Updates on Treating

MDS and Secondary AML

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Treating MDS| Agenda

- Treating Lower-risk MDS
- Treating Higher-risk MDS
- Treating sAML

Treating MDS| Agenda

- **Treating Lower-risk MDS**
- Treating Higher-risk MDS
- Treating sAML

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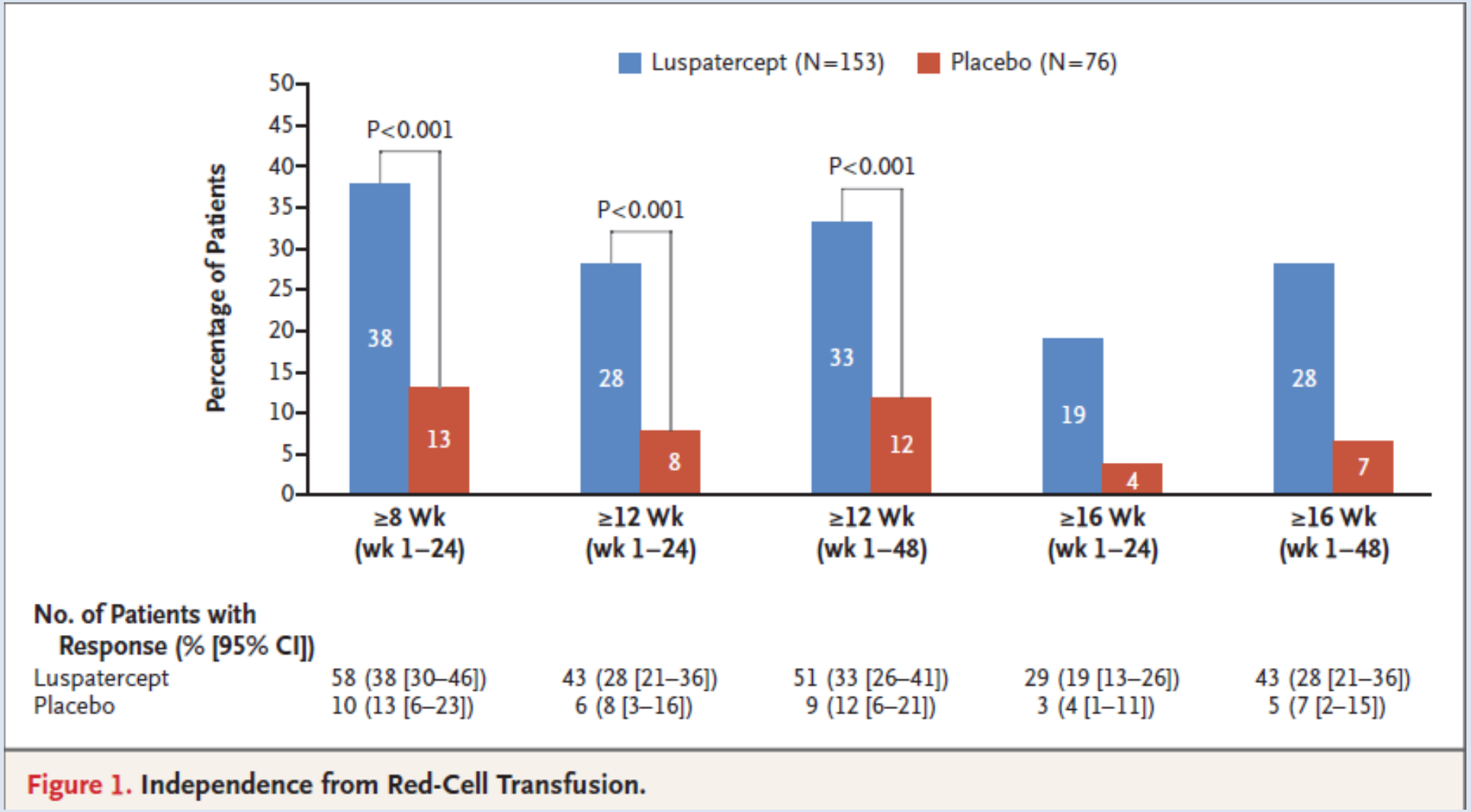
MDS | Ameliorating Anemia: LUSPAT



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])

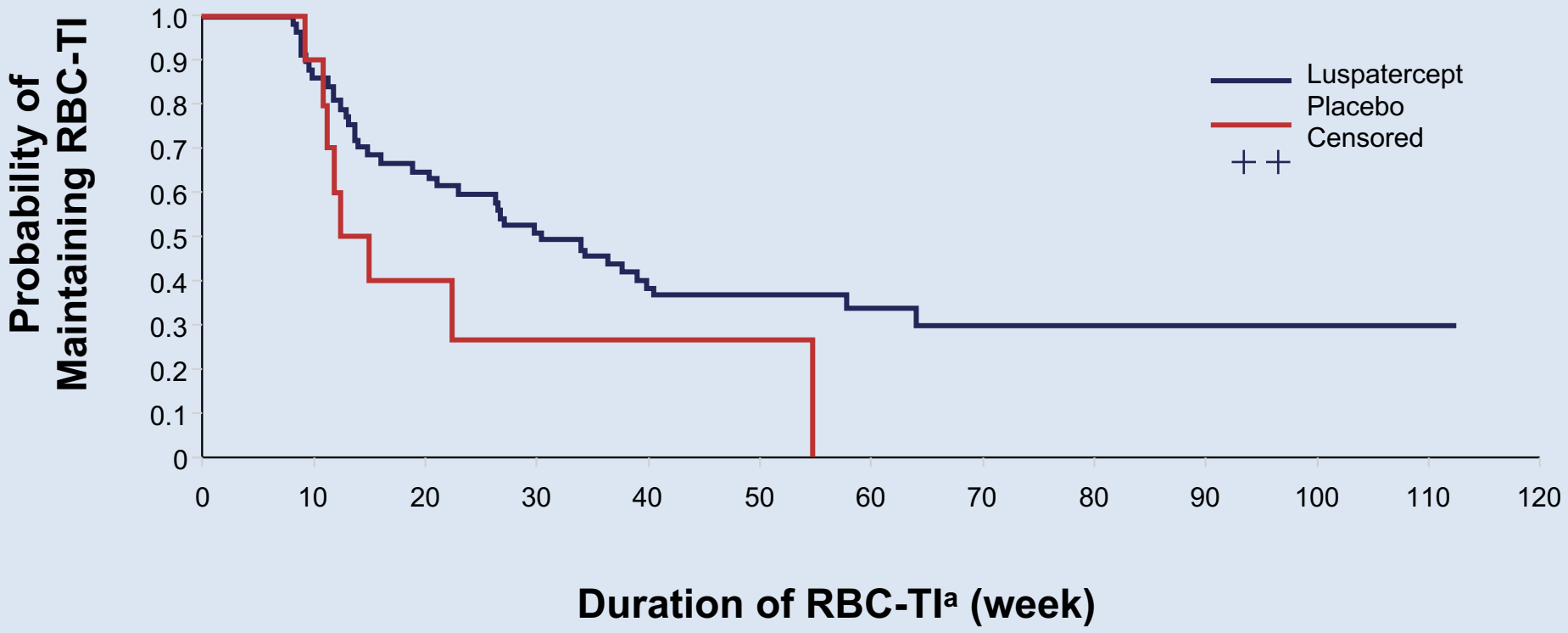
Figure 1. Independence from Red-Cell Transfusion.

Fenaux et al. NEJM 2020;382:140-151.

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Ameliorating Anemia: LUSPAT

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)



Fenaux et al. NEJM 2020;382:140-151.

Courtesy of Mikkael A Sekeres, MD, MS

MDS| Ameliorating Anemia: LUSPAT

Impact on Patient Care and Treatment Algorithm:

- Option post-ESA
- ORR/duration similar to ESA
- Few side effects

*** But – Does TI duration/definition offset time investment for shots?
Is it worth the $$? ***

Implications for Future Research:

- Compare up-front to ESA
- Is having RS such a big deal?
- Combine with ESA, LEN, HMA…

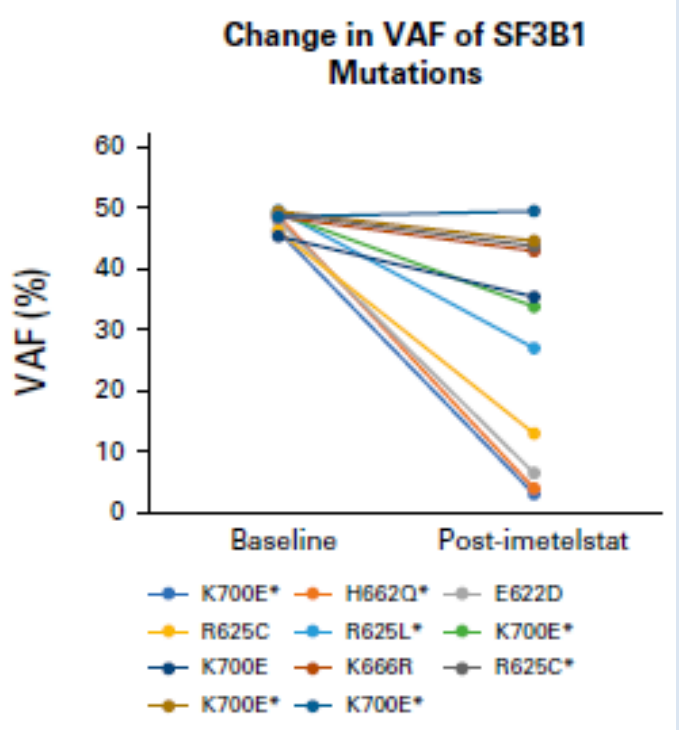
Fenaux et al. NEJM 2020;382:140-151.

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Ameliorating Anemia: Imetel

Imetelstat in HTB Lower-risk MDS

Parameter	Overall Population (n = 57)
8-week TI[a], No. (%)	21 (37)
Median time to onset, weeks (range)	8.3 (0.1-100.6)
Median duration of TI[b], weeks (range)	65 (17.0-140.9)
24-week TI[a], No. (%)	13 (23)
HI-E per IWG 2006, No. (%)	37 (65)
≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks	15 (26)
Transfusion reduction by ≥ 4 units/8 weeks	37 (65)
Response per IWG 2018, No. (%)	
Major response: 16-week TI	16 (28)
Major response: 8-week TI	21 (37)
Minor response[c]	28 (49)



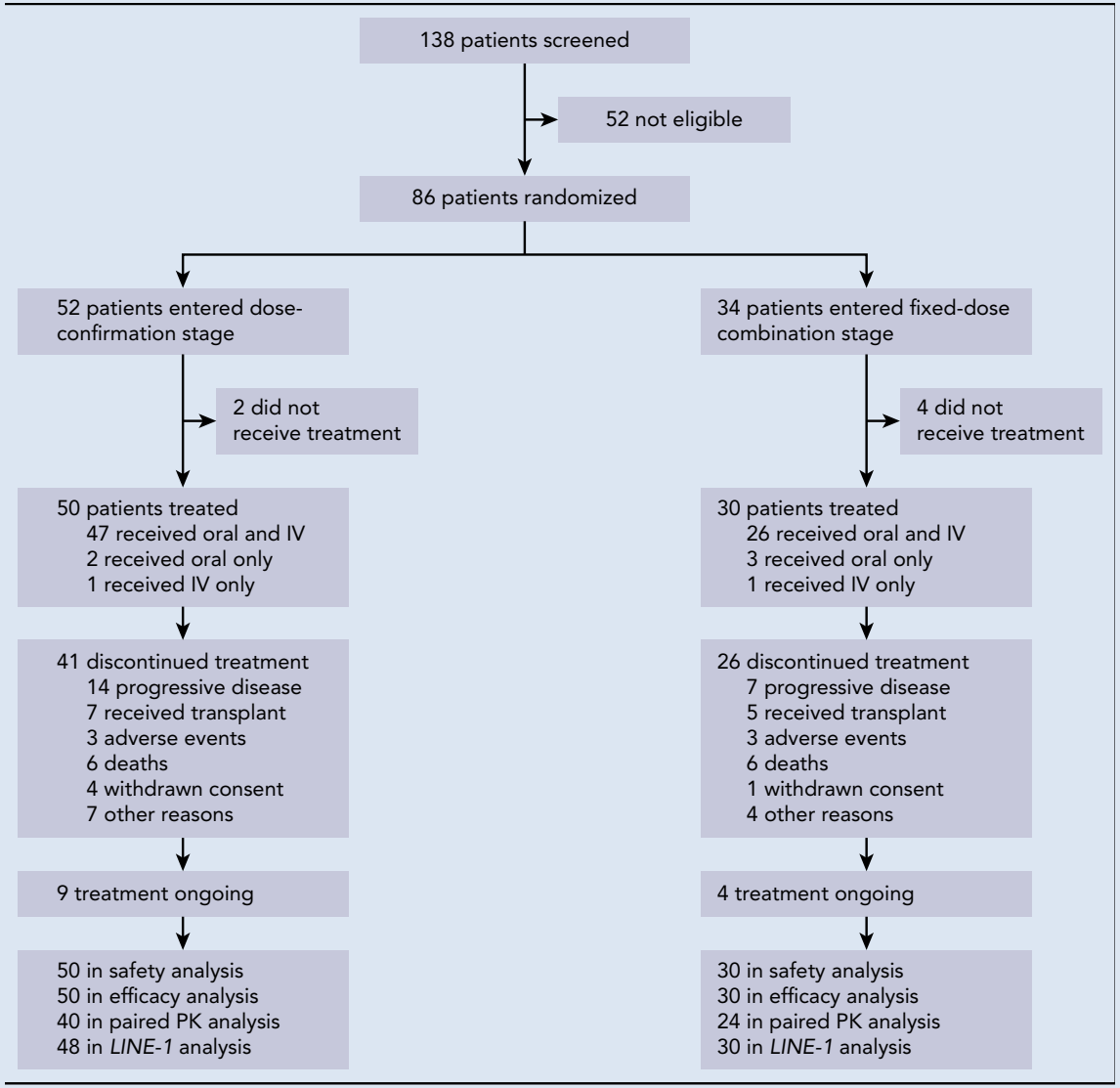
Steensma et al. JCO 2020

Courtesy of Mikkael A Sekeres, MD, MS

Treating MDS| Agenda

- Treating Lower-risk MDS
- **Treating Higher-risk MDS**
- Treating sAML

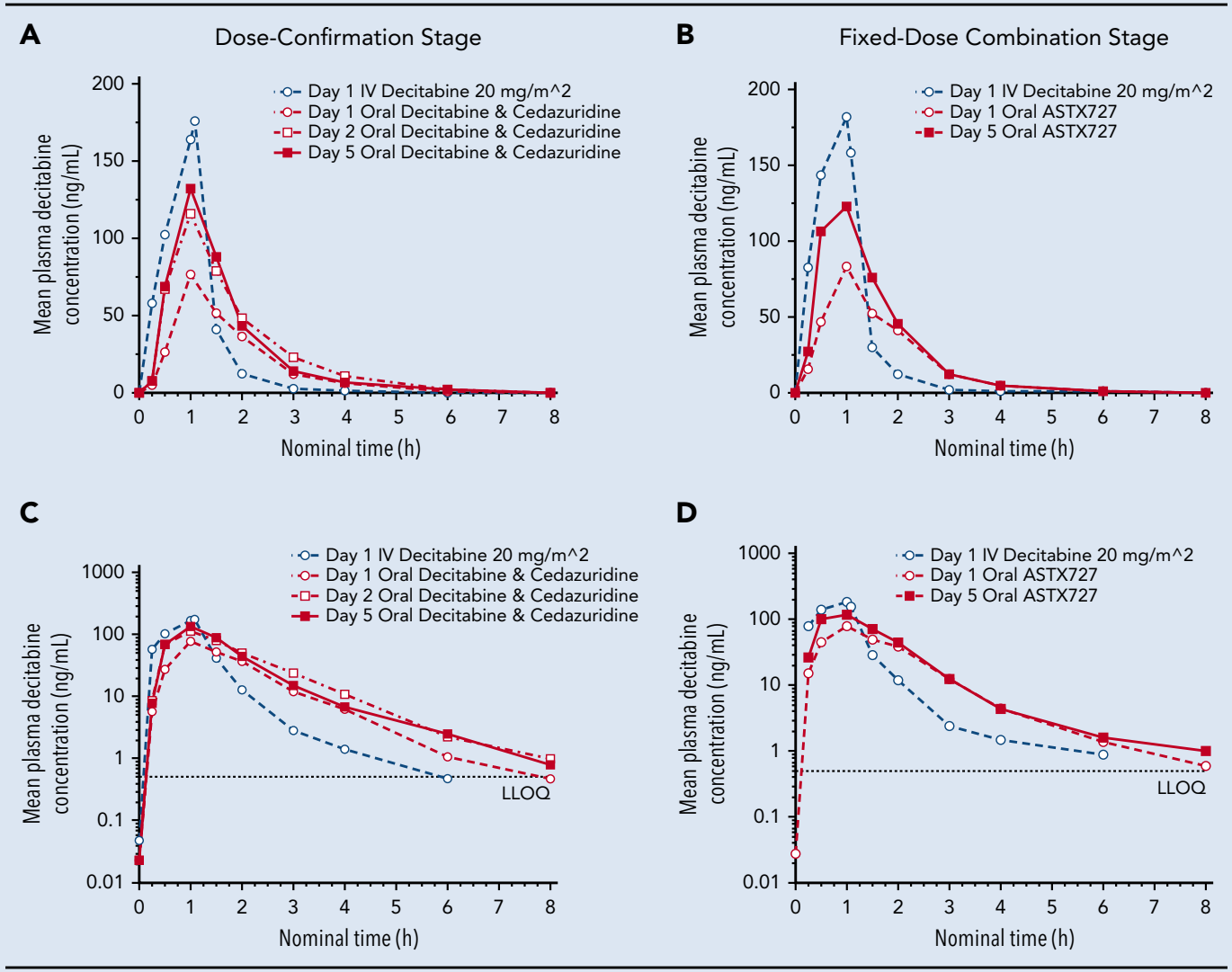
Higher-risk MDS | HMAs: DAC/CED



Garcia-Manero et al. Blood 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | HMAs: DAC/CED



Garcia-Manero et al. Blood 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | HMAs: DAC/CED

Oral Cedazuridine/Decitabine Phase 2
In Int-1, Int-2, High, CMML

Type of response	Phase 2 overall (N=80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero et al. Blood 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS| HMAs

Impact on Patient Care and Treatment Algorithm:

- DAC/CED has similar ORR to AZA or DAC
- Lower-risk MDS patients included in studies
- Crossover to IV occurred

*** But – Long-term follow-up pending. Impact on OS?
Is it worth the $$? ***

Implications for Future Research:

- Identifying molecular subtypes who did particularly well
- Combine with molecularly targeted drugs
- Give as easy maintenance post-HCT, post-IC

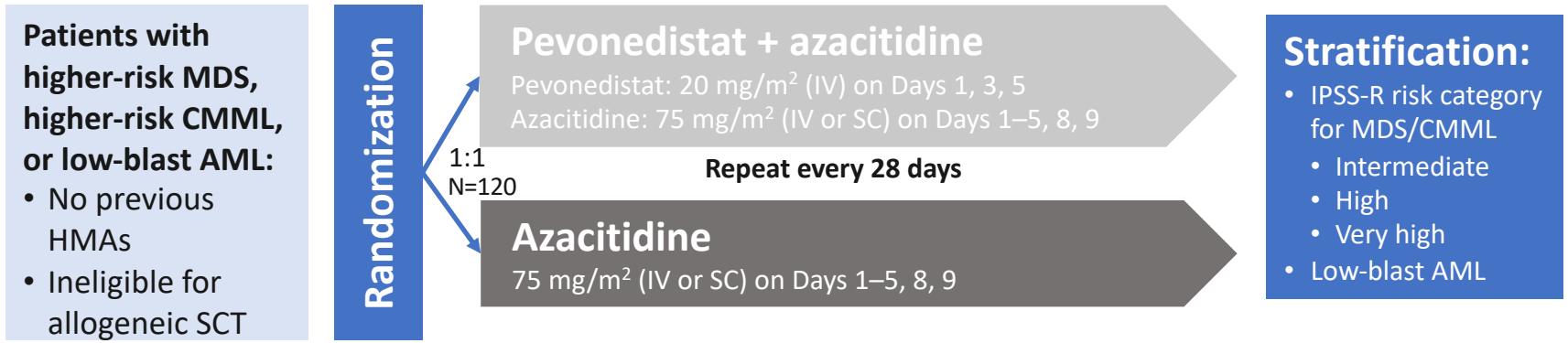
Garcia-Manero et al. Blood 2020; Fenaux P, et al. Lancet Oncology 2009;10:223-232; Lubbert et al. JCO 2011;29:1987.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Study design: AZA +/- Pevonedistat

NCT02610777: Phase 2, 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): Trial 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; HMAs, hypomethylating agents; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; ORR, objective response rate; SC, subcutaneous; SCT, stem cell transplant

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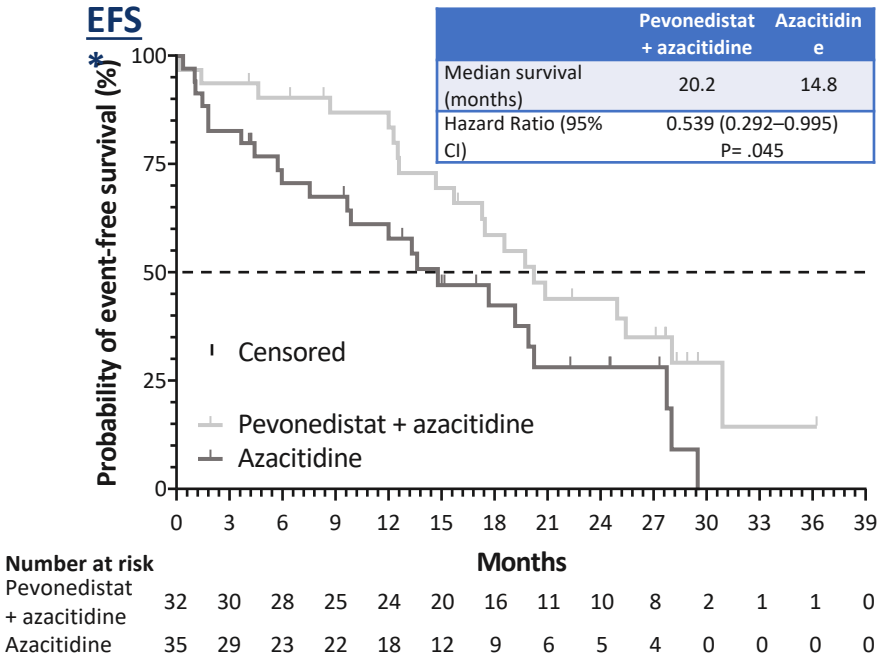
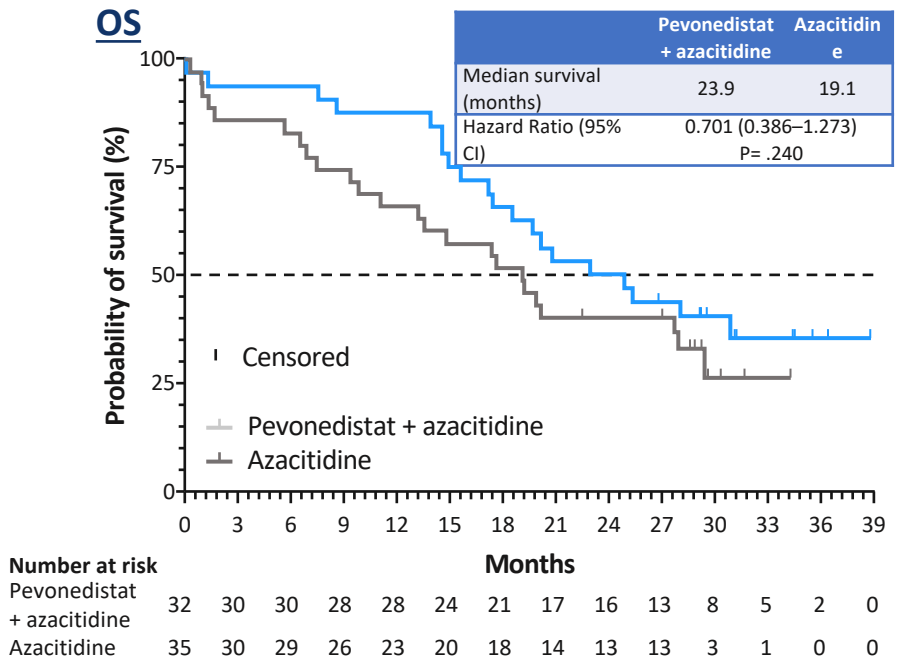
Higher-risk MDS | Combinations

EFS and OS: Higher-risk MDS





*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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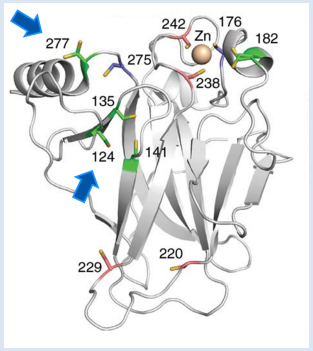
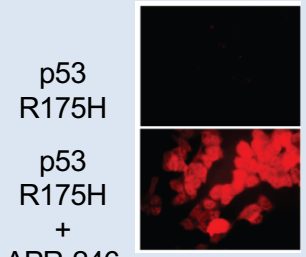
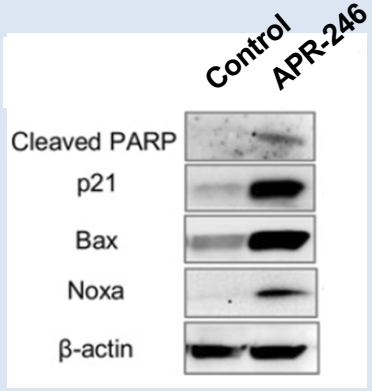
Higher-risk MDS | Targeting *TP53*



APR-246 binds covalently to p53…



…restores wt p53 conformation & activity…



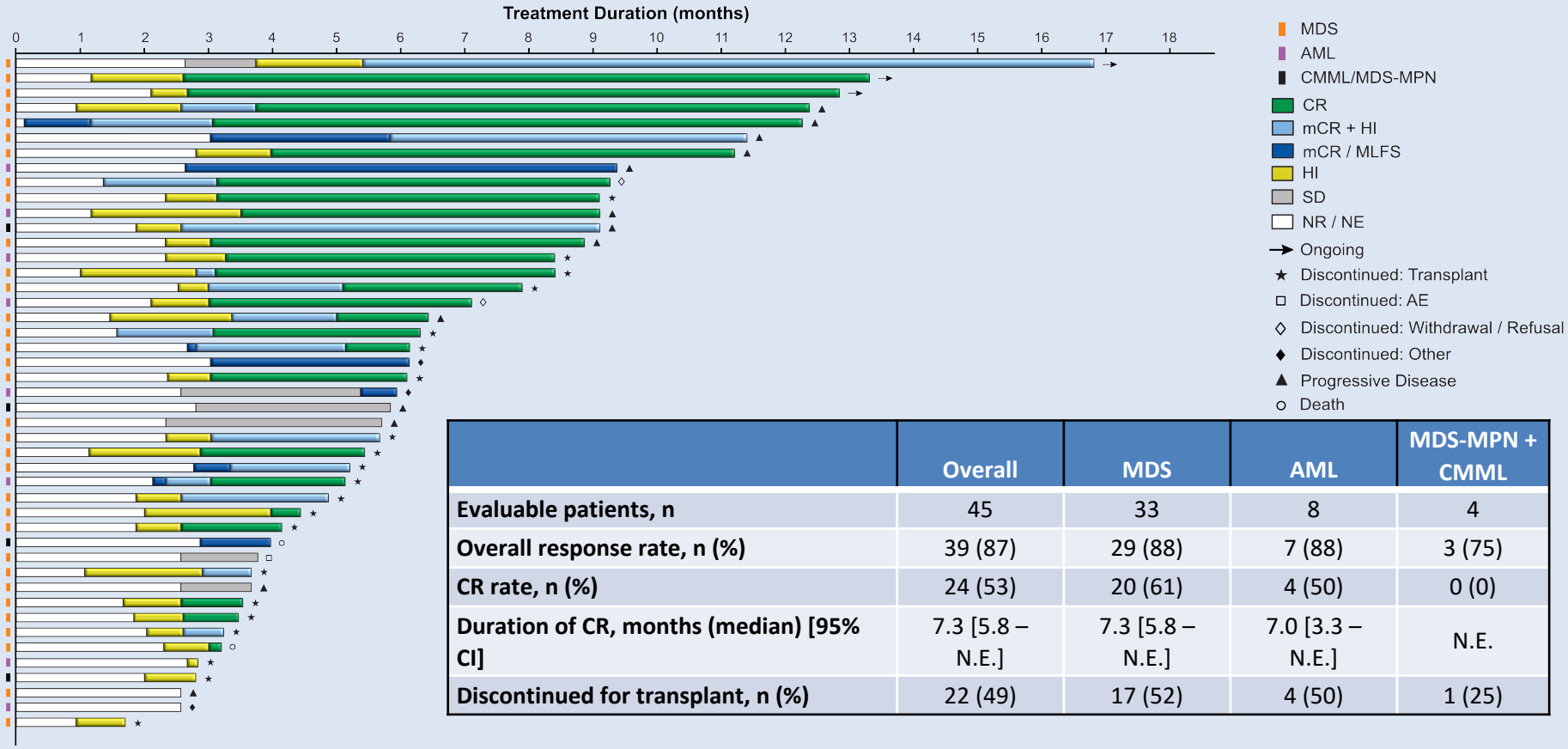
…and triggers cell cycle arrest and apoptosis

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.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Targeting *TP53*



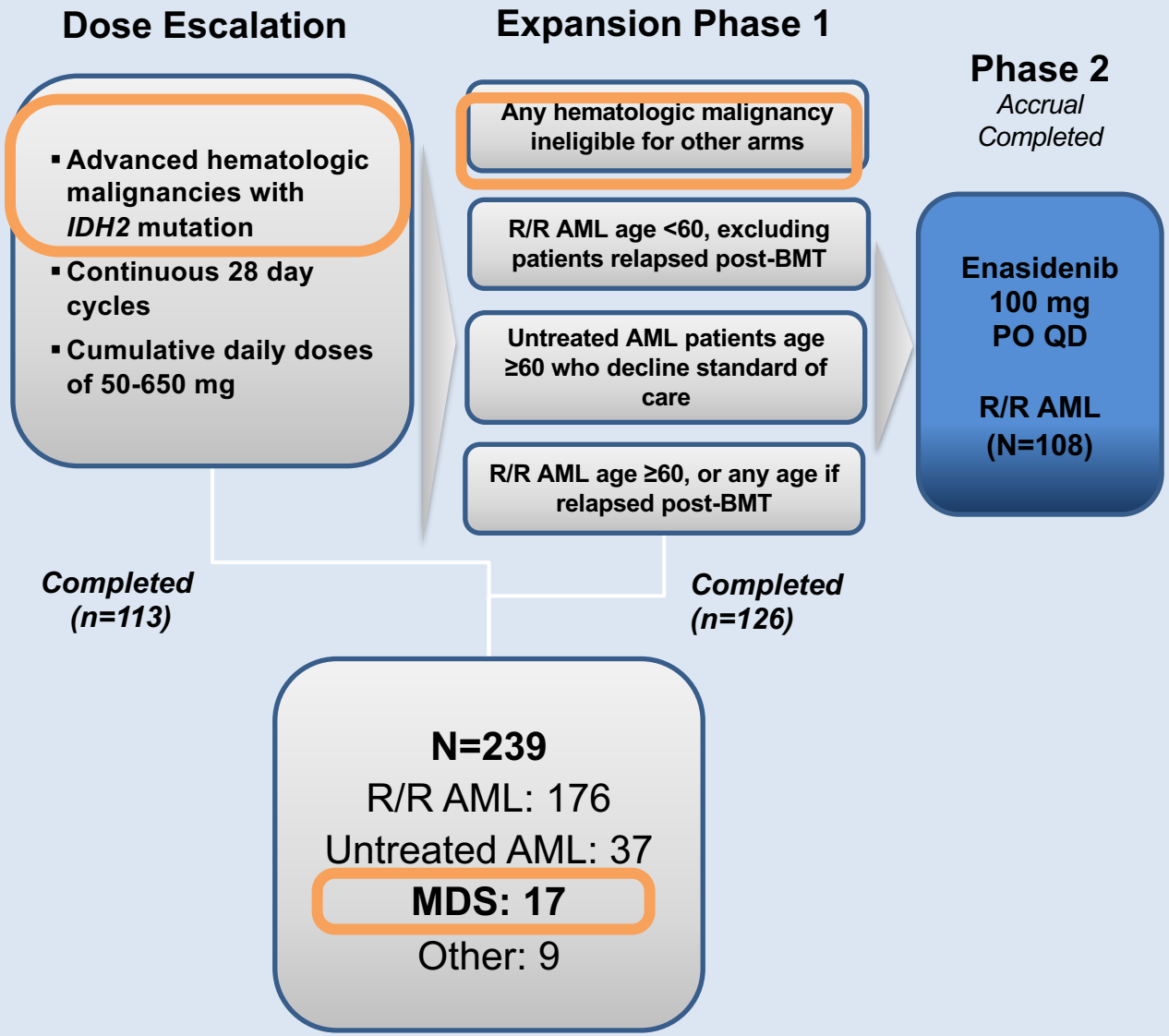
	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22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

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Targeting *IDH2*



Stein et al. Lancet Haematology 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Targeting *IDH2*

	MDS Patients (N=17) n (%)
Overall response rate (CR + PR + mCR + HI)	**10/17 (59)**
Best Response	
Complete remission	1/11 (9)
Partial remission	1/11 (9)
Marrow CR	3/11 (27)
Any hematologic improvement (HI)†	5/17 (29)
HI-E	3/15 (20)
HI-P	4/12 (33)
HI-N	4/10 (40)

Stein et al. Lancet Haematology 2020.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Phase Ib of AZA + VEN in R/R higher-risk MDS

Patients:

N=38
Median age = 74 years
Median 8 cycles prior HMA
Median follow-up = 6.8 months

Responses:

CR N=3
HI N=9
TI N=13 for median of 4.1 months
Median PFS = 9.1 months

Zeiden et al. EHA 2020;S118.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Phase Ib of AZA + VEN in <u>treatment-naïve</u> higher-risk MDS
Ven given in escalating dose (100, 200, and 400 mg) for 14 days of a 28-day cycle

Patients:
N=57
Median age = 71 years
Median follow-up = 13 months

Responses:
CR 42%
Marrow CR with HI 14%
Median response duration 14.8 months
TI N=13 for median of 4.1 months
Median PFS = 17.5 months
EORTC QLQ C30 improvement in fatigue and dyspnea

Garcia et al. ASH 2020;656a.

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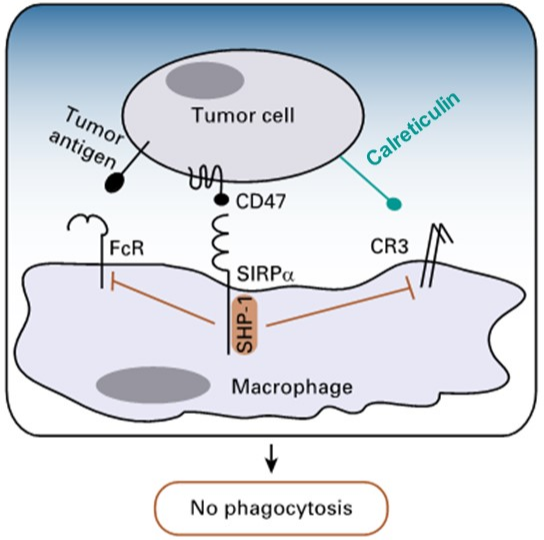
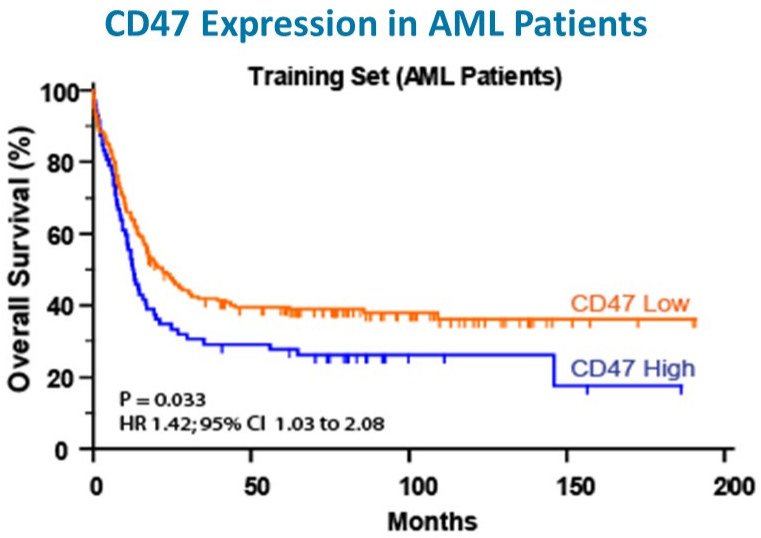
Higher-risk MDS | Combinations

CD47 Is a 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 AML patients

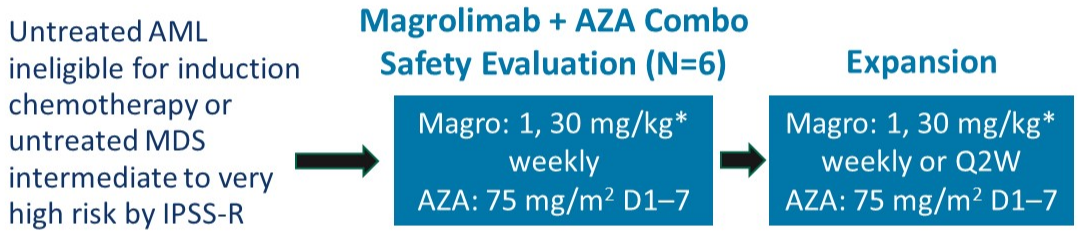
Figure at left adapted from Veillette A, Tang Z. *J Clin Onc.* 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol.* 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell.* 2009;138(2):286-299.

Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

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



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 was utilized to mitigate on-target anemia
- Data from the expansion cohort is presented

*Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing or 30 mg/kg Q2W starting Cycle 3+.
IPSS-R: Revised International Prognostic Scoring System.

Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

Patient Characteristics (N=68): Magrolimab + AZA in Untreated (1L) MDS and AML

Characteristic	1L MDS 5F9+AZA (N=39)	1L AML 5F9+AZA (N=29)
Median age (range)	70 (47–80)	74 (60–89)
ECOG Performance Status: 0	11 (28%)	7 (24%)
1	26 (67%)	20 (69%)
2	2 (5%)	2 (7%)
Cytogenetic Risk: Favorable	0	0
Intermediate	11 (28%)	2 (7%)
Poor	25 (64%)	21 (72%)
Unknown/missing	3 (8%)	6 (21%)
WHO AML classification: MRC		19 (66%)
Recurrent genetic abnormalities	NA	2 (7%)
Therapy related		3 (10%)
Not otherwise specified		5 (17%)
WHO MDS classification:		
RS and single/multilineage dysplasia	1 (3%)	NA
Multilineage dysplasia	7 (18%)	
RS with multilineage dysplasia	3 (8%)	
Excess blasts	22 (56%)	
Unclassifiable/unknown/missing	6 (15%)	
IPSS-R (MDS): Intermediate	13 (33%)	NA
High	19 (49%)	
Very High	6 (15%)	
Unknown/missing	1 (3%)	
Therapy related MDS	12 (31%)	
Unknown/missing	1 (3%)	
Harboring a TP53 mutation	5 (13%)	13 (45%)

MRC, myelodysplasia-related changes; NA, not applicable; all patients enrolled on study are shown; WHO, World Health Organization.

- 64%–72% of MDS and AML patients were poor cytogenetic risk
- 66% of AML patients had underlying myelodysplasia (MRC)
- 31% of MDS patients were therapy related
- 45% of AML patients were *TP53* mutant

Sallman et al. ASCO 2020;7507a.

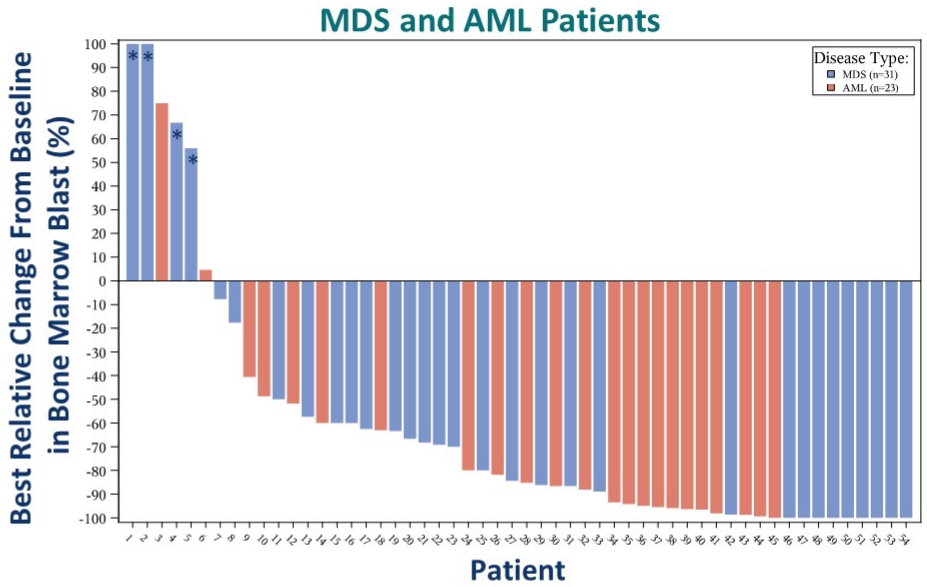
Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations

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.

Sallman et al. ASCO 2020;7507a.

Courtesy of Mikkael A Sekeres, MD, MS

Treating MDS| Combinations

Impact on Patient Care and Treatment Algorithm:

- Modest ORR for AZA + Ven in previously treated
- Good ORR for AZA + Ven in untreated higher-risk MDS
- Good ORR for AZA + Mag in untreated Intermediate/Higher-risk MDS

*** But – Is ORR really better than AZA monotherapy in selected patients?
Is durability of response any better?
Is it worth the $$? ***

Implications for Future Research:

- Identifying molecular subtypes who did particularly well
- Optimizing Ven dose and schedule
- Combine with molecularly targeted drugs (Triplet therapy)

Zeiden et al. EHA 2020;S118.
Garcia et al. ASH 2020;656a.
Sallman et al. ASCO 2020;7507a.

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Treating MDS| Agenda

- Treating Lower-risk MDS
- Treating Higher-risk MDS
- **Treating sAML**

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Treating sAML| CPX-351

- In total, 309 patients were randomized to receive CPX-351 (n = 153) or 7+3 (n = 156) and were included in the intent-to-treat population for efficacy analyses; the safety population included 153 and 151 patients, respectively[6]

Table 1. Baseline Characteristics in Older Adults With Newly Diagnosed High-risk/Secondary AML[6]

Characteristic, n (%)	CPX-351 (n = 153)	7+3 (n = 156)
Demographic characteristics		
Age		
Mean (SD), years	67.8 (4.2)	67.7 (4.1)
60 to 69 years, n (%)	96 (63)	102 (65)
70 to 75 years, n (%)	57 (37)	54 (35)
Male, n (%)	94 (61)	96 (62)
ECOG performance status, n (%)		
0	37 (24)	45 (29)
1	101 (66)	89 (57)
2	15 (10)	22 (14)
Clinical characteristics		
AML subtype, n (%)		
t-AML	30 (20)	33 (21)
AML with antecedent MDS		
With prior HMAs	50 (33)	55 (35)
Without prior HMAs	21 (14)	19 (12)
AML with antecedent CMML	11 (7)	12 (8)
de novo AML with MDS karyotype	41 (27)	37 (24)
Prior HMA therapy, n (%)[a]	62 (41)	71 (46)
Cytogenetic risk by NCCN, n (%)	143	146
Favorable	7 (5)	5 (3)
Intermediate	64 (45)	58 (40)
Unfavorable	72 (50)	83 (57)
Median bone marrow blasts (range), %	35 (5, 93)	35 (3, 97)
WBC count <20,000/μL, n (%)	131/153 (86)	131/155 (85)

AML, acute myeloid leukemia; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; t-AML, therapy-related AML; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; CMML, chronic myelomonocytic leukemia; NCCN, National Comprehensive Cancer Network; WBC, white blood cell.
[a]Includes patients in the prespecified randomization strata of antecedent MDS with prior HMA exposure as well as patients in other strata (eg, t-AML, antecedent CMML) who had previously received HMAs.

Lancet et al. ASCO 2020; 7510a; ASH 2020; 635a

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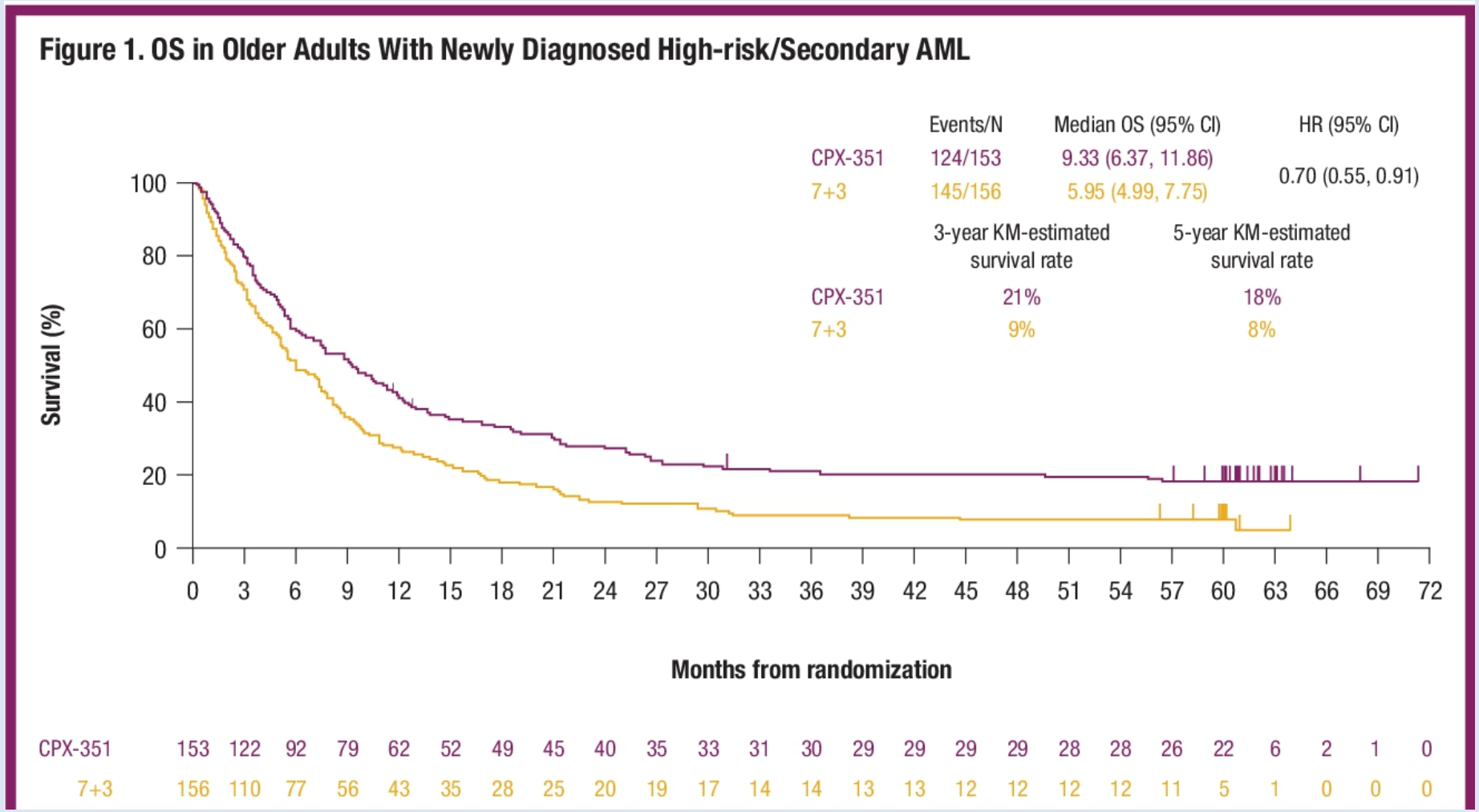
Treating sAML| CPX-351



Lancet et al. ASCO 2020; 7510a; ASH 2020; 635a

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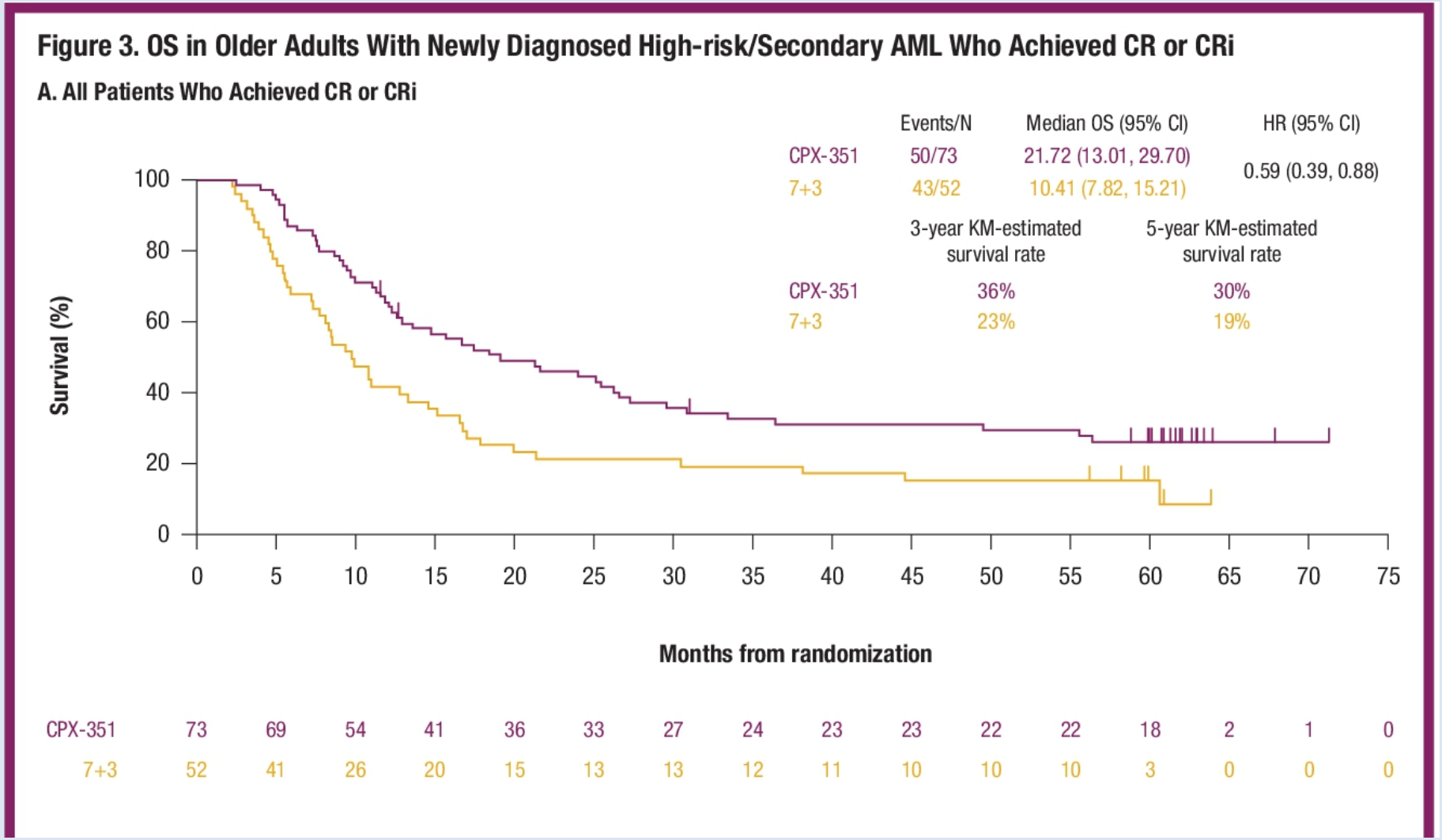
Treating sAML| CPX-351



Lancet et al. ASCO 2020; 7510a; ASH 2020; 635a

Courtesy of Mikkael A Sekeres, MD, MS

Treating sAML| CPX-351

	$N = 52$
Best response	
CR	
n (%)	15 (29)
95% CI	17.1–43.1
CRi	
n (%)	8 (15)
95% CI	6.9–28.1
CR + CRi	
n (%)	23 (44)
95% CI	30.5–58.7
Time to CR or CRi	
n	23
Median (range), d	37.0 (15–72)
Mean (SD), d	41.5 (15.24)

Roboz et al. Leuk Lymph 2020;61:1188-94.

Courtesy of Mikkael A Sekeres, MD, MS

Treating sAML| CPX-351

Impact on Patient Care and Treatment Algorithm:

- Continued improved OS among patients with sAML
- Particularly improved OS for those achieving CR/CRi and in those undergoing HCT.
- Suggests deeper responses.

*** But – did comparison arm perform as well as historically?
Was drug intensity similar?
Is it worth the $$? ***

Implications for Future Research:

- Identifying molecular subtypes who did particularly well
- Outpatient therapies
- Combine with molecularly targeted drugs

Lancet et al. ASCO 2020; 7510a; ASH 2020; 635a
Roboz et al. Leuk Lymph 2020;61:1188-94.

Courtesy of Mikkael A Sekeres, MD, MS

Treating sAML| Magrolimab

Phase Ib of AZA + Mag in <u>treatment-naïve AML</u>

Patients:

N=52
Median age = 73 years
TP53 + in 65%
Median follow-up = ???
34 evaluable for response

Responses:

CR 44%, 48% among TP53+
CRi 12%, 19% among TP53+
Median response duration 9.9 months
Median OS for TP53+ = 12.9 months, for non-TP53 18.9 months

Sallman et al. ASH 2020;330a

Courtesy of Mikkael A Sekeres, MD, MS

Treating sAML| Magrolimab

Impact on Patient Care and Treatment Algorithm:

- Good ORR for AZA + Mag in AML
- Good responses in TP53+
- Response duration good, c/w other single arm combo studies

*** But – Is ORR really better than AZA monotherapy in selected patients?
Is durability of response any better?
Is it worth the $$? ***

Implications for Future Research:

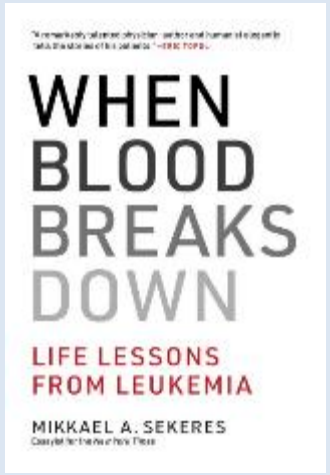
- Identifying molecular subtypes who did particularly well
- Combine with molecularly targeted drugs (Triplet therapy)
- Is it better than AZA + Ven???

Sallman et al. ASH 2020;330a

Courtesy of Mikkael A Sekeres, MD, MS

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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Appendix 1

- Additional Recent Data Set Provided by Dr Sekeres

Courtesy of Mikkael A Sekeres, MD, MS

Venetoclax/azacitidine has been evaluated in a Phase I study

Ongoing Phase 1b, open-label, dose-escalation,* multicenter study[1,2]

Higher-risk MDS
No prior therapy, not eligible for intensive chemotherapy or HSCT

N=82

Dose-escalation phase

Venetoclax + azacitidine
Venetoclax: escalating doses (oral) 100–400 mg/day
Azacitidine: 75 mg/m^2 (IV or SC) on Days 1–7

Safety expansion phase

Venetoclax + azacitidine
Venetoclax: 400 mg/day (oral)
Azacitidine: 75 mg/m^2 (IV or SC) on Days 1–7

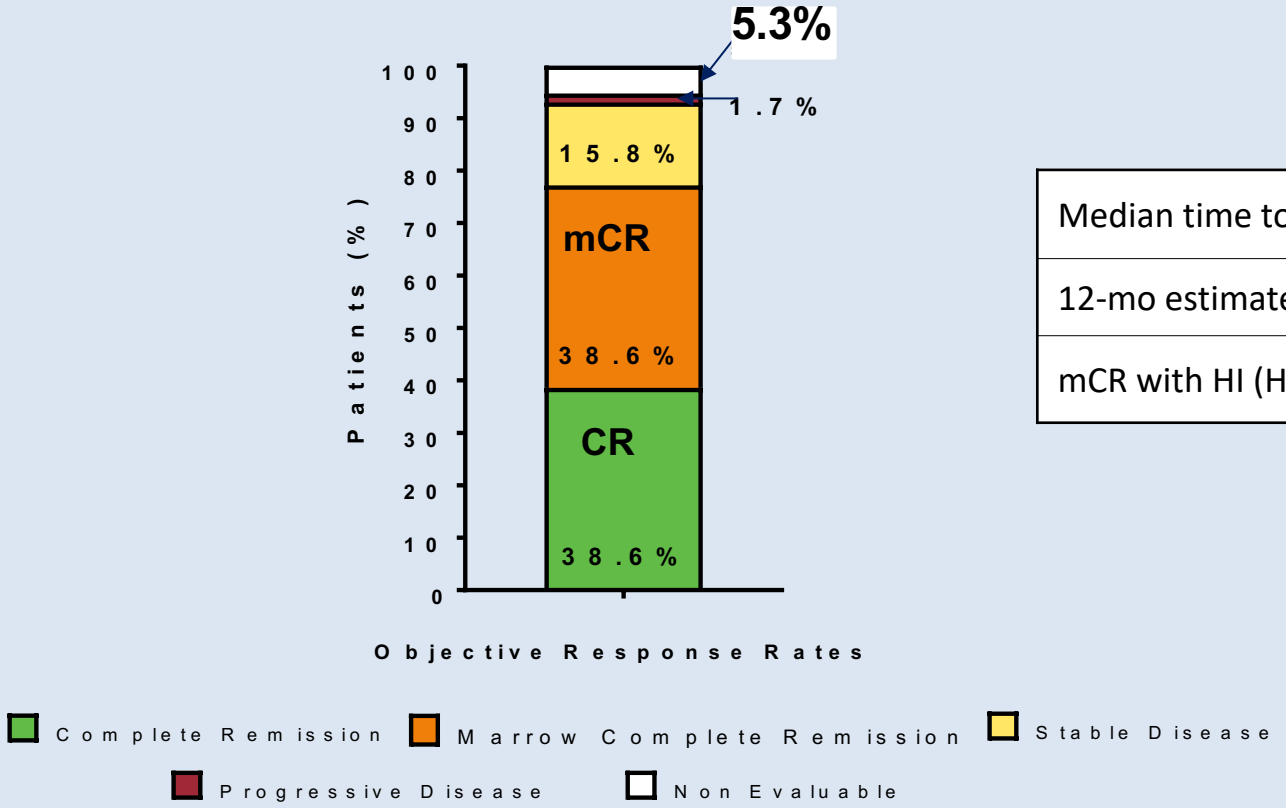
Primary endpoints:
- Safety
- RP2D

Secondary endpoints include:
- ORR
- PFS
- TTR
- DoR
- OS

1. Wei AH, *et al*. *Blood* 2019;134 (Suppl. 1):Abstract #568; 2. ClinicalTrials.gov, NCT02942290
*Originally a 3-arm, randomized study; amended to dose-escalation safety study after two deaths
TTR, time to response

Courtesy of Mikkael A Sekeres, MD, MS

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.

Courtesy of Mikkael A Sekeres, MD, MS

Appendix 2

- AML Overview slides
- Prognostic/Predictive Tools slides
- Additional Historic Data Sets Provided

Courtesy of Mikkael A Sekeres, MD, MS

Treating MDS| Agenda

- **Prognostic/Predictive tools**
- Treating Lower-risk MDS
- Treating Higher-risk MDS
- Treating sAML

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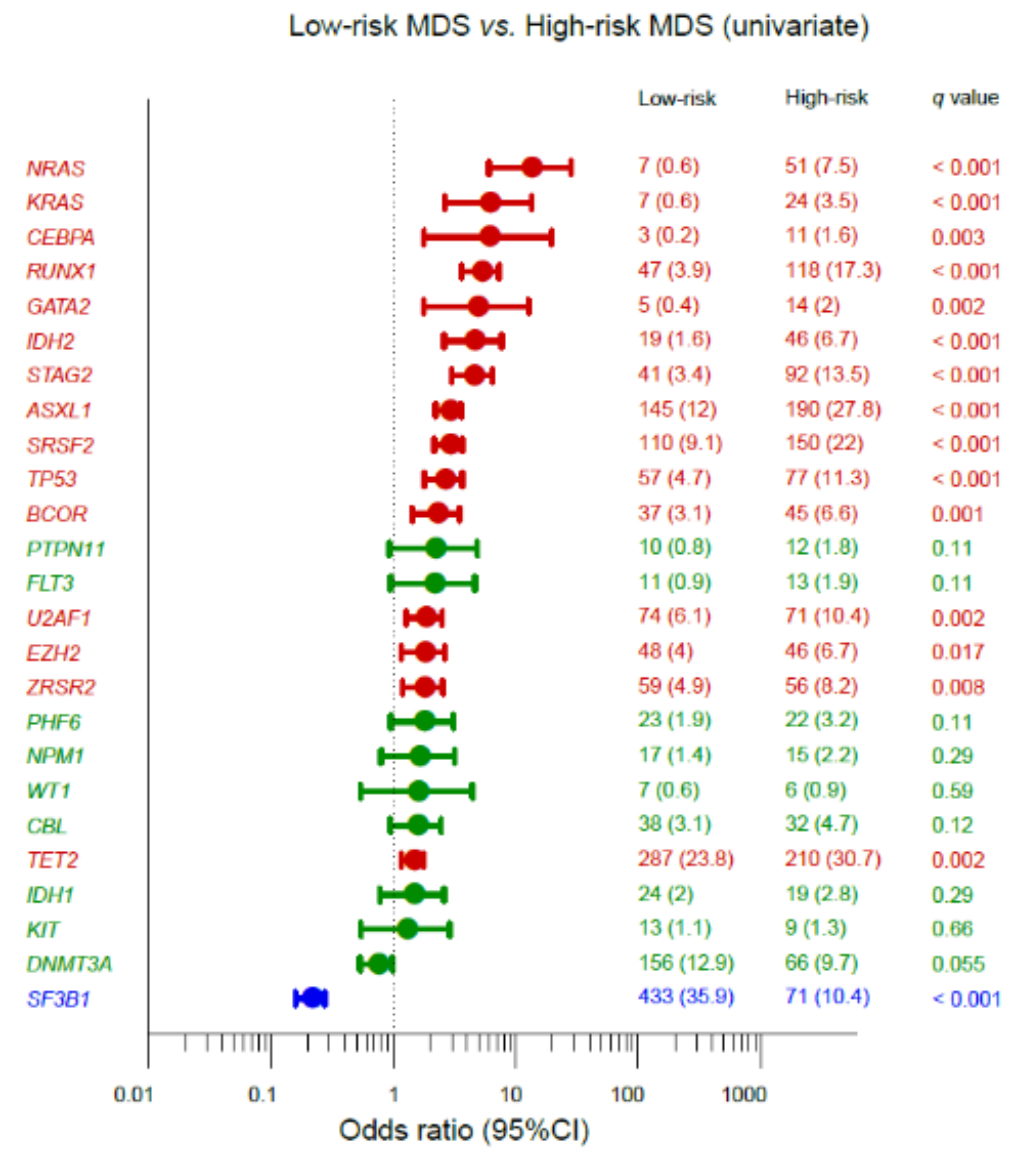
Courtesy of Mikkael A Sekeres, MD, MS

@MikkaelSekeres

Predictive Tools| Mutation Risk

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



Courtesy of Mikkael A Sekeres, MD, MS

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

MDS | Machine Learning

Data

Demographic

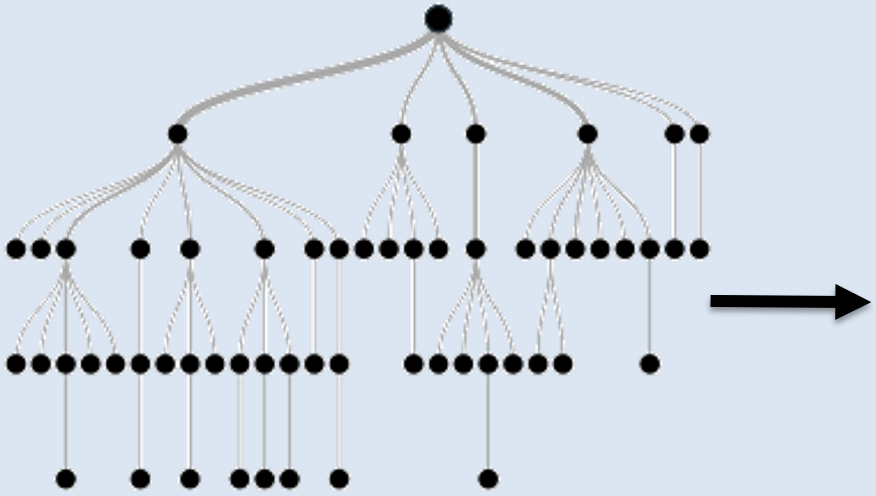
Clinical

Genomic

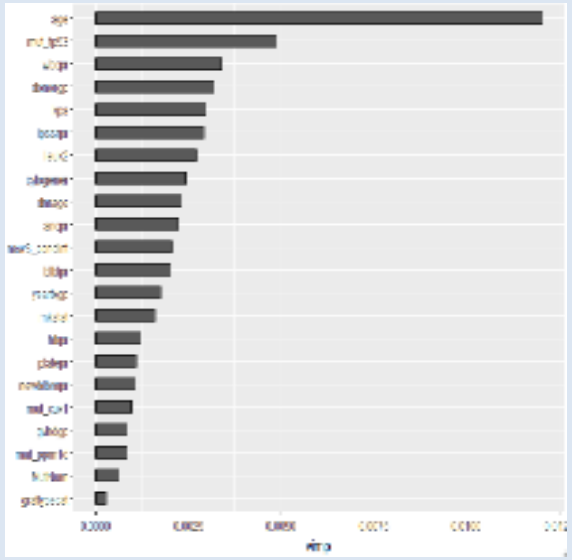
Training
CC + MLL

Validation
Moffitt

Random Survival Forest



Important Variables



Nazha A, et al. ASH 2018 [#793]

Courtesy of Mikkael A Sekeres, MD, MS

MDS | Machine Learning

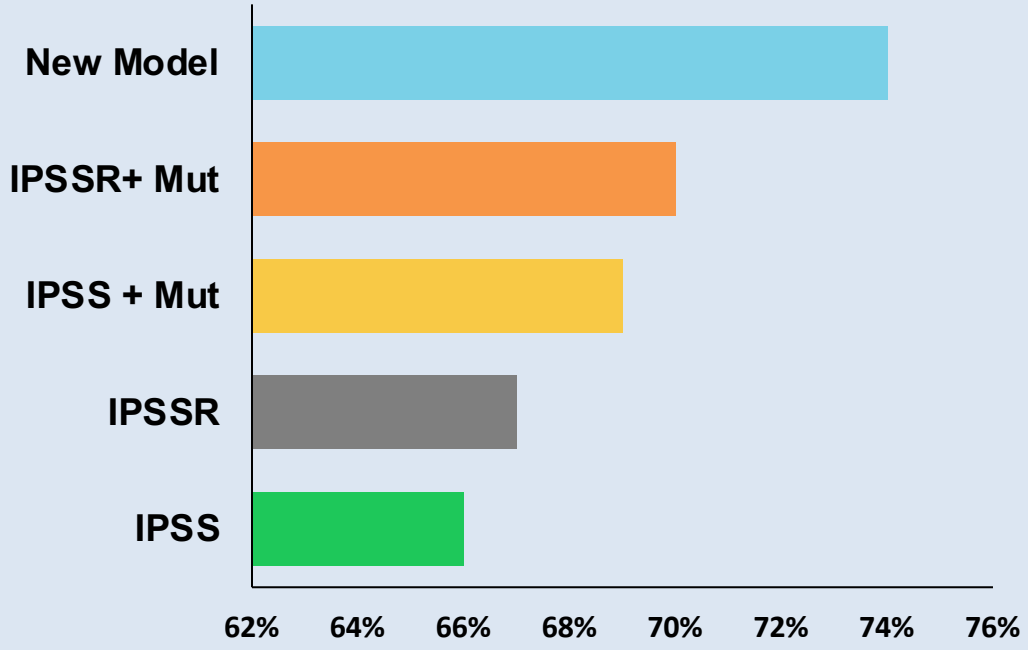
Parameter	Training No. (%) / [range]	Validation No. (%) / [range]	*p*
Total	1471	831	
Median age, years	71 [19-99]	69 [4-93]	NS
Clinical Variables			
Median WBC, 10^9/L	4.2 [0.6-82.6]	4 [0.1-25.6]	NS
Median ANC, 10^9/L	2.1 [0-65.1]	2 [0-8.5]	NS
Median Hb, g/dL	9.9 [3.9-15.6]	10 [3.4-17.1]	NS
Median Plts, 10^9/L	120 [4-975]	117 [7-1280]	NS
Median BM Blasts %	4 [0-19]	3 [0-19]	NS
2008 WHO Category			
RCMD / RCUD	578 (38)	350 (42)	NS
RARS	209 (11)	128 (15)	
RAEB-1 / RAEB-2	573 (37)	302 (36)	
MDS-U	49 (9)	18 (2)	
MDS with del (5q)	62 (5)	33 (4)	

Nazha A, et al. ASH 2018 [#793]

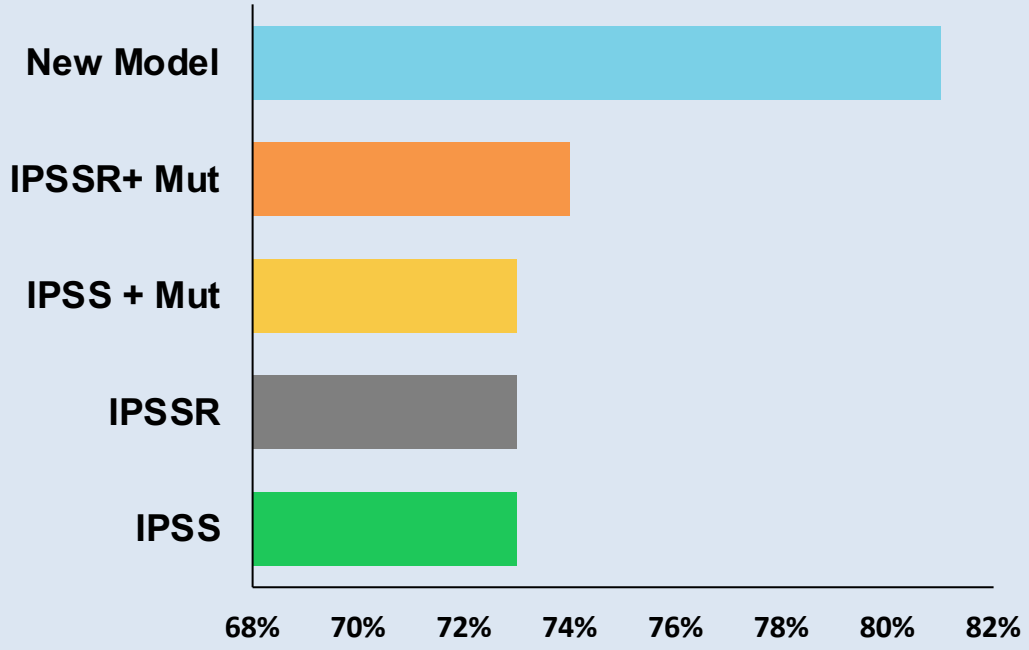
Courtesy of Mikkael A Sekeres, MD, MS

MDS | Machine Learning

Overall Survival



Leukemia-Free Survival



Nazha A, et al. ASH 2018 [#793]

Courtesy of Mikkael A Sekeres, MD, MS

Predictive Tools | Mutations/Response

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*

Results: Association Rules

31% pts
≥ 3 mutations/sample

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

ORR to HMAs = **43%**

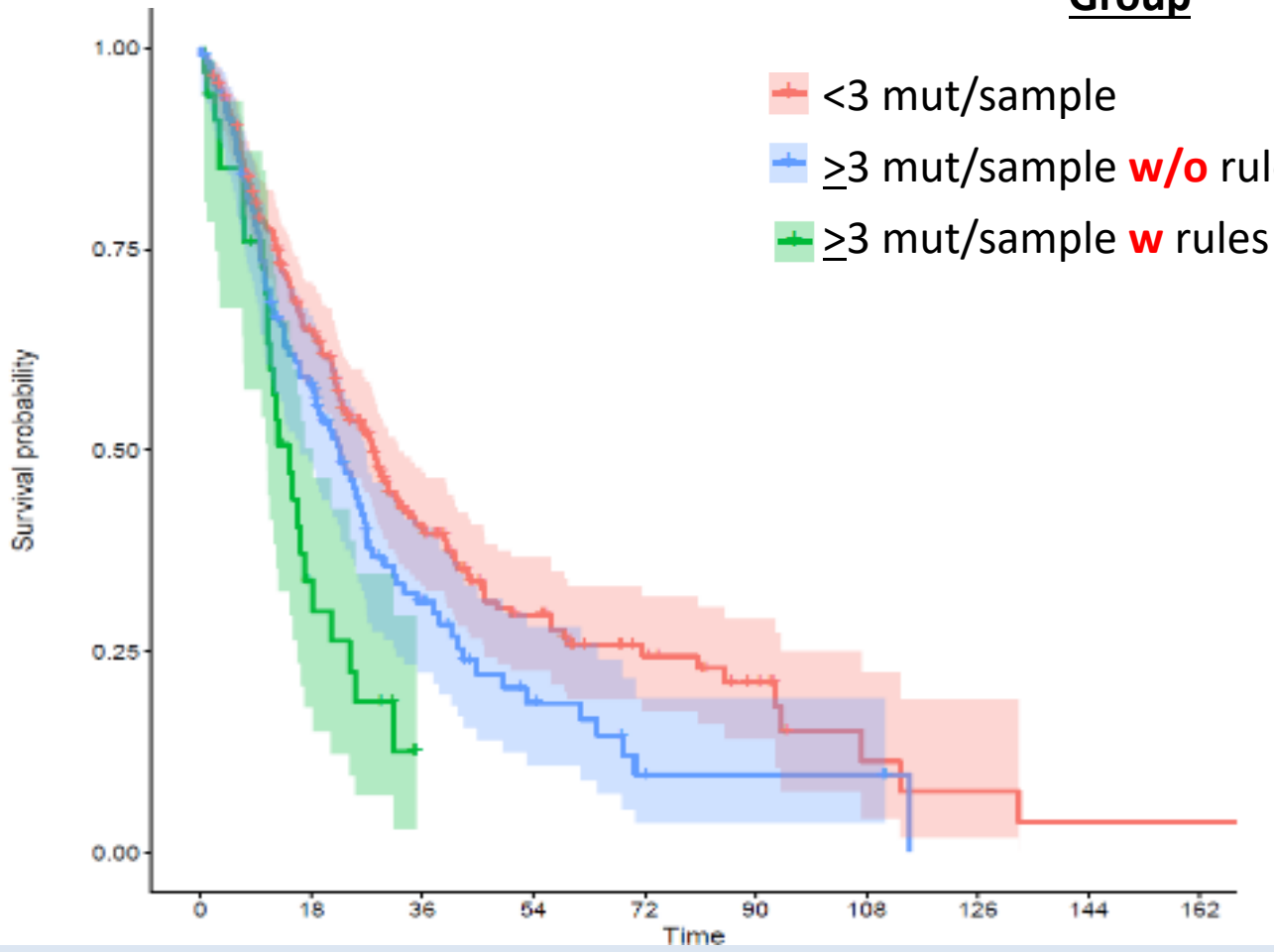
Median # mutations per patient = **3 (range, 0-9)**

Accuracy: **87%**

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

Courtesy of Mikkael A Sekeres, MD, MS

Predictive Tools | Mutations/Response



Group	Median OS (m)
<3 mut/sample	**28.2**
≥3 mut/sample **w/o** rules (69%)	**22.8**
≥3 mut/sample **w** rules (31%)	**14.6**

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

Courtesy of Mikkael A Sekeres, MD, MS

Treating MDS| Disease Biology

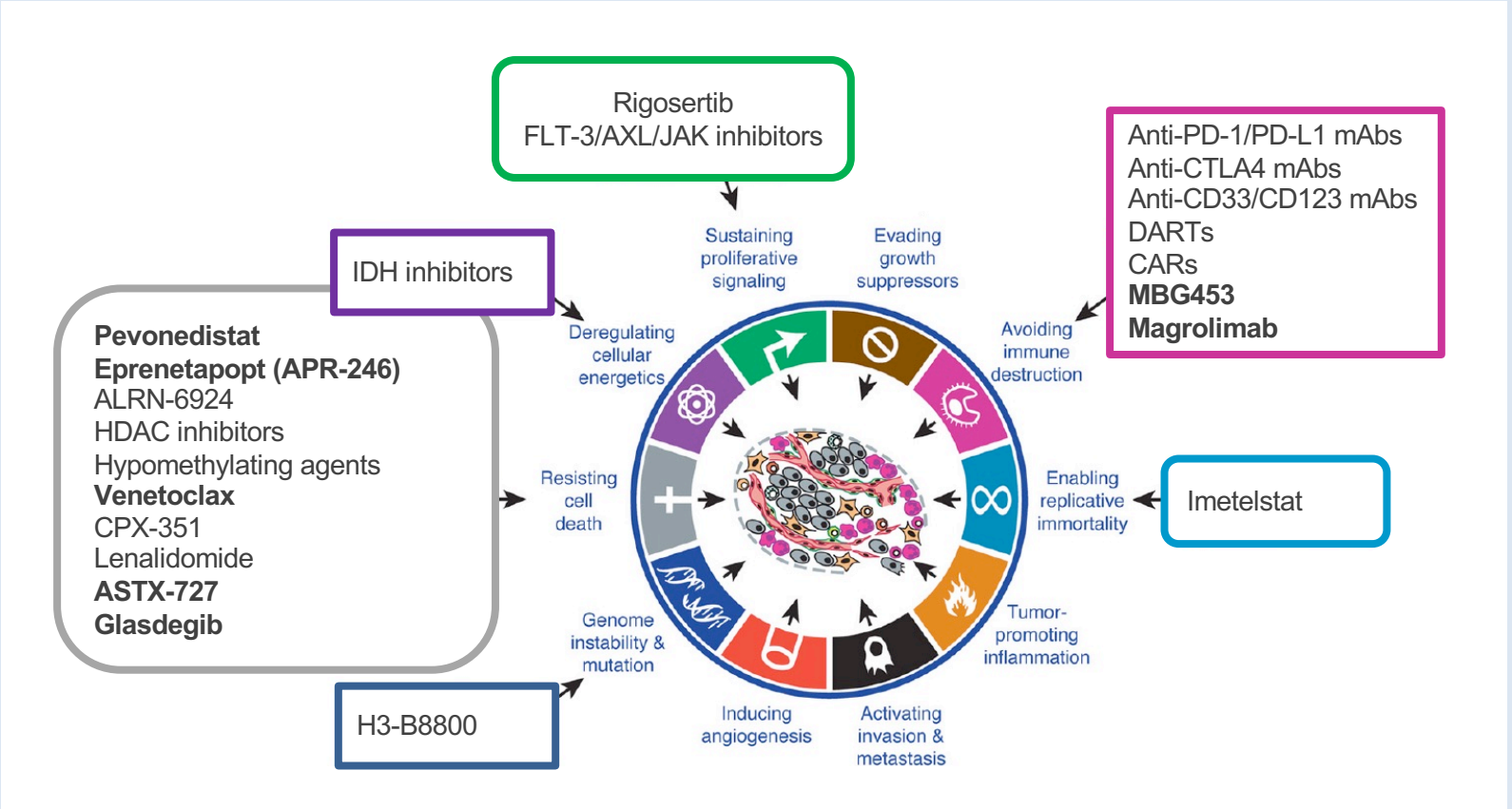
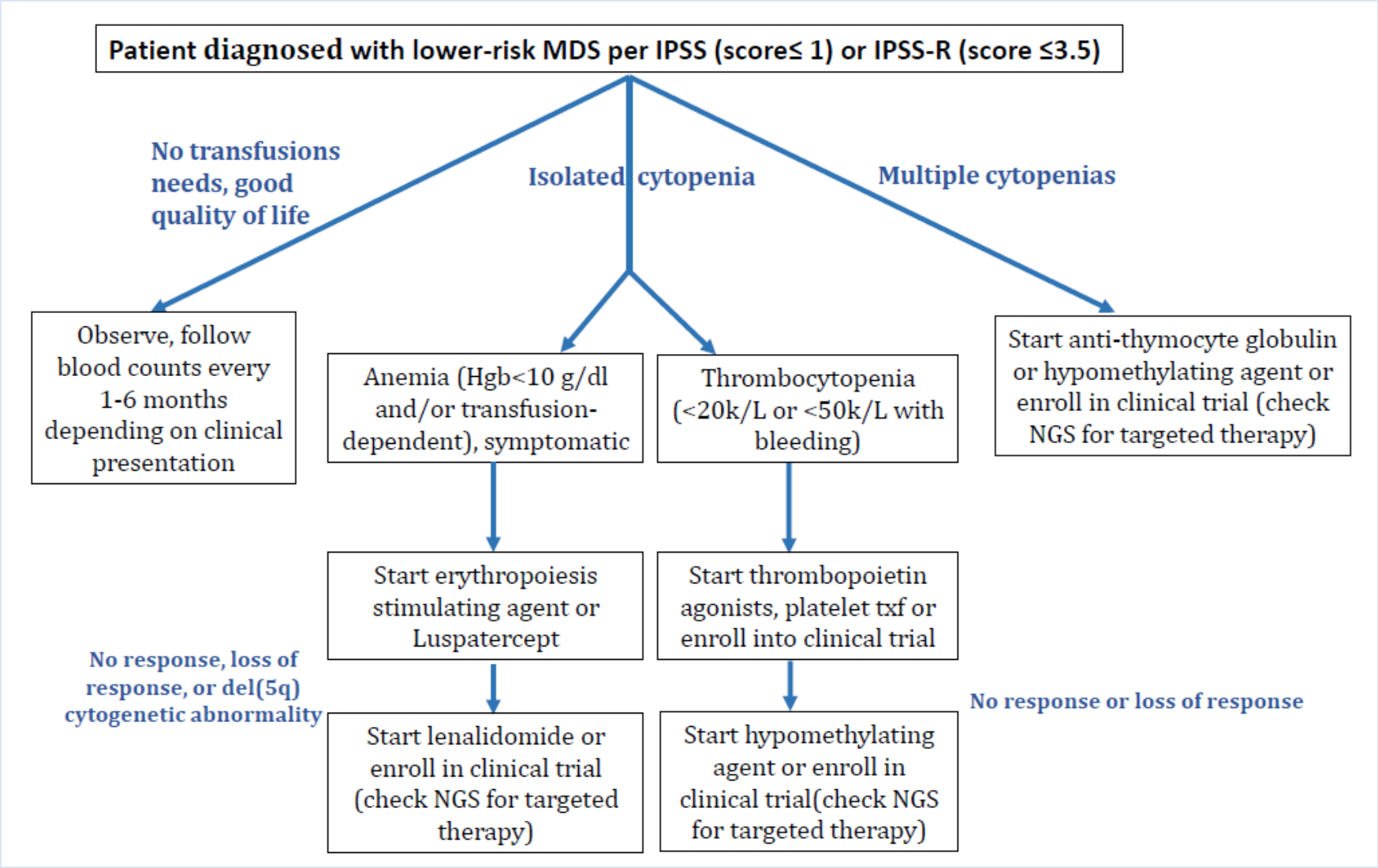


Figure adapted from Hanahan D, Weinberg RA. *Cell* 2011;144:646–74

Courtesy of Mikkael A Sekeres, MD, MS

BH3, bcl homology domain 3; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DARTs, dual affinity retargeting agents; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, poly adenosine diphosphate ribose polymerase; VEGF, vascular endothelial growth factor

MDS | Treatment – Lower-risk



Sekeres and Patel Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

Lower-risk MDS | Modifying MLD: HMA

- Regimens:
  - DAC 20 mg/m^2 IV D1-3 every 4 weeks
  - AZA 75 mg/m^2 IV/SC D1-3 every 4 weeks
- 113 pts with LR-MDS treated and evaluable for response
- Median duration of follow-up = 14 months (range: 2-30 months)
- Randomized follow-up study NCT02269280

Jabbour et al. for MDS CRC Blood 2017;130:1514

Courtesy of Mikkael A Sekeres, MD, MS

Lower-risk MDS | Modifying MLD: HMA

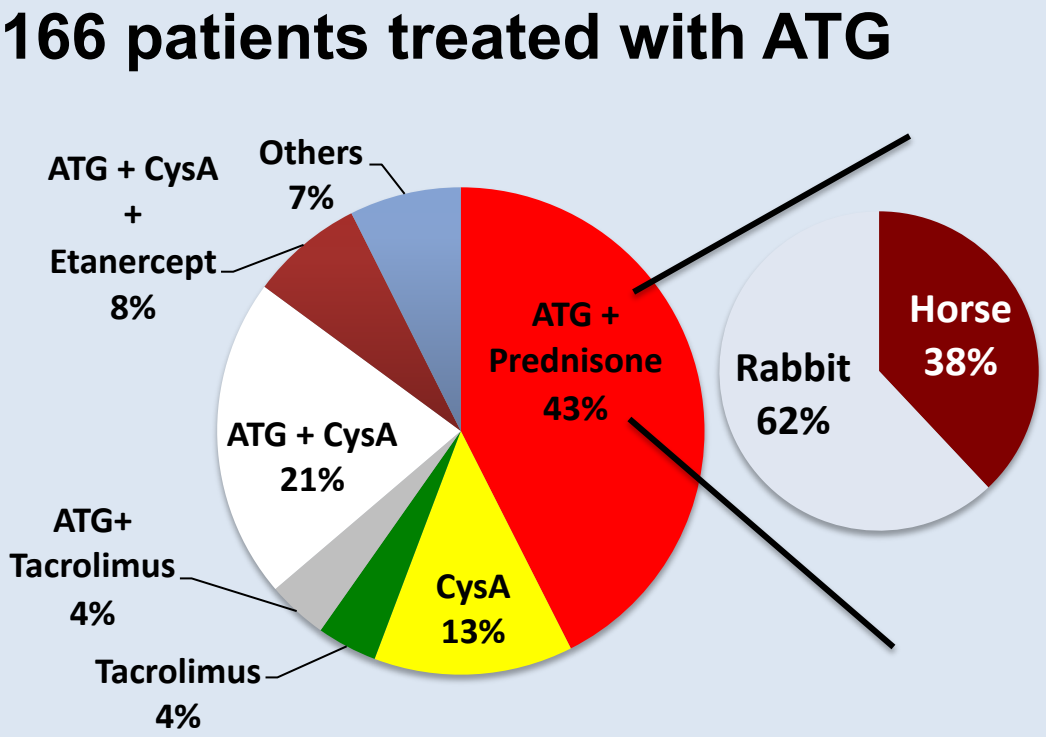
Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabbour et al. for MDS CRC Blood 2017;130:1514

Courtesy of Mikkael A Sekeres, MD, MS

Lower-risk MDS | Modifying MLD: ATG



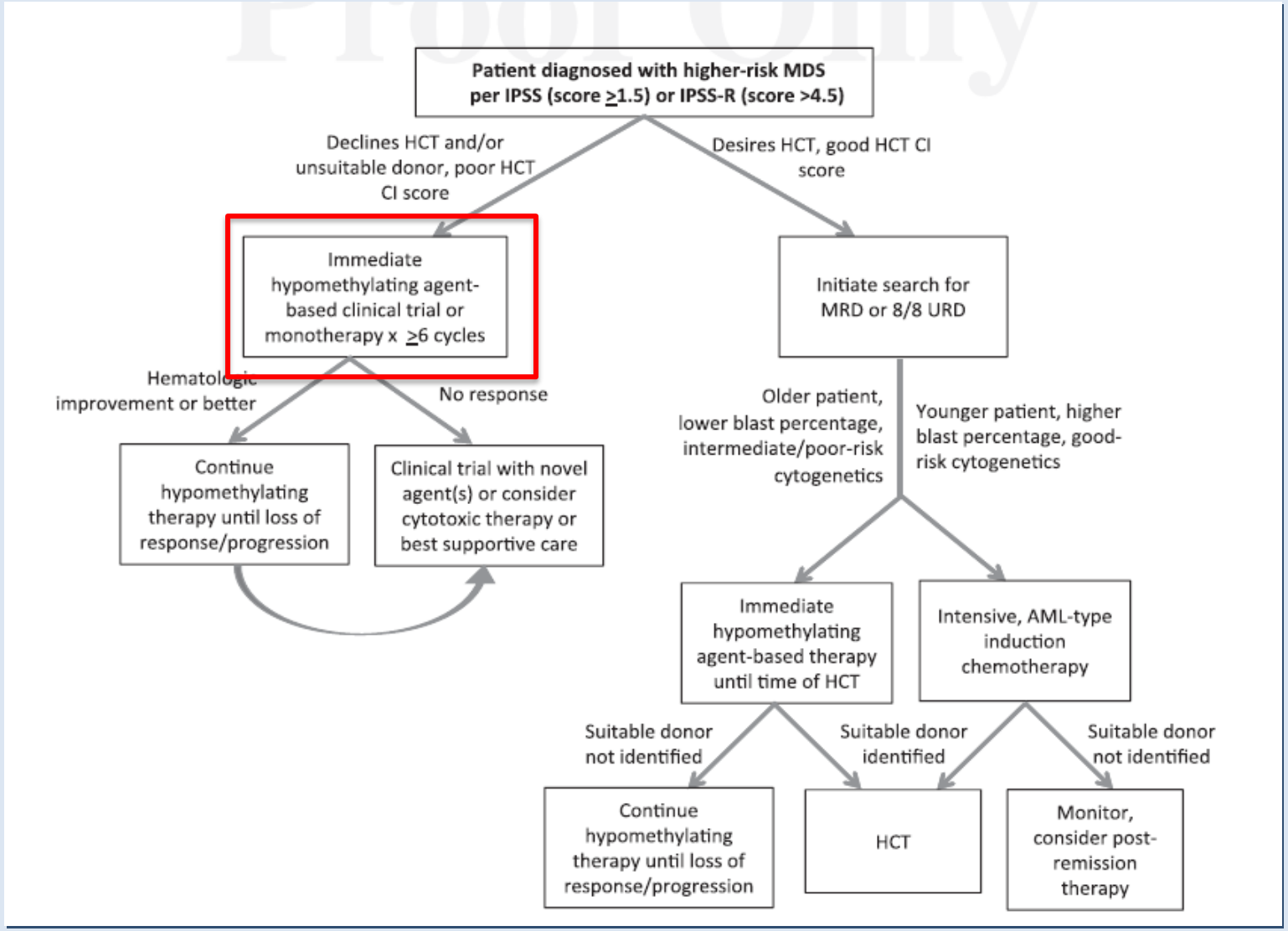
Response	%	95%CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR	48.8	39.8-57.9

Type of IST used (N=217) and responses

Stahl M et al. Blood Advances 2018;2:1765.

Courtesy of Mikkael A Sekeres, MD, MS

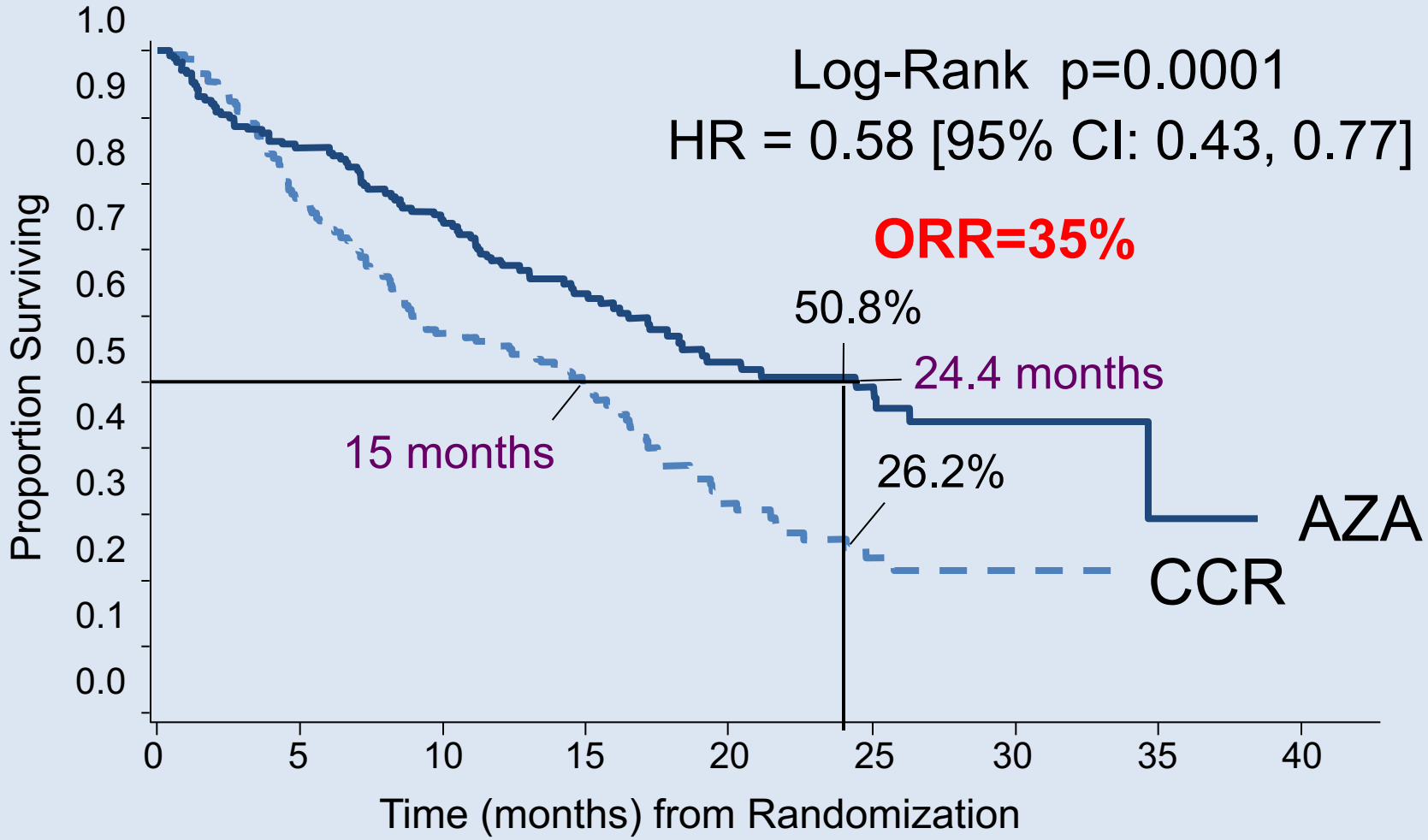
Higher-risk MDS | HMA and HCT



Sekeres and Cutler Blood 2014;123:829.

Courtesy of Mikkael A Sekeres, MD, MS

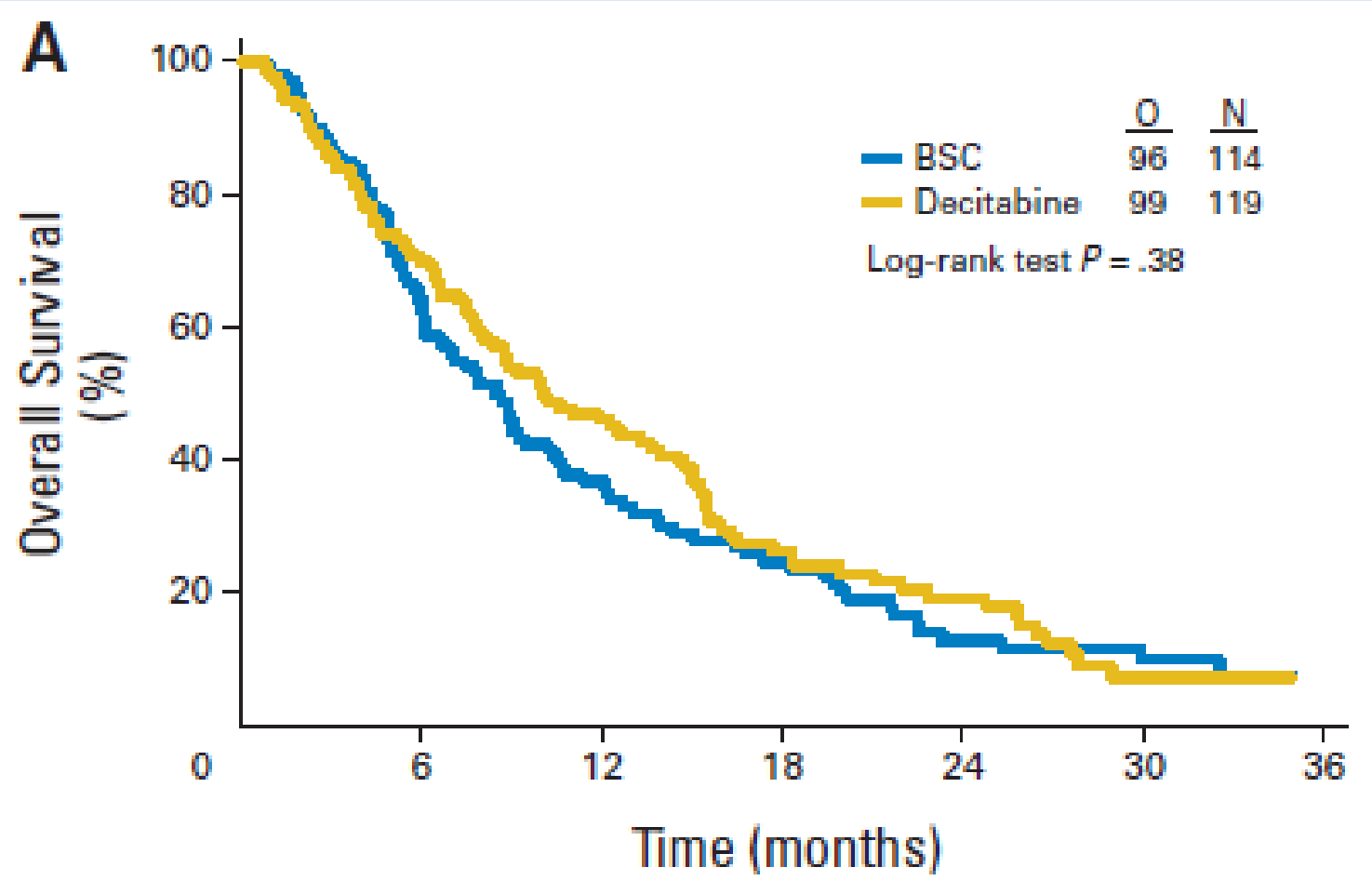
Treating MDS| AZA



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

Courtesy of Mikkael A Sekeres, MD, MS

Treating MDS| DAC

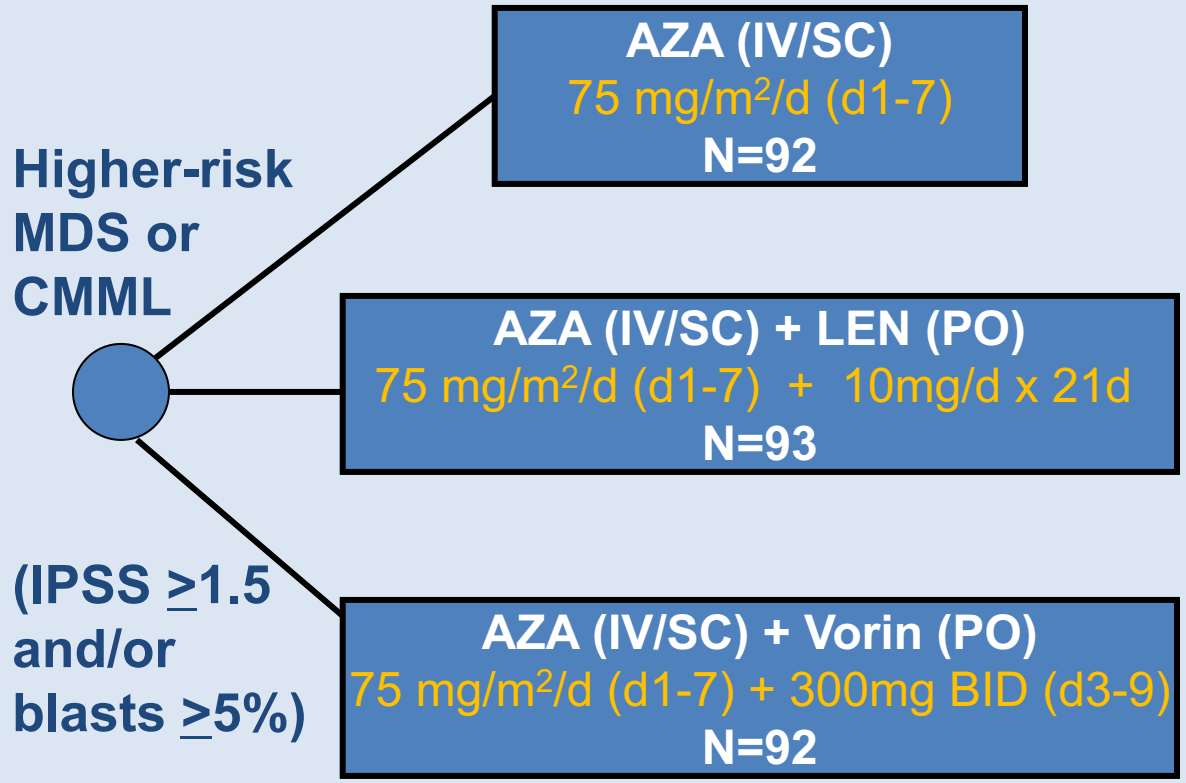


Median OS 10.1 vs. 8.5 months

Lubbert et al. JCO 2011;29:1987.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations



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.

Courtesy of Mikkael A Sekeres, MD, MS

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.

Courtesy of Mikkael A Sekeres, MD, MS

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.

Courtesy of Mikkael A Sekeres, MD, MS

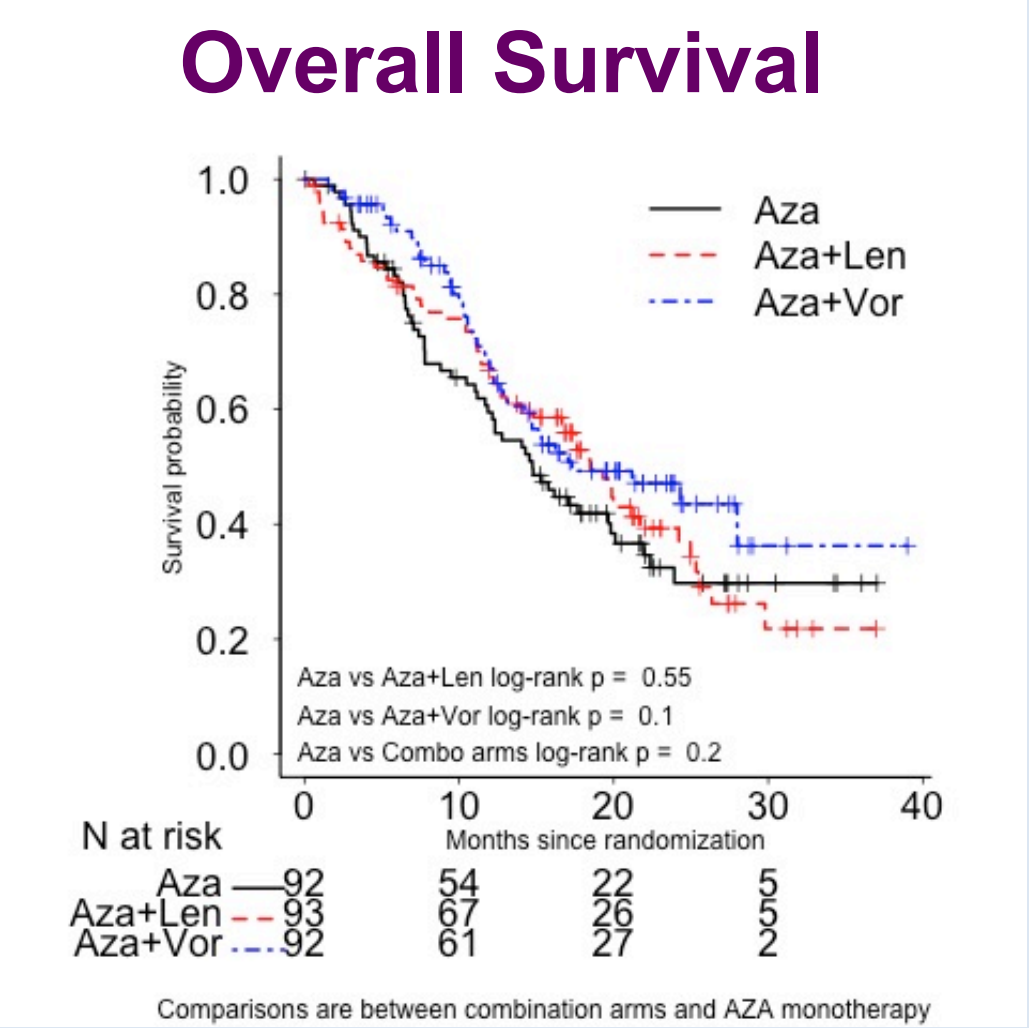
Higher-risk MDS | Combinations

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.

Courtesy of Mikkael A Sekeres, MD, MS

Higher-risk MDS | Combinations



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

Courtesy of Mikkael A Sekeres, MD, MS