Novel Therapeutic Strategies for MDS Based on Molecular Profile

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Myelodysplastic Syndromes (MDS) in the United States

10-20K **New cases per year, although some estimates are much higher (40-50 K)**

1 in 3 patients will progress to AML

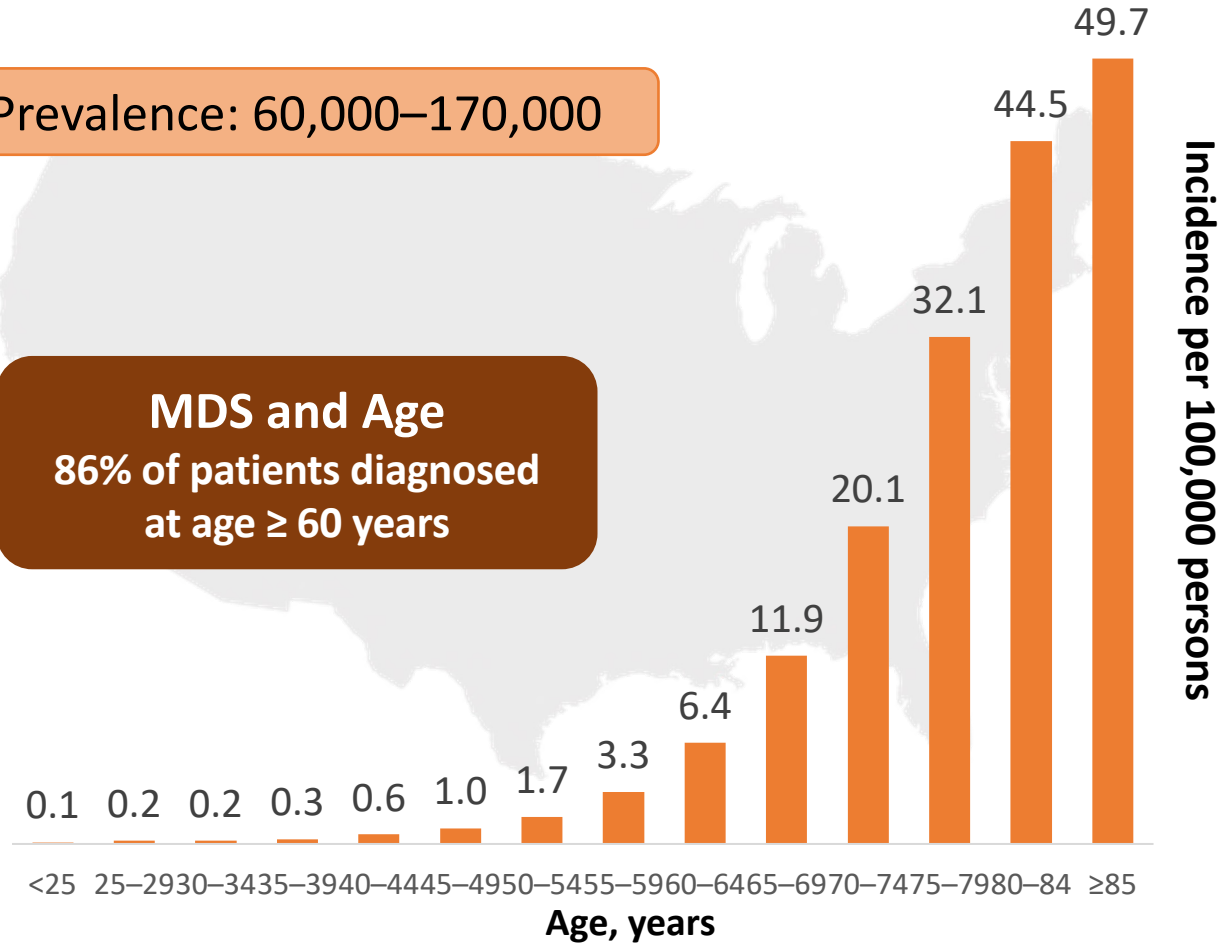
Approximately 5%-10% of cases occur after exposure to previous radiation/chemotherapy

More than 90% of patients harbor somatic mutations

Anemia is the most common clinical feature

Prevalence: 60,000–170,000

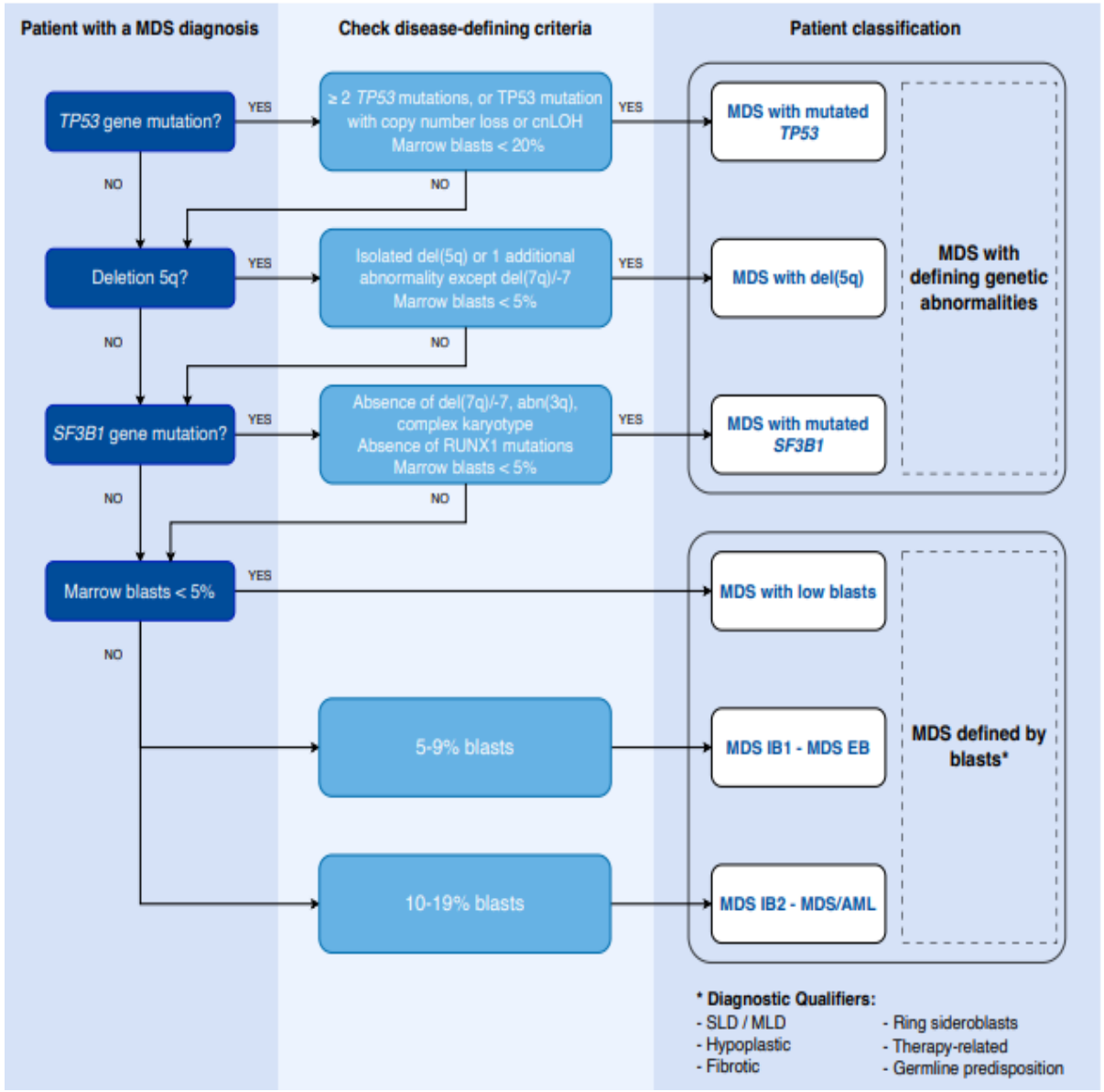
MDS and Age
86% of patients diagnosed at age ≥ 60 years



AML = Acute Myeloid Leukemia

Ma X. *Am J Med*. 2012;125(7):S2–S5; Cogle CR. *Curr Hematol Malig Rep.* 2015;10(3):272-281; American Cancer Society. www.cancer.org. Accessed 10/24/23. Leukemia and Lymphoma Society. www.lls.org Accessed 10/24/23.

Harmonized WHO/ICC 2022 classification



Conceptual classification of MDS: RSK classification

Chronic phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB

Accelerated phase MDS

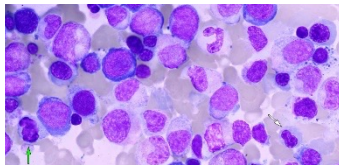
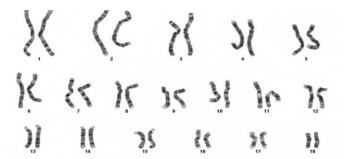
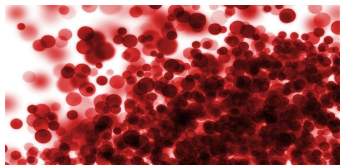
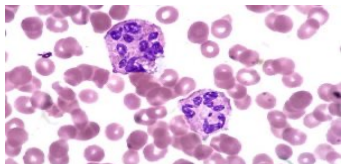
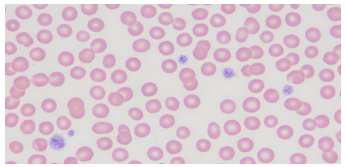
- MDS-EB (5-19% myeloblasts) (cutoff to be refined)
- Bi-allelic *TP53* MDS
- MDS-f

AML-MDS related (AML-MR)

- ≥20% myeloblasts (cutoff to be refined) with prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations.

Komrokji et al, Manuscript submitted Lancet Hematology

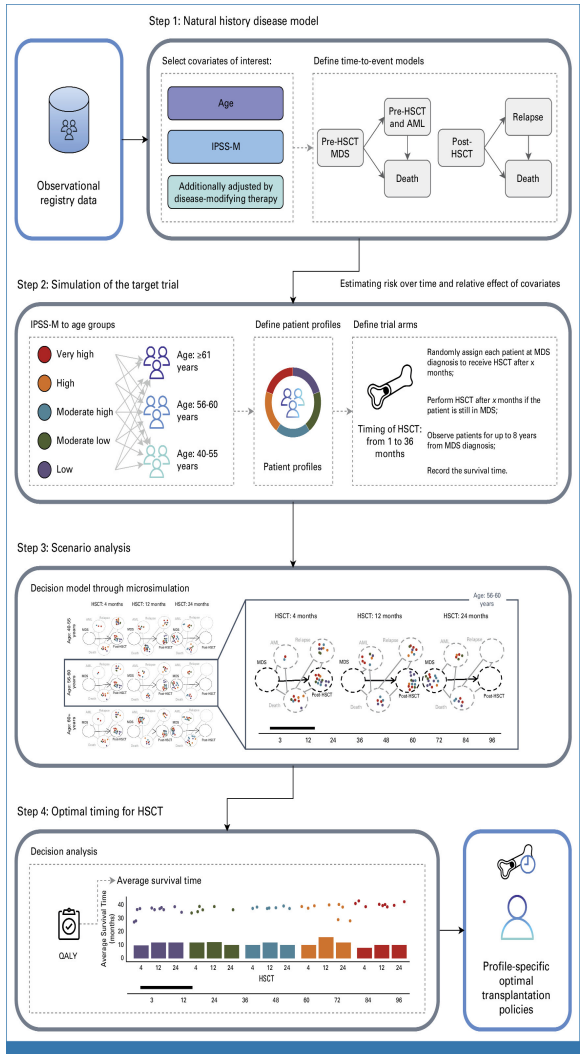
Risk stratification and clinical decisions in MDS – IPSS-M

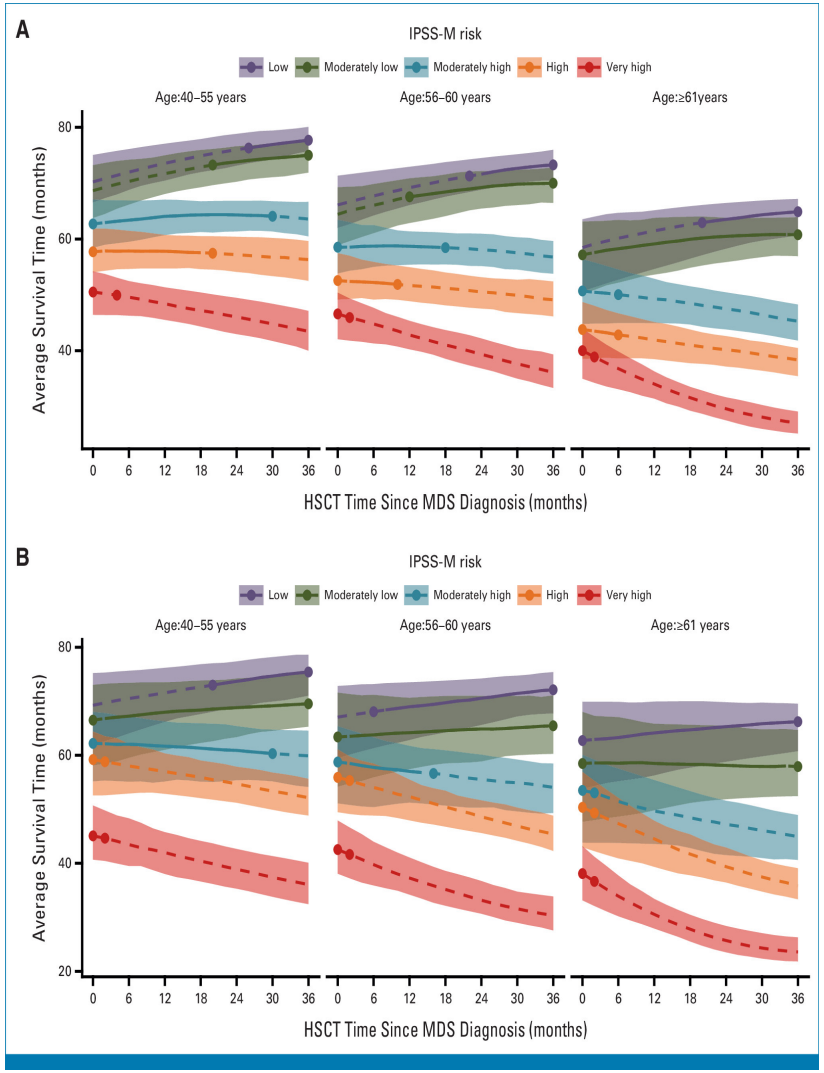
Diagnosis[1]	Classification[1]	Incidence (%)[1]	Median OS (yrs)[1]	Progression risk (yrs)*,[1]	Treatment goal[2]	Current SoC[2]
	Very low *(Very low/low)*	14	10.6	2.8	Hematologic improvement (lower risk of infection & bleeding)	Transfusion ESAs Watch & wait
	Low *(Very low/low/int)*	33	6.0	5.1		
	Moderate low *(Low/int)*	11	4.6	11.4	?	
	Moderate high *(Low/int/high)*	11	2.8	18.9	Alter disease natural history (higher risk of infection & bleeding)	HMAs/ICT +/- ASCT
	High *(Int/high/very high)*	14	1.7	29.2		
	Very high *(High/very high)*	17	1.0	42.8		

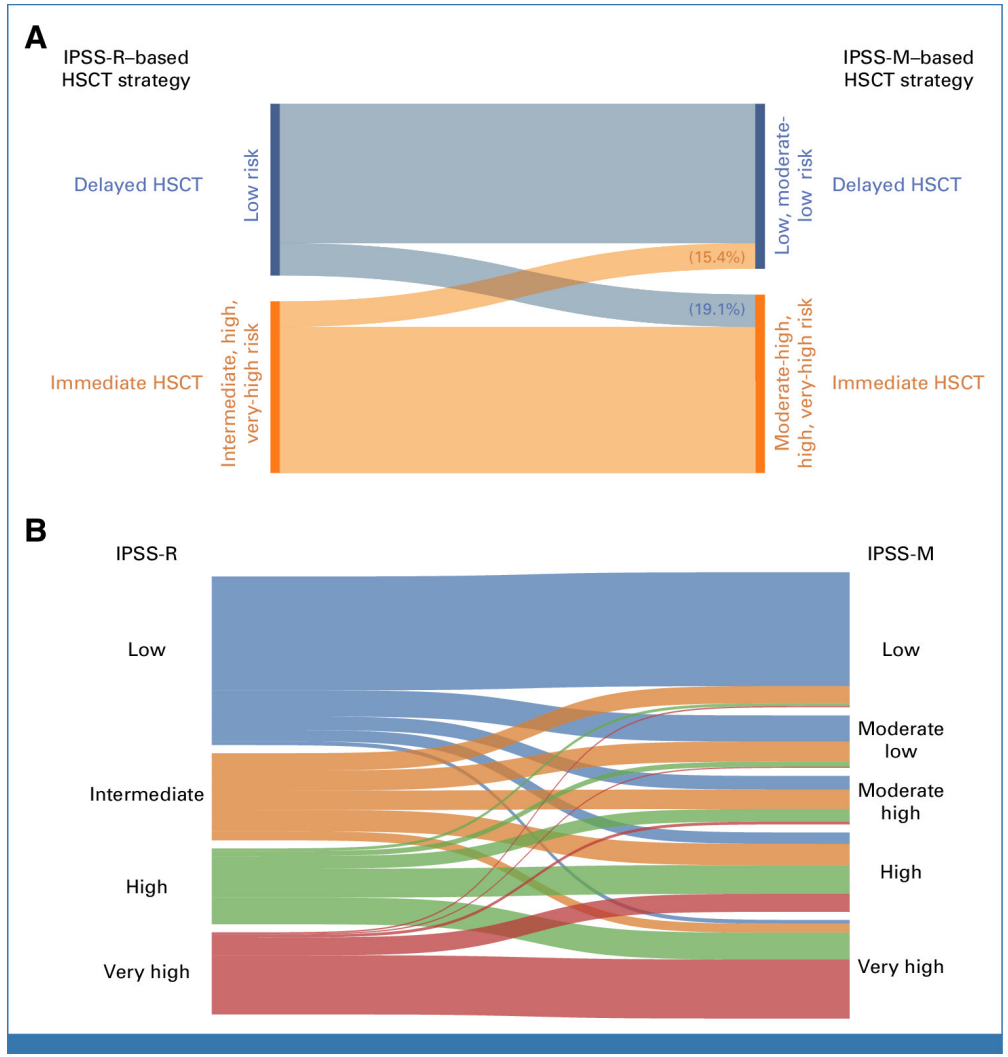
* 4 years

1. Bernard E, *et al. NEJM Evid* 2022; **1**:7; 2. Fenaux P, *et al. Ann Oncol* 2021;**32:1**42–156.

Comparison of IPSS-R versus IPSS-M for timing of Allo-SCT







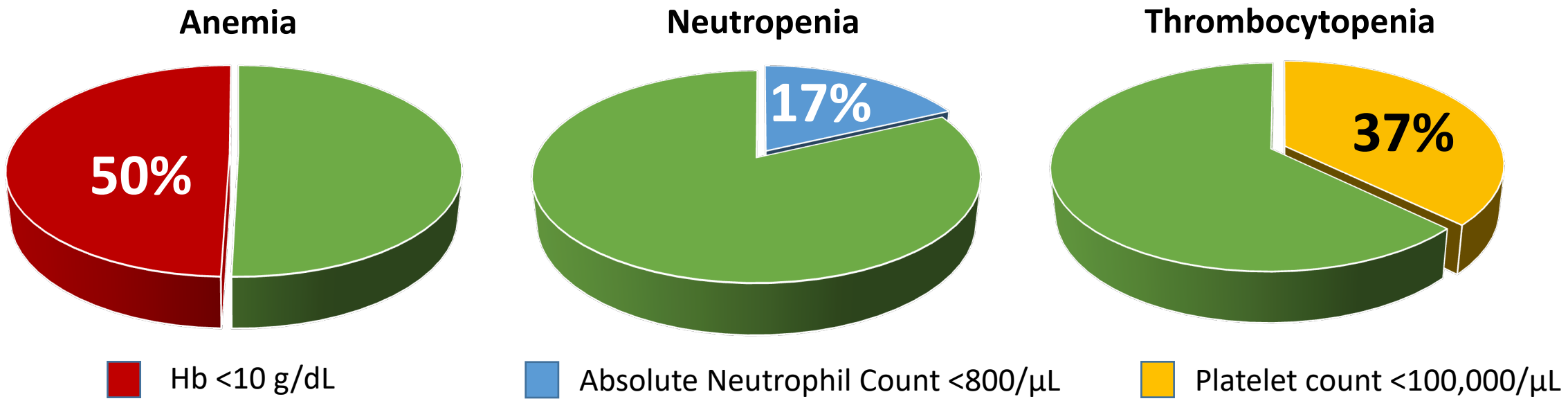
Cristina Tentroi et al *Journal of Clinical Oncology* 2024 May 9

Anemia is the hallmark of lower risk MDS and main indication for treatment

- Lower-risk MDS is characterized foremost by anemia[1]
- 50% of MDS patients will need RBC transfusions during the course of their disease[2]

Frequency of cytopenias in patients with Lower-risk MDS:[3,4]

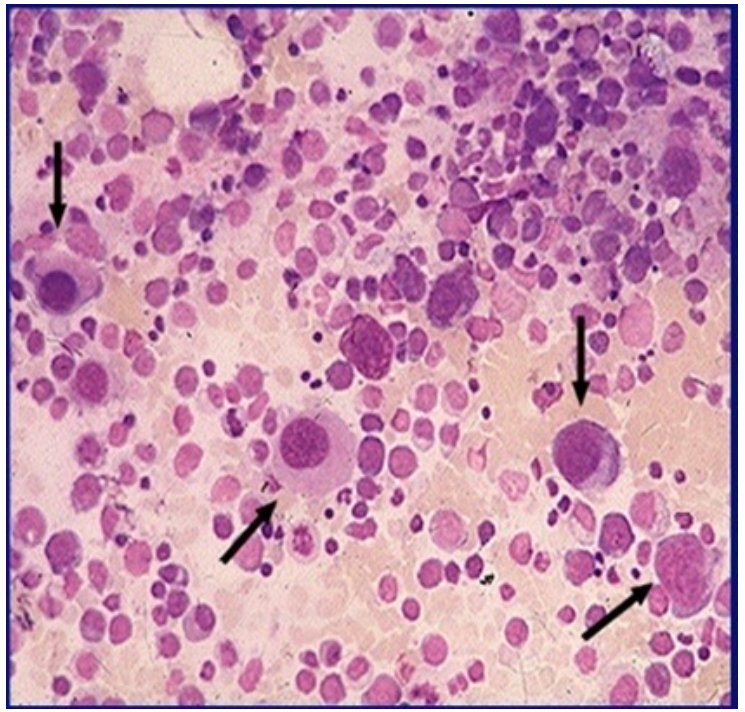
- Data from FISiM Italian registry



1. Fenaux P, et al. *Br J Haematol*. 2019;189(6):1016-1027; 2. Germing U, et al. *Hemasphere*. 2019;3(6):e314; 3. Lanino L, et al. *Am J Hematol*. 2023; 10.1002/ajh.26960; 4. Santini V. *Hemato*. 2022;3(1):153-162

5q- Syndrome: Clinical Characteristics

- First described by Van den Berghe in 1974.
- Isolated del(5q) as sole cytogenetic abnormality
- Female predominance
- Median age at diagnosis: 68 yrs
- Macrocytic anemia, mild leukopenia, normal or increased platelet count.
- Erythroid hypoplasia accompanied by megakaryocytic dysplasia with small oligo- or mononuclear forms, less than 5% myeloblasts are the hallmark features in the bone marrow biopsy and aspirate



Lenalidomide in MDS-del(5q)

Phase II MDS 003 Trial

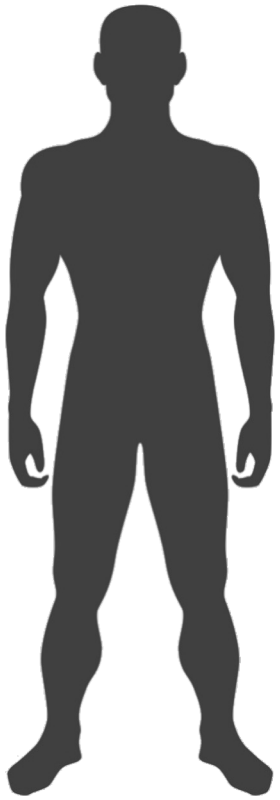
FDA Approval: 12/17/2005

Patient Population

- ✓ *Low-risk, or intermediate-risk MDS (IPSS)*
- ✓ *5q31 deletion ± additional cytogenetic abnormalities*
- ✓ *Transfusion-dependent anemia*

Most Common Grade 3–4 AEs with Lenalidomide

- *Neutropenia (55%)*
- *Thrombocytopenia (44%)*
- *Anemia (7%)*
- *Leukopenia (6%)*
- *Rash (6%)*
- *Fatigue (3%)*
- *Febrile neutropenia (1%)*



Lenalidomide

N = 148

67%

Transfusion Independence by week 24

76%

Total transfusion response by week 24

4.6wk

Median time to response

Long-Term Outcomes

Median Follow-Up 3.2 yrs

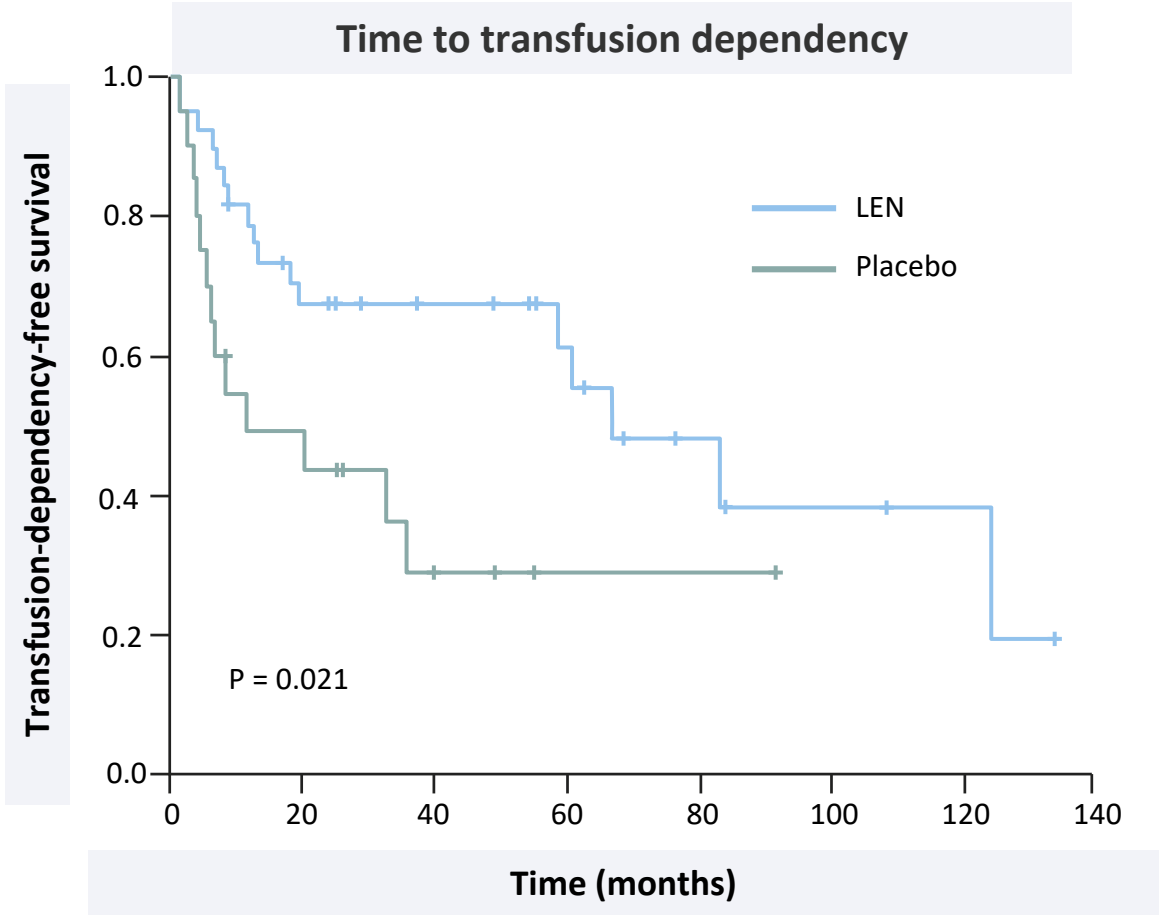
2.2 years

Median duration of transfusion independence

List A, et al. *N Engl J Med*. 2006;355:1456-1465; List A, et al. *Leukemia.* 2014;28(5):1033-1040.

Sintra-REV: Phase 3, multicenter trial investigating LEN versus placebo in non-transfusion-dependent LR-MDS del(5q) patients

- Patients were randomized 2:1 to receive LEN 5 mg/day (n = 40) or placebo (n = 21) on days 1 to 28 of every 28-day cycle
- Treatment phase: 108 weeks
- Follow-up phase: 108 weeks
- Median follow up: 60.6 months (IQR: 32.3–73.9)
- **Primary endpoint** (time to transfusion dependency):
  - LEN – 66.3 months (95% CI: 37.0, 95.5)
  - Placebo – 11.6 months
    (HR 0.414; 95% CI: 0.196, 0.875; P = 0.021)



NCT01243476. Accessed June 2023. https://clinicaltrials.gov/ct2/show/NCT01243476;
Cadenas FL, et al. *Blood.* 2022;140(Suppl. 1):1109–11.

Lenalidomide Discontinuation: HARMONY Alliance study (n=118)

- 42% of patients lost RBC-TI
- 48 patients were re-treated with LEN because of loss of response. Forty-two patients were evaluable for response and 28 of them (67%) achieved RBC-TI again

Prognostic factors for event-free survival on multivariate analysis

Variables	HR	95,0% CI		
		Lower	Upper	p value
Age at diagnosis*	1.04	1.01	1.07	0.005
RBC unit/8 weeks >4 at lenalidomide start	1.28	1.05	1.56	0,013
IPSS-R very low vs low/intermediate	0.33	0,16	0.70	0.004
Lenalidomide cycles ≥12	0.55	0.32	0.95	0.031
Hemoglobin level at lenalidomide stop*	0.82	0.69	0.98	0.028

Crisà *et al ASH 2023*

MDS with mutated *SF3B1*

Cytopenia defined by standard hematologic values

Somatic *SF3B1* mutation

Isolated erythroid or multilineage dysplasia[*]

Bone marrow blasts <5% and peripheral blood blasts <1%

WHO criteria for MDS with isolated del(5q), MDS/MPN-RS-T or other MDS/MPNs, and primary myelofibrosis or other MPNs are not met

Normal karyotype or any cytogenetic abnormality other than del(5q); monosomy 7; inv(3) or abnormal 3q26, complex (≥3)

Any additional somatically mutated gene other than *RUNX1* and/or *EZH2*[†]

[*]RS are not required for the diagnosis.
[†]Additional *JAK2V617F*, *CALR*, or *MPL* mutations strongly support the diagnosis of MDS/MPN-RS-T.

Malcovati et al, Blood, 2020

Anemia Management: Luspatercept

Phase III MEDALIST Trial

FDA Approval: 04/06/2020

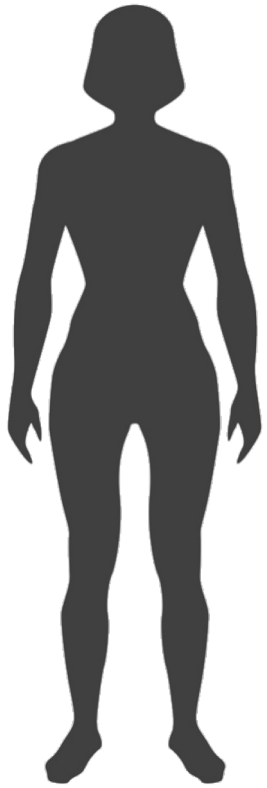
Patient Population

- ✓ *Very-low-risk, low-risk, or intermediate-risk MDS (IPSS-R) with ring sideroblasts*
- ✓ *Receiving regular RBC transfusions*

Most Common Grade 3–4 AEs with Luspatercept

- *Fatigue (5%)*
- *Asthenia (3%)*
- *Back pain (2%)*
- *Nausea (1%), headache (1%), arthralgia (1%), dyspnea (1%), bronchitis (1%), UTI (1%)*

Luspatercept ***N = 153***	***Placebo*** ***N = 76***
38%	**13%**
Transfusion Independence ≥ 8 Weeks (Weeks 1–24)	**Transfusion Independence ≥ 8 Weeks (Weeks 1–24)**
28%	**8%**
Transfusion Independence ≥ 12 Weeks (Weeks 1–24)	**Transfusion Independence ≥ 12 Weeks (Weeks 1–24)**
33%	**12%**
Transfusion Independence ≥ 12 Weeks (Weeks 1–48)	**Transfusion Independence ≥ 12 Weeks (Weeks 1–48)**



***P* < .001**
For All Comparisons

Oral Abstract 915:
Long-Term Data

IPSS-R = Revised International Prognostic Scoring System; RBC = Red Blood Cell; UTI = Urinary Tract Infection
Fenaux P, et al. *New Engl J Med*. 2020;82:140-151.

Luspatercept for Frontline Treatment

Phase III COMMANDS Trial

FDA Approval: 08/28/2023

Patient Population

- ✓ *Very-low-risk, low-risk, or intermediate-risk MDS (IPSS-R) with ring sideroblasts*
- ✓ *Require RBC transfusions*
- ✓ *ESA naïve*

Most Common TRAEs with Luspatercept

- *Diarrhea (17.6%)*
- *COVID-19 (14.8%)*
- *Hypertension (15.9%)*
- *Asthenia (13.7%)*
- *Anemia (12.1%)*

Luspatercept

N = 147

59%

RBC TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (wk 1-24)

Epoetin alfa

N = 154

31%

RBC TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (wk 1-24)

Response Rates from ASH 2023 – Data cut-off 3/31/23

	Luspatercept	Epoetin alfa
Overall, n/N (%)	110/182 (60.4%)	63/181 (34.8%)
SF3B1 mutated, n/N (%)	80/114 (70.2%)	33/101 (32.2%)
SF3B1 non-mutated, n/N (%)	29/65 (44.6%)	26/72 (36.1%)
sEPO ≤ 200 U/L, n/N (%)	96/145 (66.2%)	59/144 (41.0%)
sEPO > 200 U/L, n/N (%)	14/37 (37.8%)	4/37 (10.8%)
RS positive, n/N (%)	87/133 (65.4%)	38/130 (29.2%)
RS negative, n/N (%)	23/49 (46.9%)	25/50 (50.0%)

Luspatercept

128.1 weeks

Median Duration of TI ≥ 12 wks

Epoetin alfa

89.7 weeks

Median Duration of TI ≥ 12 wks

HR 0.534 (95% CI, 0.330-0.864)

IPSS-R = Revised International Prognostic Scoring System; RBC = Red Blood Cell; ESA = Erythroid Stimulating Agent; Hb = Hemoglobin; TI = Transfusion Independence; sEPO = serum Erythropoietin

Garcia-Manero G, et al. 2023. ASCO Oral Presentation 7003; Platzbecker U, et al. *Lancet.* 2023;402(10399):373-385; Della Porta MG, et al. 2023. EHA Oral Presentation S102; Garcia-Manero G, et al. *Blood.* 2023;142(Suppl 1):193.

Elritercept (KER-050) is Designed to Target Disorders of Ineffective Hematopoiesis Including MDS

Responders/N (%)	$mITT_{24}$[a]		$mITT_{24}$ + EPO < 500 U/L[b]	
	All (N=81)	HTB (N=46)	All (N=66)	HTB (N=35)
Overall Response[c]	**45/81 (55.6)**	**23/46 (50.0)**	**40/66 (60.6)**	**20/35 (57.1)**
Modified IWG 2006 HI-E[d]	**40/81 (49.4)**	**22/46 (47.8)**	**35/66 (53)**	**19/35 (54.3)**
RS+	33/57 (57.9)	19/33 (57.6)	29/51 (56.9)	16/29 (55.2)
non-RS	7/24 (29.2)	3/13 (23.1)	6/15 (40)	3/6 (50)
TI ≥8 weeks[e]	**26/63 (41.3)**	**16/46 (34.8)**	**25/50 (50.0)**	**15/35 (42.9)**
RS+	**22/45 (48.9)**	**13/33 (39.4)**	**21/40 (52.5)**	**12/29 (41.4)**
non-RS	**4/18 (22.2)**	**3/13 (23.1)**	**4/10 (40)**	**3/6 (50)**

Response rates in $mITT_{24}$ participants with HTB were similar to those observed in the overall $mITT_{24}$ population, with higher rates observed in the EPO < 500 U/L population particularly in non-RS participants. These data support potential for elritercept to treat a broad array of patients with LR-MDS.

[a] Includes data for Weeks 0-24 in $mITT_{24}$ participants; [b] Includes data for Weeks 0-24 in $mITT_{24}$ participants with baseline EPO < 500 U/L, excluding one participant with del5q MDS; [c] Defined as achieving modified IWG 2006 HI-E and/or TI; [d] Modified IWG 2006 HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on treatment compared to 8-week pre-treatment period; [e] TI-evaluable participants received at least 2 RBC units in the 8-week pre-treatment period.

EPO = erythropoietin; HI-E = erythroid response; HTB = high transfusion burden; IWR = International Working Group; LR-MDS = low risk myelodysplastic syndrome; LTB = low transfusion burden; $mITT_{24}$ = modified intent to treat 0-24 weeks; NT = non transfused; RBC = red blood cell; RS= ring sideroblastic; TI = transfusion independence.

Imetelstat

Phase III IMerge Trial

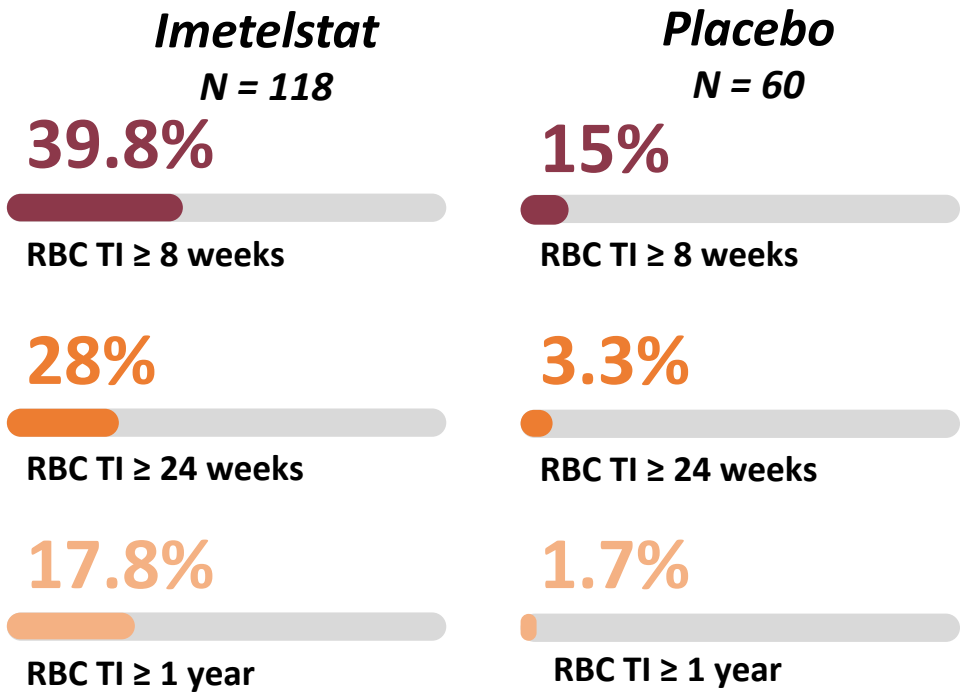
Patient Population

- ✓ *Low-risk or intermediate-risk MDS (IPSS) with ring sideroblasts*
- ✓ *Require RBC transfusions*

Most Common Grade 3/4 AEs with Imetelstat

- *Thrombocytopenia (62%)*
- *Neutropenia (68%)*
- *Anemia (19%)*
- *Leukopenia (8%)*

FDA Approval: 06/06/24



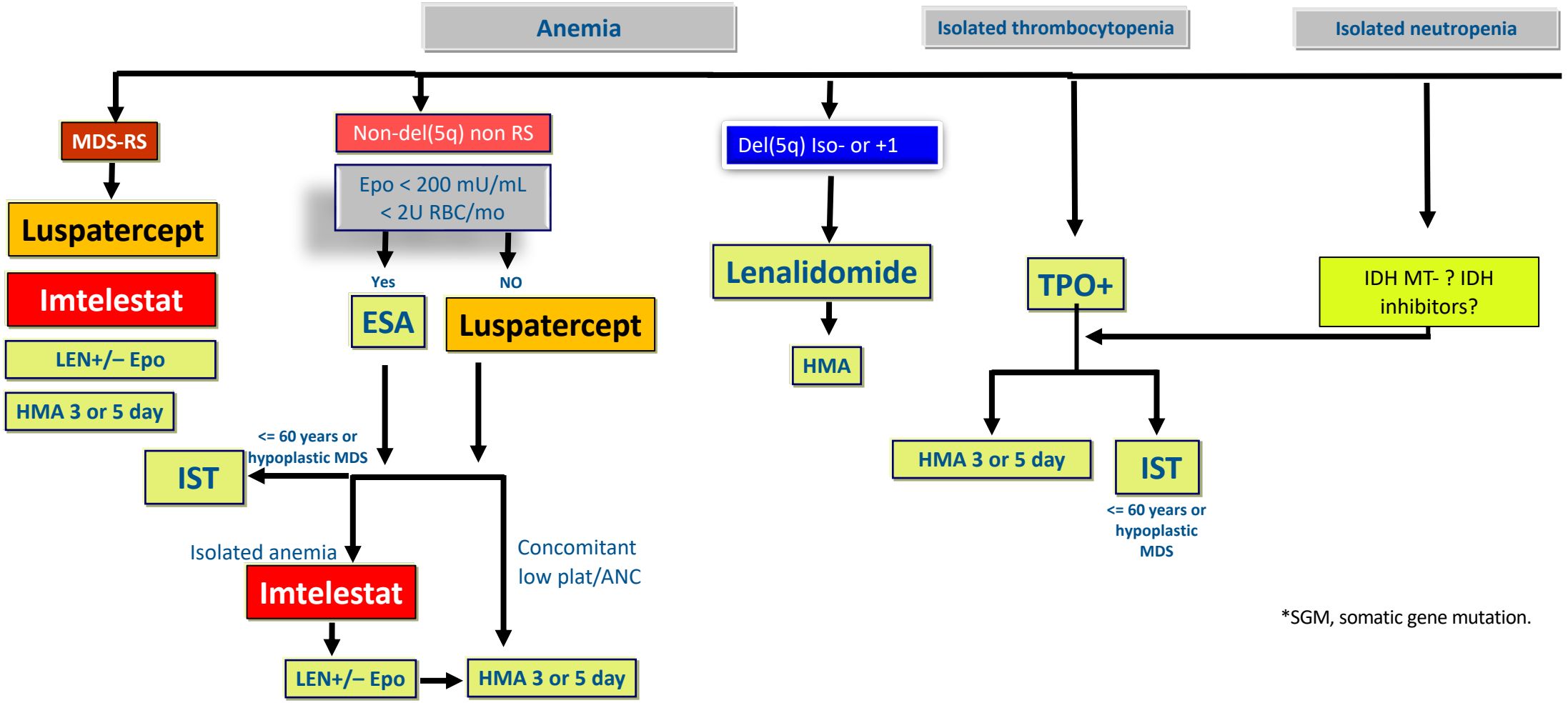
***Superior RBC-TI response rates in patients with SF3B1, TET2, ASXL1, DNMT3a, or CUX1* mutations treated with imetelstat**

1-year RBC-TI		
	Imetelstat	Placebo
IPSS		
Low	10/80 (12.5%)	1/39 (2.6%)
Int-1	5/38 (15.8%)	0/21 (0%)
IPSS-R		
Very low	0/3 (0%)	0/2 (0%)
Low	10/87 (11.5%)	1/46 (2.2%)
Int	4/20 (20.0%)	0/8 (0%)
IPSS-M		
Very low/low	10/69 (14.5)	0/33 (0%)

IPSS = International Prognostic Scoring System; RBC = Red Blood Cell; TI = Transfusion Independence

Zeidan AM, et al. 2023. ASCO Oral Presentation 7004; Santini V, et al. 2023. EHA Presentation S164; Platzbecker U, et al. 2023. EHA Presentation S165; Komrojki RS, et al. *Blood.* 2023; Abstract 194; Santini V, et al. *Blood.* 2023; Abstract 4603; Platzbecker U, et al. *Blood.* 2023; Abstract 4605; Platzbecker U, et al. *The Lancet.* 2024;403(10423):249-260.

How Do I Manage LR-MDS in 2024



*SGM, somatic gene mutation.

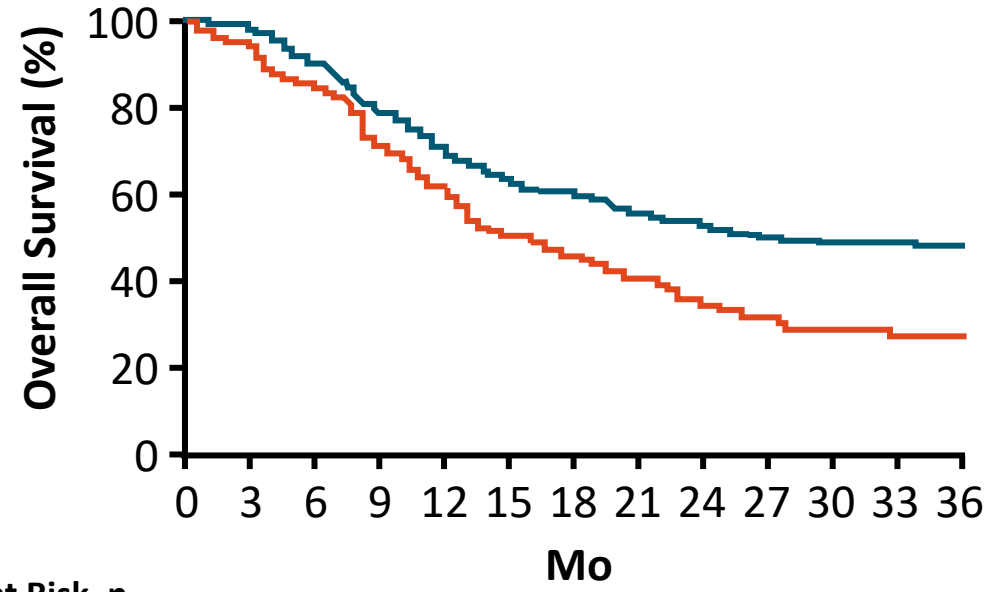
- **Allogeneic stem cell transplant maybe considered after standard therapy failure or in younger patients with higher-risk disease features by IPSS-M.**
- **Iron chelation should be considered in patients with evidence of iron overload.**

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

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

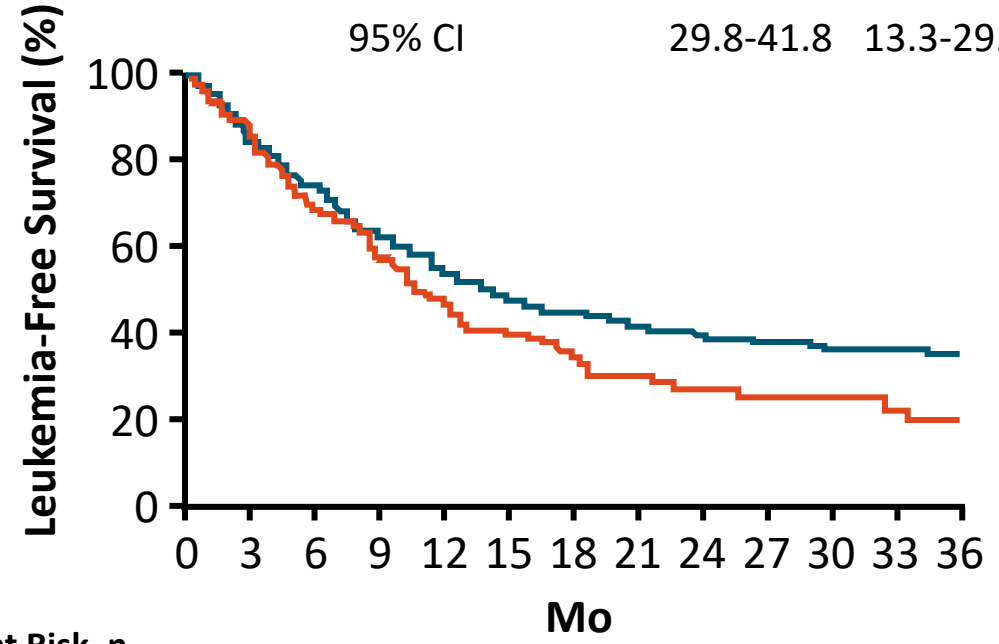


Patients at Risk, n

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

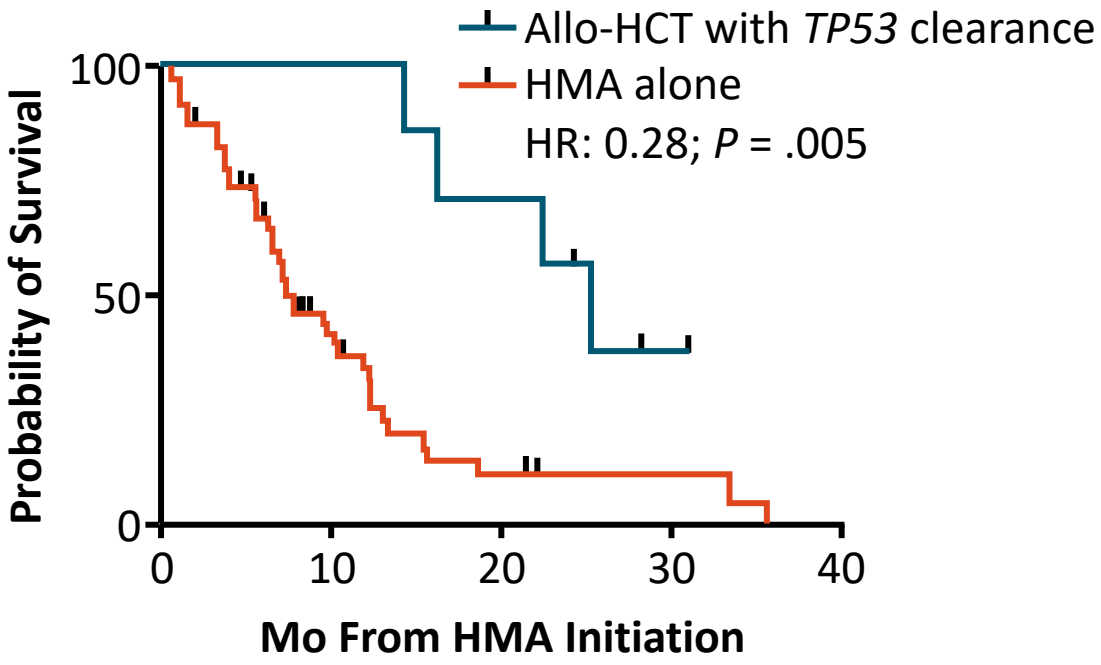


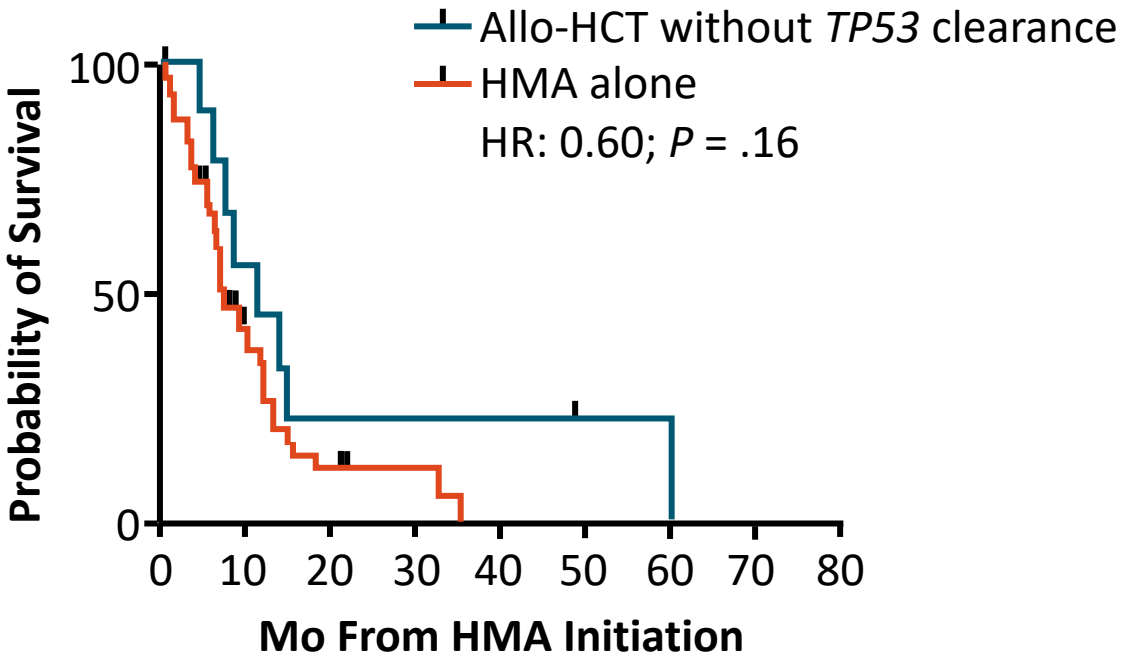
Patients at Risk, n

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.

Managing *TP53* mutant 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

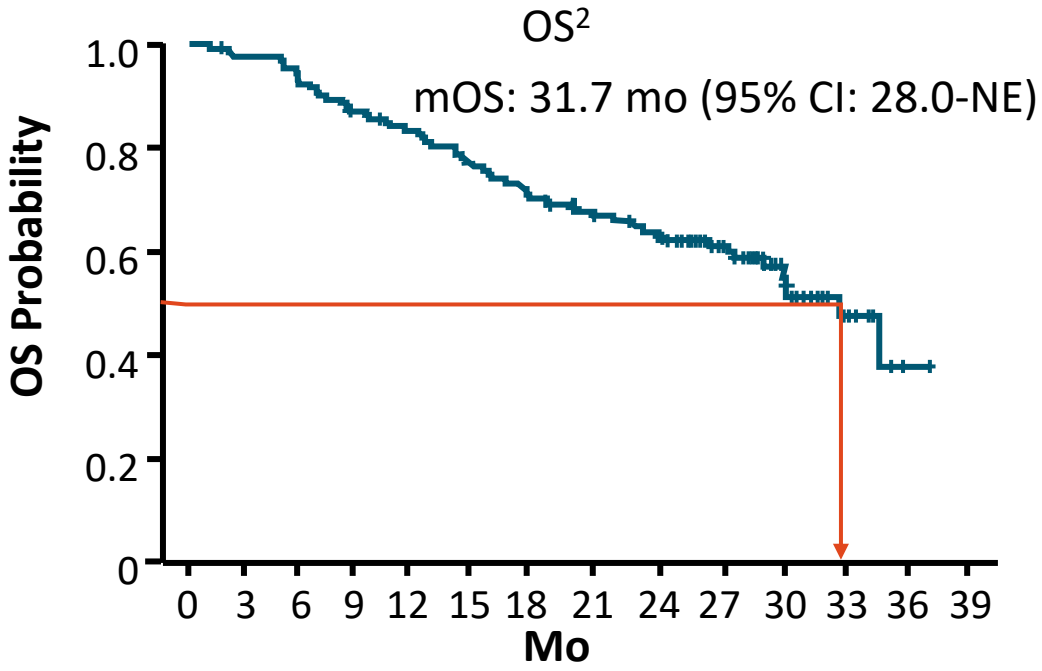
Hunter. Blood Adv. 2021;5:1017.

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.

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.

Oral decitabine/cedazuridine + venetoclax in 1L HR MDS or CMML

Key eligibility criteria

- ≥ 18 years of age
- IPSS intermediate 2 or high risk
- WHO 2016, with > 5% blasts in bone marrow
- Treatment-naive MDS or CMML

Phase 1: dose escalation
3 pts ASTX727 100/35mg day 1-5 + VEN 200mg 1-14

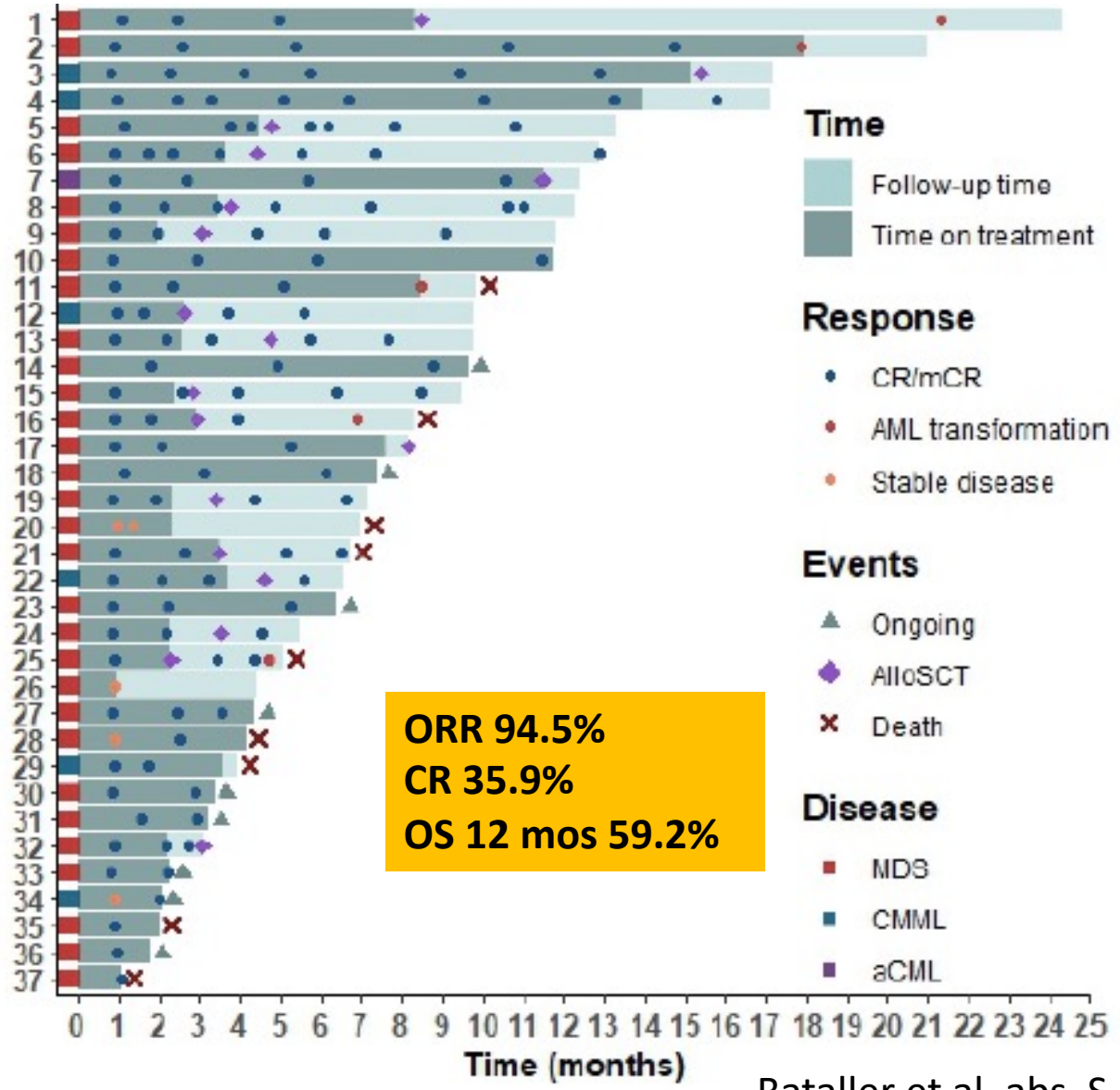
6 pts ASTX727 100/35mg day 1-5 + VEN 400mg 1-14

Phase 2: dose expansion

28 pts ASTX727 100/35mg day 1-5 + VEN 400mg 1-14

ORR

Median age 71 yrs
MDS EB2 65%, CMML 2 16%
IPSS-M very high 68.7%
mTP53 20%. 7/8 multiallelic
Median n cycles 2
Median Time to response 1 cycle



ORR 94.5%
CR 35.9%
OS 12 mos 59.2%

Bataller et al, abs S 172

Ongoing Phase 2 trial (NCT05184842)

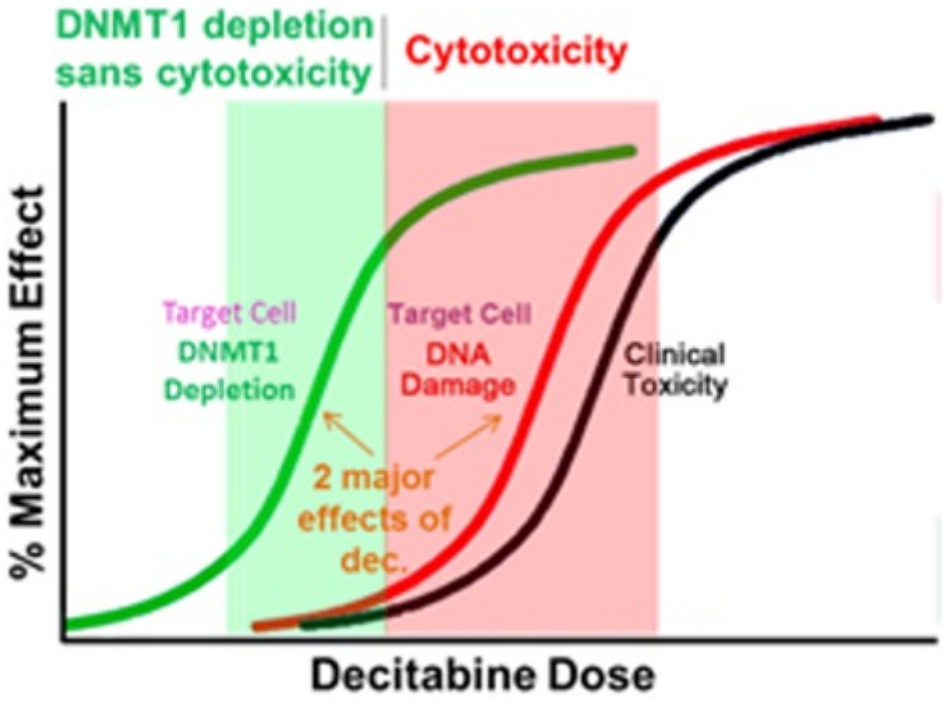
Metronomic Once Weekly Dosing of Decitabine and Venetoclax in MDS/AML

Treatment (28-day cycles):

- Venetoclax 400 mg on days 1, 8, 15, 22
- Decitabine 0.2 mg/kg SQ on days 1, 8, 15, 22

(for aggressive disease can add a second dose of decitabine on days 2, 9, 16 and 23)

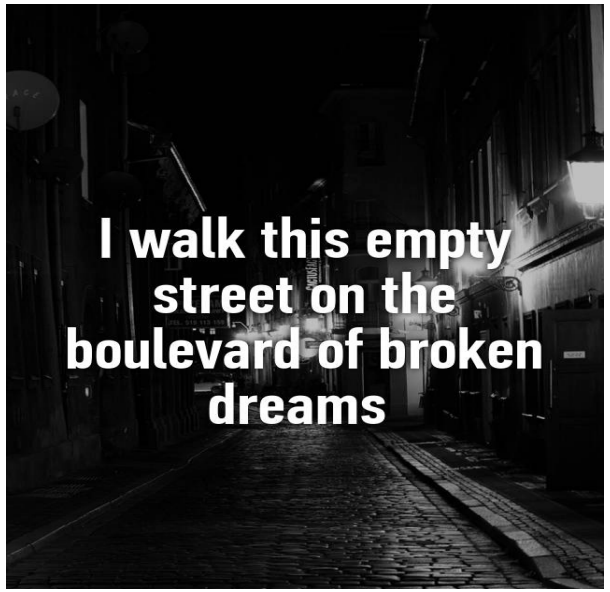
Week 1-12 (Induction phase) → Week 13 and beyond (Long-term treatment phase)



Courtesy of Dr Goldfinger

Lessons Learned from Phase III clinical trials in HR-MDS

Drug	Patient characteristics	Intervention	Study outcomes
Venetoclax	Newly-diagnosed HR-MDS Estimated enrollment: 500	Venetoclax + AZA vs. placebo + AZA	Primary Outcome: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 36 Months) - Overall survival (OS) (Up to 5 years)
MBG453 (Sabatolimab)	Newly-diagnosed HR-MDS or CMML-2 Estimated enrollment: 500	MBG453+ AZA vs. placebo + AZA	Primary Outcome: - Overall Survival (Up to 5 years after last patient randomized)
Pevonedistat	Newly-diagnosed HR-MDS, CMML, or Low-Blast AML Estimated enrollment: 502	Pevonedistat + AZA vs. AZA alone Open-label	Primary Outcome: - Event-Free Survival (From randomization until transformation to AML, or death due to any cause; up to 6 years)
Magrolimab	Newly-diagnosed HR-MDS Estimated enrollment: 520	Magrolimab + AZA vs. AZA + placebo	Primary Outcomes: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 24 Months) - Overall survival (OS) (Up to 5 years)
APR-246	Newly-diagnosed TP53-mutated HR-MDS Estimated enrollment: 154	APR-246 + AZA Vs. AZA alone Open-label	Primary Outcome: - Complete response rate (CR) with APR 246 + azacitidine vs. azacitidine only
SY-1425 (Tamibarotene)	Newly-diagnosed RARA-positive HR-MDS Estimated enrollment: 190	SY-1425 + AZA Vs. placebo + AZA	Primary outcome: - Complete response rate (CR) with SY-1425 + azacitidine vs. azacitidine only



- Bi-allelic *TP53* MDS specific clinical trials.
- Survival= CR rate x duration
- Studies are under-powered to detect small improvements

Targeting IDH mutant MDS

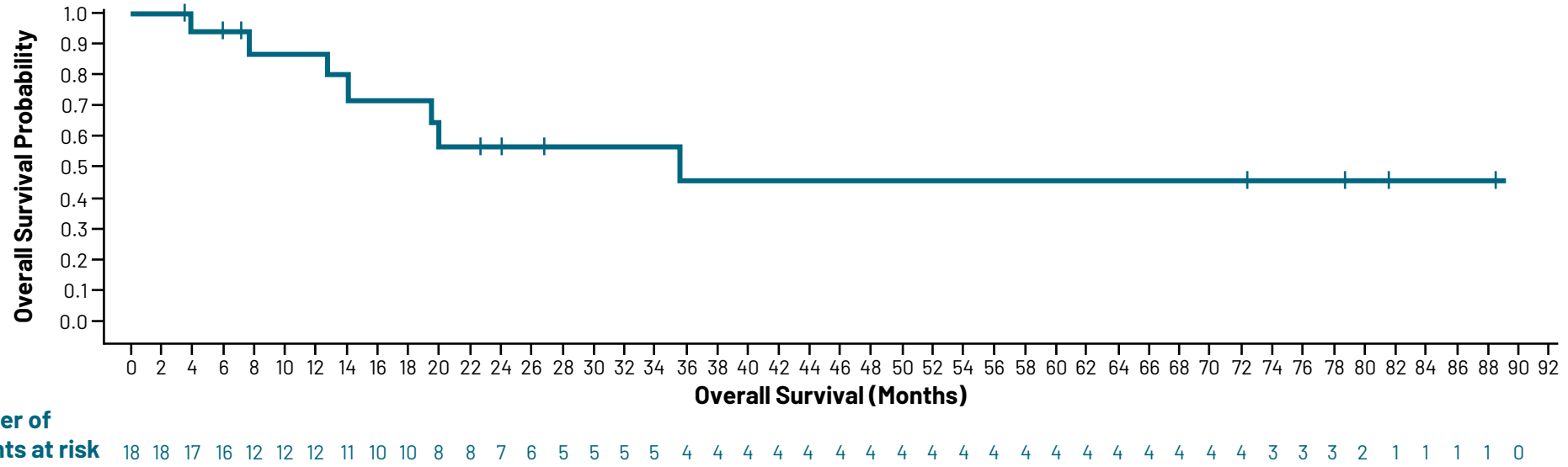
- IDH-1/IDH-2 mutations occur in 5-10% of MDS patients.
- Enriched in patients with neutropenia.
- Recent correlation of IDH-1 mutant myeloid diseases with sero-negative Rheumatoid arthritis and connective tissue disease.

Komrokji et al. Haematologica. 2023 Apr 1;108(4):1168-1172.

Overall Survival with Ivosidenib of Approximately 3 Years Was Observed

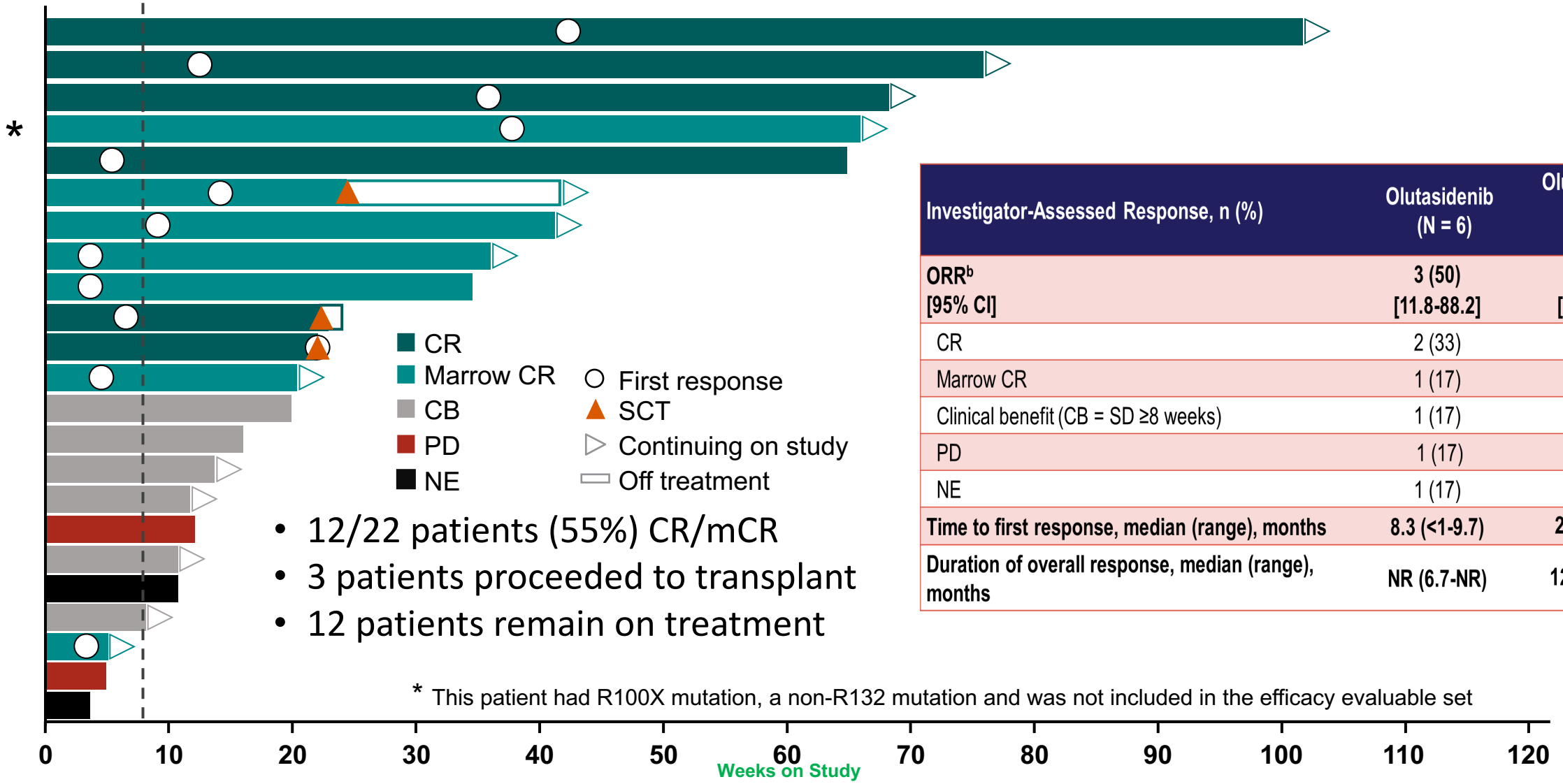
	Ivosidenib (500 mg Daily) (N=18)
mOS, months (range)	**35.7 (3.7-88.7)**
95% CI	13.1-NE

- **Median OS follow-up** was **27.1 months**
- **87% survival rate at 12 months** per Kaplan-Meier estimation
- **Because there was no control arm in this study, OS results should be interpreted cautiously**



DiNardo CD et al Blood Adv. 2024 Apr 19

Efficacy of FT-2102 (Olutasidenib) in IDH1-mutated MDS

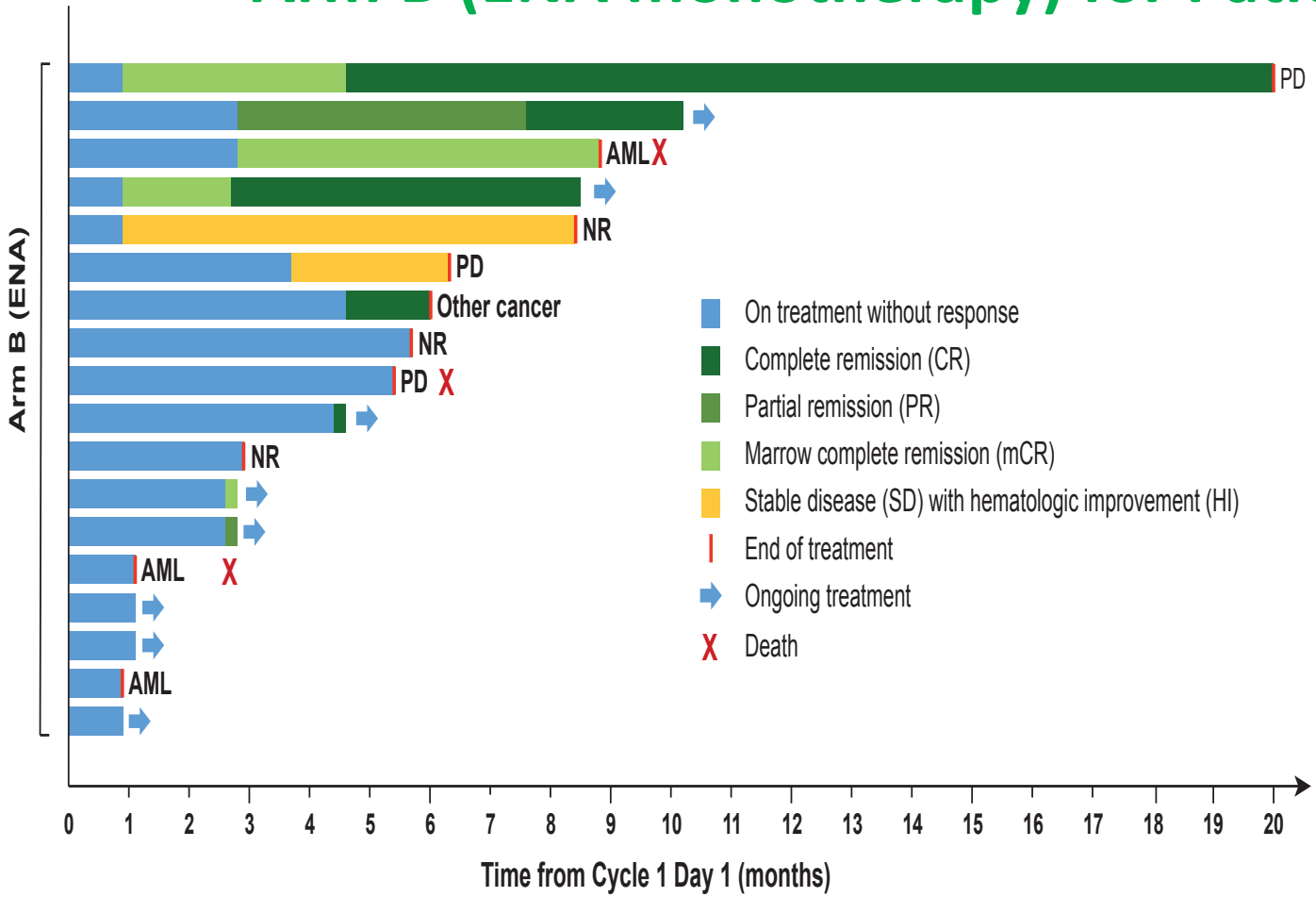


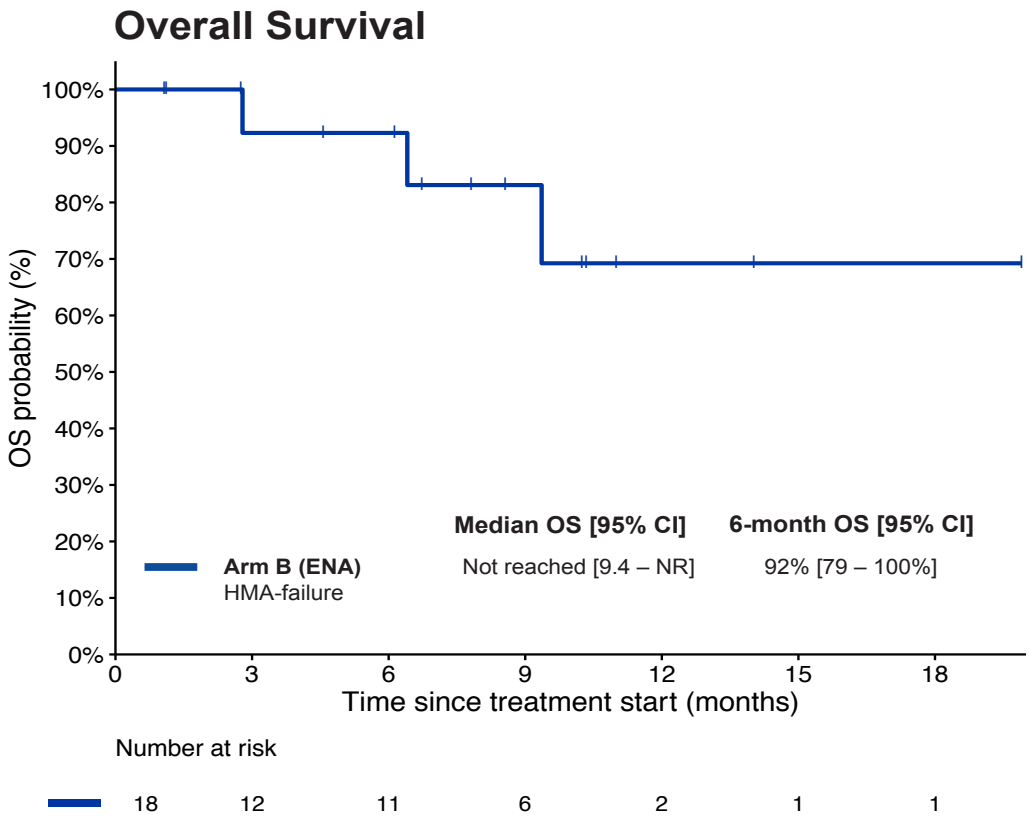
Investigator-Assessed Response, n (%)	Olutasidenib (N = 6)	Olutasidenib + AZA (N = 16)[a]
ORR[b] [95% CI]	**3 (50) [11.8-88.2]**	**9 (56) [29.9-80.2]**
CR	2 (33)	4 (25)
Marrow CR	1 (17)	5 (31)
Clinical benefit (CB = SD ≥8 weeks)	1 (17)	5 (31)
PD	1 (17)	1 (6)
NE	1 (17)	1 (6)
Time to first response, median (range), months	**8.3 (<1-9.7)**	**2.8 (<1-5.1)**
Duration of overall response, median (range), months	**NR (6.7-NR)**	**12.9 (<1-NR)**

* This patient had R100X mutation, a non-R132 mutation and was not included in the efficacy evaluable set

Cortes J, et al. ASH 2019

Phase II Study of Enasidenib in Patients With *IDH2*-Mutated HR-MDS
Arm B (ENA monotherapy) for Patients with HMA-failure





Median Follow-Up: 6.6 months [range, 1.1 – 19.9 months]

Median time to **INITIAL** response: **2.8 months** [range, 0.9 — 4.6 months]

Median time to **BEST** response: **4.6 months** [range, 2.7 — 7.6 months]

Richard-Carpentier G et al, ASH 2019; DiNardo CD et al, SOHO 2020

Targeting R/R *IDH1*/*IDH2*^{mut} MDS with ivosidenib/enasidenib

IDIOME: phase 2 study of Ivo in 3 cohorts (N=26)[1]

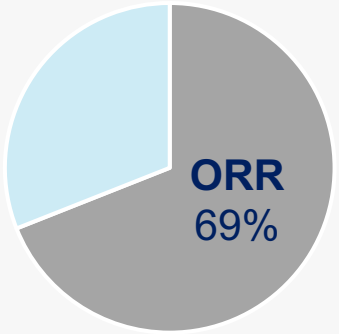
- **A**: HR-MDS, failed AZA (n=13)
- **B**: Untreated HR-MDS (n=11)
- **C**: LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

Differentiation syndrome, n=4, febrile neutropenia, n=1



IDEAL: phase 2 study of Ena in 3 cohorts (N=26)[2]

- **A**: HR-MDS, failed AZA (n=11)
- **B**: Untreated HR-MDS (n=9)
- **C**: LR-MDS, failed ESA (n=6)

ORR
42%

Median follow-up: 8.6 months

Median OS: 17.3 months

Differentiation syndrome, n=3; nausea/diarrhea, n=4; thrombocytopenia, n=5

Ivosidenib in R/R *IDH1*/*IDH2*^{mut} MDS[3]

Updated results of a phase 1 dose-escalation study (500 mg QD)

Efficacy outcomes	N=16
ORR	81%
CR	44%
mCR	31%
PR	6%
HI	69%
12-month duration CR+PR	60%

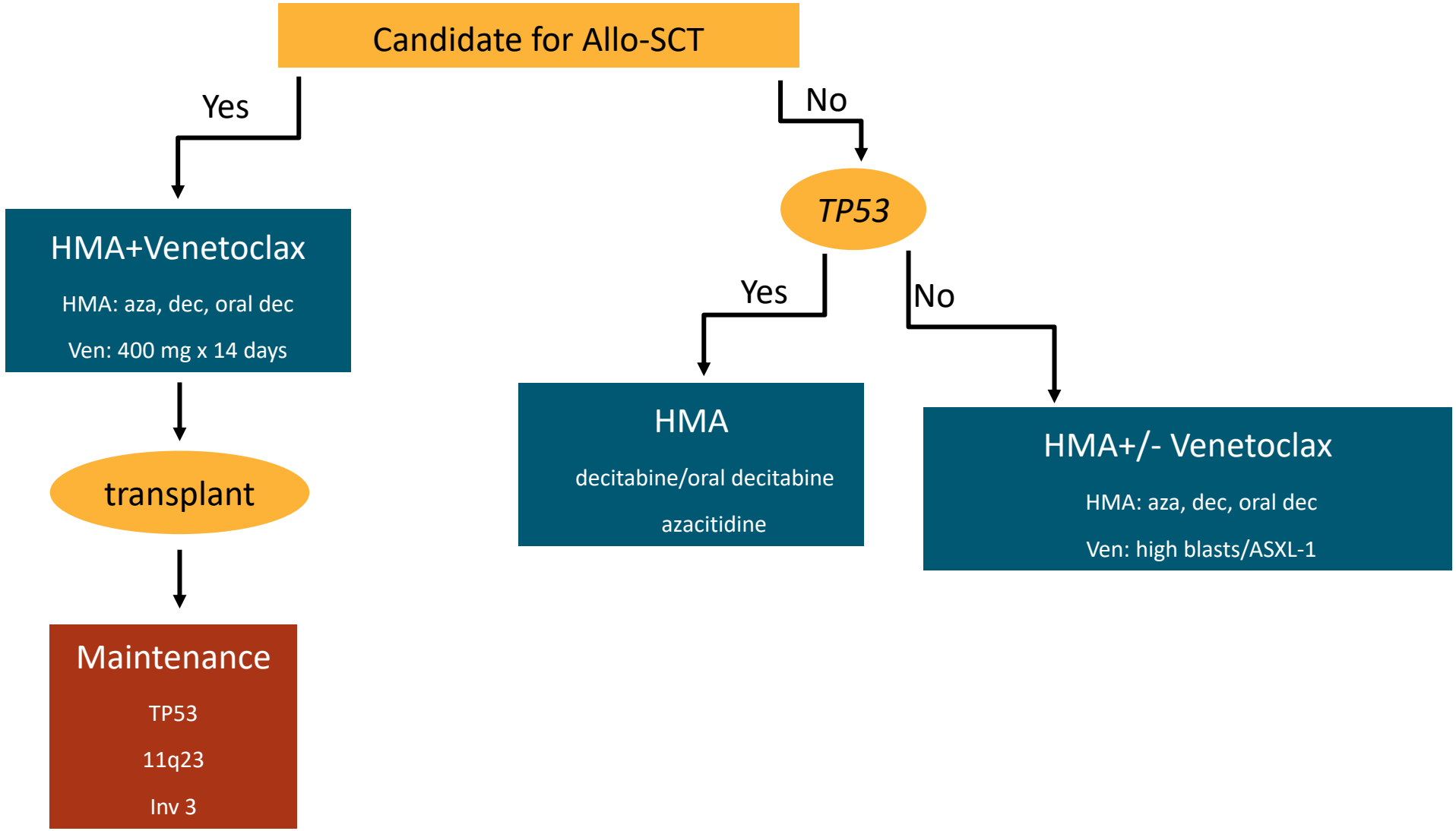
Safety outcomes	N=16
Grade ≥3 AEs	69%
Grade ≥3 TRAEs	13%
SAEs	44%

	Cohort B (n=23)
ORR after 3 cycles	78.3% (95% CI, 56.3 – 92.5)
Median DOR	NR, after median follow-up of 25.2 months
Median OS	NR, after median follow-up of 25.2 months
12-month OS rate	91.3% (95% CI, 80.5-100)

1. Sebert M, *et al.* ASH 2021. Abstract 62 (oral presentation);
2. Ades L, *et al.* ASH 2021. Abstract 63 (oral presentation)
3. Sallman DA, *et al.* ASCO 2022. Abstract 7053 (Poster 284)

Sebert M, et al. 29th European Hematological Association Congress. Madrid, Spain. June 13-16, 2024. Abstract S182.

How do I treat Higher risk MDS?

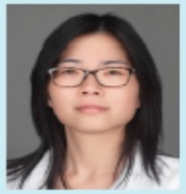


Thank You

Rami.Komrokji@moffitt.org

MEET THE TEAM


Dr. Rami Komrokji


Dr. Onyee Chan


Dr. Andrew Kuykendall


Dr. Jeffrey Lancet


Dr. Eric Padron


Dr. David Sallman


Dr. Kendra Sweet


Dr. Sara Tinsley

Moffitt MDS team: Only perfect counts !!!

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- Our patients and their caregivers
- Moffitt MDS team