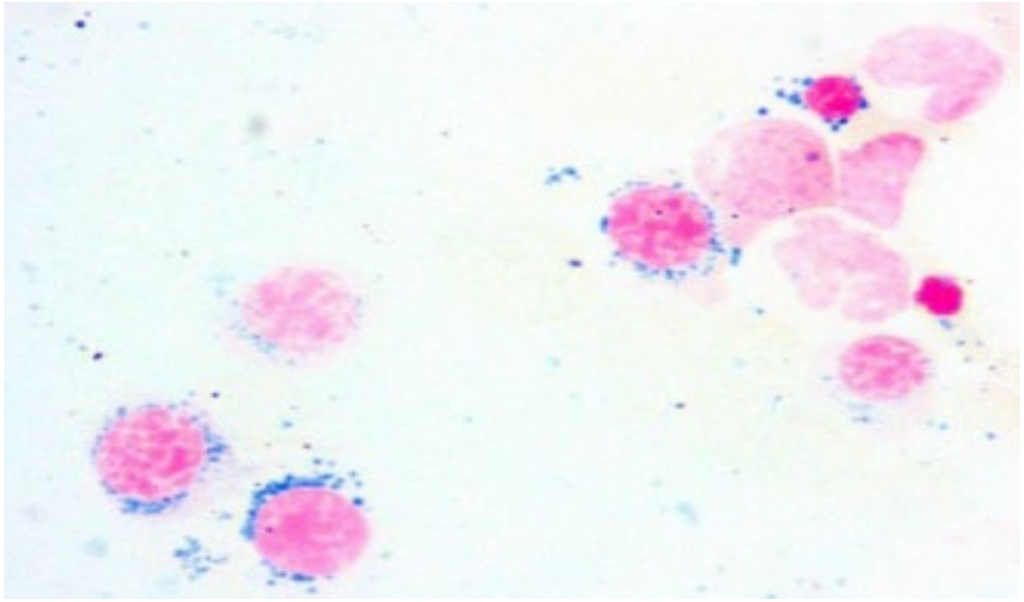
Myelodysplastic Syndromes: New Thoughts on Prognosis and Therapy



Richard M. Stone, MD

Lunder Family Chair in Leukemia

Director, Translational Research, Leukemia Division, Medical Oncology

Chief of Staff

Dana-Farber Cancer Institute

Professor of Medicine

Harvard Medical School

Boston, MA

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, New thoughts: Outline

- Increasingly sophisticated prognostication
- Therapy of lower risk disease
  - Lenalidomide in 5q-
  - Erythropoietin (EPO) +/- G-CSF; Lenalidomide +EPO
  - Luspatercept
  - Others; e.g Low dose decitabine
- Therapy of higher risk disease
  - HMA (including now: Oral decitabine/cytidine deaminase inhibitor=ASTX727), alloSCT if possible, remains the standard
    - Maybe
      - » add venetoclax, IDH inhibitor
    - Horizon
      - » aCD47,CPI, TP53 refolding, NAEi

MDS, New thoughts: Diagnosis

Will there be a lot fewer MDS pts?

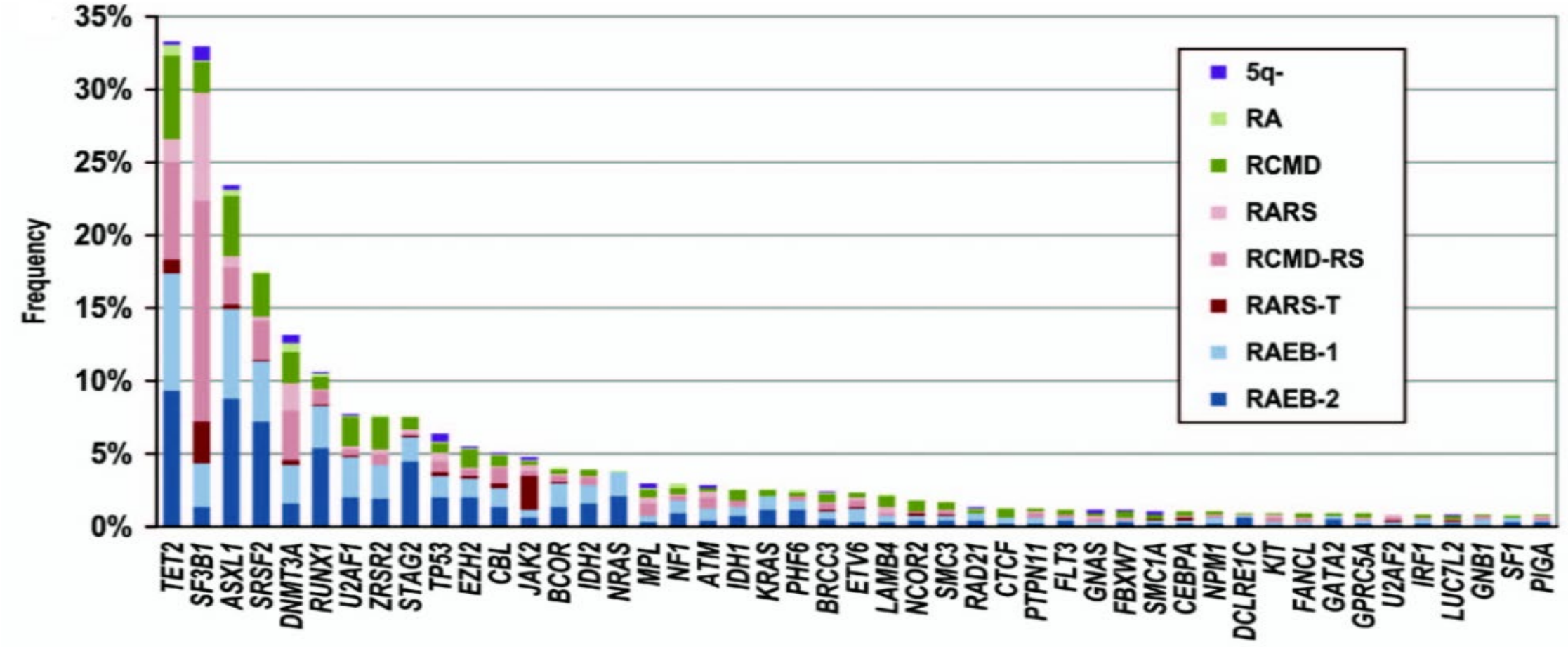
WHO: < 20% blasts is MDS

ICC: < 10% blasts is MDS (Arber D et al, *Blood* 2022)

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, which will facilitate optimizing the management of such patients. In the future, genetic features rather than an arbitrary blast cutoff may drive treatment decisions in this group (Estey, E et al , *Blood* 2022)

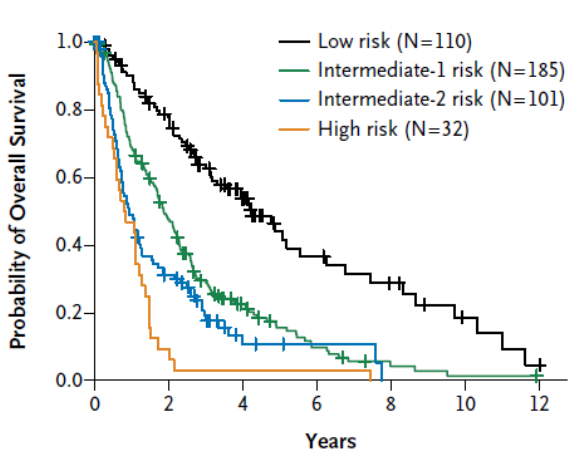
Recurrent Genetic Mutations in MDS

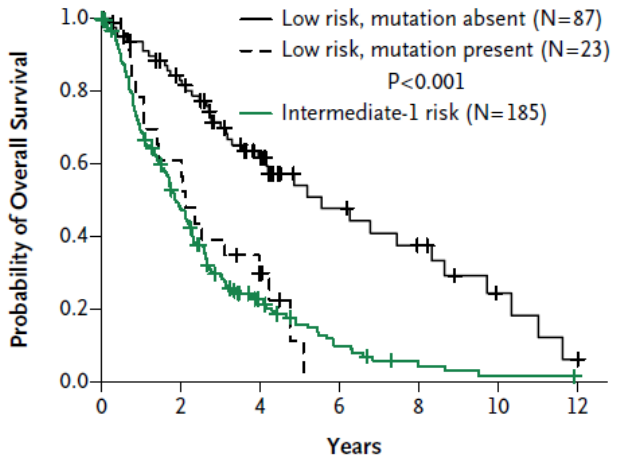
~90% of patients have a mutation by NGS

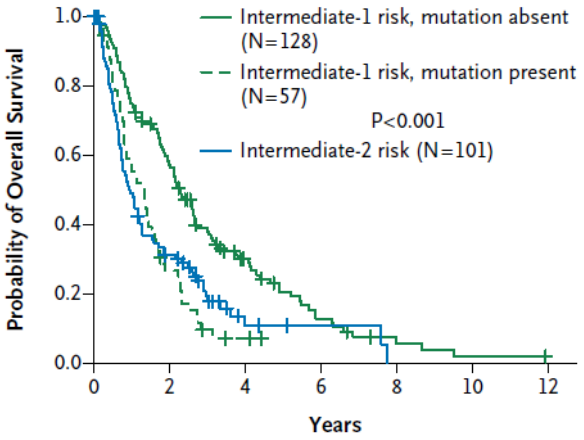


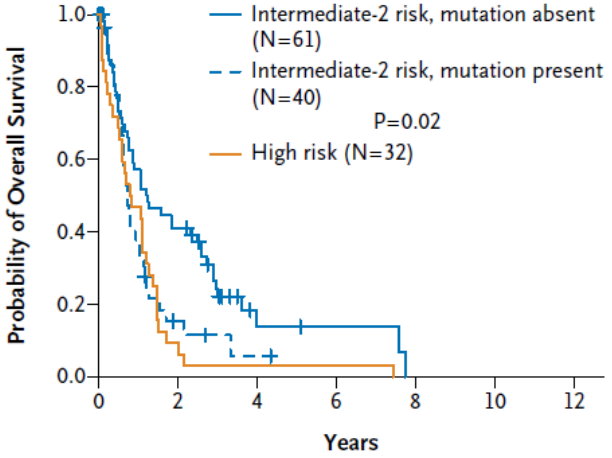
Haferlach et al., *Leukemia* (2014) 28, 241–247

Impact of Mutations by IPSS Group









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

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 blasts, 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)

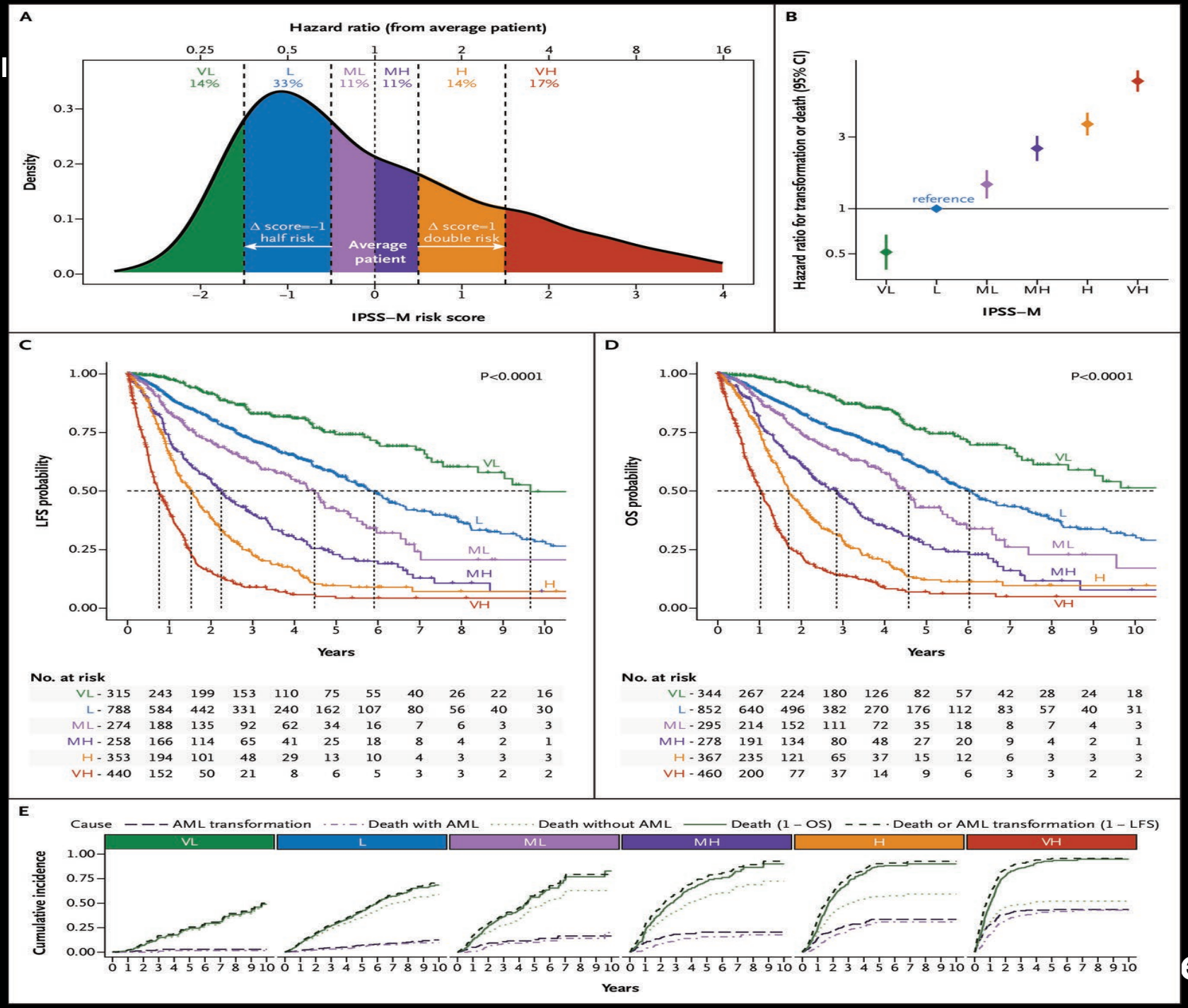
-6 subgroups

-works in s-MDS and t-MDS

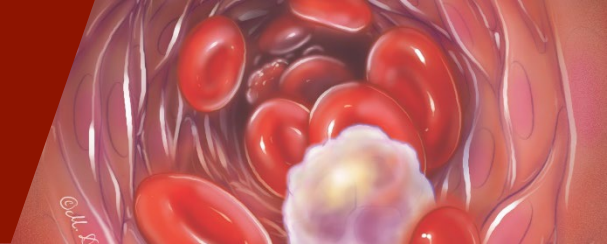
-outperforms IPSS-R

-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)
- Higher risk (HMA, chemo [*NPM1* mut] alloSCT)

Future

Integrate muts in prognostic algorithm

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

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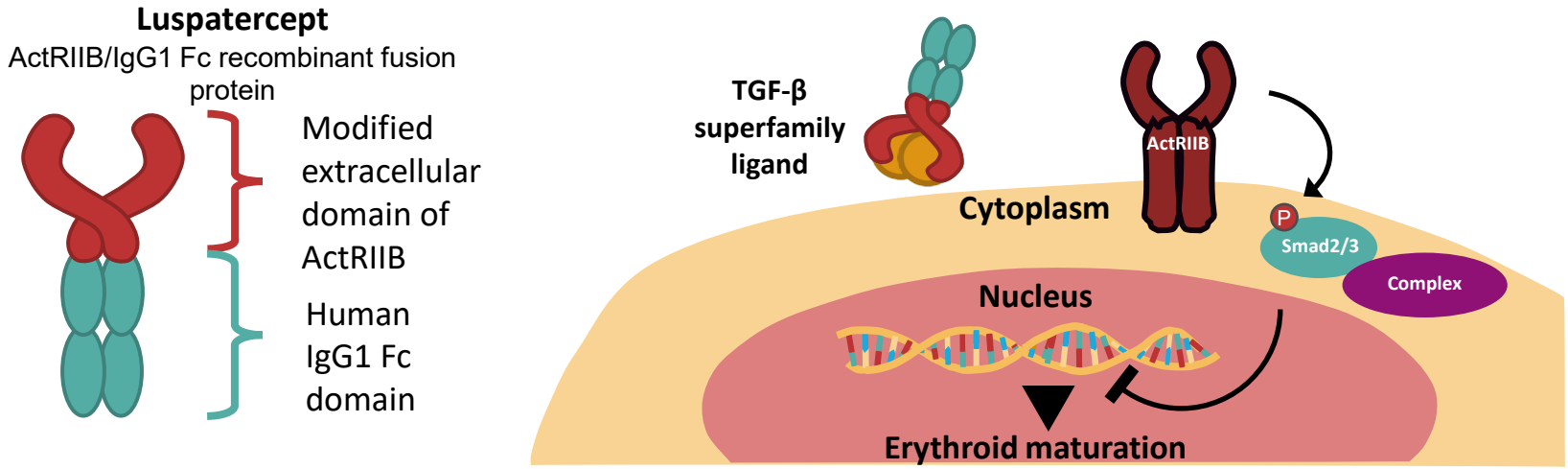
MEDALIST Luspatercept Trial

- 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]

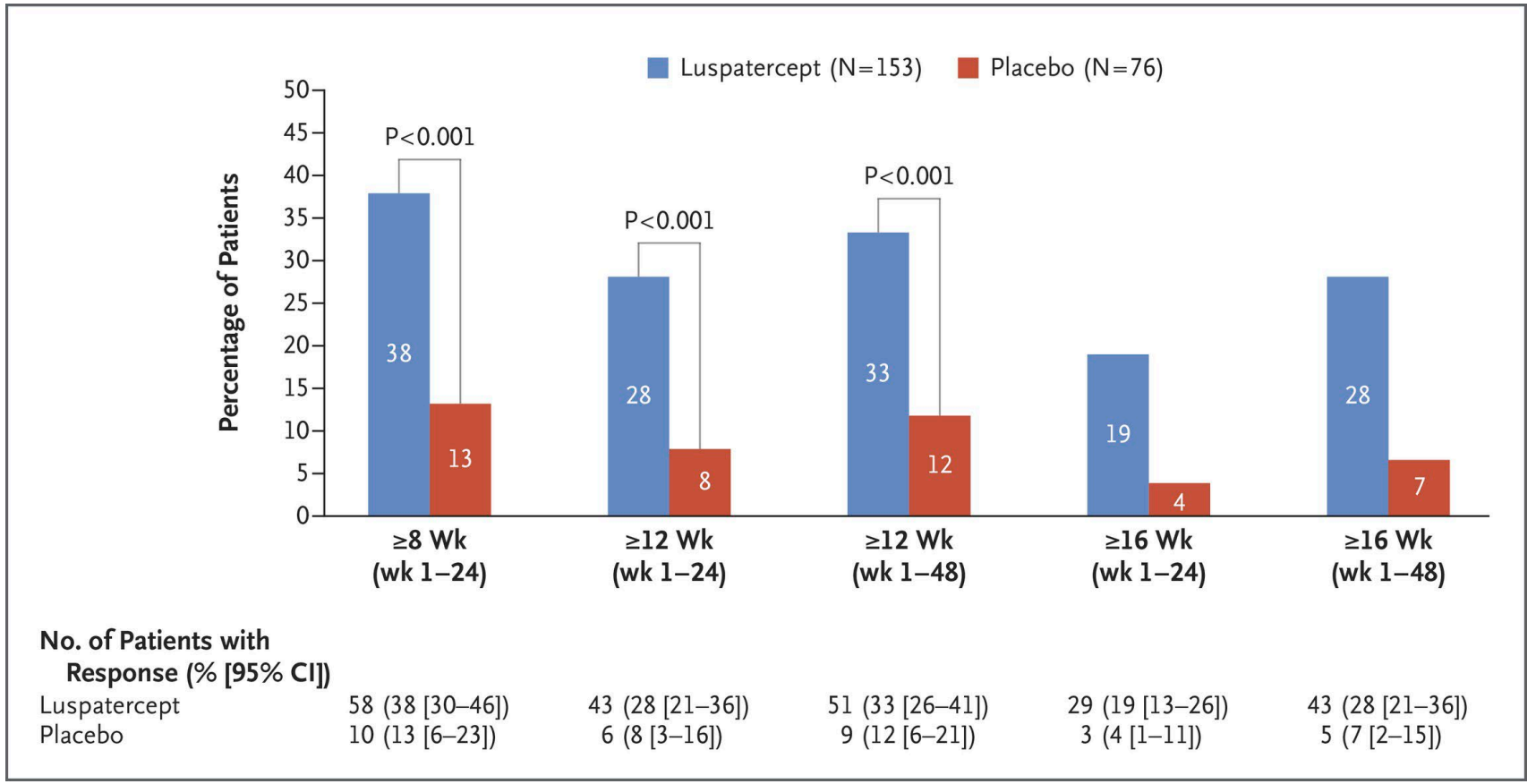


1. Suragani RN, et al. *Nat Med*. 2014;20:408.;
2. Platzbecker U, et. A. Lancet Oncol 2017; 18:1338.

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

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



No. of Patients with Response (% [95% CI])					
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

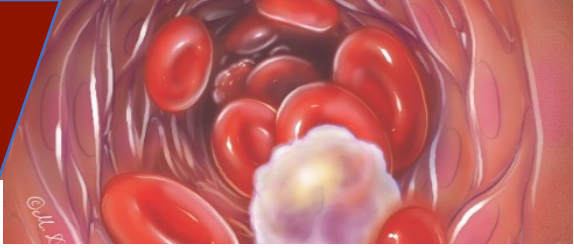
MDS: New Approaches for Lower Risk

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

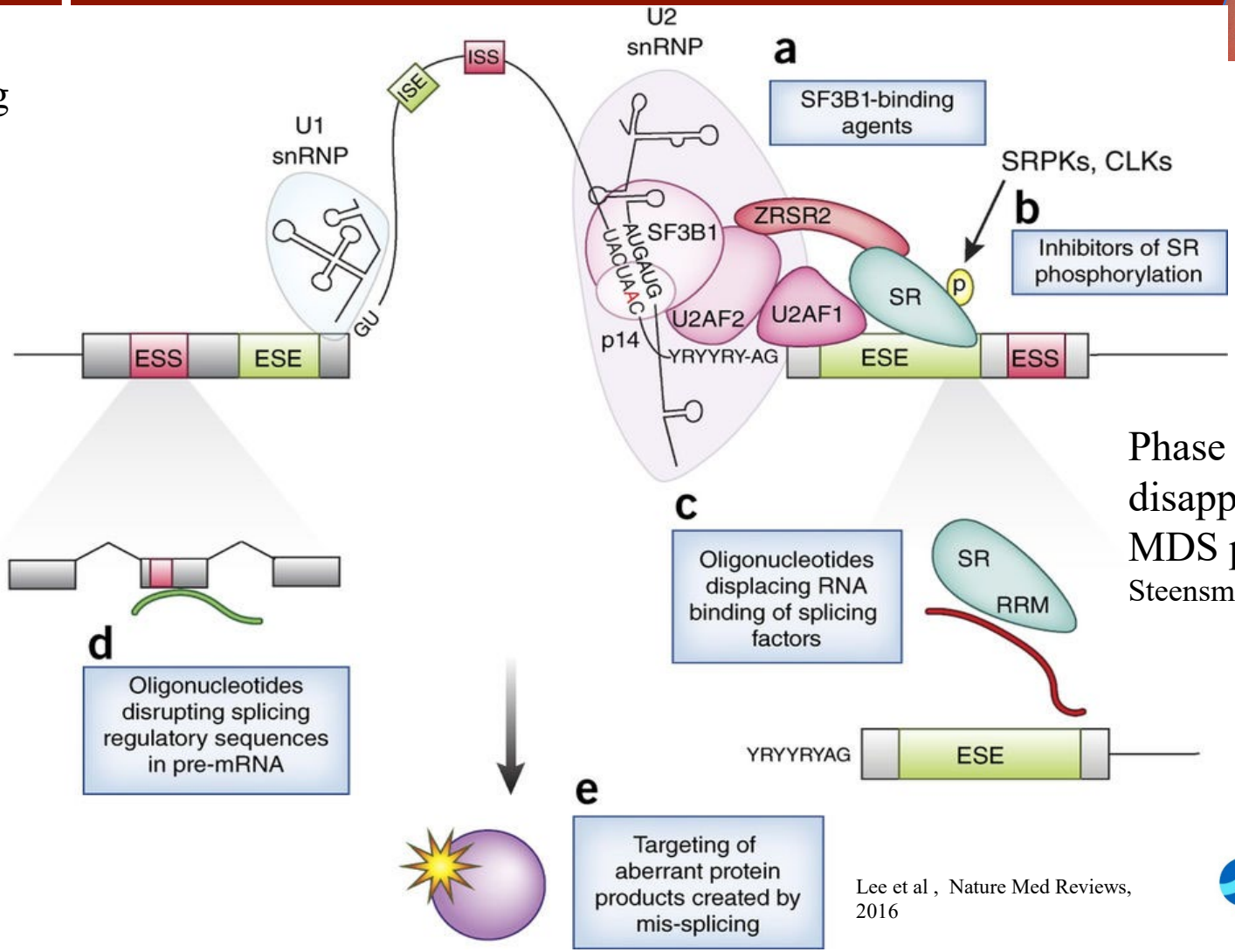
  - Some responses in MDS: Henry et al, ASH 2019

- **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**

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

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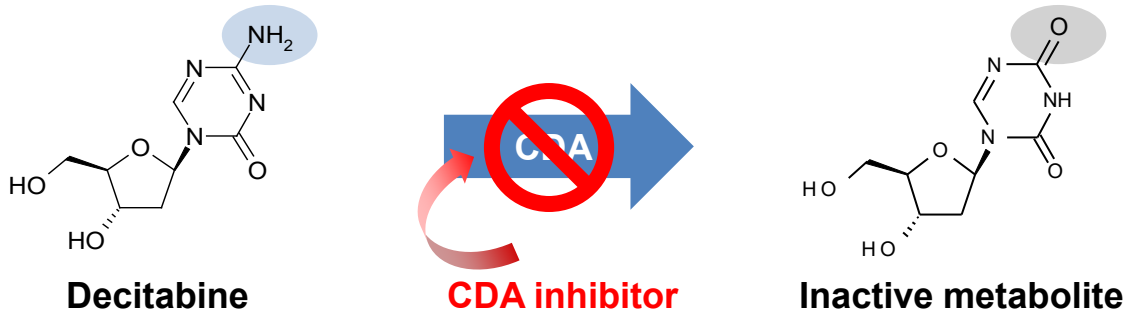
*SF3B1, U2AF1, SRSF2, ZRSR2

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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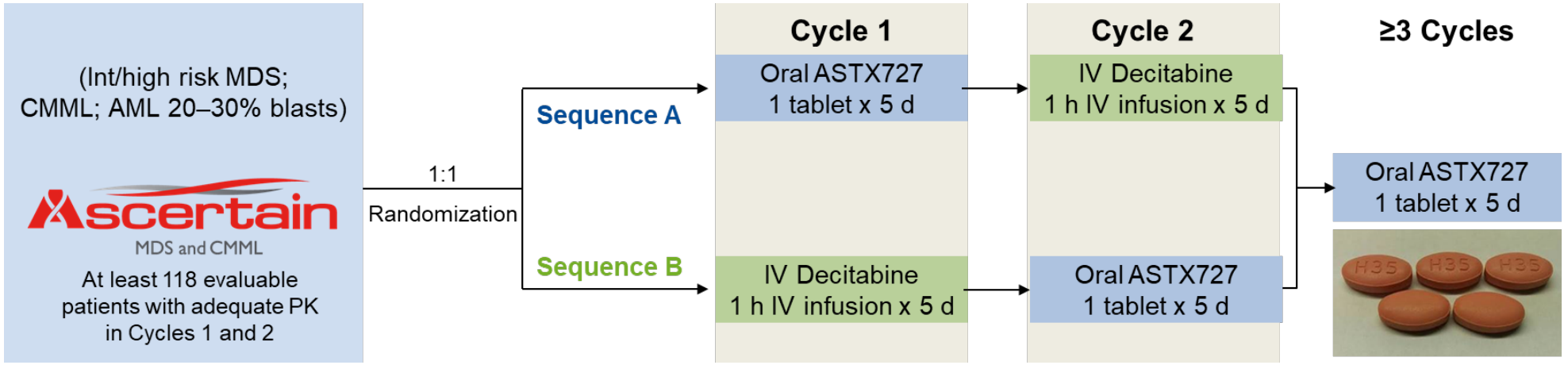


Major entry criteria:

- 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]

Place video here

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

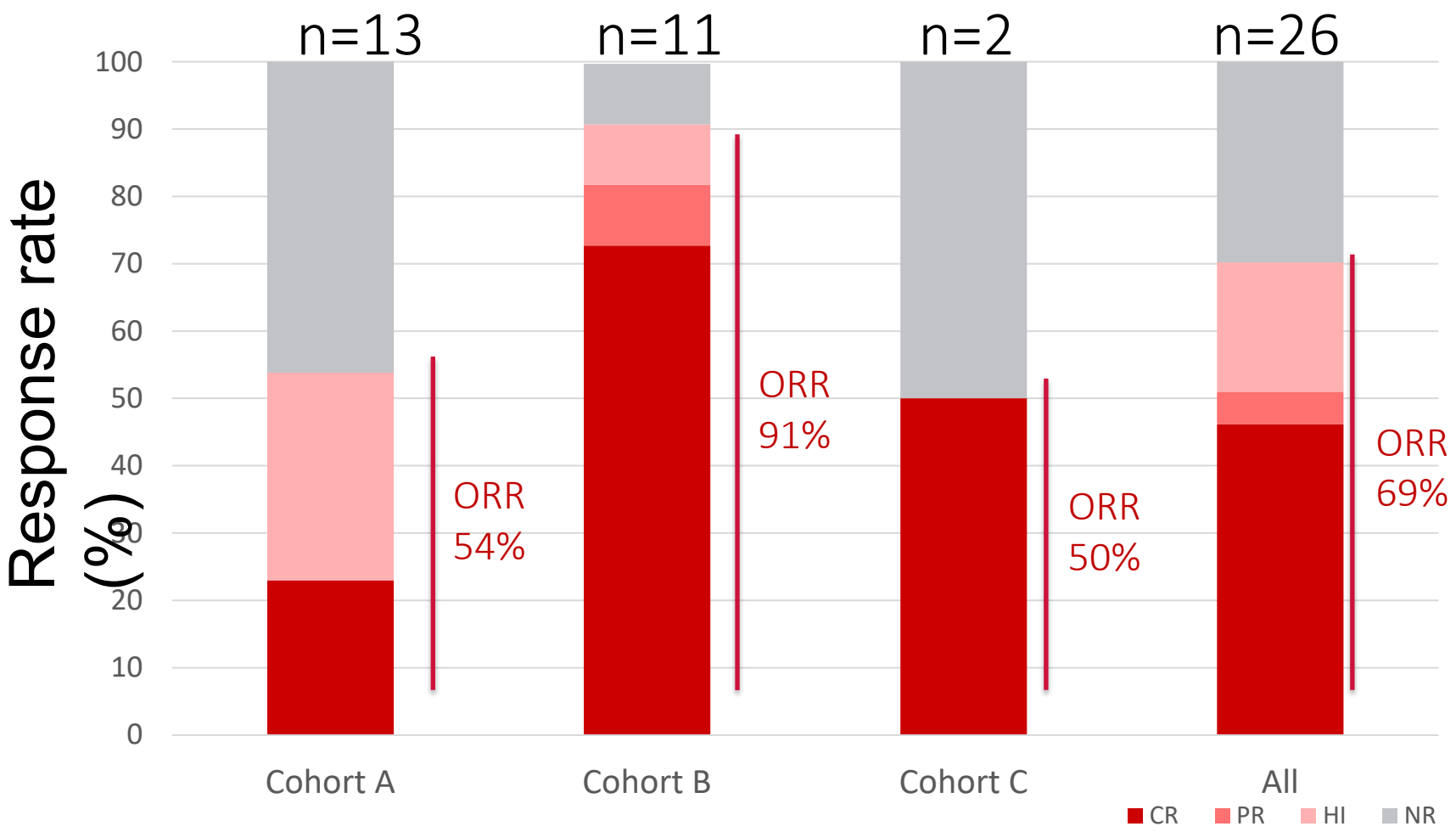
	Total (N = 31)	Arm A (Untreated) Aza + ENA (N = 13)	Arm B (HMA-Failure) ENA (N = 18)
ORR, n (%)	**21 (68)**	**11 (85)**	**10 (56)**
Complete remission	8 (26)	3 (23)	5 (28)
Partial remission	1 (3)	0 (0)	1 (6)
Marrow complete remission	9 (29)	7 (54)	2 (11)
HI only	3 (10)	1 (8)	2 (11)
No response, n (%)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

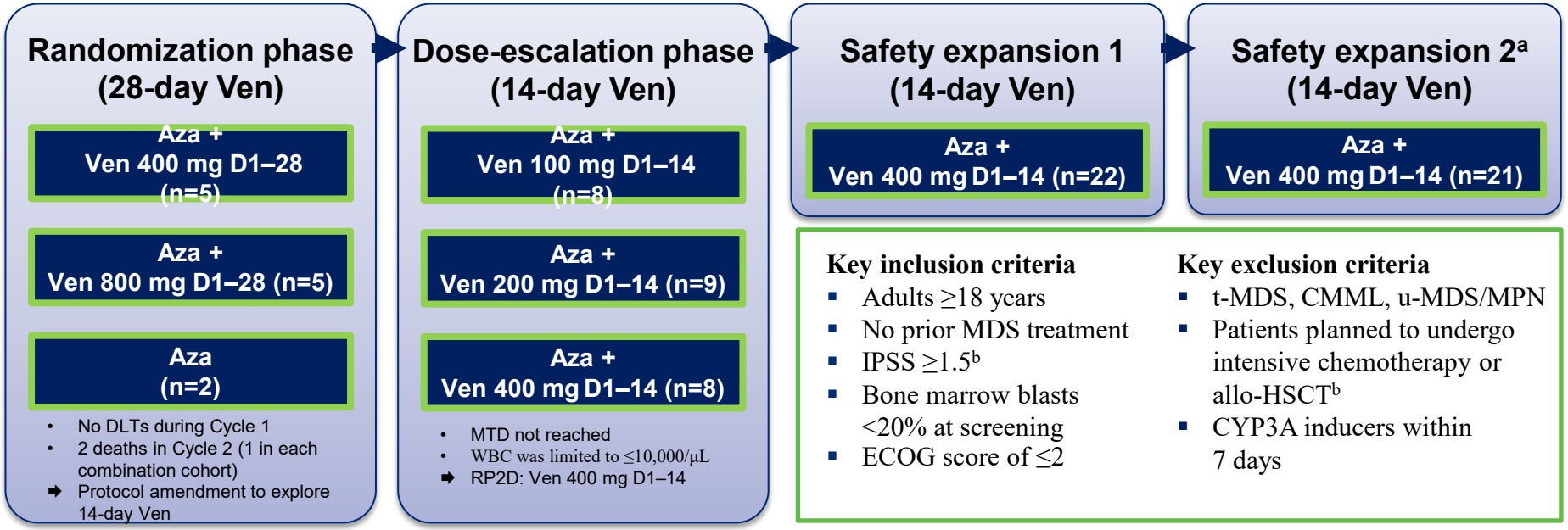
Overall response rate, *IDH1* mut MDS (Sebert ASH, 2021)



- 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



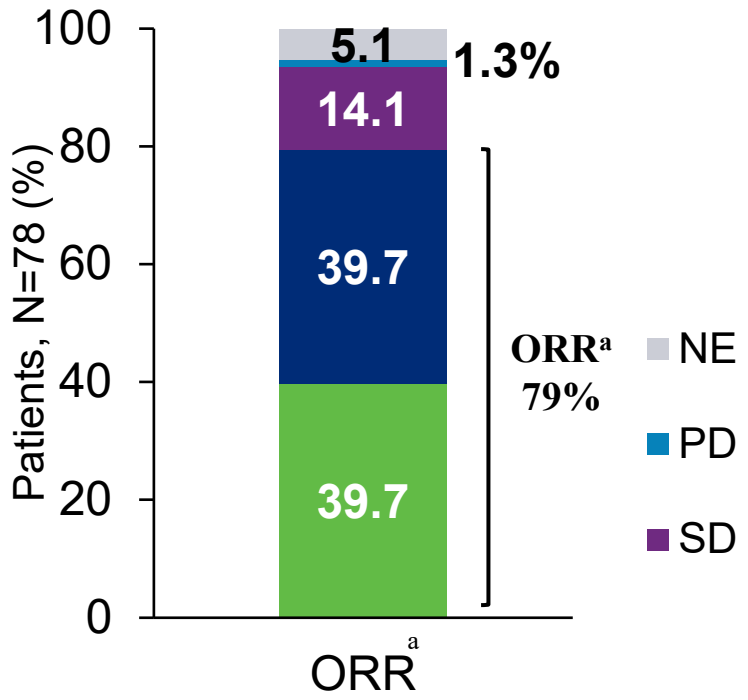
[a]Safety expansion 3 cohort is currently recruiting patients; [b]Study protocol has been amended to allow patients with higher-risk IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT

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)

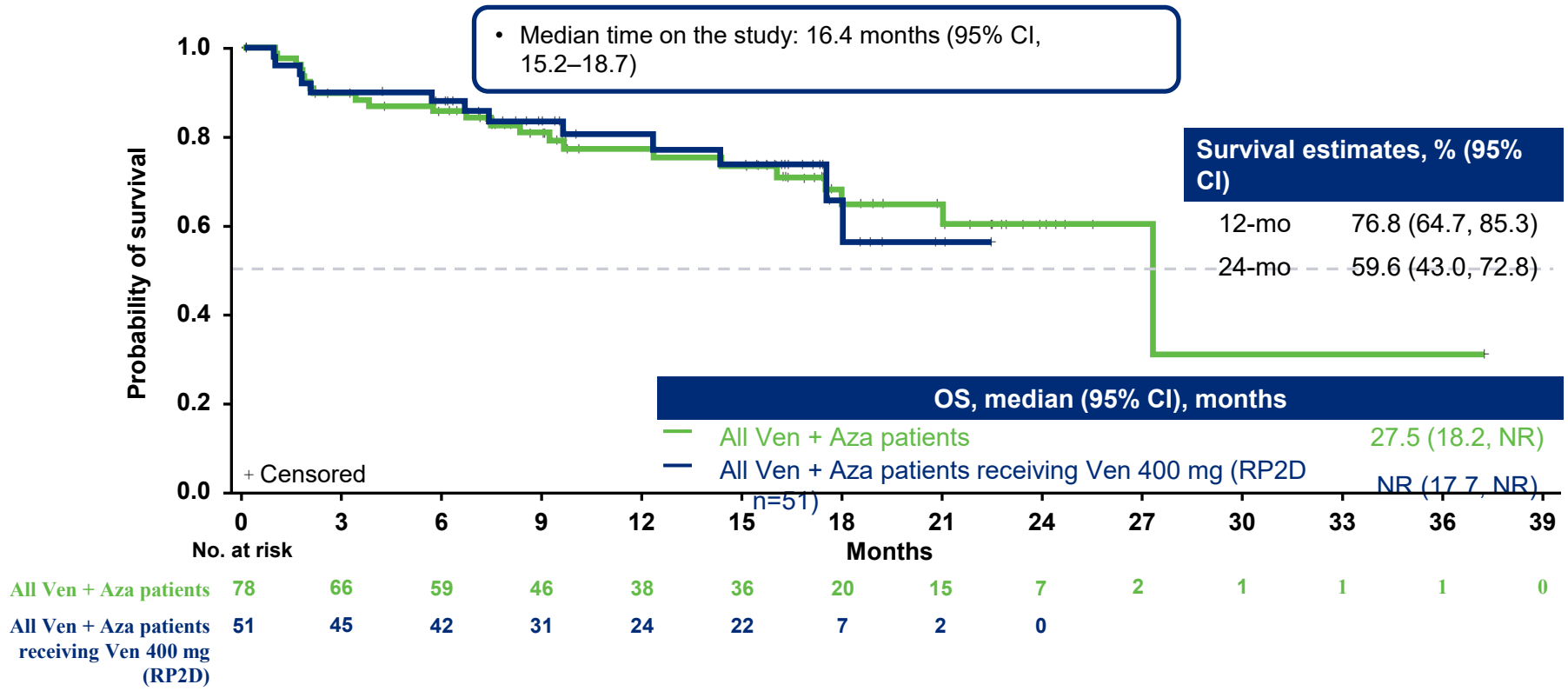
- A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant

[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

OS for All Patients



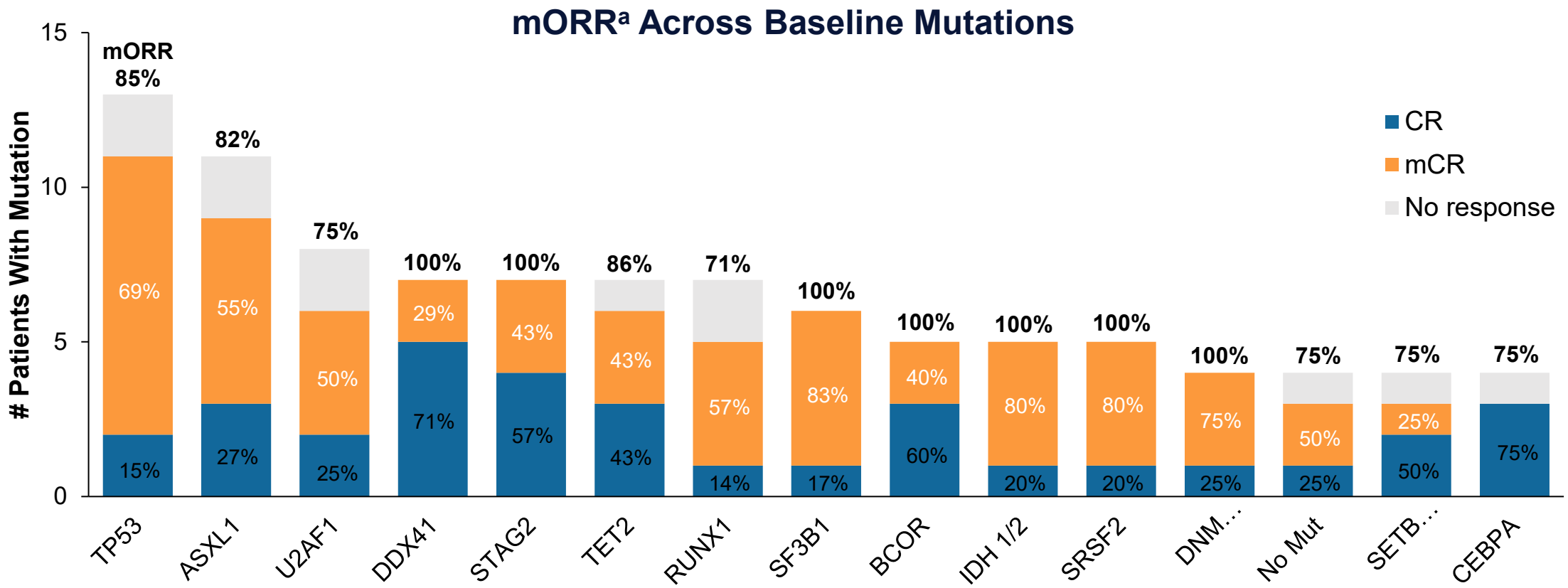
Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax

Data cutoff: June 30, 2020

Garcia et al ASH 2020

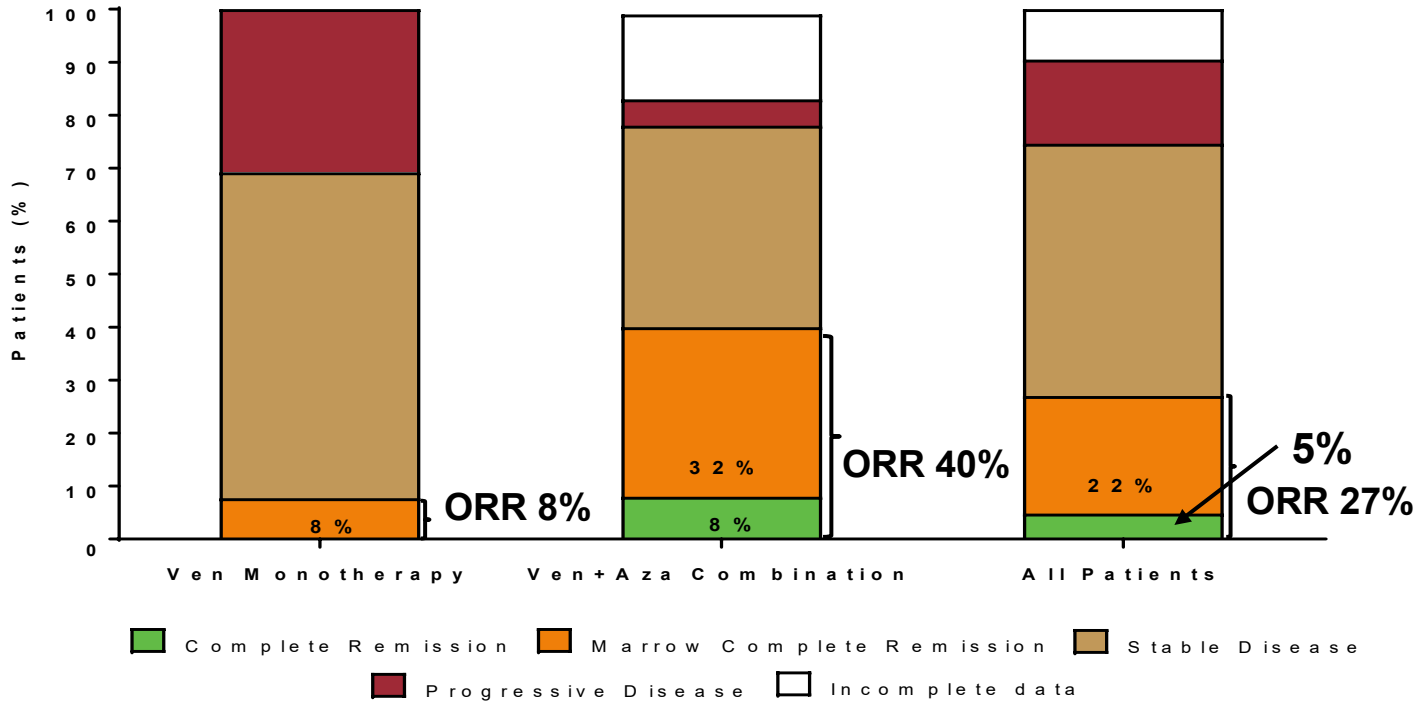
Aza/Ven Phase 1b: Broad activity across mutational spectrum that is durable among responders

Garcia
ASH 2021, abstract 241.



Broad activity that is durable among responders at RP2D

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

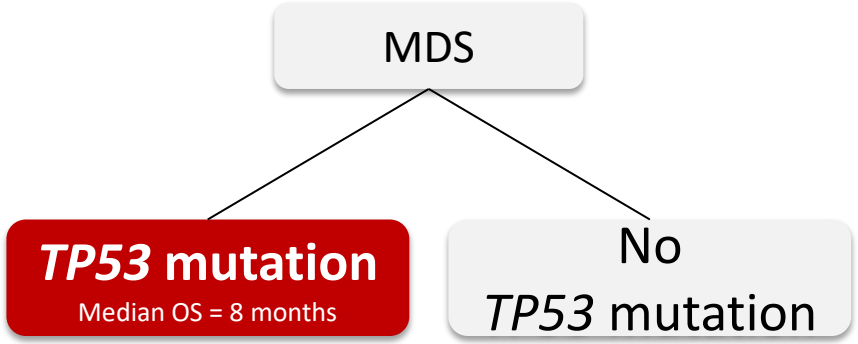


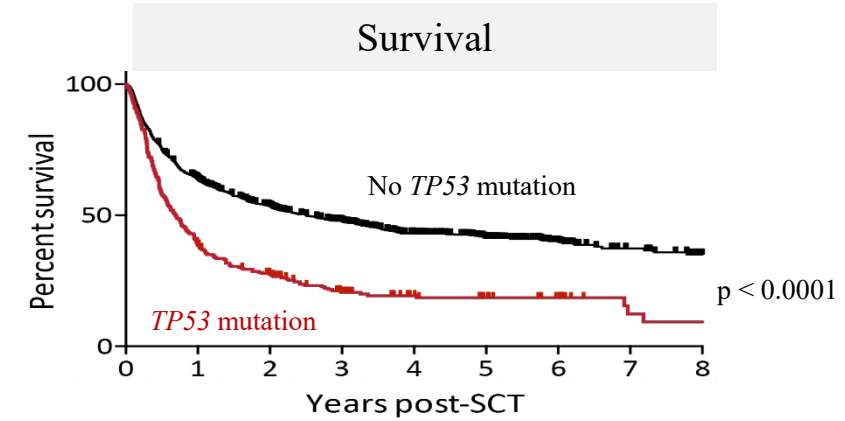
Data cutoff: Aug 30, 2019.

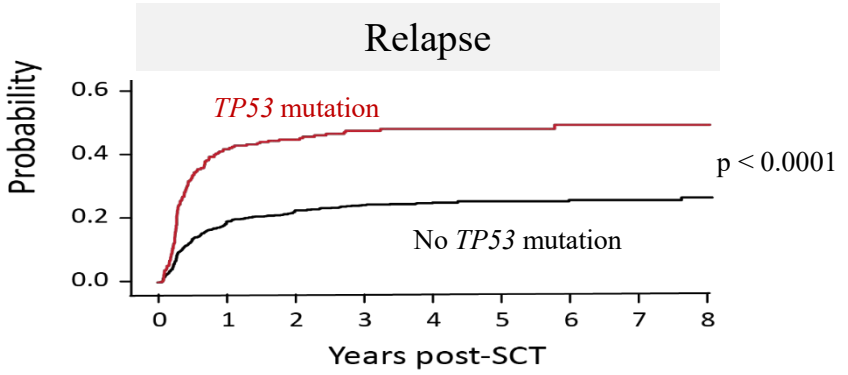
ClinicalTrials.gov. NCT02966782.
Zeidan A, et al. ASH 2019. Abstract 565.

TP53 mutated MDS

Poor prognosis Post-SCT due to early relapse



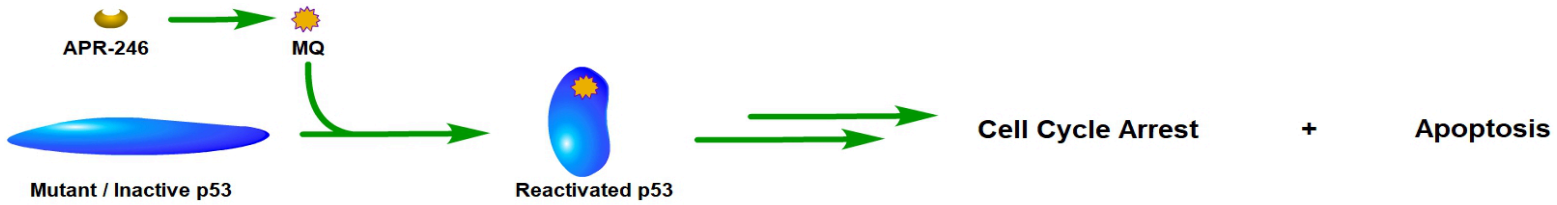


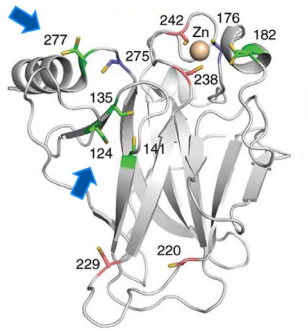


Cutler C, ASH 2020: donor v no donor higher risk MDS: n=384 48 v 27% 3 y OS in age 50-75

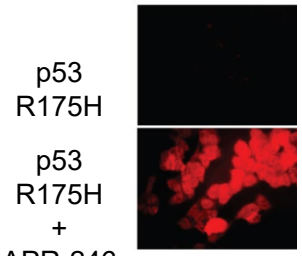
Lindsley C, et al. *N Engl J Med.* 2017;376(6):536-547.

Targeting TP53 Mutations in MDS/AML via APR-246

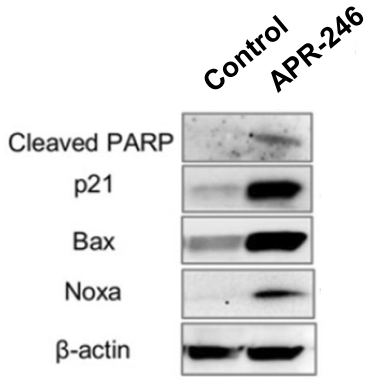




APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



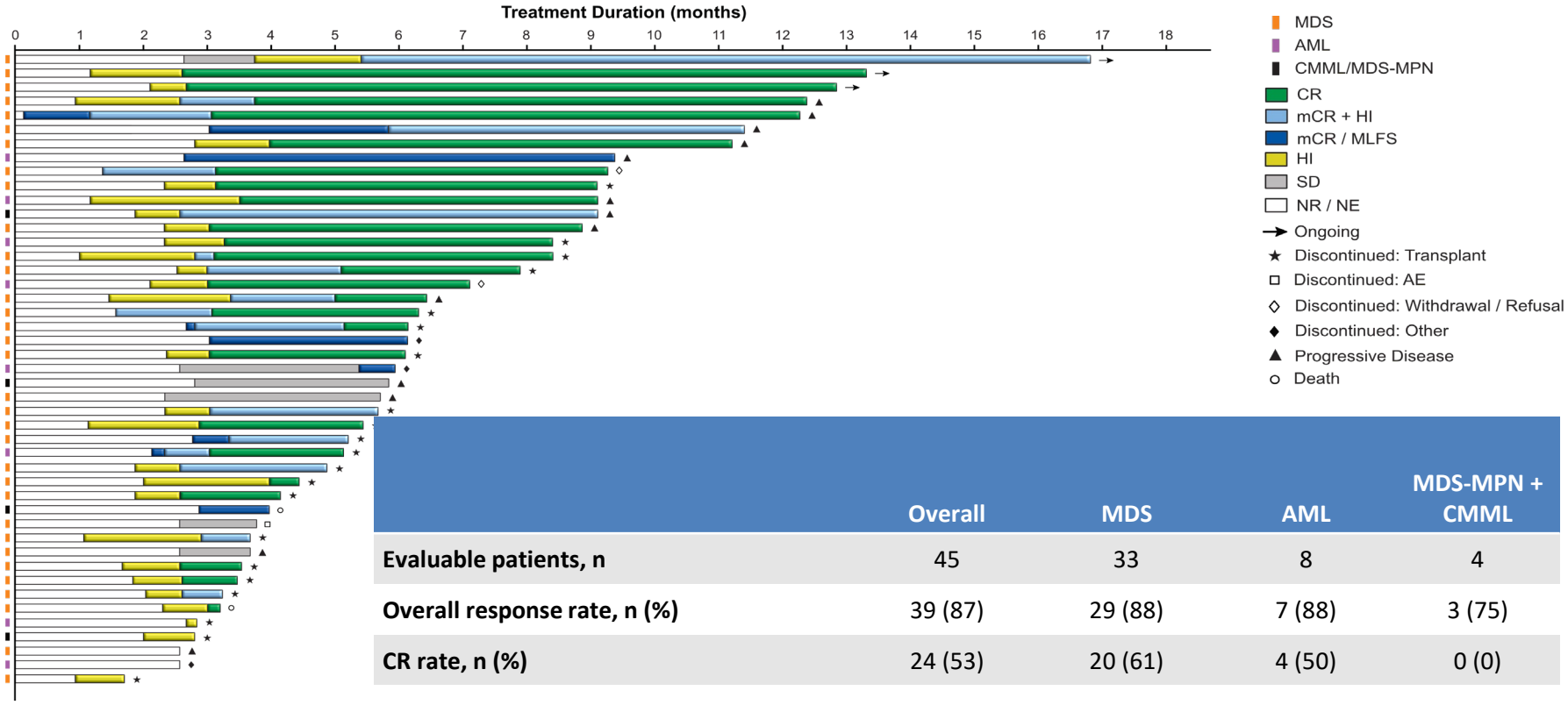
…and triggers cell cycle arrest and apoptosis

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



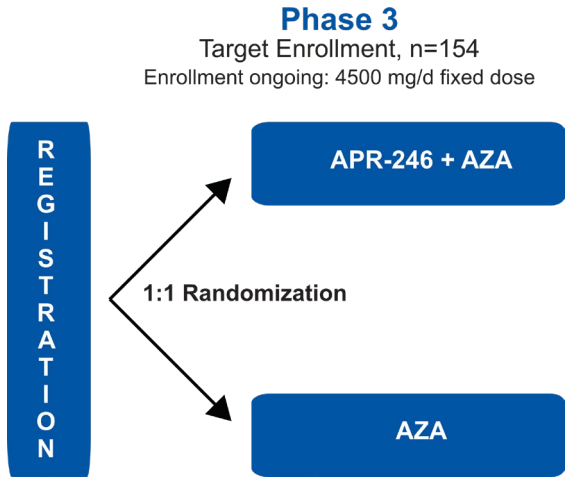
	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22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

- Median duration of follow-up = 10.8 months

Sallman D, et al, ASH 2019

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

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



- ClinicalTrials.gov. NCT03745716.

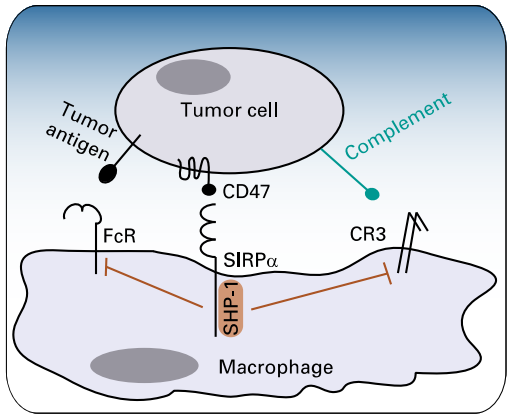
- Intermediate-/high-/very high-risk *TP53*-mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

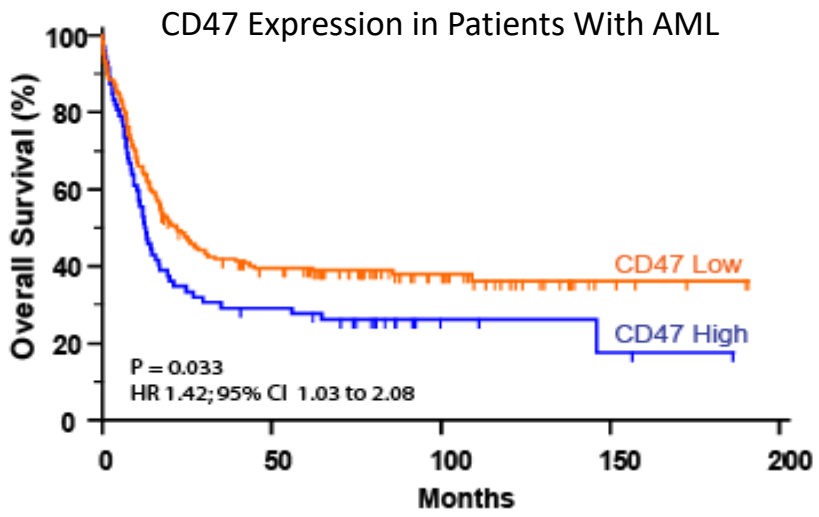
- Status
  - Enrollment commenced in January 2019
  - Currently targeting full enrollment in first quarter 2020
  - Fast Track Designation for MDS: granted by FDA in April 2019
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019

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

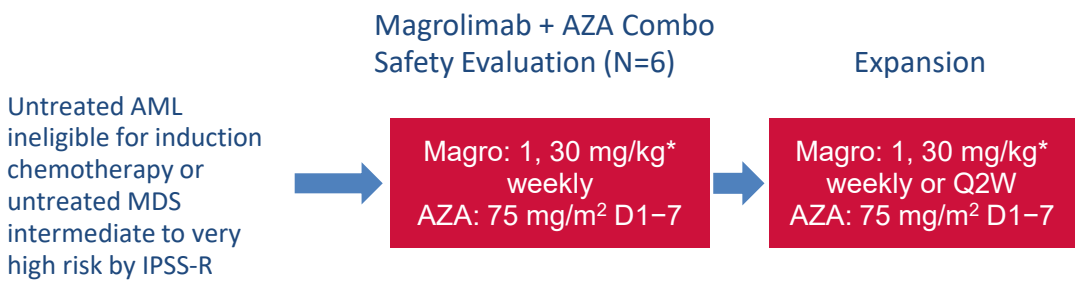




- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in patients with AML

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.

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.

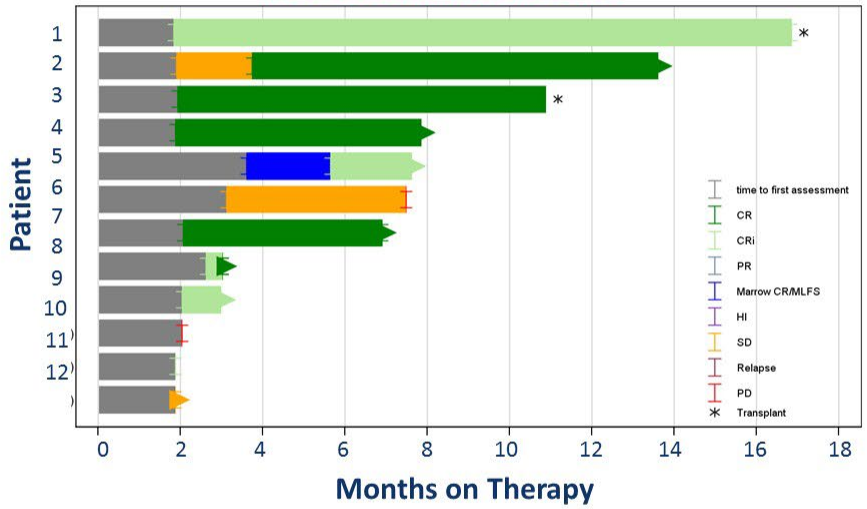
Magrolimab + AZA Eliminates Disease in AML and MDS Patients With *TP53* Mutation

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



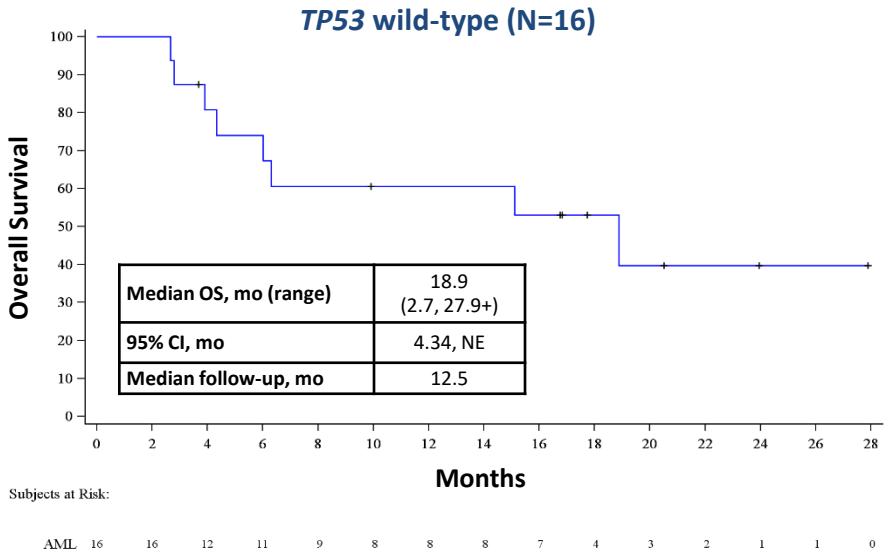
- Magrolimab + AZA has a high response rate with deep responses in *TP53*-mutant AML and MDS patients
- The estimated 6-month survival is 91% and 100% in AML and MDS patients, respectively
- Median duration and survival has not been reached, which compares favorably to current therapies
  - Venetoclax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

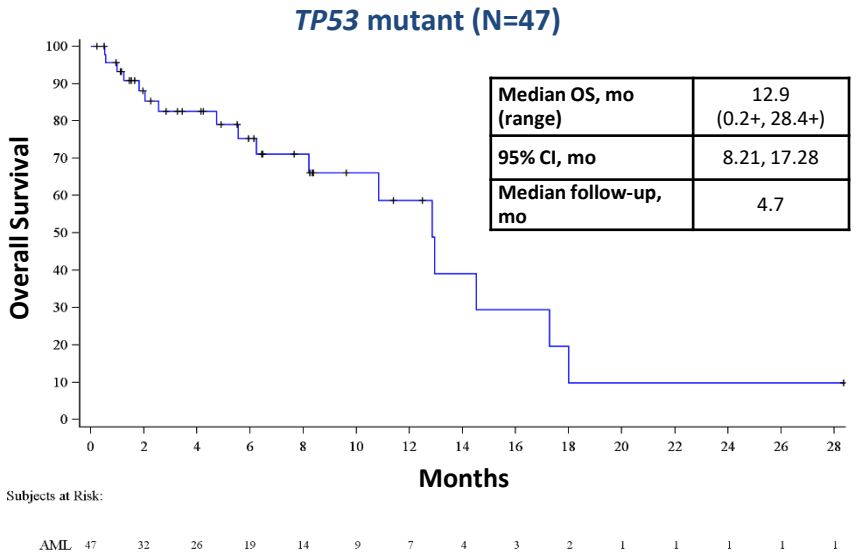
1. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

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

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%

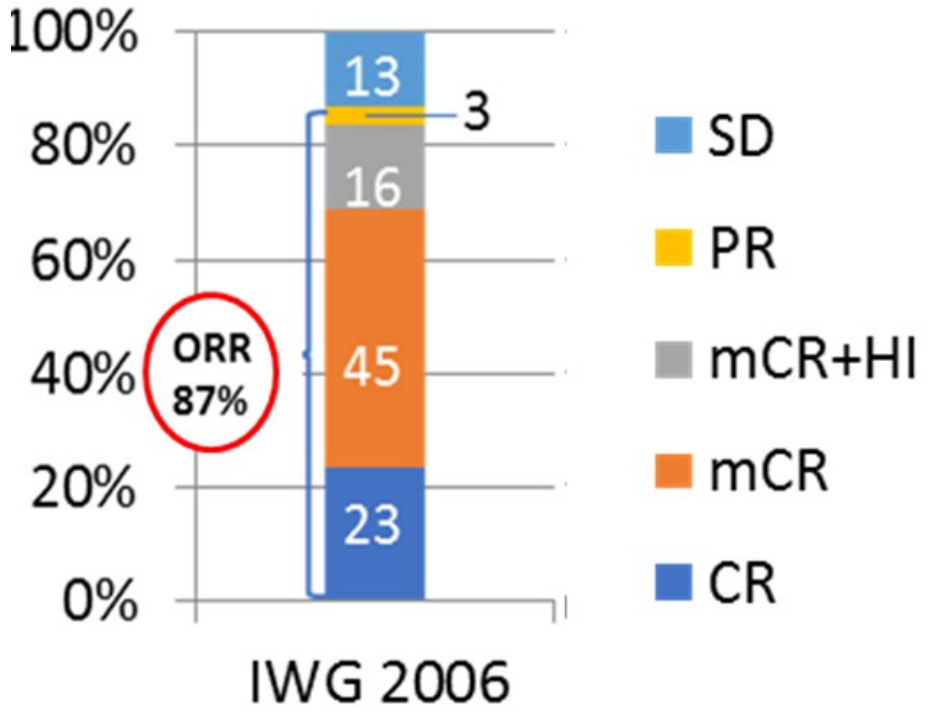
Brunner A, et al, ASH 2020

CPX-351 As First Line Treatment in Higher Risk MDS, Phase II Trial By the GFM

Peterlin P et al.,
ASH 2021, abstract 243.

31 patients (5 CMML2; 26 MDS-EB2)

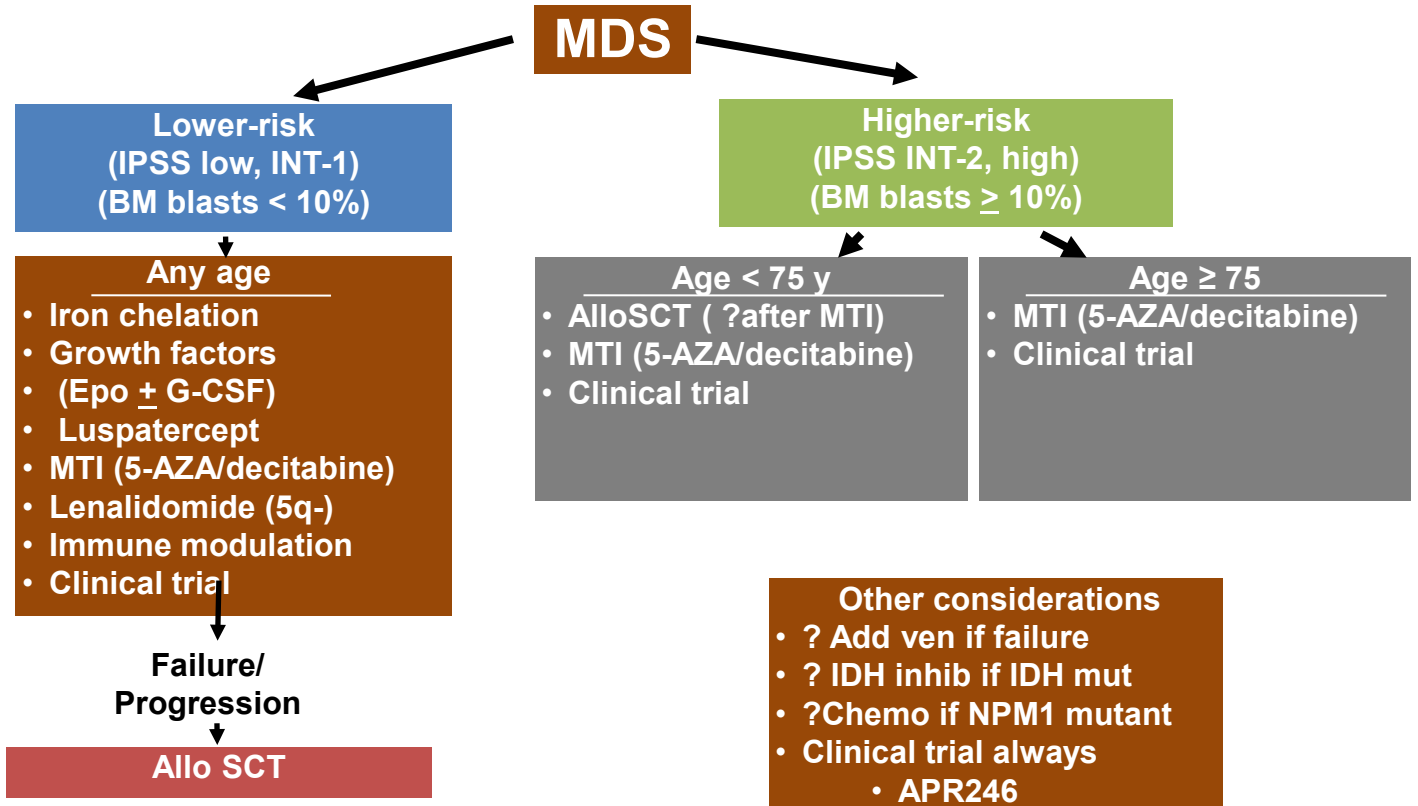
- **Hematological recovery**:
  - Platelets >20G/L : median 16 (range 0-55) days
  - Platelets >50G/L : median 28 (range 8-51) days
  - ANC >1G/L : median 26 (range 2-60) days
- **Adverse events during induction treatment :**
  - Grade 3 mucositis, n=1
  - Grade 1-2 alopecia, n=4
  - No death; No ICU transfers
- **Consolidation**
  - 12 of 31 patients received at least one consolidation cycle
  - 19 of 31 did not get CPX-351 consolidation
    - **10/31 went to transplant after responding to induction**
    - 9 had toxicity (thus 9/31 or 29% got no further therapy!)
    - Persistent cytopenia (n=5)
    - Cardiac toxicity (n=2)
    - Failure to achieve CR or PR (n=2)



CPX-351 has high activity during induction but is this regimen "too intense"? Only a third of patients were bridged to transplant.

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

Proposed Treatment Algorithm for Patients With MDS: 2022



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

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

* In memory

The End

Questions or need help?

Email: rstone@partners.org
Phone: 617-632-2214
Administrative Assistant: 617-632-2168
New Patients: 617-632-6028
Page: 617-632-3352 #42194