Individualized Patient Care Strategies for Myelodysplastic Syndromes

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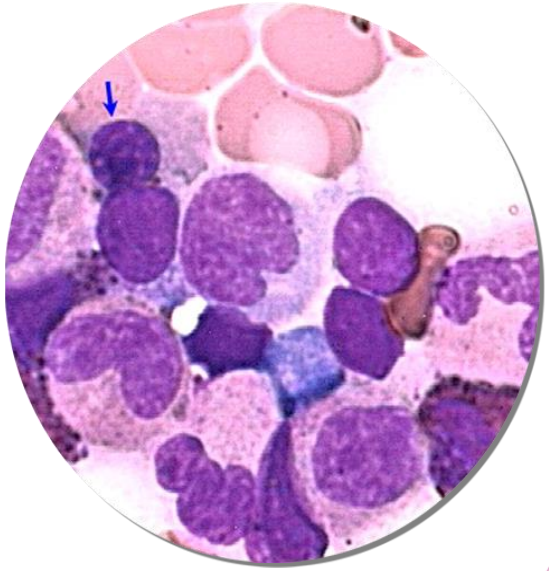
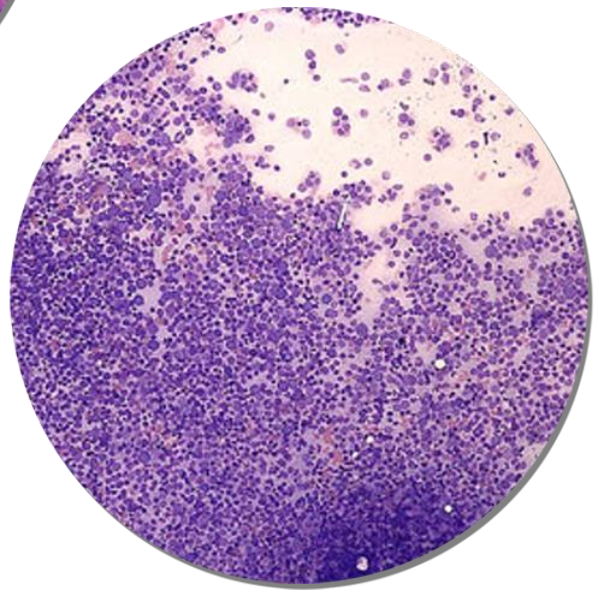
Diagnosis and Risk Stratification

Myelodysplastic Syndromes

- A group of malignant hematopoietic neoplasms characterized by[1]:
  - Bone marrow failure with resultant cytopenia and related complications
  - Evidence of clonality by cytogenetic abnormalities or somatic gene mutations
  - Dysplastic cytologic morphology is the hallmark of the disease
  - Tendency to progress to AML
- Overall incidence 3.7-4.8/100,000[2]
  - In US, true estimates ≈37,000-48,000
- Median age: 70 yr; incidence: 34-47/100,000 >75 yr[3]





1. Haferlach. Pathobiology. 2019;86:24. 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.

Minimal Diagnostic Criteria

Cytopenia(s):

- Hb <11 g/dL, *or*
- ANC <1500/µL, *or*
- Platelets <100 x 10^9/L

+

MDS "decisive" criteria:

- >10% dysplastic cells in 1 or more lineages, *or*
- 5%-19% blasts, *or*
- Abnormal karyotype typical for MDS, *or*
- Evidence of clonality (by FISH or another test)

+

Other causes of cytopenias and morphological changes EXCLUDED:

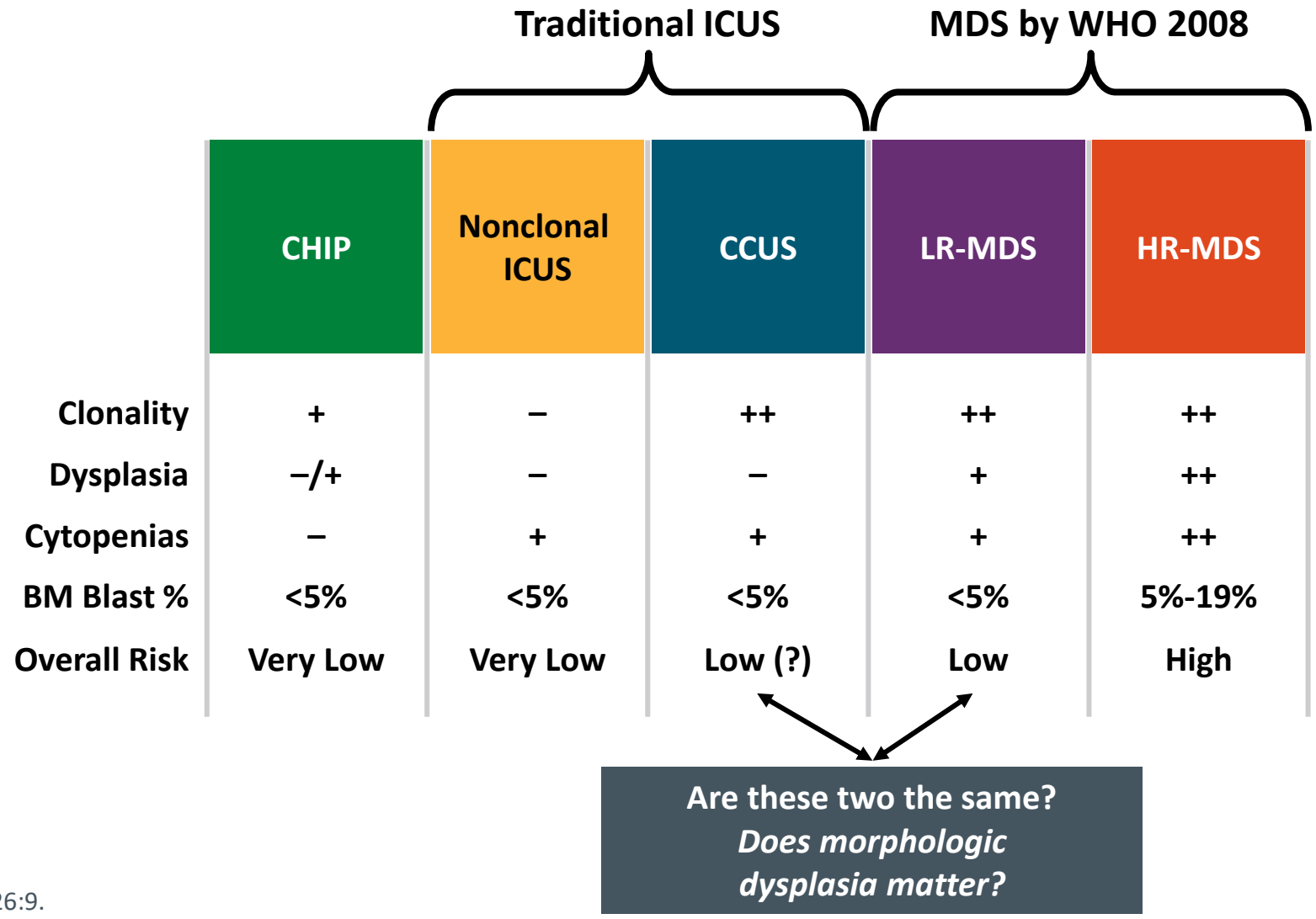
- *Vitamin B12/folate deficiency*
- *HIV or other viral infection*
- *Copper deficiency*
- *Alcohol abuse*
- *Medications (esp. methotrexate, azathioprine, recent chemotherapy)*
- *Autoimmune conditions (ITP, Felty syndrome, SLE, etc.)*
- *Congenital syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

Valent. Leuk Res. 2007;31:727. Slide courtesy of D. Steensma.

Oncogenic Gene Mutations in MDS

Gene	%	Location	Function
SF3B1	28	2q33	Splicing factor
TET2	21	4q24	Control of cytosine hydroxymethylation
ASXL1	14	20q11	Epigenetic regulator
SRSF2	12	17q25	Splicing factor
RUNX1	9	21q22	Transcription factor
TP53	8	17p13	Transcription factor
U2AF1	7	21q22	Splicing factor
EZH2	6	7q36	Polycomb group protein
NRAS	4	1p13	Signal transduction
JAK2	3	9p24	Tyrosine kinase
ETV6	3	12p13	Transcription factor
CBL	2	11q23	Signal transduction
IDH2	2	15q26	Cell metabolism, epigenetic regulation
NPM1	2	5q35	Phosphoprotein
IDH1	1	2q33	Isocitrate dehydrogenase
KRAS	<1	12p12	Signal transduction
GNAS	<1	20q13	G protein
PTPN11	<1	12q24	Protein phosphatase
BRAF	<1	7q34	Raf kinase
PTEN	<1	10q23	Phosphatase
CDKN2A	<1	9q121	Cell cycle control

How Do We Classify These Patients?



Steensma. Blood. 2015;126:9.

2016 WHO Classification of MDS

	Dysplastic Lineages	Cytopenias	RS as % of Erythroids	BM and PB Blasts	Cytogenetics
MDS-SLD	1	1 or 2	<15%/<5%[1]	<5% BM, <1% PB[2]	Any[3]
MDS-MLD	2 or 3	1-3	<15%/<5%[1]	<5% BM, <1% PB[2]	Any[3]
MDS-RS					
▪ With SLD	1	1 or 2	≥15%/≥5%[1]	<5% BM, <1% PB[2]	Any[3]
▪ With MLD	2 or 3	1-3	≥15%/≥5%[1]	<5% BM, <1% PB[2]	Any[3]
MDS with isolated del(5q)	1-3	1 or 2	None or any	<5% BM, <1% PB[2]	Del(5q) alone or with 1 other abnormality (except -7/del7q)

[1]If *SF3B1* mutation is present
[2]Also no Auer rods
[3]Unless fulfills all criteria for MDS with isolated del(5q)

Arber. Blood. 2016;127:2391.

2016 WHO Classification of MDS

	Dysplastic Lineages	Cytopenias	RS as % of Erythroids	BM and PB Blasts	Cytogenetics
MDS-EB					
▪ MDS-EB1	0-3	1-3	None or any	5-9% BM or 2-4% PB[1]	Any
▪ MDS-EB2	0-3	1-3	None or any	10-19% BM or 5-19% PB or Auer rods	Any
MDS, unclassifiable					
▪ With 1% PB blasts	1-3	1-3	None or any	<5% BM, =1% PB[1,2]	Any
▪ With SLD and pancytopenia	1	3	None or any	<5% BM, <1% PB[1]	Any
▪ Based on karyotype	0	1-3	<15%	<5% BM, <1% PB[1]	MDS-defining

[1]Also no Auer rods
[2]1% PB blasts must be documented on at least 2 separate occasions

Arber. Blood. 2016;127:2391.

Slide credit: clinicaloptions.com

Risk Group Stratification

The International Prognostic Scoring System-Revised (IPSS-R)

The revised IPSS, known as the "IPSS-R," covers the same disease factors as the IPSS, but the factors are identified in a more detailed way. The IPSS-R shows five disease factors:

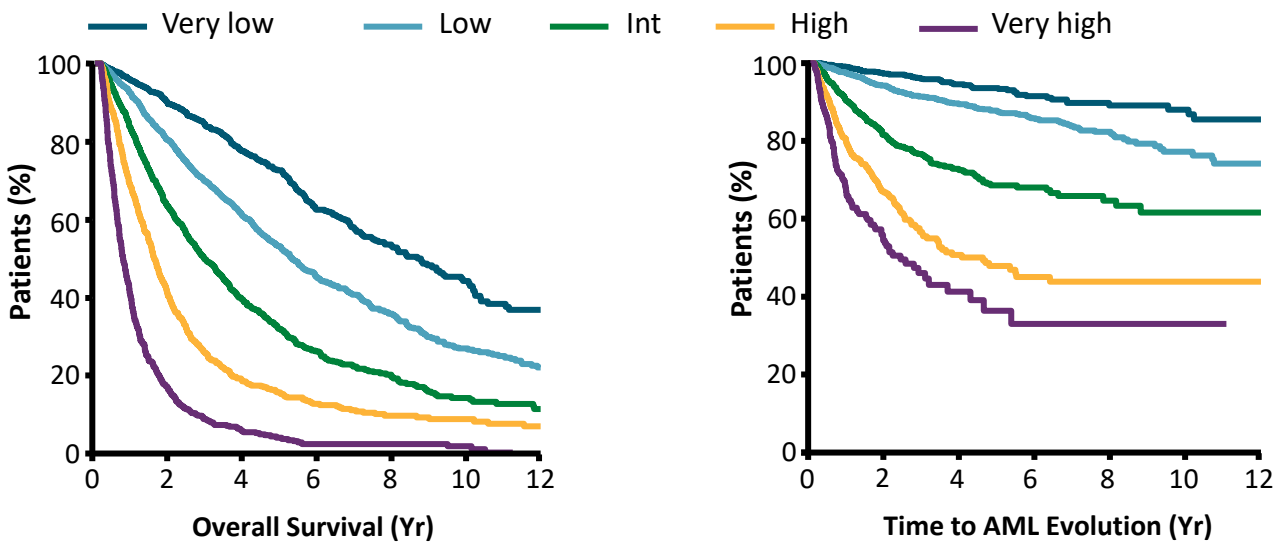
- Blasts
- Cytogenetics
- Hemoglobin
- Platelet count
- Absolute neutrophil count

Prognostic Factors Scored	Risk Groups Based on Total Risk Score
Percent of blast cells in bone marrow ○ Less than or equal to 2 = 0 points ○ Greater than 2 to less than 5 = 1 point ○ 5 to 10 = 2 points ○ Greater than 10 = 3 points	○ 1.5 or less points = Very Low ○ 2 to 3 points = Low ○ 3.5 to 4.5 points = Intermediate ○ 5 to 6 points = High ○ 6.5 or more points = Very High
Cytogenetics (chromosome changes) ○ –Y, del(11q) = 0 points ○ Normal, del(5q), del(12p), del(20q), double including del(5q)* = 1 point ○ del(7q), +8, +19, i(17q), any other single or double independent clone** = 2 points ○ –7, inv(3), +(3q), del(3q), double including –7/del(7q), complex: 3 abnormalities = 3 points ○ More than 3 abnormalities = 4 points	
Hemoglobin concentration (g/dL) ○ Equal to or greater than 10 = 0 points ○ 8 to less than 10 = 1 point ○ Less than 8 = 1.5 points	
Platelet count (x 10^9/L of blood) ○ Equal to or greater than 100 = 0 points ○ 50 to less than 100 = 0.5 points ○ Less than 50 = 1 point	
Absolute neutrophil count ([ANC] x 10^9/L of blood) ○ Equal to or greater than 0.8 = 0 points ○ Less than 0.8 = 0.5 points	

* del(5q) plus another cytogenetic abnormality
** A single clone can have many abnormalities, all of them occurring simultaneously in the same cell.

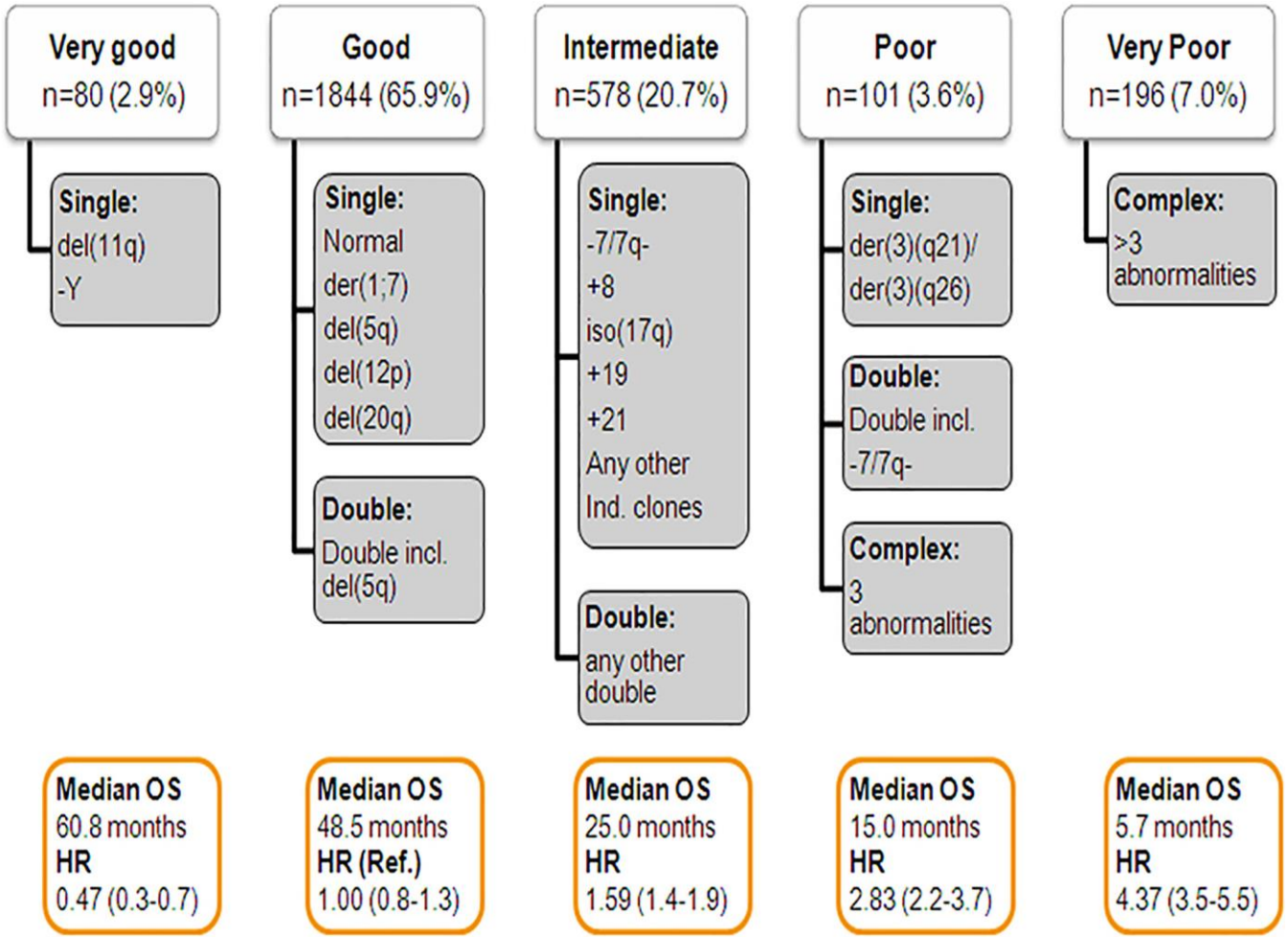
Risk Groups for the IPSS-R

Risk Group	Points	% of Patients	Median Survival, Yr	Time Until 25% of Patients Develop AML, Yr
Very low	≤1.5	19%	8.8	Not reached
Low	>1.5-3	38%	5.3	10.8
Intermediate	>3-4.5	20%	3.0	3.2
High	>4.5-6	13%	1.6	1.4
Very High	>6	10%	0.8	0.73

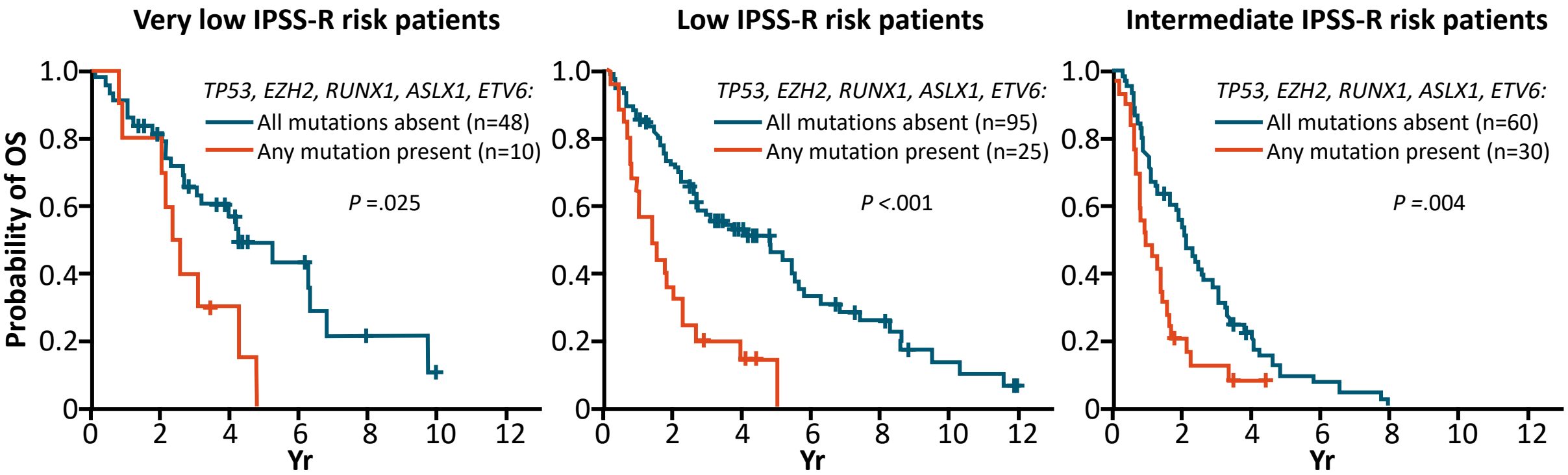


Bejar. Haematologica. 2014;99:956.

MDS Cytogenetics

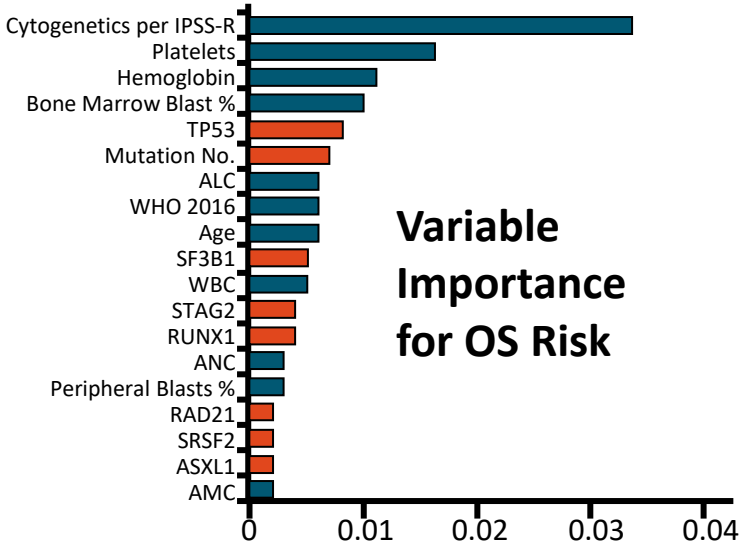


Somatic Gene Mutations Improve Precision of the IPSS-R

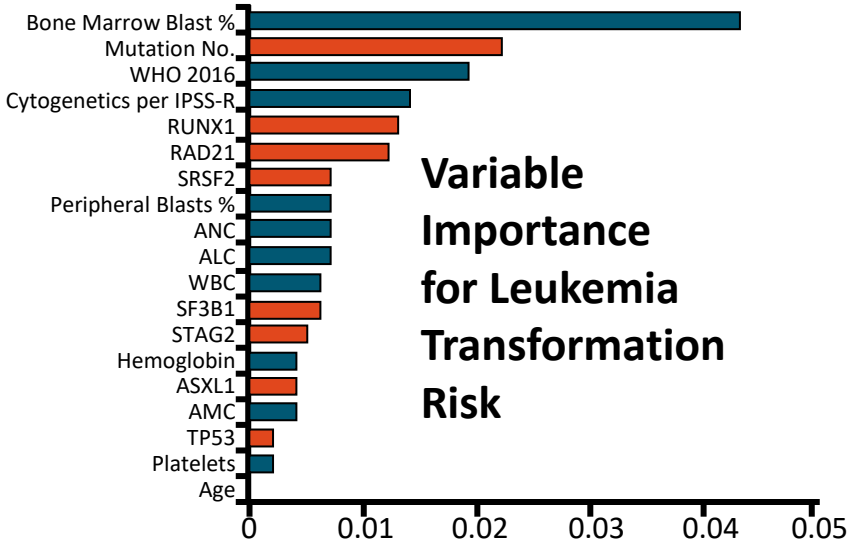


Bejar. Haematologica. 2014;99:956.

New Personalized Prediction Model to Risk Stratify Patients With MDS

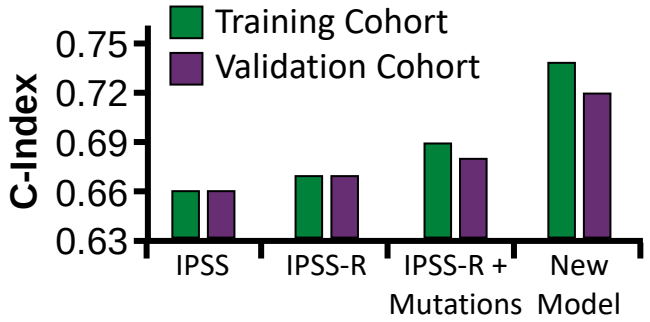


Variable Importance for OS Risk

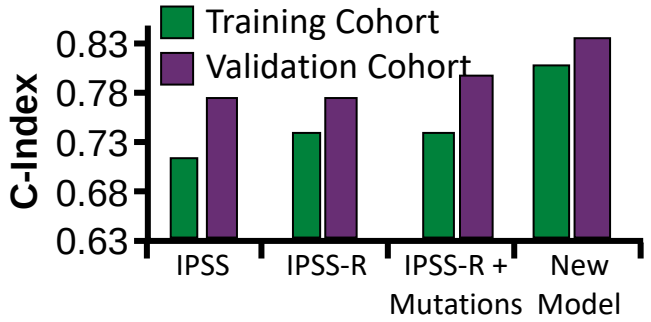


Variable Importance for Leukemia Transformation Risk

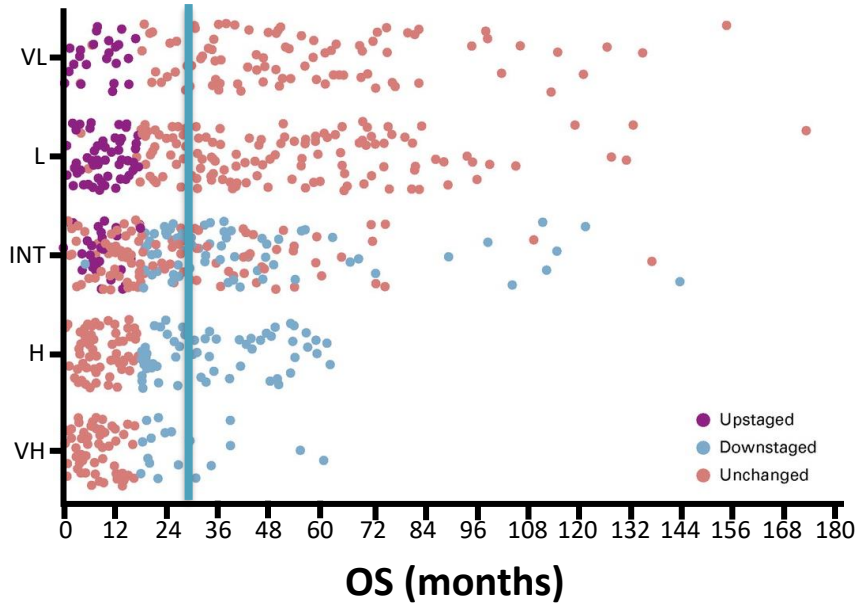
Concordance Index for OS



Concordance Index for Leukemia Transformation

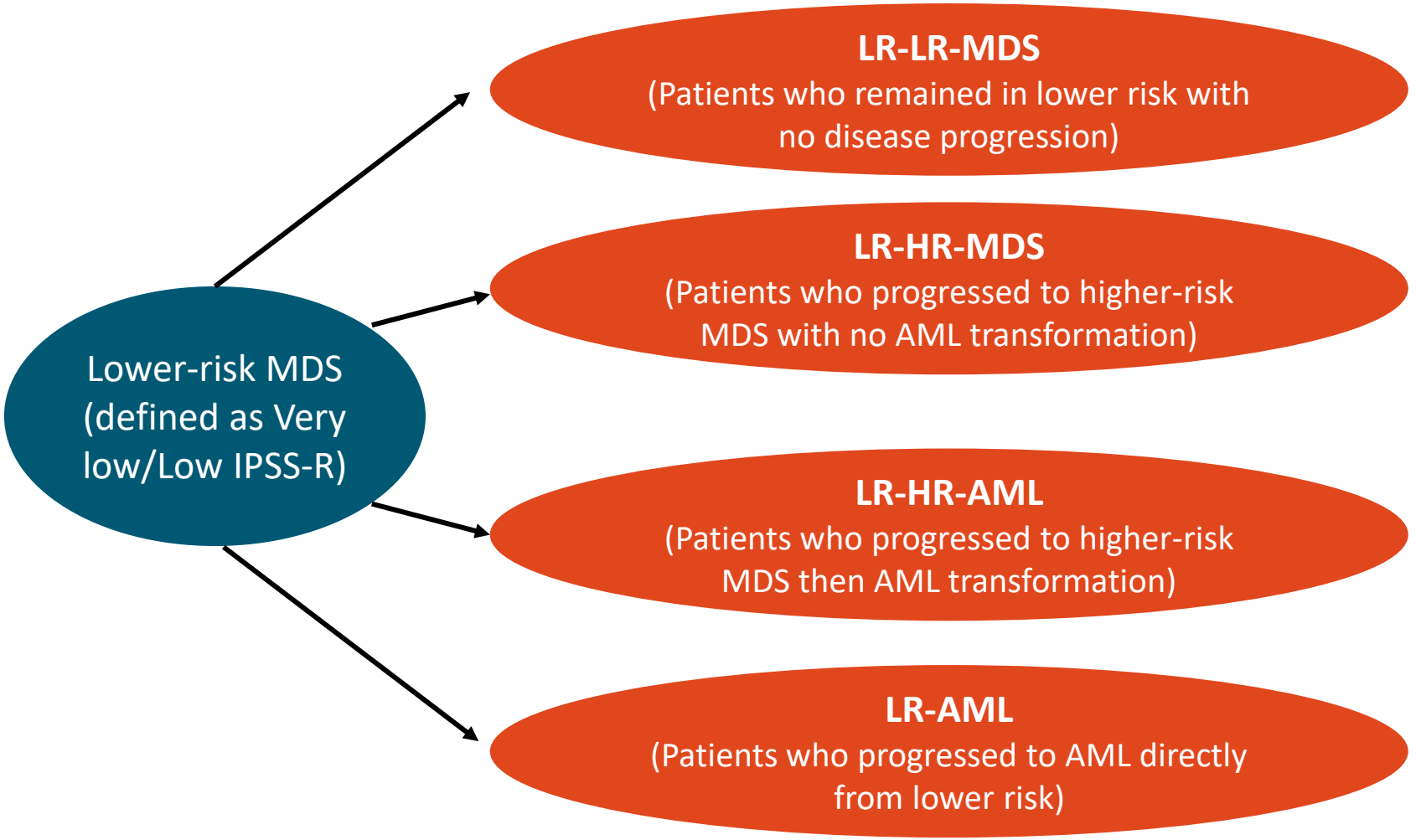


OS Based on IPSS-R Category in Training Cohort With New Model



Nazha. J Clin Oncol. 2021;39:3737.

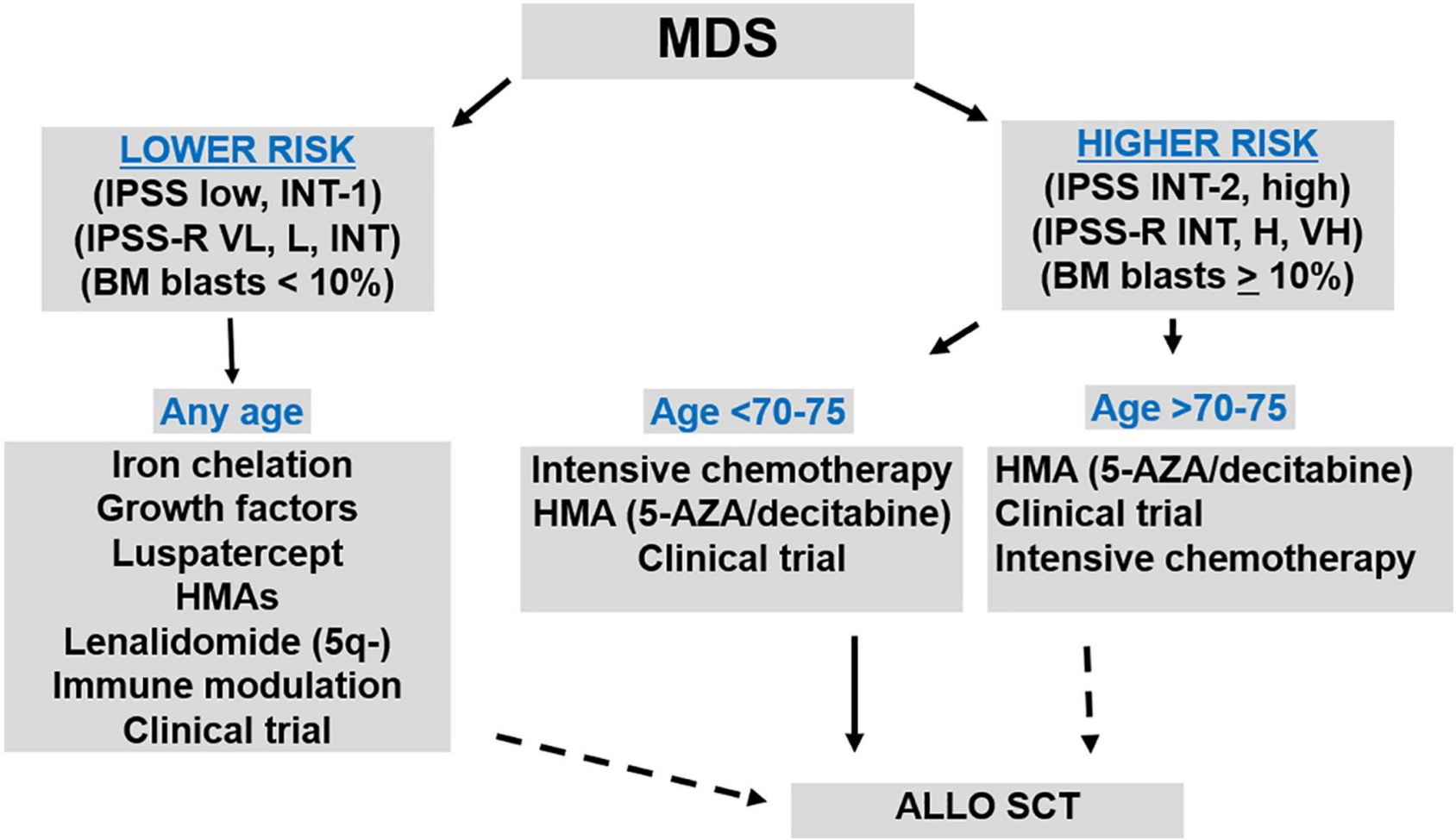
Understanding Patterns of Disease Progression in LR-MDS



Jain, Komrokji. Unpublished data.

Management of Lower-Risk MDS

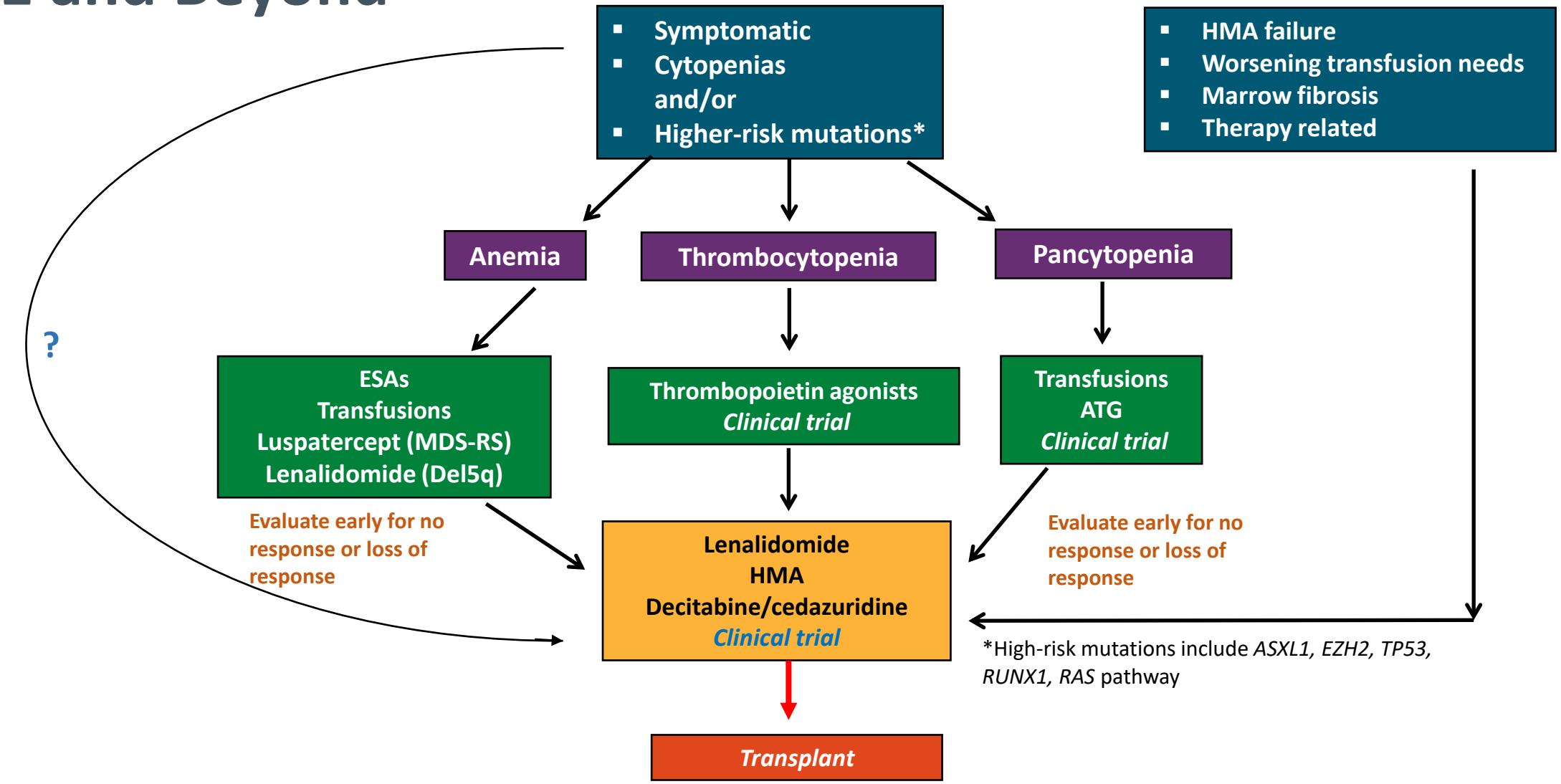
Risk Adapted Therapy



Therapeutic Goals Are Constant for Patients With Lower-Risk MDS

- Establish appropriate monitoring plan
- Decrease transfusion needs
- Decrease impact to QoL
- Lower risk of transformation to AML
- *Maximize benefit*

Lower-Risk MDS Treatment Paradigm Considerations in 2021 and Beyond



*High-risk mutations include *ASXL1, EZH2, TP53, RUNX1, RAS* pathway

Clinical Features That “Upstage”

- **Cytopenia**
  - Symptomatic neutropenia
  - Decrease in platelets >25%
  - Ongoing red blood cell transfusion dependence
  - Anemia or thrombocytopenia refractory to transfusions
- **Inherited predisposition**
- **Lack of response to treatment**
  - Primary OR Secondary

- **Etiology of MDS**
  - Treatment related
- **Fibrosis in the core biopsy**
  - Grade 2 or higher
- **Karyotype**
  - Clonal emergence of unfavorable karyotype
- **Somatic mutations**
  - ≥3 mutations
  - Bad actors: *TP53, RUNX1, ASXL1*fs

What to Do With Intermediate-Risk MDS

- Addition of intermediate risk group to the IPSS-R = clinical challenge
- Most often considered still LR BUT highly heterogeneous
- Analysis of 298 intermediate risk patients to assess “higher-risk” features
  - Age above 66 yr
  - Peripheral blood blasts of ≥2%
  - RBC transfusion
- This group could potentially be eliminated once molecular testing results are formally incorporated to prognostic scoring systems

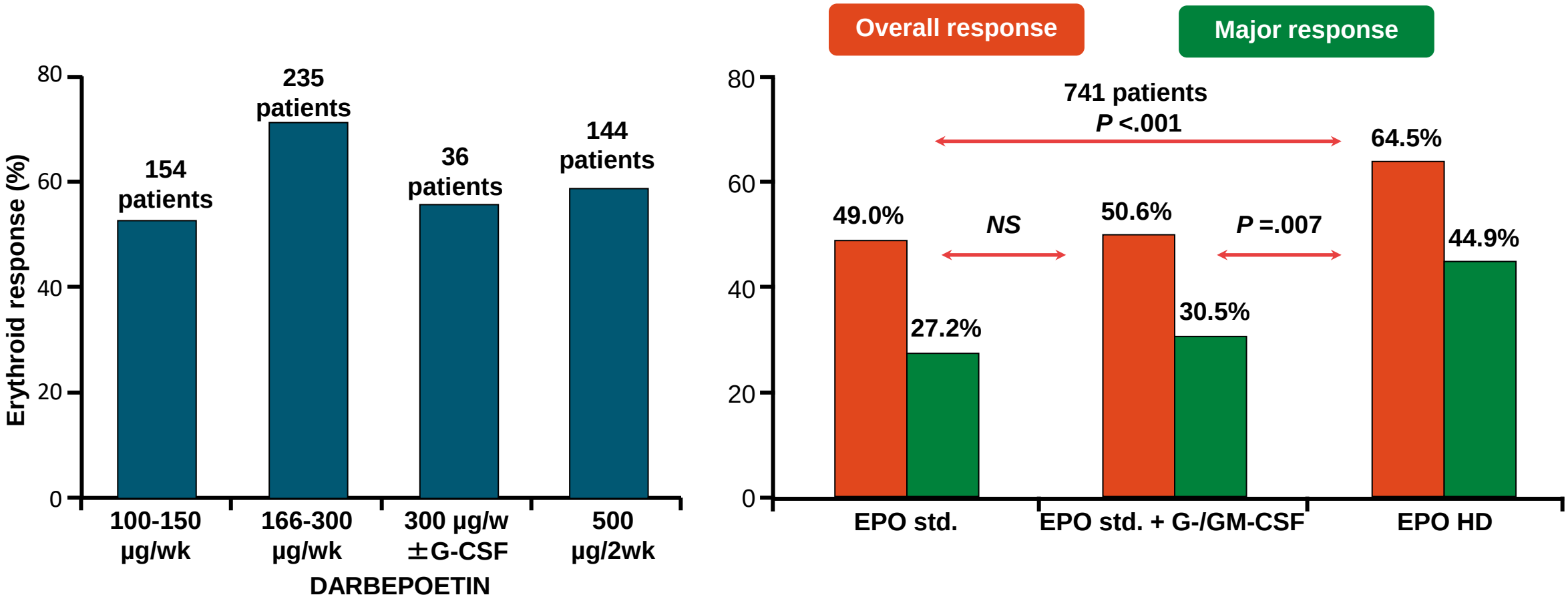
Benton. Am J Hematol. 2018;93:1245.

Erythropoietin-Stimulating Agents in MDS

- Majority of responses occur within 8-12 wk
  - Fixed-dose versus weight-based EPO regimen
- Median duration of response ~2 yr
  - Longer responses if EPO <500, IPSS lower risk, Int-1, blasts <5%, no multilineage dysplasia (RA)
  - Supplemental iron may be needed at relapse
- Early ESA failure (no response or relapse <6 mo)

Park. Blood. 2008;111:574. Jadersten. JCO. 2008;26:3607.

Meta-analysis of Erythroid Response to Erythropoietin Stimulating Agents



Higher dosing regimens of both epoetin alfa (weekly dose 60-80 K IU) and darbepoetin alfa (weekly dose 150-300 mcg) correlate with higher erythroid response rates

Moyo. Ann Hematol. 2008;87:527. Mundle. Cancer. 2009;115:706. Santini. Semin Hematol. 2012;49:295.
Santini. Oncologist. 2011;16:35. Nilsson-Ehle. Eur J Haematol. 2011;87:244.

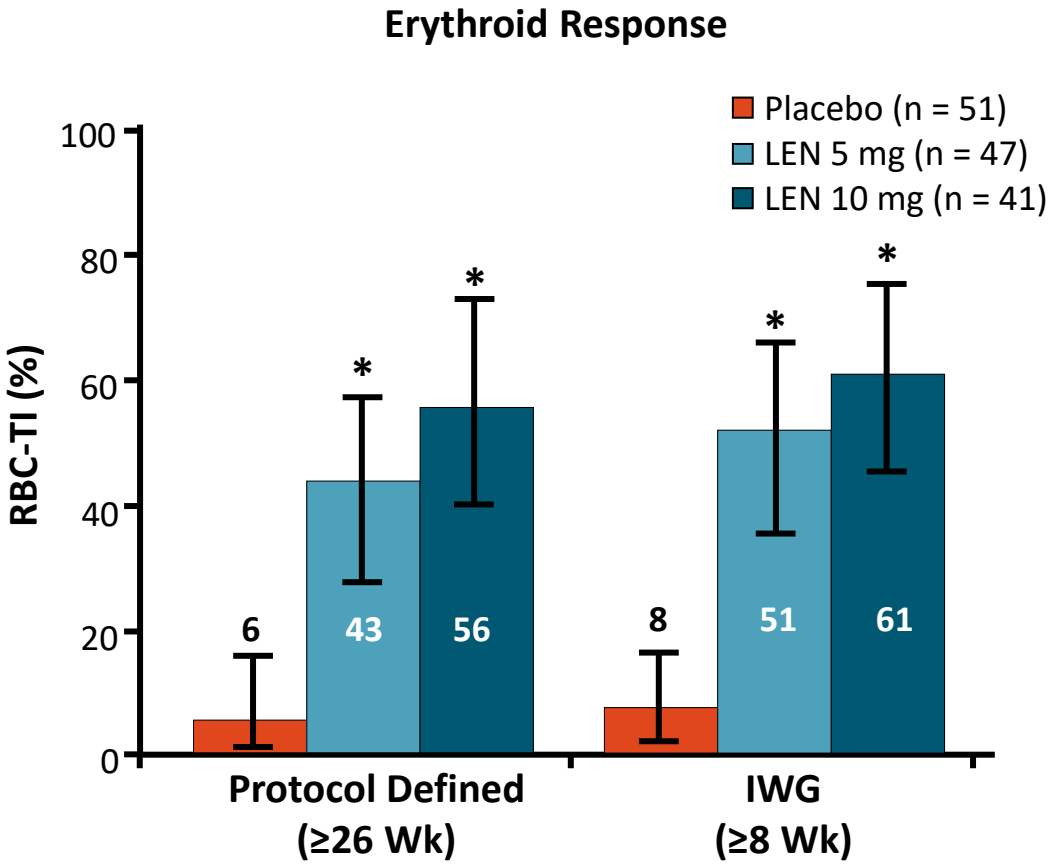
Thrombopoietin Receptor Agonists: Romiplostim and Eltrombopag

- For use with immunocytopenias, or eltrombopag in select cases of isolated thrombocytopenia
- Avoid use outside of clinical trials
- Phase II trial with ELT and LEN (N=52) showed efficacy and safety in patients with low-risk/intermediate-risk MDS[1]
  - ORR of 35% in ITT population, median DoR: 1.5 yr, acceptable safety profile
- Randomized phase II of 250 patients: romiplostim vs placebo (2:1) for 58 wk[2]
  - Increased platelet counts and decreased the number of bleeding events and platelet transfusions.
  - Stopped early due to concern for increased blasts, evolution to AML (HR 2.5)
    - Longer term F/U – no impact on OS (HR 0.86 favoring romiplostim)
    - Survival and AML rates were similar with romiplostim and placebo

1. Gonzalez-Lugo. ASH 2021. Abstr 65. 2. Giagounidis. Cancer. 2014;120:1838.

MDS-004: Lenalidomide vs Placebo in Patients With Lower-Risk del(5q) MDS

- Randomized, double-blind phase III trial in transfusion-dependent patients with del(5q) mutated MDS, N = 205
- Most common grade 3/4 AEs: neutropenia, thrombocytopenia, leukopenia, anemia, DVT

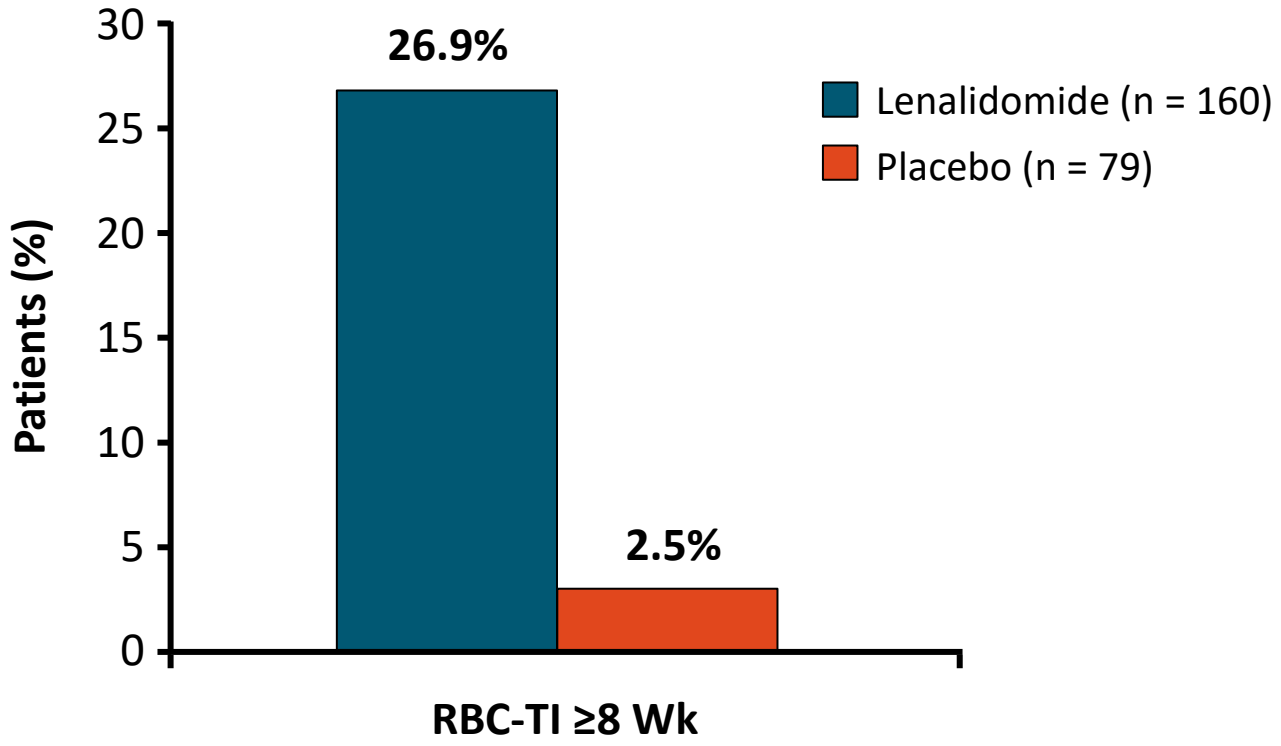


**P* <.001 vs placebo.

Fenaux. Blood 2011;118:3765. NCT00179621.

Lenalidomide vs Placebo in RBC-TD Lower-Risk MDS Without del(5q): RBC-TI ≥8 Wk

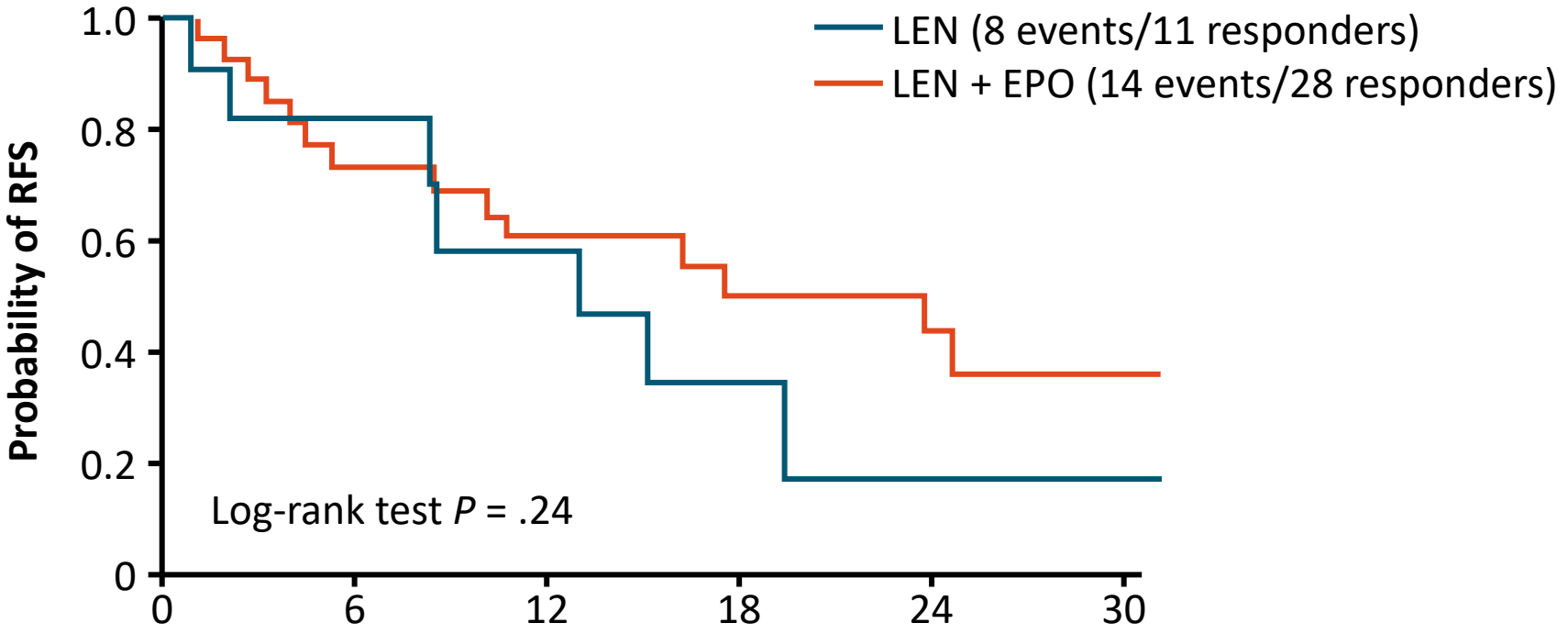
- Phase III MDS-005 study
- N = 239 patients with non-del(5q) MDS and ineligible for or refractory to ESAs
- Results
  - Significantly more patients achieved RBC-TI for ≥8 wk with lenalidomide vs placebo (*P* <.001)
  - Median DoR in lenalidomide-treated patients with RBC-TI for ≥8 wk: 30.9 wk



Santini. JCO. 2016;34:2988.

Phase III ECOG 2905 Study of Lenalidomide ± EPO Alfa in MDS Non-del(5q) Refractory to Erythropoietin: RFS

- Randomized, phase III trial of patients with low- or intermediate 1–risk by IPSS; symptomatic anemia or RBC-TD (N = 247; n = 195 evaluable)



Patients at Risk, n						
LEN	11	8	5	2	1	1
LEN + EPO	28	18	13	10	6	5

List. JCO. 2021;39:1001.

Phase III Lenalidomide in Patients With IPSS Low/Int-1-Risk MDS Without del(5q) Unresponsive or Refractory to ESAs

- **Therapy = 10 mg daily po or PBO (239 patients: LEN = 160, PBO = 79)**
  - **Median age: 71 yr (range: 43-87 yr)**
  - **83.7% with prior therapy including ESA**
- AEs: Myelosuppression: grade 3/4 neutropenia LEN 61.9% vs PBO 11.4%
- Grade 3/4 thrombocytopenia LEN 35.6% vs PBO 3.8%
- Discontinuations due to AEs were reported in 31.9% LEN and 11.4% PBO patients

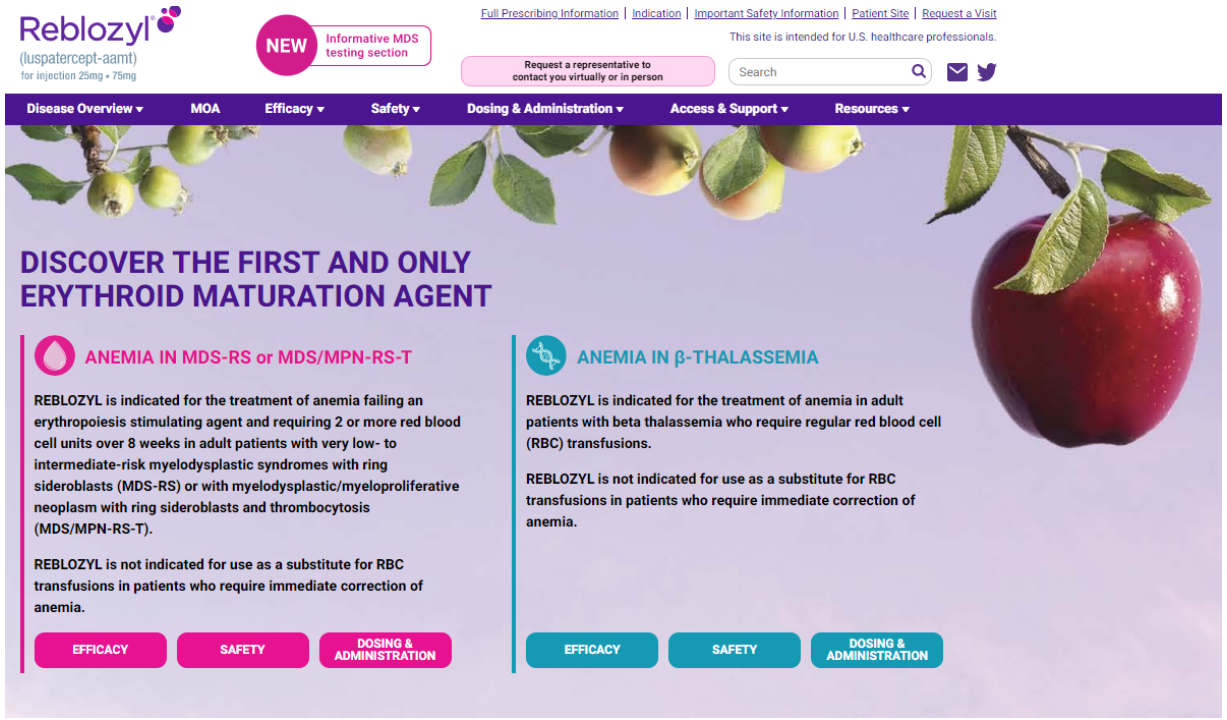
Response	Lenalidomide	Placebo
RBC-TI ≥56 d	26.9%	2.5%
TI duration (wk)	30.9	NE
RBC-TI ≥168 d	17.5%	NE

- 90% of responders did so within 4 cycles (16 wk)

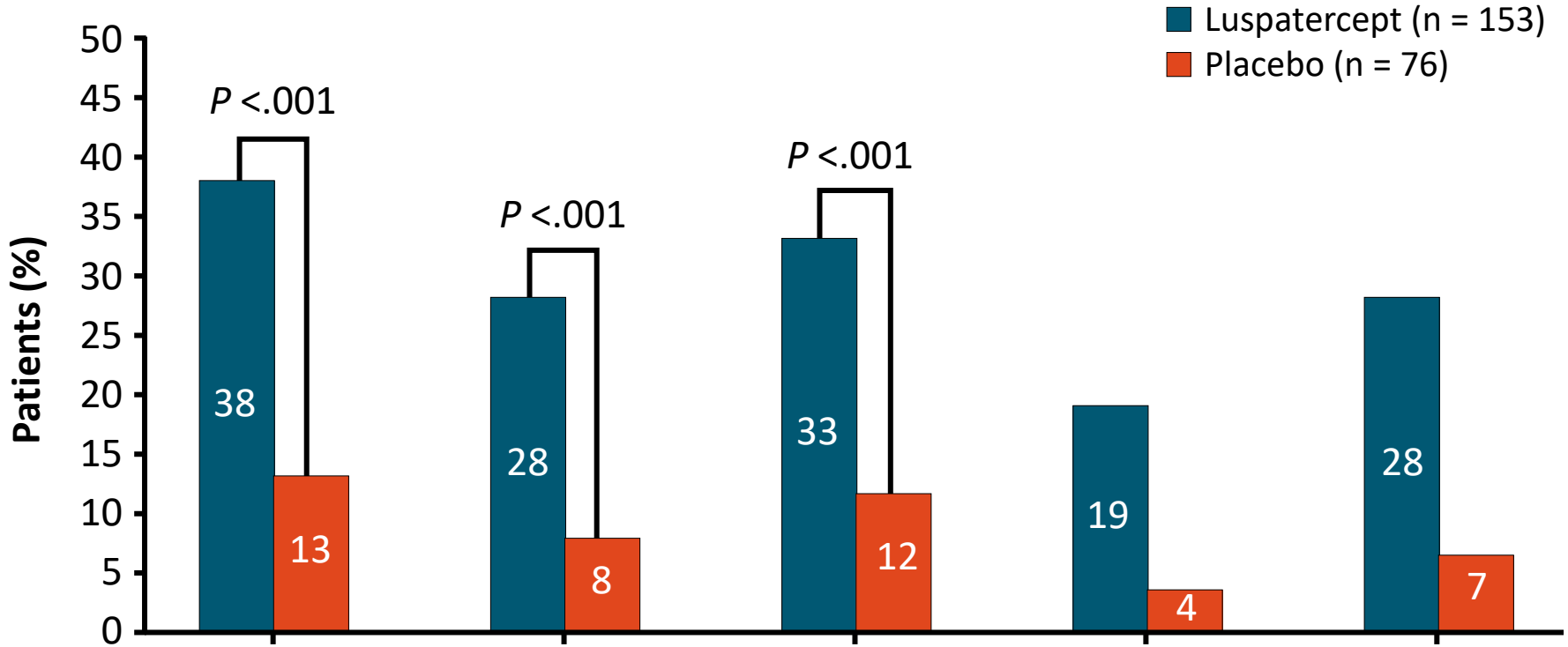
Santini. JCO. 2016;34:2988.

Luspatercept

- First-in-class erythroid maturation agent inhibits abnormal SMAD2/3 signaling by neutralizing select TGF-β superfamily ligands and improves late-stage erythropoiesis in MDS models[1]
- Phase II study in patients with LR non-del(5q) MDS, luspatercept yielded high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes[2]



MEDALIST: Red Cell Transfusion Independence With Luspatercept in MDS-RS



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 (13 [3-16])	6 (12 [6-21])	3 (4 [1-11])	5 (7 [2-15])

Fenaux. NEJM. 2020;382:140.

MEDALIST: RBC-TI ≥8 Wk

RBC-TI ≥8 Wk Over Entire Tx	Luspatercept (n=153)	Placebo (n=76)	Luspatercept vs Placebo	
			OR (95% CI)	*P* Value
BL RBC transfusion requirement, n/N (%)				
≥6 U/8 wk	14/66 (21.2)	2/33 (6.1)	4.17 (0.89-19.60)	.0547
≥4 to <6 U/8 wk	20/41 (48.8)	2/23 (8.7)	10.00 (2.07-48.28)	.0013
<4 U/8 wk	39/46 (84.8)	8/20 (40.0)	8.36 (2.51-27.83)	.0002

- More luspatercept-treated patients achieved RBC-TI ≥8 wk over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden

Fenaux. NEJM. 2020;382:140. Fenaux. ASH 2019. Abstr 841.

MEDALIST: Safety

TEAE of Any Grade, %	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	26.8	13.2
Diarrhea	22.2	9.2
Asthenia	20.3	11.8
Nausea	20.3	7.9
Dizziness	19.6	5.3
Back pain	19.0	6.6
Cough	17.6	13.2
Peripheral edema	16.3	17.1
Headache	15.7	6.6
Dyspnea	15.0	6.6
Bronchitis	11.1	1.3
Constipation	11.1	9.2
UTI	11.1	5.3
Fall	9.8	11.8

TEAE, %	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥1 TEAE	98.0	92.1
▪ ≥1 serious TEAE	31.4	30.3
▪ ≥1 grade 3/4 TEAE	42.5	44.7
▪ TEAEs leading to death	3.3	5.3
▪ ≥TEAE causing discontinuation	8.5	7.9

- 4 patients progressed to acute myeloid leukemia: 3 in luspatercept arm, 1 in placebo arm
- The most common grade 3/4 TEAEs in luspatercept arm were anemia (6.5%), fatigue (4.6%), and fall (4.6%)

Fenaux. NEJM. 2020;382:140.

Low-Dose HMAs in Lower-Risk MDS: Response Rates

Response, %	Decitabine (n = 70)	Azacitidine (n = 39)	*P* Value
ORR	70	49	.03
▪ CR	37	36	.90
▪ mCR	9	5	NR
▪ HI	24	8	NR
▪ SD	26	44	NR
▪ PD	4	8	NR
	(n = 28)	(n = 16)	
CCyR	25	6	.12
PCyR	36	19	
▪ CCyR + PCyR	61	25	.02

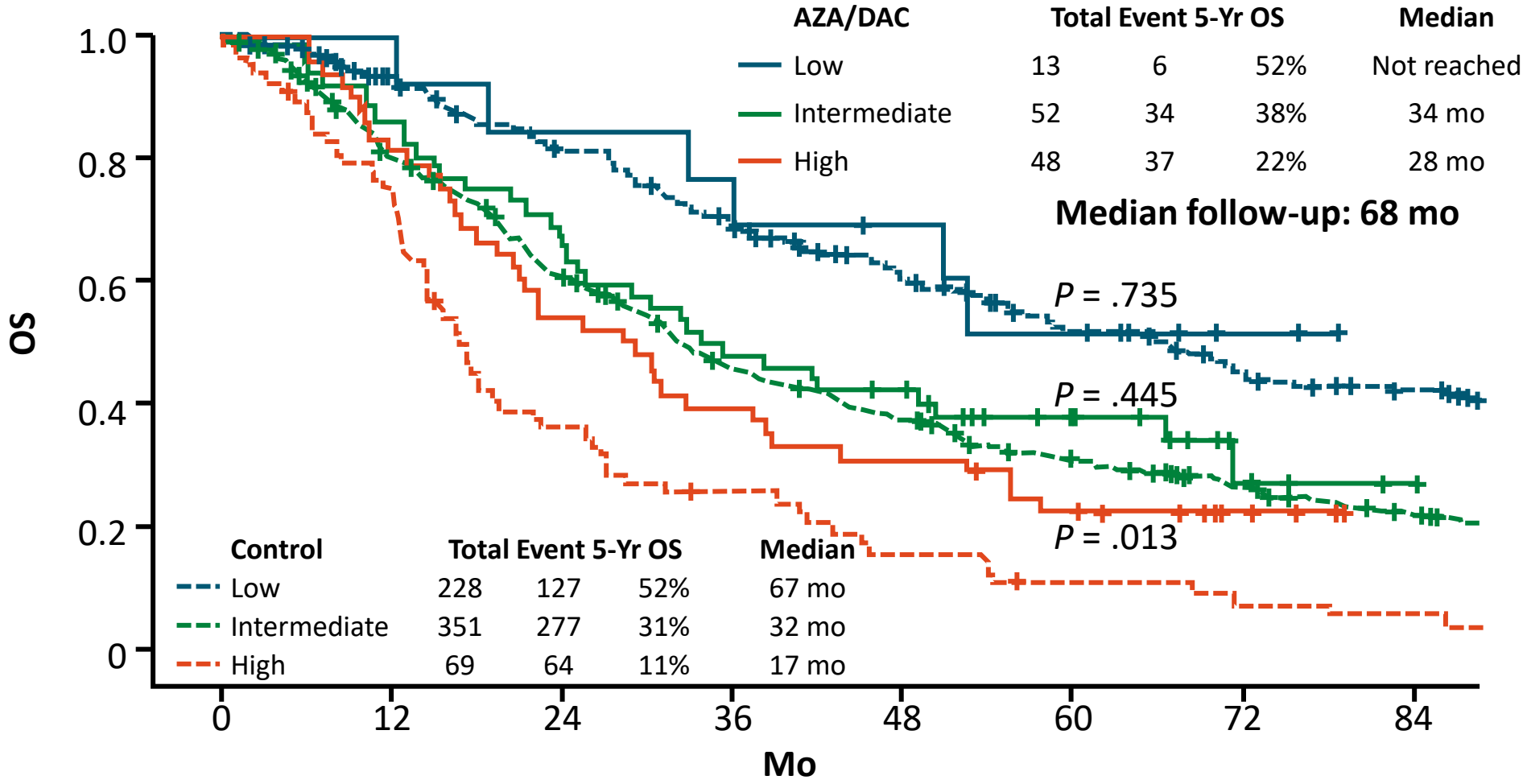
Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	*P* Value
Blasts ≥5%	(n = 37)	(n = 11)	
▪ ORR	100	36	<.001
▪ CR	52	18	.06
Blasts <5%	(n = 45)	(n = 27)	
▪ HI: ≥1 lineage	36	48	.29
▪ HI: all lineages	22	26	.72
TI at response*	32	16	.20

*Based on baseline transfusion-dependent patients: DEC = 38, AZA= 19.

- Strongest predictors of response included BM blasts ≥5%, MDS/MPN or CMML diagnosis, high MDS LR-MDS score, and IPSS intermediate-1 risk

Jabbour. Blood. 2017;130:1514.

Low-Dose Decitabine vs Azacitidine in LR-MDS: Historical Comparison



Sasaki. ASH 2020. Abstr 2196.

AZA-MDS-003 CC-486 (Oral Aza) in MDS: Study Design

KEY INCLUSION CRITERIA

Age ≥18 yr

IPSS Low or INT-1 MDS

ECOG PS score 0-2

+

RBC transfusion dependence:

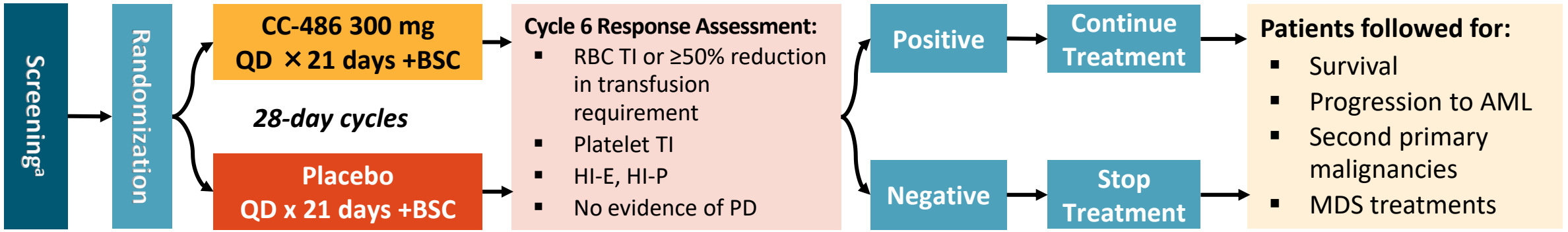
- Average of ≥2 RBC units/28 days for ≥56 days
- No ≥28-day transfusion-free period in 56 days prior to randomization

+

Thrombocytopenia:

- Platelet count ≤75 x 10^9/L, confirmed at 2 visits ≥21 days apart
- Confirmatory count obtained within 14 days before randomization

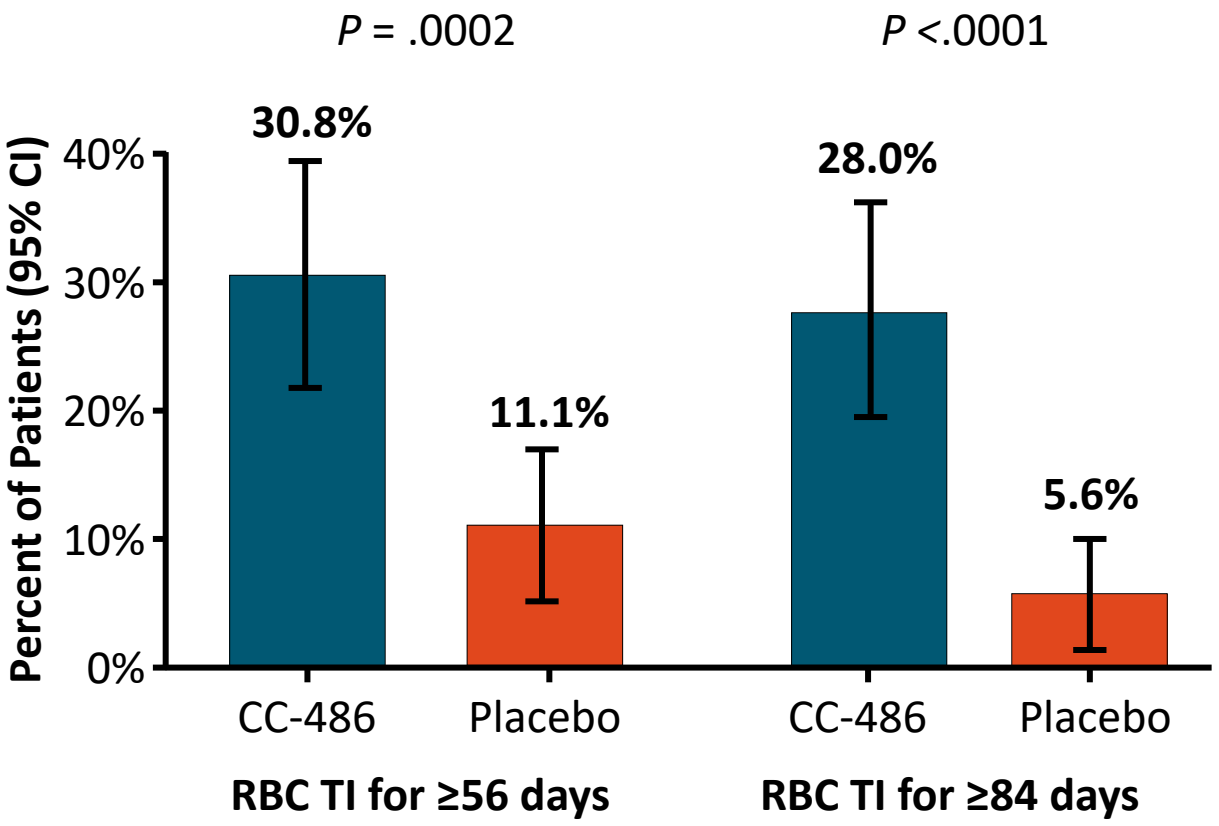
STUDY DESIGN



[a]The screening phase was initially defined as 84 days from randomization to allow repeated confirmation of RBC-TD and concomitant thrombocytopenia, but later amended to shorten the interval to 56 days. ClinicalTrials.gov NCT01566695.

Garcia-Manero. JCO. 2021;39:1426.

AZA-MDS-003: RBC TI

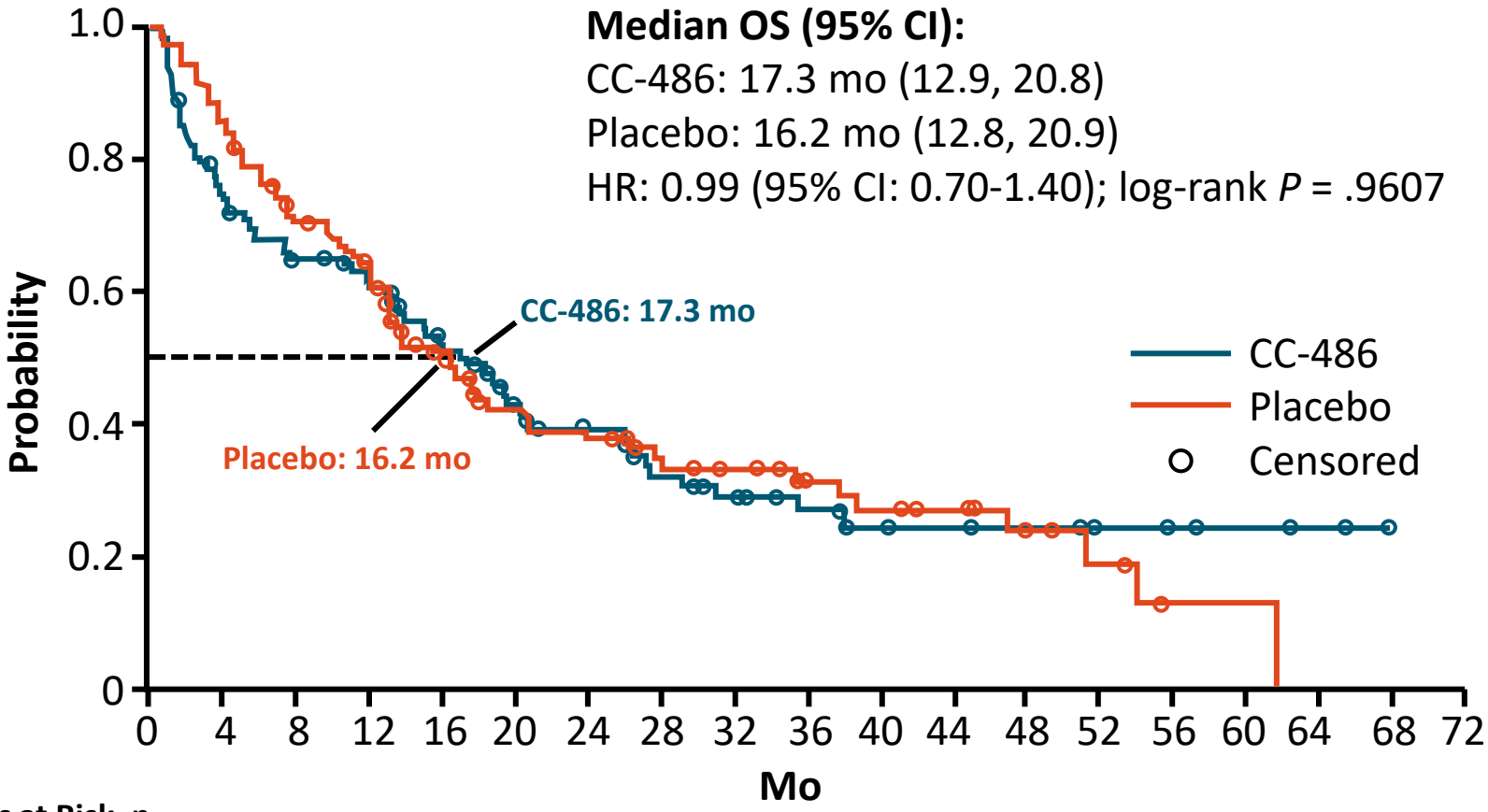


	CC-486 n = 107	Placebo n = 108[a]
RBC TI for >56 days, n (%) [95% CI]	33 (30.8) [22.1-39.6]	12 (11.1) [5.2-17.0]
Odds ratio [95% CI]	3.6 [1.7-7.4]	
P value	.0002	
RBC TI for >56 days, n (%) [95% CI]	30 (28.0) [19.5-36.5]	6 (5.6) [1.2-9.9]
Odds ratio [95% CI]	6.6 [2.6-9.9]	
P value	<.0001	

- Median number of treatment cycles
  - CC-486: 5 (range: 1-70)
  - Placebo: 6 (range: 1-69)

Garcia-Manero. JCO. 2021;39:1426. Cheson. Blood. 2006;108:419.

AZA-MDS-003: Overall Survival



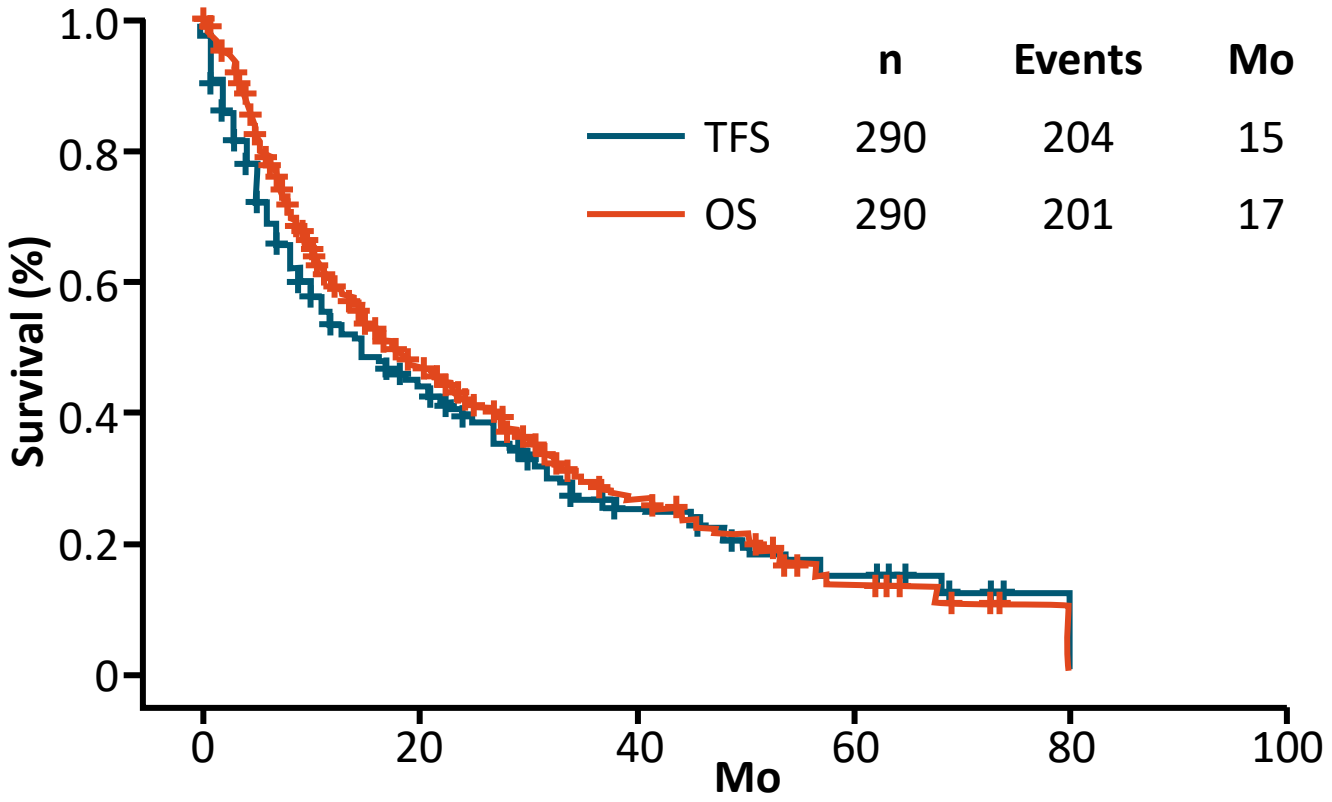
Patients at Risk, n

CC-486	107	78	66	47	35	29	21	17	13	10	8	7	5	4	3	2	0
Placebo	108	92	74	63	43	31	28	22	19	14	12	10	6	4	1	1	0

- Overall death rate similar between arms
- Early deaths (days 1-56): CC-486, n = 16; placebo, n = 6
  - Most related to infection
  - Patients who died in the CC-486 arm had median baseline ANC of 0.57 x 10^9/L and platelet count of 15.5 x 10^9/L
- Progressed to AML:
  - CC-486: n = 8 (7.5%)
  - Placebo: n = 18 (16.7%)

Garcia-Manero. JCO. 2021;39:1426.

LR-MDS Post-HMA Failure: Outcomes



Salvage	N (%)	% Response
No therapy	90 (31)	NA
Conventional	83 (29)	18
SCT	26 (9)	62
Investigational	91 (31)	16

- **Conventional therapies included cytarabine-based regimen and HMA**

- Median follow-up: 16 (1-80) mo
- Median TFS and OS: 15 and 17 mo

Jabbour. Cancer. 2015;121:876.

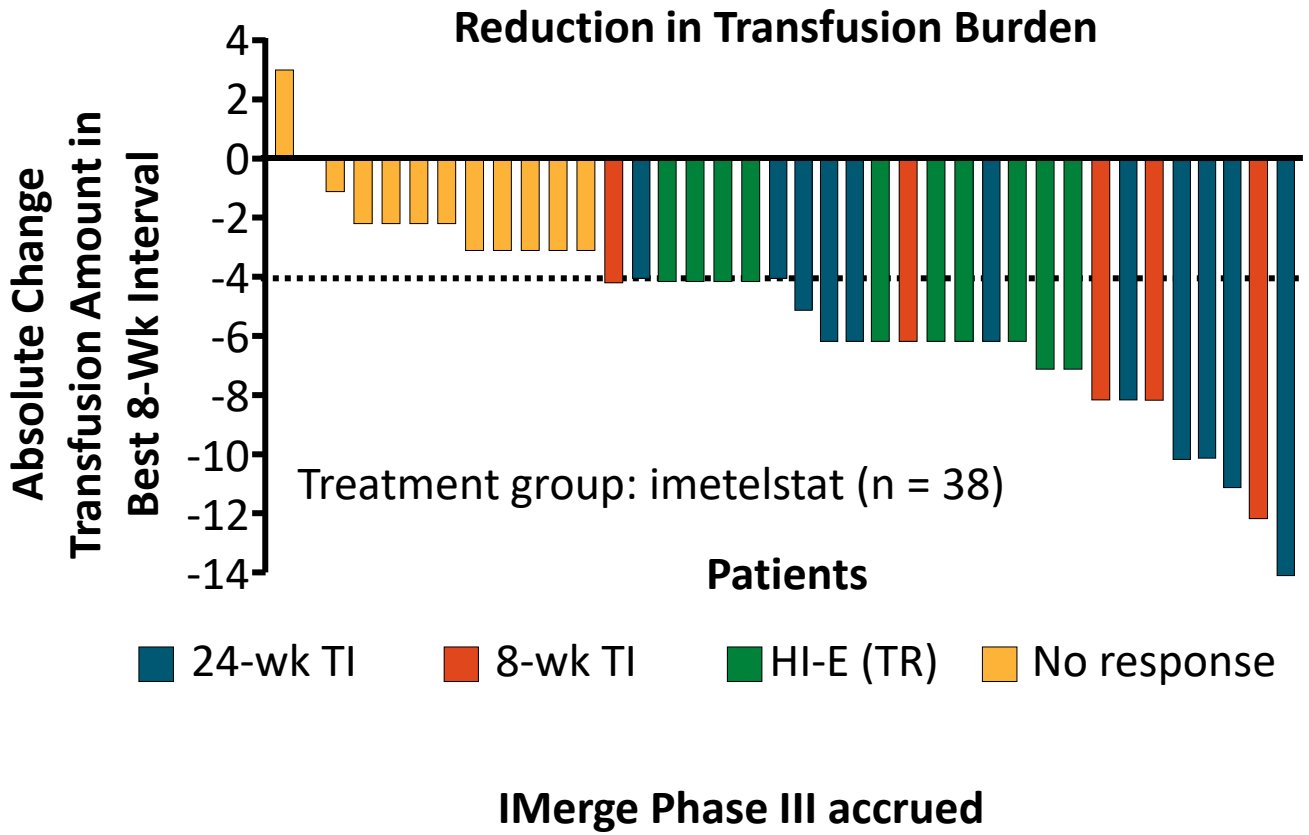
Immunosuppressive Therapy in LR-MDS: Randomized Study of ATG/CSA vs BSC

Parameter	ATG (n = 45)	BSC (n = 43)	*P* Value
Hematologic response			
CR + PR (%)	29	9	.016
Median duration (mo)	16.4		
2-yr survival (%)	49	63	.83
2-yr transformation-free survival (%)	46	55	.73

Passweg. JCO. 2011;29:303.

Imetelstat: Phase II MDS3001 Trial

- Imetelstat: telomerase inhibitor
- Phase II/III; open-label phase II results reported in which 57 patients with lower-risk MDS, ESA relapsed/refractory, treated with imetelstat
- Primary endpoint: 8-wk RBC transfusion independence rate:
  - 37% overall
  - 42% non-del(5q) and HMA/ lenalidomide naive



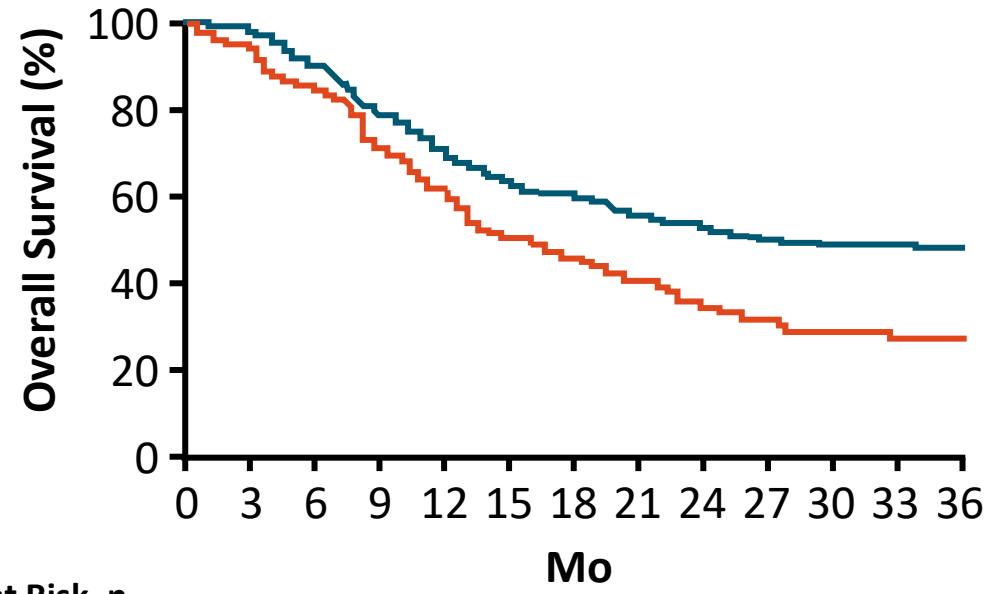
Steensma. JCO. 2021;39:48.

Management of Higher-Risk MDS

BMT CTN 1102: RIC Plus Allo-HSCT vs BSC in Older Patients With Higher-Risk MDS

Overall Survival

	Donor	No Donor
3-yr estimate, %	47.9	26.6
95% CI	41.3-54.1	18.4-35.6

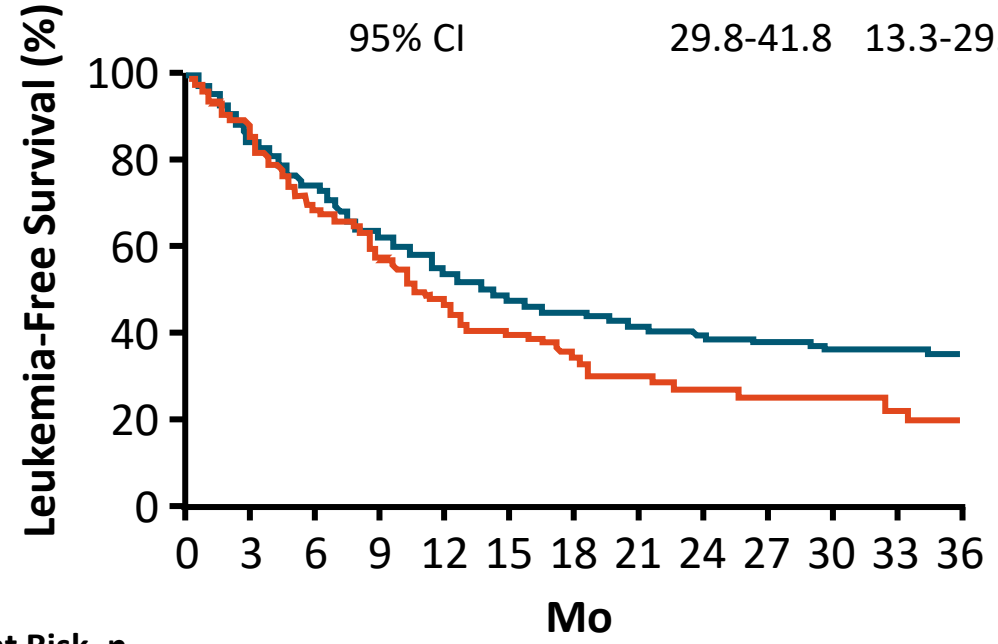


Patients at Risk, n

Donor	260	253	233	201	176	155	129	117	102	86	76	72	27
No donor	124	116	103	84	71	56	49	40	30	22	15	14	7

Leukemia-Free Survival

	Donor	No Donor
3-yr estimate, %	35.8	20.6
95% CI	29.8-41.8	13.3-29.1



Patients at Risk, n

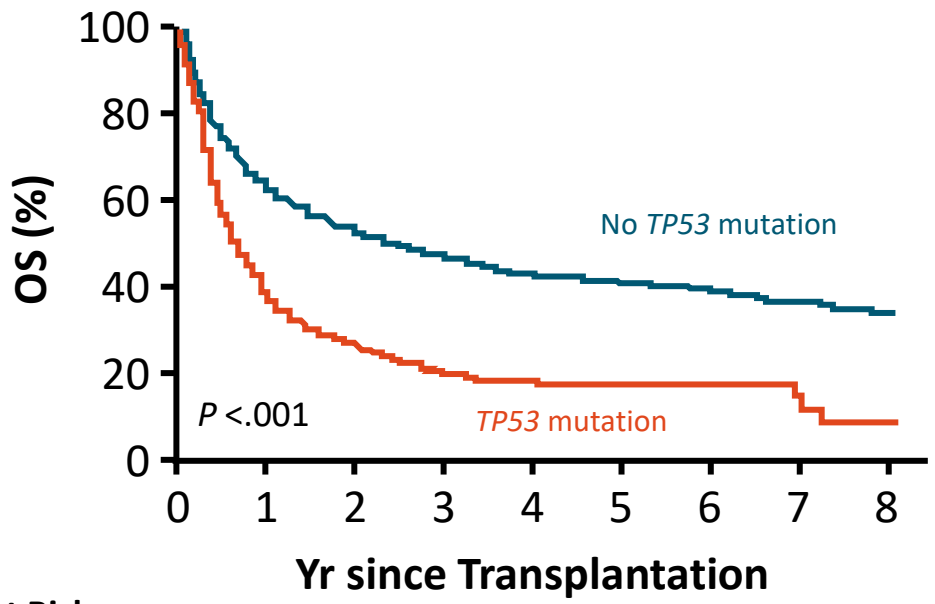
Donor	260	219	192	160	135	119	97	88	76	66	58	56	22
No donor	124	106	83	68	56	44	37	29	24	18	14	12	5

Nakamura. JCO. 2021;39: 3328.

Slide credit: clinicaloptions.com

Impact of *TP53* Mutation and Age on AlloHCT in High-Risk MDS

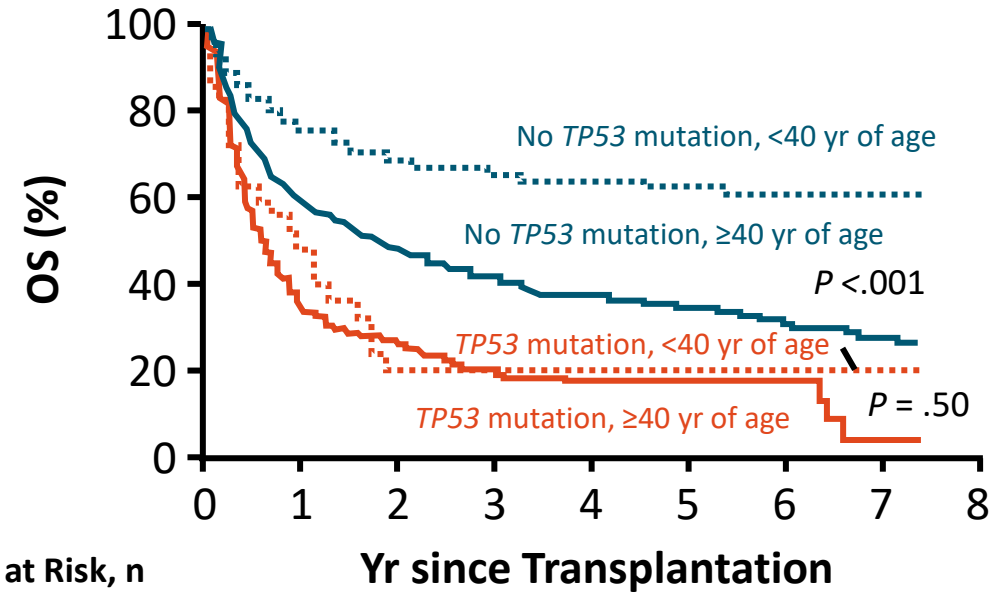
OS by *TP53* Mutation Status



Patients at Risk, n

No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

OS by *TP53* Mutation and Age



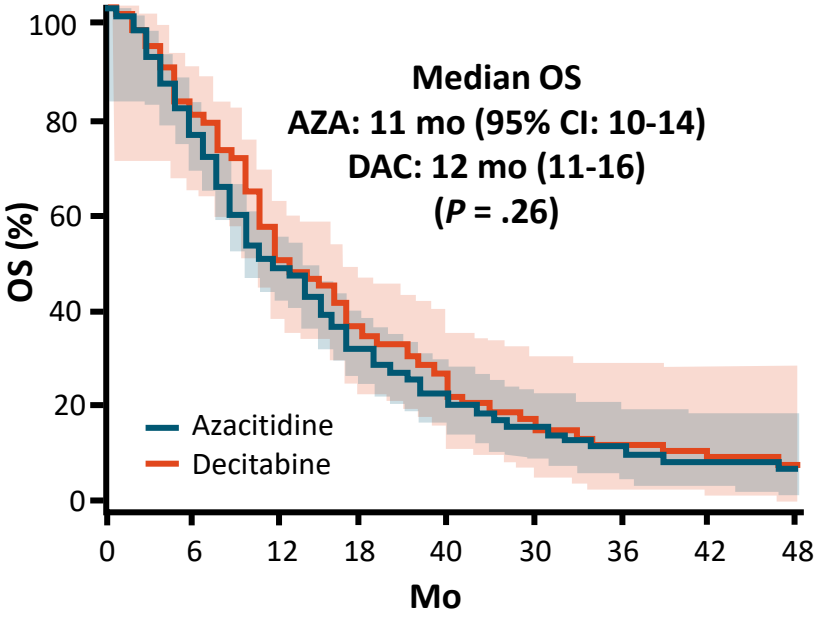
Patients at Risk, n

No *TP53* mutation									
<40 yr of age	214	159	133	115	100	78	42	23	13
≥40 yr of age	1010	598	396	255	161	105	67	30	19
TP53 mutation									
<40 yr of age	27	14	7	5	5	5	4	4	3
≥40 yr of age	262	95	59	34	21	15	10	3	2

Lindsley. NEJM. 2017;376:536.

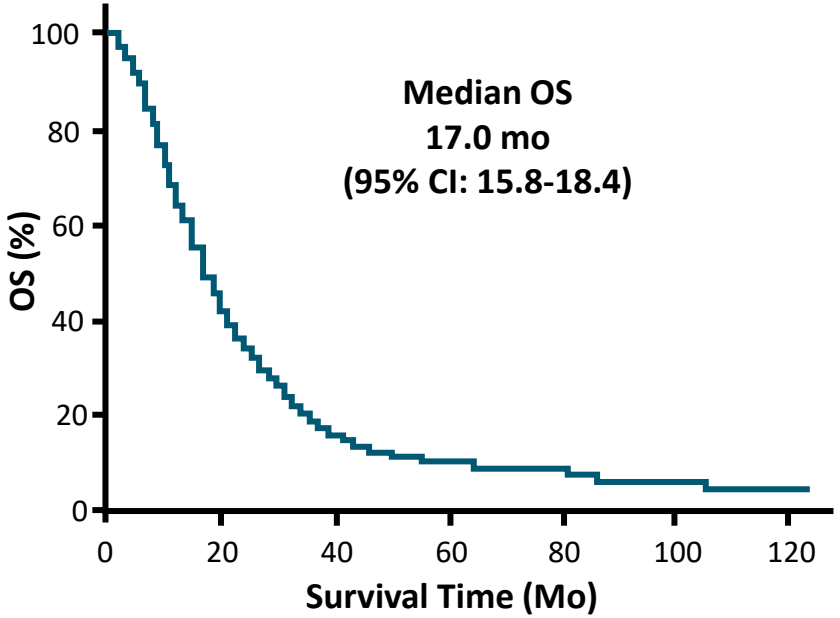
Survival of Patients With HR-MDS Remains Poor Despite Use of HMAs

OS: AZA vs DAC



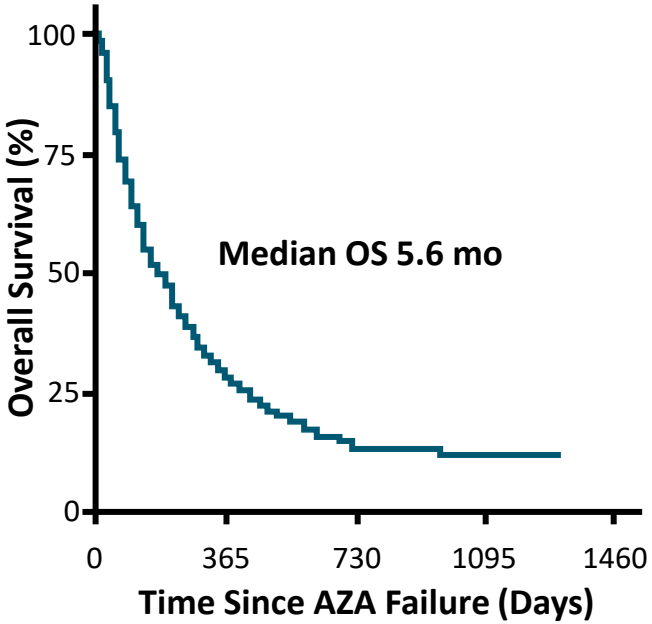
532 patients ≥66 yr at diagnosis who received ≥10 days of HMA therapy

OS: Median 5 Cycles HMA



636 HR-MDS of all ages in the MDS Clinical Research Consortium who received HMA (median 5 cycles), 72% received ≥4 cycles. 68% received AZA.

OS: Post-AZA Failure

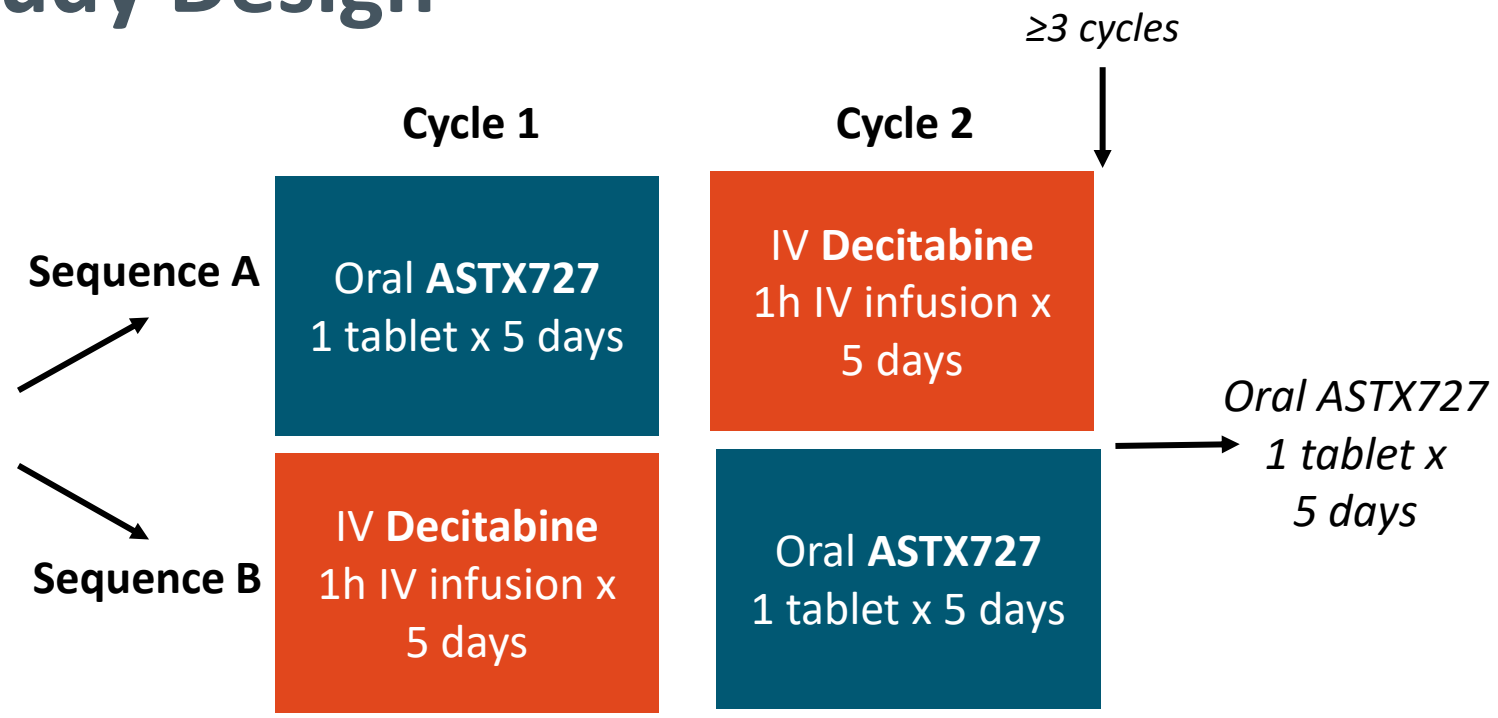


Survival post-AZA failure for patients with HR-MDS

Zeidan. Br J Haematol. 2016;175:829. Zeidan. Leukemia. 2016;30:649. Prebet. JCO. 2011;29:3322.

ASCERTAIN: Phase III ASTX727 (Oral Decitabine/ Cedazuridine) Trial Study Design

Patients with int-/high-risk MDS; CMML; AML 20%-30% blasts; candidates for IV decitabine; ECOG PS 0/1; life expectancy of ≥3 mo; adequate organ function; 1 prior cycle of HMA is allowed (N = 133)



- Primary endpoint: total 5-day decitabine AUC equivalence (oral/IV 90% CI between 80% and 125%)
- Secondary endpoints: response rate; transfusion independence; duration of response; leukemia-free, OS; safety; max LINE-1 demethylation

Garcia-Manero. ASH 2019. Abstr 846.

ASCERTAIN Primary Endpoint: 5-Day Decitabine AUC Equivalence

Decitabine 5-day AUC0-24 (h ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo LSM Oral/IV, % (90% CI)	Intra-subject (% CV)
		N	Geo LSM	N	Geo LSM		
Primary Analysis	Paired*	123	864.9	123	855.7	98.9 (92.7-105.6)	31.7

*Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Primary endpoint met: oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All PK AUC analyses (sensitivity and secondary) confirmed findings from primary analysis

Garcia-Manero. ASH 2019. Abstr 846.

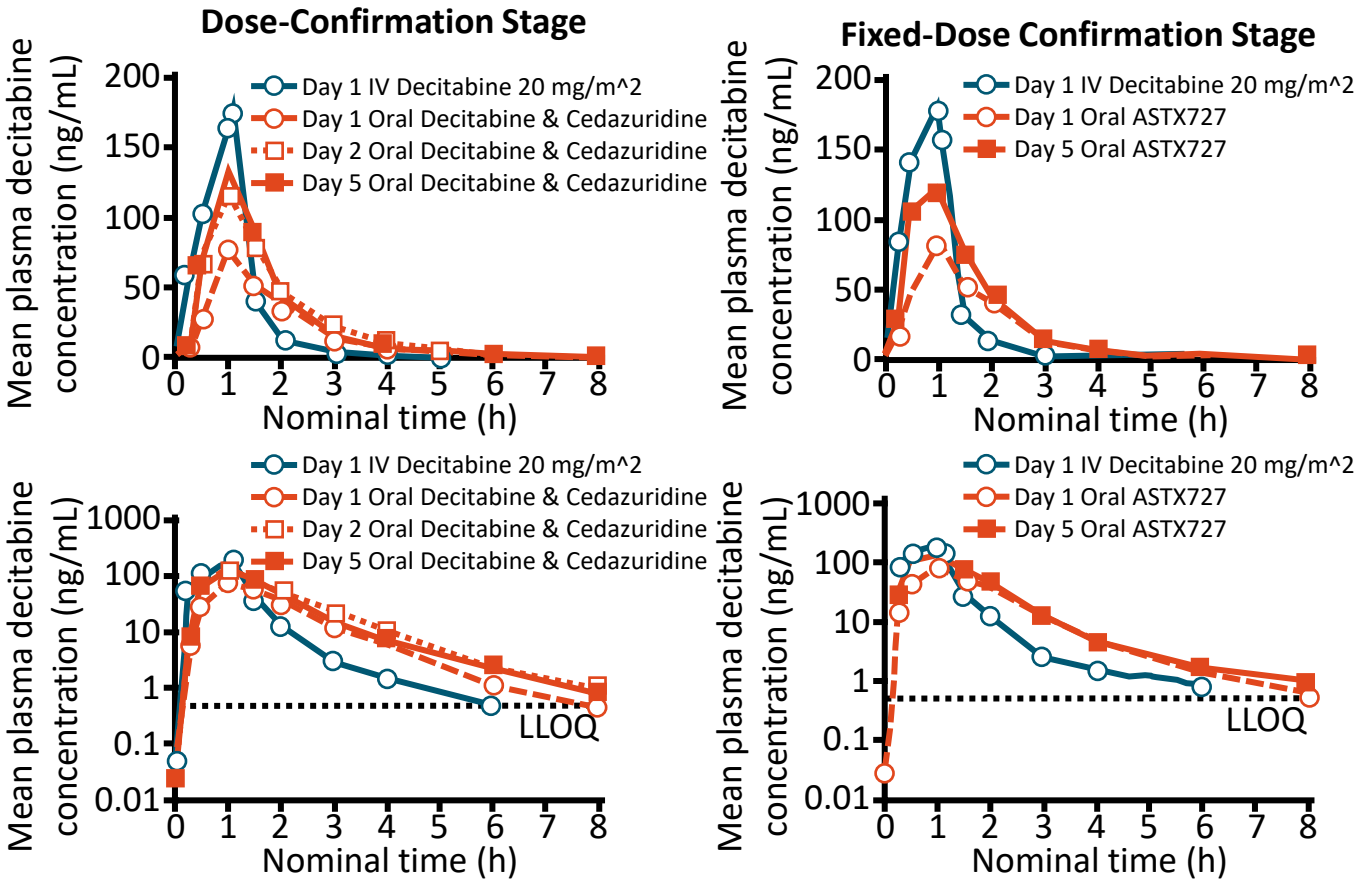
ASCERTAIN: Oral Decitabine Efficacy

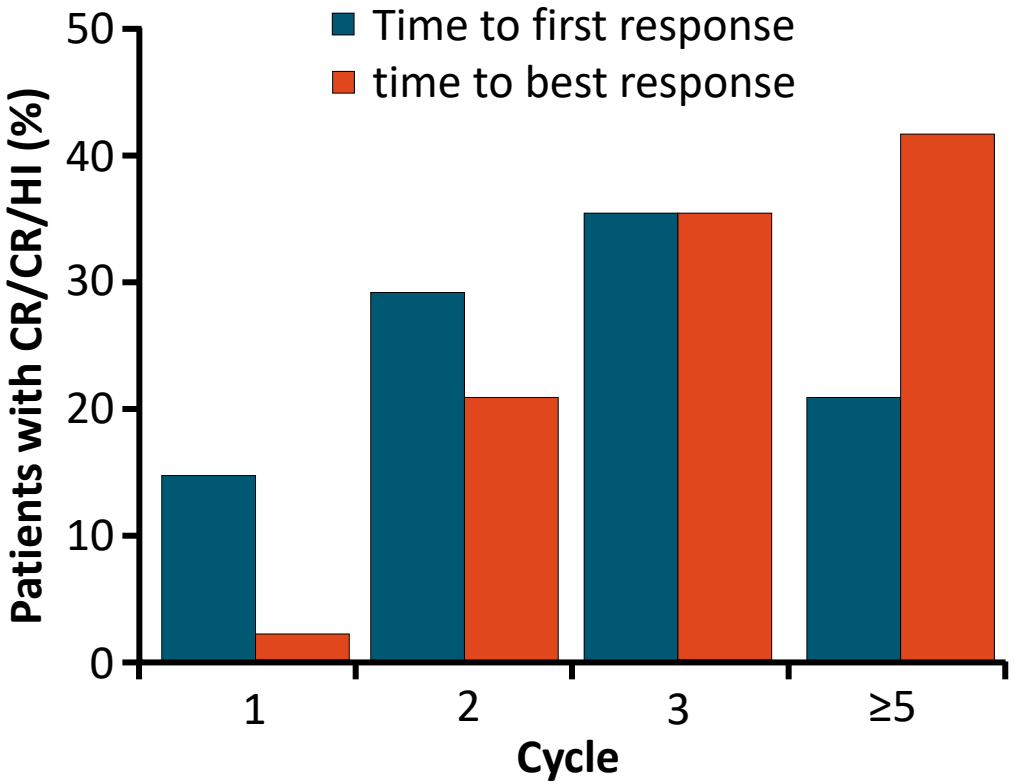
Response category, n (%)	Treated Patients (N = 133)	95% CI
Complete response (CR)	29 (22)	(15.1-29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3)	(24.5-41.0)
▪ mCR with hematologic improvement	22 (16.5)	(10.7-24.0)
Hematologic improvement (HI)	10 (7.5)	(3.7-13.4)
▪ HI-erythroid	2 (1.5)	(0.2-5.3)
▪ HI-neutrophils	1 (0.8)	(0-4.1)
▪ HI-platelet	7 (5.3)	(2.1-10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7)	(52.8-69.9)
Progressive disease	6 (4.5)	(1.7-9.6)
No response	28 (21.1)	(14.5-29.0)
Non-evaluable	17 (12.8)	(7.6-19.7)

- Median CR duration was 14.0 mo
- Median duration of best response was 12.7 mo
- 34 (26%) of subjects proceeded to HCT
- **Median OS has not been reached with median follow-up of 24.7 mo**

Savona. ASH 2020. Abstr 1230.

Oral Cedazuridine/Decitabine in High-Risk MDS





Approved July 2020 for high-risk MDS and CMML

Garcia-Manero. Blood. 2020:136:674.

Investigational Agents in MDS

Magrolimab + AZA in Patients With MDS and AML: Background

- CD47 is an adverse prognostic factor in AML and plays a role in evasion of macrophage phagocytosis[1,2]
- Magrolimab is a first-in-class anti-CD47 macrophage immune checkpoint inhibitor that promotes tumor cell elimination via macrophage phagocytosis
  - Synergistic effects observed in combination with AZA in vitro and in vivo[3]
- Initial study assessed safety and efficacy of magrolimab plus AZA in untreated patients with MDS and AML[4]

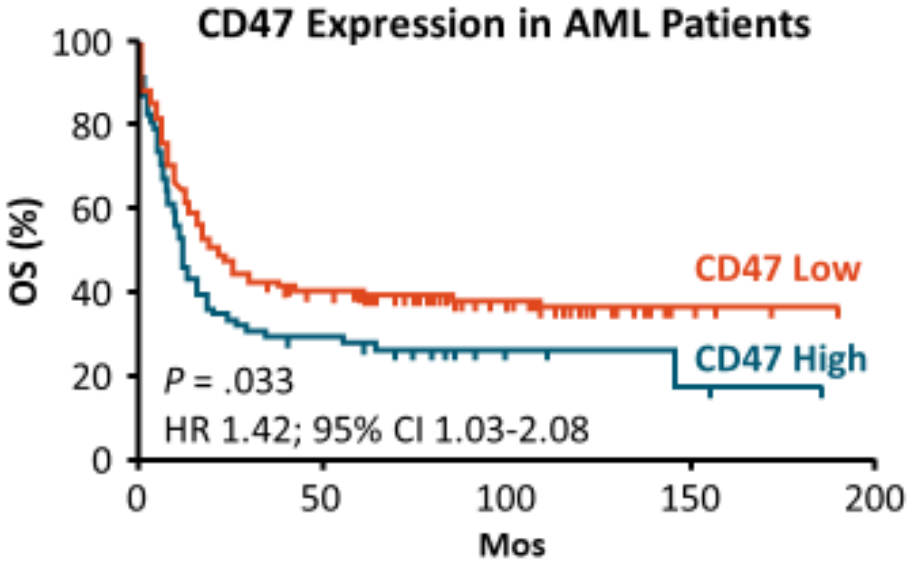


Image not available

1. Chao. Curr Opin Immunol. 2012;24:225. 2. Majeti. Cell. 2009;138:286.
3. Feng. Blood. 2018;132(suppl 1):2729. 4. Sallman. ASCO 2020. Abstr 7507.

Phase Ib Study of Magrolimab + AZA in Patients With Intermediate or High-Risk MDS or AML: Response

Best Overall Response, n (%)	MDS (n = 33)	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)*	1 (4)
Hematologic improvement	7 (21)	NA
SD	3 (9)	8 (32)
PD	0	1 (4)

- Median TTR: 1.9 mos; median OS: NR (either arm)
- 6-mo CR rate, MDS patients: 56%
- 9 of 58 (16%) patients received alloSCT

Outcome, n (%)	MDS (n = 33)	AML (n = 25)
RBC transfusion independence	11/19 (58)	9/14 (64)
Complete cytogenetic response	9/26 (35)	6/12 (50)
MRD negativity in responders	6/30 (20)	8/16 (50)
Median DoR, mo	NR (0.03+ to 10.4+)	NR (0.03+ to 15.1+)
Median follow-up, mo (range)	5.8 (2.0 to 15.0)	9.4 (1.9 to 16.9)

*4 patients had marrow CR and hematologic improvement.

Sallman. ASCO 2020. Abstr 7507.

Magrolimab + AZA in Patients With MDS or AML: Response in Patients With *TP53* Mutation

Outcome	MDS *TP53* Mutant (n = 12)	AML *TP53* Mutant (n = 4)
ORR, n (%)	9 (75)	3 (75)
CR, n (%)	5 (42)	2 (50)
CRi/marrow CR, n (%)	4 (33)	1 (25)
Complete cytogenetic response, n/N (%)*	4/8 (50)	3/3 (100)
MRD negativity in responders, n/N (%)	4/9 (44)	0
Median DoR, mos	NR (0.03+ to 15.1)	NR (0.03+ to 5.2+)
6-mo survival probability, %	91	100
Median follow-up, mos (range)	8.8 (1.9 to 16.9)	7 (4.2 to 12.2)

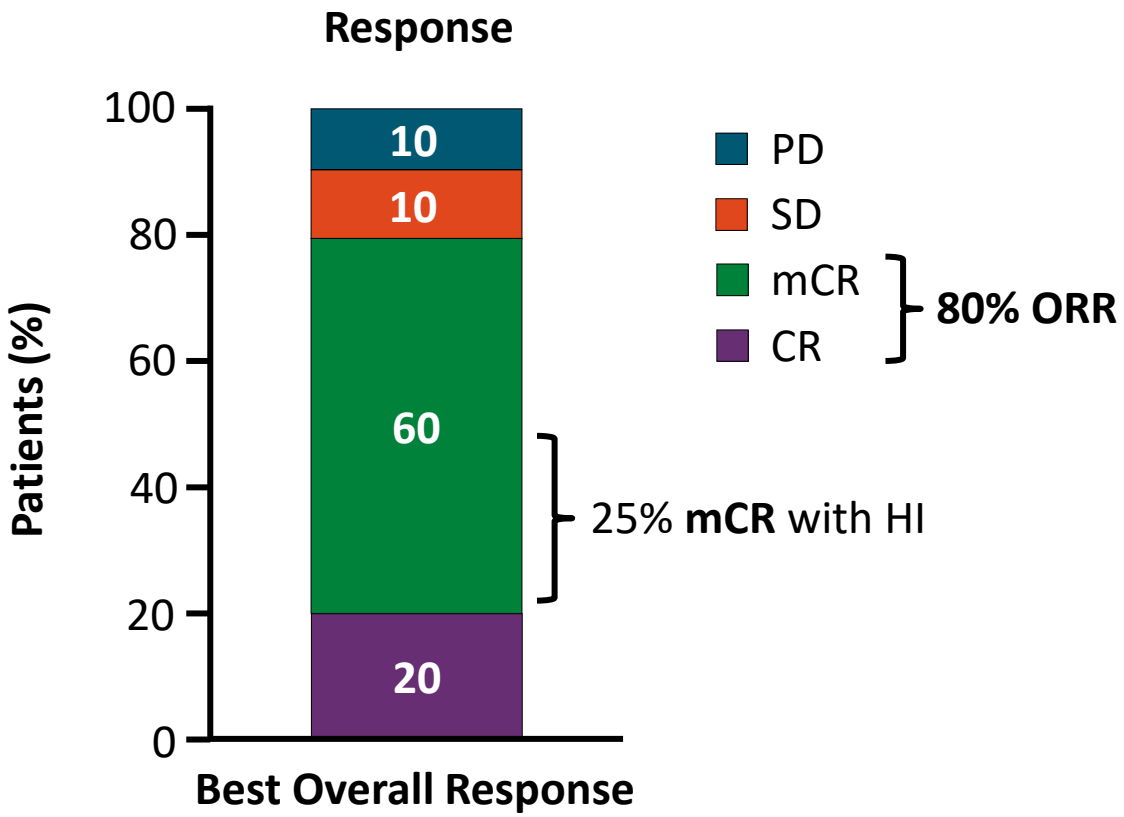
*Responders with cytogenetic abnormalities at baseline.

- 9 of 58 (16%) patients received alloSCT

Sallman. ASCO 2020. Abstr 7507.

CPX-351 in HR-MDS

- Multicenter, dose-escalation, safety-expansion phase I study (N = 20)
- 75% of patients proceeded to allo-HCT; 15% pending allo-HCT
- 0 deaths within 30 days of induction
- 1 patient died from PD to sAML within 60 days of induction
- 1 patient did not proceed to allo-HCT due to poor performance status post induction and was taken off the study



Jacoby. ASH 2021. Abstr 540.

Eltanexor Phase I/II Study in HMA-Refractory MDS: Preliminary Safety and Activity

- Oral selective inhibitor of nuclear export less emetogenic than selinexor
- N = 20 with intermediate-2 MDS with 5% to 19% myeloblasts or high-risk MDS
  - Responses in 15 evaluable patients; 7 achieved marrow CR, 5 achieved SD
  - Median OS 11.86 mo in patients with marrow CR vs 8.67 with no marrow CR

Lee. ASCO 2021. Abstr e19037. NCT02649790.

TIM-3 Is an Inhibitory Receptor Expressed on Immune and Leukemic Cells

Immune Effectors

- An inhibitory receptor expressed on macrophages, monocytes, NK cells, dendritic cells, and T cells[1,2]
- Involved in regulating innate and adaptive immune responses[1,2]

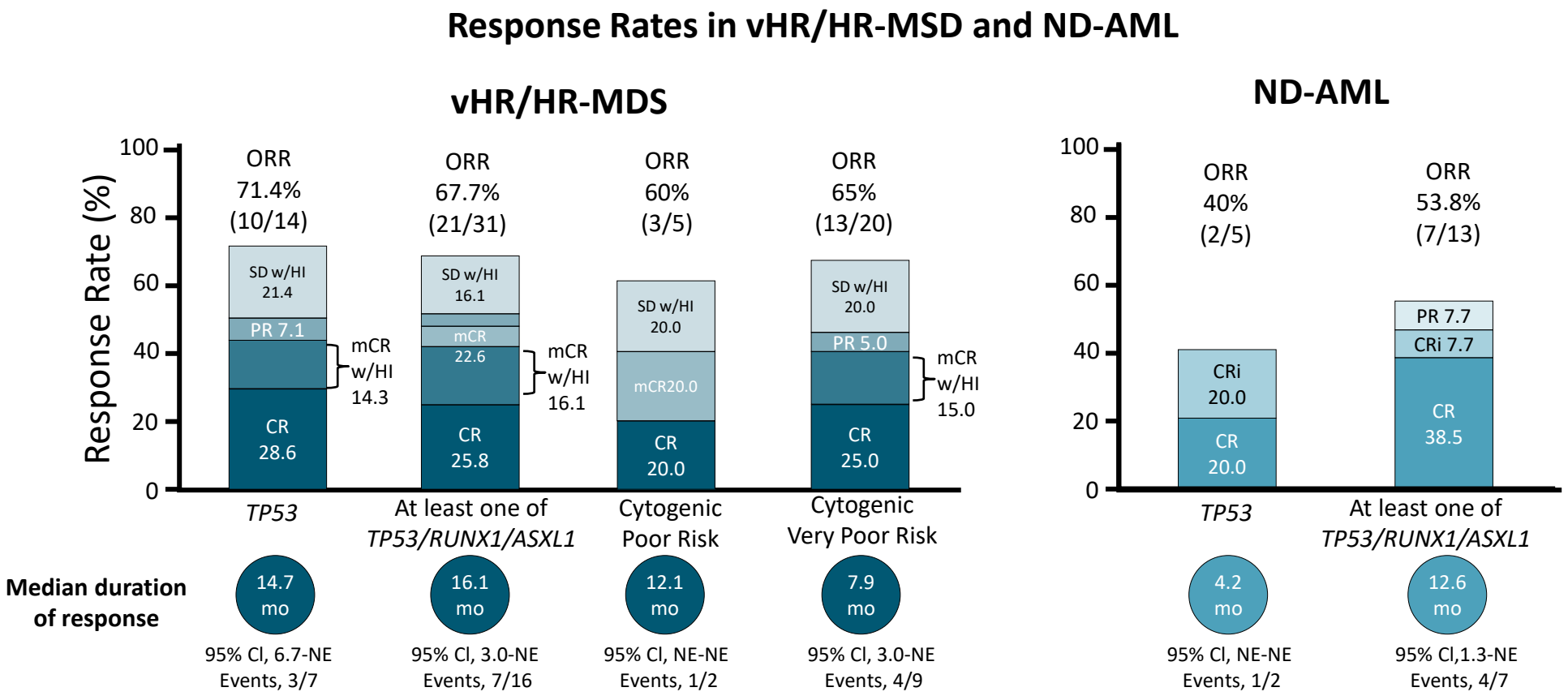
Leukemic Cells

- Expressed on LSCs and blasts but not on normal HSCs,[1-5] making it a promising target in MDS/AML[2,4,6]
- TIM-3/Galectin-9 interaction forms an autocrine stimulatory loop promoting LSC self-renewal[2,7]

Images not available

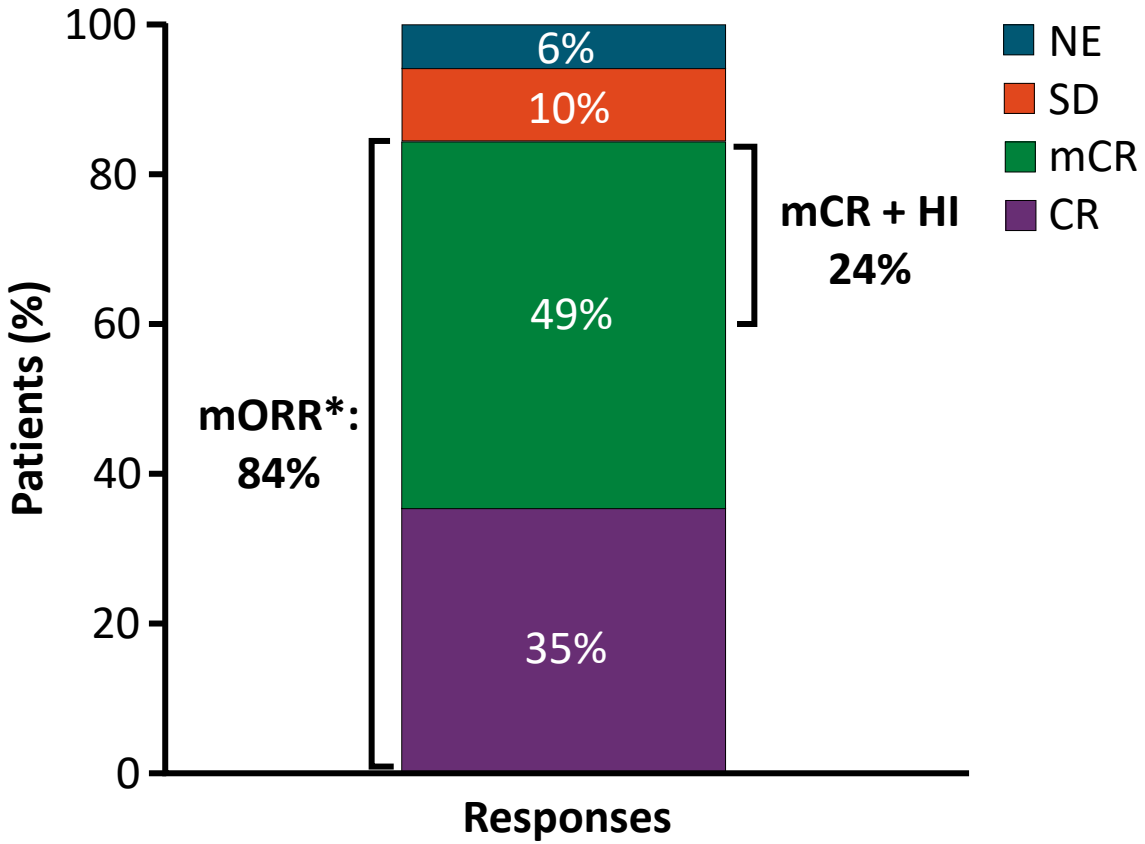
1. Wolf. Nat rev Immunol. 2020;20:173. 2. Acharya. J Immunother Cancer. 2020;8:e000911. 3. Haubner. Leukemia. 2019;33:64. 4. Asayama. Oncotarget. 2017;8:88904. 5. Kikushige. Cell Stem Cell. 2015;17:341. 6. Borate. EHA. 2020. Abstr S185. 7. Sabatos-Peyton. SITC. 2020. Abstr 439.

Sabatolimab + HMA Demonstrates Durable Response in vHR/HR-MDS and ND-AML



Garcia-Manero. SOHO 2021. MDS 420.

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Responses

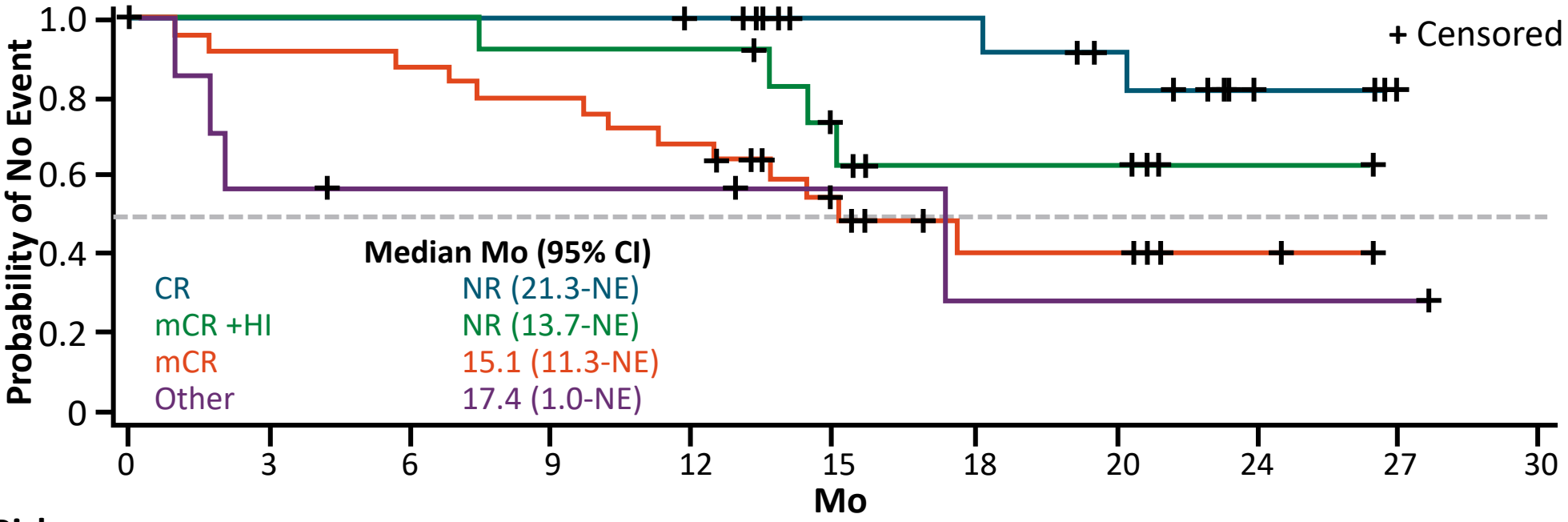


*mORR: CR + mCR + PR.

- Median time to response: 0.9 mo (95% CI: 0.7-5.8)
- Median duration of response: 12.4 mo (95% CI: 9.9-NR)

Garcia. ASH 2021. Abstr 241.

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Overall Survival by Best Response at RP2D



Patients at Risk, n

CR	18	18	18	18	17	12	12	9	3	1	0
mCR +HI	12	12	12	11	11	8	4	4	1	0	
mCR	25	23	22	20	17	11	5	5	2	0	
Other	8	4	3	3	3	2	1	1	1	1	0

Garcia. ASH 2021. Abstr 241.

Venetoclax and HMA in Higher-Risk MDS: Efficacy of First-line Therapy

Best Response, %	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
ORR	77	40	<.005
▪ CR	34	13	
▪ mCR	37 (62 + HI)	11	
▪ PR	3	1	
▪ HI	3	15	
***ASXL-1* mut**	**(n = 16)**	**(n = 106)**	
ORR	87	32	<.005
▪ CR	44	8	
***TP53* mut**	**(n = 12)**	**(n = 137)**	
ORR	75	44	.038
▪ CR	25	17	.47

Outcome	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
Median OS, mo			
▪ From diagnosis (95% CI)	21 (11-32)	20 (19-22)	.86
▪ From start of treatment*	19.4	17.2	.88
AML transformation, %	23	37	.08
AHSCT cohort†	**(n = 13)**	**(n = 256)**	
Median OS, mo (95% CI)	NR	38 (27-50)	.20
2-yr OS, %	91	51	

*Median time from diagnosis to treatment was 1 mo in both arms.
†Patients who went on to AHCST.

Komrokji. ASH 2021. Abstr 536.

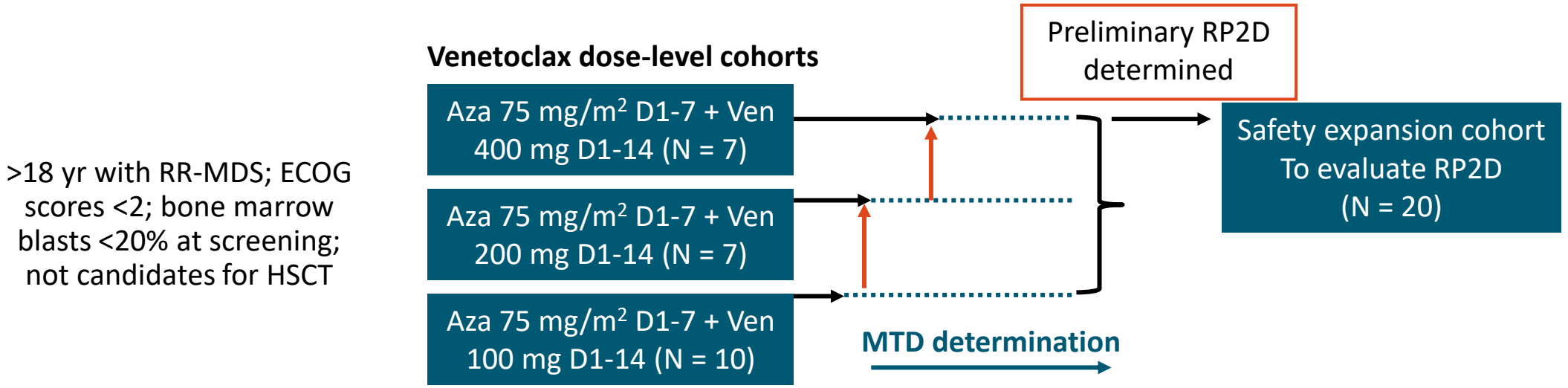
Venetoclax and HMA in Higher-Risk MDS: Efficacy in R/R MDS Population

Best Response, %	1L HMA (n = 1127)	HMA + Ven for R/R (n = 31)	1L HMA + Ven (n = 35)	*P* Value
ORR	77	61	40	
▪ CR	34	13	13	
▪ mCR	37 (62 + HI)	48	11	
Median OS from diagnosis, mo (95% CI)	20 (19-22)	33 (31-36)	21 (11-32)	.02

- 31 patients with R/R MDS received median 6 cycles of first-line HMA
- 9 patients who received HMA + venetoclax for R/R MDS underwent AHSCT
  - Median OS: 31 vs 33 mo with no AHSCT (*P* = .70)

Komrokji. ASH 2021. Abstr 536.

Venetoclax in Combination With Azacitidine for the Treatment of Relapsed/Refractory MDS: Design

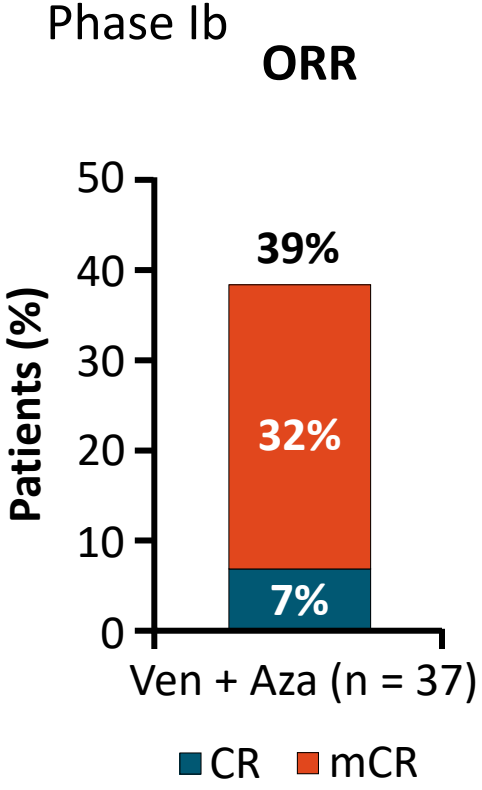


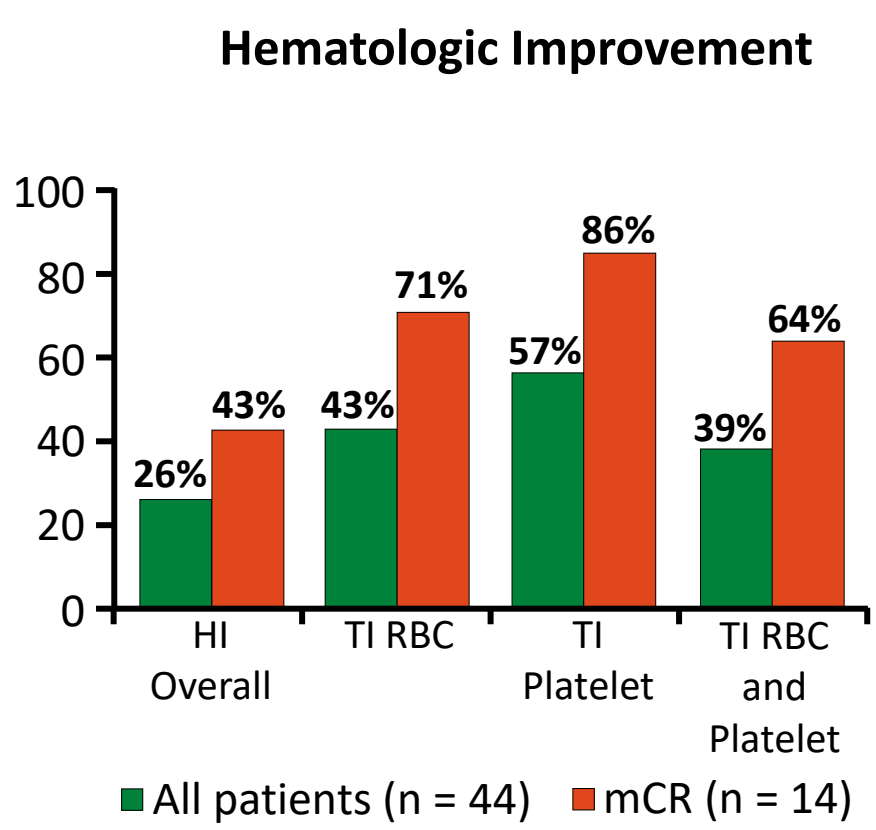
- Key endpoints: ORR, DoR, HI, TI, exploratory biomarkers
- In this ongoing phase Ib study, 44 patients with R/R MDS were enrolled to receive venetoclax and azacitidine combination

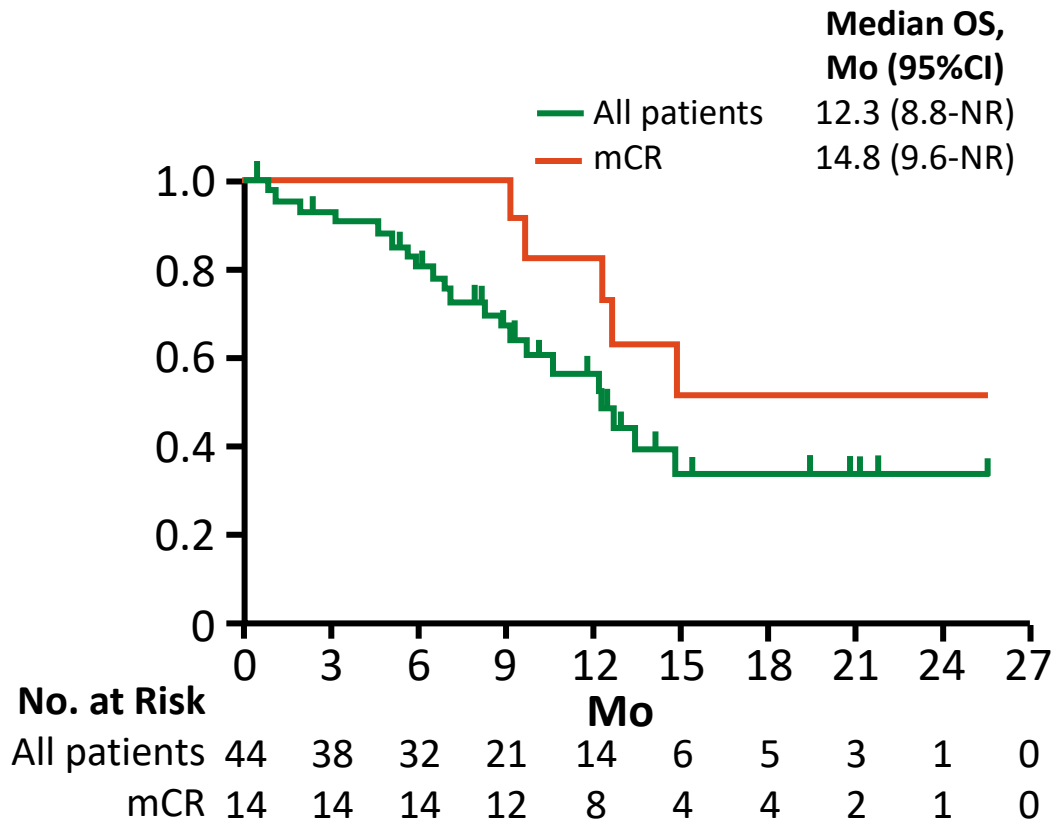
Zeidan. ASH 2020. Abstr 3109.

Venetoclax in Combination With Azacitidine for Relapsed/Refractory MDS

Phase Ib

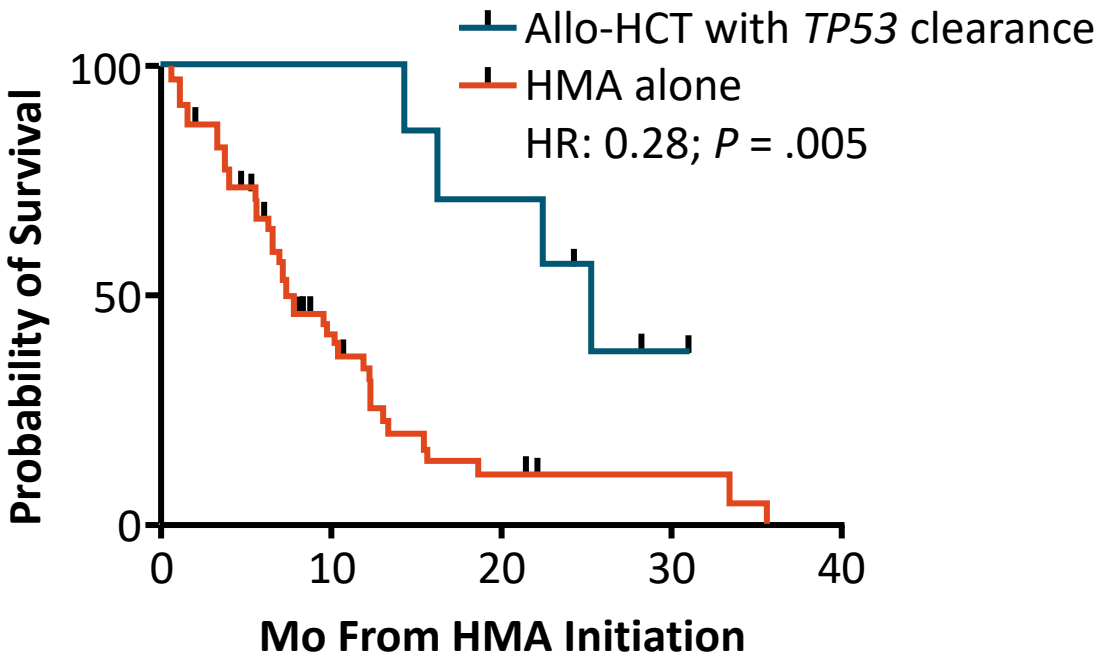


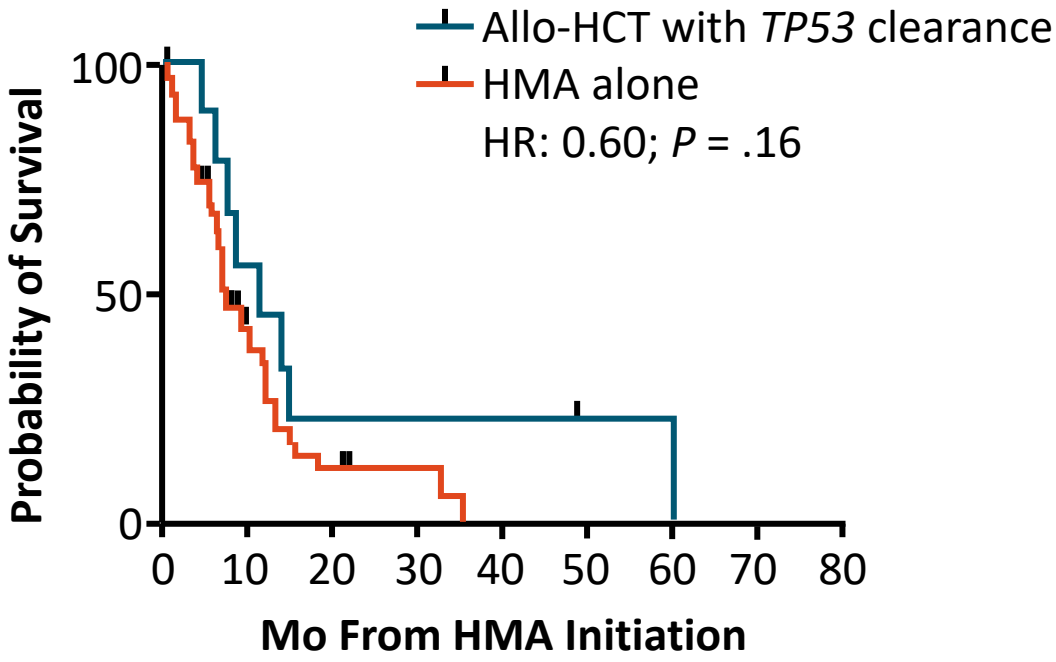




Zeidan. ASH 2020. Abstr S188.

Baseline and Serial Molecular Profiling Predicts Outcomes With HMAs in MDS





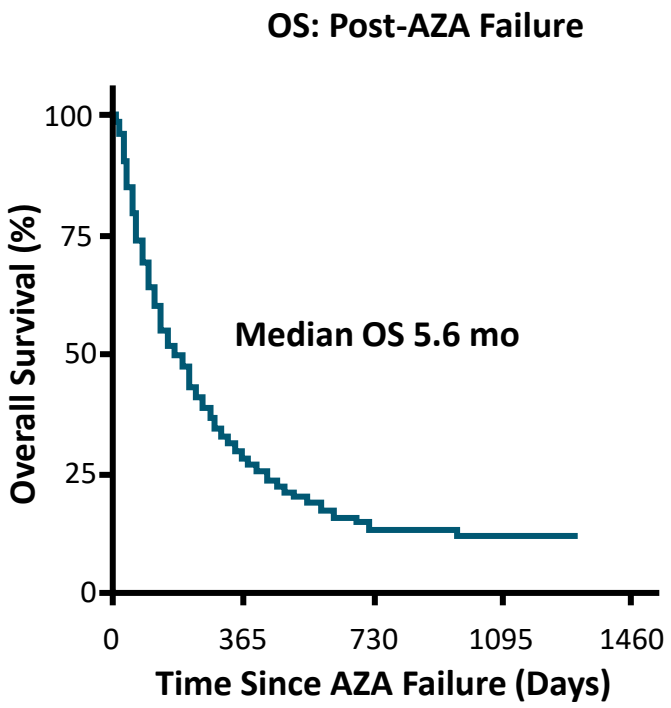
Proposed treatment algorithm for *TP53* mutated MDS:

TP53 mutated, higher-risk MDS → Frontline therapy with a hypomethylating agent → Serial next generation sequencing to assess molecular response

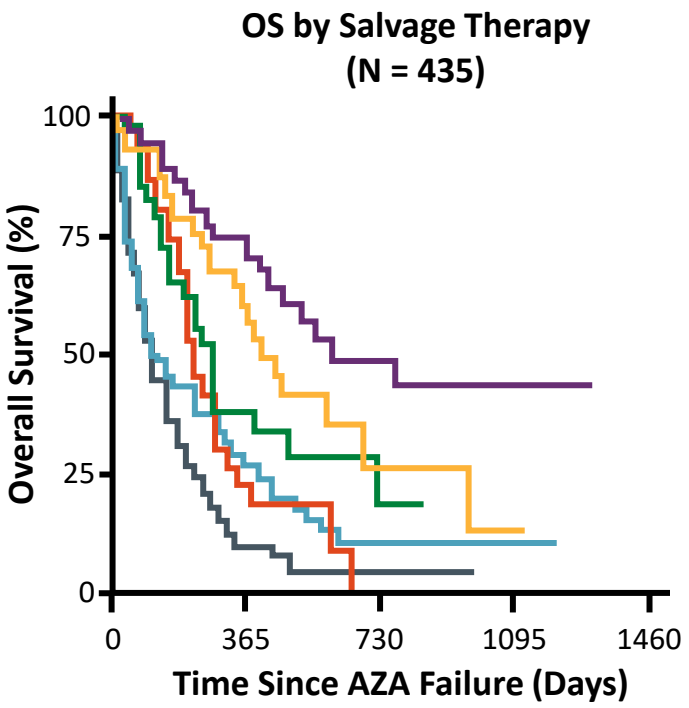
- Clearance of *TP53* mutation → Proceed to allogeneic transplant (if candidate)
- Persistent *TP53* mutation detected → Clinical trial evaluating novel therapy

Hunter. Blood Adv. 2021;5:1017.

AlloSCT and Investigational Agents Best Salvage Therapy for Patients With HR MDS After HMA Failure



Survival post-AZA failure for patients with HR-MDS



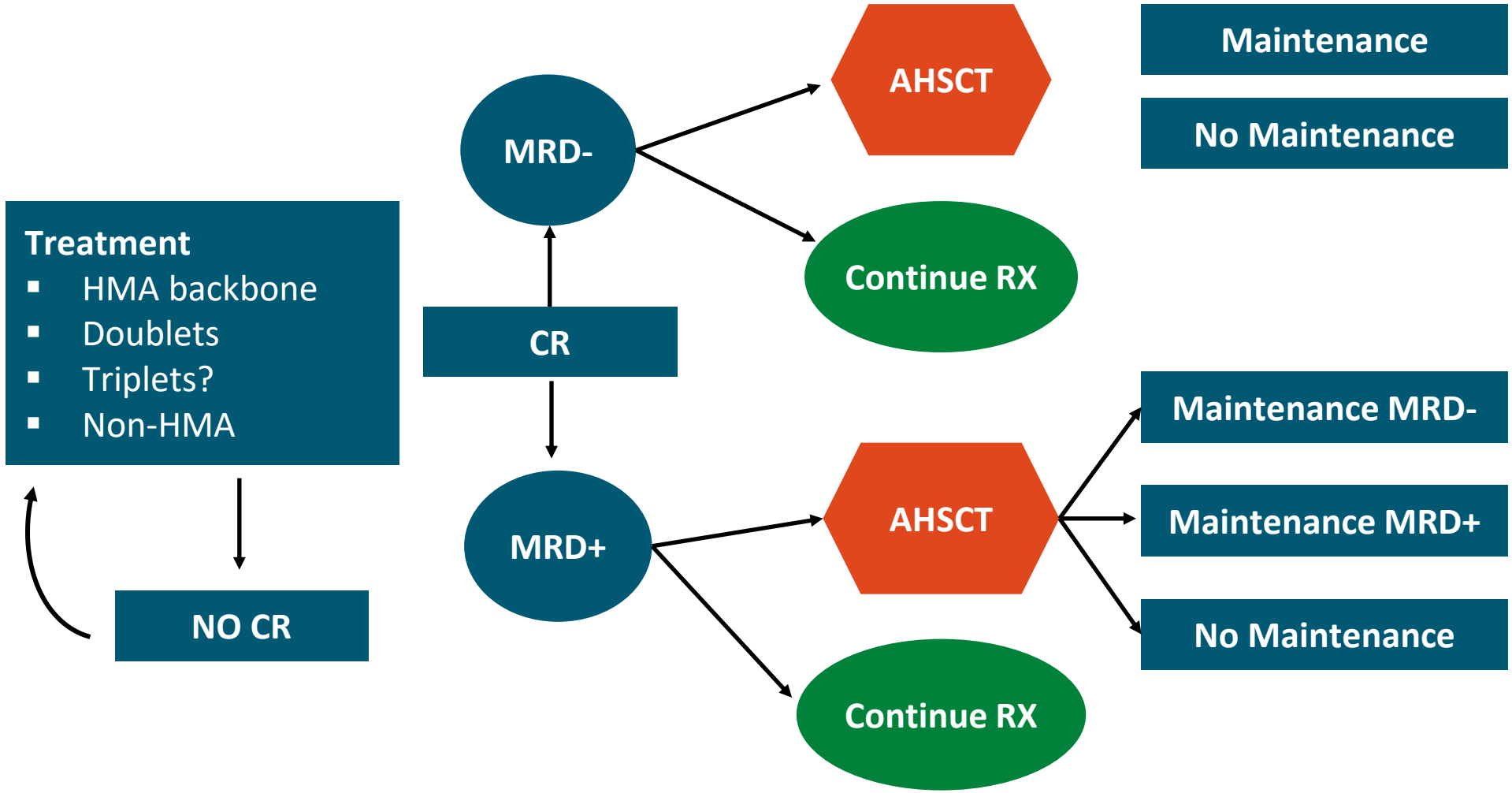
Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9
Investigational therapy	44	4/36	13.2
Allogeneic transplantation	37	13/19	19.5

Prebet. JCO. 2011;29:3322.

Treatment Options in MDS After HMA Failure

- Add additional agent to HMA
- Intensive chemotherapy
- Mini-CLA ± venetoclax: normal karyotype
- *IDH2* (5-10%): enasidenib
- *IDH1* (5%): ivosidenib
- *FLT3* (15%): multiple *FLT3* agents
- *NPM1* (1%): ara-C based

Total Therapy in HR-MDS



Questions