Myelodysplastic Syndromes

“Major Challenges Treating Myelodysplastic Syndrome”

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COI Disclosures

Speaker bureau: BMS/Celgene, Jazz, Pharma Essential, AbbVie, Servier, CTI

Advisory board/honoraria: BMS/Celgene, Jazz Pharmaceuticals, PharmaEssentia, AbbVie, Novartis, Takeda, Geron, Taiho, CTI, Servier

Patient 1

- 71-yr-old female presented with pancytopenia (Hb 8.0 g/dL, platelets 90, ANC 900)
- Original bone marrow showed increased ring sideroblasts
- Patient treated in community with ESA for 3 mo then azacitidine for 6 mo but remains RBC TD

Patient 2

- 71-yr-old female presenting with anemia (Hb 8.0 g/dL, platelets 200, ANC 4000)
- Original workup no evidence of bleeding and no nutritional deficiencies

Patient 3

- 71-yr-old female presenting with anemia (Hb 8.0 g/dL, platelets 150, ANC 1200)
- Original workup no evidence of bleeding and no nutritional deficiencies

Patient 1

- Repeat bone marrow demonstrated RS >15%, no increased myeloblasts
- Normal karyotype, no somatic mutation detected by NGS
- Further workup revealed severe copper deficiency

Patient 2

- Bone marrow aspirate and biopsy revealed >15% RS and erythroid dysplasia
- Normal karyotype, *SF3B1* K700E (VAF 30%) detected by NGS

Patient 3

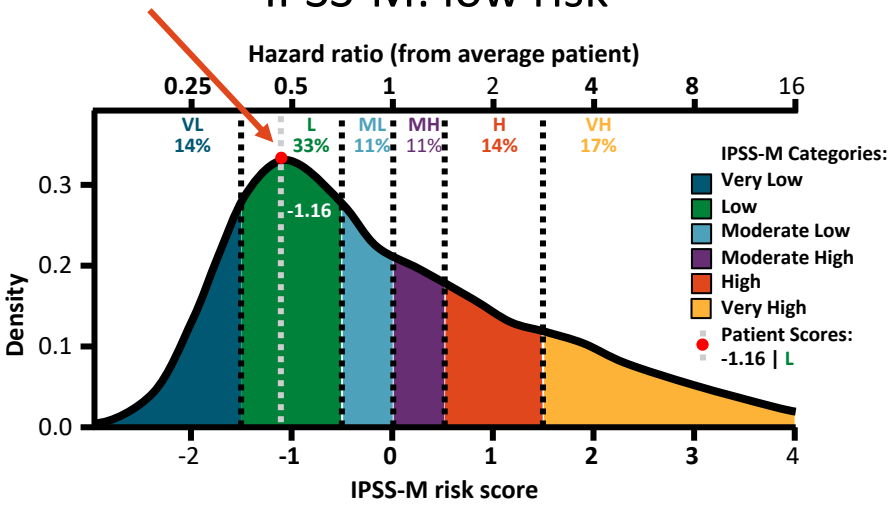
- Bone marrow aspirate and biopsy revealed >15% RS and 10-15% myeloblasts
- Complex karyotype including del5q and -7, *TP53* (VAF 65%) detected by NGS

Patient 1

- 71-yr-old female presented with pancytopenia (Hb 8.0 g/dL, platelets 90, ANC 900)
- Diagnosis: copper deficiency

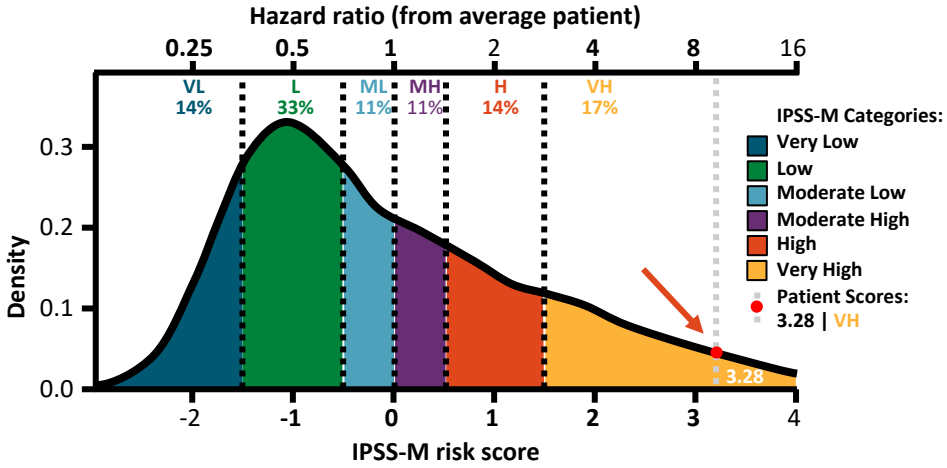
Patient 2

- 71-yr-old female presenting with Anemia (Hb 8.0 g/dL, platelets 200, ANC 4000
- Diagnosis: MDS-RS
- IPSS-R: low-risk
- IPSS-M: low risk



Patient 3

- 71-yr-old female presenting with Anemia (Hb 8.0 g/dL, platelets 150, ANC 1200)
- Diagnosis: MDS-EB2
- IPSS-R: very high risk
- IPSS-M: very high risk



Patient 1

- Treatment:

1. Copper replacement.

Patient 2

- Treatment:

1. ESA
2. Luspatercept
3. Lenalidomide
4. HMA

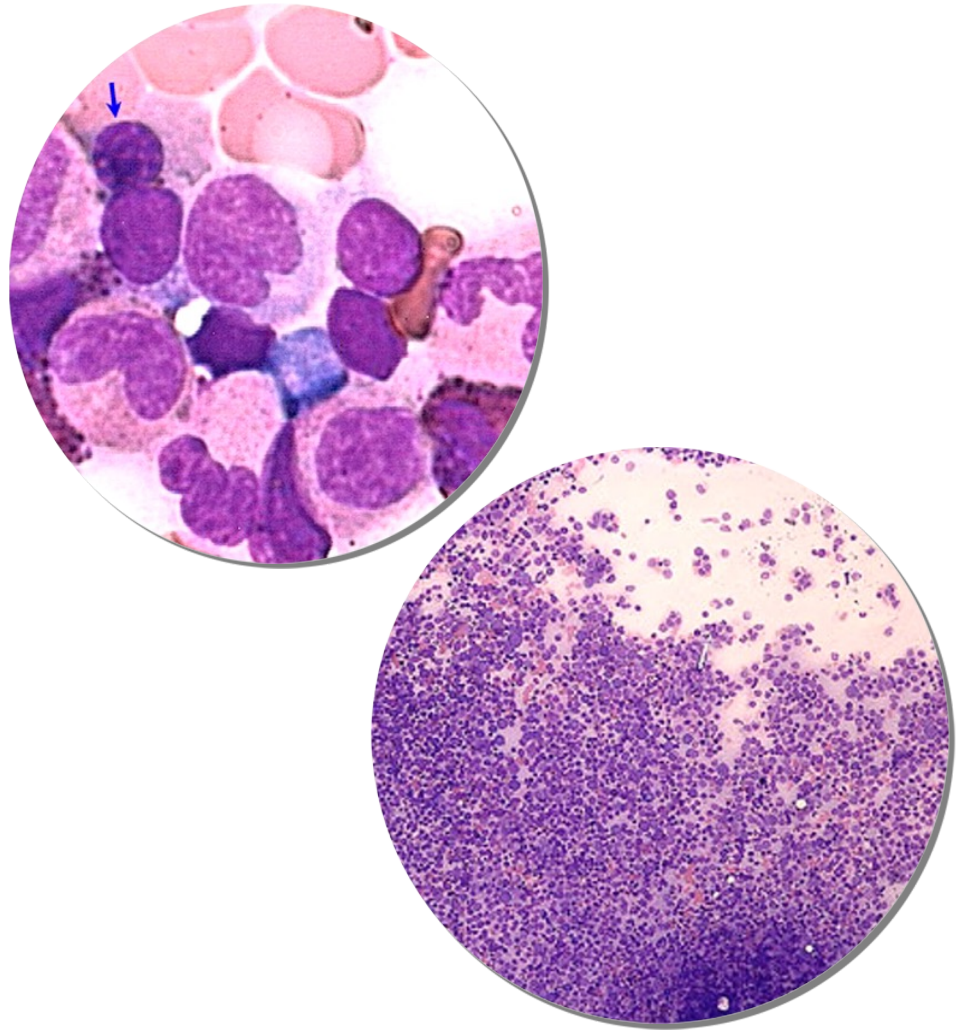
Patient 3

- Treatment:

1. Clinical trials
2. HMA
3. Allo-SCT if TP53 mutation is cleared

Myelodysplastic Syndromes (MDS)

- 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 yrs; incidence: 34-47/100,000 >75 yrs[3]



1. Bennett J et al. *Clinical Oncology*. New York, NY: Churchill Livingstone; 2004:2849-2881; 2. SEER data. 2000-2009. 3. SEER 18 data. 2000-2009.

MDS Minimal Diagnostic Criteria

Prerequisite Criteria

Both 1 and 2 must be fulfilled

1. Cytopenia(s)

2. EXCLUDE other causes of cytopenias and morphological changes:

- *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.)*
- *Hereditary BMF syndromes (Fanconi anemia etc.)*
- *Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)*

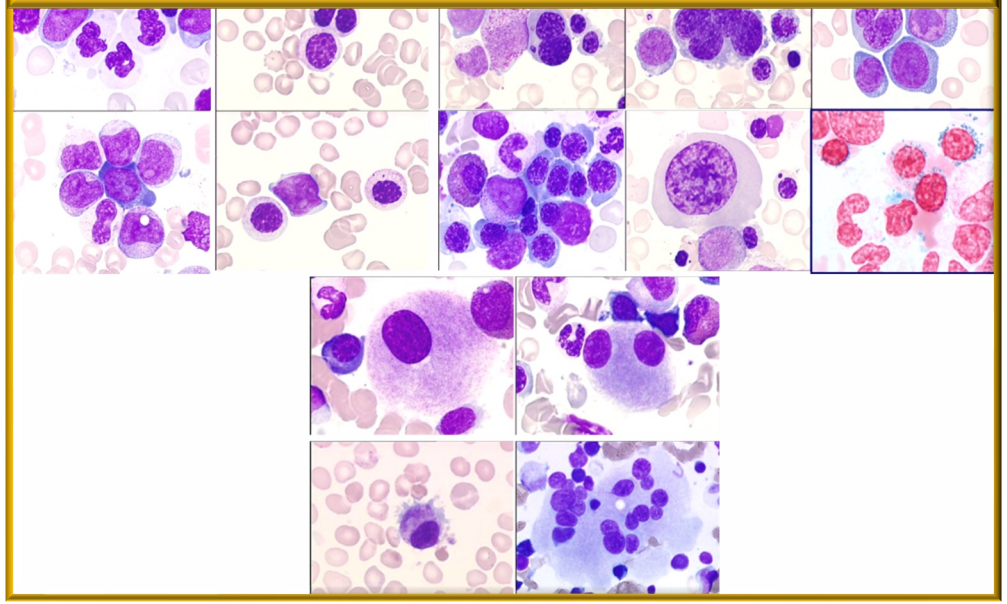
MDS Major Criteria

i. Dysplasia of at least 10% of cells in one or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in ring sideroblasts (RS) of ≥ 15% (or ≥ 5% in the presence of a SF3B1 mutation)

ii. An increase in myeloblasts of 5-19% in dysplastic BM smears or 2-19% myeloblasts in peripheral blood smears

iii. An MDS-related (5q-, -7, complex….) karyotype

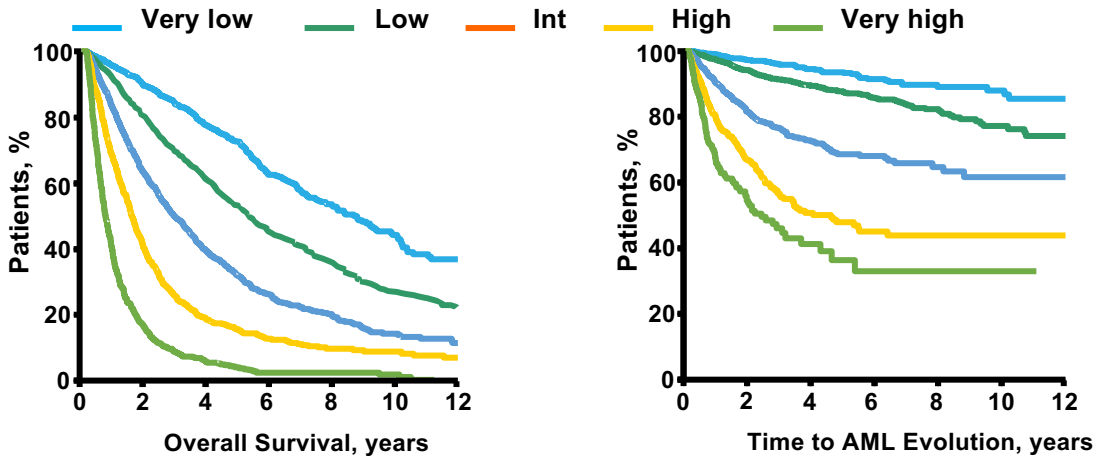
At least one of these major MDS criteria has to be met (together with pre-requisite-criteria) to arrive at the diagnosis of MDS



Valent, et al. *Oncotarget*. 2017 Sep 26; 8(43): 73483–73500.

Risk Groups for the IPSS-R

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
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



Adapted from Greenberg PL, et al. *Blood.* 1997;89:2079-2088.

Development of IPSS-M: Model Development Steps 1 and 2

Step	Development
Encoding for clinical and molecular variables	▪ Continuous encoding of clinical variables; linear function for BM blasts, Hg ▪ Platelet values capped at 250 x 10^9/L; ANC not included ▪ Maintained 5 IPSS-R cytogenetic categories ▪ Gene mutations incorporated as binary variables aside from *TP53* allelic state and *SF3B1* subsets accounting for comutations
Determination of independent IPSS-M prognostic variables	▪ Model fit with a Cox multivariable regression adjusted for confounder variables (age, sex, primary vs therapy-related MDS) ▪ Continuous clinical parameters ▪ IPSS-R cytogenetic categories ▪ 17 genetic variables from 16 main effect genes ▪ 1 genetic variable from 15 residual genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*)

Bernard. ASH 2021. Abstr 61.

Development of IPSS-M: Association Between Gene Mutations and Clinical Endpoints in Discovery Cohort

- After adjusting for age, sex, MDS type (primary vs therapy related), and IPSS-R raw score, multiple genes were associated with adverse outcomes including LFS (14 genes), OS (16 genes), and AML transformation (15 genes)[1]
- Strongest associations found with:
  - *TP53* multi-hit (multiple mutations, mutation with deletion or copy-neutral LoH)[2] (7% of patients)
  - *MLL* partial tandem duplication (2.5% of patients)
  - *FLT3* mutations (1.1% of patients)

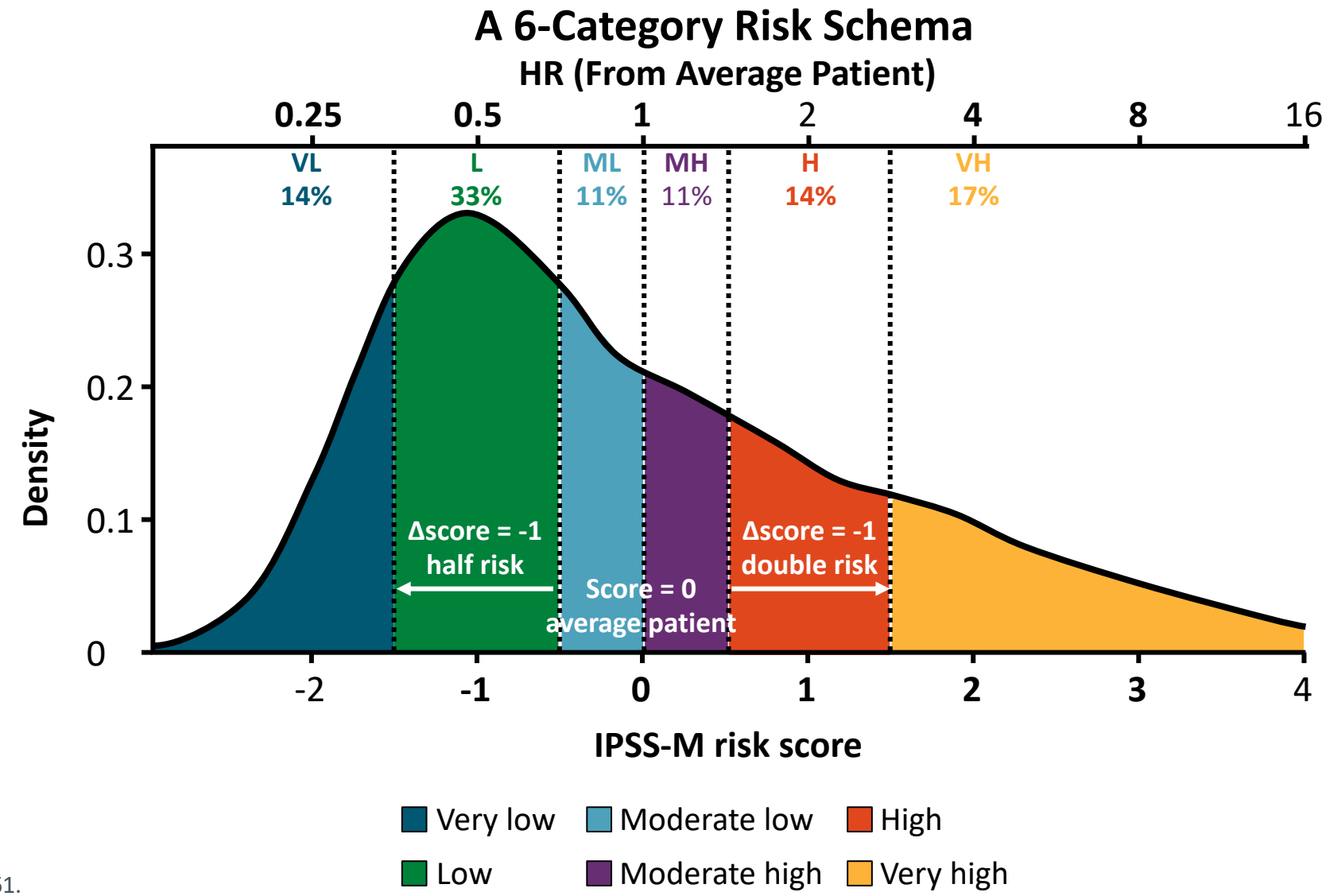
1. Bernard. ASH 2021. Abstr 61. 2. Bernard. Nat Med. 2020. 26:1549.

Development of IPSS-M: Association Between Gene Mutations and Clinical Endpoints in Discovery Cohort

- *SF3B1* mutations were associated with favorable outcomes, modulated by pattern of comutations
  - *SF3B1*^{5q}: concomitant isolated del(5q) (7%)
  - *SF3B1*$^{\beta}$: co-occurrence of mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2* (15%)
  - *SF3B1*$^{\alpha}$: any other *SF3B1* mutations

Bernard. ASH 2021. Abstr 61.

The IPSS-M Risk Categories

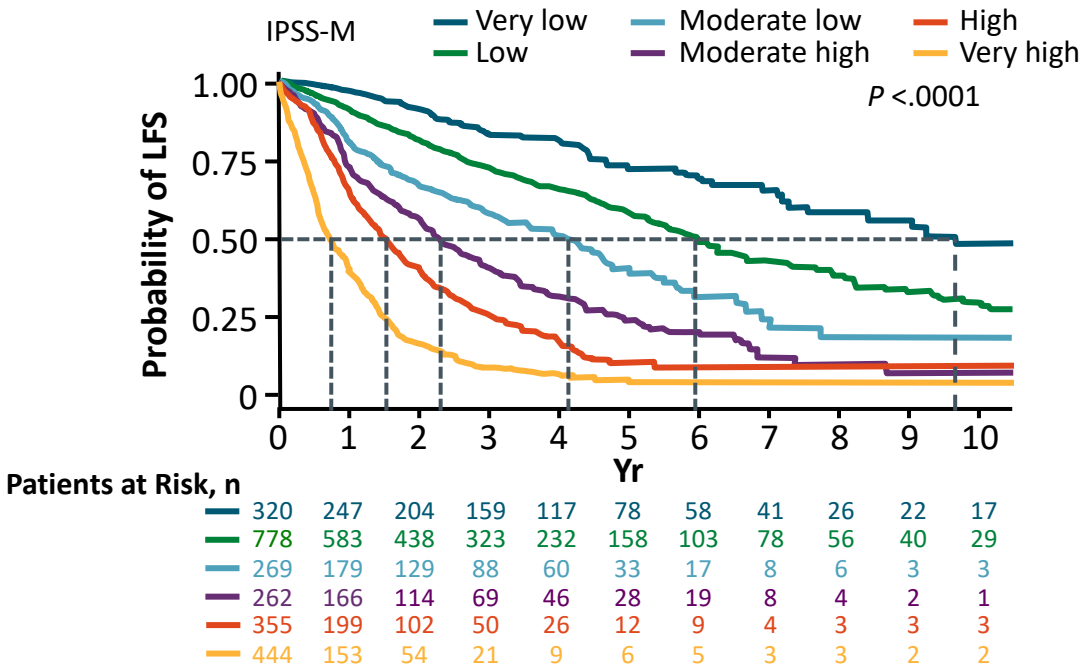


Bernard. ASH 2021. Abstr 61.

Molecular IPSS for MDS

- Discovery cohort: diagnostic MDS samples (N = 2957) with <20% blasts and WBC <13 x 10^9/L were profiled for mutations in 156 driver genes
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders

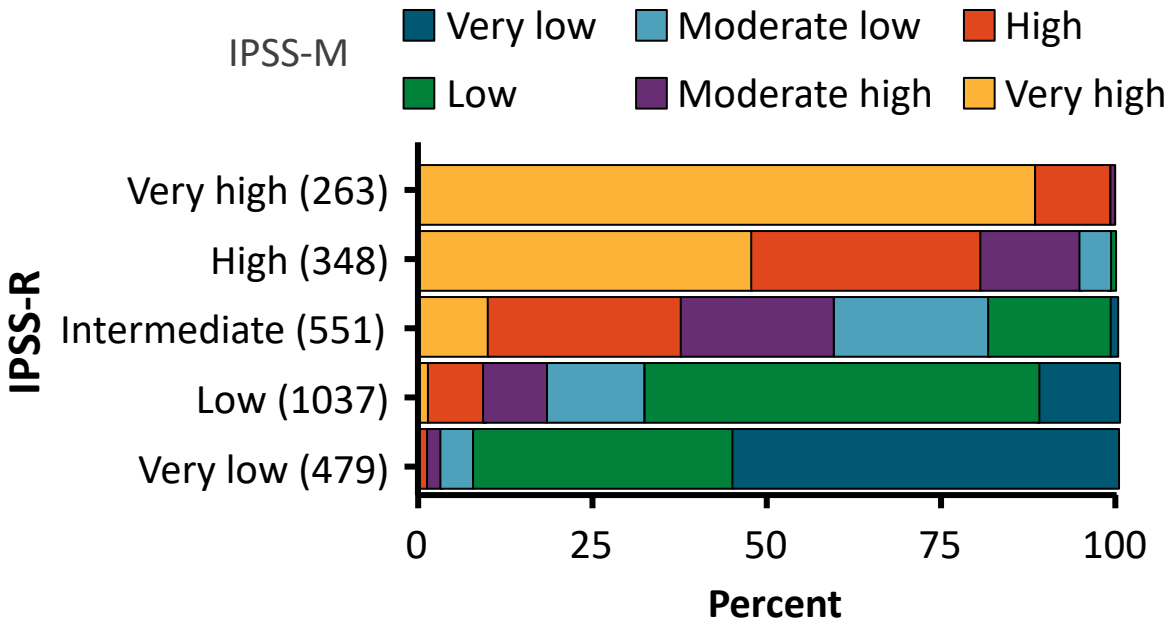
Leukemia-Free Survival



Bernard. ASH 2021. Abstr 61.

Restratification of Patients From IPSS-R to IPSS-M Categories

- 46% (n = 1,223) of patients were restratified
- 7% (n = 196) of patients were restratified by more than 1 strata



Management of Lower-Risk MDS

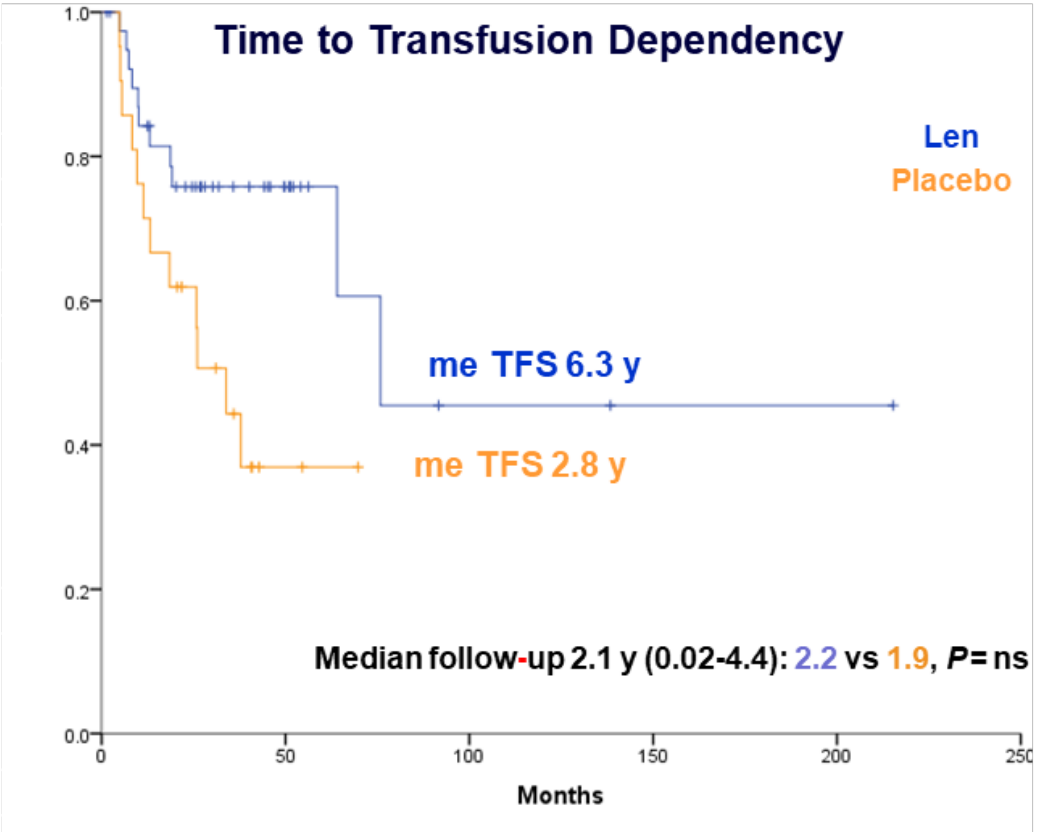
Lenalidomide in MDS

- Lenalidomide is standard of care for lower risk MDS with del(5q)[1,2]
  - Transfusion independence by IWG (67%)
  - 90% of patients respond within 3-4 month and duration of response is almost 3 years
  - MDS-004 supports 10 mg as appropriate starting dose
    - Higher TI for 10 mg
    - Greater proportion of cytogenetic responses vs 5 mg (41% vs 17%)
    - No significant differences in hematological toxicity
- MDS-001, MDS-002, and MDS-005 provided evidence that lenalidomide could be a choice for anemia treatment in lower-risk non-del(5q) pts with adequate platelets and neutrophil count[3,4]

1. Fenaux P et al. Blood. 2011;118(14):3765-3776; 2. List AF et al. *N Engl J Med*. 2006;355(14):1456-1465; 3. List AF et al. *N Engl J Med*. 2005;352(6):549-557; 4. Raza A et al. *Blood*. 2008;111(1):86-93; 5. Sekeres MA et al. *J Clin Oncol*. 2008;26(36):5943-5949.

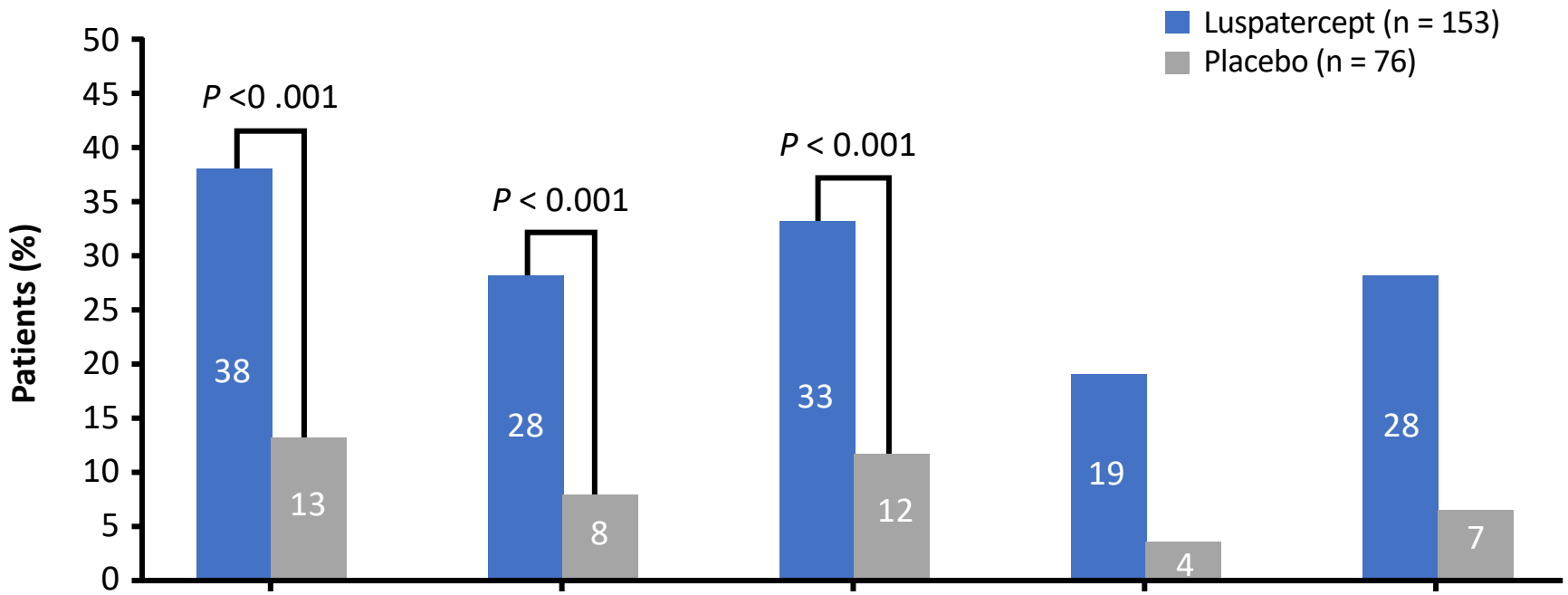
Sintra-REV Trial

	Total (N = 61)	Len (n = 40)	Placebo (n = 21)	*P* value
Age, median (range)	72 (37-89)	72 (37-86)	71 (46-89)	ns
Gender M/F	11/50	8/32	3/18	ns
Hb (g/dL), median (range)	9.8 (7.7-11.7)	9.6 (8.8-11.7)		ns
Neutrophils, median (range)	2.15 x 10^9/L (0.8-14.2)			ns
Platelets, median (range)	243 x 10^9/L (78-706)			ns
% Blasts in PB, median (range)	0 (0-2)	0 (0-1)	0 (0-2)	ns
% Blasts in BM, median (range)	1.5 (0-7)	1.5 (0-5)	2 (0-7)	ns
WHO 2008 classification, n (%)				
RCUD	2 (3.3)	2 (5)	0	ns
RARS	1 (1.6)	0	1 (4.8)	
RCMD	15 (24.6)	10 (25)	5 (23.8)	
MDS with EB-1	3 (4.9)	1 (2.5)	2 (9.5)	
MDS with isolated del(5q)	40 (65.6)	27 (67.5)	13 (61.9)	
IPSS, n (%)				
0	43 (70.5)	29 (72.5)	14 (66.7)	ns
0.5	9 (14.8)	6 (15)	3 (14.3)	
1	9 (14.8)	5 (12.5)	4 (19)	
Cytogenetics				
Del(5q) isolated	56 (93.3)	38 (95)	18 (90)	ns
Del(5q) + 1 Cy abnormality	4 (6.7)	2 (5)	2 (10)	



López-Cadenas F et al. ASH 2020. Abstract 536.

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 P, et al. N Engl J Med 2020;382:140-151.

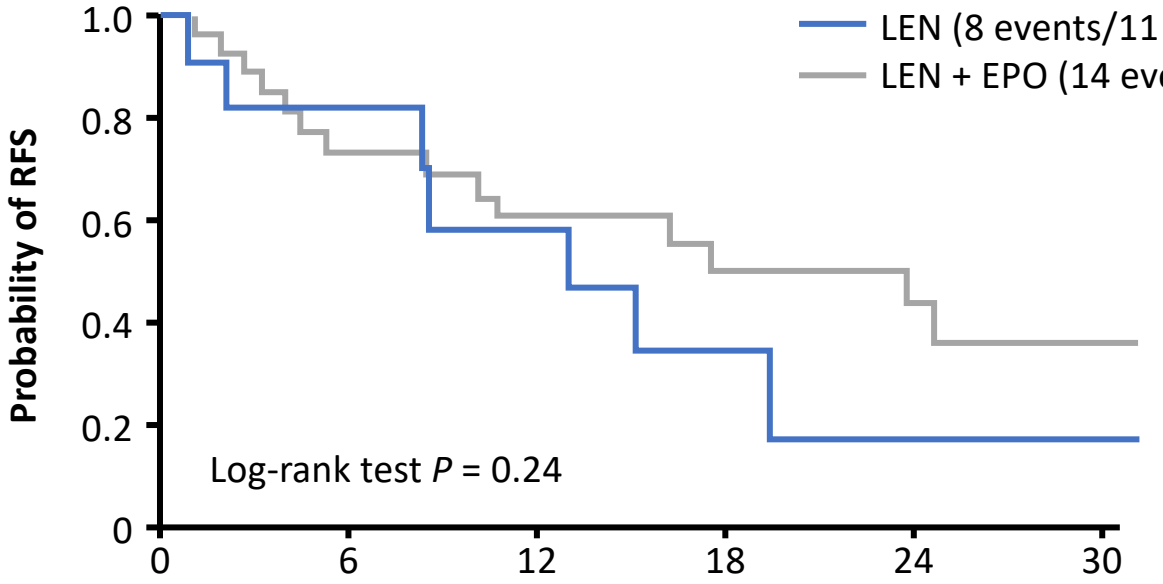
Immunosuppressive Therapy (IST)

- One course ATG ± CSA
- Positive variable for IST response[1,2]
  - Age is the strongest variable for response
  - HLA-DR 15 status
  - Short Duration of disease.
  - Low transfusion burden
  - Trisomy 8
  - Hypoplastic MDS
  - PNH clone
- Negative predictors of response
  - Bone marrow fibrosis
  - Del(5q)
  - SF3B1
- Responses are durable and trilineage responses are observed[3]

1. Sauntharajah Y et al. *Blood*. 2002;100(5):1570-1574; 2. Sloand EM et al. *J Clin Oncol*. 2008;26(15):2505-2511; 3. Sloand E et al. ASH 2004. Abstract 1431.

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

Randomized, Phase III trial of patients with Low- or Intermediate-1 risk by IPSS; symptomatic anemia either untransfused with hemoglobin < 9.5 g/cL 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

- There was no statistically significant difference in the frequency of Grade ≥ 3 non-hematologic AEs between treatment arms
- The toxicity associated with LEN and EPO alfa was similar to treatment with LEN alone

List AF, et al. J Clin Oncol 2021;39:1001-1009.

Low-Dose HMAs in LR-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
CCyR	25	6	.12
PCyR	36	19	
CCyR + PCyR	661	25	.02

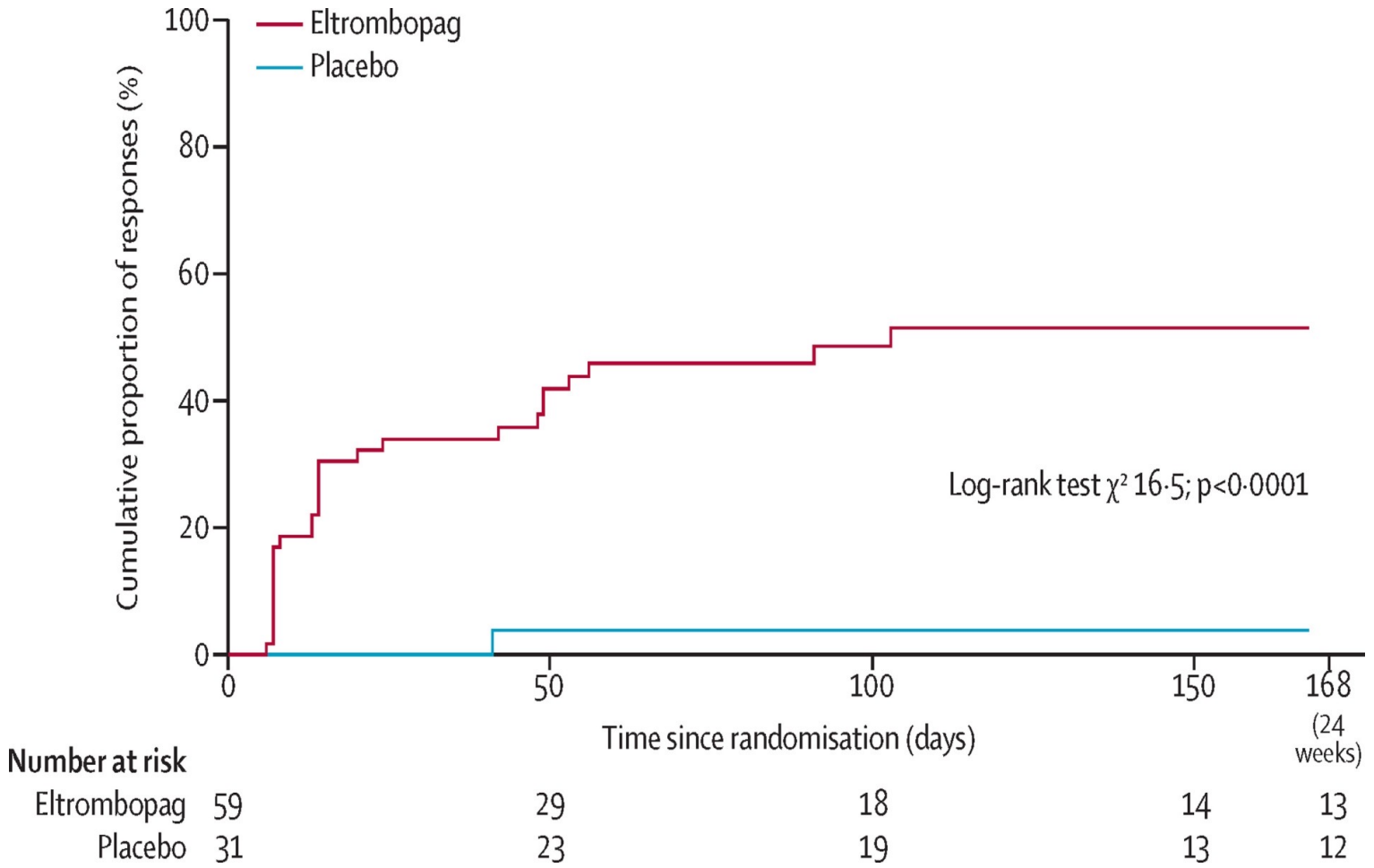
Response,* %	Decitabine (n = 70)	Azacitidine (n = 39)	*P* value
Blasts ≥5%	(n = 21)	(n = 11)	
ORR	100	36	<.001
CR	52	18	.06
Blasts <5%	(n = 45)	(n = 27)	
HI – ≥1 lineage	36	48	.29
HI – All lineages	22	26	.72
TI at response	32	16	.20

*Median treatment cycles (range): 9 (1-41)

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

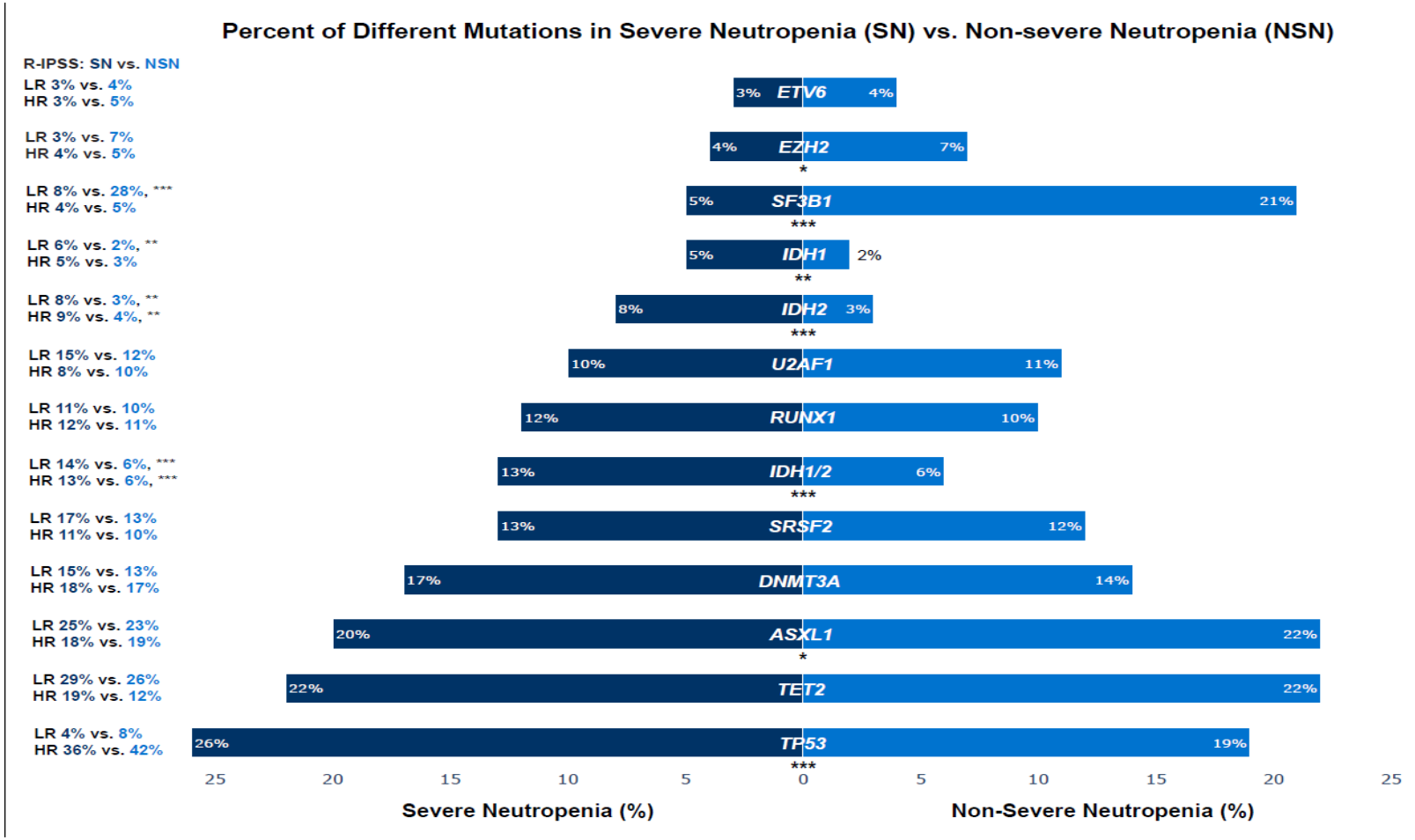
Jabbour EJ et al. ASH 2016. Abstract 226.

Eltrombopag Responses



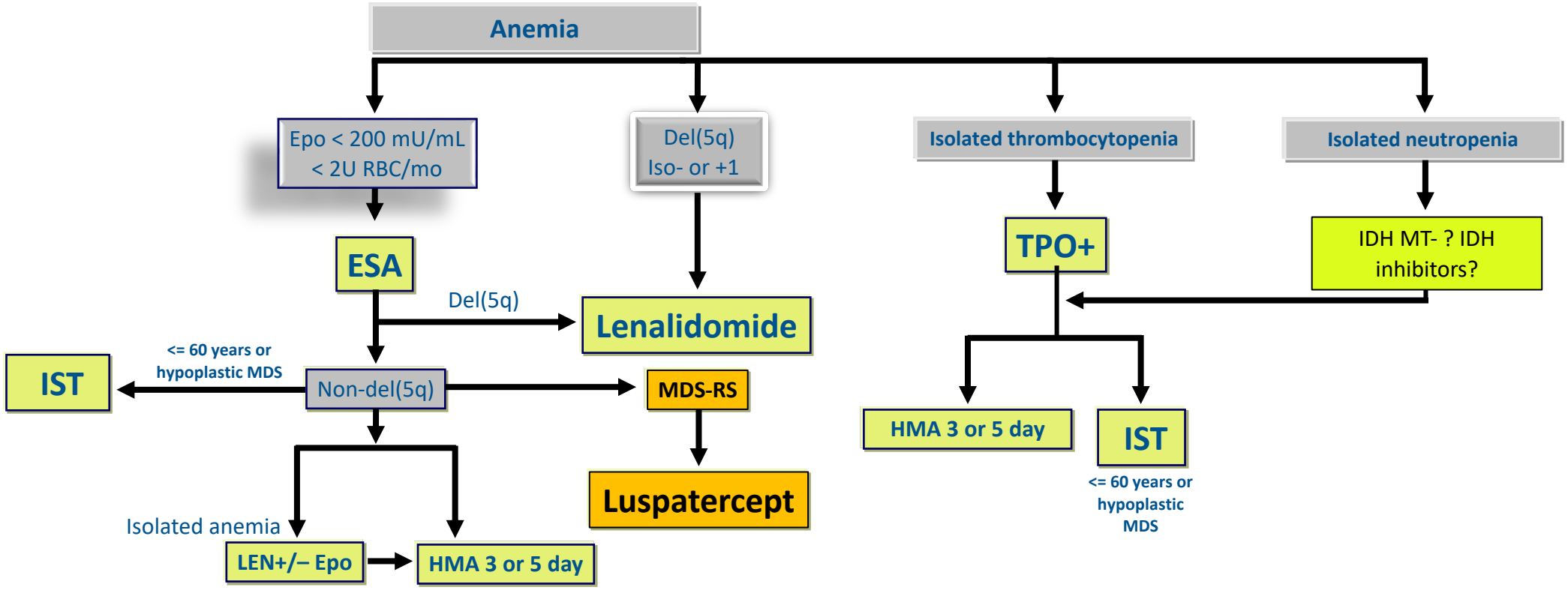
Oliva EN et al. *Lancet Haematol.* 2017;4(3):e127-e136.

IDH Mutations are Enriched in Myelodysplastic Syndrome Patients with Severe Neutropenia: A Potential Targeted Therapy



Komrokji et al. ASH 2021

How Do I Manage LR-MDS in 2022



*SGM, somatic gene mutation.

- **Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features.**
- **Iron chelation should be considered in patients with evidence of iron overload.**

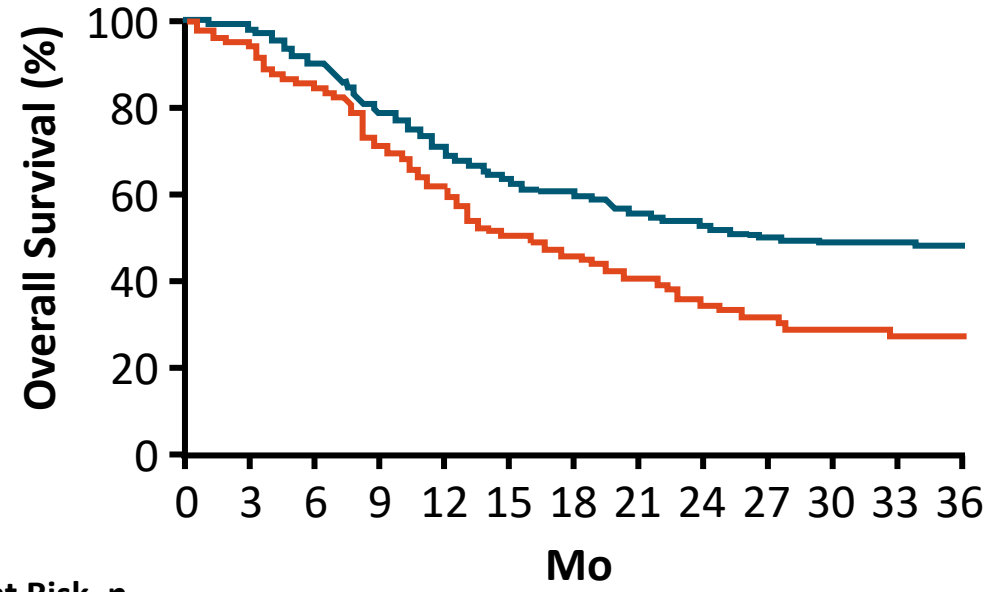
Adapted from Volpe VO, Komrokji RS. Ther Adv Hematol 2021;12:1-10.

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

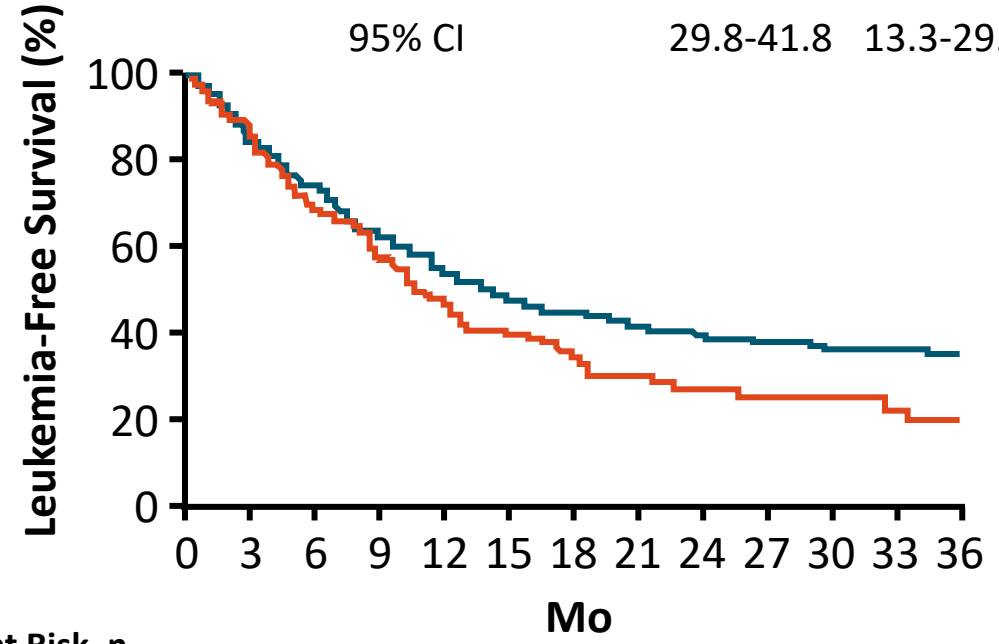


Patients at Risk, n

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

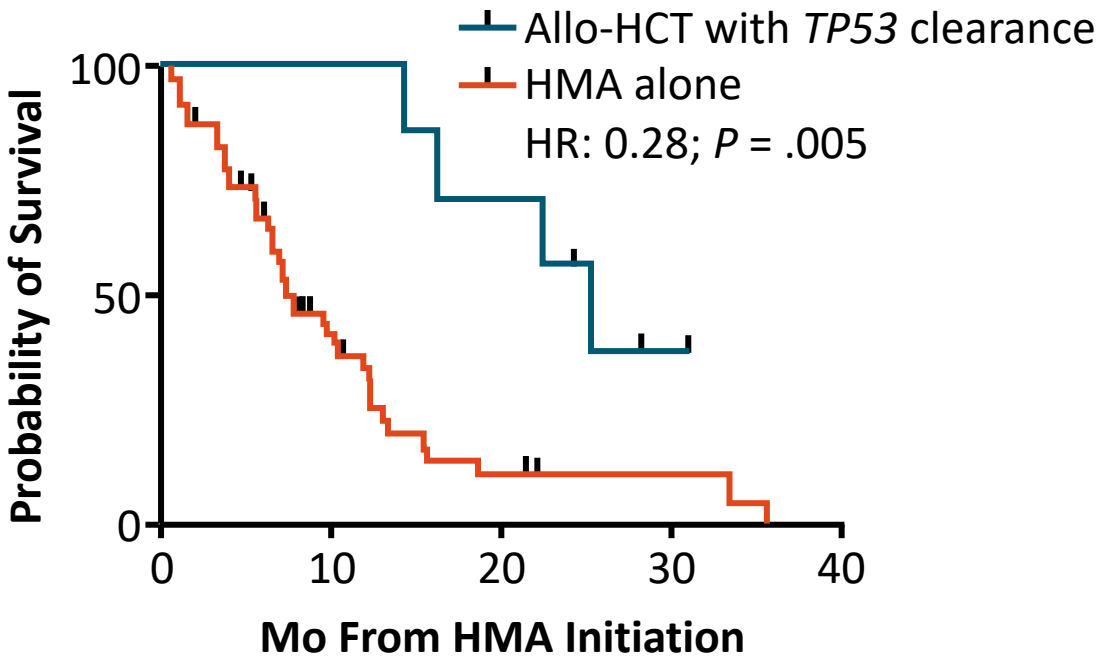


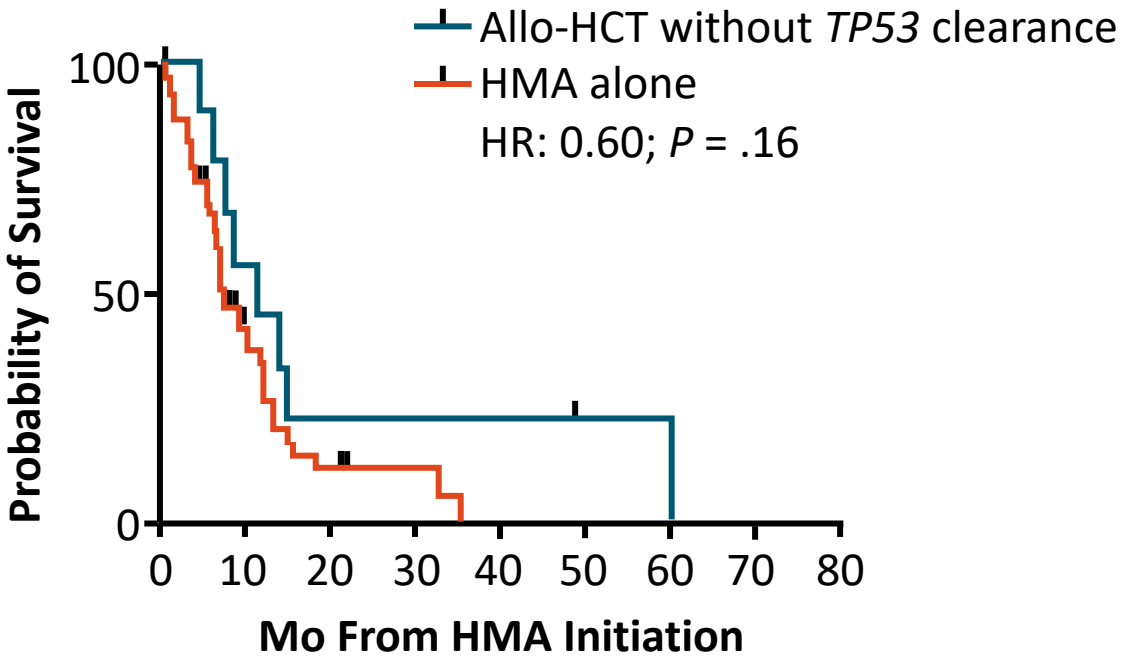
Patients at Risk, n

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.

Baseline and Serial Molecular Profiling Predicts Outcomes With HMAs in MDS





Proposed treatment algorithm for *TP53* mutated MDS:

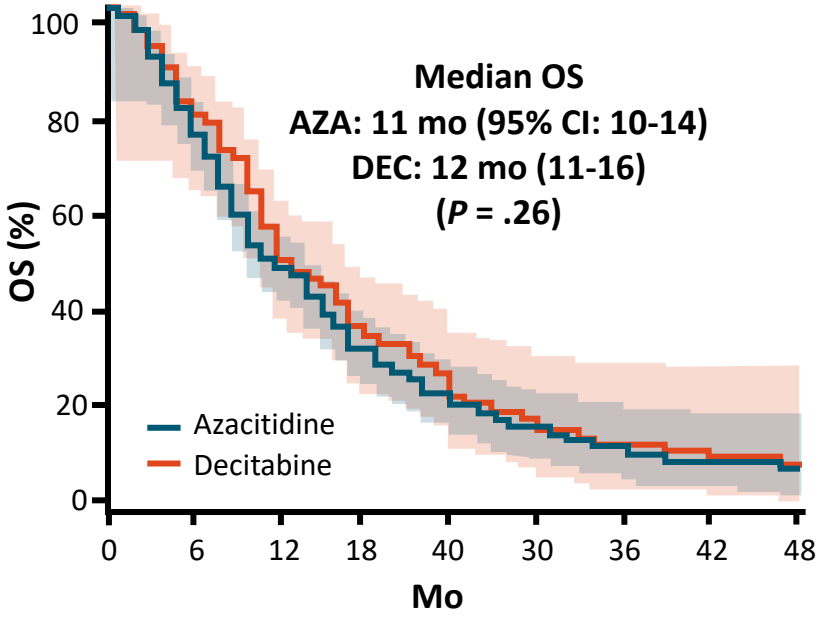
TP53 mutated, higher-risk MDS → Frontline therapy with a hypomethylating agent → Serial next generation sequencing to assess molecular response

- 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.

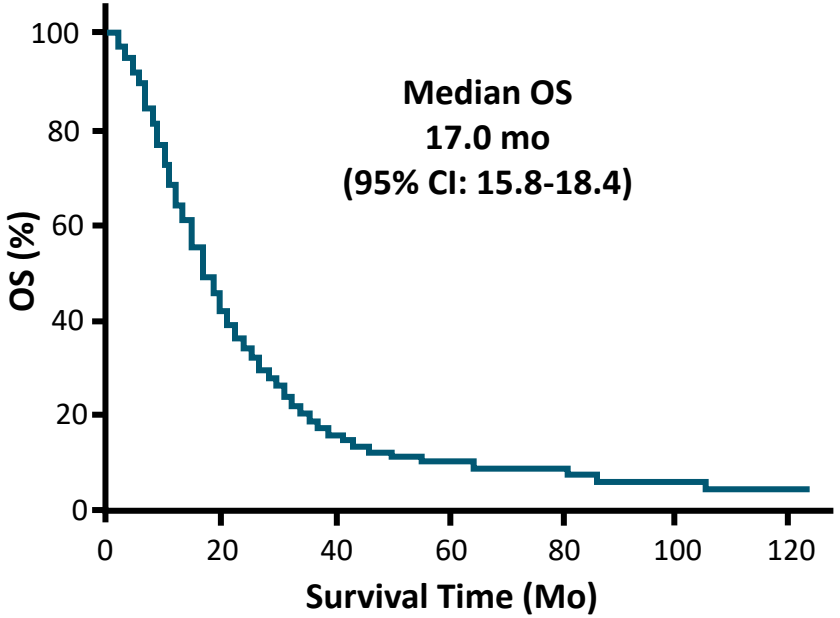
Survival of Patients With HR-MDS Remains Poor Despite Use of HMAs

OS: AZA vs DEC



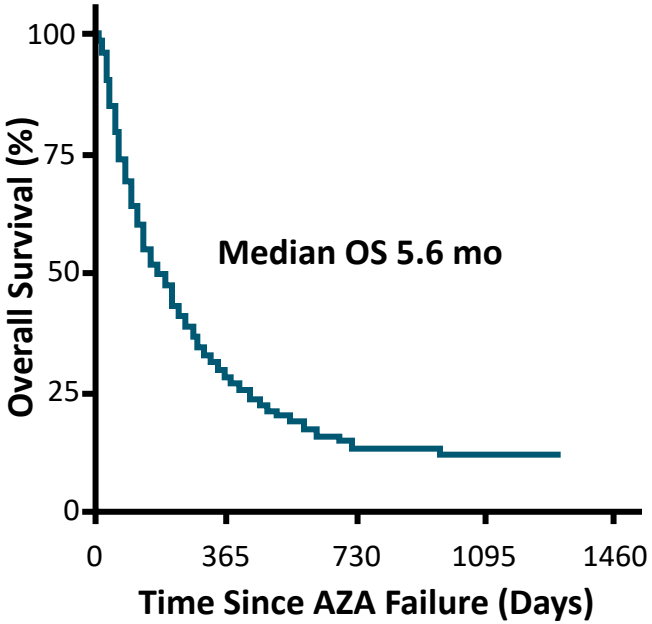
532 patients ≥66 yr at diagnosis who received ≥10 days of HMA therapy

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 Study of Oral HMA ASTX727 (Cedazuridine/Decitabine) vs IV Decitabine

- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver
- Cedazuridine is a CDA inhibitor

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC N	IV DEC Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (% CV)
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.

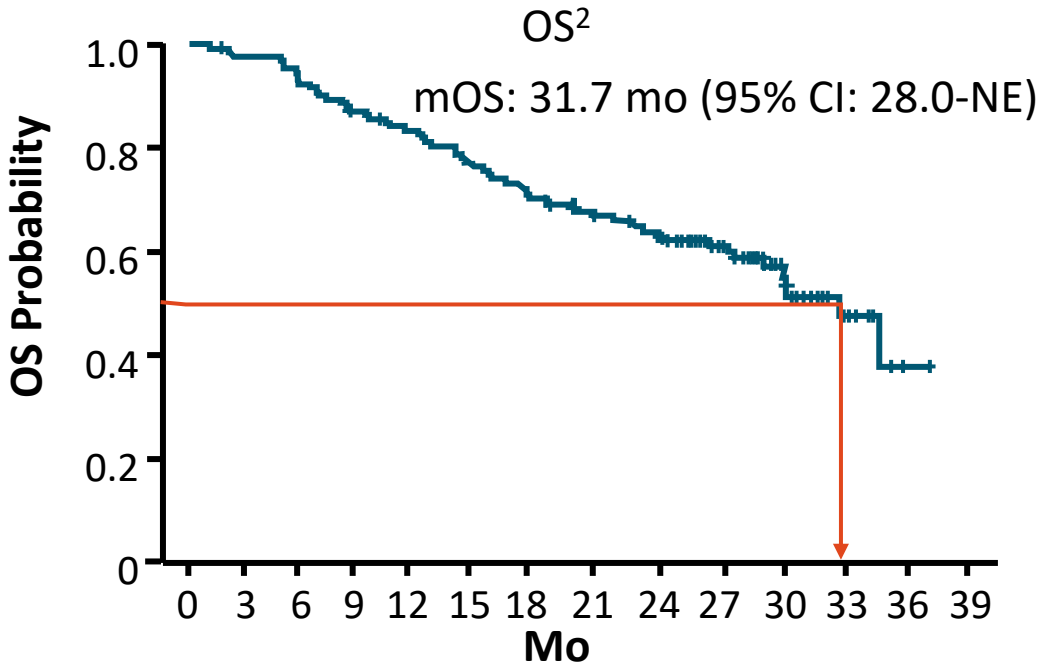
Garcia-Manero. ASH 2019. Abstr 846. Savona. ASH 2020. Abstr 1230. Savona. MDS 2021. Abstr P48.

ASCERTAIN: Update on Efficacy and Safety of Oral Decitabine/Cedazuridine in Patients With MDS and CMML

Response Category[1,2]	Treated Patients (N = 133)
CR, n (%)	29 (22)
PR, n (%)	0
mCR, n (%)	43 (32.3)
▪ mCR with HI	22 (16.5)
HI, n (%)	10 (7.5)
▪ HI-erythroid	2 (1.5)
▪ HI-neutrophils	1 (0.8)
▪ HI-platelet	7 (5.3)
Overall response (CR + PR + mCR + HI), n (%)	82 (61.7)
RBC transfusion independence, n/N (%)*	27/53 (51)
Platelet transfusion independence, n/N (%)*	6/12 (50)

*# patients TI/# patients TD at baseline.

- Median CR duration: 14.0 mo (range: 2-29)
- Median duration of best response: 12.7 mo (range: 1-33)
- Number of patients proceeding to HCT: 34 (26%)
- Leukemia-free survival: 29.1 mo (95% CI: 22.1-NE)



1. Savona. ASH 2020. Abstr 1230. 2. Savona. MDS 2021. Abstr P48.

Principal Targeted Therapies Emerging/Available in MDS

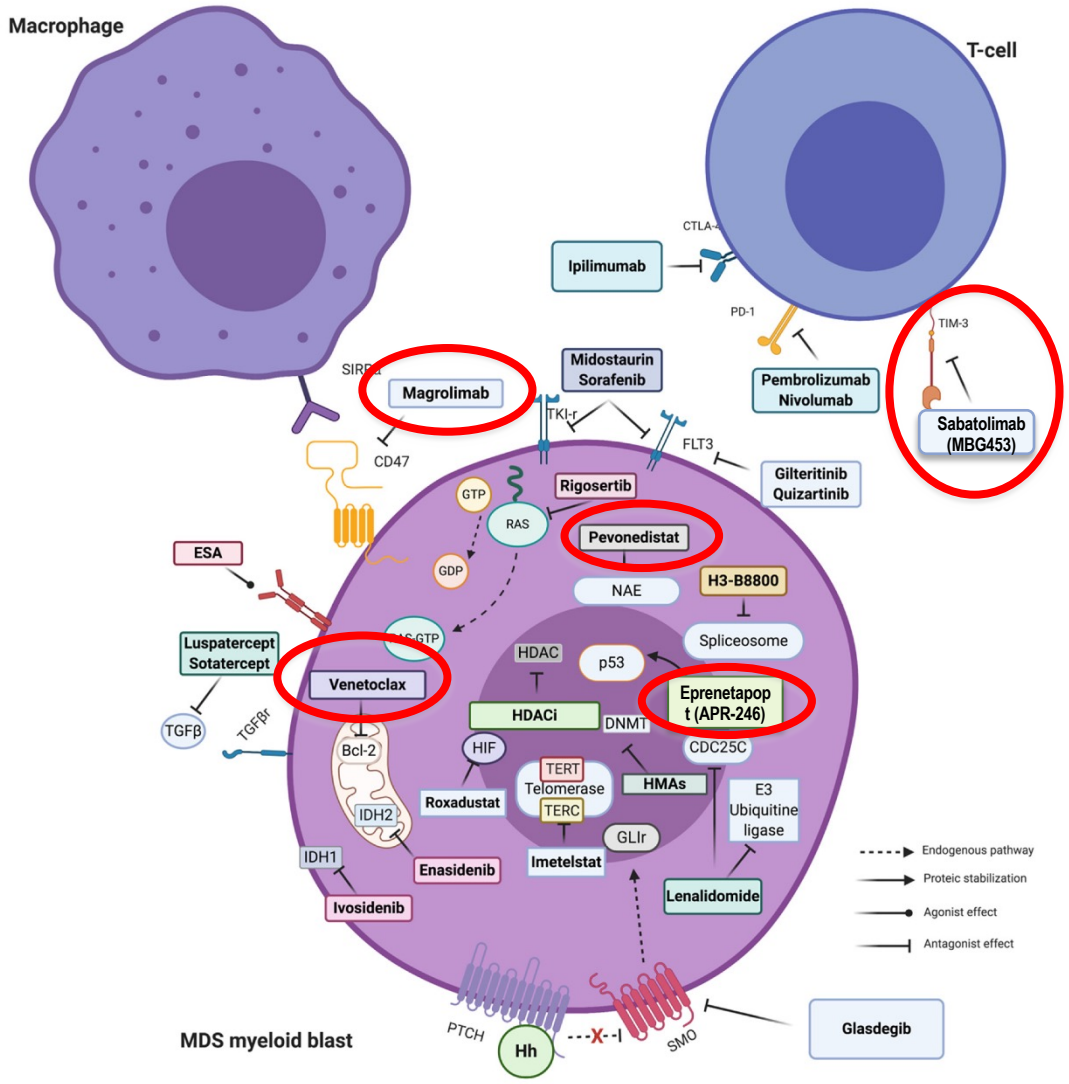


Figure from Pagliuca S, et al. *Cancers*. 2021; 13(4):784.

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

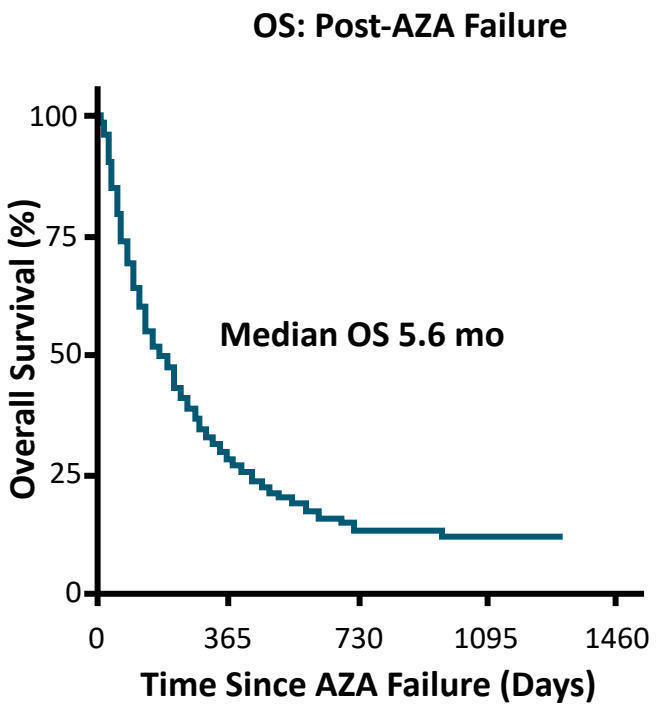
Best Response, %	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
ORR	77	40	<.005
▪ CR	34	13	
▪ mCR	37 (62% + HI)	11	
▪ PR	3	1	
▪ HI	3	15	
***ASXL-1* mut**	**(n = 16)**	**(n = 106)**	
ORR	87	32	<.005
▪ CR	44	8	
***TP53* mut**	**(n = 12)**	**(n = 137)**	
ORR	75	44	.038
▪ CR	25	17	.47

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	

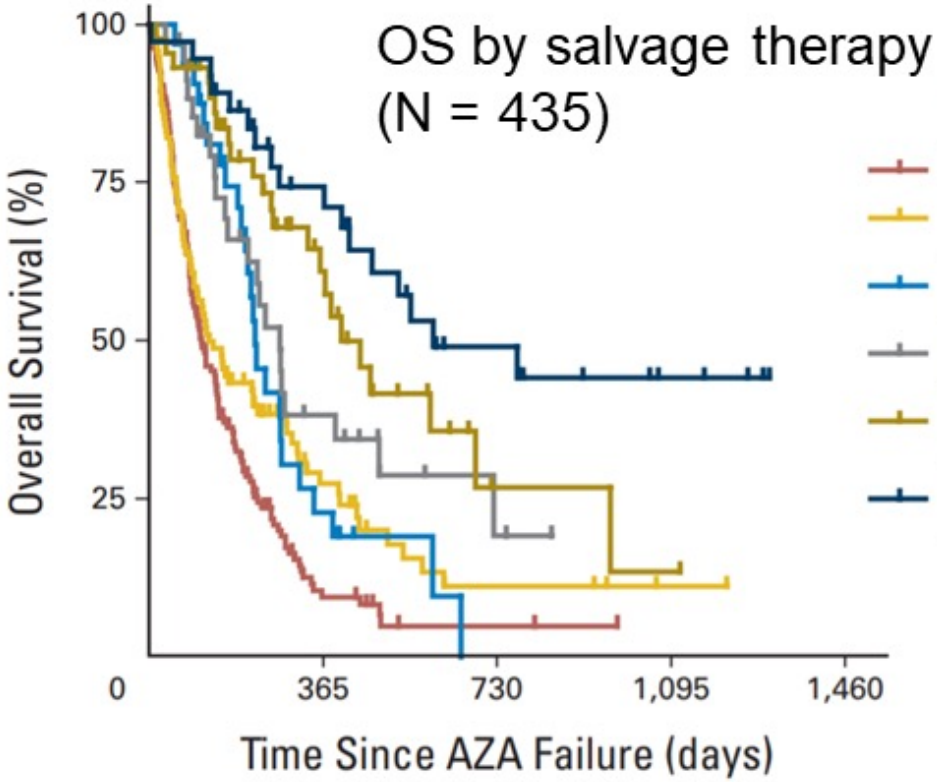
*Median time from diagnosis to treatment was 1 mo in both arms.
†Patients who went on to AHCST.

Komrokji. ASH 2021. Abstr 536.

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

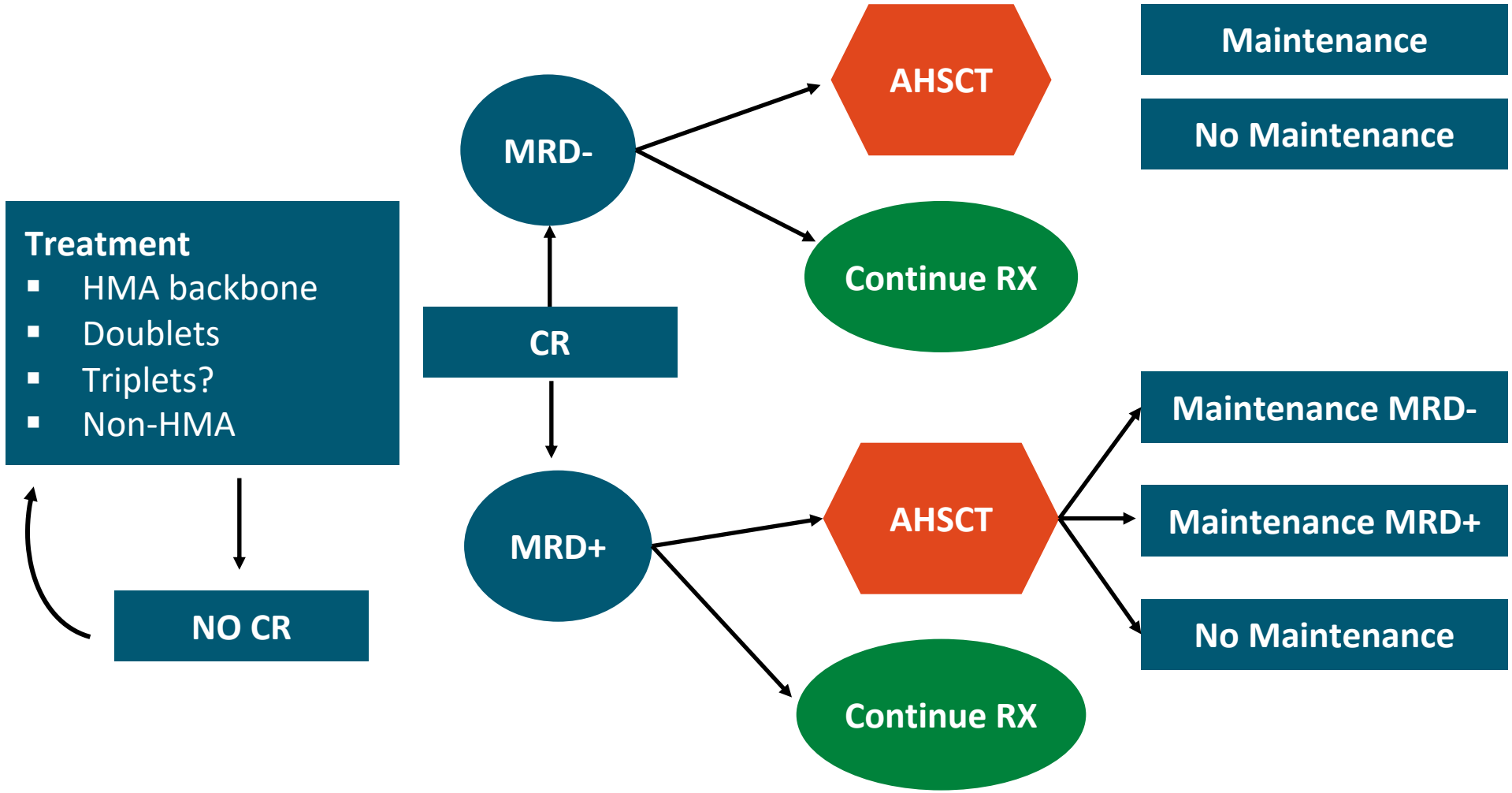
Venetoclax and HMA in Higher-Risk MDS: Efficacy in R/R MDS Population

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.

Total Therapy in HR-MDS



Thank You

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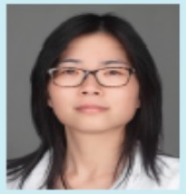
MEET THE TEAM


Dr. Rami Komrokji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Dr. Eric Padron


Dr. David Sallman


Dr. Kendra Sweet


Dr. Sara Tinsley

Moffitt MDS team: Only perfect counts !!!

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