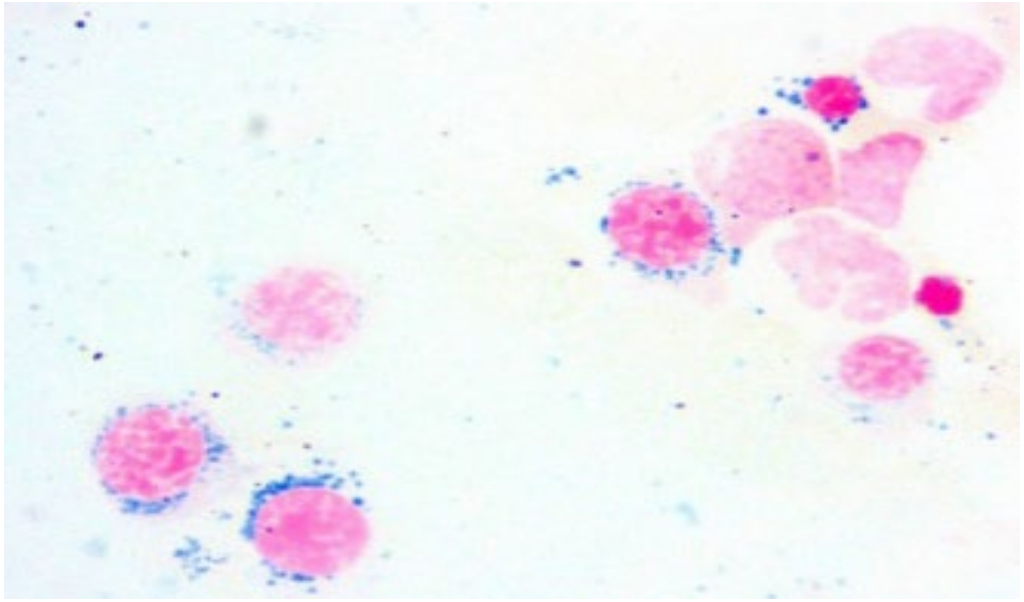
The Oracle of Apollo in Indianapolis: Prognosis and Treatment in MDS



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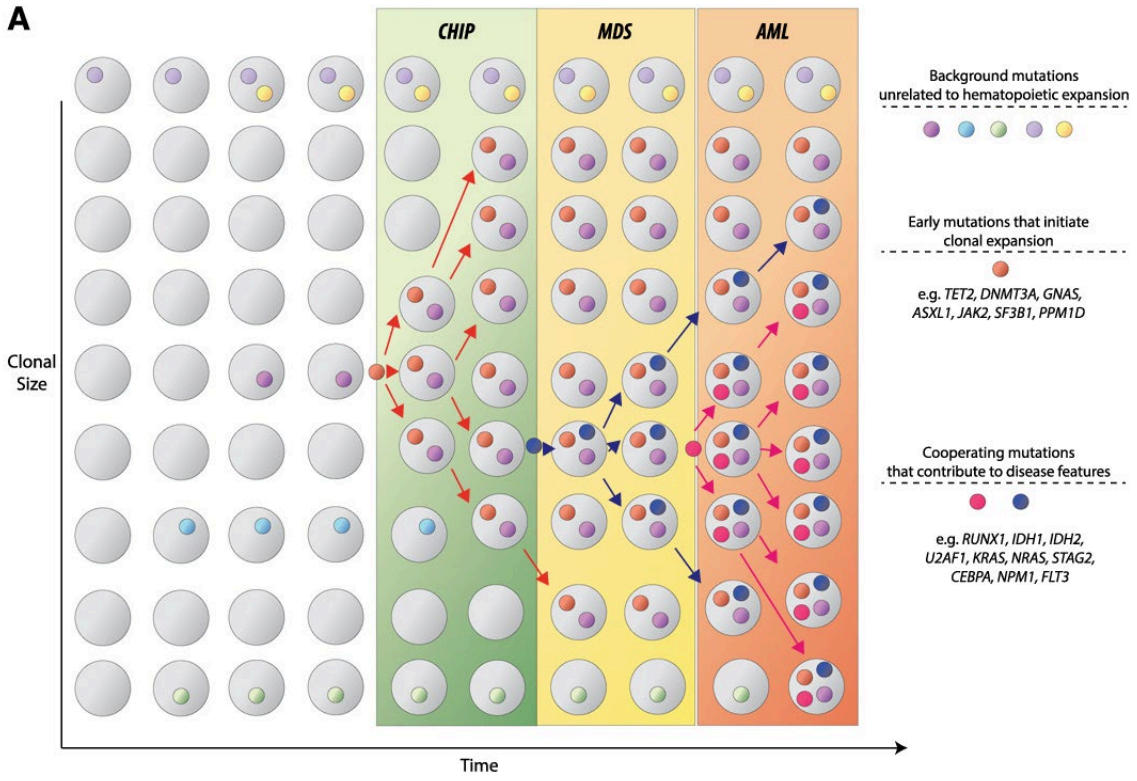
Disclosures- Richard M. Stone, MD

- **Consulting relationships past three years:**
  - **AbbVie*; Actinium, Agios*; Amgen; Argenix (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**

MDS: SMART Learning Objectives

- Apply modern prognostic algorithms in MDS
- Evaluate the 2023 Therapeutic Algorithm in lower risk and higher risk MDS
- Analyze the Developmental Therapeutic Landscape in higher risk and Lower risk MDS

Assessing risk of developing MDS: Myeloid precursor conditions (CHIP and CCUS)



Prevalence in the population → Risk for transformation into MDS/AML

	CH	ICUS	CCUS (low risk)	CCUS (high risk)	MDS
Clonality	YES	NO	YES	YES	YES
Cytopenia	NO	YES	YES	YES	YES
Dysplasia	NO	NO	NO	NO	YES
High risk features*	NO	NO	NO	YES	YES/NO
↑ Blasts	NO	NO	NO	NO	YES/NO
Risk of progression	**~ 0.5-1%/year**	**~ 1%/year**	**~ 10%/year**	**~ 20%/year**	

* High risk features:
1. DTA mutation (*DNMT3A*, *TET2*, *ASXL-1*) + 1 other myeloid mutation
2. Spliceosome mutation (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*)

Steensma Blood 2015
Stahl ASCO SEP 2022

Risk of developing myeloid malignancy for CH patients

High Risk Mutations
Absent

single DNMT3A
Absent

Maximum VAF
< 0.2 (20%)

Number of Variants
1

CHIP or CCUS
CHIP

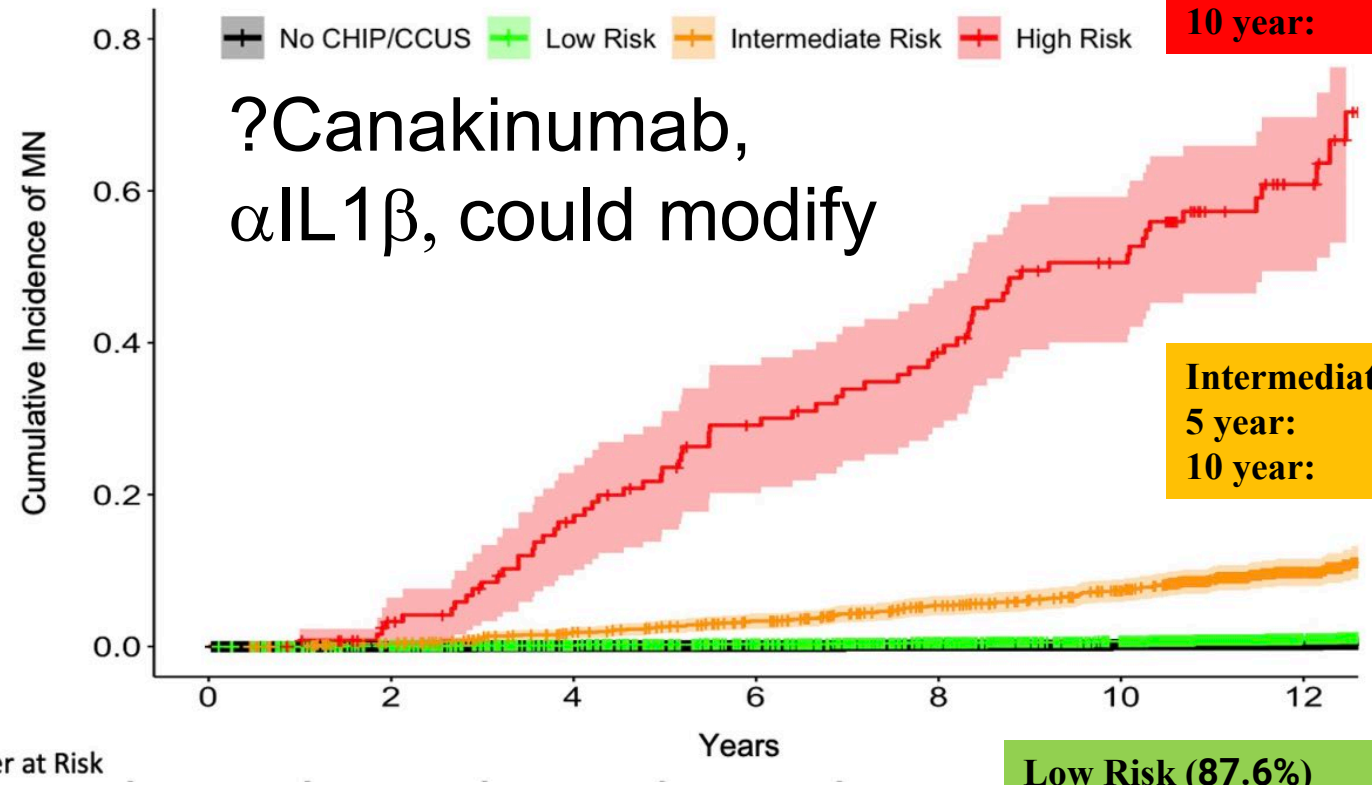
Mean corpuscular volume
< 100 fl

Red cell distribution width
< 15%

Age
< 65 years

High risk mutations:
SF3B1, SRSF2, ZRSR2,
JAK2,
TP53,
RUNX1, FLT3, IDH1, and IDH2

- UK Biobank: 193,743 healthy volunteers
- 11,337 (5.85%) had pathogenic variants



High Risk (1.13%)
5 year: 24.4 ± 4.12%
10 year: 52.2 ± 4.96%

Intermediate Risk (11.3%)
5 year: 2.76 ± 0.482%
10 year: 7.83 ± 0.807%

Low Risk (87.6%)
5 year: 0.232 ± 0.0484%
10 year: 0.669 ± 0.0827%

Weeks ASH 2022 (abstract #926)
Garcia-Manero ASH 2022 (abstract 853)

2022 ICC

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥				
MDS, NOS with multilineage dysplasia	≥2	≥				
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥				
MDS/AML	Typically ≥1‡	≥				

Table 21. Myeloid neoplasms with mutated *TP53*

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

*Defined as 2 distinct *TP53* mutations (each VAF > 10%) OR a single *TP53* mutation with (1) 17p deletion on cytogenetics; (2) VAF of >50%; or (3) Copy-neutral LOH at the 17p *TP53* locus.

†If *TP53* locus LOH information is not available.

Risk based on new 2022 WHO and ICC classification

2022 WHO

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

To acknowledge the biologic continuum between MDS and AML, the name of the previous category of MDS-EB2 in adults with 10% or more blasts is changed to MDS/AML, defined as a cytopenic myeloid neoplasm and 10-19% blasts in the blood or BM. Patients with MDS/AML should be eligible for both MDS and AML trials.

MDS, New thoughts: Prognosis

– Increasingly sophisticated

1998: IPSS: BM blasts, # of cytopenias, KT (4 groups)

-ease, even # of groups, non-dynamic

2005: WPSS: WHO subgroups KT, RBC tx

-4 subgroups

2012: IPSS-R: BM basts, KT, depth of indiv cytopenias

-5 subgroups

2022: MIPSS: marrow blasts, plt, hgb, IPSS-R KT, # of mutations, yes/no on 17 mutations (special emphasis: SF3B1 single, TP53 multihit)

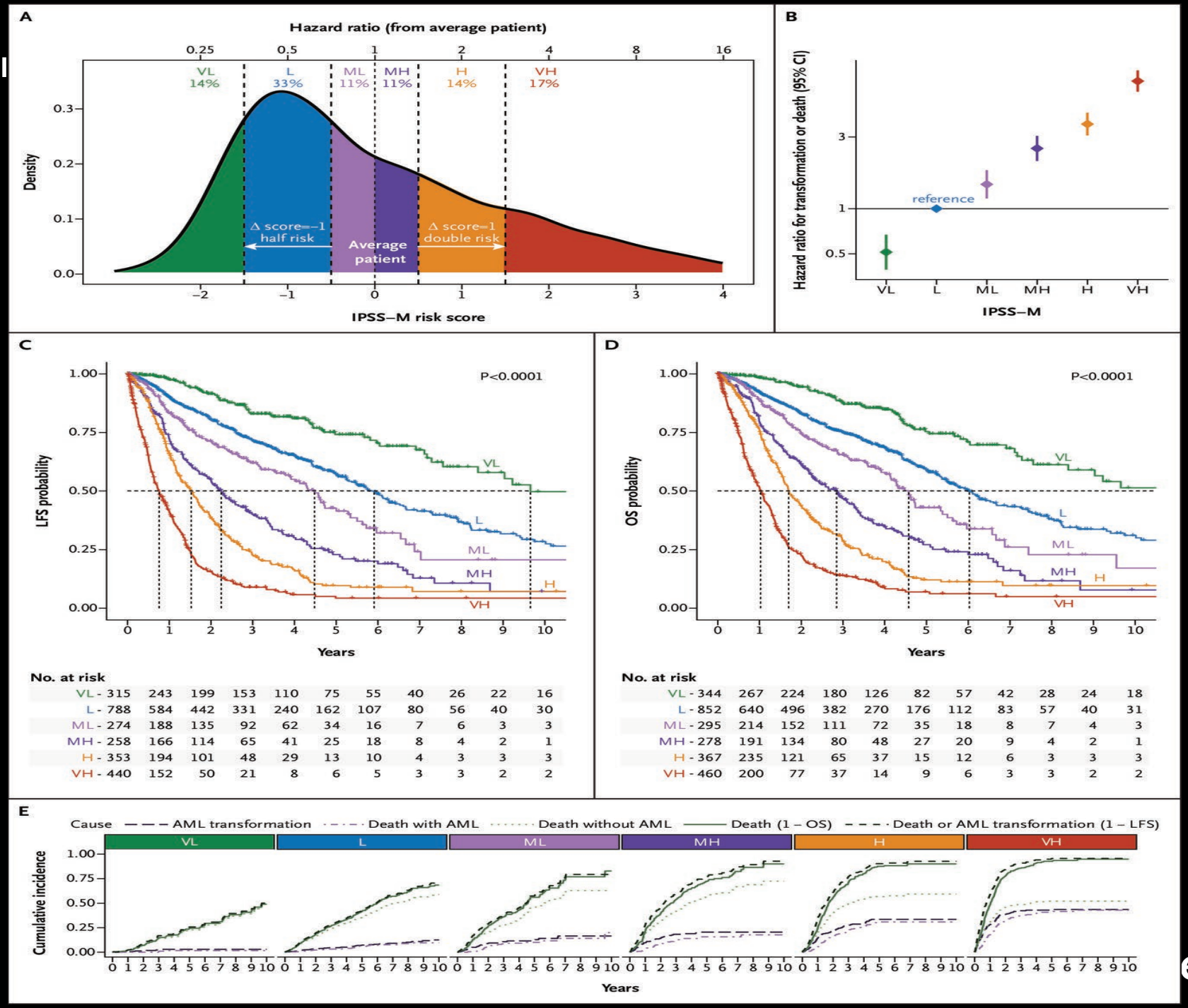
-6 subgroups

-works in s-MDS and t-MDS

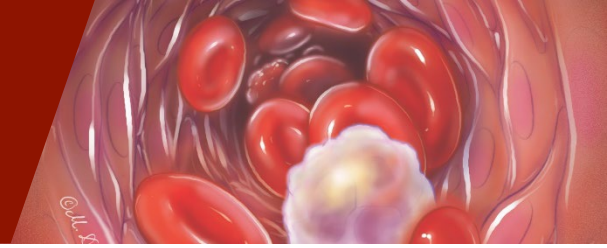
-outperforms IPSS-R

-https://mds-risk-model.com/

Bernard, E et al, *NEJM Evidence* 2022



Molecularly Guided Therapy in MDS



Current

- Lower risk: (ESA, luspatercept [*SF3B1* mut], lenalidomide [not in *TP53* mut]. HMA), short or long course HMA
- Higher risk (HMA, including oral, (+VEN coming?), chemo [*NPM1* mut] alloSCT)

Integrate muts in prognostic algorithm

FUTURE:

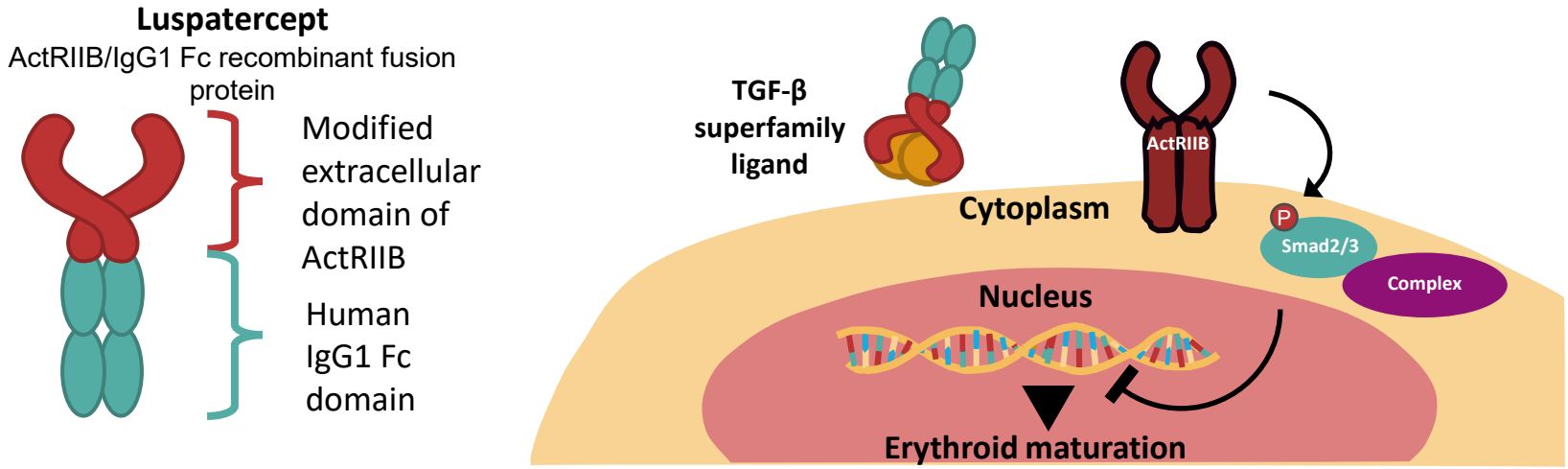
Mutational targeted rx

- Selective lethality in Spliceosome, cohesion mutations
- *TP53* refolding, magrolimab in *TP53* mut
- Enzyme inhibition in *IDH1* and *IDH2* mut
- Telomerase inhibition in telomerase complex mutations

Dana-Farber Cancer Institute

MEDALIST Luspatercept Trial

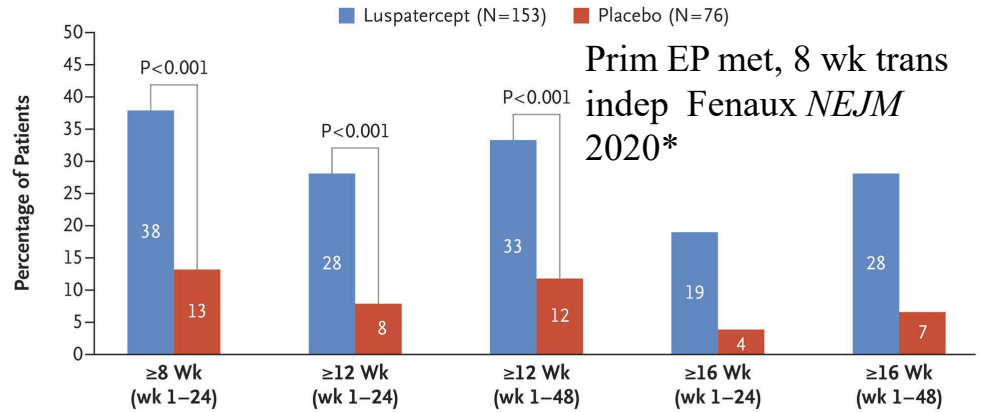
- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion-reduction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

1174 Overall Survival and Progression-Free Survival of Patients Following Luspatercept Treatment in the MEDALIST Trial

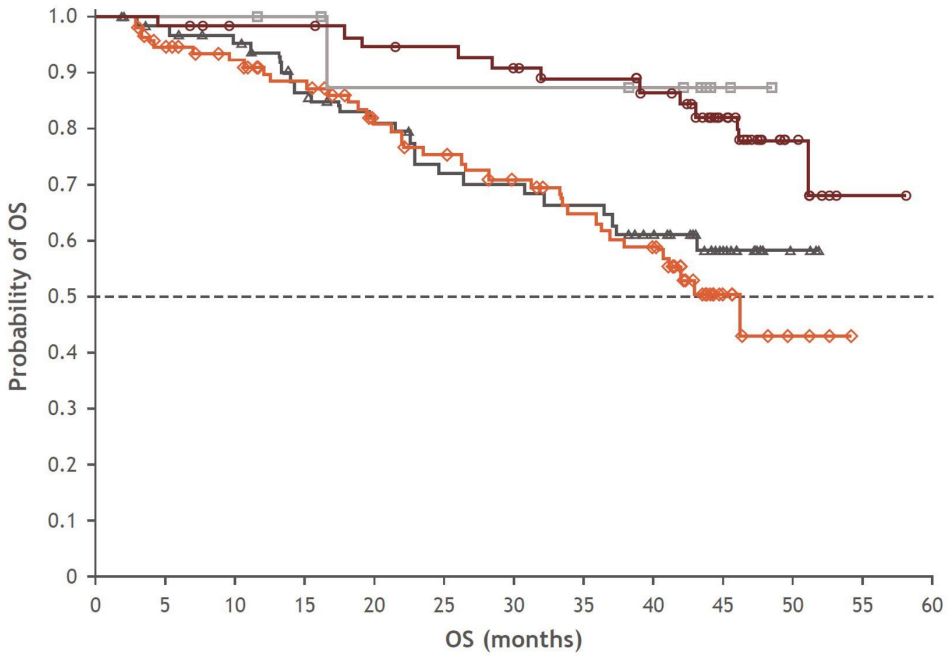


Prim EP met, 8 wk trans indep Fenaux *NEJM* 2020*

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])

- **Shows that OS in the 2 groups are the same**
  - **But some subgroups: IPSS-R very low; high BL PLT count**
- **Luspat responders lived longer than luspat non-responders**
- **OVERALL; Reassuring that luspatercept had no negative Lt effects**

Figure 1A. Kaplan–Meier estimates of OS by response and treatment arms

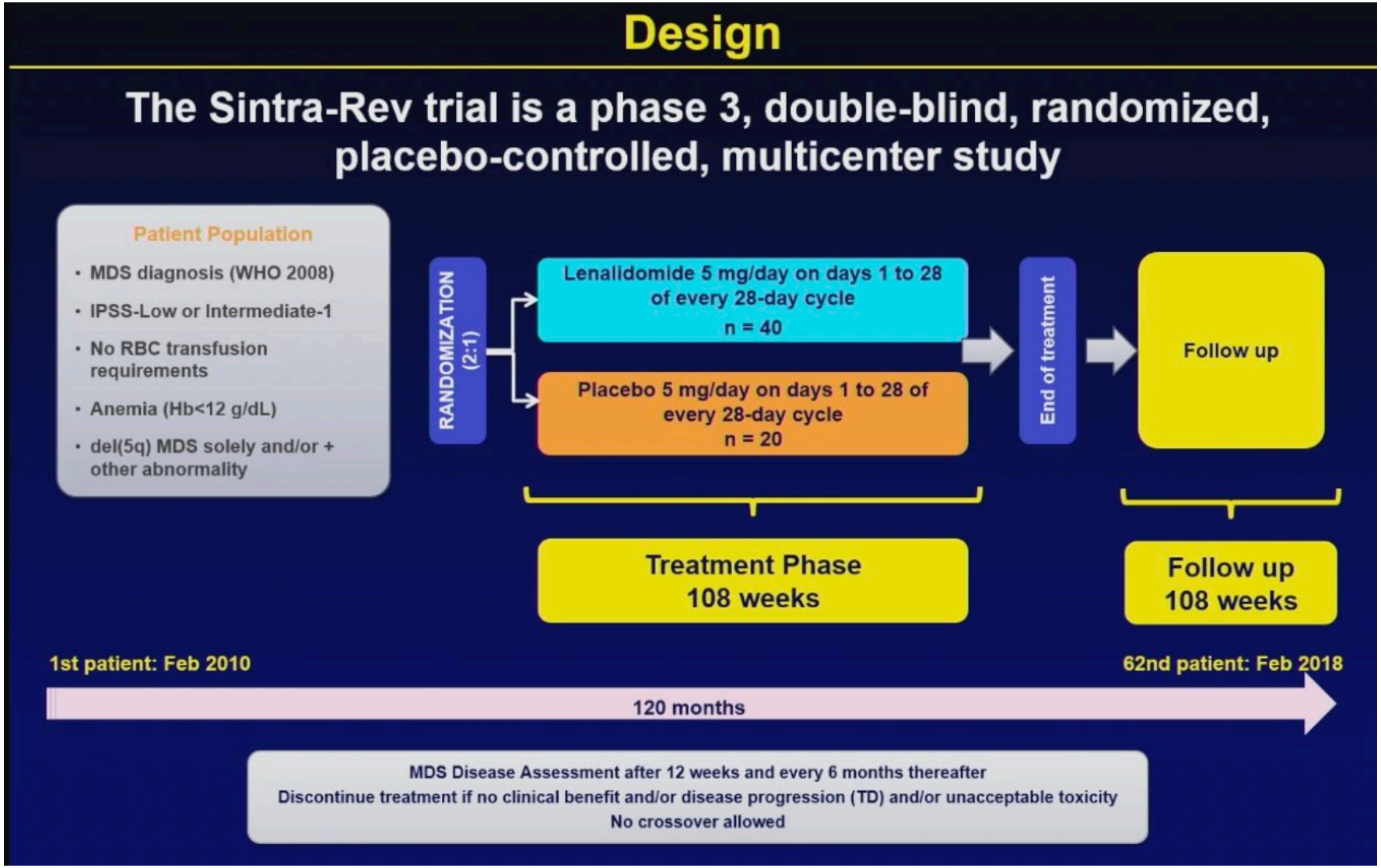


No. of patients at risk													
Luspatercept responders	58	57	54	54	51	50	47	44	39	23	9	1	0
Luspatercept non-responders	95	87	78	71	59	54	48	42	36	9	3	0	0
Placebo responders	10	10	10	9	7	7	7	7	6	2	0	0	0
Placebo non-responders	66	62	58	50	45	39	38	36	29	15	3	0	0

Luspatercept responders (events 11/58), median NA months (95% CI 51.1–NA)
Luspatercept non-responders (events 36/95), median 46.1 months (95% CI 36.3–NA)
Placebo responders (events 1/10), median NA months (95% CI 16.6–NA)
Placebo non-responders (events 23/66), median NA months (95% CI 37.0–NA)
Luspatercept responders vs placebo responders: HR 1.58 (95% CI 0.20–12.27), *P* = 0.7595
Luspatercept non-responders vs placebo non-responders: HR 1.25 (95% CI 0.74–2.11), *P* = 0.4288
Luspatercept responders vs luspatercept non-responders: HR 0.319 (95% CI 0.16–0.63), *P* = 0.0003

* Demographics not reported

460: Evaluation of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent Low Risk Del(5q) MDS Patients. Final Results of Sintra-REV Phase III International Multicenter Clinical Trial (ASH 2022)



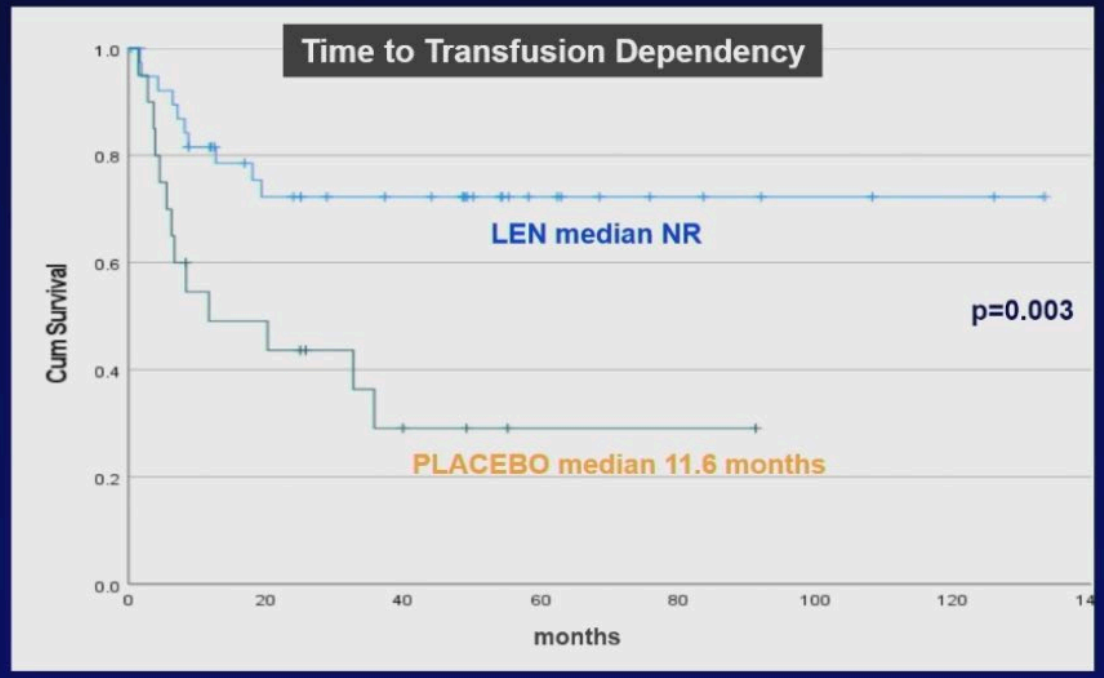
Presented are final results (completion of treatment and follow up phase)

460: Evaluation of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent Low Risk Del(5q) MDS Patients. Final Results of Sintra-REV Phase III International Multicenter Clinical Trial (ASH 2022)

Primary objective: Efficacy (ITT, N=61)

Low doses of Len delayed and decreased transfusion dependency

- TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)
- ✓ Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692), p=0.005



Median follow up 5.05y (0.3-11): 5.2 vs 4.85, p=ns

No LEN-mediated increase in AML or *TP53* mut evolution

-TP53 clones often stable or len-responsive

✓ Erythroid Response[1]

✓ Len (ITT Evaluable) 28/36 (77.8%)

✓ Median Hb at EOT 12.4 g/dL (+2.7 g/dL)

✓ Placebo 0 (0%)

✓ Cytogenetic Response[1]

✓ Len (ITT Evaluable) 32/34 (94.1%):

✓ 87.5% Complete (28/32)

✓ 12.5% Partial (4/32)

✓ Placebo 0 (0%)

- **Intriguing data favoring early intervention**

Maria Diez-Campelo, MD
Hematology Department, Hospital Universitario de Salamanca-IBSAL

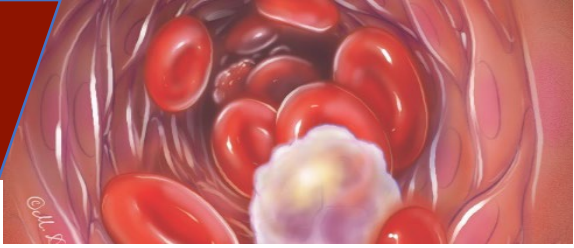
MDS: New Approaches for Lower Risk

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

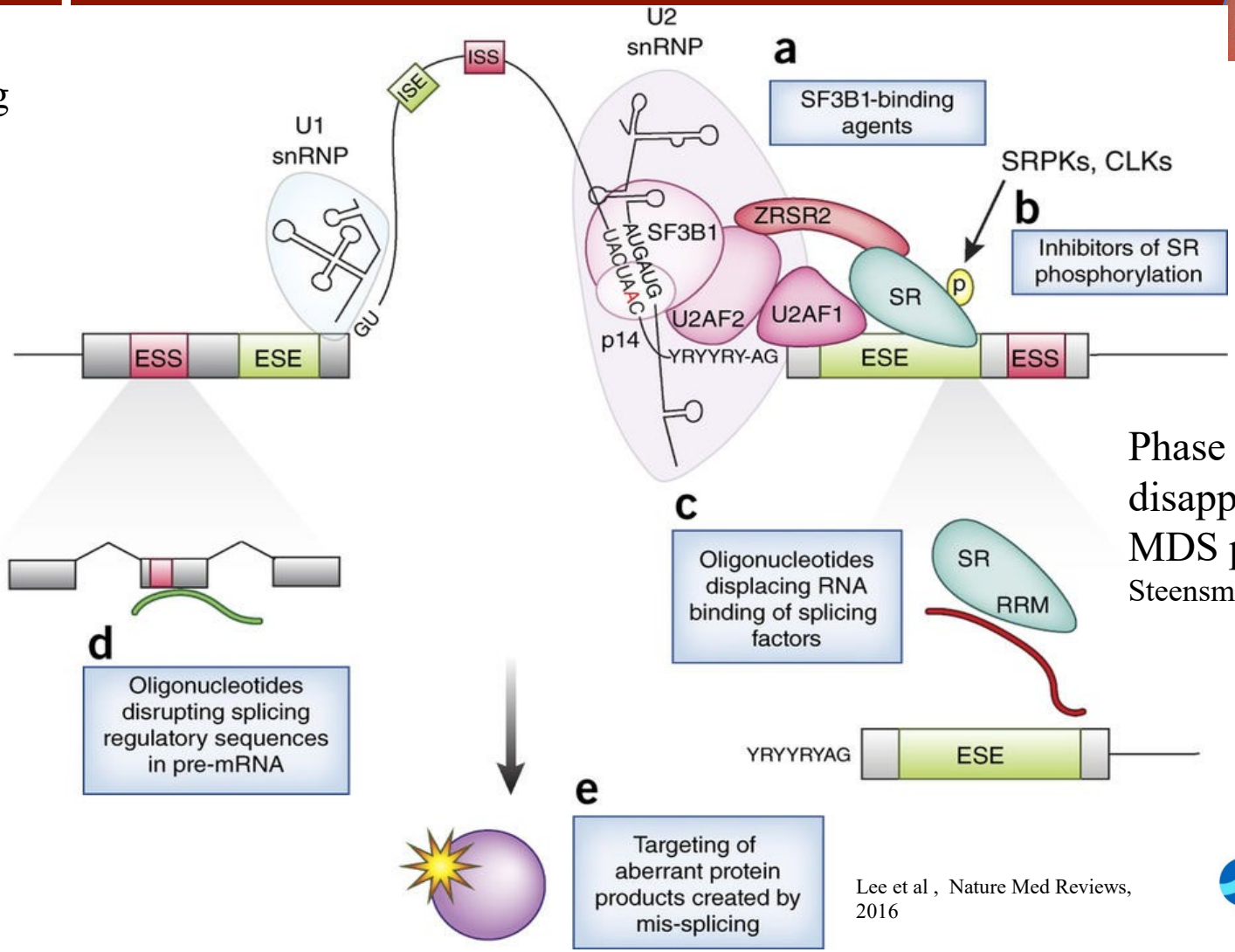
  - Some responses in MDS: Henry et al, ASH 2019

- **Short course hypomethylating agents for lower risk pts**
  - 3d decitabine higher ORR (70)% than 3d azacytidine (33%) (Sasaki et al., *NEJM Evidence* 2022)
- **Telomerase Inhibition (** Platzbecker et al ASH, #459, 2022**)**
  - **N-38, Tx Indep at 8, 12, 56 weeks: 43%, 32%, 29%**

Targeting MDS with splicing Complex mutations*



The splicing complex can be disrupted leading to synthetic lethality



Protein methyl arginase inhib

ATR inhib

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

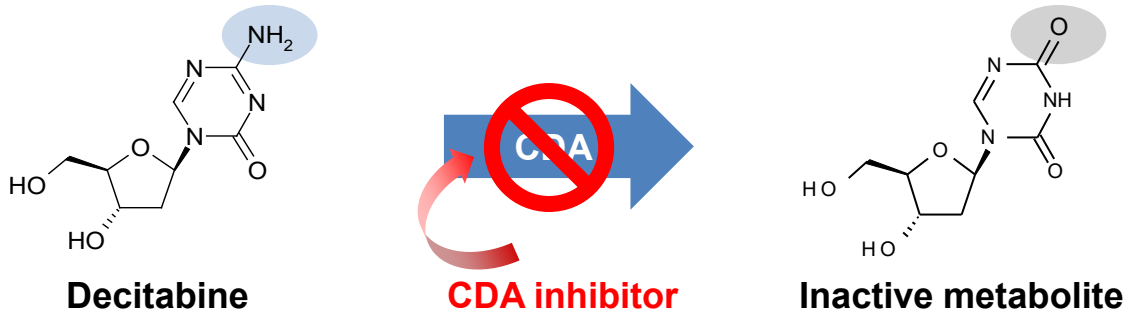
Lee et al , Nature Med Reviews, 2016

Dana-Farber Cancer Institute

*SF3B1, U2AF1, SRSF2, ZRSR2

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.

Methods/Study Design: Garcia-Manero, G, et al , ASH 2021[3]

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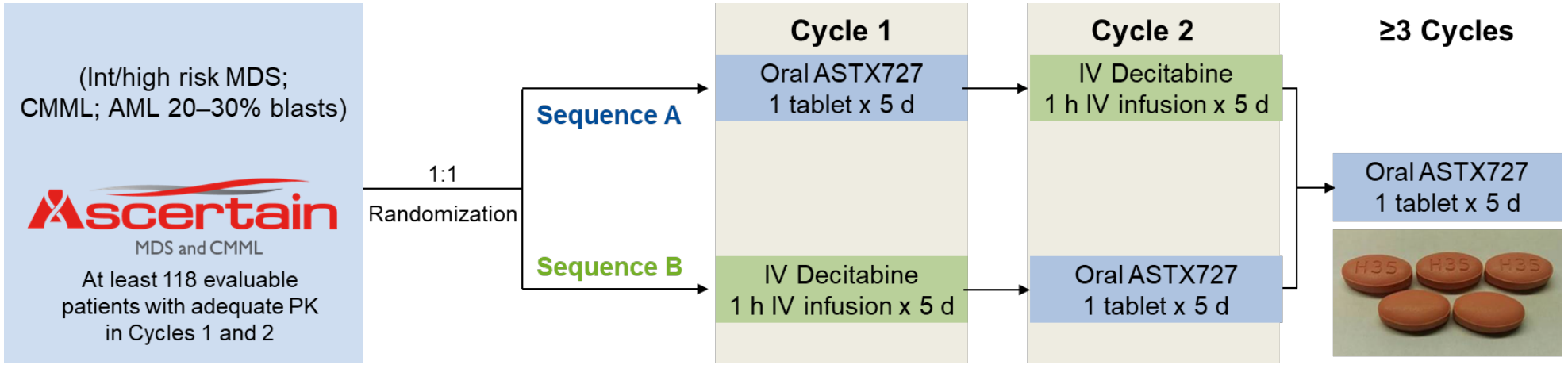

Major entry criteria:

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

Candidates for decitabine include:

Adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (**refractory anemia, refractory anemia with ringed sideroblasts**, refractory anemia with excess blasts, and chronic myelomonocytic leukemia[CMML] and **intermediate-1**, intermediate-2, and high-risk International Prognostic Scoring System groups.

-Equivalence lead to the approval of DEC-C in MDS[1]

-A total of 69 lower-risk (LR/Int-1) subjects were enrolled into ASCERTAIN) (Garcia-Manero, ASH 2021)

[3]Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1).

Results: ASCERTAIN Efficacy Response in Lower-Risk Pts[1]

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Response Category	Treated Patients (N=69[a]), n (%)	95% CI
Complete response (CR)	16 (23.2%)	(13.9, 34.9)
Partial response (PR)	0	
Marrow CR (mCR)	18 (26.1%)	(16.3, 38.1)
mCR with hematologic improvement	9 (13.0%)	(6.1, 23.3)
Hematologic improvement (HI)	5 (7.2%)	(2.4, 16.1)
HI-erythroid[3]	1 (1.4%)	(0.0, 7.8)
HI-neutrophils[3]	0	
HI-platelet[3]	4 (5.8%)	(1.6, 14.2)
Overall response (CR + PR + mCR + HI)	39 (56.5)	(44.0, 68.4)

[a] Includes 3 subjects who did not receive ASTX727 (received IV decitabine cycle 1 and did not continue)

For subjects with ≥ 5% bone marrow blasts (n=26):

- CR 7 (26.9%)
- mCR 11 (42.3%)

For the entire group (n=69):

- Median CR duration was 15.3 months
- Median duration of best response was 13.4 months
- Median time to first and best response were 3.0 months and 4.3 months, respectively
- 18 (26.0%) subjects proceeded to HCT
- c/w 37% CR rate with 3 d IV decitabine (Jabbour E, et al, Blood 2017)

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

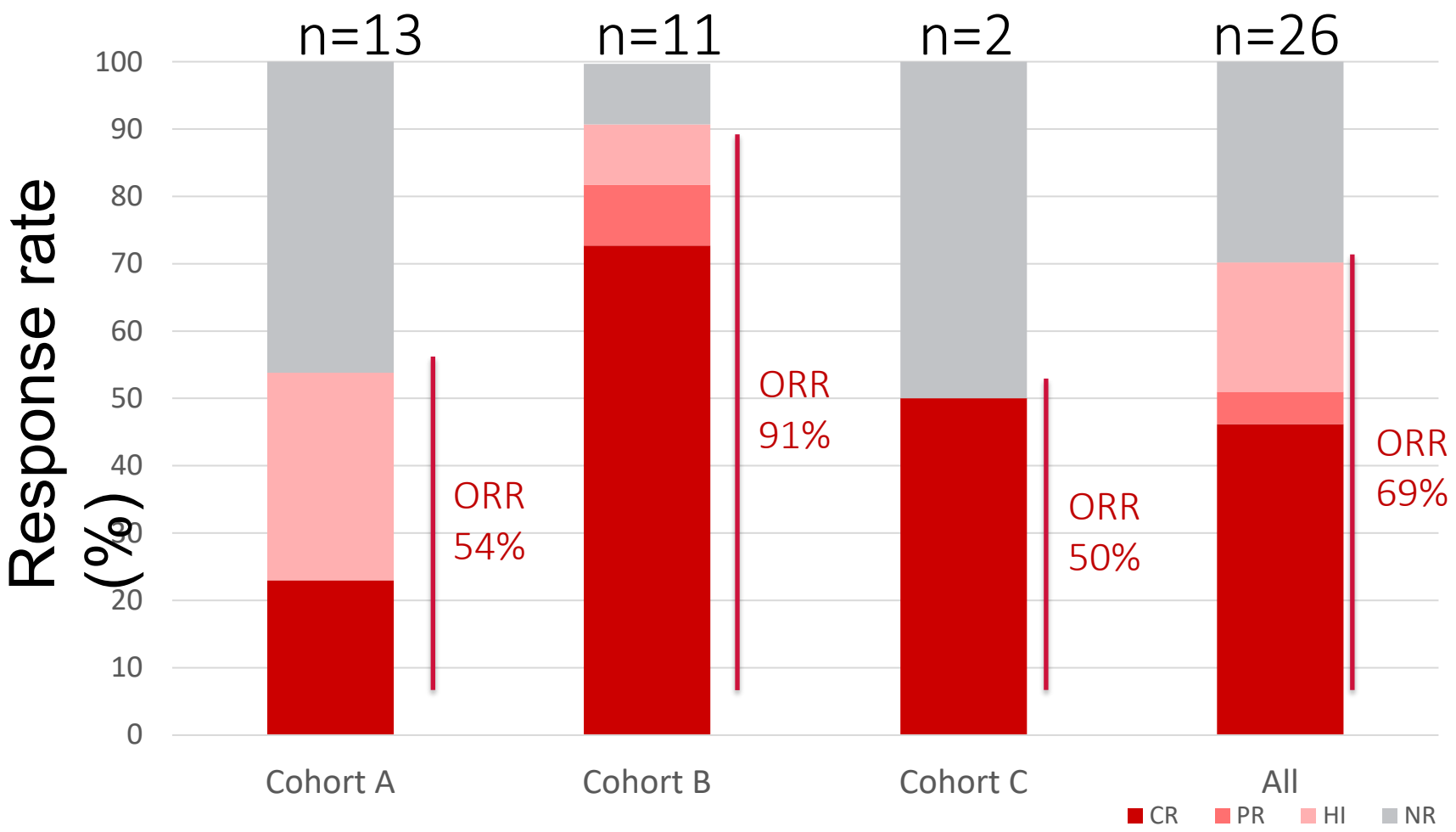
	Total (N = 31)	Arm A (Untreated) Aza + ENA (N = 13)	Arm B (HMA-Failure) ENA (N = 18)
ORR, n (%)	**21 (68)**	**11 (85)**	**10 (56)**
Complete remission	8 (26)	3 (23)	5 (28)
Partial remission	1 (3)	0 (0)	1 (6)
Marrow complete remission	9 (29)	7 (54)	2 (11)
HI only	3 (10)	1 (8)	2 (11)
No response, n (%)	**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

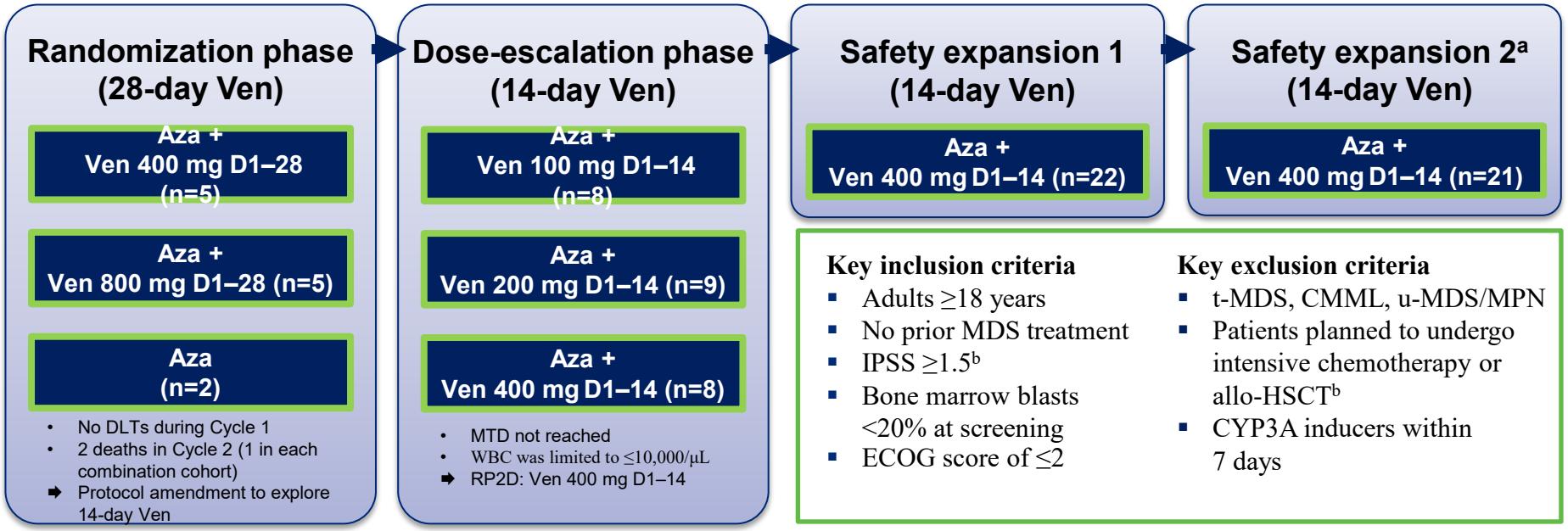
Overall response rate, *IDH1* mut MDS (Sebert ASH, 2021)



- 46% of CR (including 73% in cohort B)
- 94.4% of the responders achieved response at 3 cycles
- Only one patient received azacitidine in association with Ivo after three cycles of Ivo in cohort B, without additional response
- A. HMA failure, B. HR, naïve, C, EPO failure lower risk

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

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



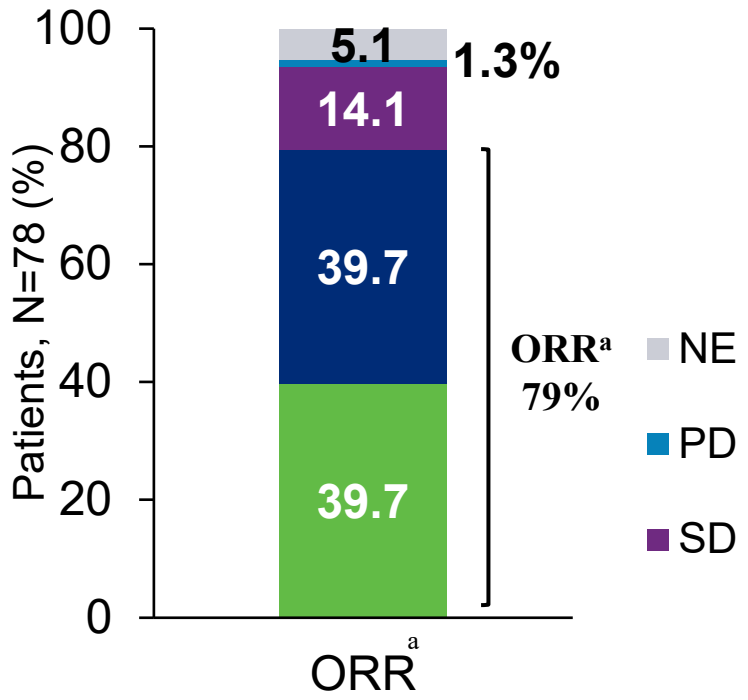
[a]Safety expansion 3 cohort is currently recruiting patients; [b]Study protocol has been amended to allow patients with higher-risk IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT

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

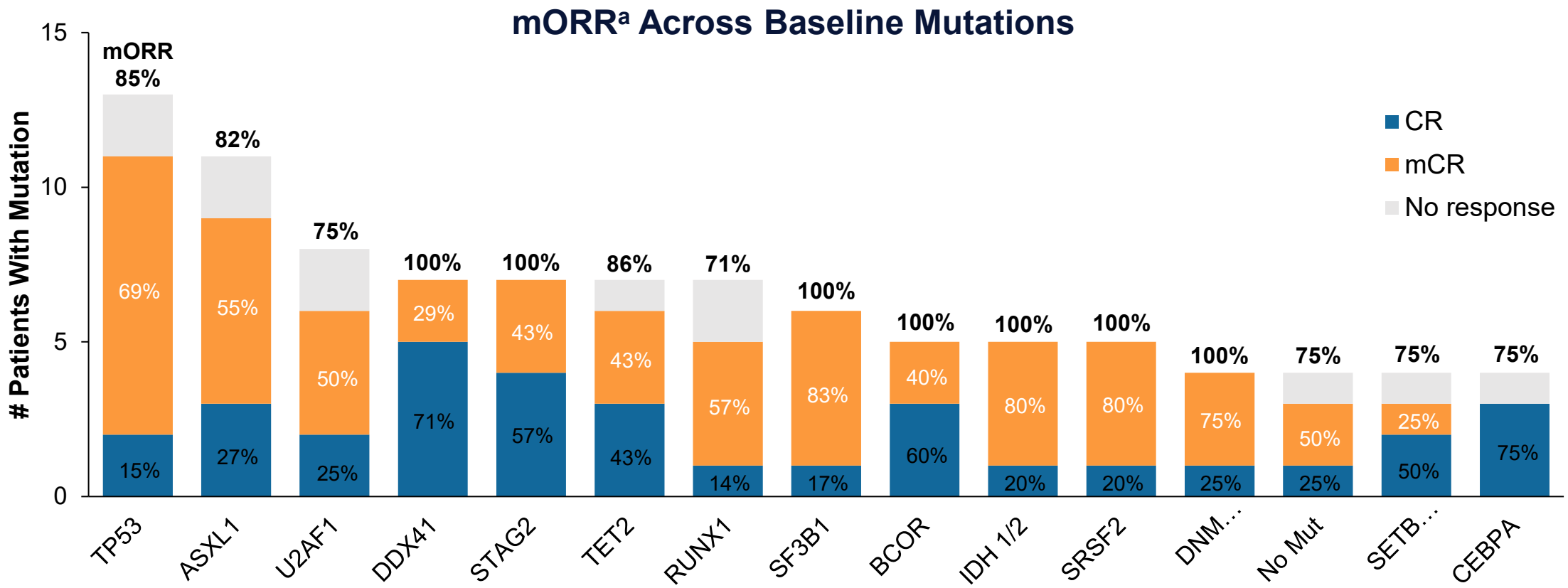
[a]Excludes patients of Arm C (Aza only); ORR includes CR + mCR + PR; PR n=0; per IWG 2006 (Cheson BD, et al. *Blood*. 2006;108(2):419–25);
[b]Excludes 5 patients from the randomization phase who received 28-day Ven
Aza, azacitidine; CR, complete remission; DoR, duration of response; IWG 2006, International 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

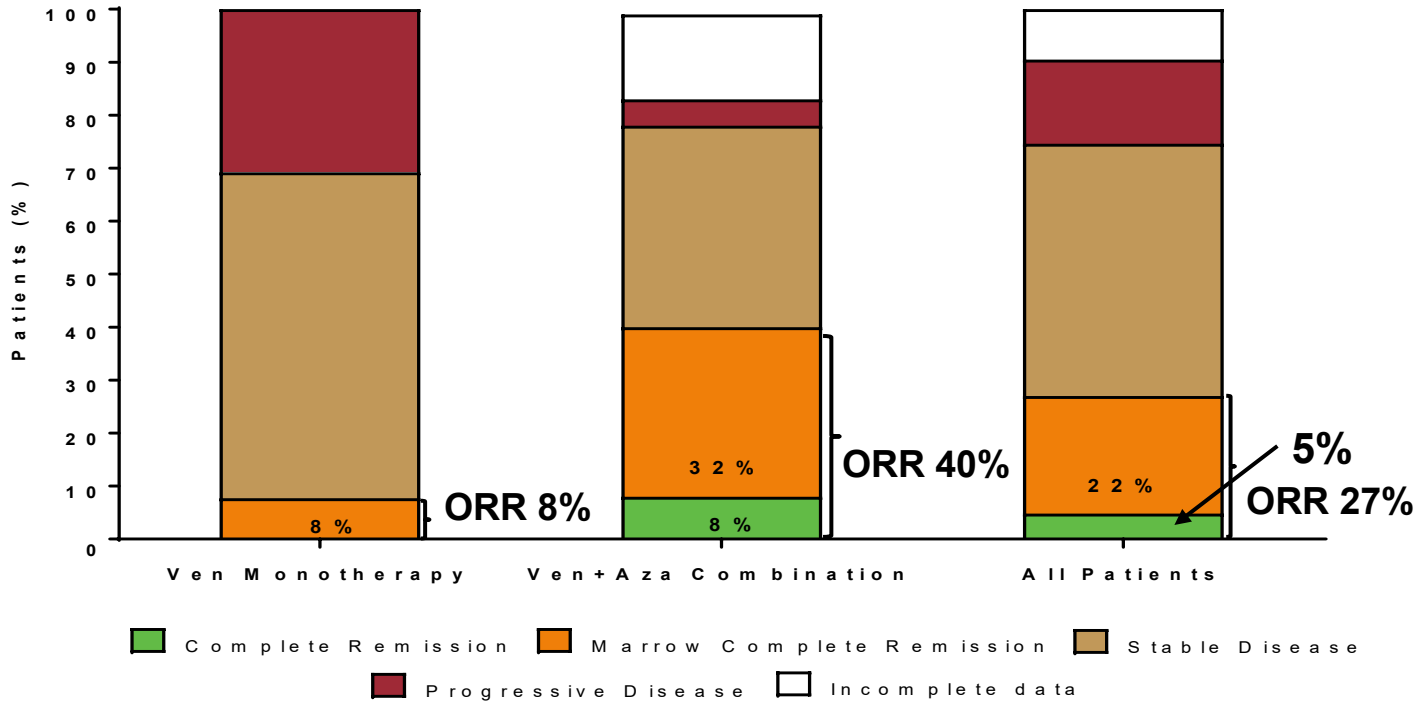
Aza/Ven Phase 1b: Broad activity across mutational spectrum that is durable among responders

Garcia
ASH 2021, abstract 241.



Broad activity that is durable among responders at RP2D

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

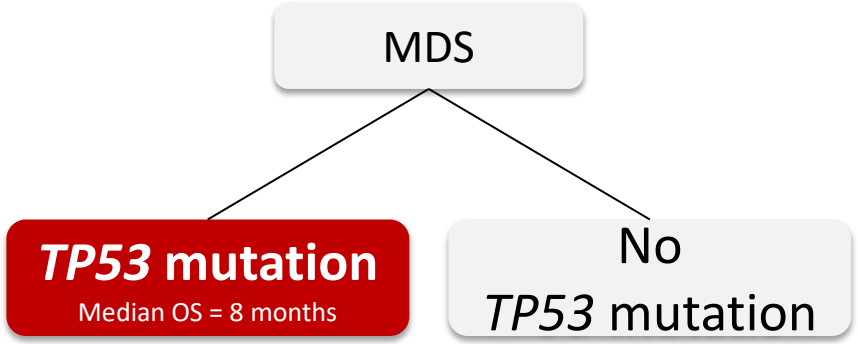


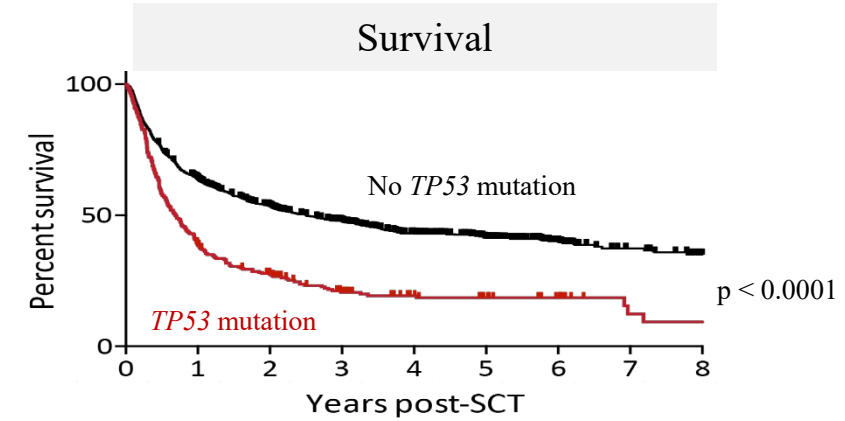
Data cutoff: Aug 30, 2019.

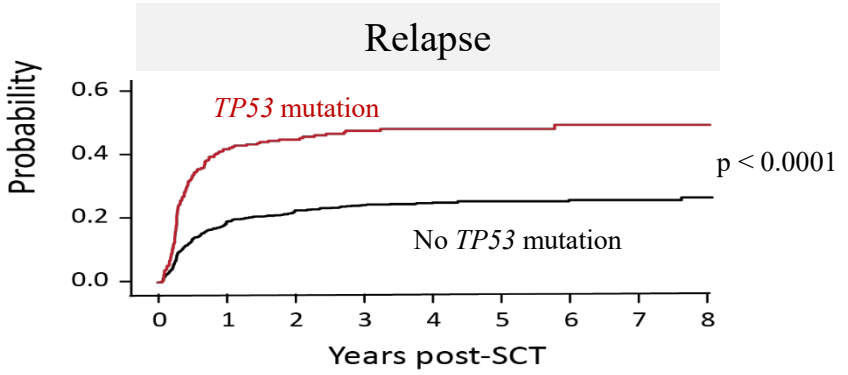
ClinicalTrials.gov. NCT02966782.
Zeidan A, et al. ASH 2019. Abstract 565.

TP53 mutated MDS

Poor prognosis Post-SCT due to early relapse





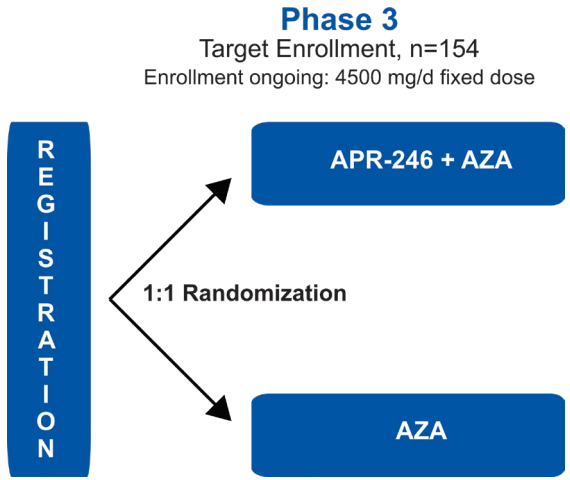


Cutler C, ASH 2020: donor v no donor higher risk MDS: n=384 48 v 27% 3 y OS in age 50-75

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

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

- Randomized study of frontline azacitidine ± APR-246 (refolding agent) in *TP53*-mutant MDS



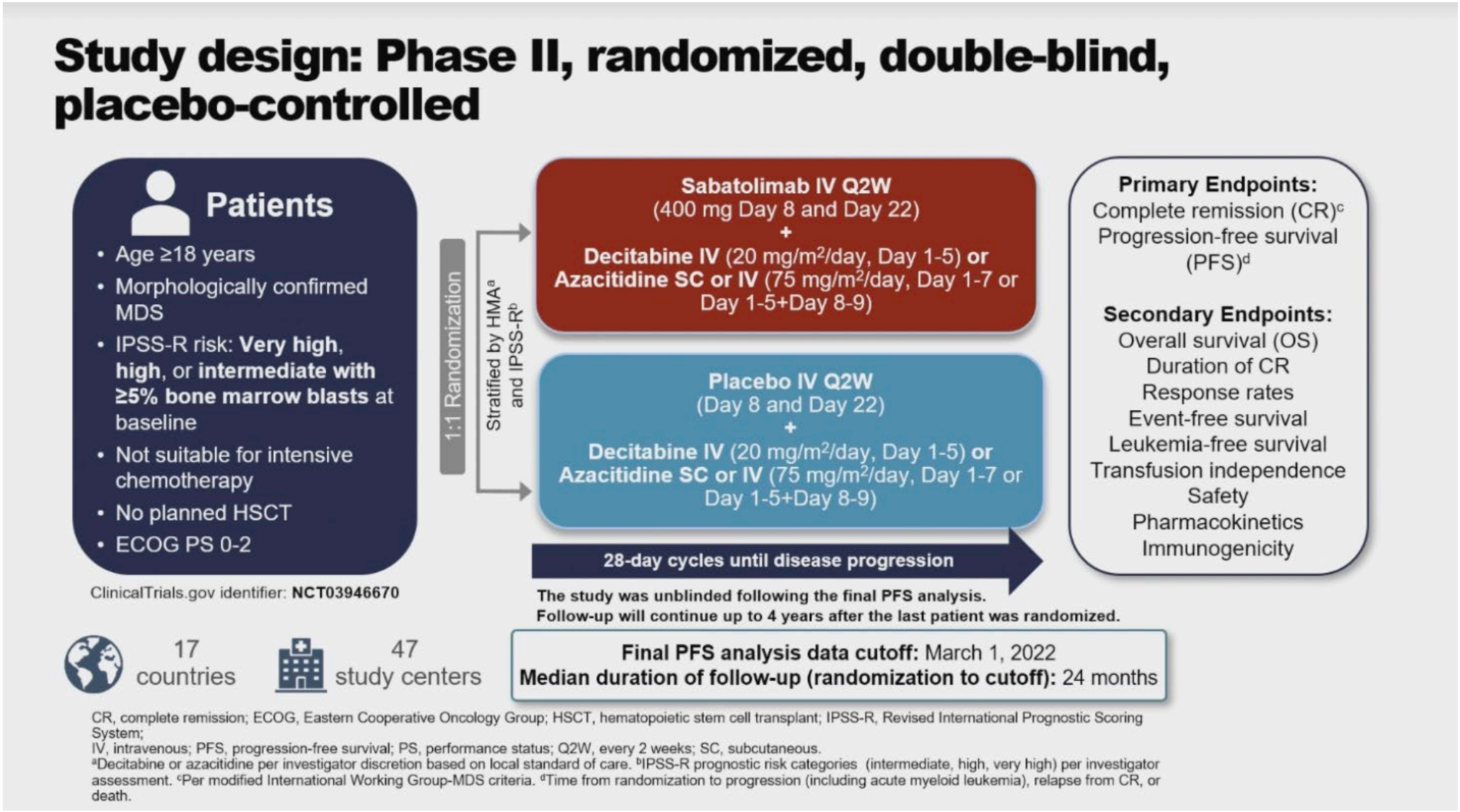
- ClinicalTrials.gov. NCT03745716.

- 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 (Not yet published so no demographics)

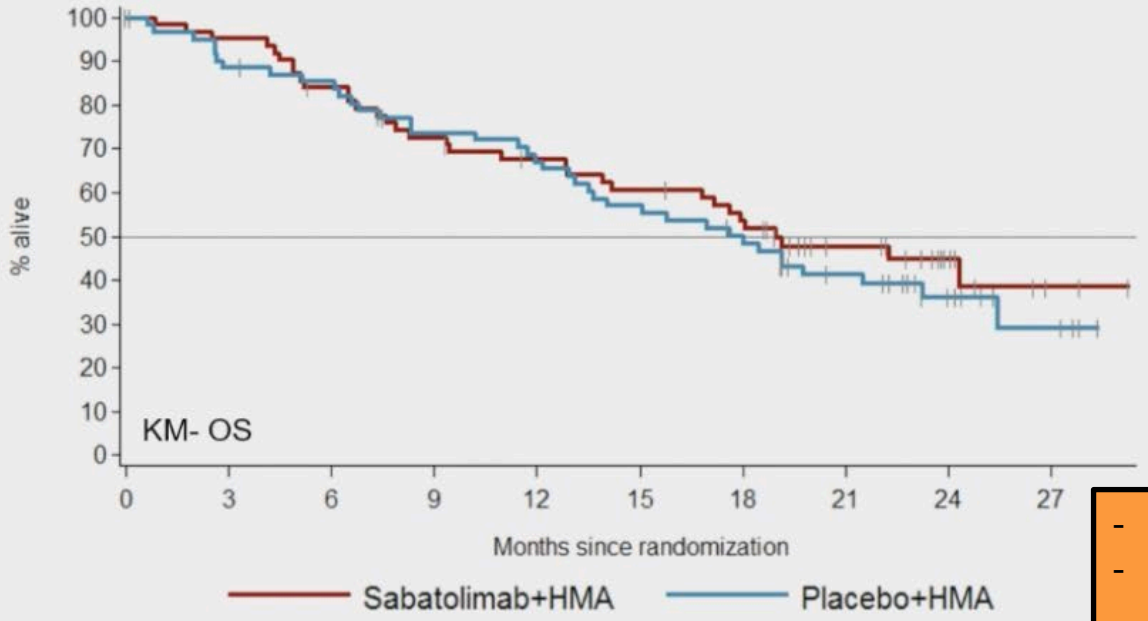
853: Primary Results of Stimulus-MDS1: A Randomized, Double-Blind, Placebo-Controlled Phase II Study of TIM-3 Inhibition with Sabatolimab Added to Hypomethylating Agents (HMAs) in Adult Patients with Higher-Risk Myelodysplastic Syndromes (MDS)



Amer Zeidan, MD
Yale University and Yale Cancer Center

853: Primary Results of Stimulus-MDS1: A Randomized, Double-Blind, Placebo-Controlled Phase II Study of TIM-3 Inhibition with Sabatolimab Added to Hypomethylating Agents (HMAs) in Adult Patients with Higher-Risk Myelodysplastic Syndromes (MDS)

Overall survival and leukemia-free survival in patients receiving sabatolimab + HMA compared with placebo + HMA



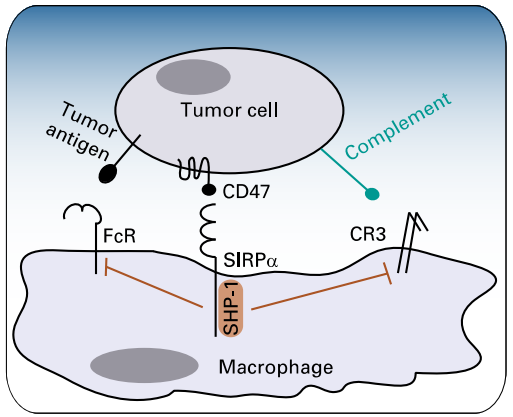
	Sabatolimab + HMA n=65	Placebo + HMA n=62
OS,[a] median (95% CI) , mo	19.0 (13.9-NE)	18.0 (13.1-23.2)
Hazard ratio (95% CI)[b]	0.905 (0.565-1.450)	
LFS, median (95% CI), mo	16.8 (8.8-NE)	13.6 (9.8-19.8)
Hazard ratio (95% CI)[b]	0.951 (0.578-1.567)	

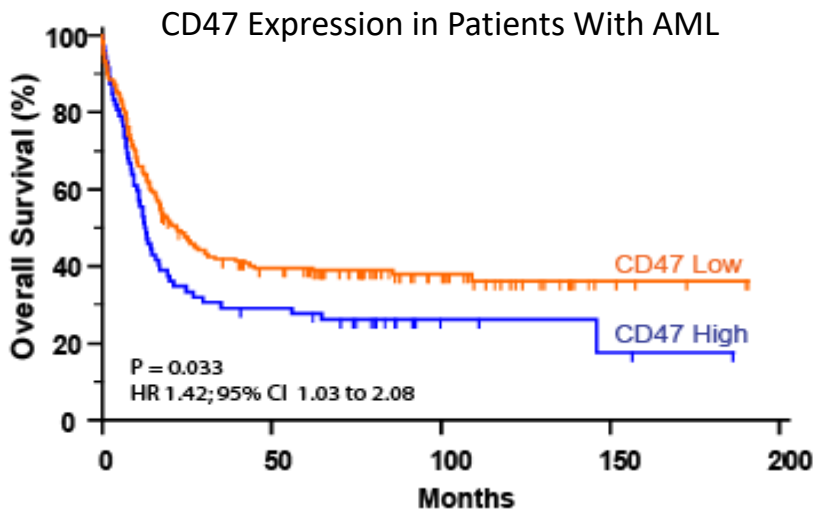
- **Negative trial**
- **Subset of patients with < 10% blasts seemed to benefit (unplanned analysis) → ? Delayed onset effect of IO?**
- **Phase III (STIMULUS-MDS2) is ongoing (endpoint: OS)**

LFS, leukemia-free survival; NE, not estimable; OS, overall survival.
[a]The median follow-up time for OS (time from the date of randomization to the date of OS event or the date of censoring for OS [i.e., the last contact date]) was 17.15 months
[b]Calculated via Cox model stratified by IPSS-R.

CD47

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

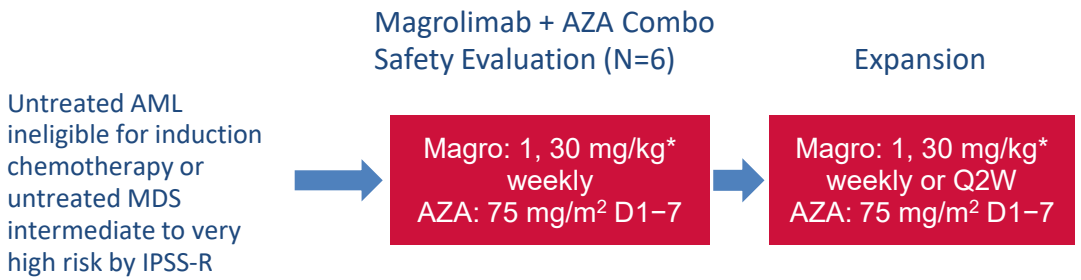




- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in patients with AML

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.

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.

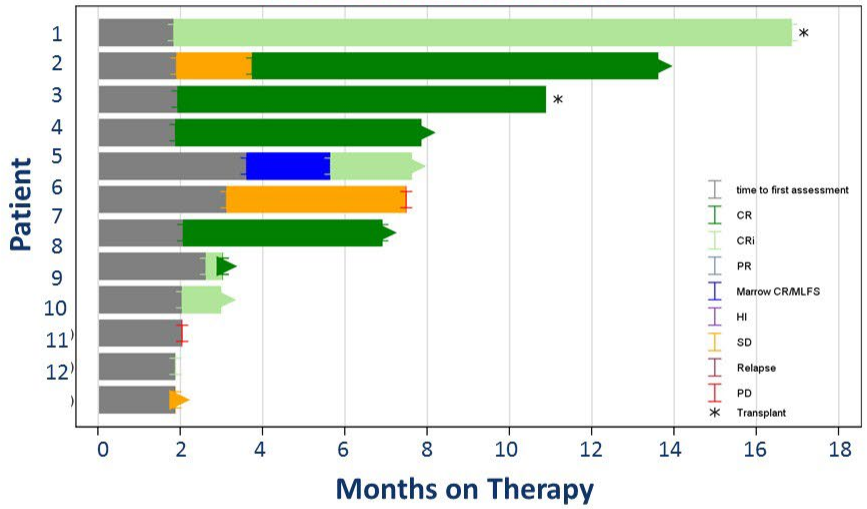
Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

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



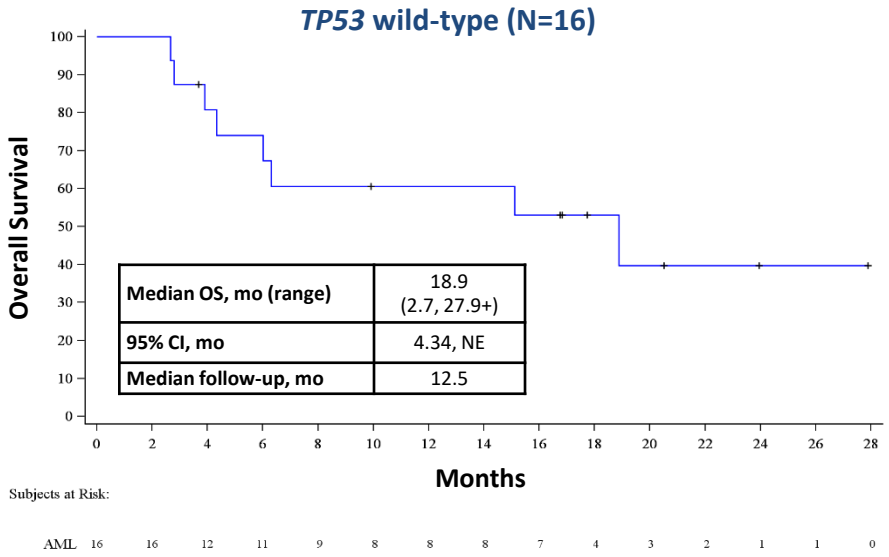
- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax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

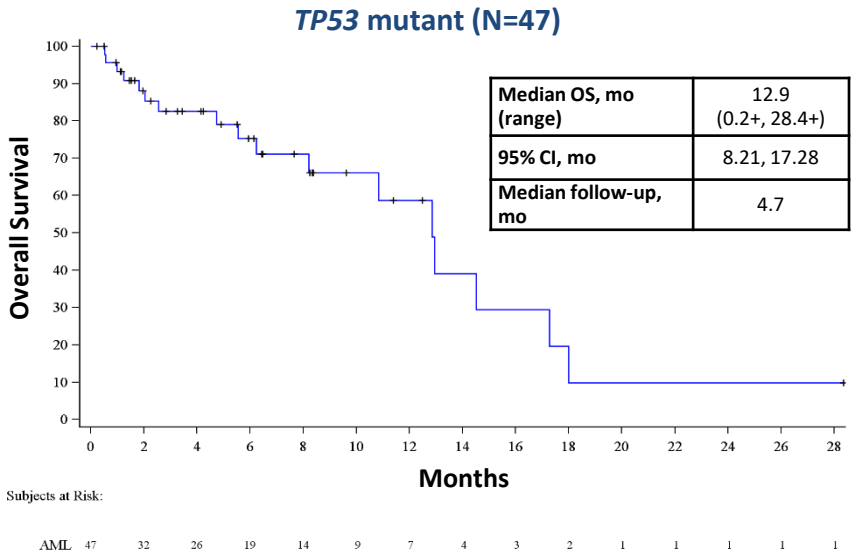
1. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

9/16 pts cleared TP53 VAF to less than 5%

Sallman D, et al, 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

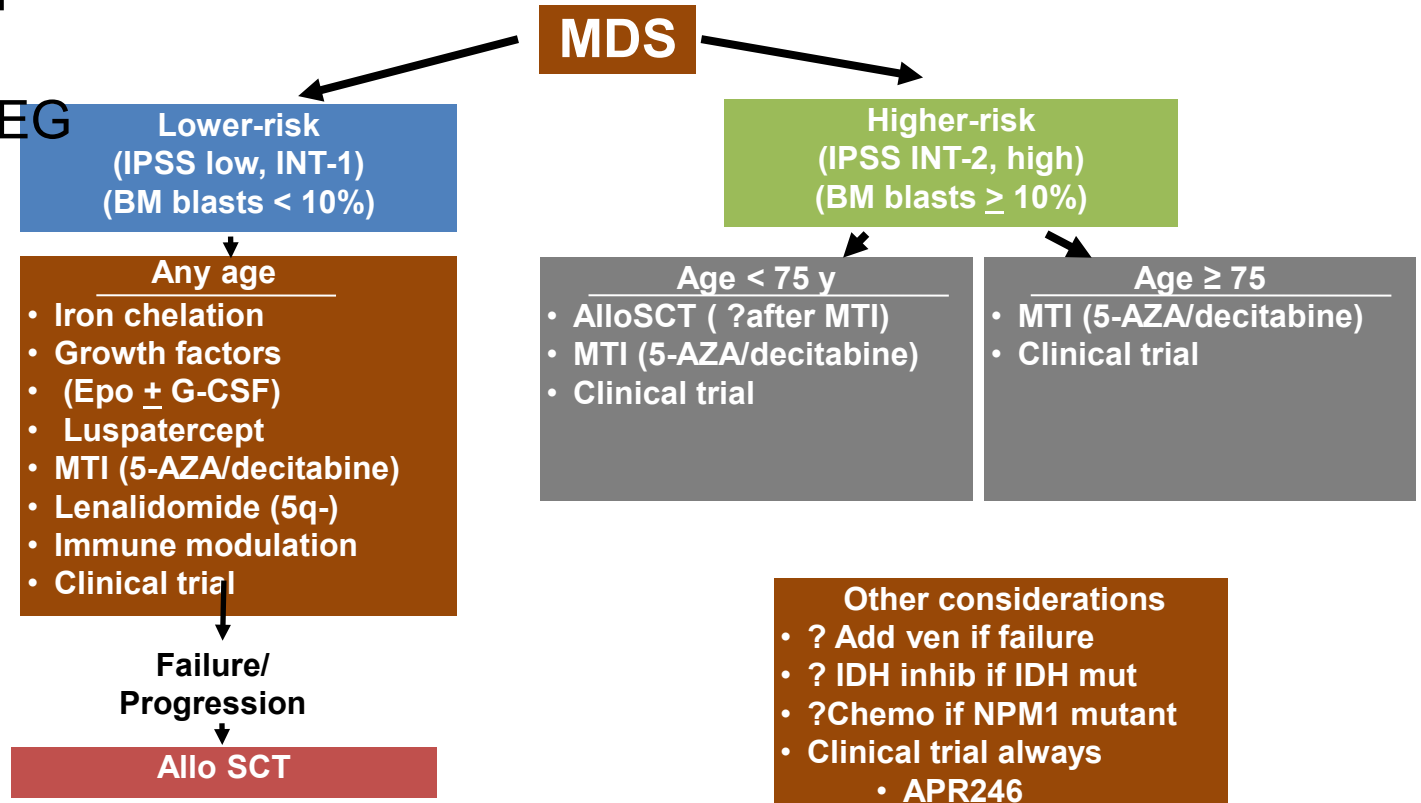
NE, not evaluable.

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

Key clin trials
-aza+/-PEV…..NEG
-aza+/- APR…..NEG
-aza+/-VEN…accrued
-aza+/-MAG…..OG
-aza+/-SAB…. OG/NEG

Proposed Treatment Algorithm for Patients With MDS: 2022



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

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Alliance

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Academic Collaborators

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- Worldwide: E. Estey*, C Schiffer, H Dohner, C Thiede, F. LoCoco* and many others.

* In memory

The End

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