Beyond Hypomethylating Agents:

Combination Therapies in MDS

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Beyond HMAs| Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- Combinations – Higher-risk
- Conclusions

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Beyond HMAs| Agenda

- **Predicting Responders to HMAs**
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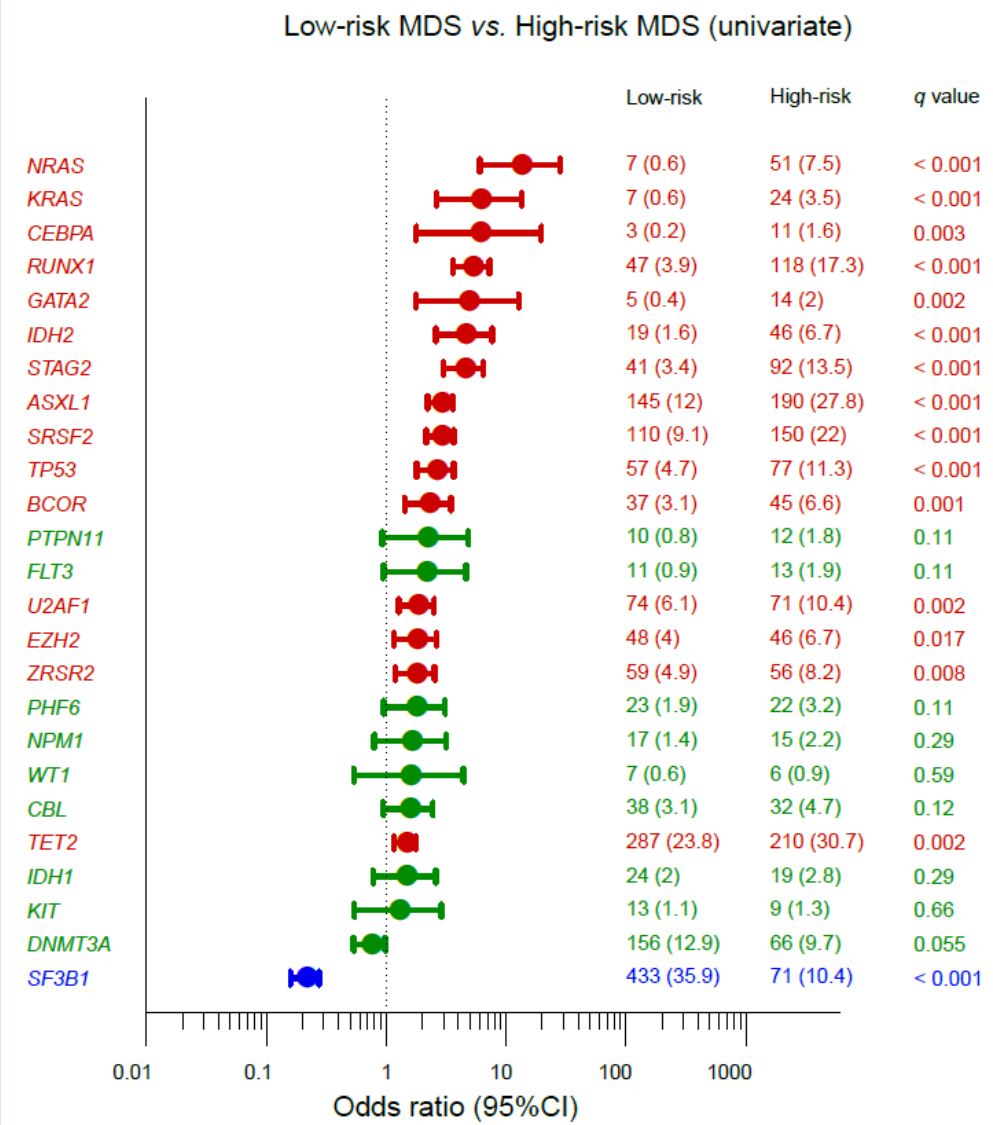
Beyond HMAs| Mutation Risk

Driver genes can be classified into molecular subtypes differentially associated with disease severity



Makishima et al. Nat Genetics 2017; 49:204.

Beyond HMAs| Mutations/Response

- Somatic mutations may predict response or resistance to HMA:
  - ***TET2*** mutations may predict response
  - ***ASXL1*** may predict resistance
  - ***TP53*** mutations may predict response

- Challenges with these data:

  ✓ Response might be higher but the mutation is not a biomarker

  ✓ Genomic data are complex

Nazha A, et al. JCO Prec Oncol 2019;3

Beyond HMAs| Mutations/Response

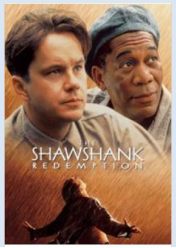
The Green Mile (1999)

Hacksaw Ridge (2016)

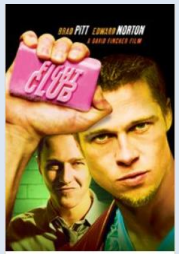
Django Unchained (2012)

?

The Lord of the Rings: The Return of the King (2003)



The Shawshank Redemption (1994)



Fight Club (1999)

?

NETFLIX

Beyond HMAs| Mutations/Response

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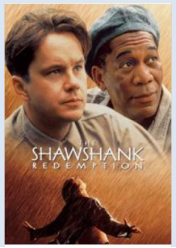

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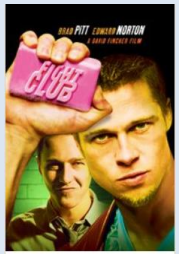
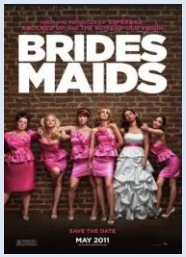


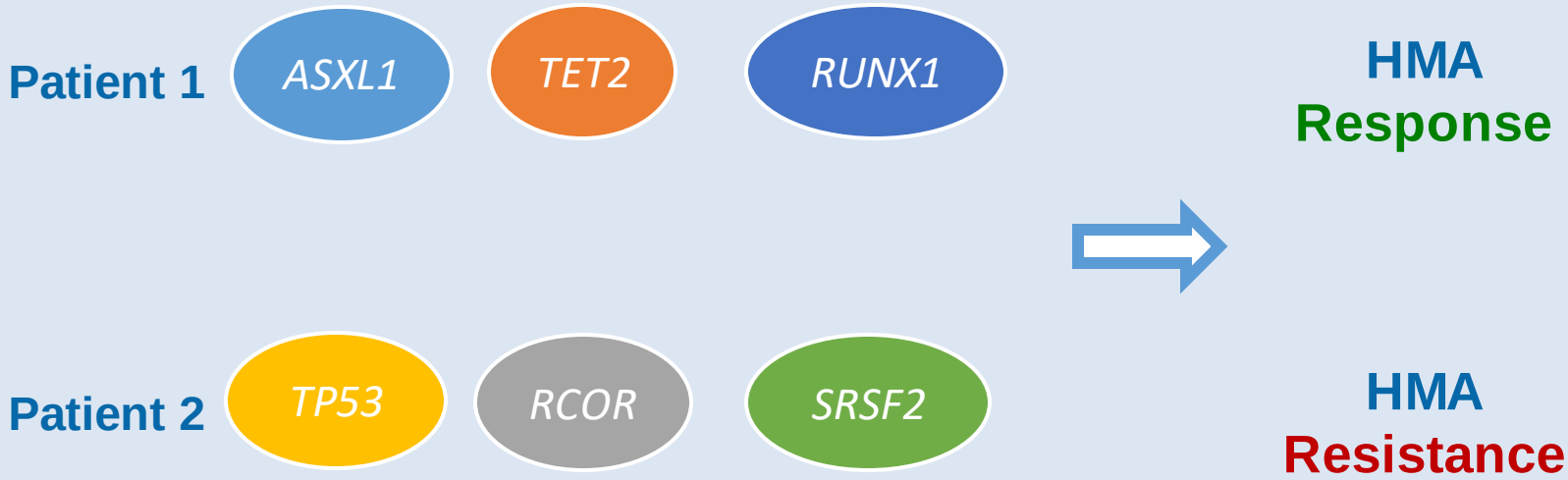
Fight Club (1999)

The Godfather



NETFLIX

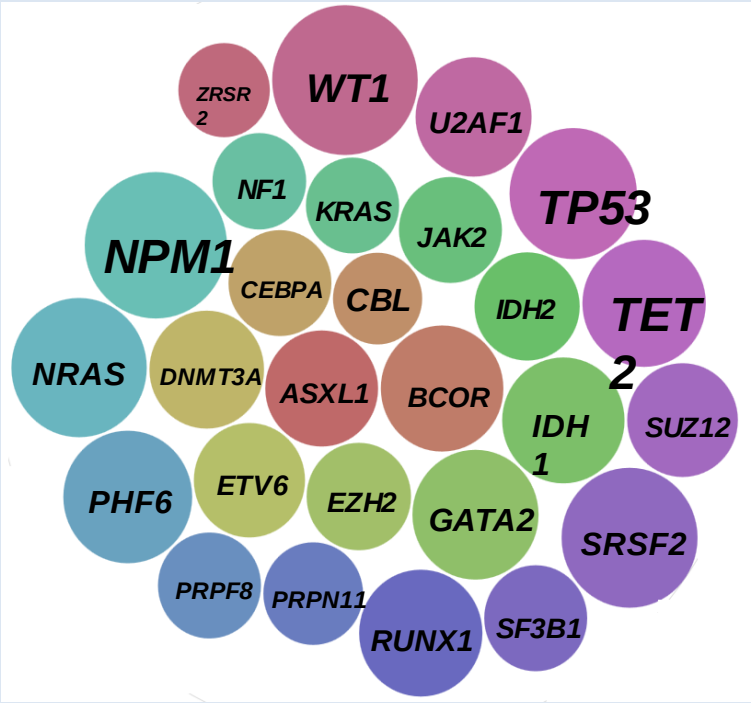
Beyond HMAs| Mutations/Response



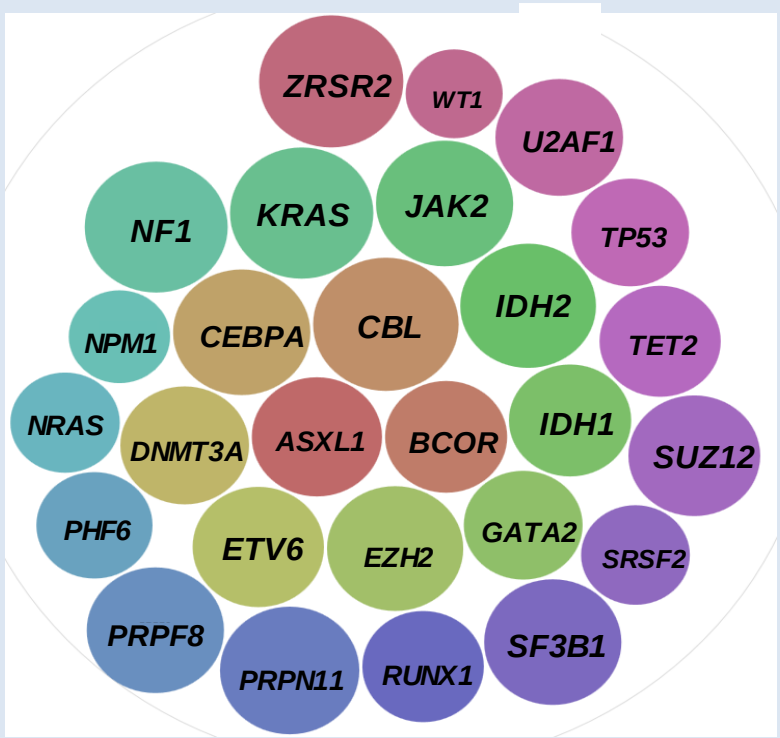
Nazha A, et al. JCO Prec Oncol 2019;3

Beyond HMAs| Mutations/Response

Responders



Non-Responders



N = 433 Patients treated with HMAs → Validated in 113 Patients enrolled in S1117

Nazha A, et al. JCO Prec Oncol 2019;3

Beyond HMAs| Mutations/Response

Results: Association Rules

Training

Association Rules (Resistance)
ASXL1, *NF1*
ASXL1, *EZH2*, *TET2*
ASXL1, *EZH2*, *RUNX1*
EZH2, *SRSF2*, *TET2*
ASXL1, *EZH2*, *SRSF2*
ASXL1, *RUNX1*, *SRSF2*
ASXL1, *TET2*, *SRSF2*
ASXL1, BCOR, RUNX1

Association Rules (Response)
TET2, *RUNX1*, *SRSF2*

31% pts
$\geq$ 3 mutations/sample

29% pts
Very Low/Low risk by IPSS-R

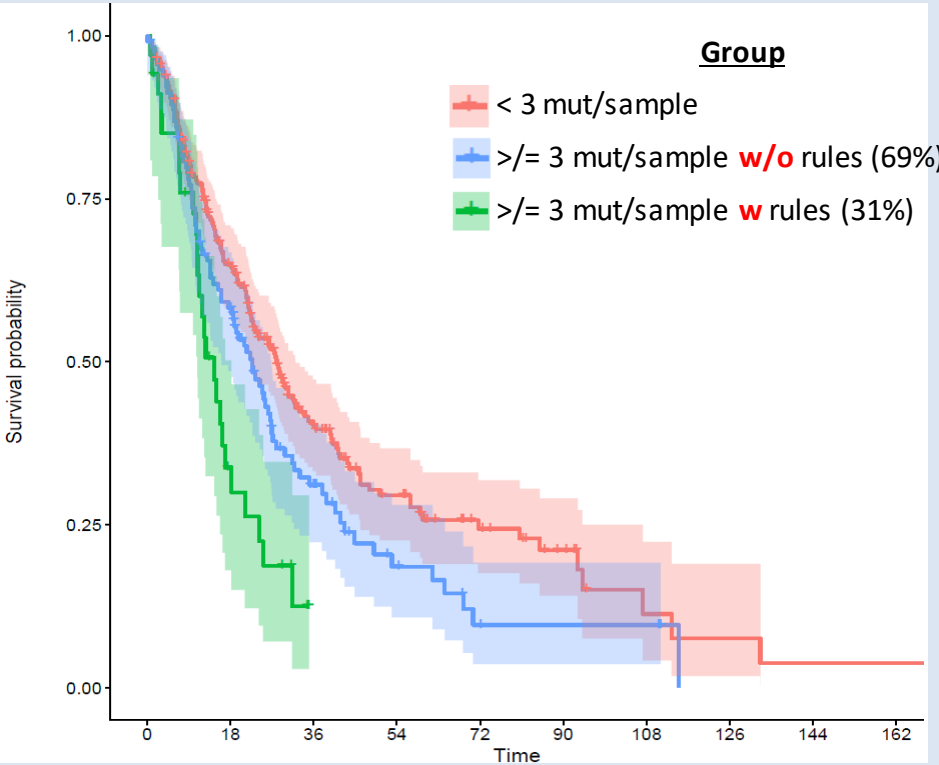
ORR to HMAs = **43%**

Median # mutations per patient = **3 (range, 0-9)**

Accuracy: **87%**

Nazha A, et al. JCO Prec Oncol 2019;3

Beyond HMAs| Mutations/Response



Median OS (m)
28.2
22.8
14.6

Nazha A, et al. JCO Prec Oncol 2019;3

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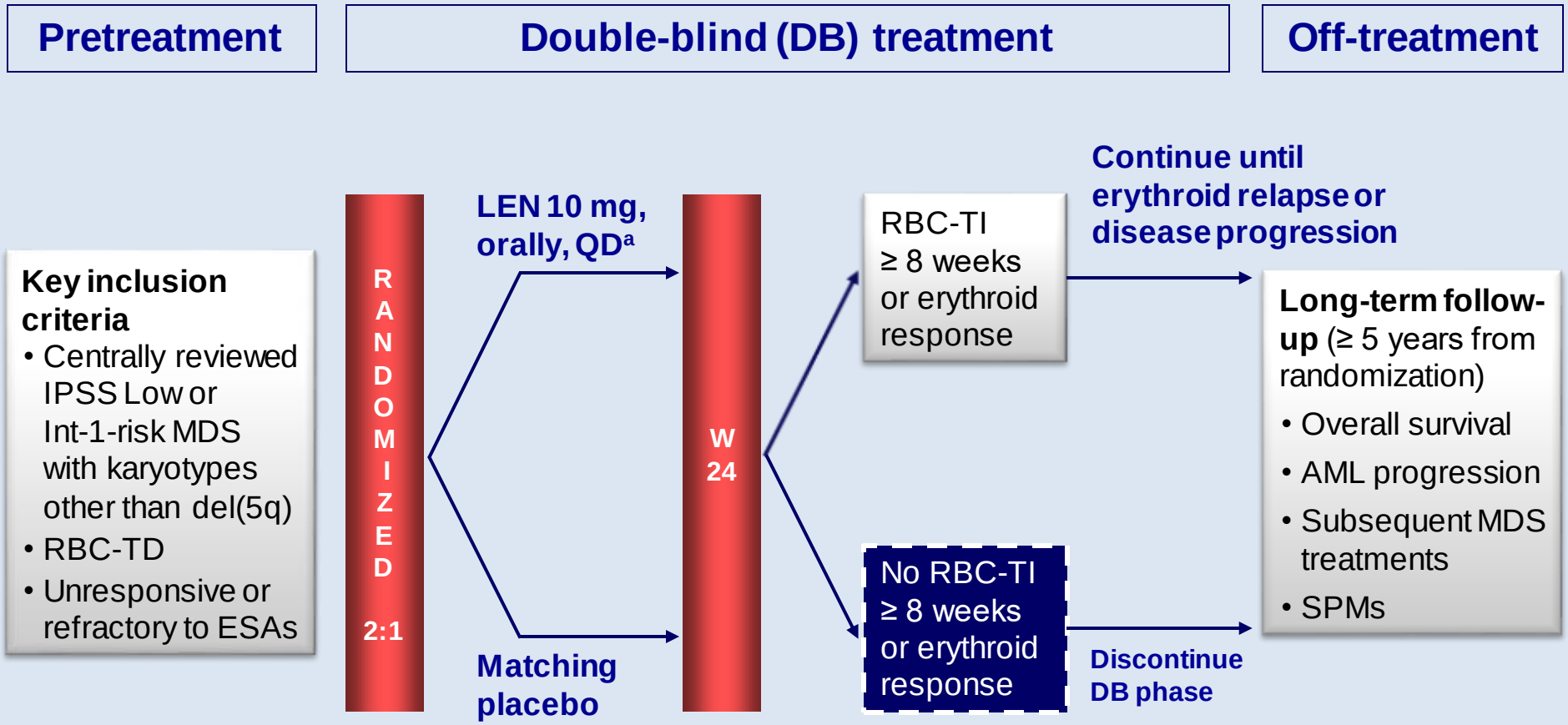
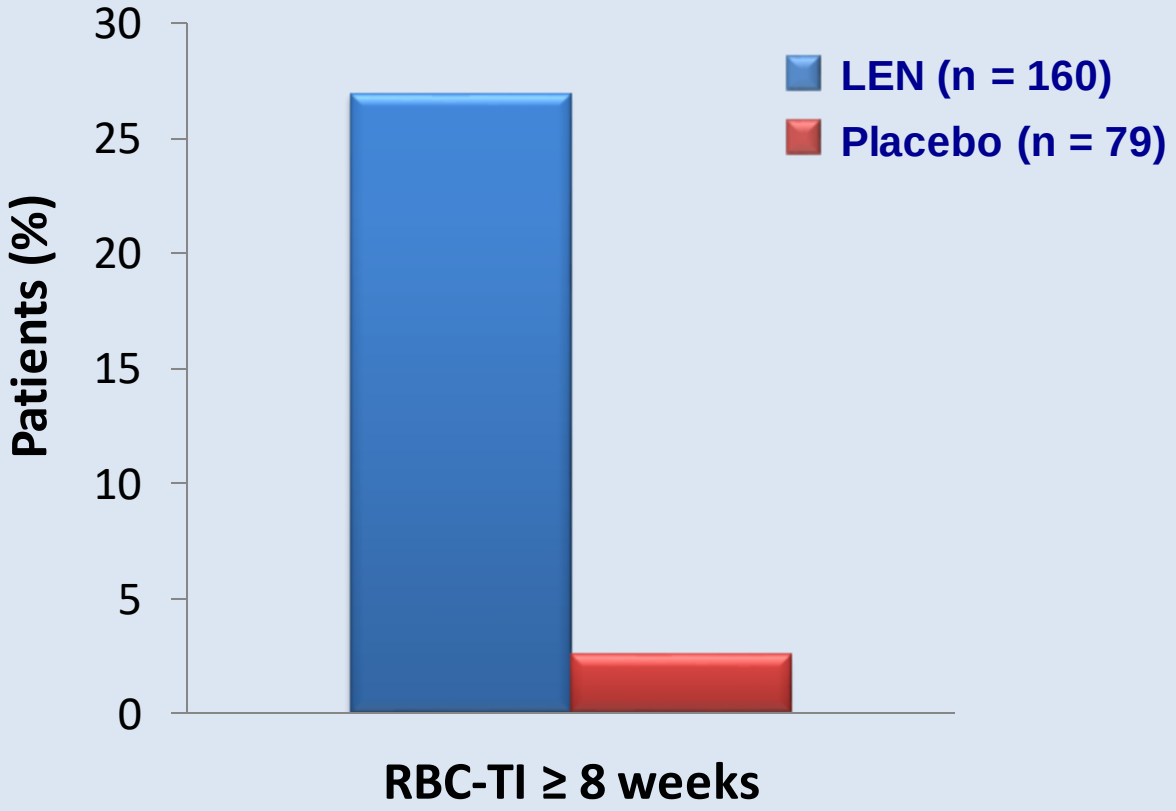
Lower-risk MDS | Ameliorating Anemia: LEN



Santini et al. JCO 2016;34:2988

Lower-risk MDS | Ameliorating Anemia: LEN

Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo (*P* < 0.001)



Santini et al. JCO 2016;34:2988

List et al, Abstract 824:Combined Treatment with Lenalidomide and Epoetin Alfa in Epo refractory Non-Deletion 5q [Del(5q)] MDS: E2905 Phase III Study

- Randomized Phase III low risk non-del(5q) ESA resistant or high endogenous EPO level (>500).
- Len 10 mg/day * 21 versus Len plus EPO 60K/week
- 205 patients randomized- 14 not treated due to EPO shortage
- Median transfusion burden 4 U/ 8 weeks
- 93% prior ESA; 18% prior DNMTi

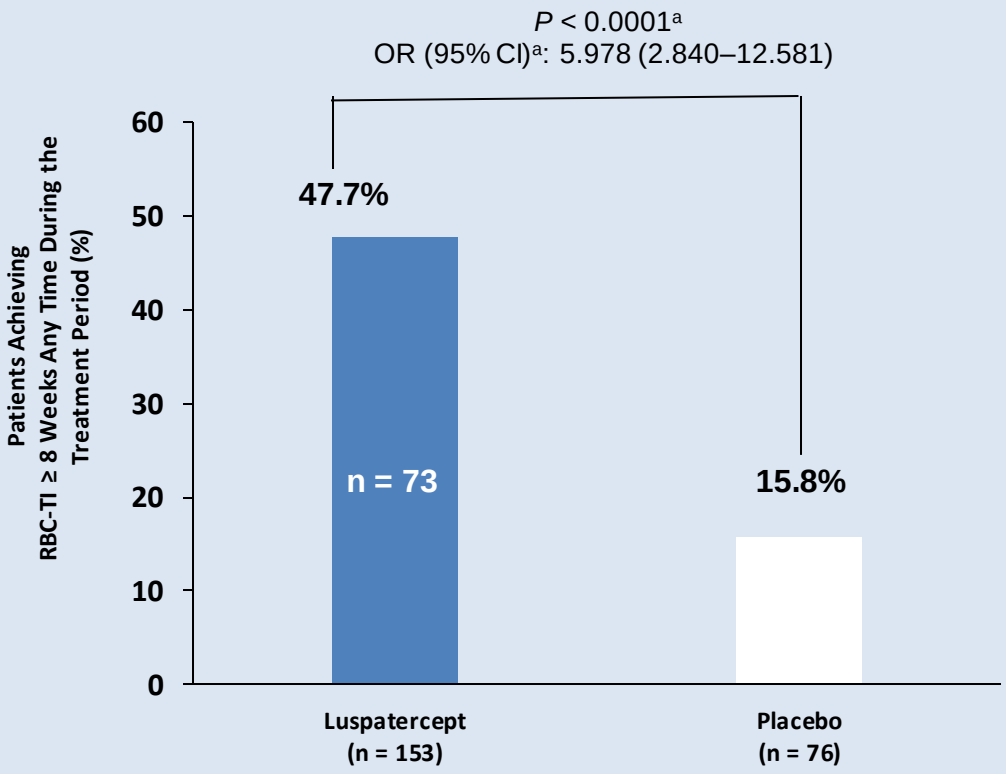
AF List et al. ASH 2019; Abstract 824

LEN +/- EPO

	Lenalidomide	Lenalidomide plus EPO
n	96	99
Major Erythroid Response	11 (11.5%)	28 (28.3%)
After 16 weeks of therapy		
n	64	73
Major Erythroid Response	10 (16%)	28 (39%)
CROSSOVER To COMBO		
Major Erythroid Response		11/44
Duration of MER		
Median (months)	13	24

AF List et al. ASH 2019; Abstract 824

Fenaux et al, Luspatercept: RBC-TI ≥ 8 weeks Achieved any time during treatment period



Fenaux et al. ASH 2019, Abstract 841

Beyond HMAs| LEN + LUS

The L2 Regimen

Dose Level	Lenalidomide Schedule	Luspatercept Schedule
1	5 mg PO days 1-21	1.0 mg/kg day 1
2	5 mg PO days 1-21	1.33 mg/kg SC day 1
3	5 mg PO days 1-21	1.75 mg/kg SC day 1

Phase IB/II
Lower-risk, Non-Del(5q)
N = 40

Beyond HMAs| Agenda

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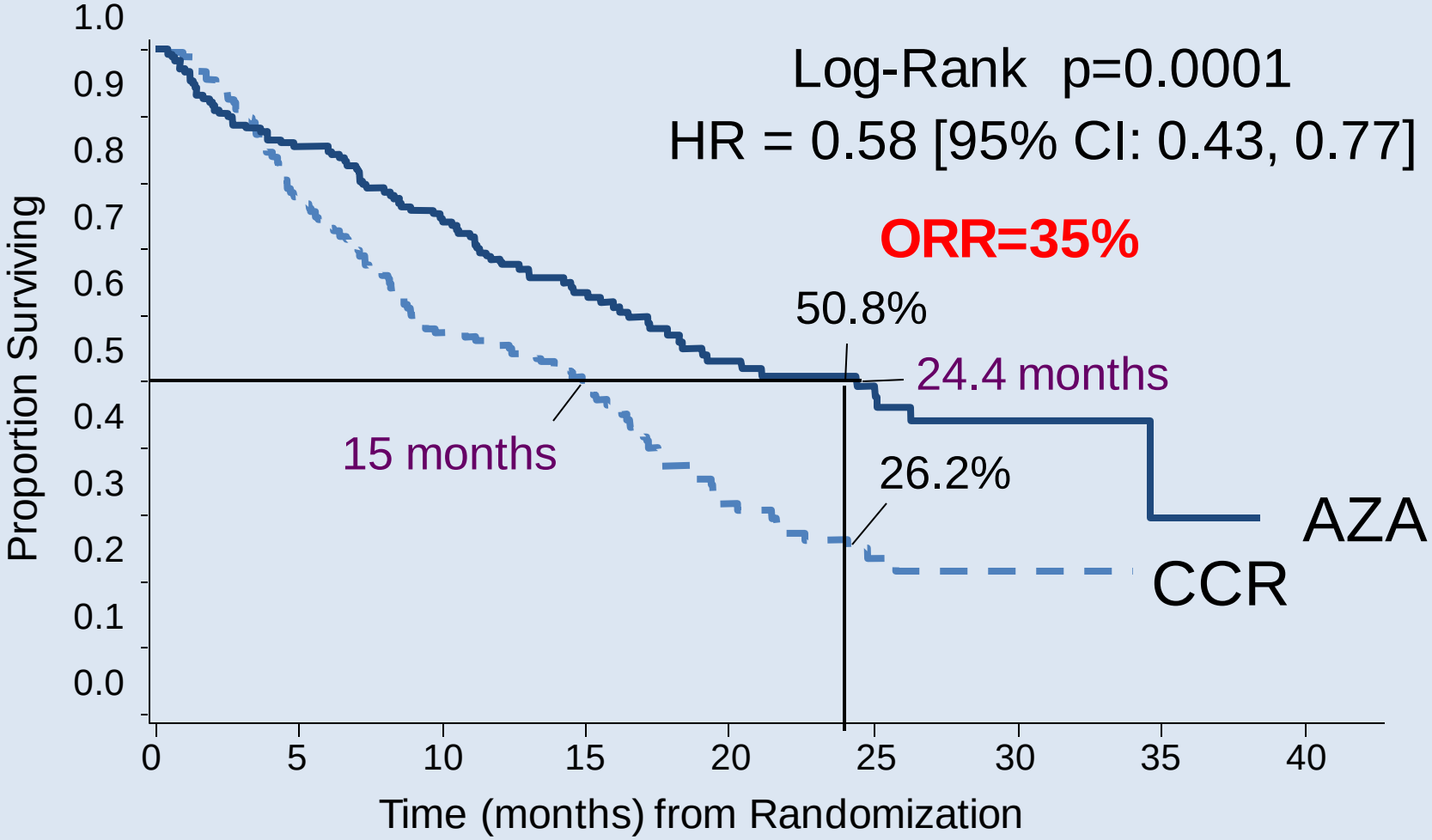
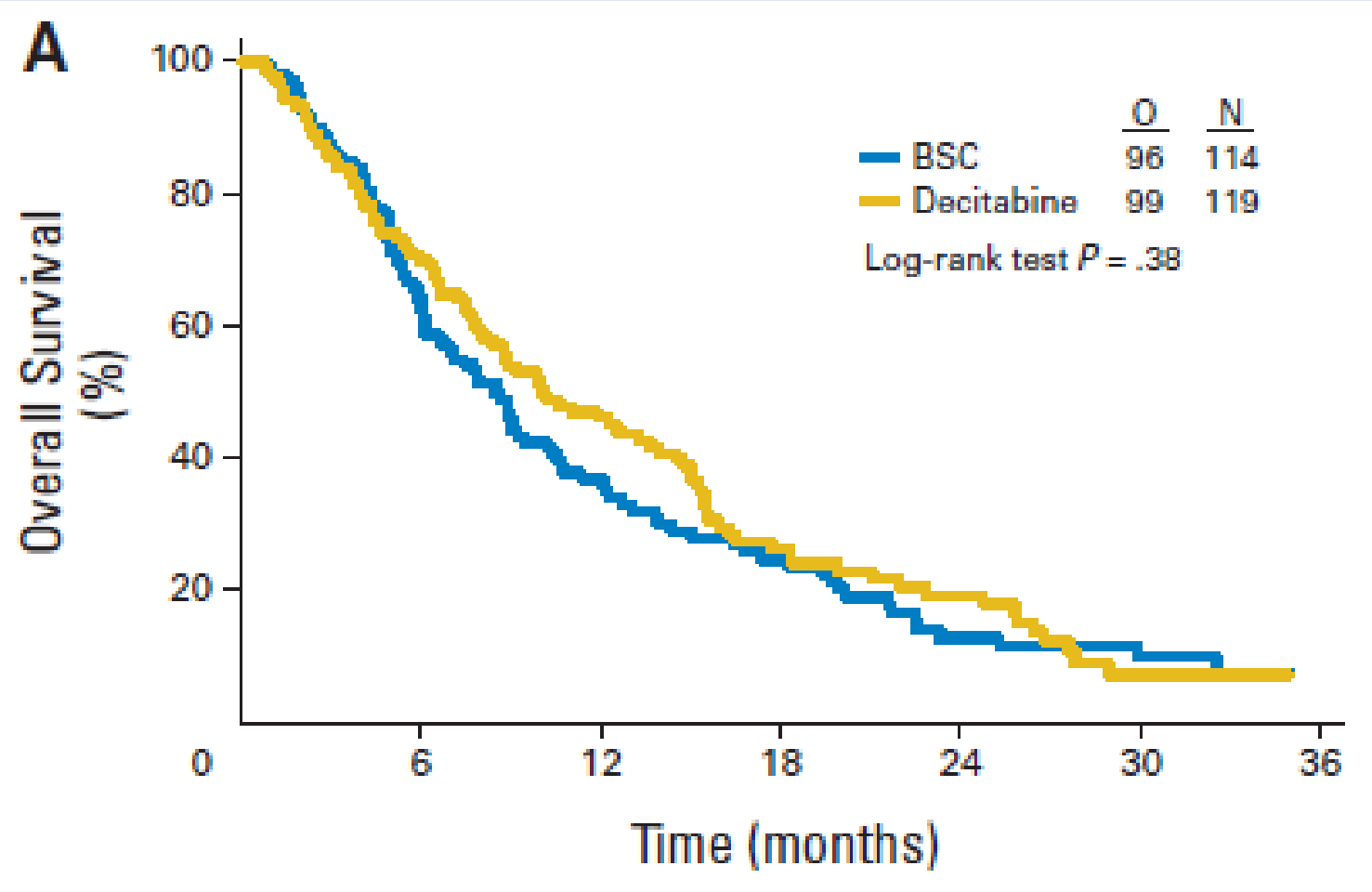
Beyond HMAs| AZA



Fenaux P, et al. Lancet Oncology 2009;10:223-232.

Beyond HMAs| DAC



Median OS 10.1 vs. 8.5 months

Lubbert et al. JCO 2011;29:1987.

ECOG E1905

Eligible patients (no prior azacitidine):

- **MDS** *(higher risk; if IPSS low/INT-1 risk, then platelets <50 x 10^9/L or ANC<500)*
- **CMML** *with WBC <12 x 10^9/L*
- **AML** *with multilineage dysplasia and WBC ≤30 x 10^9/L for ≥4 weeks*

Randomize 1:1

Azacitidine SC 50 mg/m² x 10 days every 28 days

Primary Endpoint:
IWG 2000 responses with hematological normalization (CR+PR+trilineage HI)

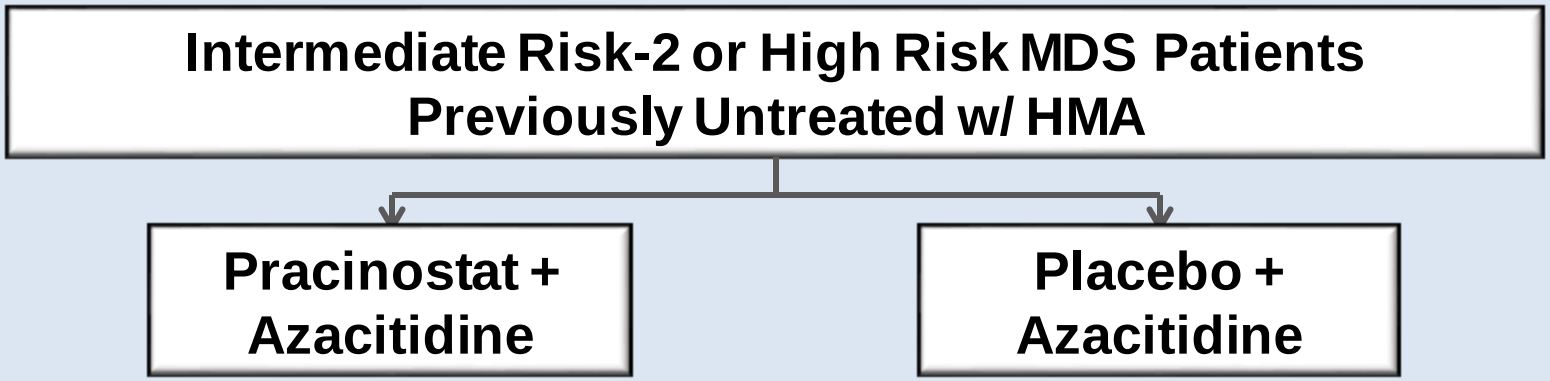
Azacitidine SC 50 mg/m² x 10 days every 28 days, plus Entinostat (MS-275) 4 mg/m2 PO days 3 and 10 each cycle

Prebet et al. JCO 2014;32:1242

E1905 study results

Response / AE	Arm A (n=68) (azacitidine monotherapy)	Arm B (n=68) (combination therapy)
Complete response (CR)	12%	7%
Partial response (PR)	9%	7%
Trilineage hematological improvement (tHI)	10%	10%
Qualifying Response (CR+PR+tHI)	**31%**	**24% (p=NS)**
Other hematological improvement	*12%*	*19%*
Any response	***43%***	***44%***
Grade IV thrombocytopenia	44%	63% (p=0.07)
Grade III/IV fatigue	13%	23% (p=0.13)

Aza + Pracinostat in MDS: Study Design



- **102 evaluable patients: one-to-one randomization**
- **Azacitidine: 75 mg/m^2 7 days I.V./sq every 28 days**
- **Pracinostat or placebo P.O. 60 mg 3 days/week for 3 weeks**
- **Cycles repeated every 28 days until disease progression, lack of benefit, or intolerance**

Garcia-Manero et al. Cancer 2017;123:994.

Aza + Pracinostat in MDS:
Summary of Response

	Pracinostat	Placebo
CR, within 180 days	18%	33%
Best Response		
Complete Remission	20%	33%
Partial Remission	0%	0%
Marrow CR	28%	22%
Stable Disease	26%	29%
Progressive Disease	6%	6%
Not evaluable	22%	10%

Garcia-Manero et al. Cancer 2017;123:994.

Aza + Pracinostat in MDS: Summary of Response

RESPONSE	Pracinostat	Placebo
Hematological improvement	35%	55%
Erythroid response (HI – E)	28%	45%
Platelet response (HI – P)	31%	53%
Neutrophil response (HI – N)	26%	39%
Clinical benefit rate (CR + PR + HI + mCR)	53%	63%
Cytogenetic response	42%	55%
Cytogenetic CR	24%	29%
Cytogenetic PR	18%	26%

Garcia-Manero et al. Cancer 2017;123:994.

Higher-risk MDS | Combinations

Higher-risk MDS or CMML

(IPSS ≥1.5 and/or blasts ≥5%)

AZA (IV/SC)
75 mg/m^2/d (d1-7)
N=92

AZA (IV/SC) + LEN (PO)
75 mg/m^2/d (d1-7) + 10mg/d x 21d
N=93

AZA (IV/SC) + Vorin (PO)
75 mg/m^2/d (d1-7) + 300mg BID (d3-9)
N=92

Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 282/277

Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

06/2012 – 06/2014

Sekeres et al. JCO 2017;35:2745-53.

Higher-risk MDS | Combinations

Variable Median and N (%)	AZA n=92 (33%)	AZA+LEN n=93 (34%)	AZA+VOR n=92 (33%)	Total n=277 (100%)
Age (yrs, range)	69 (42, 88)	70 (51, 86)	70 (28, 93)	**70 (28, 93)**
Female	31 (34)	32 (34)	22 (24)	**81 (31)**
CMML	18 (20)	19 (20)	16 (18)	**53 (19)**
tMDS	7 (8)	6 (6)	5 (5)	**19 (7)**
Baseline ANC ($x10^3$)	2 (0, 110)	1 (0, 336)	2 (0, 36)	**2 (0, 336)**
Baseline Platelet count ($x10^3$)	70 (8, 4000)	75 (3, 452)	62 (3, 1462)	**68 (3, 4000)**
Baseline Median Blast %	8 (0, 22)	10 (0, 20)	10 (1, 18)	**9 (0, 22)**

Sekeres et al. JCO 2017;35:2745-53.

Higher-risk MDS | Combinations

Toxicity Variable	AZA	AZA+LEN (P-value vs. AZA)	AZA+VOR (P-value vs. AZA)	Total n=271
Febrile neutropenia (n)	10	13 (.66)	12 (.51)	36
GI (n)	4	12 (.10)	14 (.02)	28
Rash (n)	3	14 (<.01)	1 (1)	17
Off Tx due to Toxicity/Side Effect/Complication	8%	20% (.05)	21% (.03)	18%
Non-protocol defined dose modifications	24%	43% (.002)	42% (.01)	33%

Sekeres et al. JCO 2017;35:2745-53.

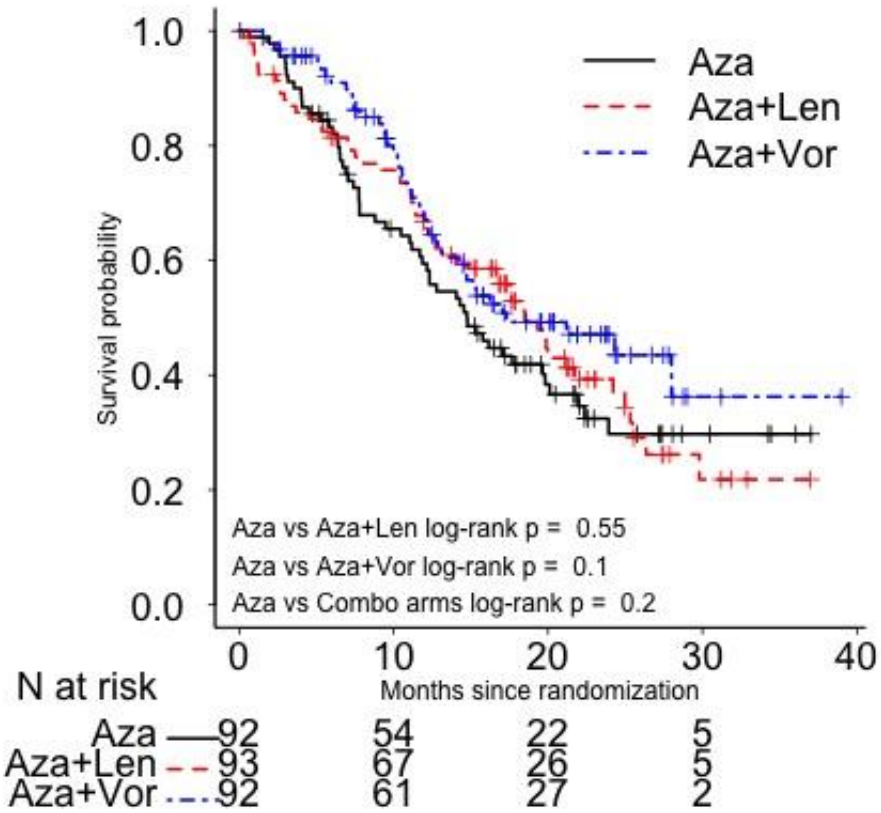
Higher-risk MDS | Combinations

Response Variable	AZA	AZA+LEN (P-value vs. AZA)	AZA+VOR (P-value vs. AZA)	Total n=277
Median Tx Duration (Wks)	25	24	20	22
Overall Response Rate (%)	38	49 (.16)	27 (.16)	38%
CR/PR/HI (%)	24/0/14	24/1/25	17/1/9	22/1/16%
CMML ORR (%)	5 (28)	13 (68) (.02)	2 (12) (.41)	37%
ORR Duration (median)	10 months	14 months (.41)	15 months (.31)	14 months
CMML ORR Duration (median)	15 months	14 months (.87)	24 months (.69)	15 months

Sekeres et al. JCO 2017;35:2745-53.

Higher-risk MDS | Combinations

Overall Survival

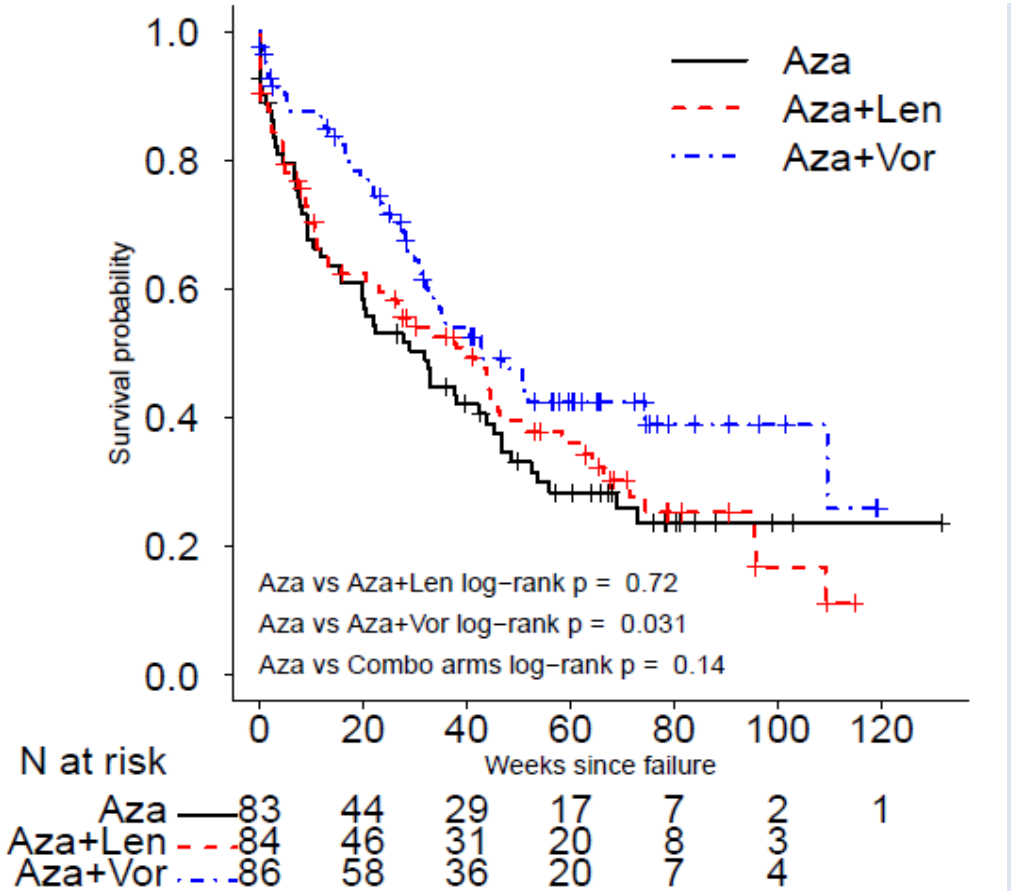


Comparisons are between combination arms and AZA monotherapy

Sekeres et al. JCO 2017;35:2745-53.

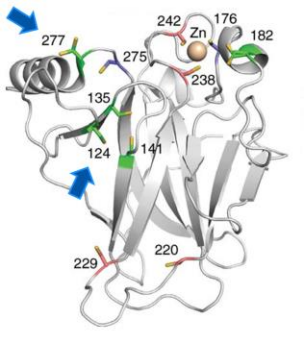
Higher-risk MDS | Combinations

Overall Survival After Failure

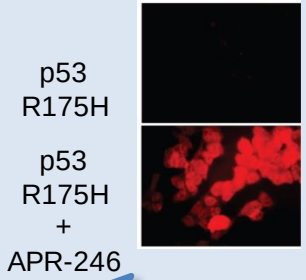


Sekeres et al. JCO 2017;35:2745-53.

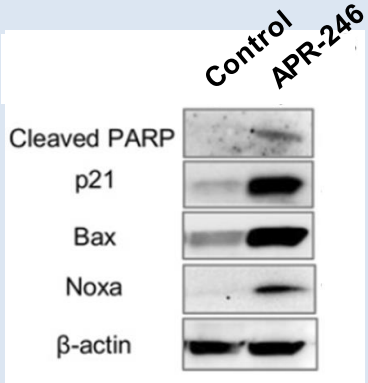
Higher-risk MDS | Targeting *TP53*



APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…

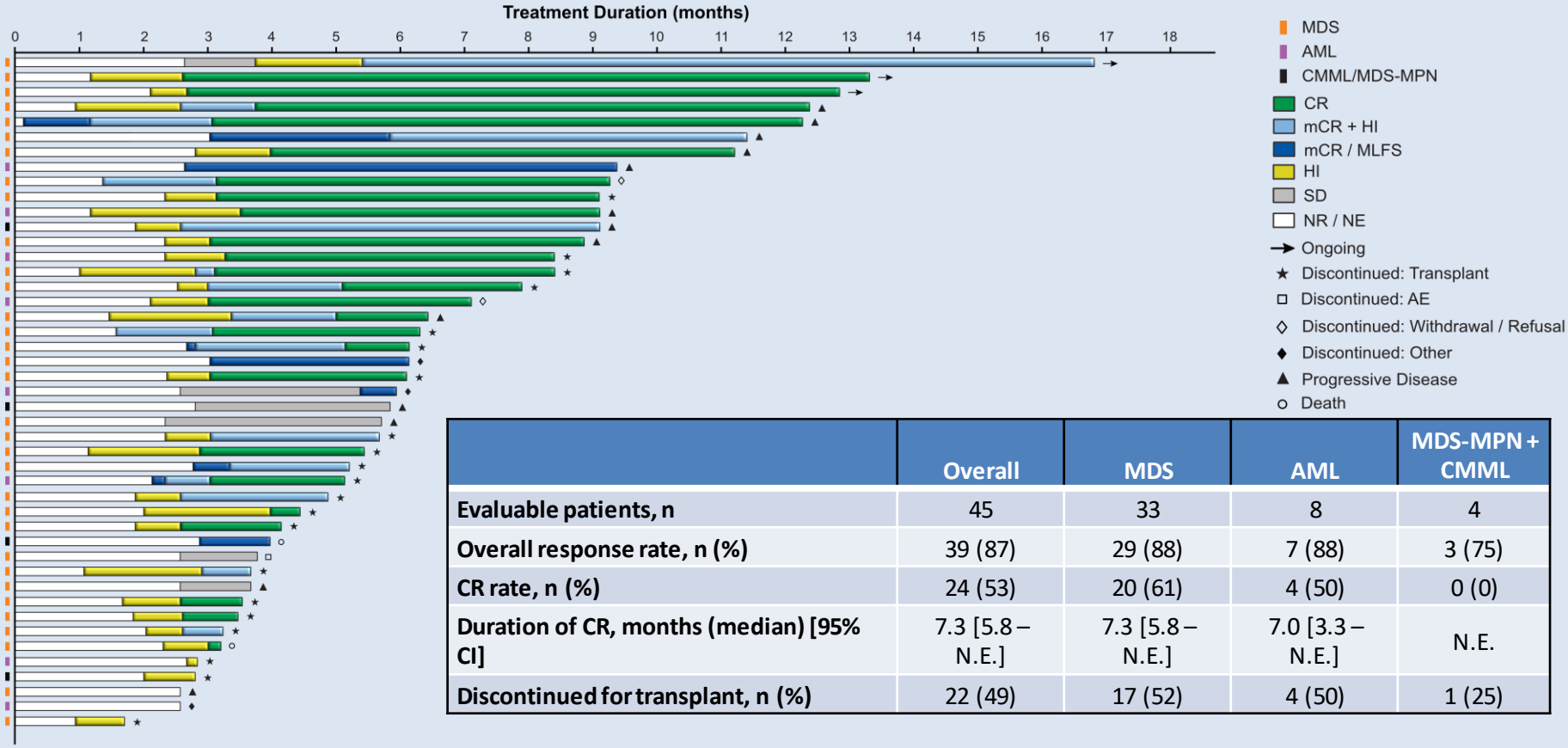


…and triggers cell cycle arrest and apoptosis

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

Sallman et al, Cluzeau et al. ASH 2019, Abstract 676-7.

Higher-risk MDS | Targeting *TP53*



	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

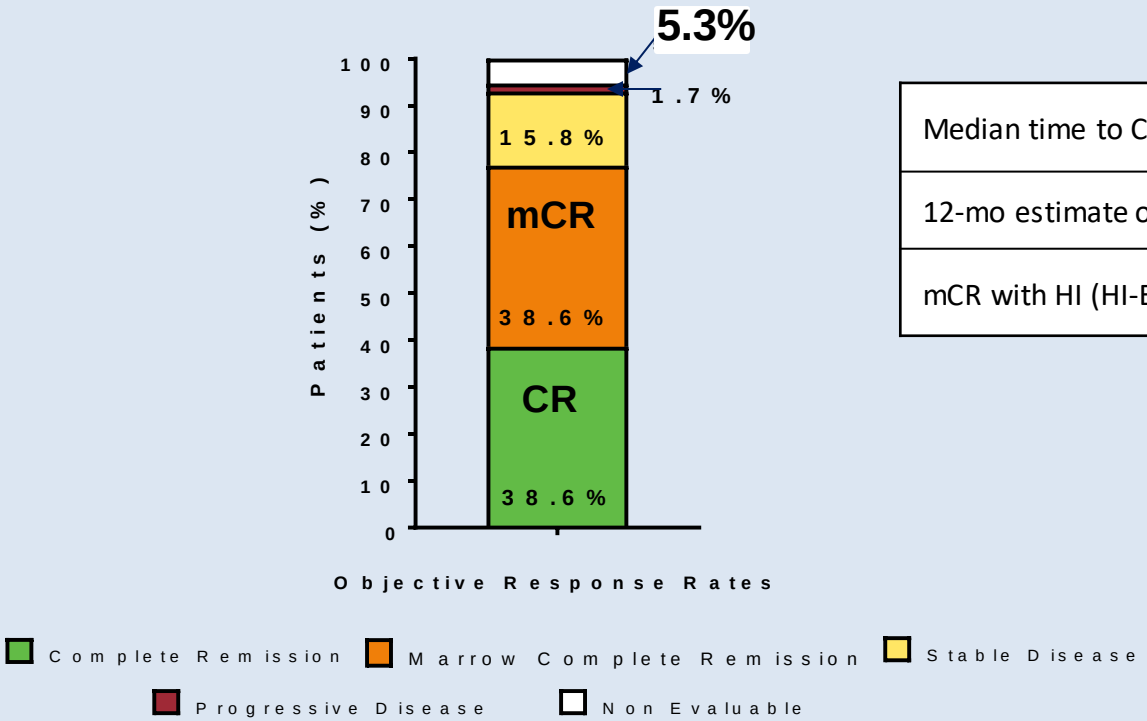
Sallman et al, Cluzeau et al. ASH 2019, Abstract 676-7.

Wei et al, Abstract 568 – AZA plus Venetoclax for HR-MDS

- Phase 1b study
- Untreated *de novo* MDS, IPSS Int-2 or high risk, not planning intensive chemo or transplant
- Ven days 1-14 (400 mg/day, no ramp up)
  - Prophylactic antimicrobials required
- 57 patients
  - Med Age 71 (26-85);
  - IPSS-R very high risk: 60%

Wei et al. ASH 2019 Abstract #568.

Wei et al, Abstract 568 – AZA plus Venetoclax for HR-MDS: Response Rates



Median time to CR, months (range)	2.2 (1.2-11.1)
12-mo estimate of DoR after CR, % (95% CI)	83.3 (2.3, 97.5)
mCR with HI (HI-E, HI-P or 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; per IWG (Cheson et al., *Blood* 2006;108:419-425)
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

Wei et al. ASH 2019 Abstract #568.

Abstract 569 – AZA plus Magrolimab for HR-MDS

- CD47 is a macrophage immune checkpoint and ”Do Not Eat Me” signal in MDS
- Magrolimab targets CD47 and synergizes with AZA in preclinical models
- Phase 1b study
- *Untreated* MDS, IPSS-R intermediate or higher risk disease
  - Magro dose ramp up to 30mg/kg weekly in C1 to mitigate on-target anemia
  - AZA given at standard 75mg/m2 D1-7 doses
- 35 patients
  - Med Age 70 (47-80);
  - IPSS-R high or very high risk disease: 65%
- Safety profile consistent with AZA monotherapy; on-target anemia seen but mitigated with ramp up (median Hgb drop 0.4 g/dL with first dose)

Sallman et al. ASH 2019 Abstract #569.

AZA plus Magrolimab for HR-MDS – Preliminary Efficacy

Best Overall Response	1L MDS N=24
CR	12 (50%)
CRi	-
PR	0
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI
Hematologic improvement (HI)	2 (8%)
SD	2 (8%)
PD	0

Parameter	1L MDS N=24
RBC transfusion independence[1]	4/9 (44%)
Complete cytogenetic response in responders[2]	5/19 (26%)
MRD negativity in responders	5/22 (23%)
Median duration of response (months)	Not reached (0.03+ – 9.76+)
Median follow-up [range] (months)	6.4 [2.0 – 14.4]

Med OS not reached
5 patients received allogeneic HSCT

Sallman et al. ASH 2019 Abstract #569.

BRIGHT MDS & AML 1012 Study Design

- BRIGHT MDS & AML 1012 (NCT02367456) is an ongoing open-label, multicenter, phase 1b trial
- Key eligibility criteria:
  - Patients were aged ≥18 years
  - Newly diagnosed AML, higher-risk MDS, and CMML
  - Clinical indication for treatment with AZA for AML or MDS
  - No prior treatment with a Smoothened inhibitor and/or a hypomethylating agent

Population

AML cohort (n=30)
- De novo or secondary AML

MDS cohort (n=30)
- MDS (intermediate, high, or very high risk by IPSS-R) or CMML

Treatment

Glasdegib + AZA
- Glasdegib 100 mg once daily
- AZA (75 mg/m^2/day) on Days 1–7 of a 28-day cycle

Endpoints

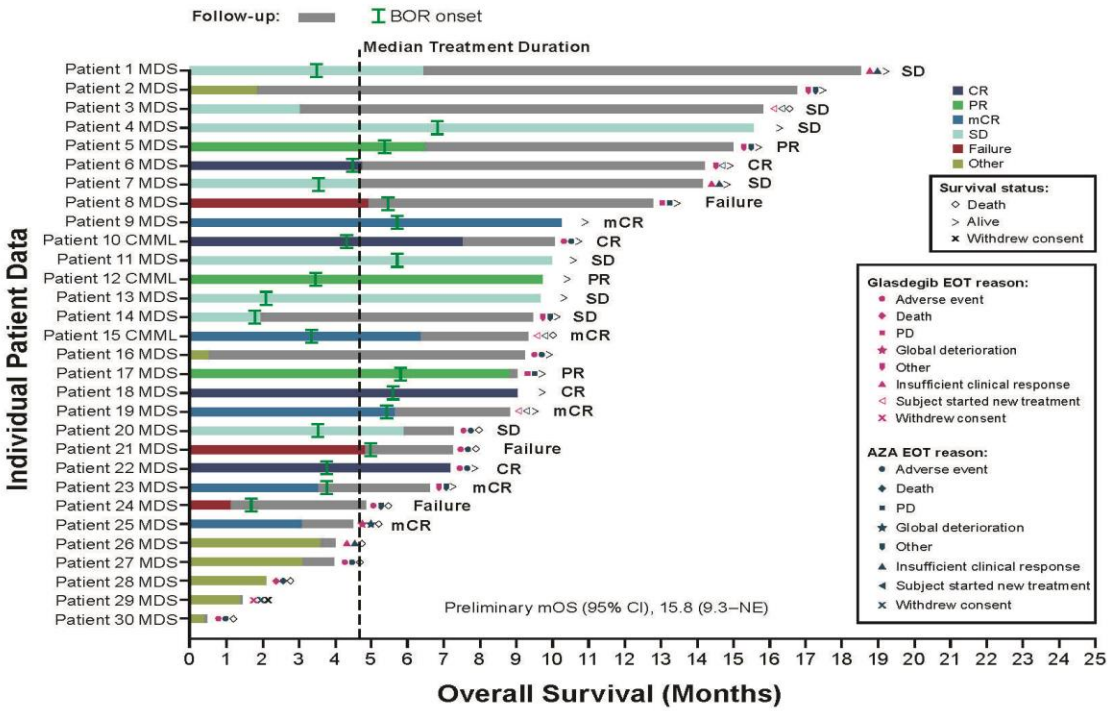
Primary
- Rate of CR

Secondary
- Overall survival
- Disease-specific efficacy measures
- Time to and duration of CR
- Safety
- Pharmacokinetic analysis

Study start date: April 28, 2015. Data cut-off: September 11, 2019.

AML=acute myeloid leukemia; AZA=azacitidine; CMML=chronic myelomonocytic leukemia; CR=complete remission; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome

MDS Cohort:
Overall Survival With Best Overall Response

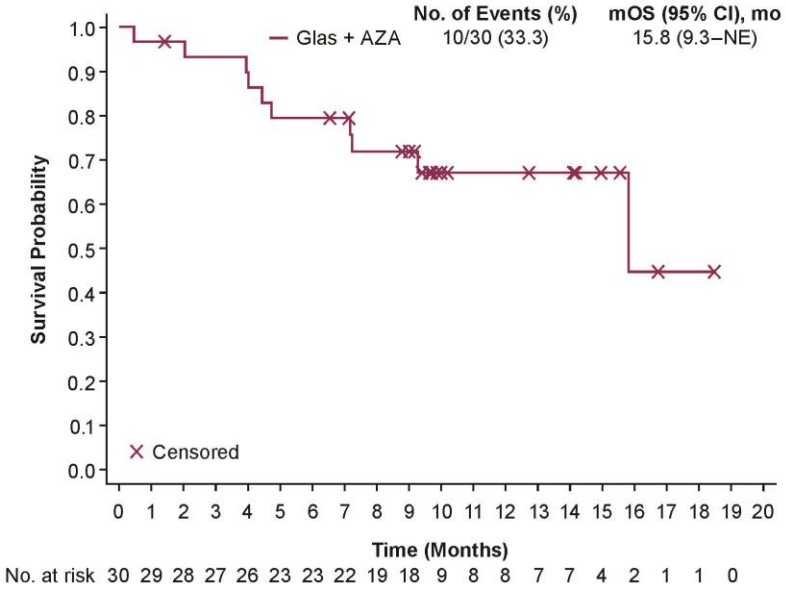


Response	n (%)
CR	4 (13.3)
PR	3 (10.0)
HI without CR or PR	3 (10.0)
CR + PR + HI without CR or PR	10 (33.3)
mCR	5 (16.7)
SD	8 (26.7)

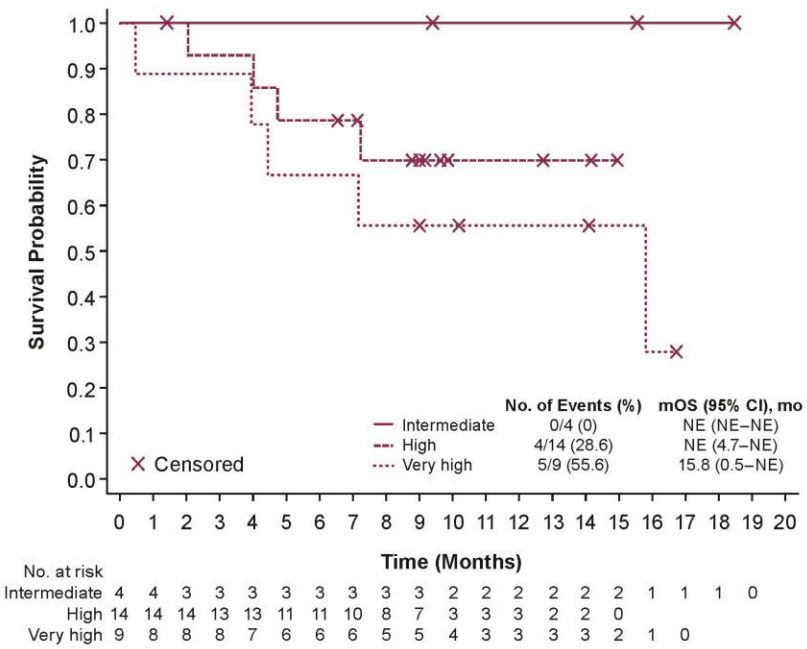
AZA=azacitidine; BOR=best overall response; CMML=chronic myelomonocytic leukemia; CR=complete remission; EOT=end of treatment; HI=hematologic improvement; mCR=marrow complete remission; MDS=myelodysplastic syndrome; PD=progressive disease; PR=partial remission; SD=stable disease

MDS Cohort: Preliminary Overall Survival

All Patients



IPSS-R Genetic Risk Category*



*Risk category based on 27 MDS patients alone.

AZA=azacitidine; CI=confidence interval; Glas=glasdegib; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome; mo, months; mOS=median overall survival; NE=not evaluable

Beyond HMAs| Other Combos

AZA + Checkpoint inhibitors

AZA + Other HDAC-I

AZA + Pevonedistat

AZA + IDHi (or IDHi alone)

AZA + mAb (or mAb alone)

AZA + Rigosertib

(or DAC + any of the above)

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Beyond HMAs| Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- Combinations – Higher-risk
- **Conclusions**

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Beyond HMAs| Conclusions

- Predicting response to HMAs coming of age
- Combos in lower-risk MDS focused on anemia
- Combos in higher-risk take different mechanism of action approaches or on genetics

Our drugs fail our patients! Our patients don't fail our drugs.

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Thanks!!!

MDS The National Myelodysplastic Syndromes Natural History Study

Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

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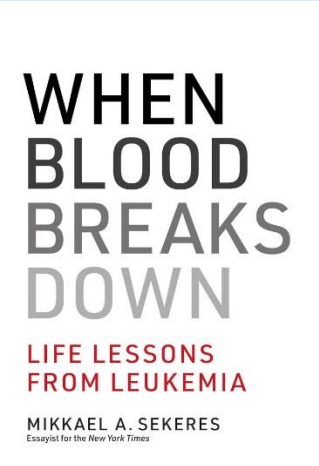

April 2020!

And Our Patients!!!