

Conquering high-risk MDS: are we close?

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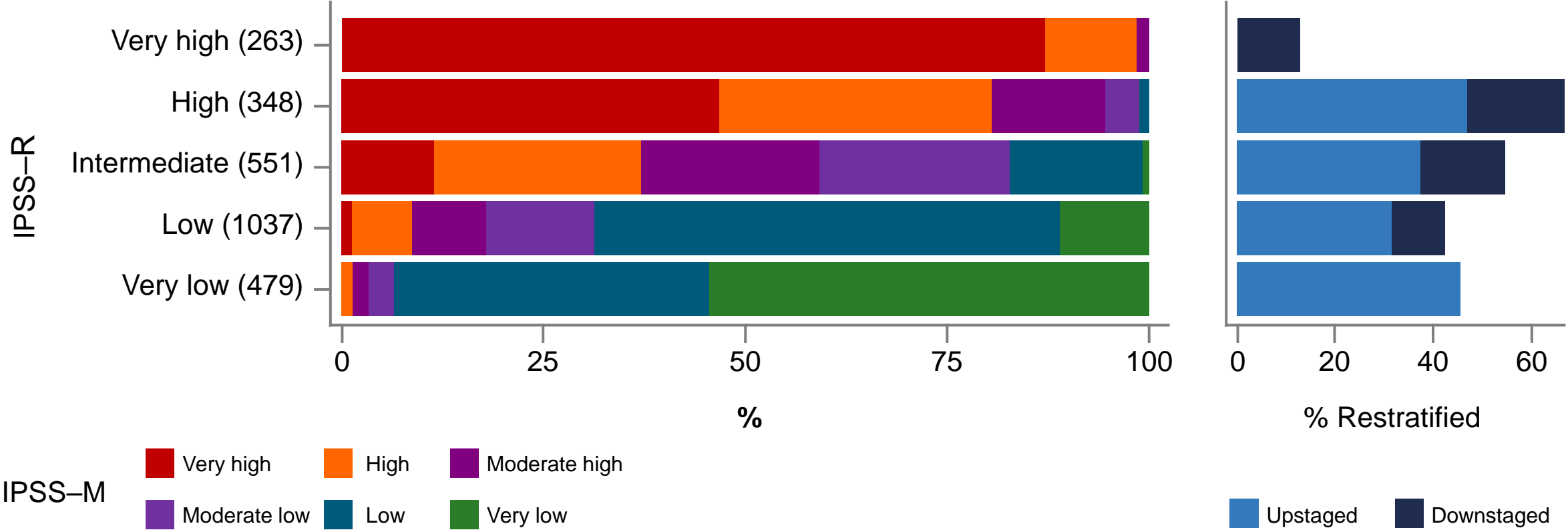
Tampa, Florida

Redefining 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 <i>(Very low/low)</i>	 14	10.6	2.8	 <p>Hematologic improvement</p> <p>(lower risk of infection & bleeding)</p>	<p>Transfusion ESAs</p> <p>Watch & wait</p>
	Low <i>(Very low/low/int)</i>	 33	6.0	5.1		
	Moderate low <i>(Low/int)</i>	 11	4.6	11.4	<p>?</p>  <p>Alter disease natural history</p> <p>(higher risk of infection & bleeding)</p>	<p>HMA/ICT +/- ASCT</p>
	Moderate high <i>(Low/int/high)</i>	 11	2.8	18.9		
	High <i>(Int/high/very high)</i>	 14	1.7	29.2		
	Very high <i>(High/very high)</i>	 17	1.0	42.8		

* 4 years

IPSS-M: Improves risk stratification of patients with MDS, providing a valuable tool for clinical decision making



Categorization by IPSS-M and restratiated 46% of patients (n=1,223/2,678) and of these, 74% (n=911) were upstaged vs IPSS-R

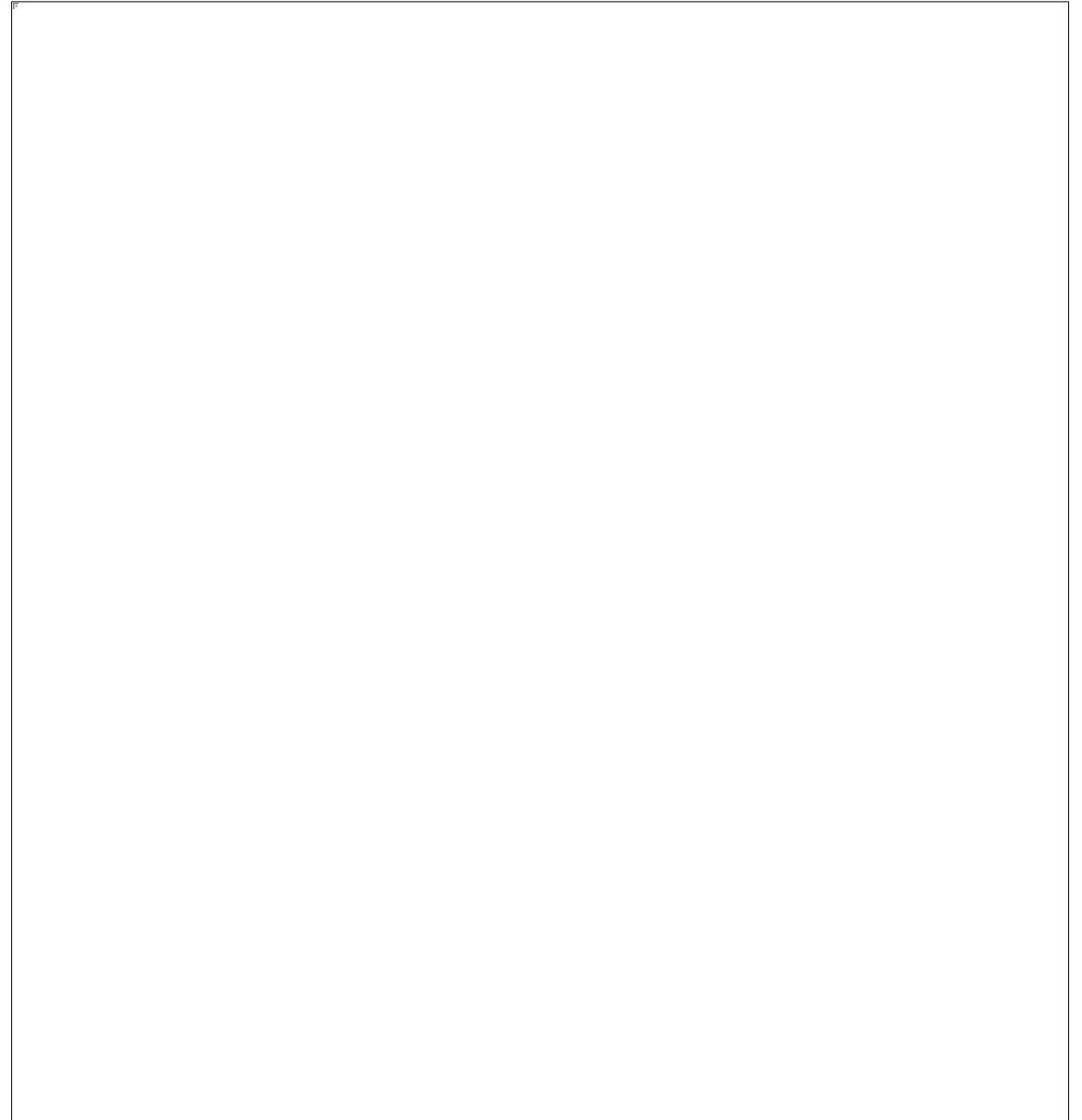
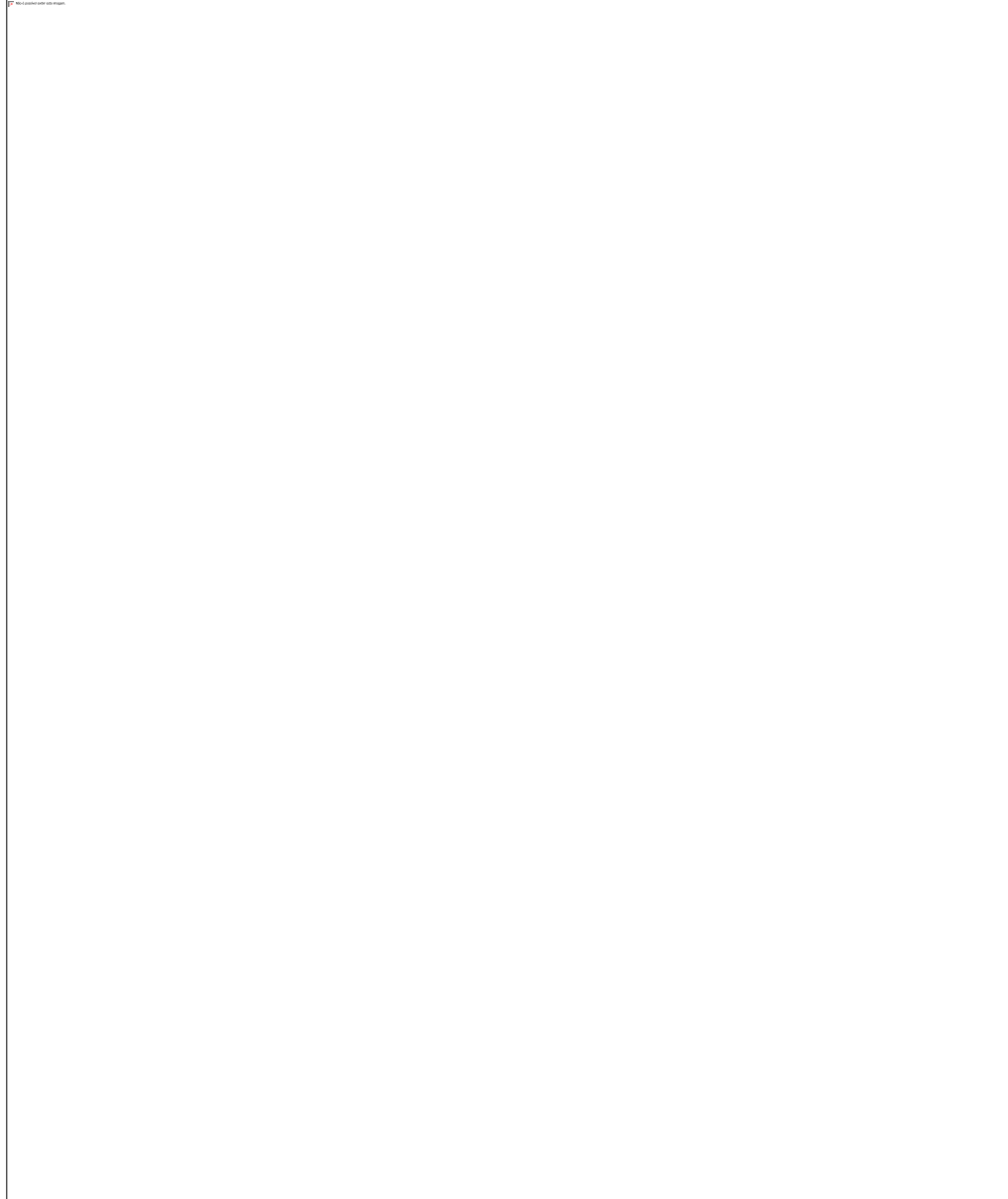
Categorization by IPSS-M 42% of patients are categorized as Higher risk MDS

IPSS-M vs. IPSS-R based transplantation strategy



- 13% of candidates to be immediately transplanted under an IPSS-R based policy would benefit from a delayed strategy under an IPSS-M based policy, while 32% of candidates to delayed transplantation by IPSS-R, would benefit from immediate HSCT by IPSS.
- The comparison of the average conditional survival time for the optimal transplantation policies obtained using different scoring systems (IPSS-R/IPSS-M) resulted in a significant gain of live expectancy under an IPSS-M based policy across all age groups ($P=0.002$)

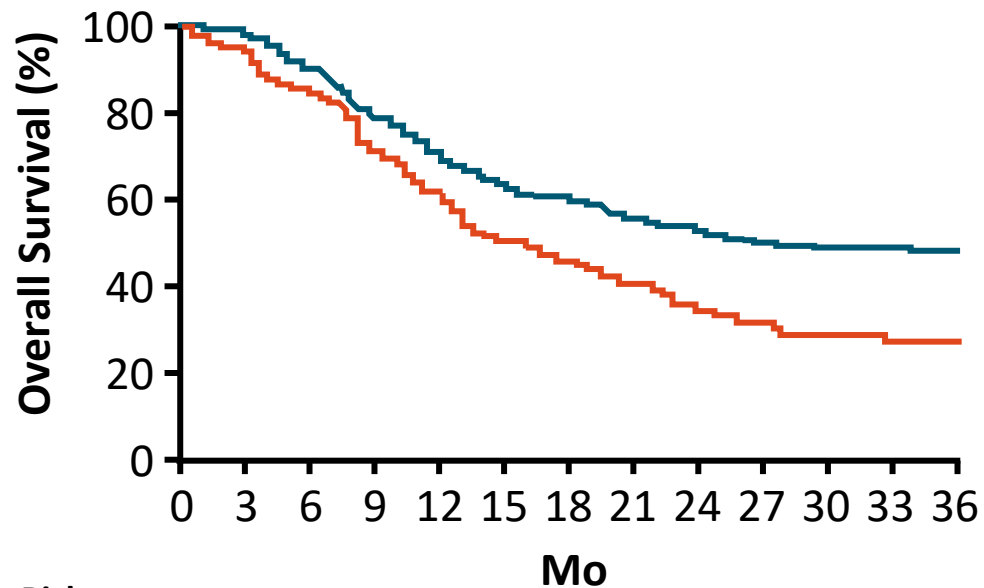
IPSS-M in the context of AH SCT and HMA



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

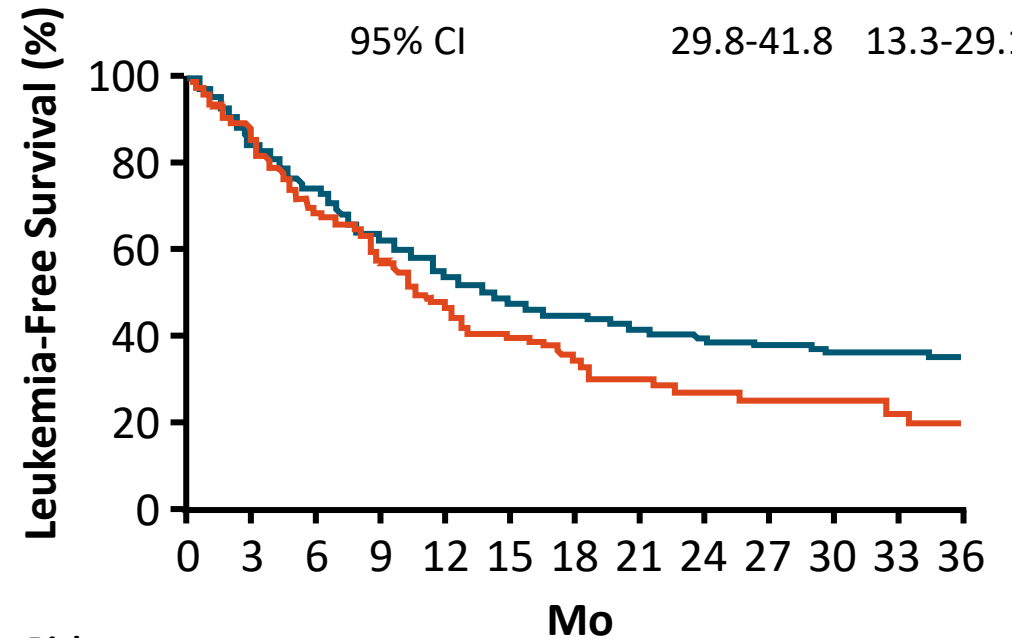


Patients at Risk, n

	0	3	6	9	12	15	18	21	24	27	30	33	36
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

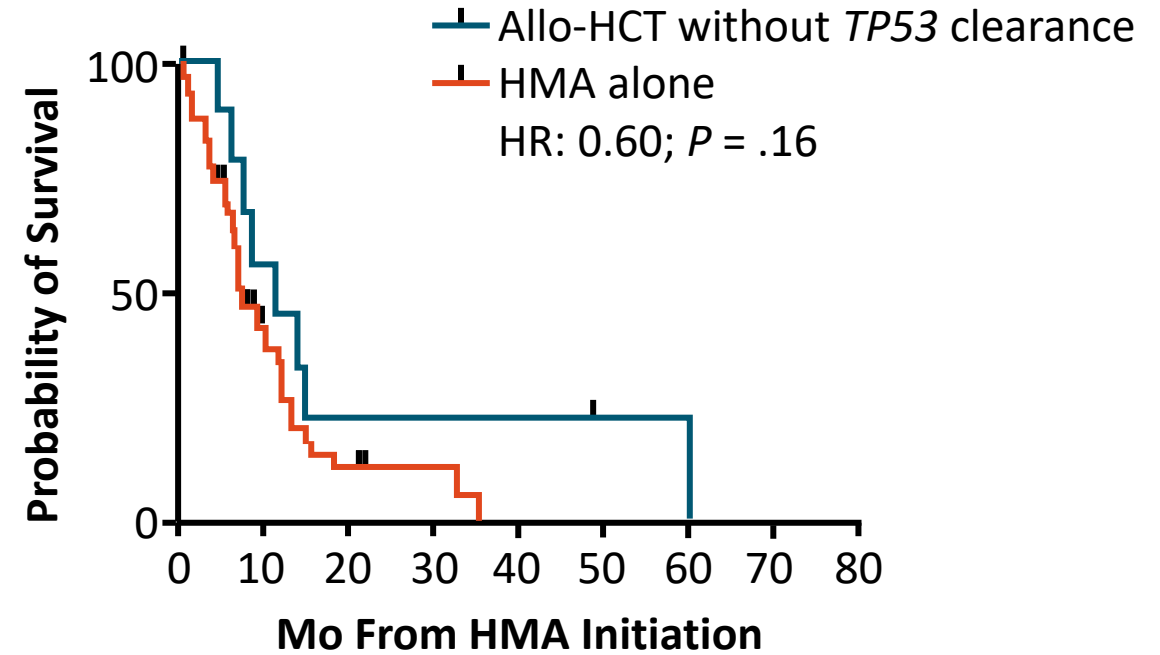
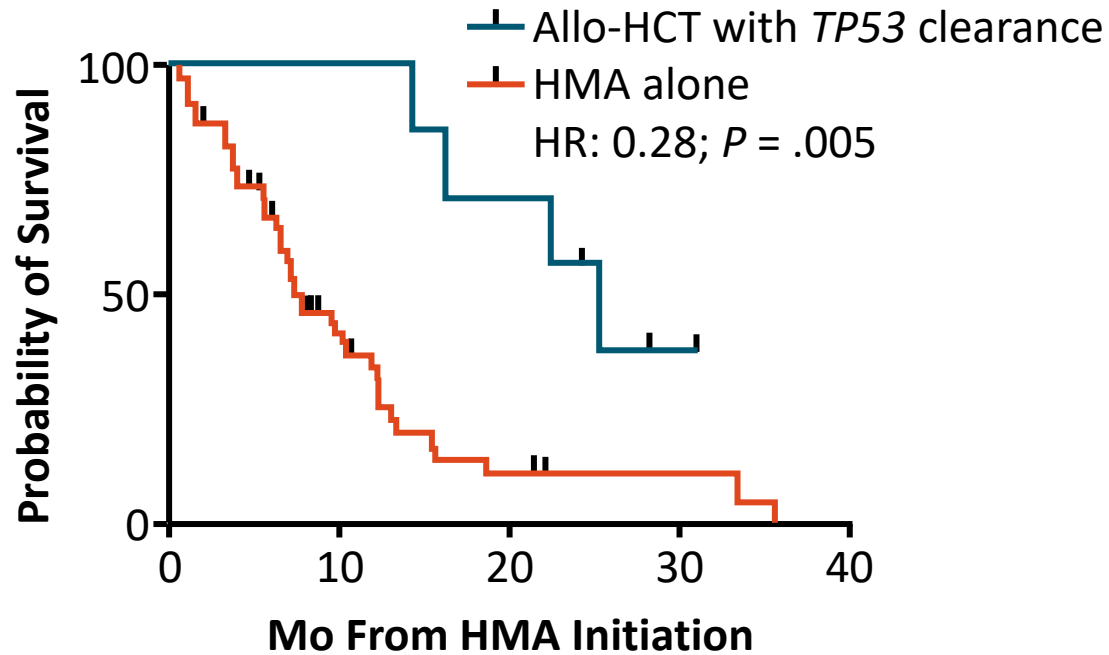
	Donor	No Donor
3-yr estimate, %	35.8	20.6
95% CI	29.8-41.8	13.3-29.1



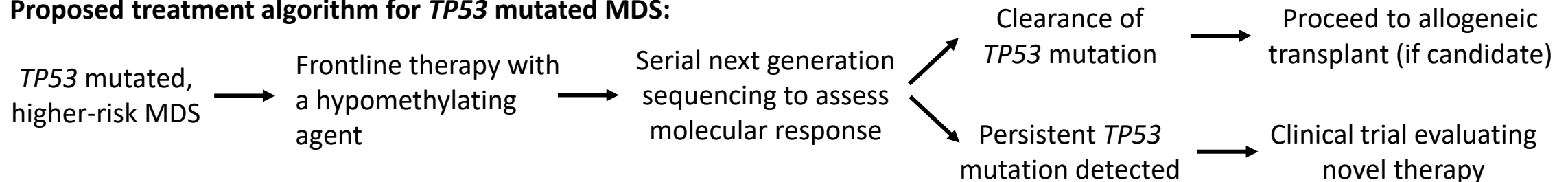
Patients at Risk, n

	0	3	6	9	12	15	18	21	24	27	30	33	36
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

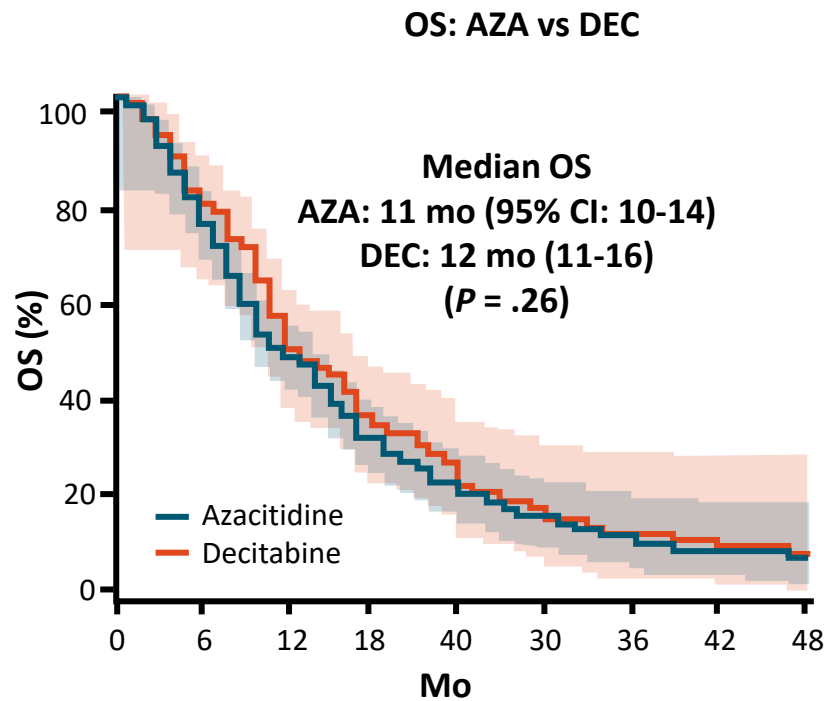
Baseline and Serial Molecular Profiling Predicts Outcomes With HMAs in MDS



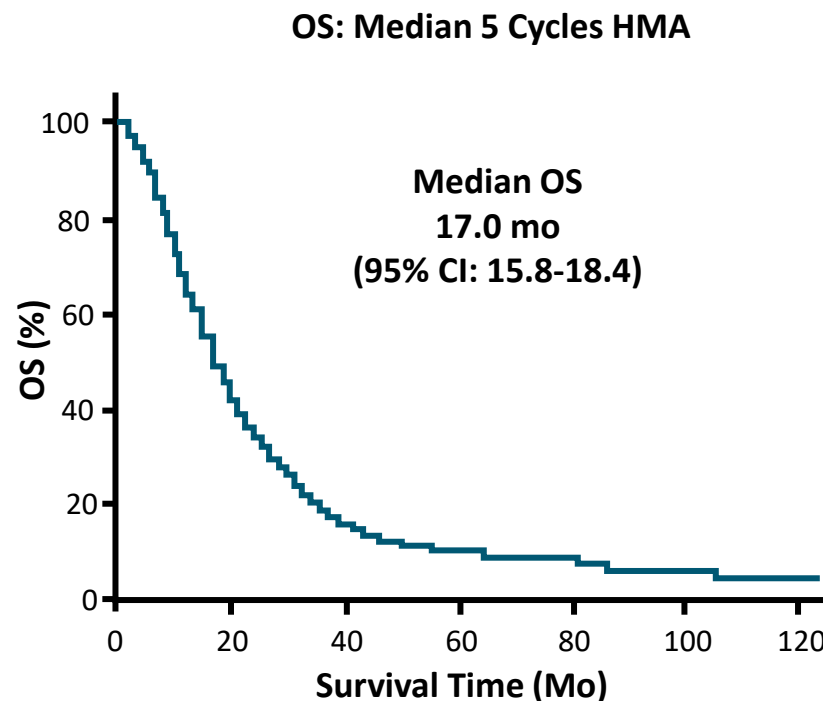
Proposed treatment algorithm for *TP53* mutated MDS:



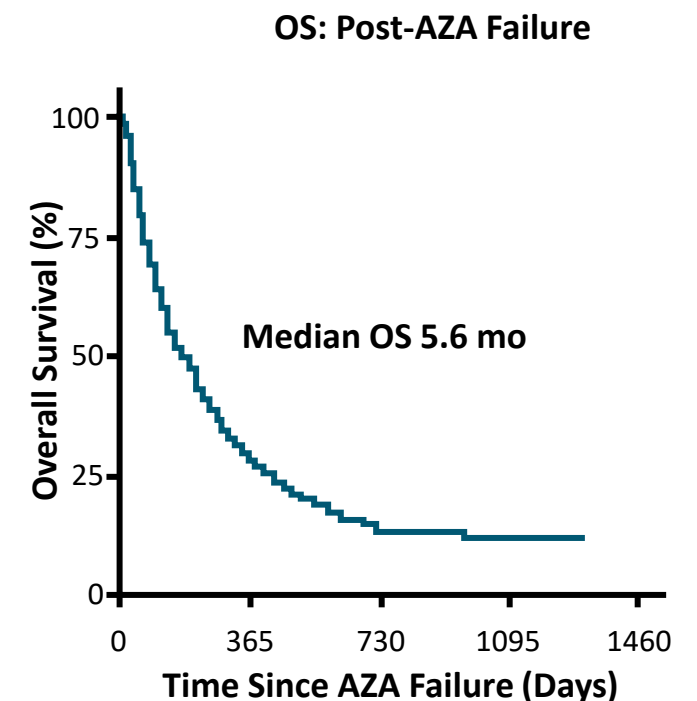
Survival of Patients With HR-MDS Remains Poor Despite Use of HMAs



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



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.



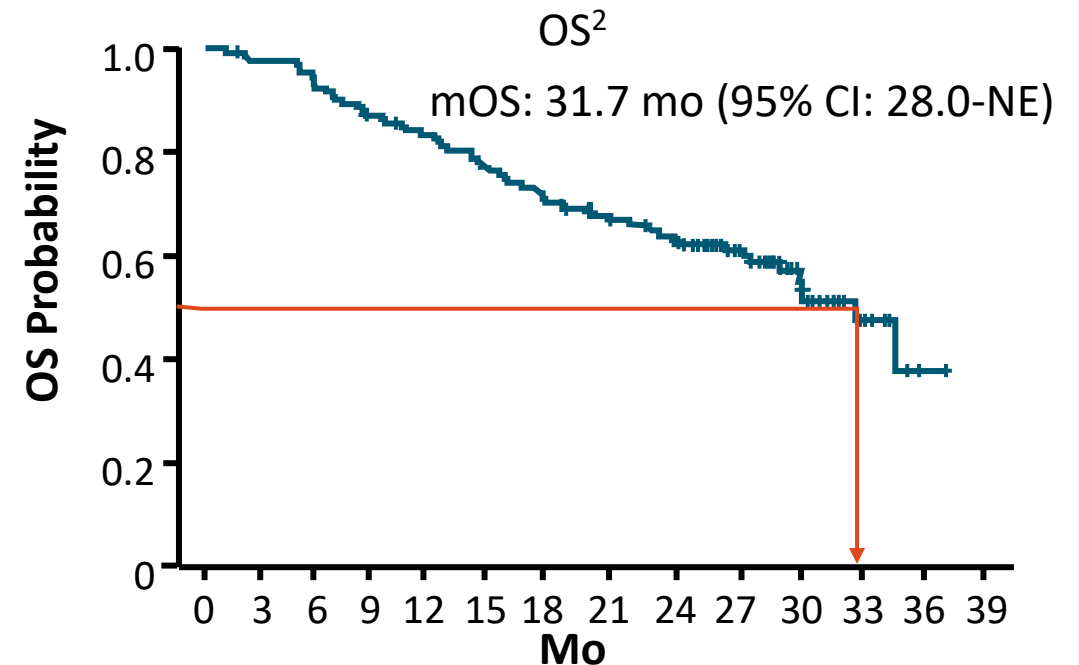
Survival post-AZA failure for patients with HR-MDS

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)

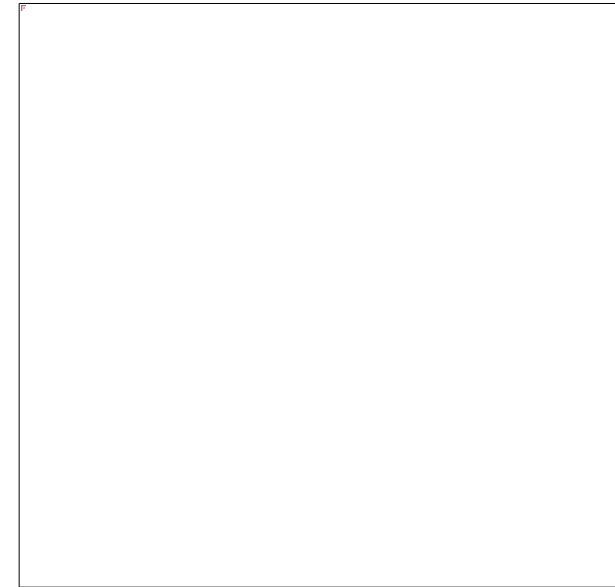
*# patients TI/# patients TD at baseline.

- 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)



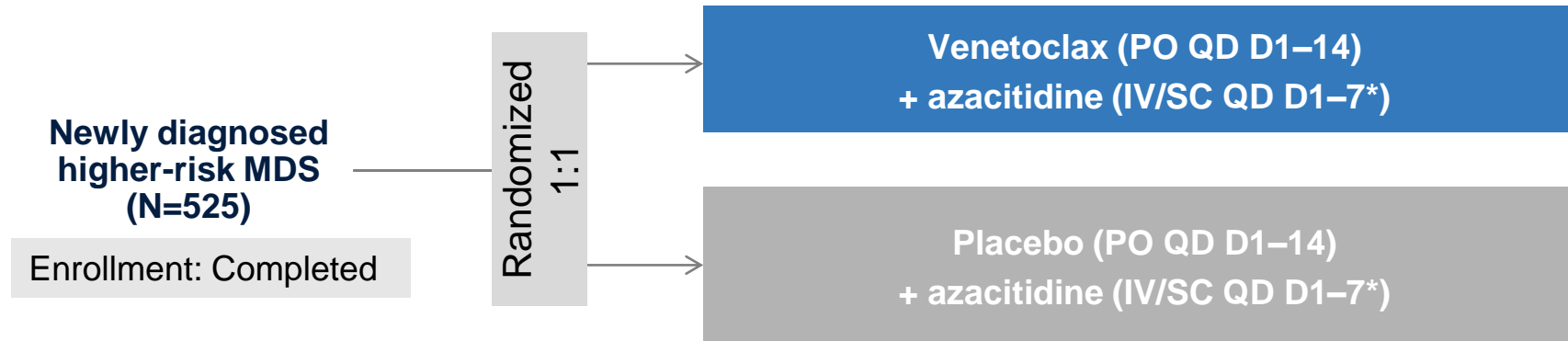
Lessons Learned from Phase III clinical trials in HR-MDS

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

VERONA: Phase 3 study of Ven+Aza in higher-risk MDS



Key inclusion criteria

- ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
- <20% BM blasts
- ECOG PS 0–2
- IPSS-R score of >3 (Intermediate, high, very high)
- No planned HSCT at the time of C1D1

Primary endpoints

- CR
- OS

Secondary endpoints

- Modified overall response (mOR)
- Transfusion independence (TI)
- ORR
- QoL

Phase Ib Study of Venetoclax in Combination With Azacitidine for Frontline Treatment of Patients With HR-MDS

Trial Design

Key Eligibility Criteria

- No prior MDS treatment
- IPSS ≥ 1.5
- BM blasts $< 20\%$ at screening
- ECOG score of ≤ 2
- Treatment cohorts (28-day cycles); Aza 75 mg/m² D1-7

Randomization Phase (28-Day Ven):

- Aza + Ven 400 mg D1-28 (n = 5)
 - Aza + Ven 800 mg D1-28 (n = 5)
 - Aza (n = 2)
- Protocol amendment was made to explore 14-day Ven

Dose-escalation Phase (14-Day Ven):

- Aza + Ven 100 mg D1-14 (n = 8)
 - Aza + Ven 200 mg D1-14 (n = 9)
 - Aza + Ven 400 mg D1-14 (n = 8)
- Ven RP2D was established at 400 mg D1-14

Safety Expansion 1 (14-Day Ven):

- Aza + Ven 400 mg D1-14 (n = 22)

Safety Expansion 2 (14-Day Ven):

- Aza + Ven 400 mg D1-14 (n = 21)

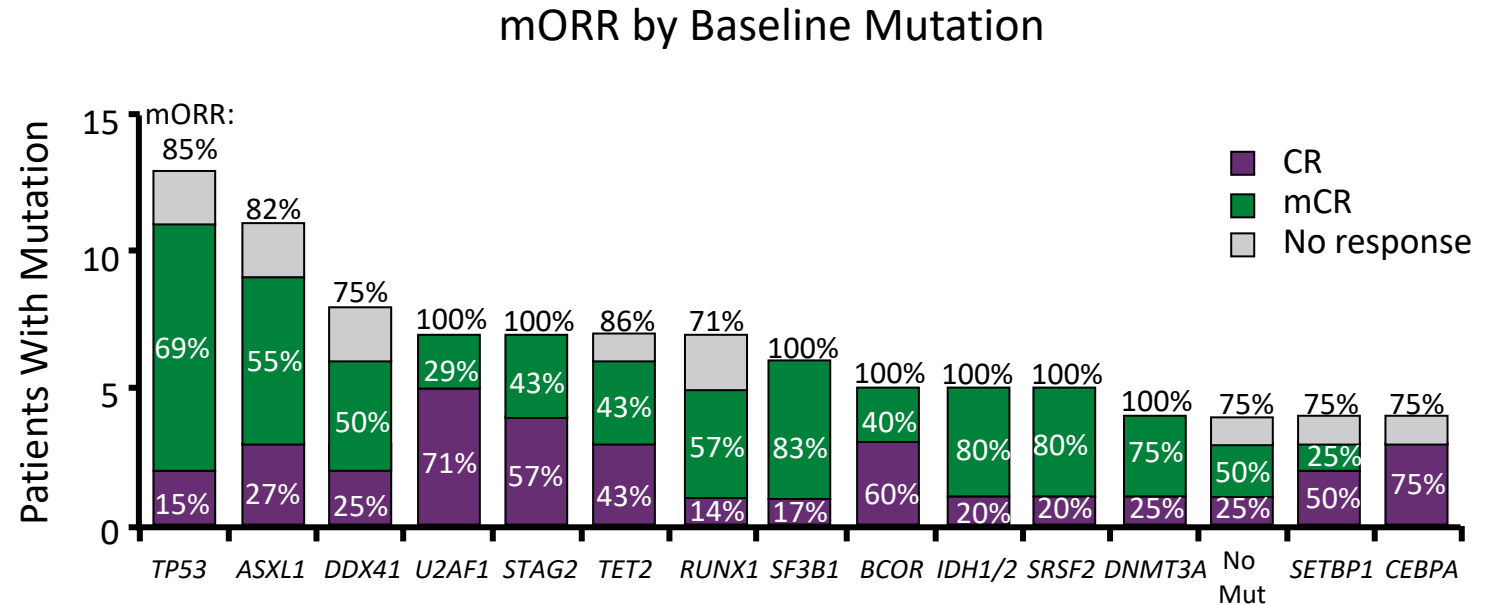
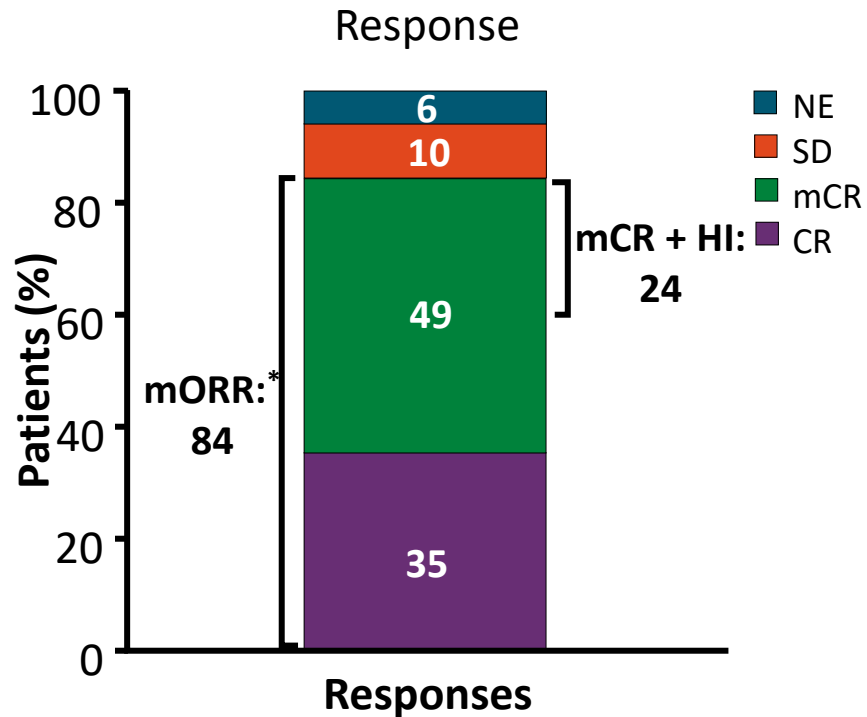
Baseline Characteristics

Patient Characteristics		N = 78
Median age, yr (range)		70 (26-87)
ECOG PS, n (%)	0	33 (42)
	1	38 (49)
	2	7 (9)
BM blasts, n (%)	$\leq 5\%$	7 (9)
	$> 5\%$ to $\leq 10\%$	21 (27)
	$> 10\%$ to $\leq 20\%$	49 (63)
	$> 20\%$	1 (1)
IPSS	Good	31 (40)
karyotype	Intermediate	16 (20)
risk, n (%)	Poor	31 (40)

Patient Characteristics (cont'd)		N = 78	
IPSS risk, n (%)	Intermediate-2	57 (73)	
	High	21 (27)	
IPSS-R risk	Intermediate	14 (18)	
	High	16 (20)	
	Very high	48 (62)	
Baseline Cytopenias, n (%)		Grade 3	Grade 4
Neutropenia		24 (31)	22 (28)
Thrombocytopenia		20 (26)	6 (8)
Leukopenia		30 (38)	3 (4)
Anemia		10 (13)	0

Primary endpoints: Safety, establish RP2D
Secondary endpoints: ORR, OS

Phase Ib Study of Venetoclax in Combination With Azacitidine: Efficacy



- 51 patients received the RP2D Ven 400 mg D1-14
- Median follow-up: 23 mo (range 0.1-44.2)
- ORR: 84% at RP2D
- Median TTR: 0.9 mo (95% CI: 0.7-5.8)
- Median DoR: 12.4 mo (95% CI: 9.9-NR)

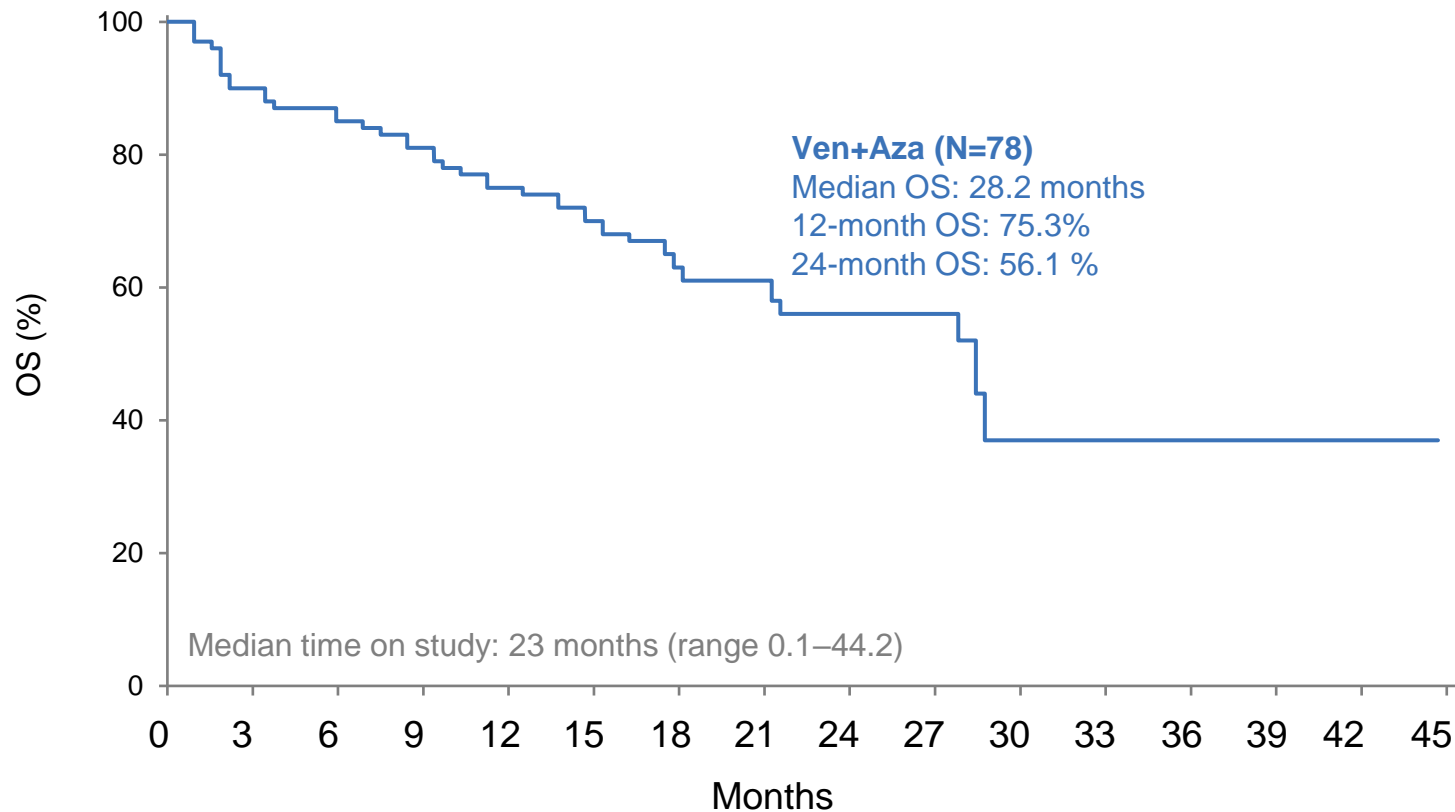
- Multi-hit/bi-allelic *TP53* mutations were found in 7 of 13 patients with *TP53* mutation
- Responses in multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation
 - CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff: December 15, 2020.

Ven+Aza associated with rapid, durable response in HR-MDS

Phase 1b, dose-escalation study in untreated patients (N=78)

Key secondary endpoint: Overall survival



Key outcomes	N=78
ORR (%)	80%
DoR for CR, median (95% CI), mo	13.8 (8.9–NR)
mCR+HI,[†] n/N (%)	13/31 (42)
OS, median (95% CI), mo	28.2 (17.7–NR)
TI rate,[‡] n/N (%) [95% CI]	20/43 (46.5) [31.2–62.3]

Most common Grade ≥3 AEs	N=78
Neutropenia	60%
Febrile neutropenia	51%
Thrombocytopenia	50%
Leukopenia	45%
Anemia	24%

23% of the study population moved to post-study alloHSCT* prior to other post-study systemic cancer therapies

ORR, overall response rate (CR+mCR)

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
AHCT 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 AHCT.

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

ORR

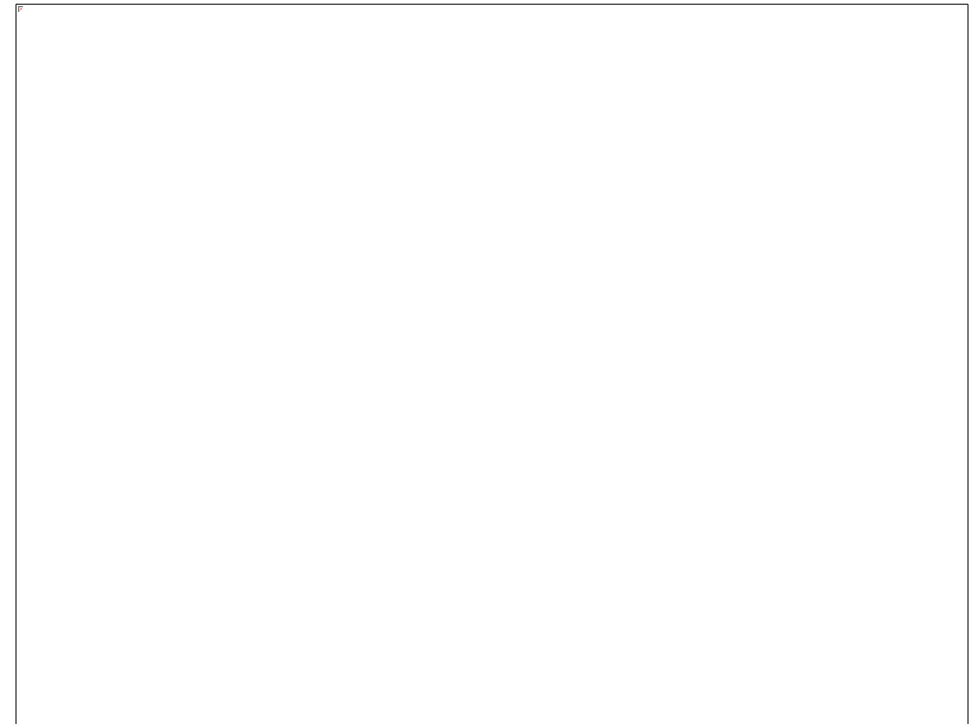
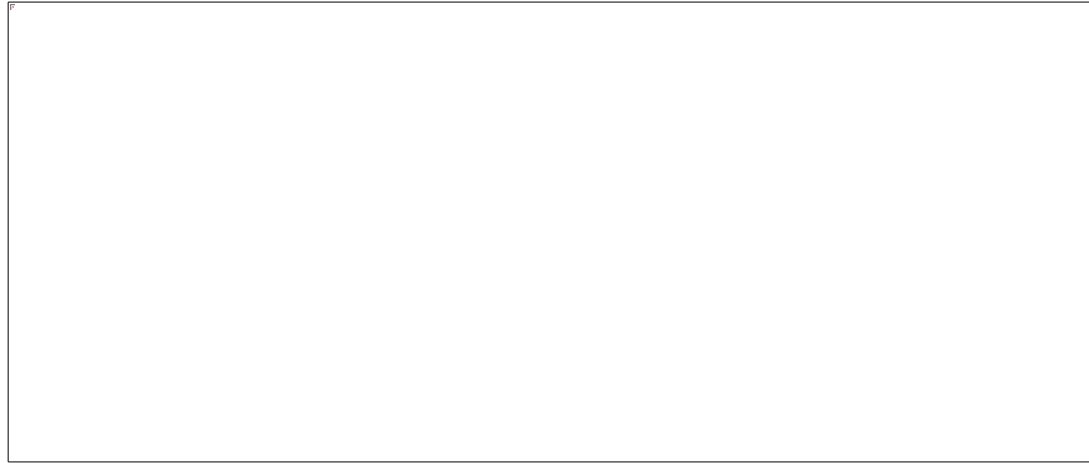
Phase 2: dose expansion
28 pts ASTX727 100/35mg
day 1-5 + VEN 400mg 1-14

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%

Ongoing Phase 2 trial (NCT05184842)

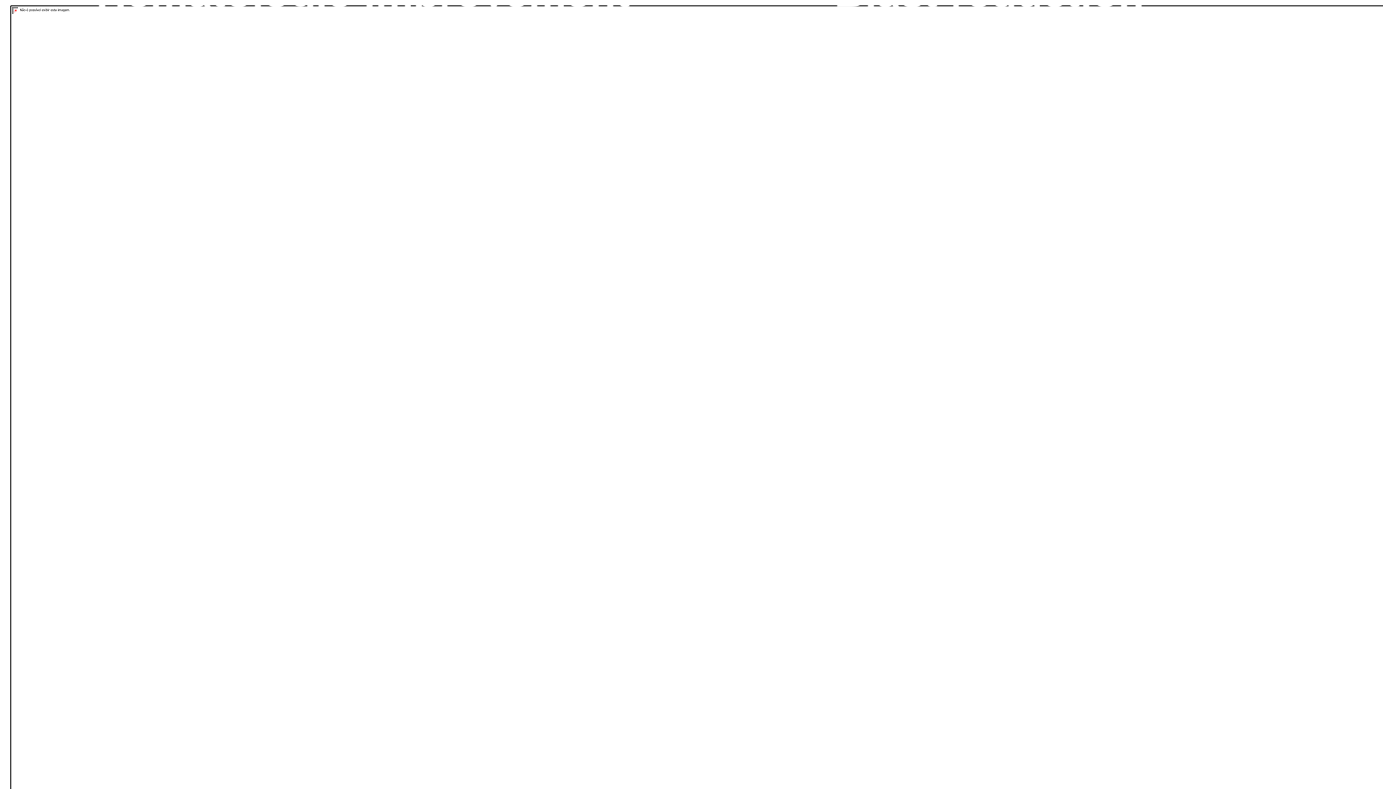
Metronomic Once Weekly Dosing of Decitabine and Venetoclax in MDS/AML



Courtesy of Dr Goldfinger

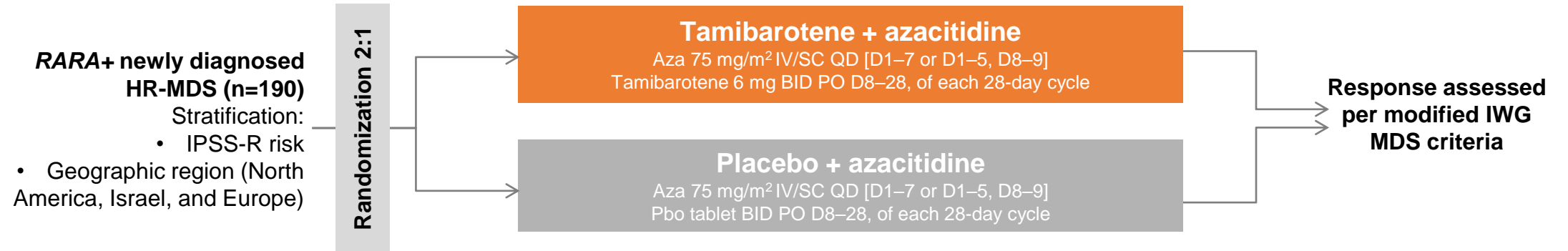
Interim Results:

AML patients who completed 12 -week induction	n=14
Age, median (IQR)	75 (62-87)
Female, n (%)	9 (64)
Median bone marrow blasts at diagnosis, n (range)	29 (15-90)
Adverse risk by ELN, n (%)	7 (50)
Response in evaluable AML patients, n (%)	n=14
CR	8 (57)
PR	1 (7)
MLFS	1 (7)
MRD negative CR (MFC , Hematologics)	6 (43)
Therapy tolerability in evaluable AML patients, n (%)	n=14
Treatment delays/interruptions	3 (21)
Grade ≥ 3 non-heme Adverse Events	0
60-day mortality	0
30-day mortality	0
Patients hospitalized	5 (36)



Tamibarotene + Aza vs Pbo+Aza

Phase 3, double-blind, randomized trial in patients with *RARA+* newly diagnosed HR-MDS



Key inclusion criteria

- Adults ≥18 years old
- *RARA+* based on the investigational biomarker test
- Newly diagnosed with HR-MDS by 2016 WHO classification and classified by IPSS-R as very high, high, or intermediate risk
- Blast count >5% at study entry

Key exclusion criteria

- Patients suitable for transplant at the time of screening

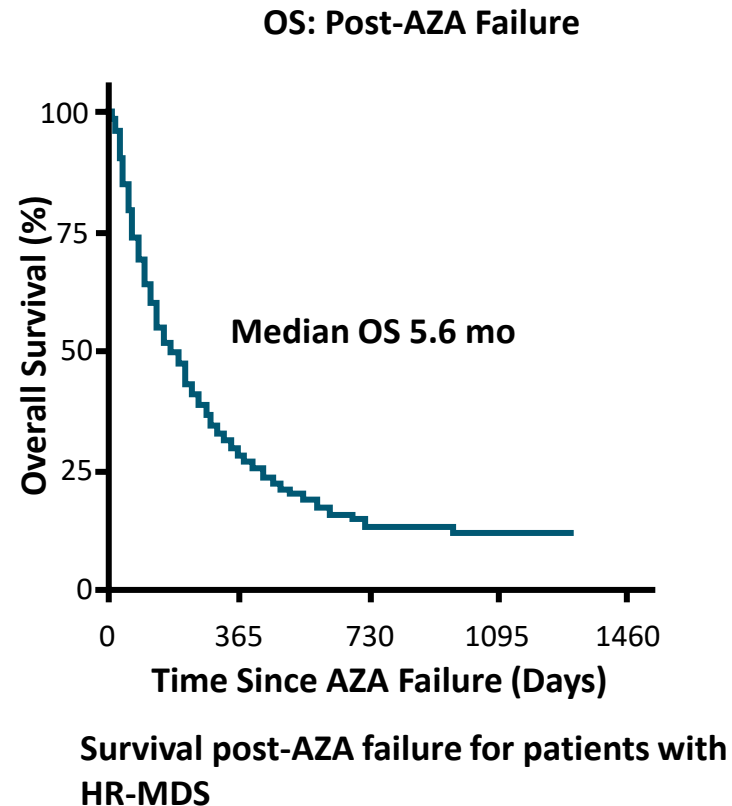
Primary endpoint

- Proportion of participants with CR [Timeframe: up to 5 years]

Key secondary endpoints

- ORR
- EFS, OS
- Transfusion independence

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



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 ($P = .70$)

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

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

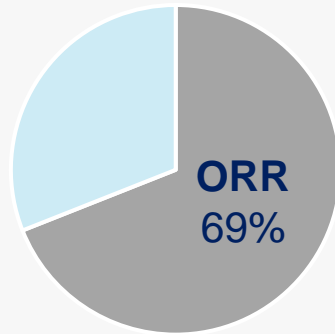
- **A:** HR-MDS, failed AZA (n=13)
- **B:** Untreated HR-MDS (n=11)
- **C:** LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

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



Ivosidenib in R/R *IDH1/IDH2*^{mut} MDS³

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

Efficacy outcomes	N=16	Safety outcomes	N=16
ORR	81%	Grade ≥3 AEs	69%
CR	44%	Grade ≥3 TRAEs	13%
mCR	31%	SAEs	44%
PR	6%		
HI	69%		
12-month duration CR+PR	60%		

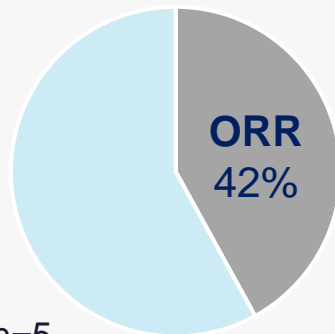
IDEAL: phase 2 study of Ena in 3 cohorts (N=26)²

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

Median follow-up: 8.6 months

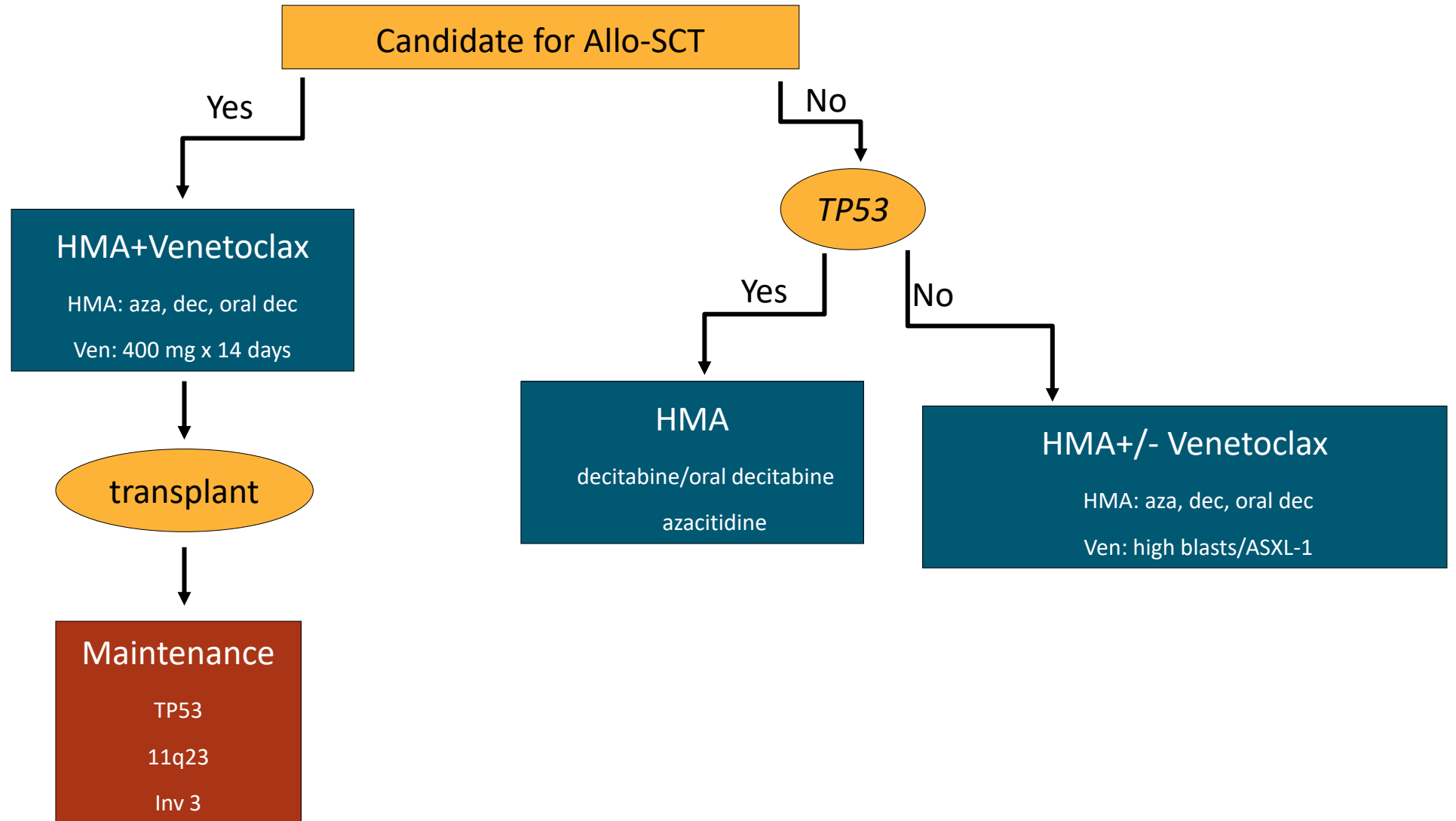
Median OS: 17.3 months

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



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)

How do I treat Higher risk MDS 2024?





Moffitt MDS team: Only perfect counts !!!

Acknowledgements:

- Our patients and their caregivers
- Moffitt MDS team