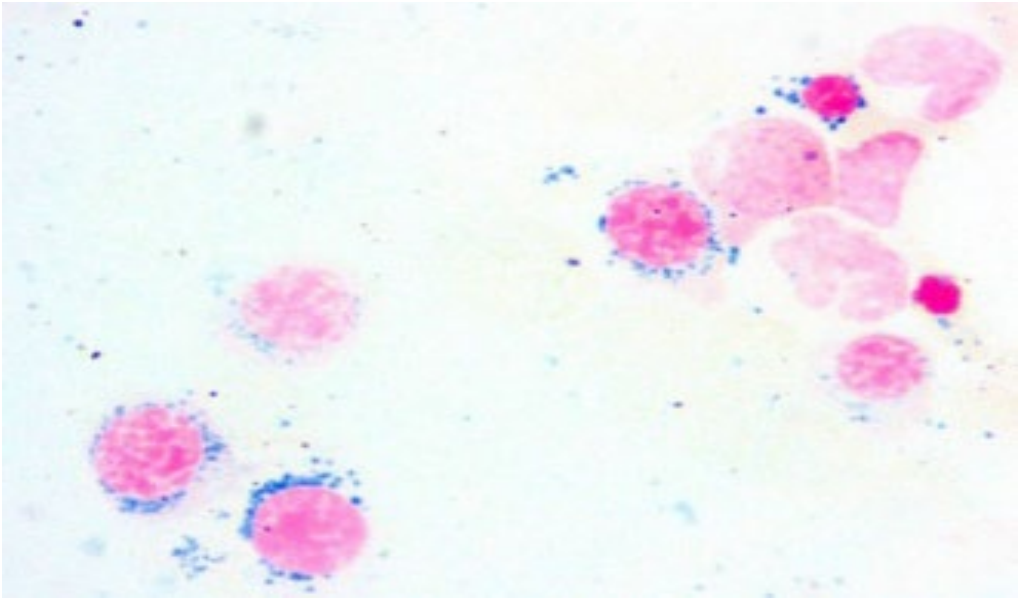
Myelodysplastic Syndromes: What is new in 2020?



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Disclosures- Richard M. Stone, MD

- **Consulting relationships past three years:**
  - **AbbVie*; Actinium, Agios*; Amgen; Argenix (DSMB); Arog*; Astellas; AztraZenaca; Biolinerx, Celgene (includes DSMB and steering committee); Elevate Bio, Fujifilm, Janssen; 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**

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Myelodysplastic Syndromes: Outline

- Genetics and Prognosis
- 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
- Therapy of Higher risk disease
  - HMA (including now: Oral decitabine/cytidine deaminase inhibitor=ASTX727), alloSCT if possible, remains the standard
    - Maybe
      - » add ventoclax, IDH inhibitor-CSF
    - Horizon
      - » CPI, TP53 refolding, aCD47

Recently Approved

Risk Assessment in Myelodysplastic Syndromes

Key Information for MDS Risk Assessment in 2020
Host Factors
• **Age**
• **Comorbid** conditions
• **Performance status**
Disease Factors
• Proportion of marrow **blasts**
• Number and degree of peripheral blood **cytopenias**
• **Cytogenetics** / karyotype
• **Transfusion** burden
• Other marrow features: presence of heavy marrow **fibrosis**, ring sideroblasts (if low risk/only anemic – to distinguish RA from RARS)

While not yet routinely part of risk assessment, molecular features will become critical soon.

Internarional Prognostic Scoring System (IPSS) (1997) Risk Stratification

	Score				
Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5%	5%-10%	--	11%-20%	21%-30%
Karyotype class*	Good	Intermediate	Poor	--	--
# of cytopenias**	0 or 1	2 or 3	--	--	--

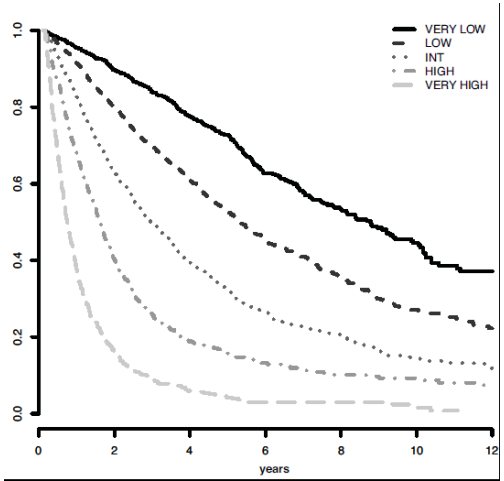
* Karyotype class: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes; ** Cytopenias: Hb < 10 g/dL, ANC < 1800/uL, platelets < 100,000/uL

Risk Groups				
	Low	Int-1	Int-2	High
IPSS	0	0.5-1.0	1.5-2.0	2.5-3.5

Adapted from Greenberg P, et al. *Blood*. 1997:89(6):2079-2088.

IPSS-R

Risk group	Points	% patients (n=7,012; AML data on 6,485)	Median survival, years	Median survival for pts under 60 years	Time until 25% of patients develop AML, years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermed	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7



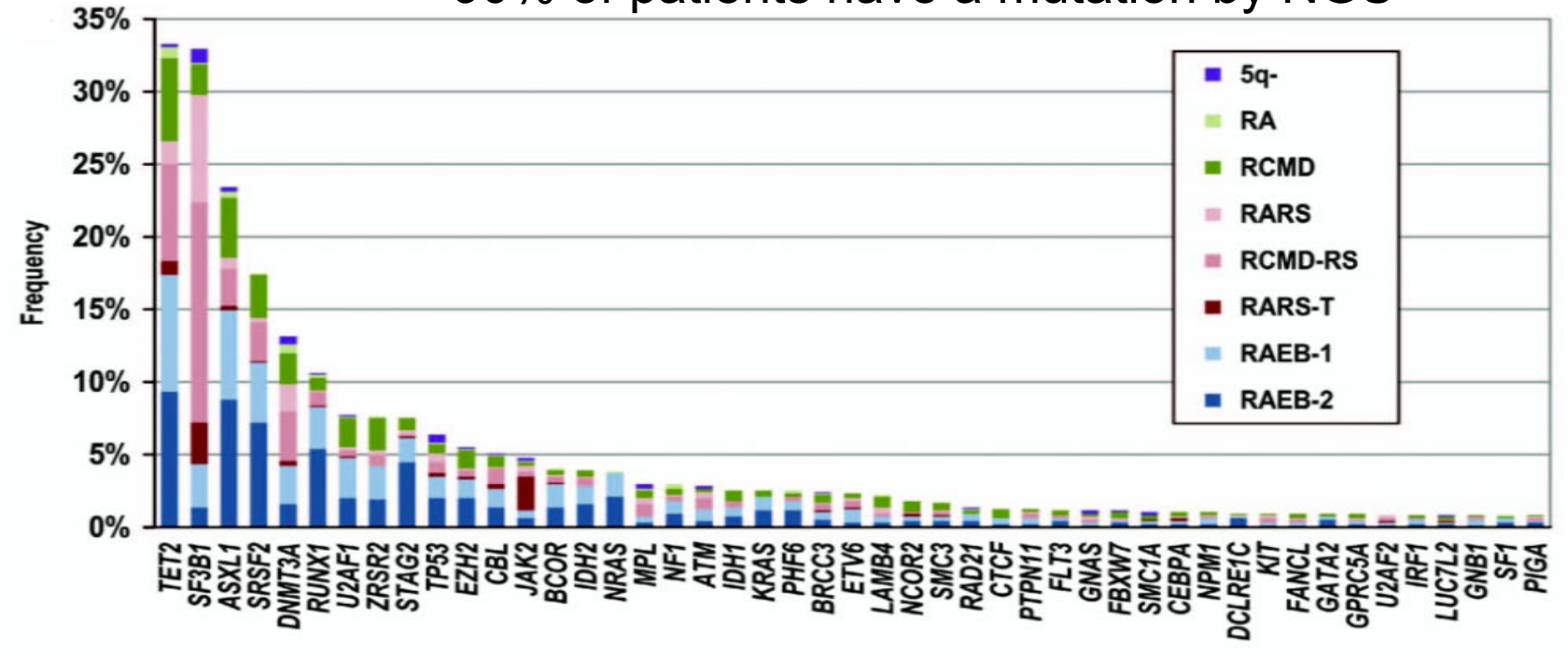
Based on cytogenetics, marrow blasts, hgb, ANC, plt

Using IPSS-R:
27% of IPSS lower risk "upstaged"
18% of IPSS higher risk "downstaged"

Greenberg P et al *Blood* 2012 Sep 20;120(12):2454-65.

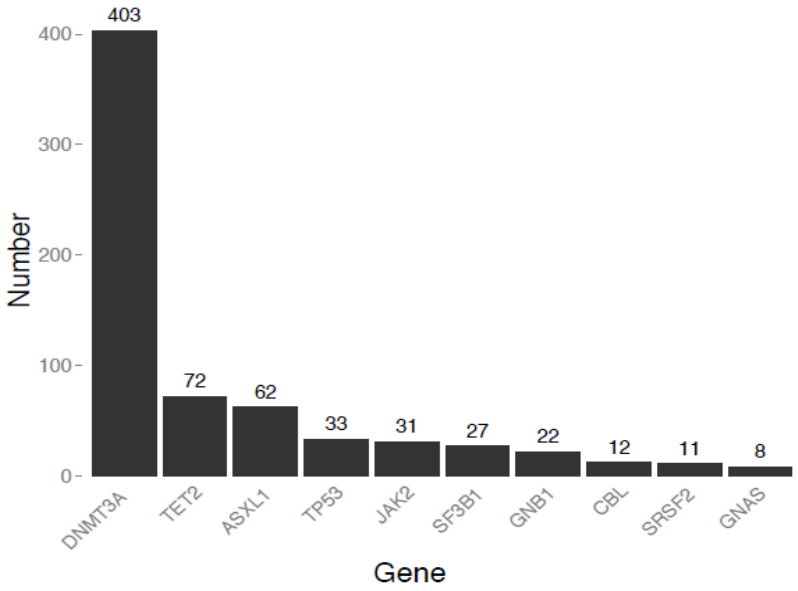
Recurrent Genetic Mutations in MDS

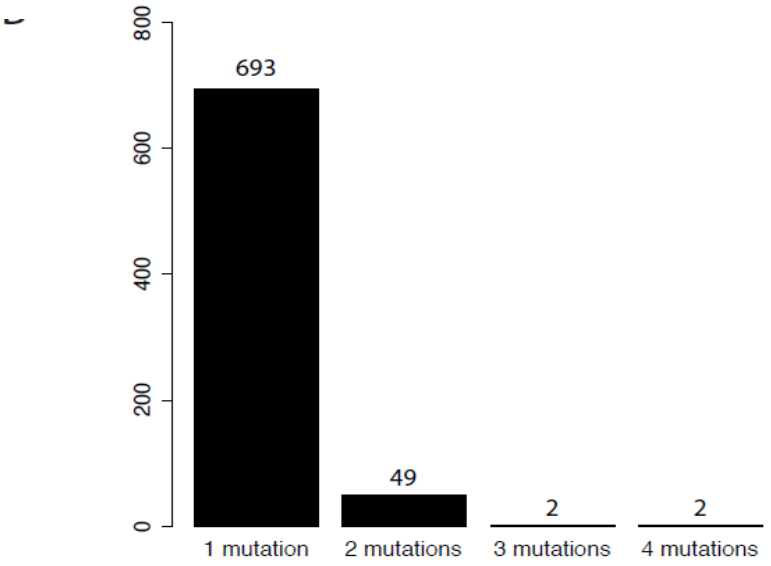
~90% of patients have a mutation by NGS



Haferlach et al., *Leukemia* (2014) 28, 241–247

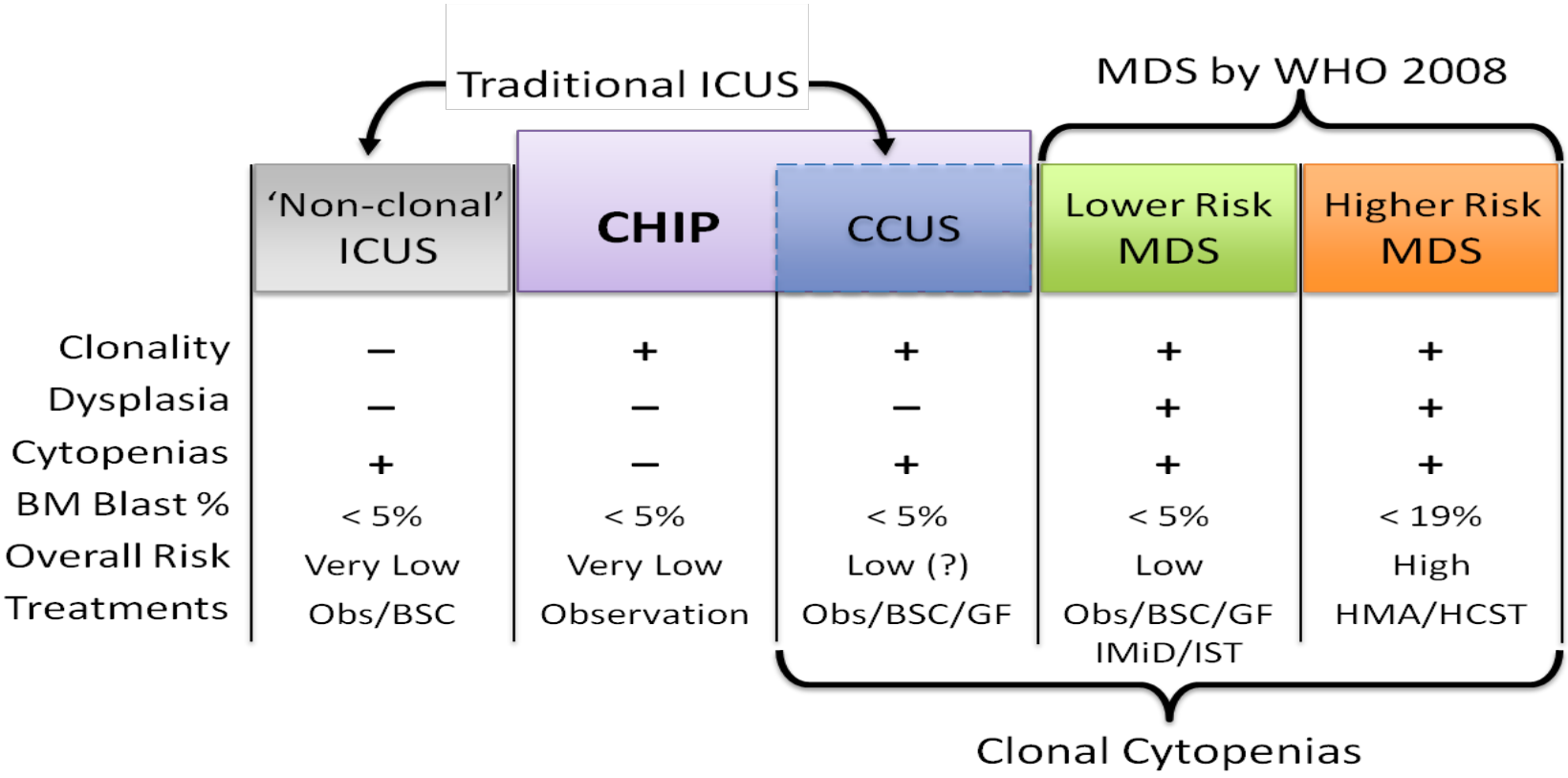
“CHIP” Mutation Distribution
(increases with age ;12% by age 80)



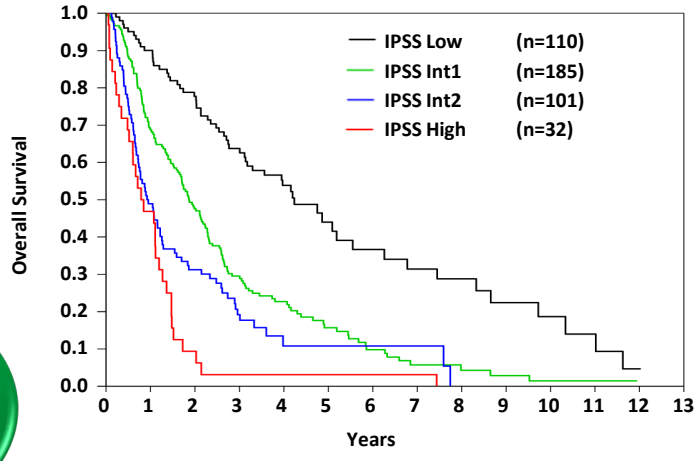


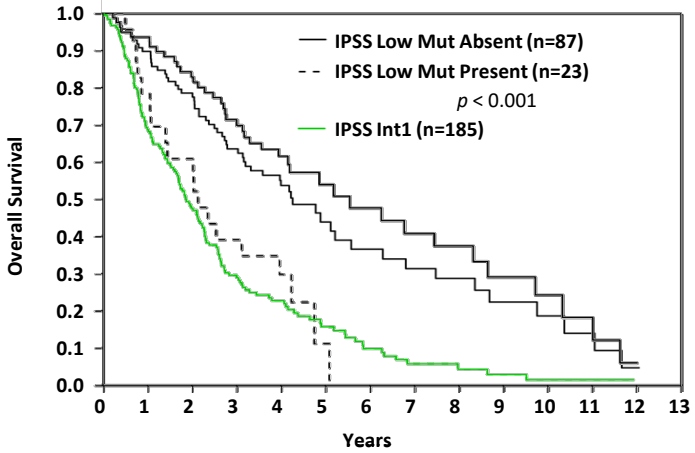
Jaiswal S et al *N Engl J Med* 2014

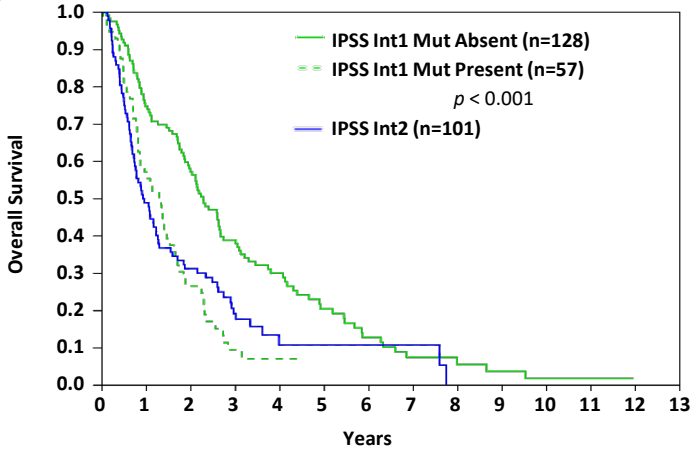
Clonal **H**ematopoiesis of **I**ndeterminate **P**otential (CHIP)

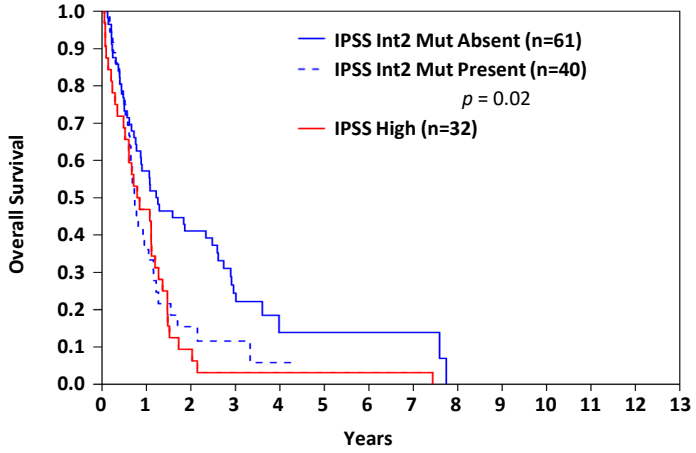


Impact of Mutations by IPSS Group









Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

Lenalidomide Clinical Trials in MDS

Rx of Anemia is lower MDS beyond ESA

Eligibility:

>2 U pRBCs/8 weeks

Platelet >50 x 10^9/L

ANC >500/uL

MDS-001

N = 43, Phase I/II initiated Feb 2002

List A et al *NEJM* 2005

Del(5q)

MDS-003

N=148, Phase II initiated July 2003

List A et al *NEJM* 2006

67% transfusion independence

Median duration of response >2 years

45% complete cytogenetic remission

MDS-004

N=205, Phase III initiated July 2005

Fenaux et al *Blood* 2011

No difference in dose reductions w/ 5 vs 10 mg.
↑cytogenetic CR with 10 mg 21/28 d vs 5 mg/d

Non-del(5q)

MDS-002

N = 214, Phase II initiated July 2003

Raza A et al *Blood* 2008

26% transfusion independence

Median duration of response 41 weeks

9% complete cytogenetic remission

MDS-005

N = 239, Phase III initiated Nov. 2009

Santini et al J Clin Oncol 2016

27% v 3% TI, 31 wk resp duration
No diff in QOL overall, but resp assoc w imp QOL

MDS: New Approaches for Lower Risk-I

- **Lenalidomide (10 mg/d x 21d)+Erythropoietin (60k/wk), at 4 weeks higher major erythroid response (26%) than Lenalidomide alone (10%) in non del 5q- (p=0.018); E2905**
  - List et al., ASH 2016, abstract 223; Toma A, et al, Leukemia 2016, 30: 897-905.
- **Activin trap: luspateracept (Now approved in RARS!)**
  See subsequent slides
  - Fenaux et al., NEJM 2020

MDS: New Approaches for Lower Risk-II

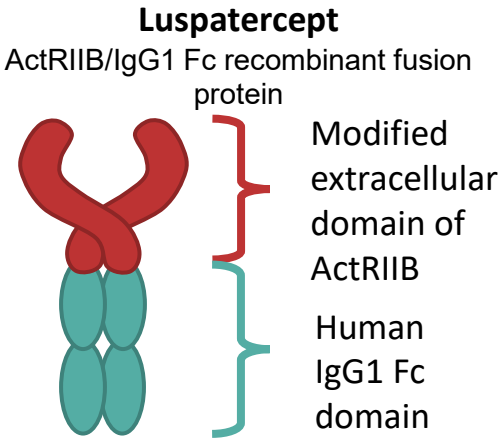
- **Reset Oxygen sensing: roxudostat**
  - **Prevents HIF1α degradation**
  - **Based on work done by Wm Kaelin DFCI, Semenza, JHU and Ratcliffe, Crick**

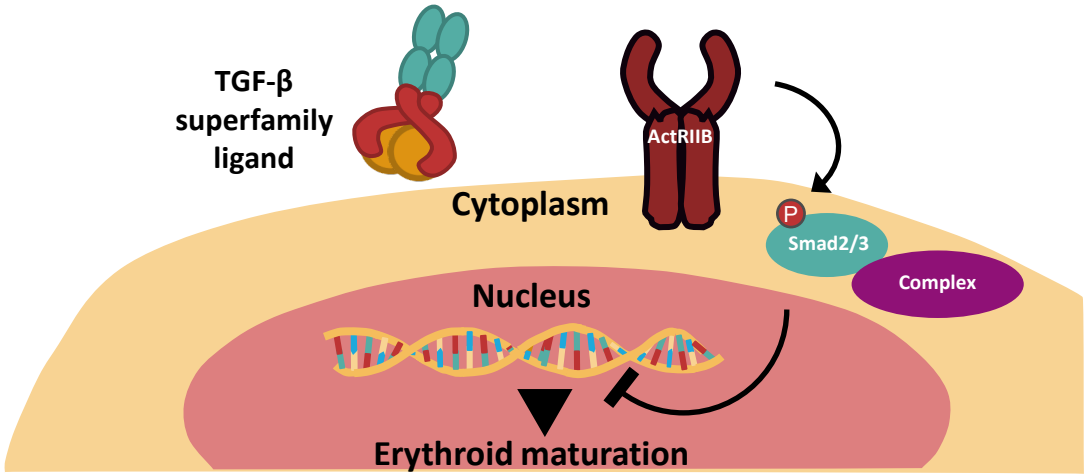
  - Some responses in MDS: Henry et al, ASH 201

- **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
- **Splicesome inhibitors in those with U2AF1, SF3B1, SRSF2, ZRSR2 mutations (First study H3B8800- not active (Steensma ASH 2019)**

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

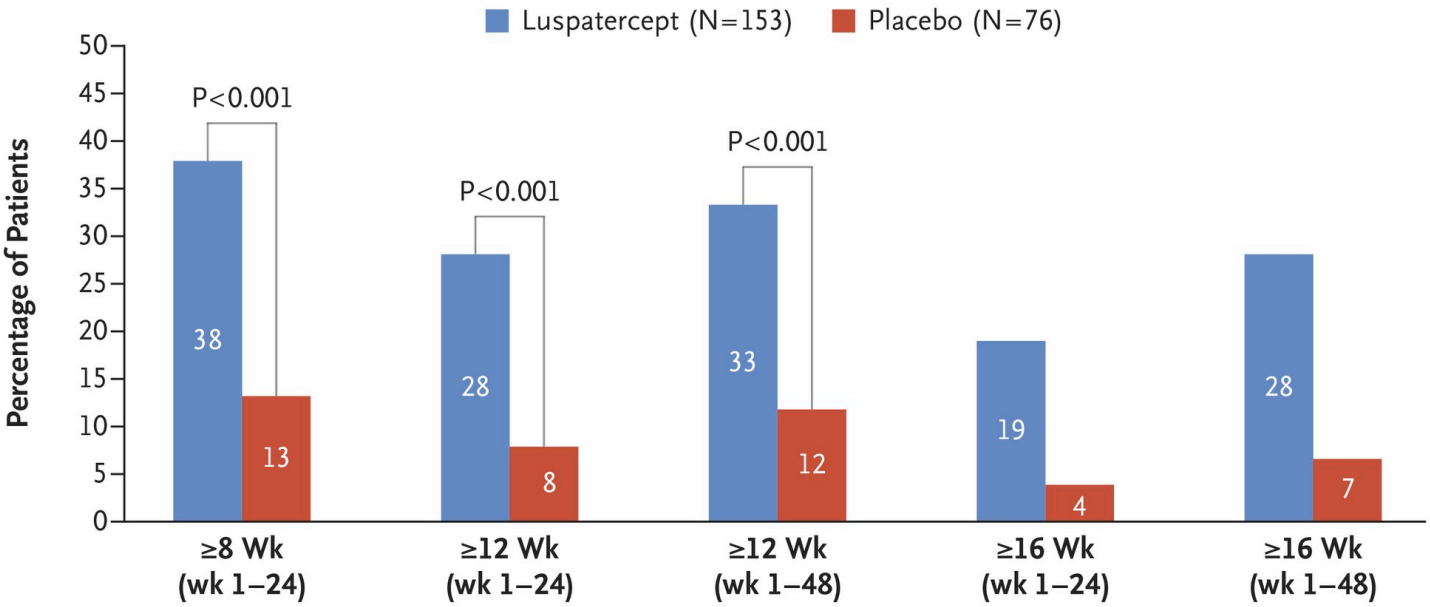
Disease & Response Assessment week 24 & q 6 months Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; No crossover allowed

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

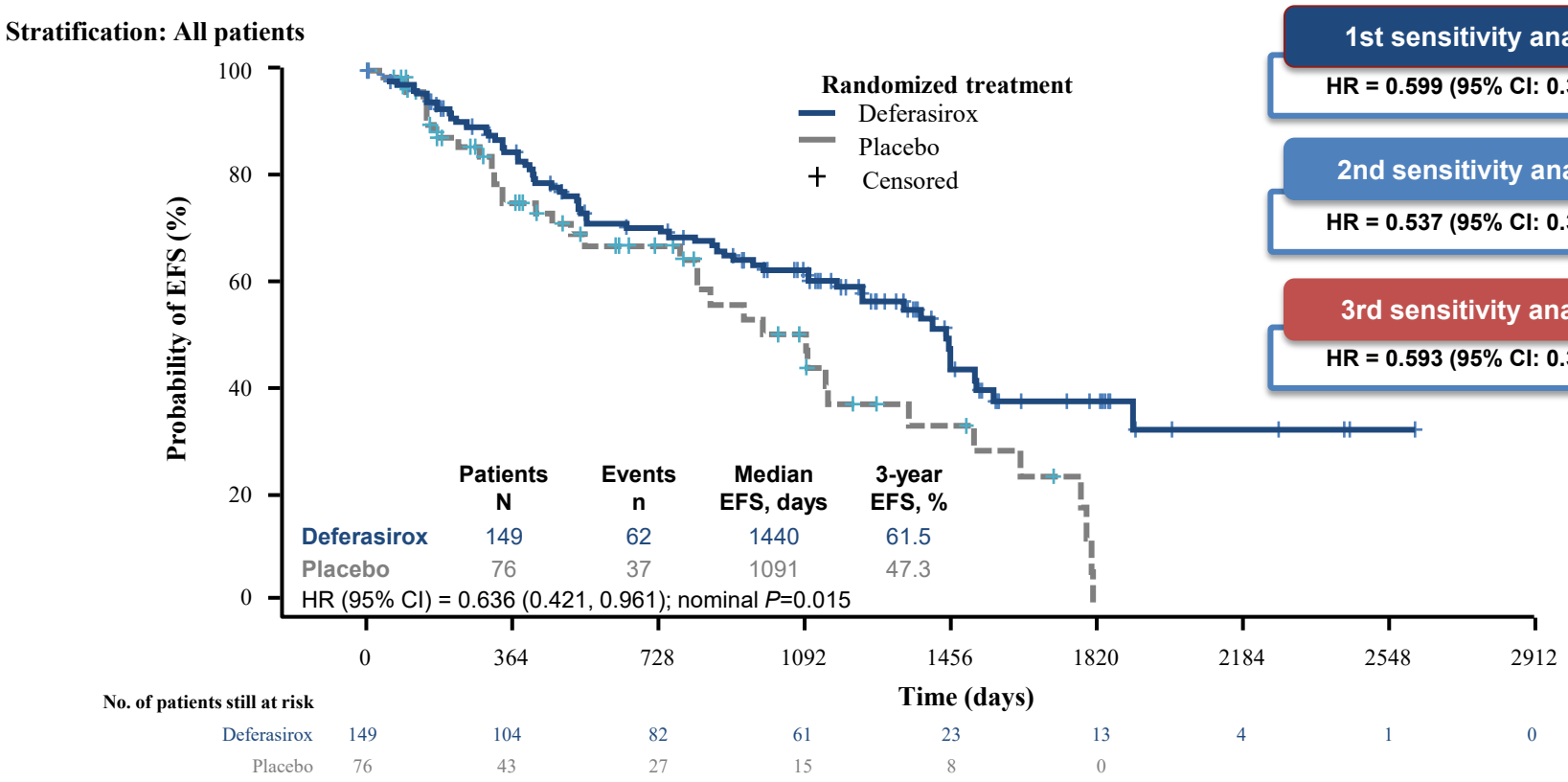


No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

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

Iron Chelation may have a role in heavily transfused lower risk pts 2:1 randomization of defersirox v placebo with primary EP of time to an event (CHF, LFT, AML)

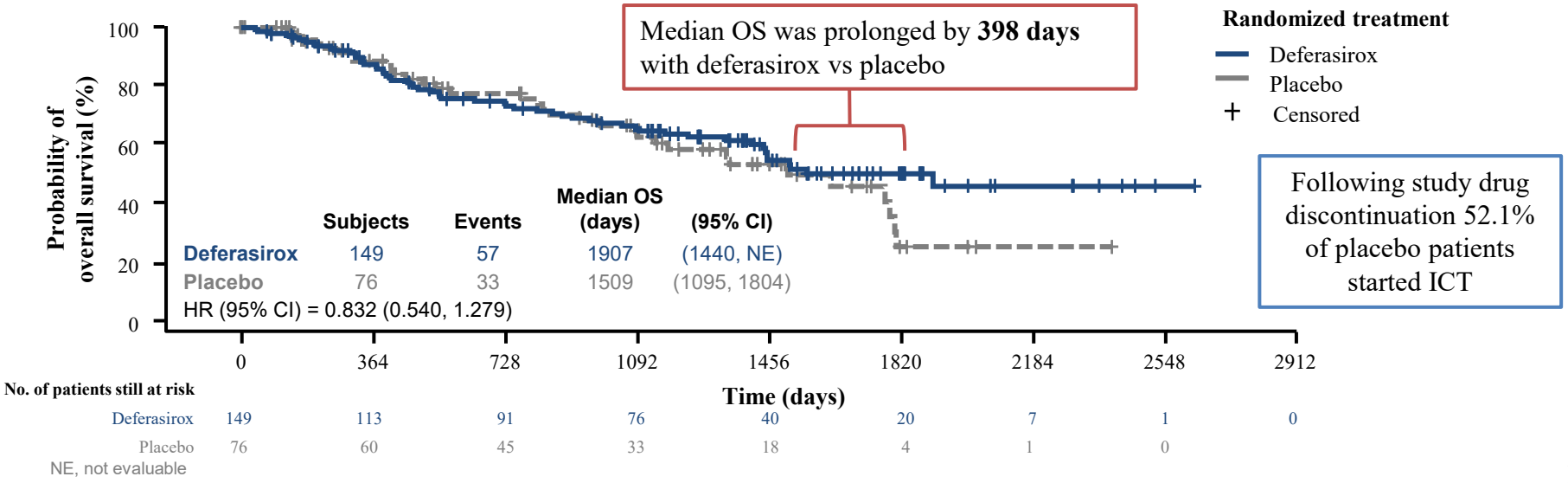


Angelucci E, et al, ASH 2018

Trend toward OS benefit

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	1907 (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	1509 (1095, 1804)		

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



NE, not evaluable

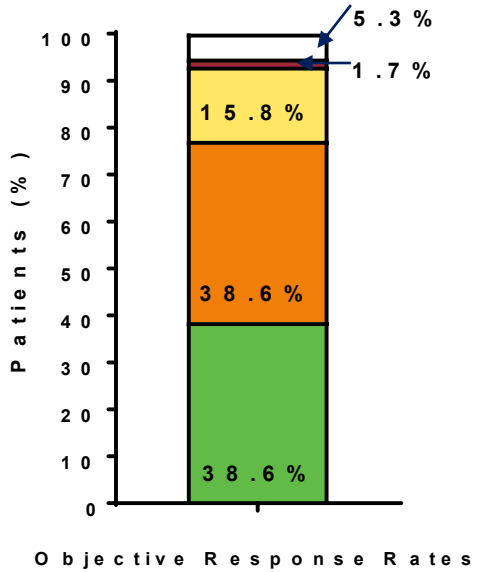
Angelucci E, et al, ASH 2018

Introduction to VEN+HMA in MDS

- 30% of MDS have Intermediate-2/high IPSS risk disease (median OS 0.4-1.2 years)[1]
- Azacitidine (Aza) has been the standard of care for higher-risk MDS based on AZA-001 showing median OS of 24.5 mo c/w doctor's choice -9.4 mo [2]
  - CR (17%), PR (12%), HI-E (40%), HI-N (19%), HI-P (33%)
- To date, no doublet has produced superior results in RCT (e.g. + HDAC inhib or len, Sekeres M, et al JCO 2017)
- The BCL-2 inhibitor venetoclax (Ven) combined with Aza induces rapid clinical responses in older patients with AML[3]
- Tolerability and efficacy of Ven combined with Aza in MDS unknown
- Phase I trial of IPSS Int-2 or high (no t-MDS,CMML, or OL), <20% blasts, results first reported ASH 2019[4]

[1]Greenberg P et al. *Blood*, 1997; [2]Fenaux P et al., *Lancet Oncol,* 2007; [3]DiNardo CD et al. *Lancet Oncol,* 2017, [4]Wei A et al, ASh 2019

Response Rates (IWG 2006)



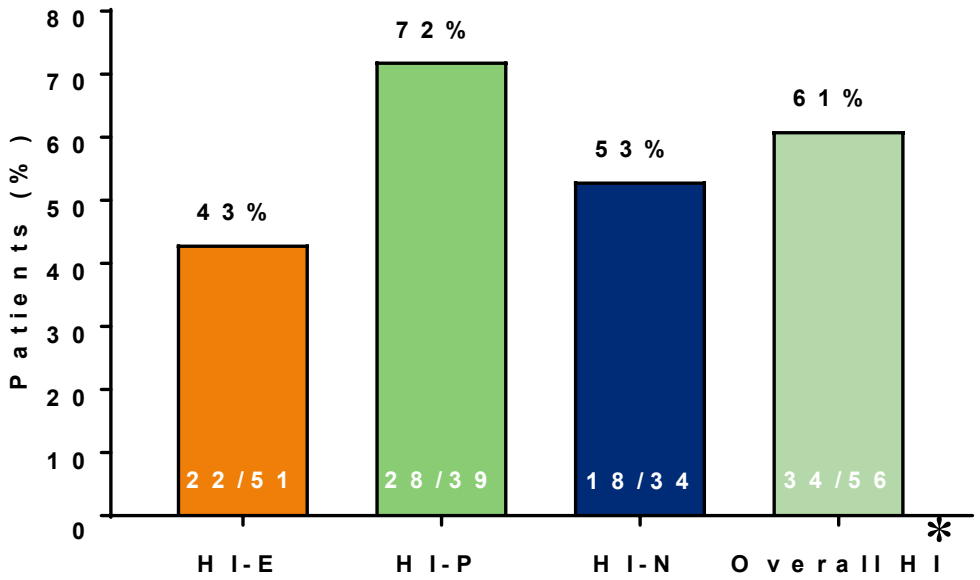
	All Ven+Aza Patients (N=57)
Median time to response for CR, months (range)	2.2 (1.2-11.1)
12-mo estimate of DoR after ORR, % (95% CI)	69.8 (47.4, 84.0)
HI+mCR (HI-E+HI-P+HI-N), n/N%	10/22 (45.5)

Excludes patients of arm C (Aza only); Objective response rate (ORR) includes [complete remission (CR) + marrow complete remission (mCR) + partial remission (PR)]; # of patients with PR=0;
DoR: Duration of response; HI: hematological improvement; HI-E: hematologic improvement in erythroids; HI-N: hematologic improvement in neutrophils; HI-P: hematologic improvement in platelet count; n: patients with favorable outcomes; N: patients eligible for evaluating outcomes

Data Cut-off: 21 AUG 2019

Wei A et al , ASH 2019

Hematological Improvement



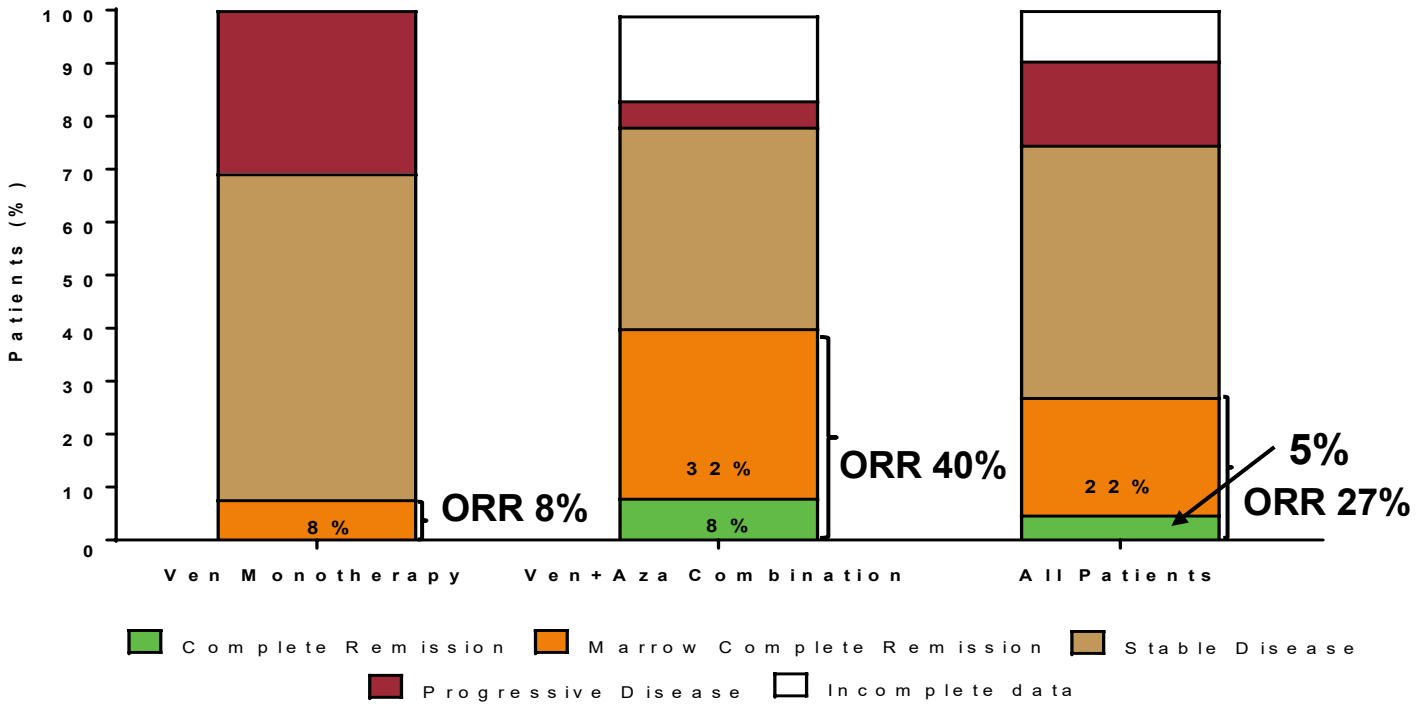
Note: Evaluation of HI-E required baseline hemoglobin <11 g/dL, HI-P platelet counts (unsupported) <100 × 10^9/L, HI-N neutrophil counts <1.0 × 10^9/L
Overall HI response rate included subjects eligible for HI assessment at baseline and achieving any component of HI-E + HI-P + HI-N

HI: hematological improvement; HI-E: hematologic improvement in erythroids; HI-N: hematologic improvement in neutrophils; HI-P: hematologic improvement in platelet count; n: patients with favorable outcomes; N= patients eligible for evaluating outcomes
*The proportion of patients with Overall HI is less than proportion of patients with HI-P as the eligibility to assess HI is dependent on the baseline cell counts and the number of patients in the groups varied

Data Cut-off: 21 AUG 2019

Wei A et al , ASH 2019

Ven (generally 400 mg/d) With or Without Aza in R/R MDS: ORR

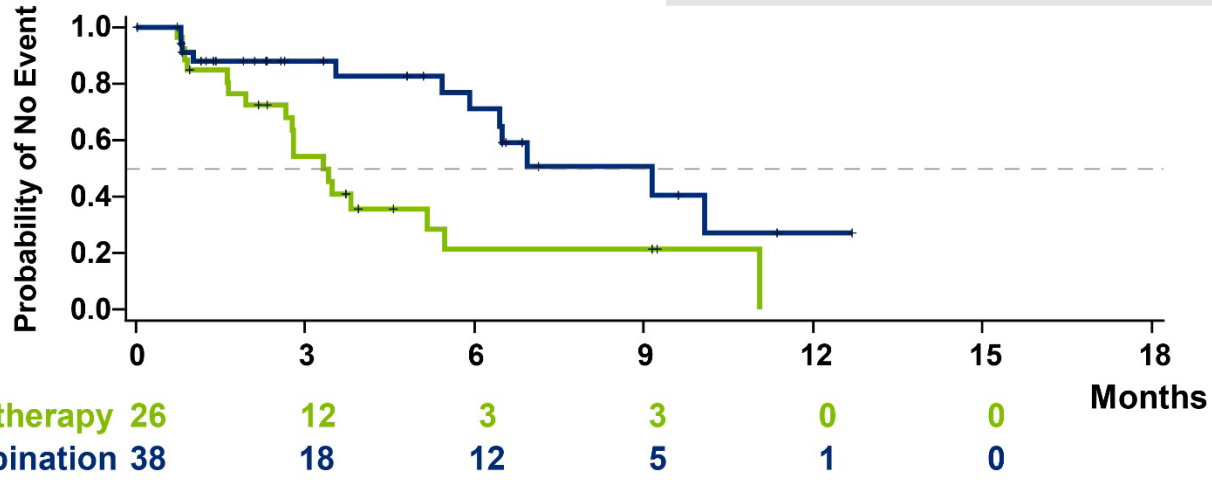


Data cutoff: Aug 30, 2019.

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

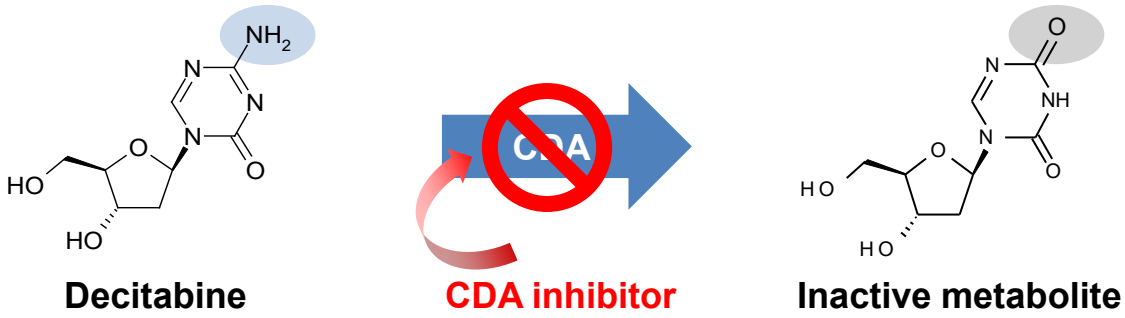
- Zeidan A, et al. ASH 2019. Abstract 565.

Data cutoff: Aug 30, 2019.

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

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



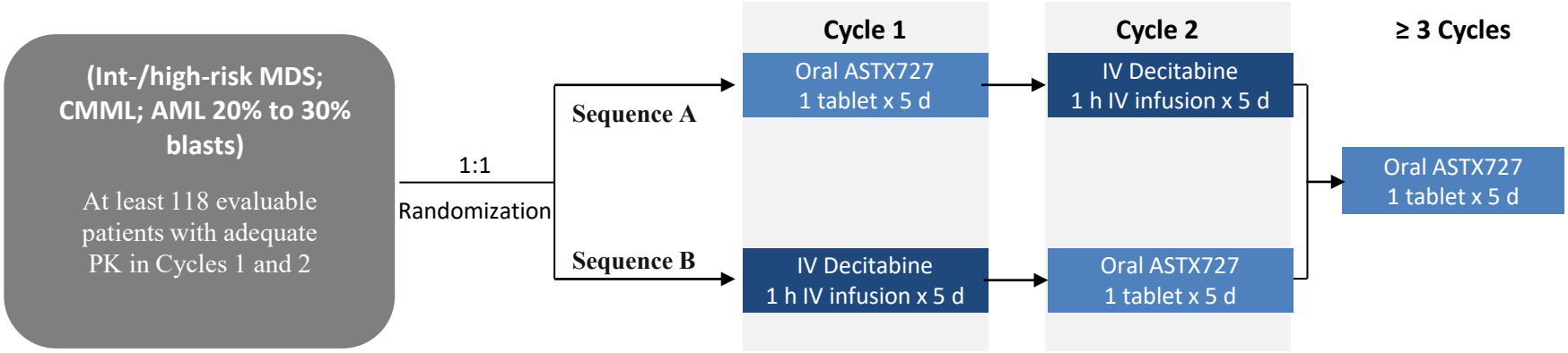
Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel CDA inhibitor

Garcia-Manero G, et al. ASH 2019. Abstract 846.

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. ASH 2019. Abstract 846.

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. ASH 2019. Abstract 846.

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

Allogeneic Transplant in MDS: Approximation of Life Expectancy (Years)

	Immediate Transplant	Transplant in 2 Years	Transplant at Progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

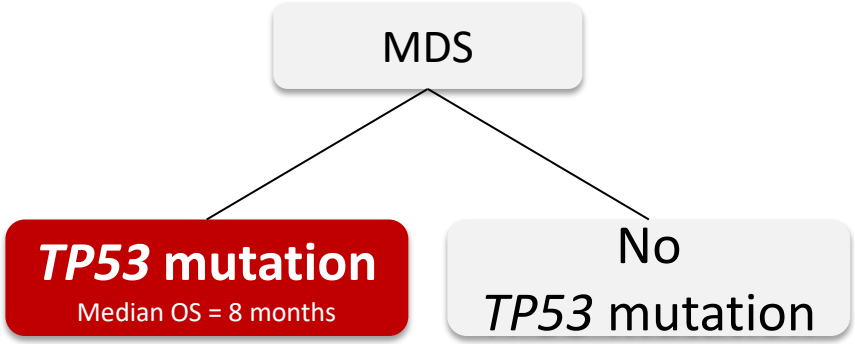
*This is for fully HLA matched T cell replete **myeloablative** SCT*

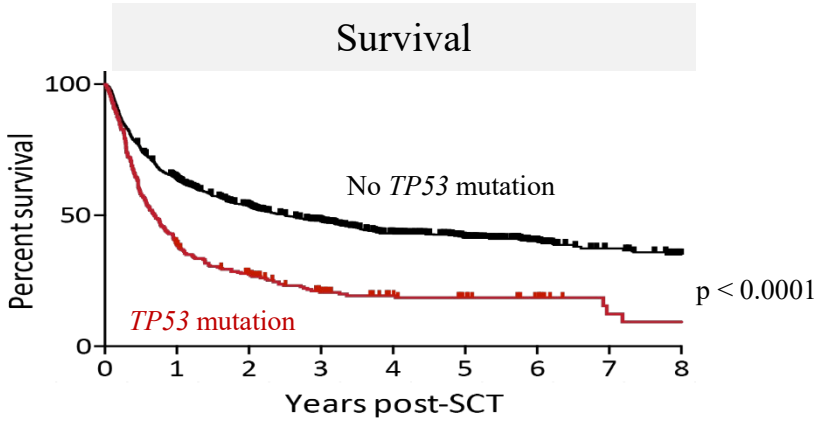
Cutler CS, et al. *Blood.* 2004;104(2):579-585.

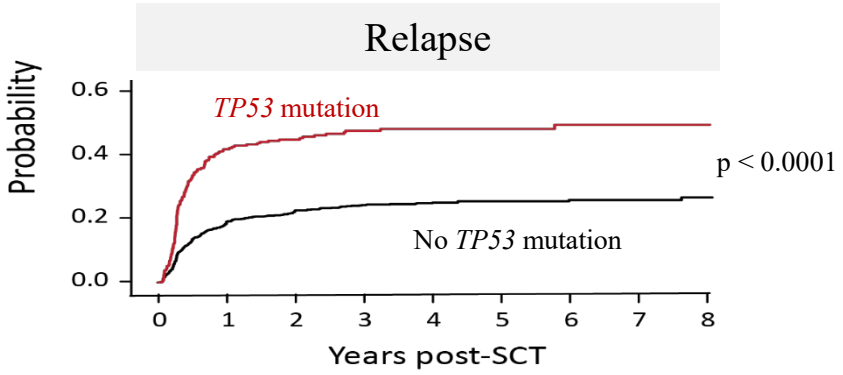
Update: Koreth J et al JCO 2013: *Same applies in era of RIC allo SCT among patients 60-70 years old*

TP53 mutated MDS

Poor prognosis Post-SCT due to early relapse



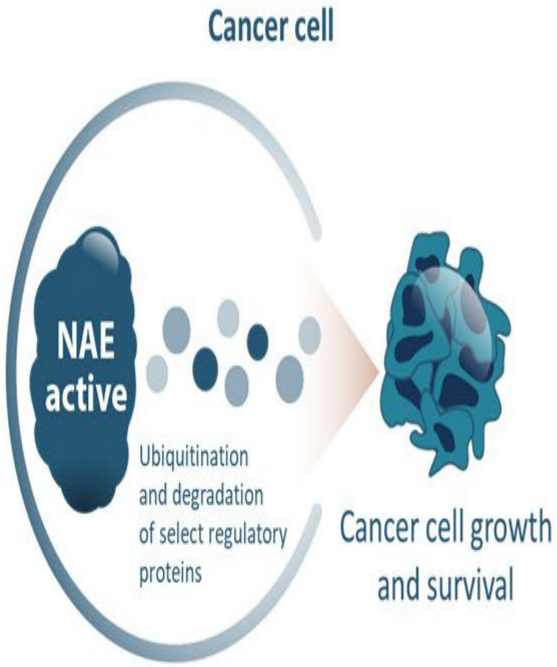


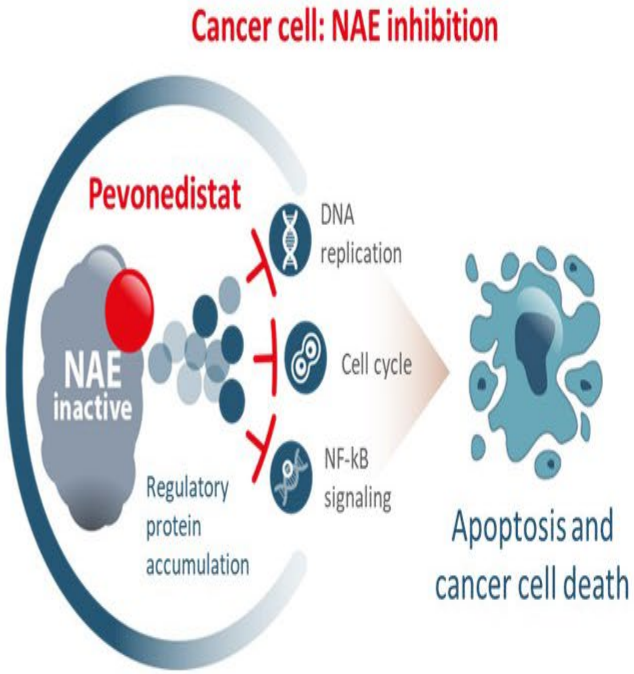


Lindsley C, et al. *N Engl J Med.* 2017;376(6):536-547.

Pevonedistat: NEDD8-A-E inhibitor in MSA

- Pevonedistat is the first small-molecule inhibitor of the NEDD8-activating enzyme (NAE)[4,5]
  - In AML, pevonedistat has shown encouraging clinical activity in combination with azacitidine and was well tolerated[6]





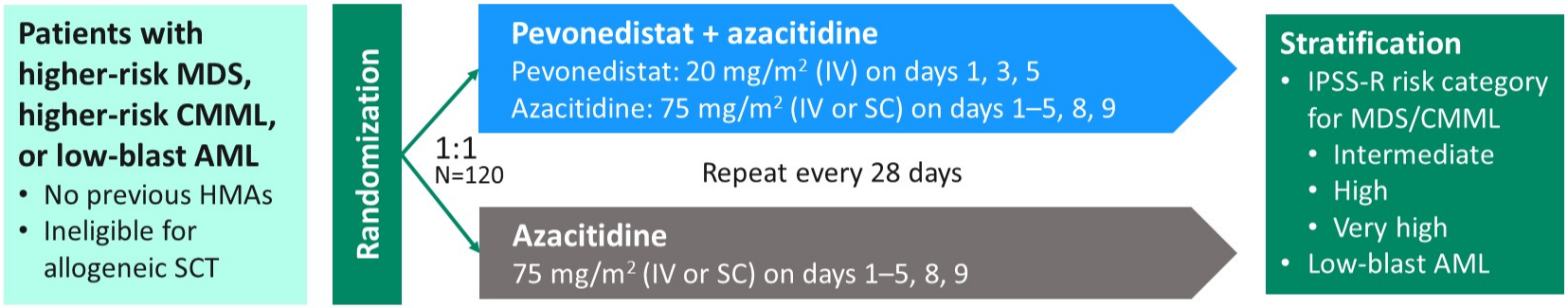
AE, adverse event; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; NEDD8, neural precursor cell expressed, developmentally downregulated 8.

1. Sekeres MA, et al. J Clin Oncol 2017;35:2745–53; 2. Garcia-Manero G, et al. Cancer 2017;123:994-1002; 3. Prebet T, et al. J Clin Oncol 2014;32:1242–8; 4. Soucy TA, et al. Nature 2009;458:732–6; 5. Brownell JE, et al. Mol Cell 2010;37:102–11; 6. Swords RT, et al. Blood 2018;131:1415–24

Ades, L et al ASCO 2020

Study design

NCT02610777: Phase II, randomized, open-label, global, multicenter study [proof of concept]



Study endpoints

- **EFS** (defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML): The study was powered on EFS as the original primary endpoint
- **OS**: Original secondary endpoint, changed to primary endpoint based on regulatory feedback after enrollment
- **ORR**: Secondary endpoint

EFS, event-free survival; HMA, hypomethylating agent; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; ORR, objective response rate; OS: overall survival; SC, subcutaneous; SCT, stem cell transplant.

About 70 pts per arm, about 8, 16 per arm with CMML, low blast AML, respectively

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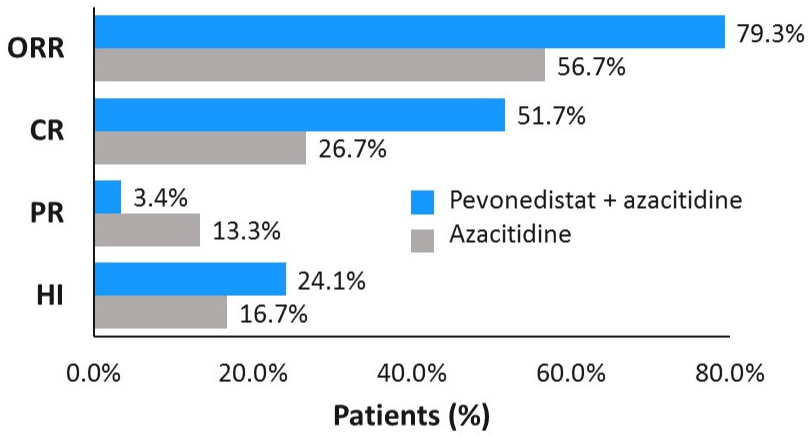
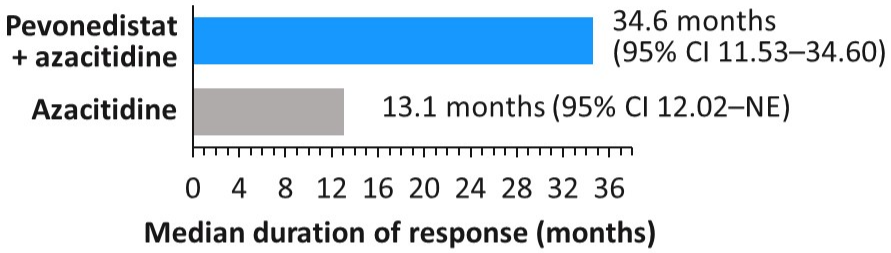
Objective response: Disease subgroups

Higher-risk MDS (response-evaluable patients, n=59)





Rate of transfusion independence:
69.2% (pevonedistat + azacitidine) versus 50.0% (azacitidine)

Low-blast AML and higher-risk CMML

- In low-blast AML, ORR was 52.9% (pevonedistat + azacitidine) versus 60.0% (azacitidine) in response-evaluable patients (n=32)
- In higher-risk CMML, ORR was 77.8% (pevonedistat + azacitidine) versus 75.0% (azacitidine) in response-evaluable patients (n=17)

Well tolerated, no increased F/N in doublet

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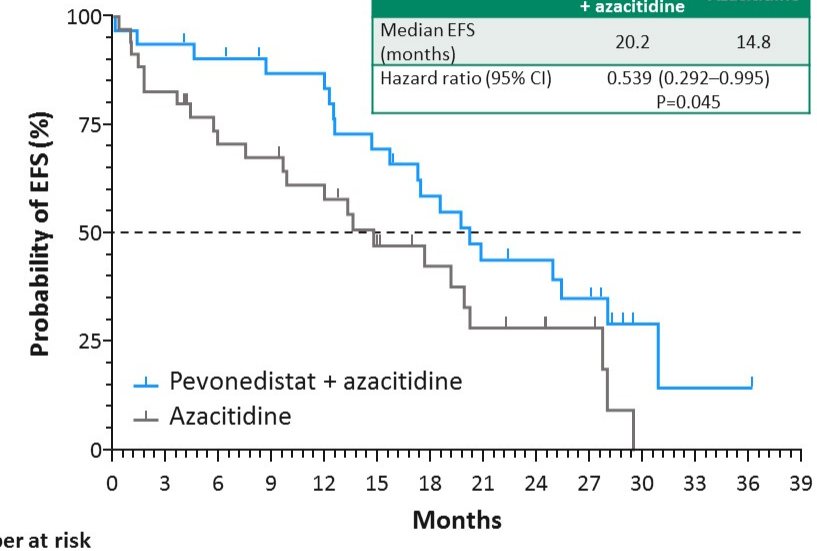
EFS and OS: Higher-risk MDS

EFS*

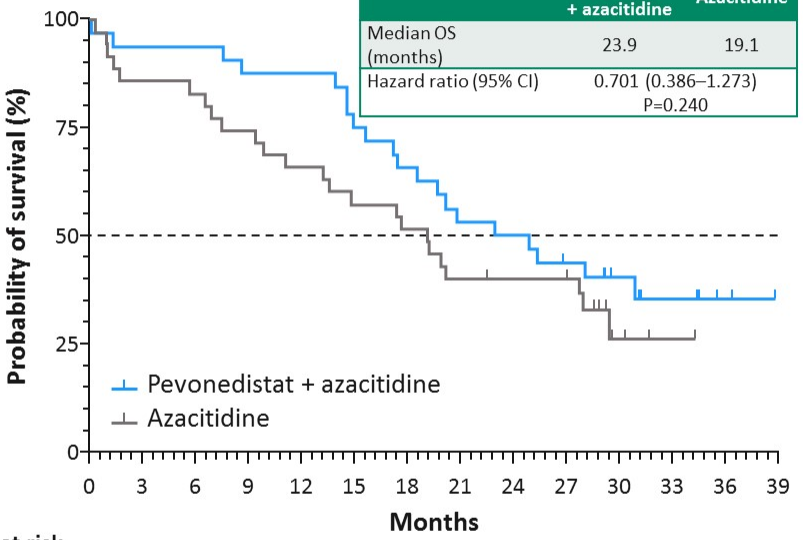


	Pevonedistat + azacitidine	Azacitidine
Median EFS (months)	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	

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	Azacitidine
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

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

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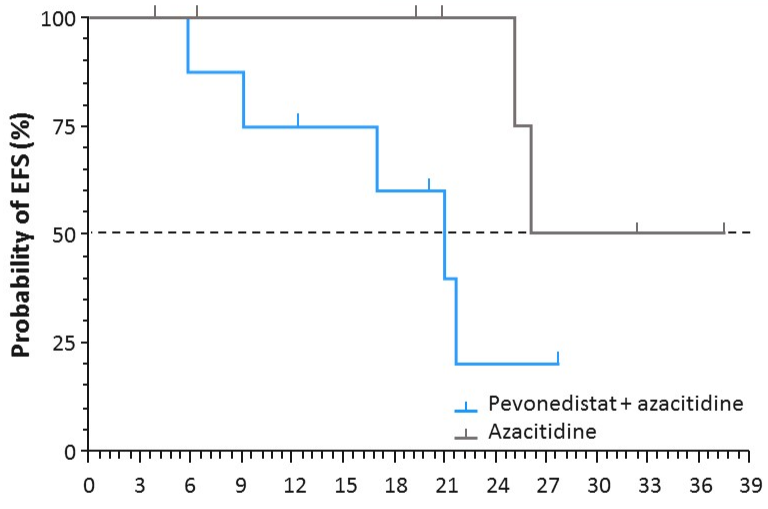
EFS and OS: Higher-risk CMML

EFS*

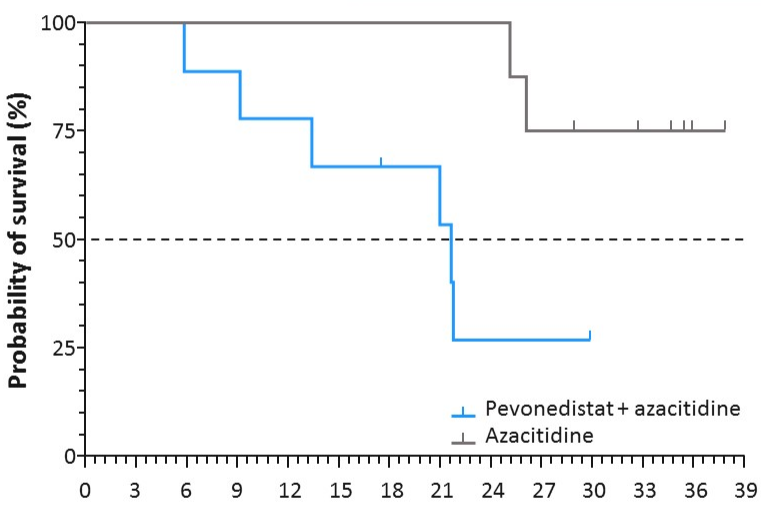
	Pevonedistat + azacitidine	Azacitidine
Median EFS (months)	21.0	NE
Hazard ratio (95% CI)	4.302 (0.791–23.407)	



Number at risk														
Pevonedistat + azacitidine	9	9	7	7	6	5	4	2	1	1	0	0	0	0
Azacitidine	8	8	7	6	6	6	6	4	4	2	2	1	1	0

OS

	Pevonedistat + azacitidine	Azacitidine
Median OS (months)	21.7	NE
Hazard ratio (95% CI)	7.519 (1.362–41.510)	P=0.010

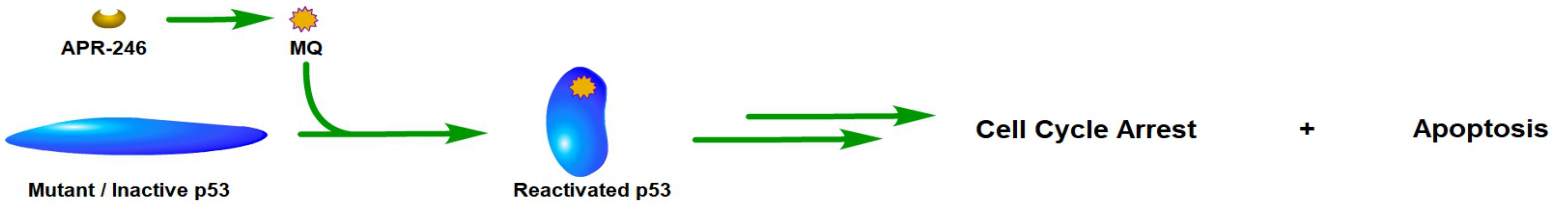


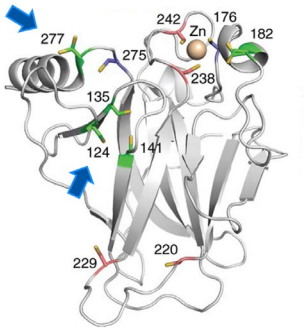
Number at risk														
Pevonedistat + azacitidine	9	9	8	8	7	6	5	4	1	1	0	0	0	0
Azacitidine	8	8	8	8	8	8	8	8	8	6	5	4	1	0

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

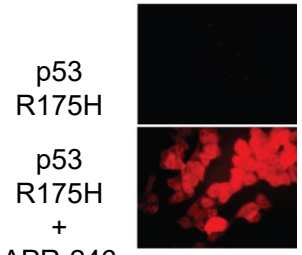
Ades, L, et al, ASCO, 2020

Targeting TP53 Mutations in MDS/AML via APR-246

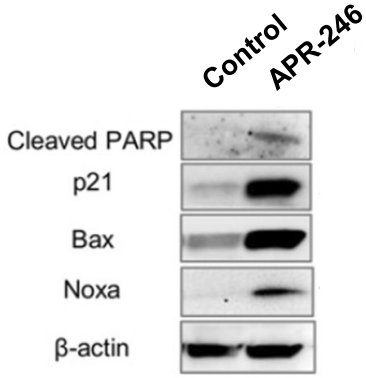




APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



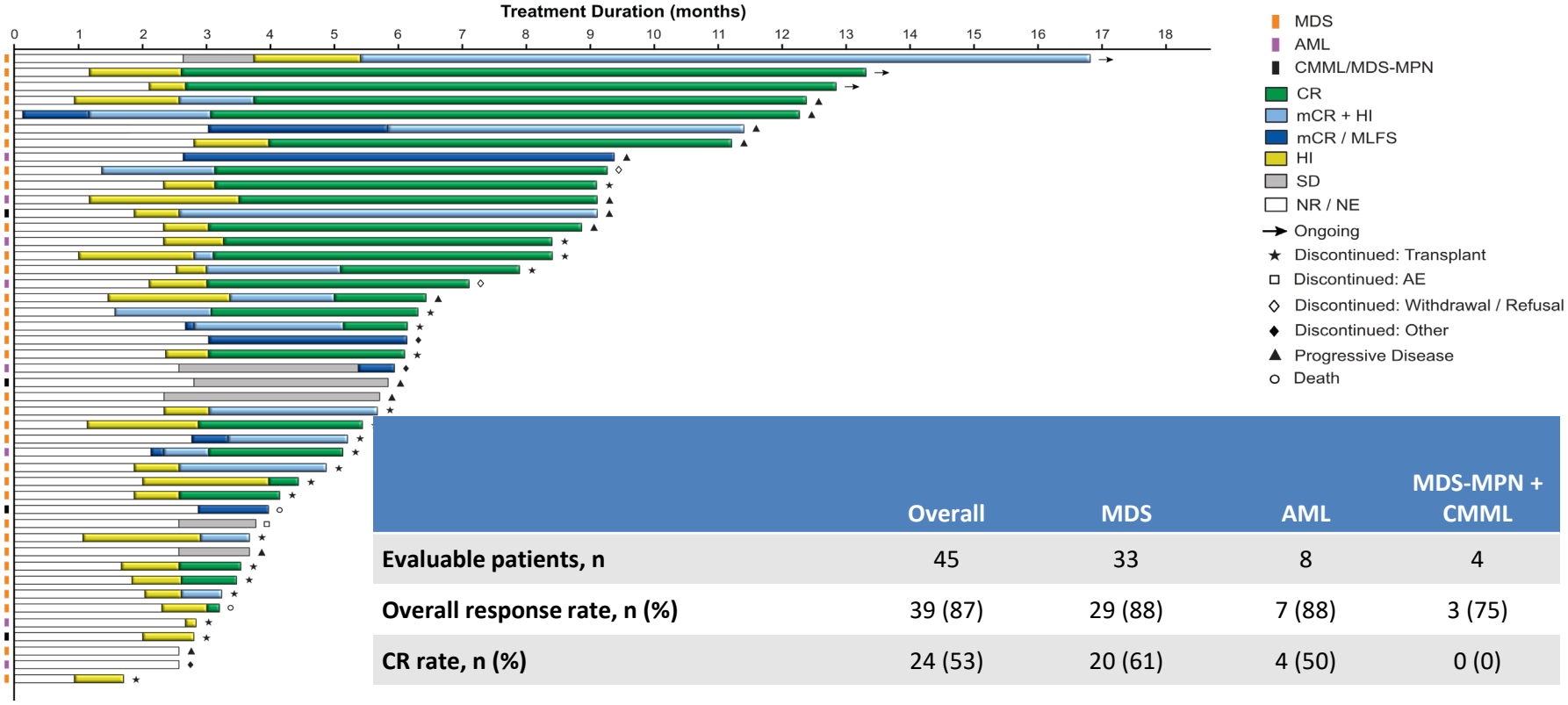
…and triggers cell cycle arrest and apoptosis

A. Fenist et al. (2010) Phar. 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

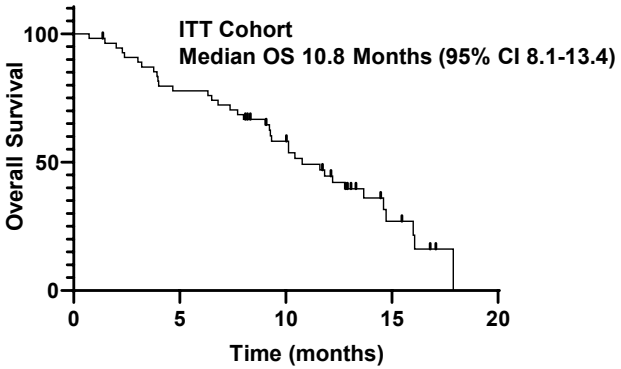


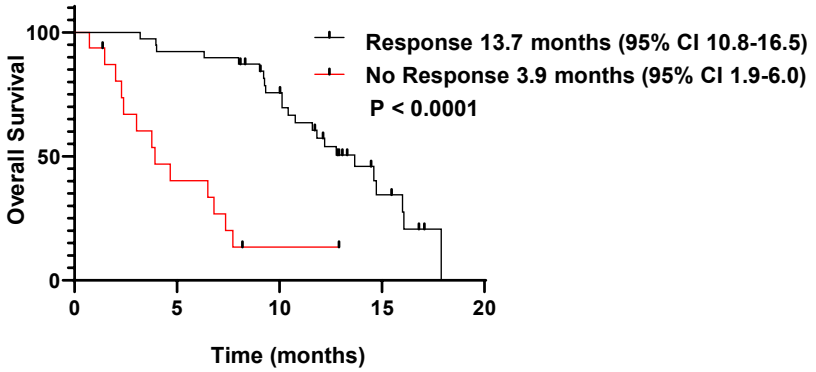
	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22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

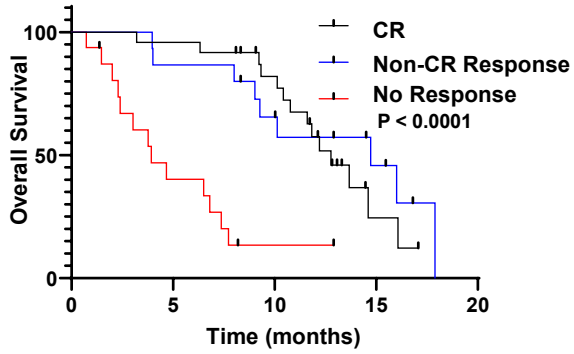
- Median duration of follow-up = 10.8 months

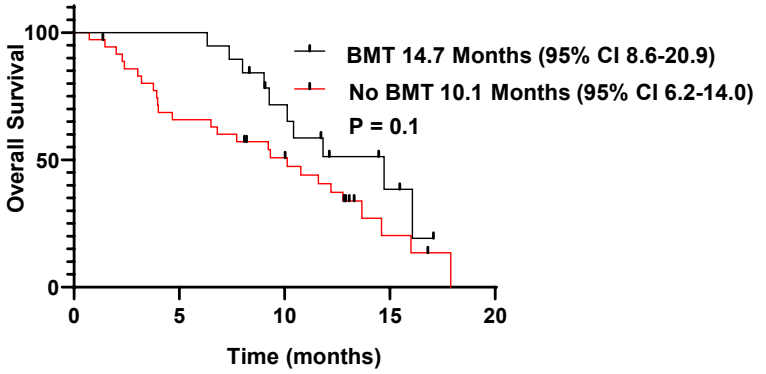
Sallman D, et al, ASH 2019

Overall Survival (ITT): APR-246+aza







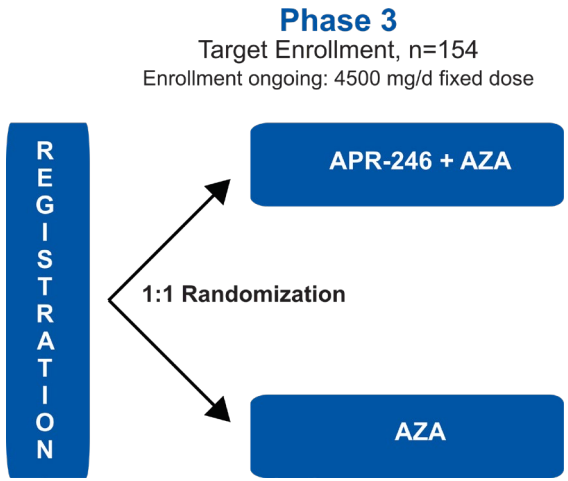


44% cleared TP53 to <5% VAF

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



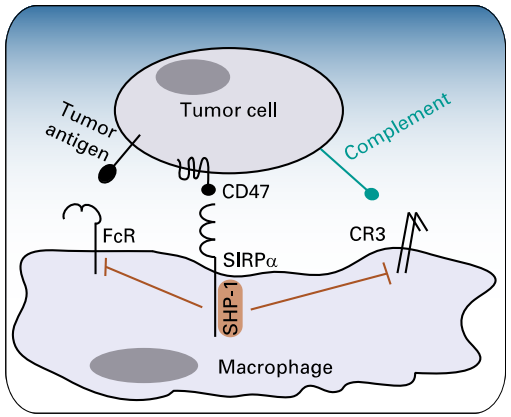
- Intermediate-/high-/very high-risk *TP53*-mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

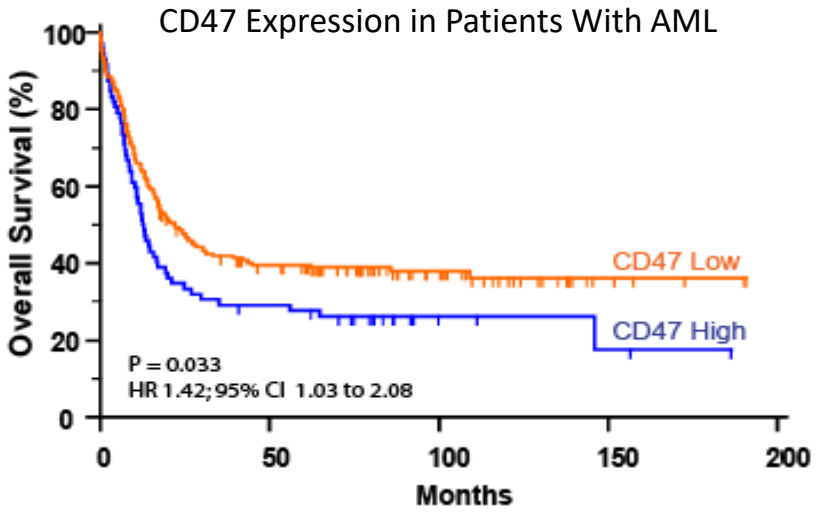
- Status
  - Enrollment commenced in January 2019
  - Currently targeting full enrollment in first quarter 2020
  - Fast Track Designation for MDS: granted by FDA in April 2019
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019

- ClinicalTrials.gov. NCT03745716.

CD47

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





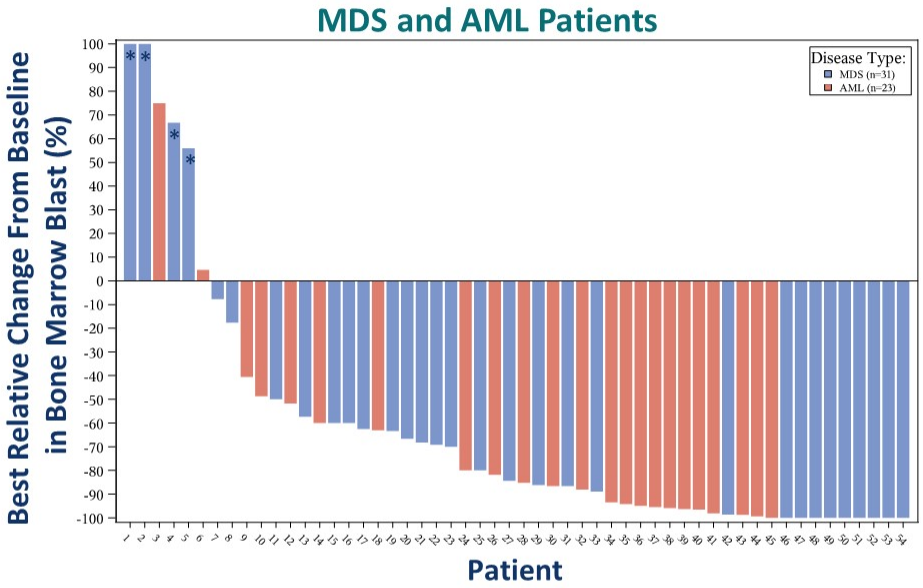
- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in patients with AML

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 + 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

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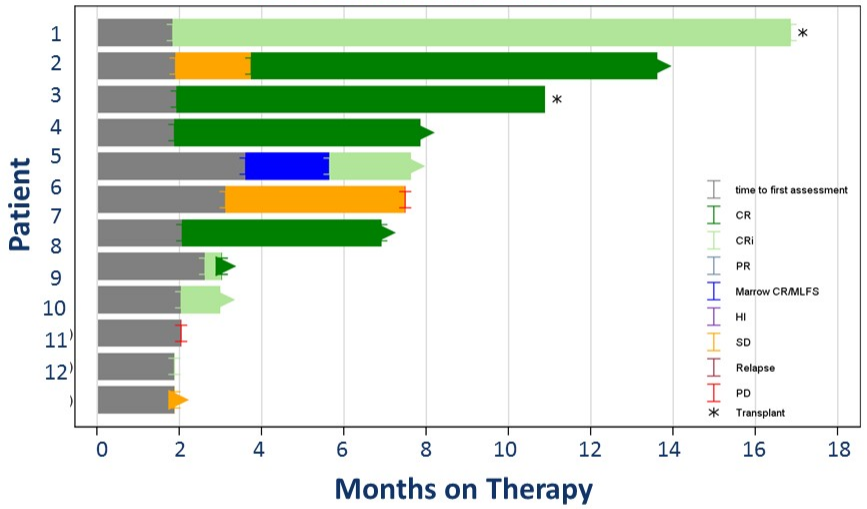
Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

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**



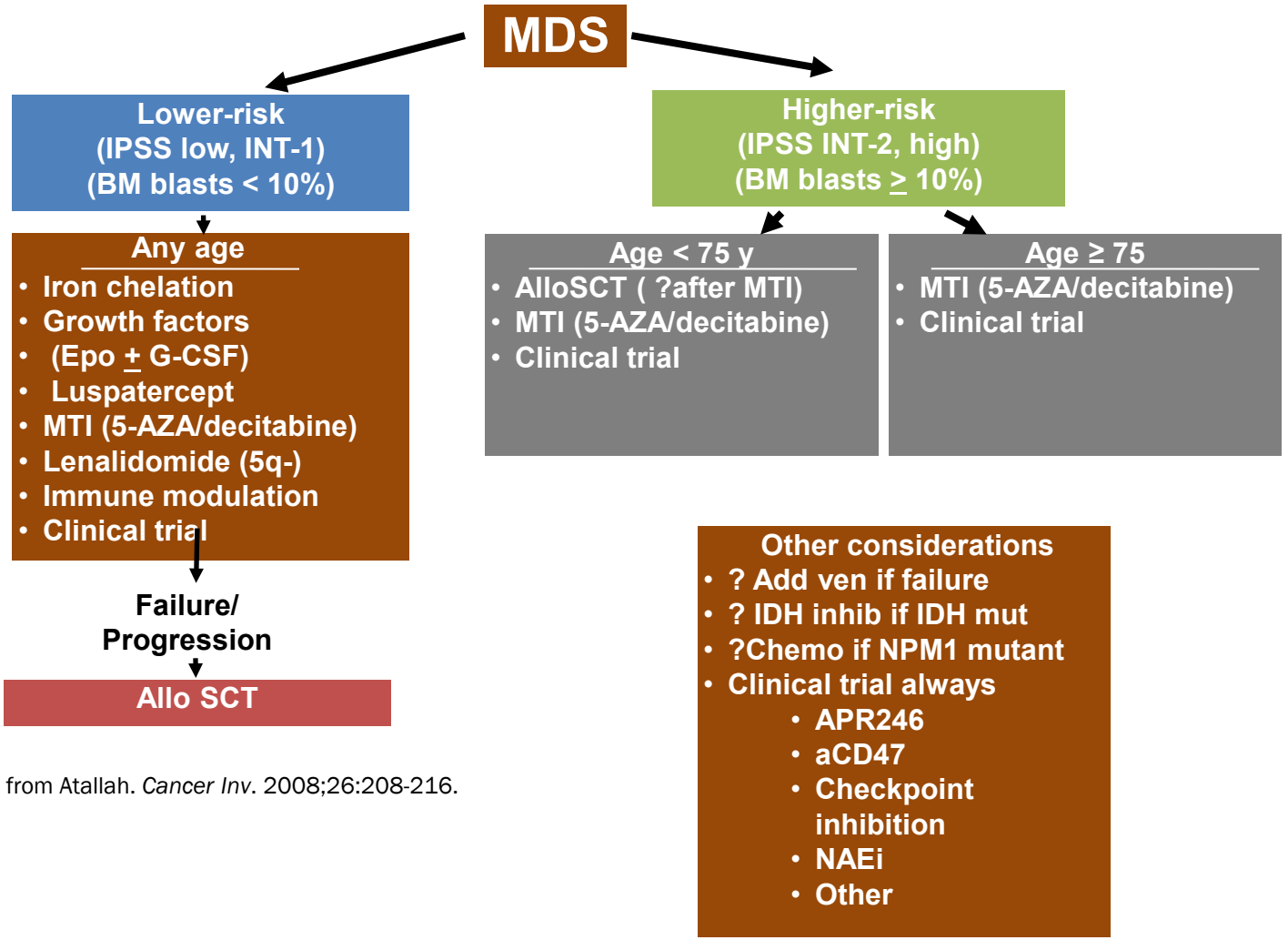
- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax + 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 VAF to less than 5%

Sallman D, et al, ASH 2020

Proposed Treatment Algorithm for Patients With MDS: 2020



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

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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,**

The End

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