2019. Abstract 678.

12 pts w R/R MDS rx w ivosidenib 500 mg/d: 5 (42%) CR

DiNardo C, *NEJM* 2019

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins

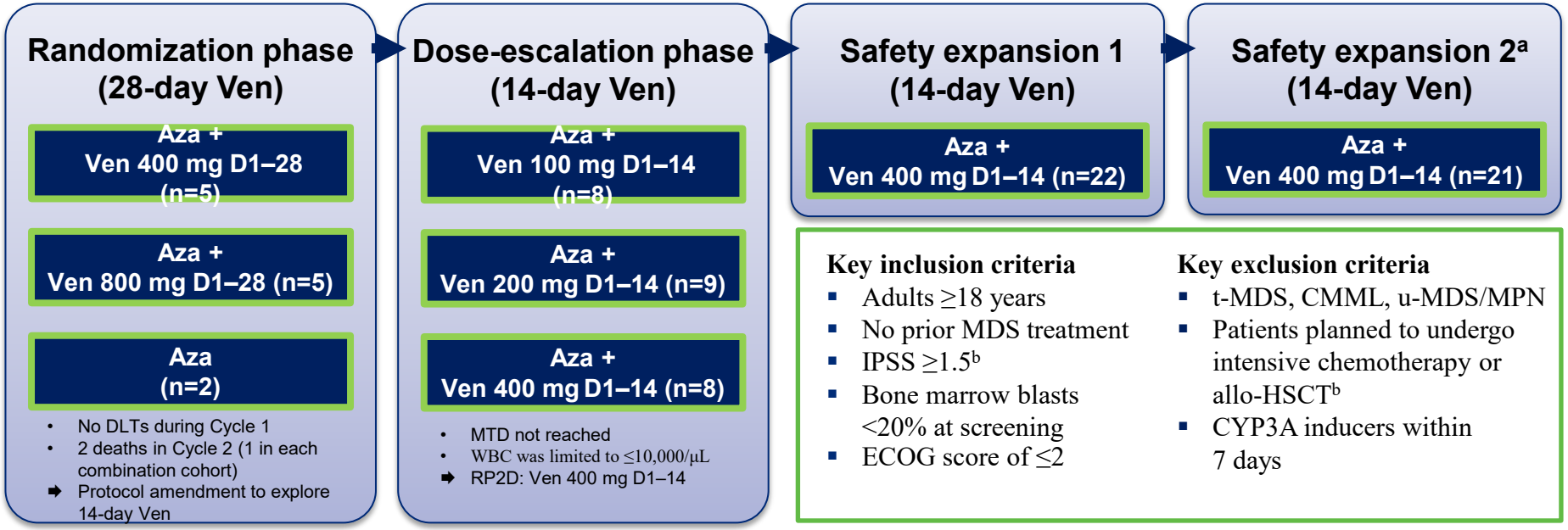


Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Phase Ib Study: Venetoclax + Azacitidine (AZA) in Higher-Risk MDS

Treatment cohorts (28-day cycles); Aza 75 mg/m^2 D1–7



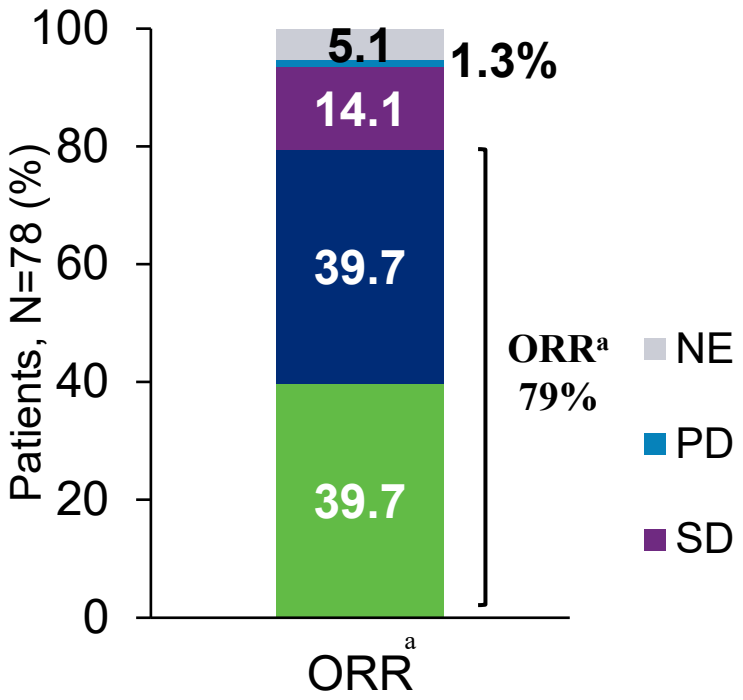
[a]Safety expansion 3 cohort is currently recruiting patients; [b]Study protocol has been amended to allow patients with higher-risk IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT

allo-HSCT, allogeneic hematopoietic stem cell transplantation; Aza, azacitidine; CMML, chronic myelomonocytic leukemia; D, Day; DLT, dose-limiting toxicity; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase 2 dose; Ven, venetoclax, WBC, white blood cell

NCT02942290

Garcia et al ASH 2020

Response Rates and Transfusion Independence



- 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)

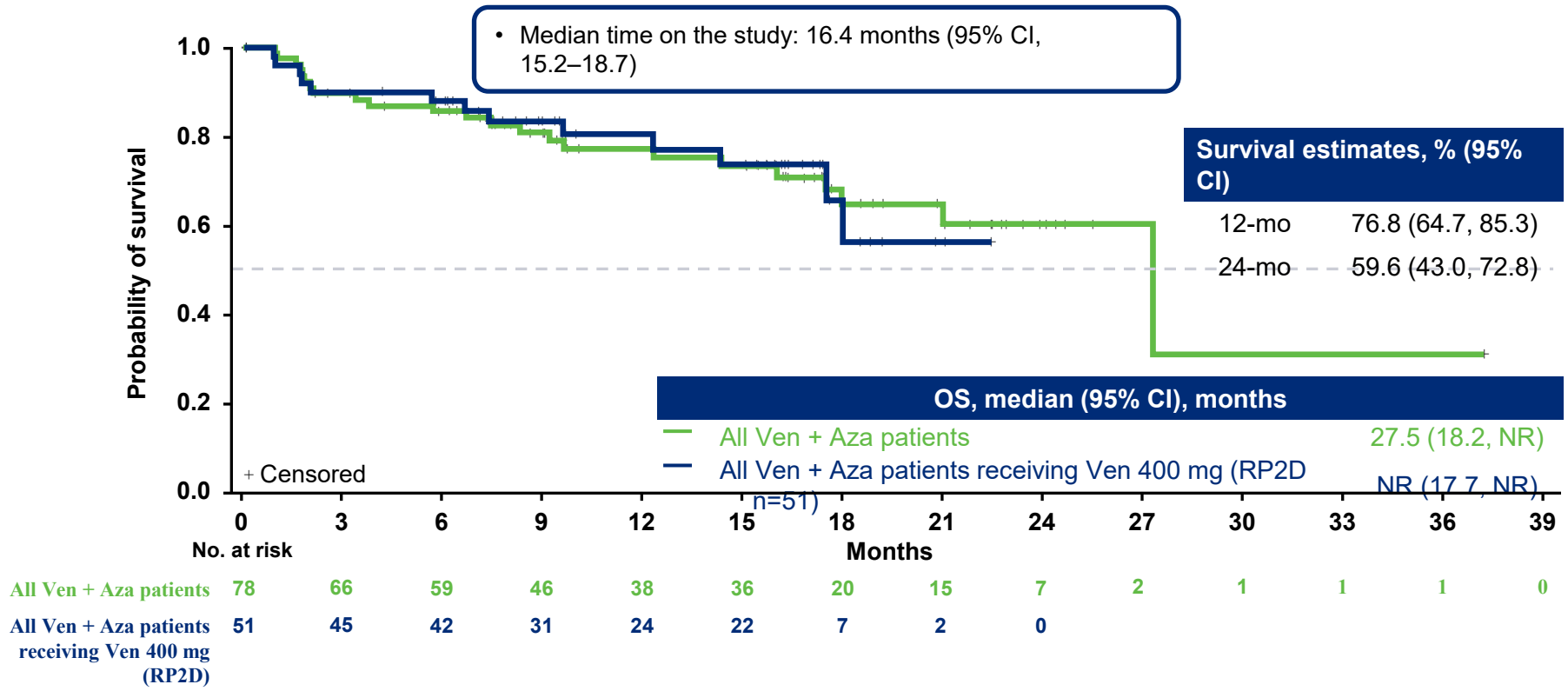
- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

[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

Garcia et al ASH 2020

OS for All Patients

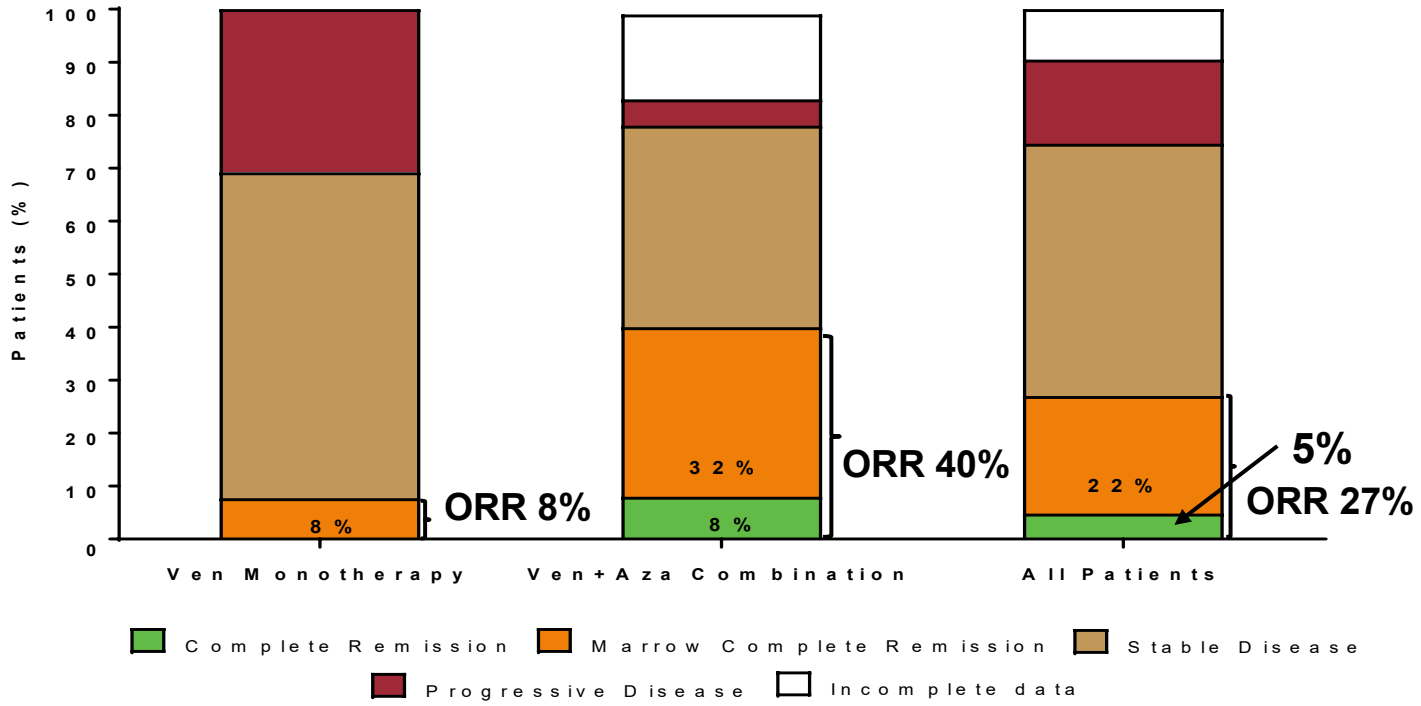


Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax

Data cutoff: June 30, 2020

Garcia et al ASH 2020

Ven+/- AZA not so active in R/R HR MDS

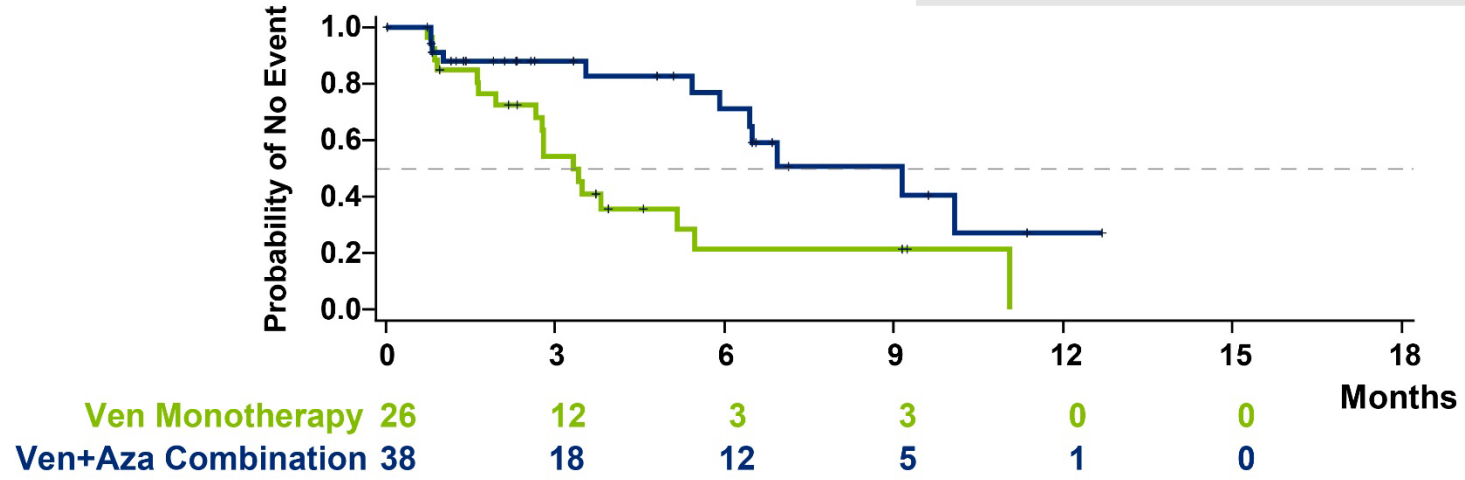


Data cutoff: Aug 30, 2019.

ClinicalTrials.gov. NCT02966782.
Zeidan A, et al. ASH 2019. Abstract 565.

Ven With or Without Aza in R/R MDS: PFS

Median PFS, Months (95% CI)	
Ven monotherapy	3.3 (2.7, 5.2)
Ven + Aza combination	9.1 (5.9, NE)



Ven monotherapy: Ven 400 mg or 800 mg; Ven + Aza combination: Ven doses 100, 200, or 400 mg + Aza 75 mg/m^2

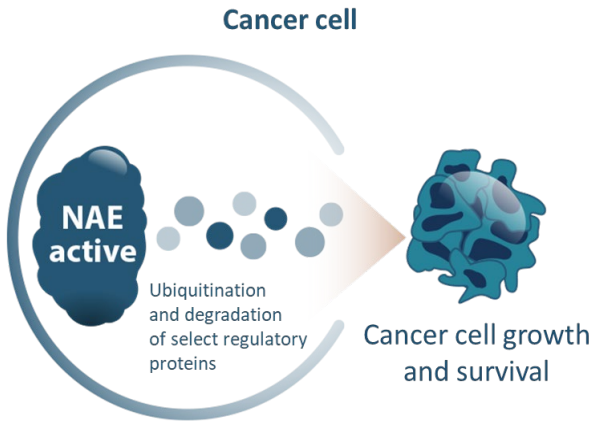
- Zeidan A, et al. ASH 2019. Abstract 565.

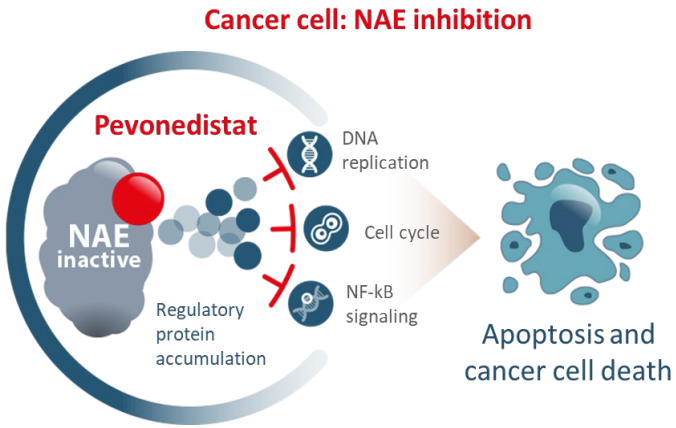
Data cutoff: Aug 30, 2019.

ClinicalTrials.gov. NCT02966782.
Zeidan A, et al. ASH 2019. Abstract 565.

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]



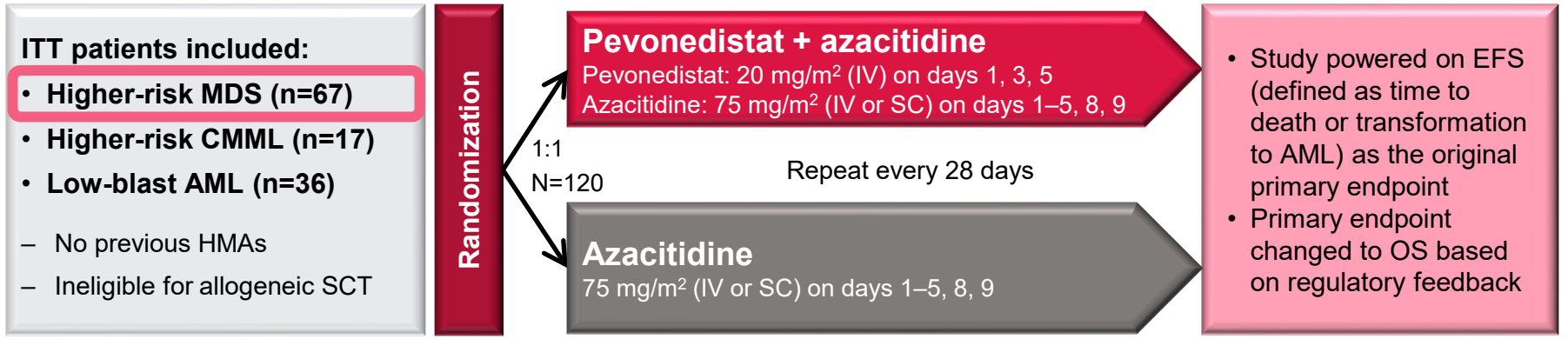


AML, acute myeloid leukemia; NAE, NEDD8-activating enzyme; NEDD8, neural precursor cell expressed, developmentally downregulated 8; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells.

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;136(Suppl. 1):653.

NCT02610777: phase 2, randomized, open-label, global, multicenter study



Results in the ITT population:[1]

- **Median EFS:** 21.0 vs 16.6 months (HR: 0.67; 95% CI: 0.42–1.05; P=0.076)
- **Median OS:** 21.8 vs 19.0 months (HR: 0.80; 95% CI: 0.51–1.26; P=0.334)

Analyses in patients with higher-risk MDS presented here:

- Focus on clinical and cytogenetic risk (IPSS-R), and genetic factors that could impact ORR and duration of response, as well as EFS and OS
- Post-hoc analysis of patients with MDS assessed as high-risk according to the combined Cleveland Clinic model formula, which incorporates both clinical and genetic factors[2]

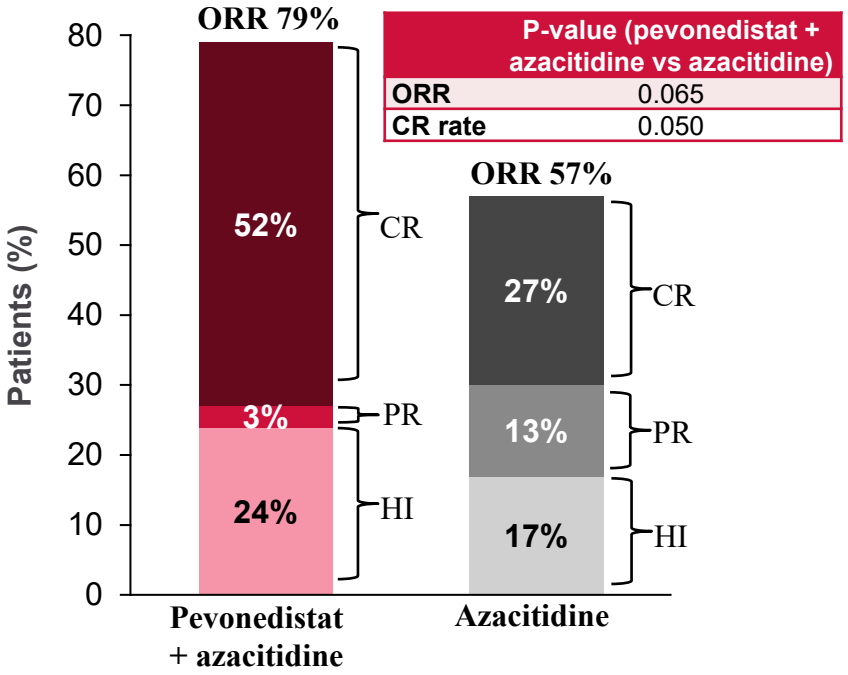
CI, confidence interval; CMML, chronic myelomonocytic leukemia; EFS, event-free survival; HMA, hypomethylating agent; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; ORR, overall response rate; OS, overall survival; SC, subcutaneous; SCT, stem cell transplant.

1. Ades L, et al. J Clin Oncol 2020;38(15_suppl):abstract 7506; oral presentation at ASCO 2020;
2. Nazha A, et al. Leukemia 2016;30:2214–20.

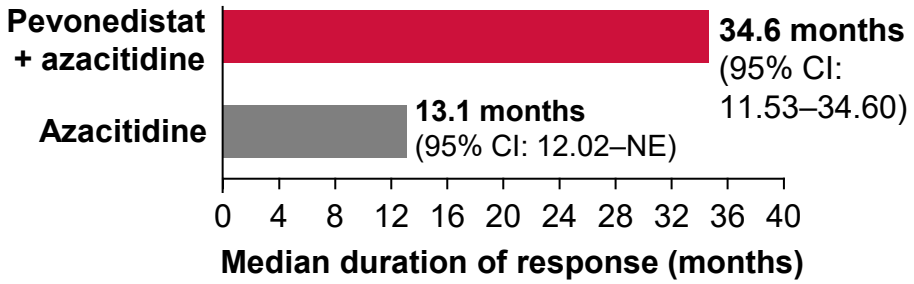
Sekeres MA, et al. Blood 2020;136(Suppl. 1):653.

CR rate was nearly doubled and median duration of response was almost tripled with pevonedistat + azacitidine

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



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



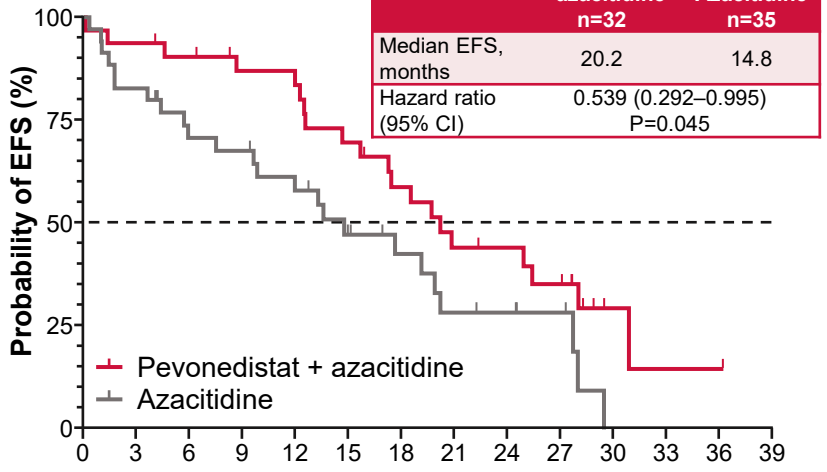
	Pevonedistat + azacitidine n=16	Azacitidine n=12
Median time to first CR or PR among responders, months (range)	3.83 (1.8–25.8)	4.29 (2.0–13.2)

CR, complete response; HI, hematologic improvement; NE, not evaluable; PR, partial response.

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

EFS and OS favored pevonedistat + azacitidine among patients with higher-risk MDS according to IPSS-R

EFS*

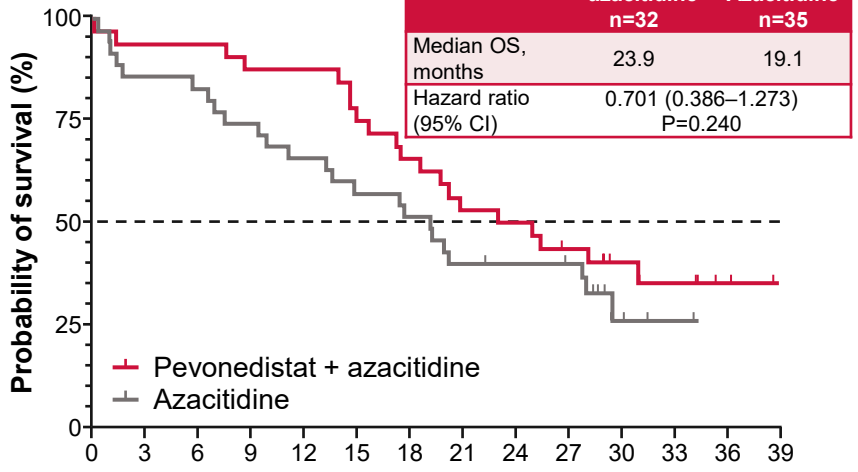


	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median EFS, months	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	

Number at risk

Pevonedistat + azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	12	9	6	5	4	0	0	0	0

OS



	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	

Number at risk

Pevonedistat + azacitidine	32	30	30	28	28	24	21	17	16	13	8	5	2	0
Azacitidine	35	30	29	26	23	20	18	14	13	13	3	1	0	0

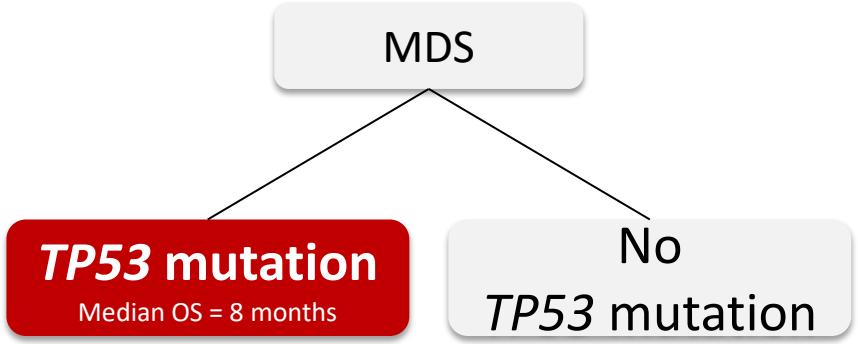
- Longer EFS was particularly evident in patients with IPSS-R-defined very-high-risk MDS (n=26; HR: 0.47; 95% CI: 0.19–1.18) and high-risk MDS (n=21; HR: 0.53; 95% CI: 0.17–1.72)

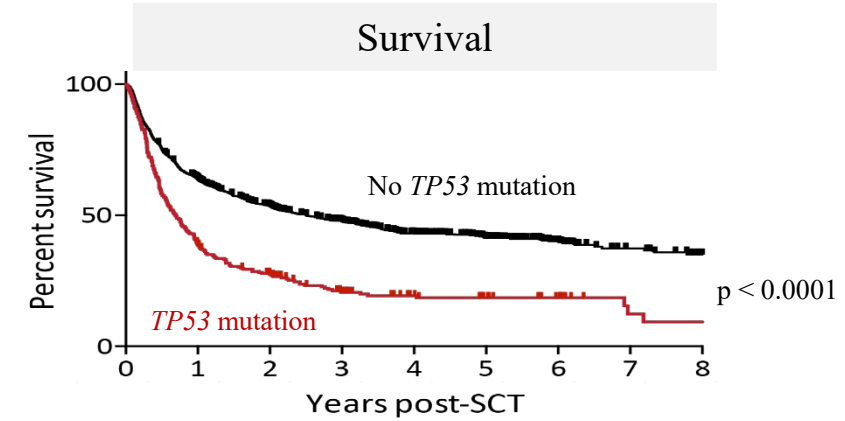
*EFS defined as time to death or transformation to AML in higher-risk MDS.

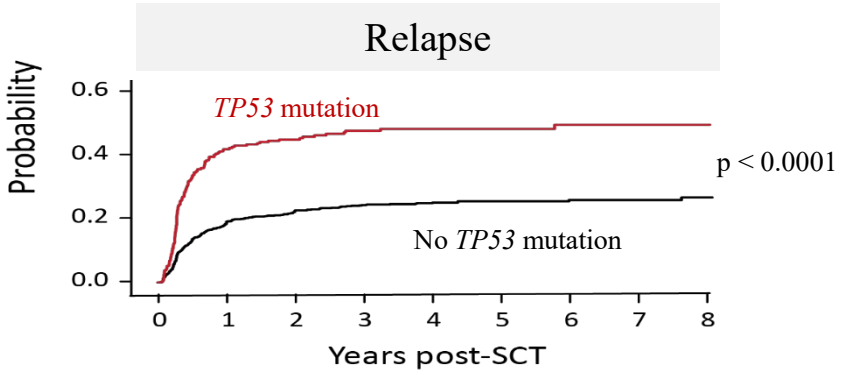
Sekeres MA, et al. Blood 2020;136(Suppl. 1):653.

TP53 mutated MDS

Poor prognosis Post-SCT due to early relapse



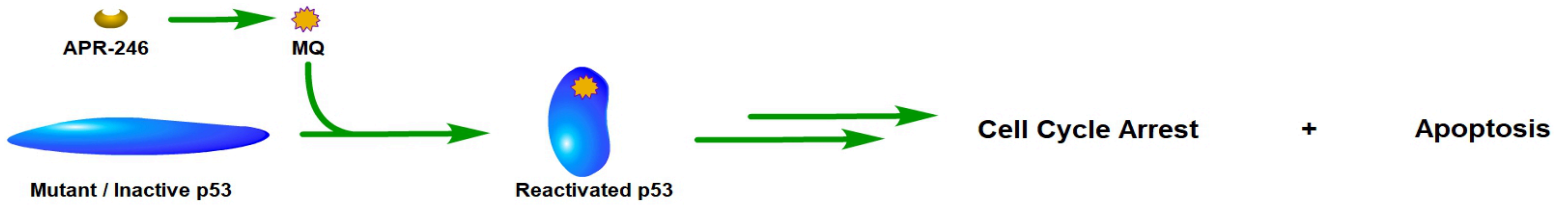


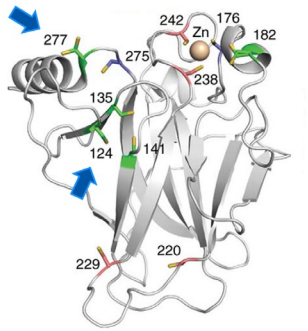


Cutler C, ASH 2020: donor v no donor higher risk MDS: n=384 48 v 27% 3 y OS in age 50-75

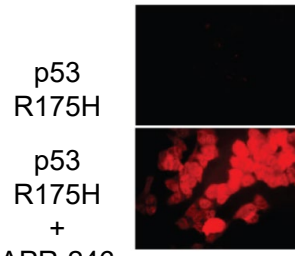
Lindsley C, et al. *N Engl J Med.* 2017;376(6):536-547.

Targeting TP53 Mutations in MDS/AML via APR-246

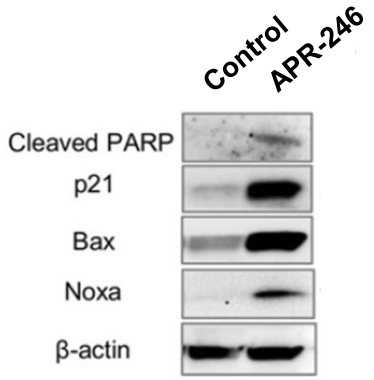




APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



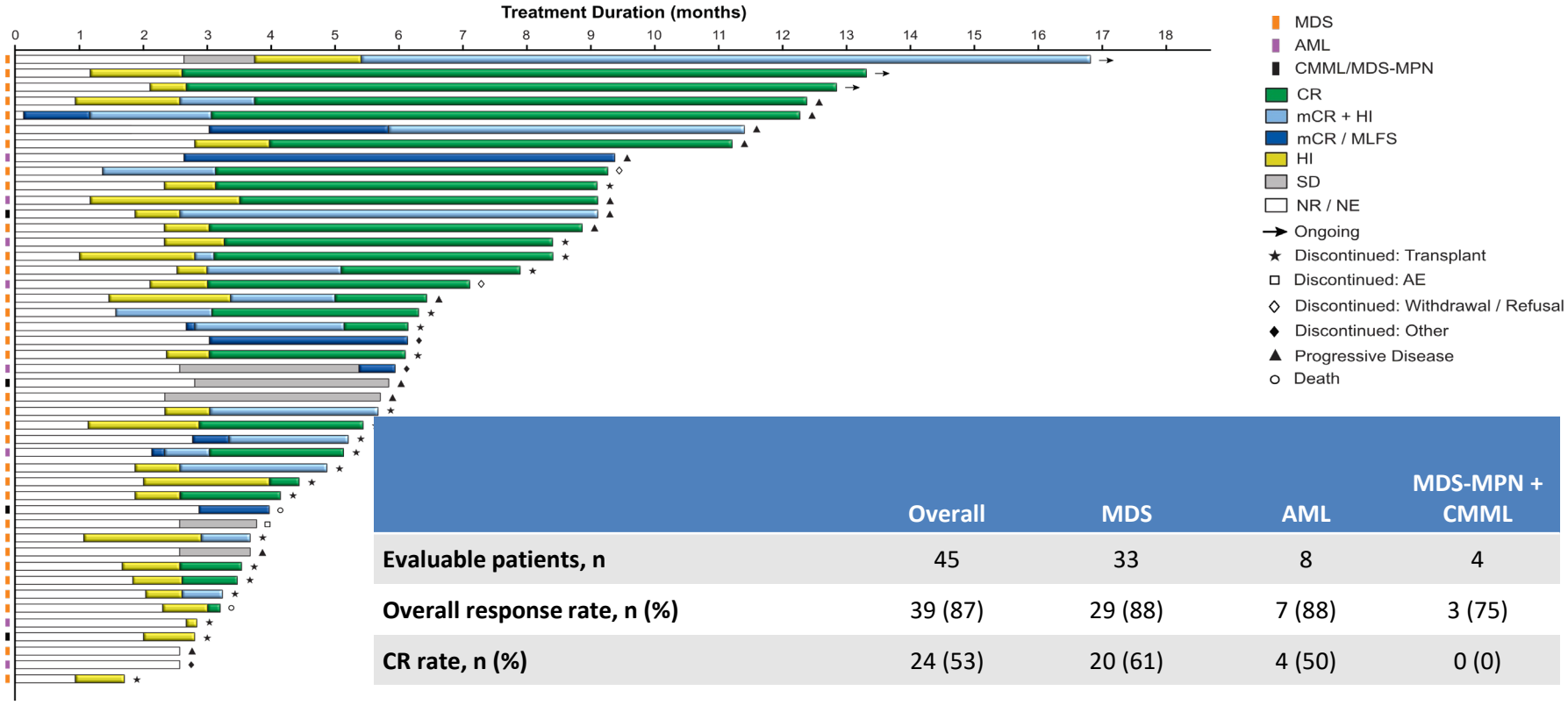
…and triggers cell cycle arrest and apoptosis

A. Fersht et al. (2010) Pnot. Sci; Q. Zhang et al. (2018) Cell Death Disease; H. Furukawa et al. (2018) Cancer Sci.

Sallman D, et al, ASH 2019

Response to Treatment in Evaluable Patients (n=45)

APR-246+AZA

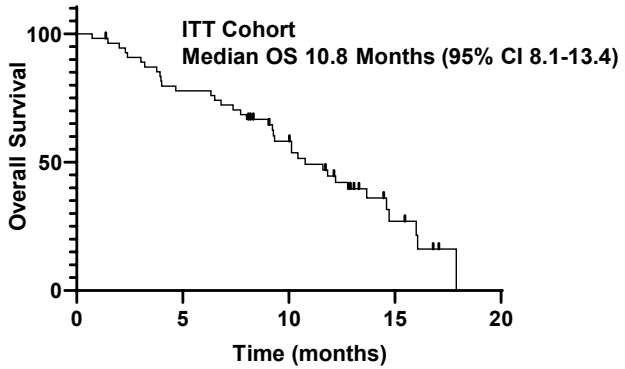


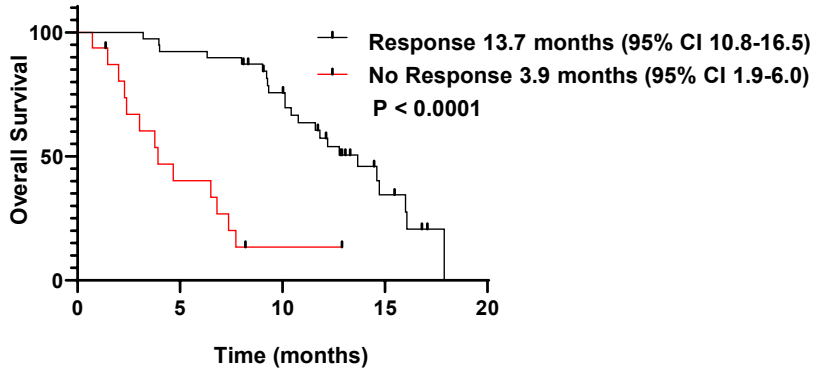
	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

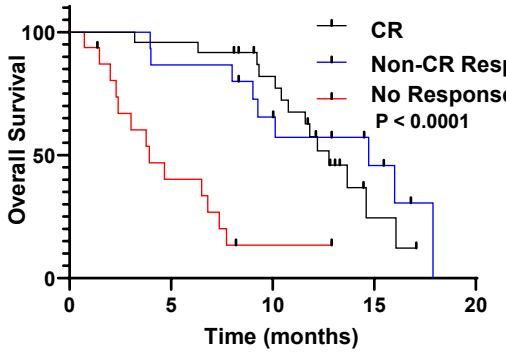
- Median duration of follow-up = 10.8 months

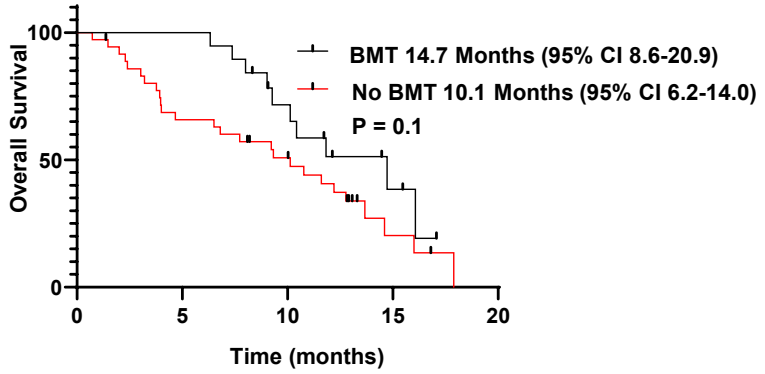
Sallman D, et al, ASH 2019

Overall Survival (ITT): APR-246+aza







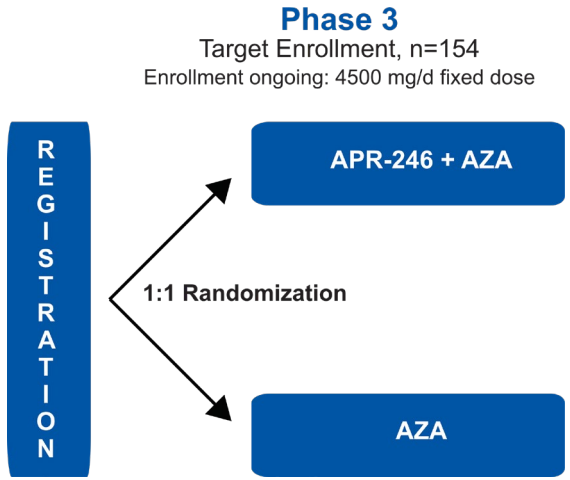


44% cleared TP53 to <5% VAF

Sallman D, et al. ASH 2019

Pivotal Phase 3 MDS Trial in *TP53*-Mutant MDS

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



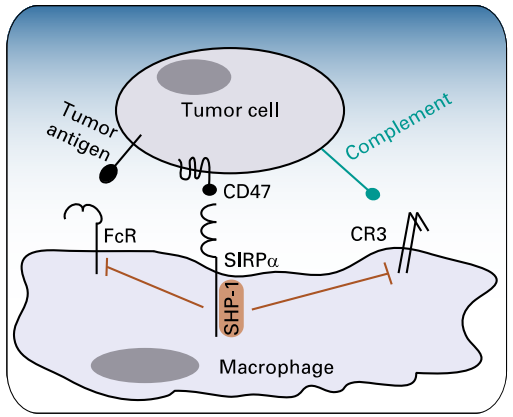
- ClinicalTrials.gov. NCT03745716.
- Intermediate-/high-/very high-risk *TP53*-mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

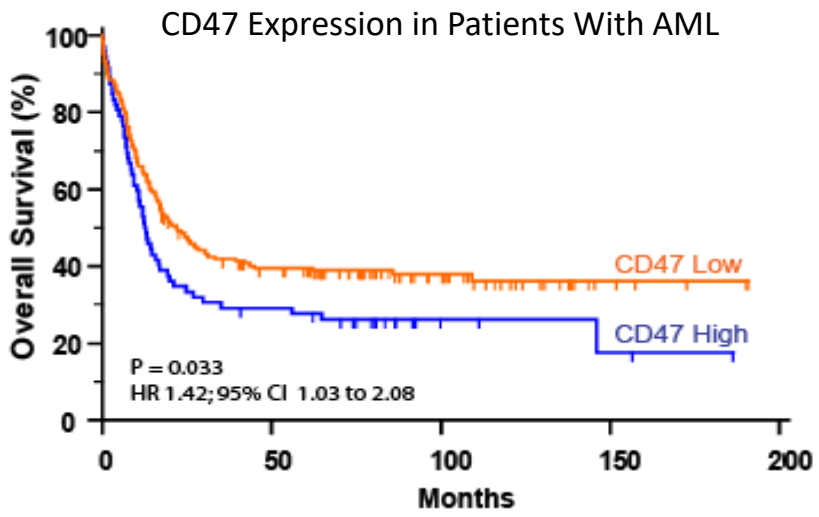
- Status
  - Enrollment commenced in January 2019
  - Currently targeting full enrollment in first quarter 2020
  - Fast Track Designation for MDS: granted by FDA in April 2019
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019

Press Release 12/20: primary EP Not met

CD47

- Major macrophage immune checkpoint and "do not eat me" signal in myeloid malignancies including MDS and AML

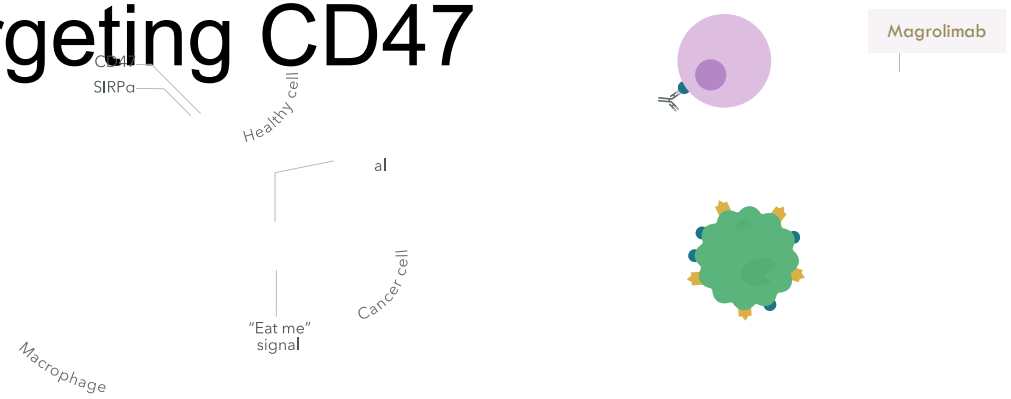




- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in patients with AML

Veillette, A, et al. *J Clin Oncol*. 37:1012-1014; Chao MP, et al. *Curr Opin Immunol.* 2012;24:225-32; Majeti R, et al. *Cell.* 2009 Jul 23;138(2):286-99.; Sallman D, et al. ASH 2019. Abstract 569.

Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47



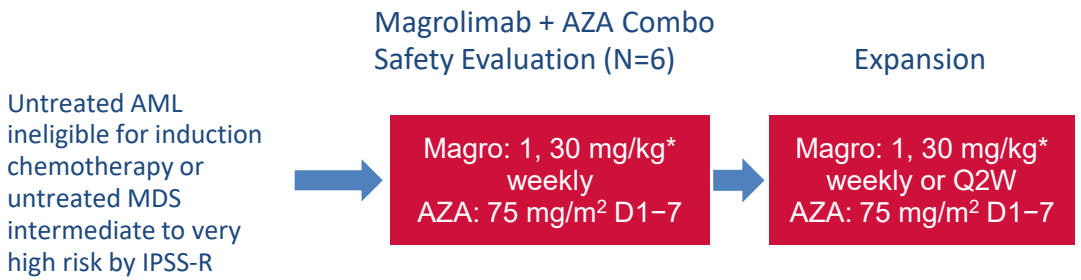
CD47 is a “do not eat me” signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion

Magrolimab, an IgG4 anti-CD47 monoclonal antibody (mAb), eliminates tumor cells through macrophage phagocytosis

Magrolimab is being investigated in multiple cancers with >500 patients dose

Sallman D, et al ASH 2020

5F9005 Study Design: Magrolimab in Combination With AZA in AML and MDS



Primary Objectives

1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary Objectives

1. Pharmacokinetics, pharmacodynamics, and immunogenicity 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

A magrolimab priming dose (1 mg/kg) and dose ramp-up were utilized to mitigate on-target anemia

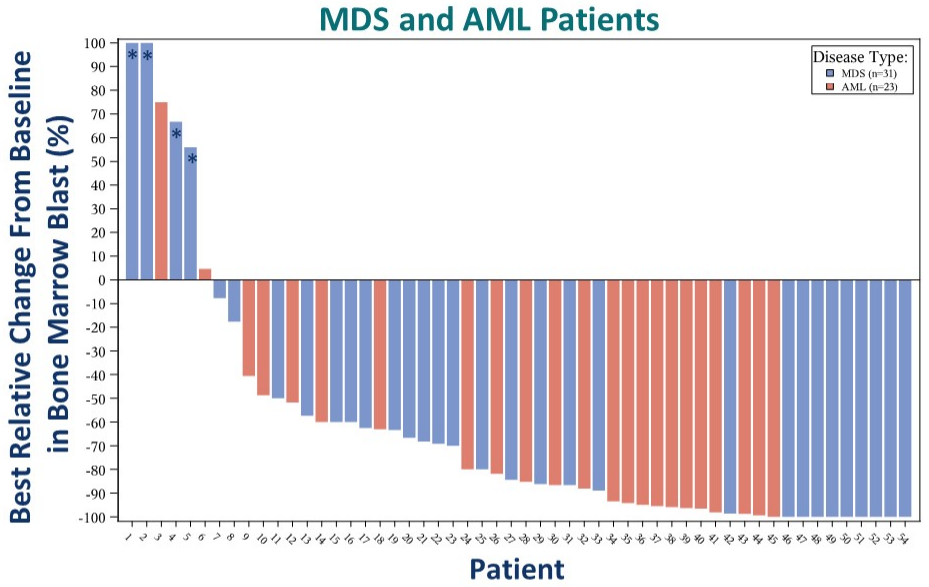
Sallman D, et al , ASH 2020

*Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing.
IPSS-R: Revised International Prognostic Scoring System.

Magrolimab + AZA Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L 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%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN 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) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (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%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Note: on target anemia mitigated by priming

Sallman D, et al, ASCO 2020

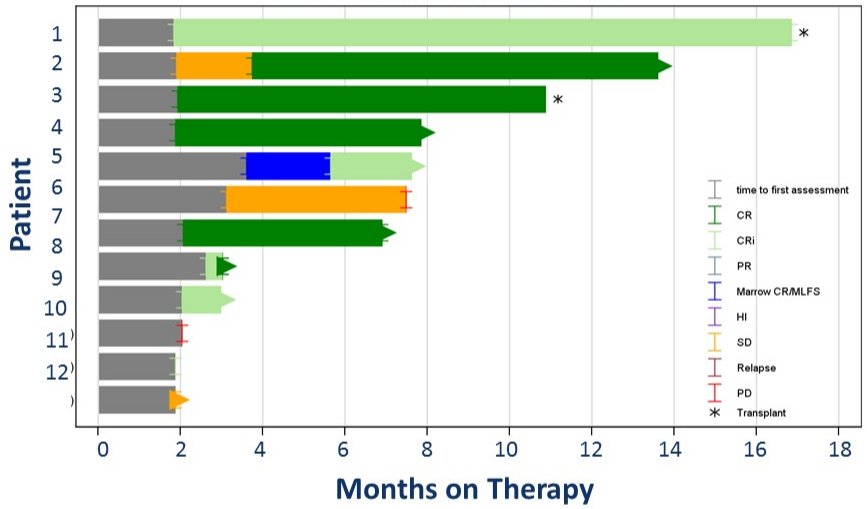
Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

Efficacy in *TP53*-Mutant Patients

Best Overall Response	AML *TP53* Mutant (N=12)	MDS *TP53* Mutant (N=4)
ORR	9 (75%)	3 (75%)
CR	5 (42%)	2 (50%)
CRi/marrow CR	4 (33%)	1 (25%)
Complete cytogenetic response *	4/8 (50%)	3/3 (100%)
MRD negative of responders	4/9 (44%)	0
Median duration of response (months)	Not reached (0.03+ – 15.1+)	Not reached (0.03+ – 5.2+)
Survival probability at 6 months	91%	100%
Median follow-up (range) (months)	8.8 (1.9 – 16.9)	7 (4.2 – 12.2)

*Responding patients with abnormal cytogenetics at baseline.

TP53-Mutant AML Patients

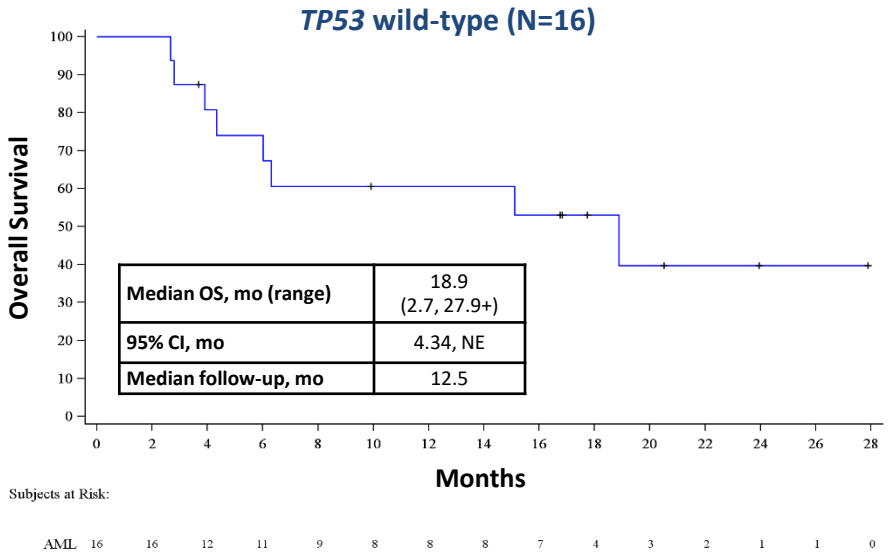


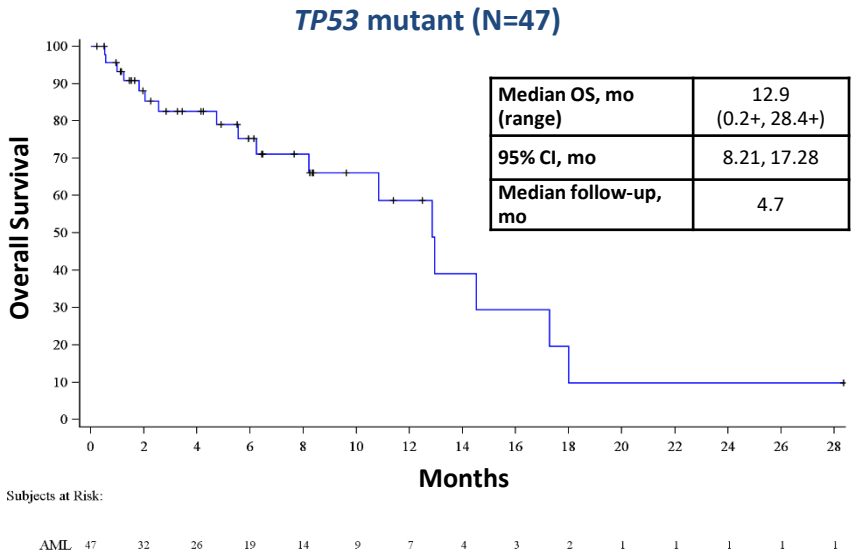
- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + AZA in AML: ORR 47%, DOR 5.6 mo, OS 7.2 mo[1]

1. DiNardo CD, et al. *Blood.* 2019;133(1):7-17.

9/16 pts cleared TP53 variant allele frequency (VAF) to less than 5% Sallman D, et al, ASCO 2020

Preliminary Median Overall Survival Is Encouraging in Both *TP53* Wild-Type and Mutant Patients





The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients

This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,[1,3] 5.2–7.2 mo in patients who are *TP53* mutant[2,3])

Additional patients and longer follow-up are needed to further characterize the survival benefit

NE, not evaluable.

1. DiNardo CD, et al. *N Eng J Med*. 2020;383(7):617-629. 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual). 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

Sallman D, et al , ASH 2020

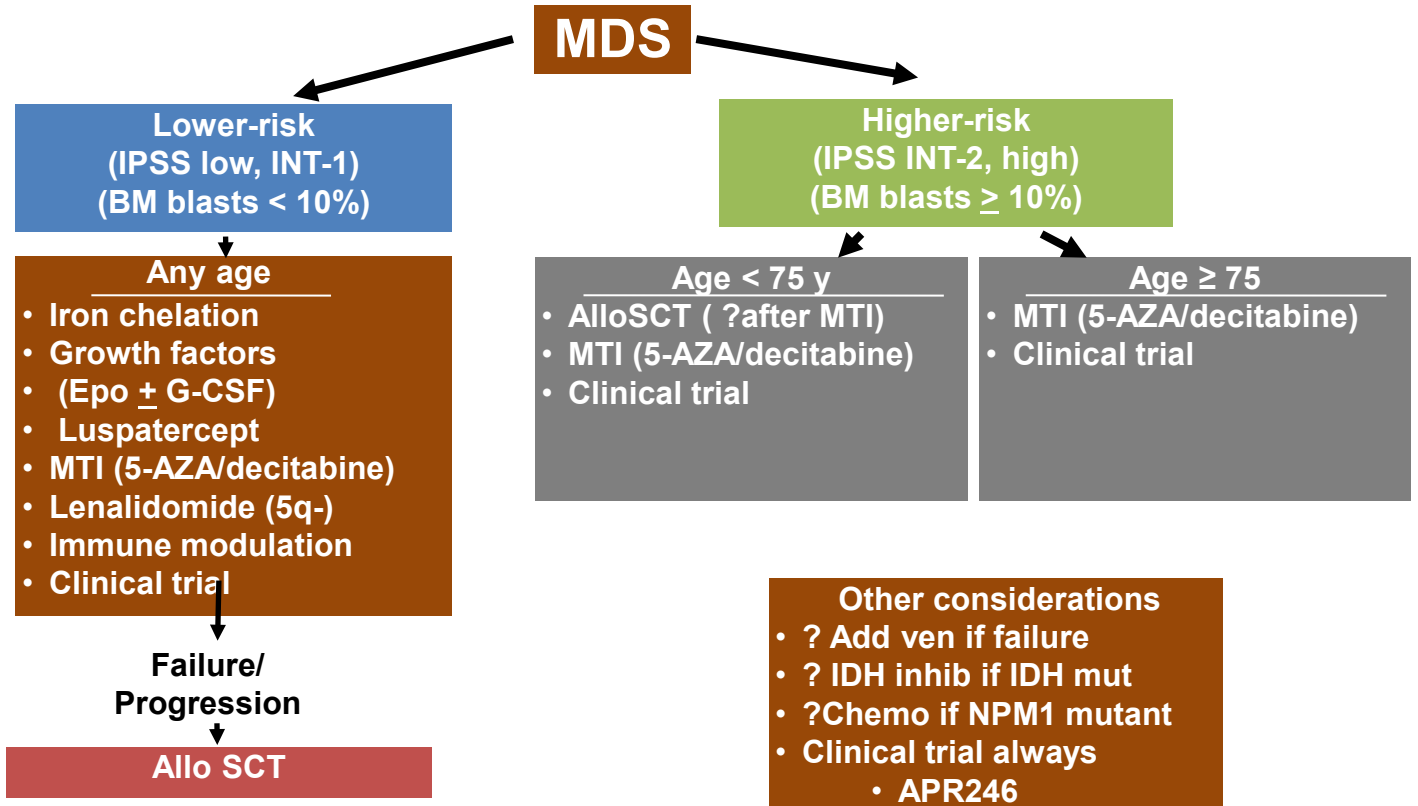
Checkpoint Inhibition: Sabatolimab (TIM-3 Antibody) +HMA for High Risk MDS

- 48 AML, 39 MDS, 12 CMML
- Most common Aes F&N, anemia/thrombocytopenia/neutropenia
- Few immune AAs >g3
- 2.1mo median TTR
- Estimated 12mo PFS 44%

	TIM-3 Ab+ decitabine	TIM-3 Ab +azacitidine
n	19	20
evaluable	18	17
CR	33%	12%
Marrow CR	17%	29%
SD	11%	23%
ORR	61%	65%

Brunner A, et al, ASH 2020

Proposed Treatment Algorithm for Patients With MDS: 2021



- Modified from Atallah. *Cancer Inv*. 2008;26:208-216.

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  - **Andrian Penicaud, PA, Kat Edmonds, NP, Sarah Cahill, PA, Mary Girard, PA, Elizabeth Herrity, DNP**
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  - **Worldwide: C Schiffer, T Fischer, H Dohner, K Dohner, C Thiede, R Schlenk, and others**
- **Slides**
  - **G Garcia-Manero, D Steensma, D Sallman, J Garcia**

The End

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