Treatment of Higher Risk Myelodysplastic Neoplasm (HR MDS)

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Disclosures

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Discussion of off-label use: venetoclax and azacitidine

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Topics to be discussed

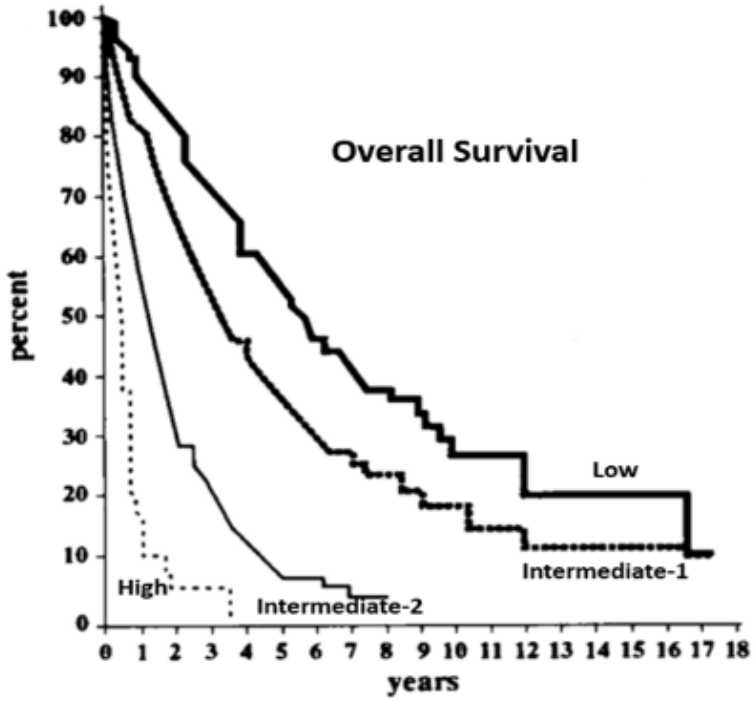
1. Currently available (nontransplant) frontline therapies for higher risk MDS

2. VERONA trial: venetoclax + azacitidine versus placebo + azacitidine

3. Next steps

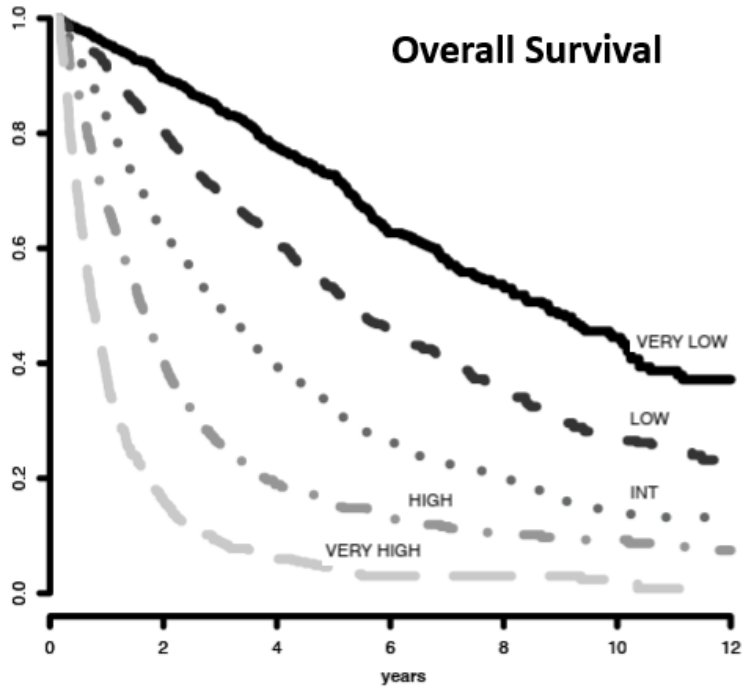
Definition Higher Risk MDS

IPSS



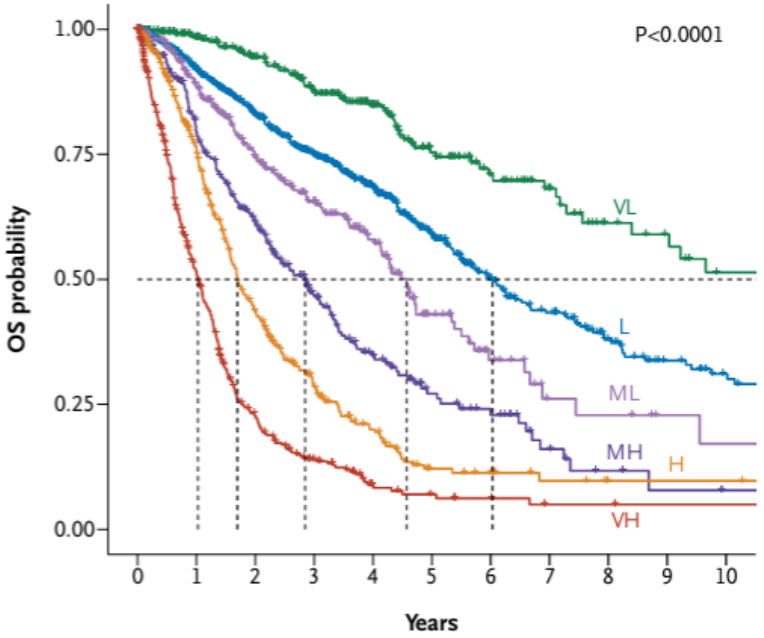
- Intermediate-2 and High risk
- Median OS: Int-2 (22%) 1.2y; High (14%) 0.4y

IPSS-R



- Intermediate (>3-4.5; but scores of >3.5 are consider higher risk), High and Very high risk
- Median OS: Int (20%) 3y; High (13%) 1.6y; Very high (10%) 0.8y

IPSS-M



- Moderate high, High and Very high risk
- Median OS: MH (11%) 2.8y; H (14%) 1.7y; VH (17%) 1y

H, high; Int, Intermediate; IPSS, International Prognostic Scoring System; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; L, low; MH, moderate high; ML, moderate low; OS, overall survival; VH, very high; VL, very low.

Greenberg, P. et al. *Blood.* 1997;89(6):2079-88; Greenberg, P. et al. *Blood* 2012;120(12):2454-65; Bernard, E. et al. *NEJM Evid.* 2022;1(7):EVIDoa2200008

Front-line Therapy for Treatment-Naïve HR-MDS

Lower intensity therapy: (a) azacitidine (AZA); (b) decitabine (DEC);
(c) decitabine/cedazuridine (DEC-C)

Intensive chemotherapy

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AZA monotherapy efficacy and safety

AZA-MDS-001: Phase III, multicentre trial of AZA *versus* conventional care regimens (CCRs) in patients with IPSS higher risk MDS (defined by FAB classification incl. WHO AML with <30% bone marrow blasts)

AZA-MDS-001

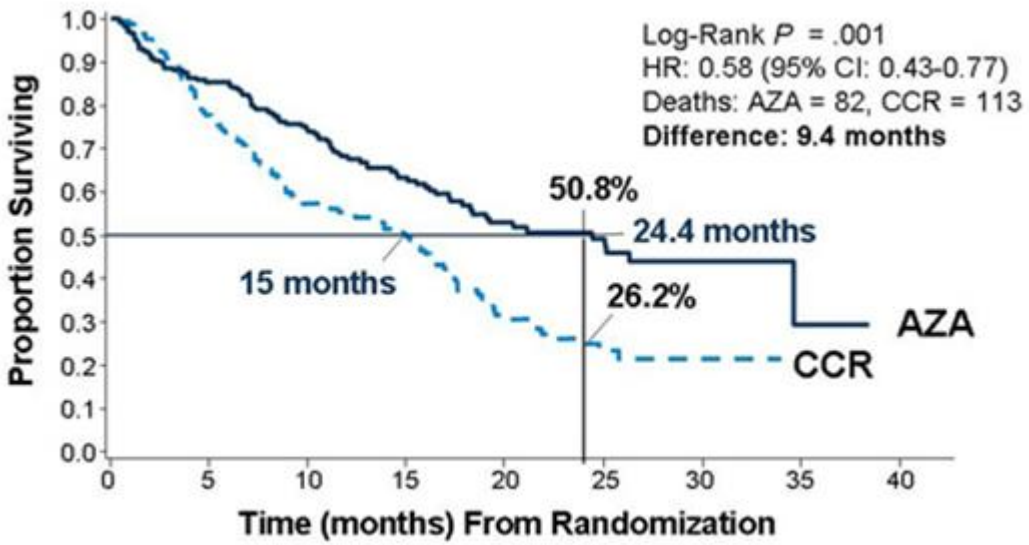
Phase III (open-label)
IPSS Intermediate-2 or High risk MDS
N=358

Randomized 1:1

- **AZA 75 mg/m² SC for 7 consecutive days per 28-day treatment cycle for at least 6 cycles**
- **CCR: BSC; LDAC SC or IC IV**

Primary endpoint: overall survival

Overall survival: AZA versus CCRs



	AZA (n=179)	CCR (n=179)	P
OR (CR+PR)	29%	12%	0.0001
CR	17%	9%	0.015
RBC-TI	45%	11%	<0.0001
DOR, months	13.6	5.2	0.0002
AML transformation (months)	17.8	11.5	<0.0001

The most frequent Grade 3 or 4 AEs in the AZA, LDAC and IC groups, respectively, were:

- Neutropenia (91%, 89% and 90%)
- Thrombocytopenia (85%, 96% and 95%)

Deaths during the first 3 months of therapy: 11% AZA vs 9% CCR

Real World Data:
Overall survival 10-19 months with azacitidine

Health Canada approved (2009) for the treatment of adults with IPSS intermediate-2 and high-risk MDS or AML with 20-30% blasts and multi-lineage dysplasia who are not eligible for haematopoietic stem cell transplantation

AE, adverse event; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimen; CR, complete remission; DOR, duration of response; IC, cytarabine + daunorubicin/idarubicin; IV, intravenous; LDAC, low-dose cytarabine; OR, overall response; OS, overall survival; PR, partial response; RBC-TI, red blood cell transfusion independency; SC, subcutaneous;

Fenaux, P. et al. *Lancet Oncol*. 2009;10(3):223–32.

IV Decitabine monotherapy efficacy and safety

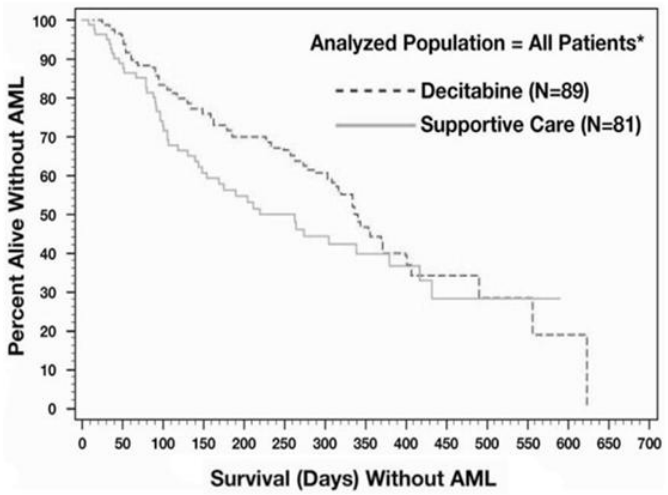
Phase III, multicentre trial of IV decitabine *versus* best supportive care (BSC) in patients with IPSS Intermediate-1/2 or high risk MDS (defined by FAB classification incl. WHO AML with <30% bone marrow blasts)

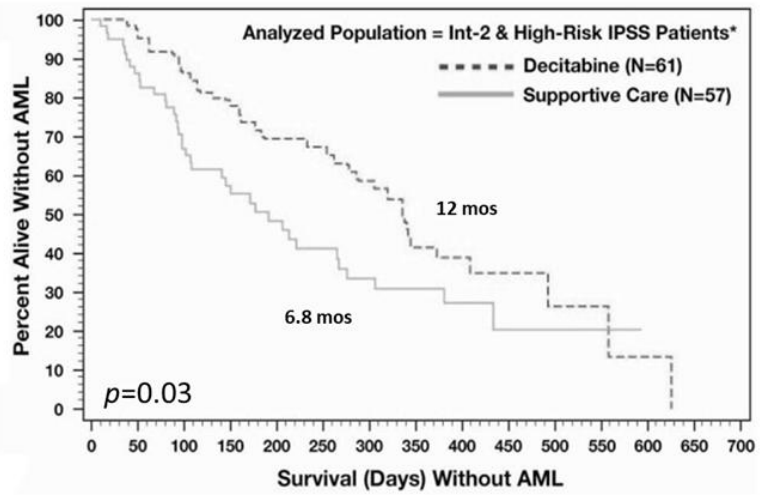
Phase III (open-label)
IPSS Intermediate-1/2 or High risk MDS
N=170

Randomized 1:1

- IV Decitabine 15 mg/m^2 IV q8hr for 3 consecutive days per 6-week* treatment cycle for maximum 10 cycles
- BSC

Primary endpoint:
- overall response rate
- time to AML or death





	DEC IV (n=89)	BSC (n=81)	P
OR (CR+PR)	17%	0%	<0.001
CR	9%	0%	
Hematologic Improvement	13%	7%	
DOR, months	10.3	NS	
AML transformation or death (months)[a]	12.1	7.8	0.16
Median OS (months)	14	14.9	0.636

[a] subgroup analysis IPSS Intermediate-2/High risk 12 mos *vs* 6.8 mos (P =0.03)

QoL: DEC superior for global health status, physical functioning, fatigue & dyspnea

- 52/170 (30% of patients had IPSS Intermediate-1 risk MDS)
- Median 3 cycles DEC (range, 0-9)

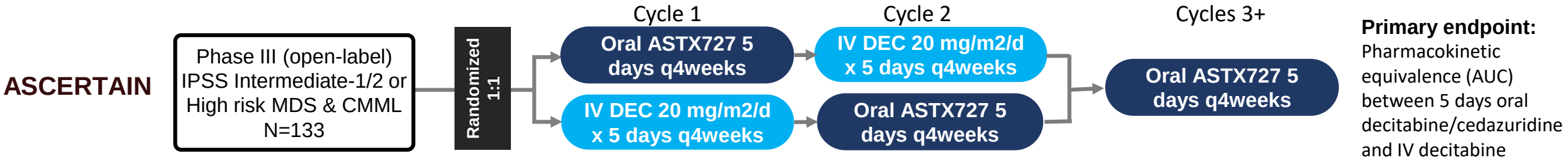
* 2 dose regimens are approved, but default dose/schedule is DEC 20 mg/m2/day IV x 5 consecutive days every 4 weeks

Health Canada approved (2019) for the treatment of adults with IPSS intermediate-1, intermediate-2 and high-risk MDS, French-American-British (FAB) subtypes (RA, RARS, RAEB, RAEB-t, and CMML) who are not eligible for haematopoietic stem cell transplantation

AE, adverse event; BSC, best supportive care; DEC, decitabine; CR, complete remission; DOR, duration of response; IV, intravenous; NS, not specified; OR, overall response; OS, overall survival;
Kantarjian, H. et al. *Cancer*. 2006;106(8):1794–80.

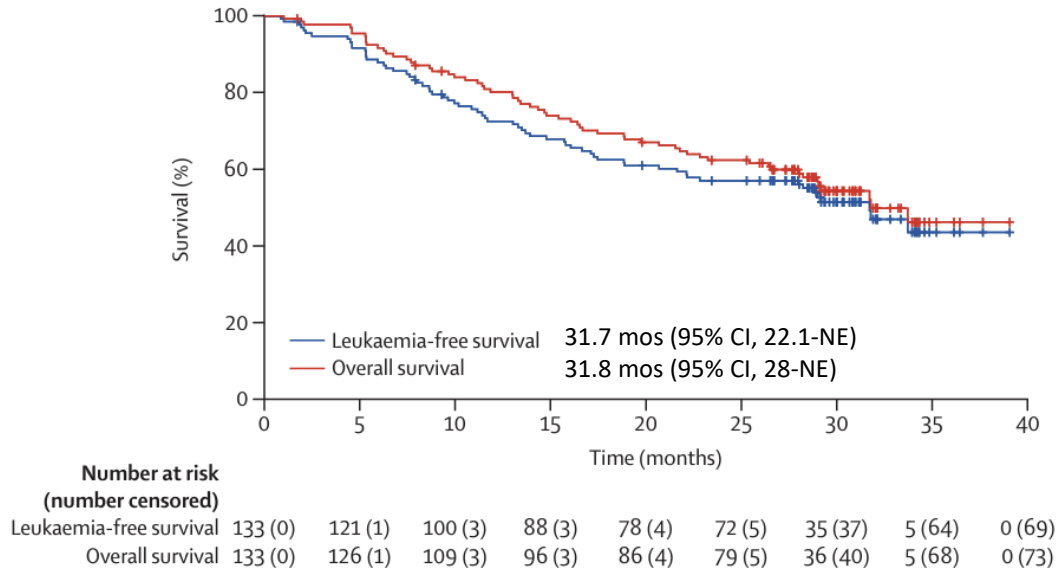
Oral decitabine 35 mg/cedazuridine 100 mg (ASTX727; DEC-C) *versus* IV decitabine

ASCERTAIN: Phase III, cross-over study of oral decitabine/cedazuridine (ASTX727) *versus* IV decitabine in patients with IPSS intermediate-2 or high risk MDS and CMML



Primary endpoint: Pharmacokinetic equivalence (AUC) between 5 days oral decitabine/cedazuridine and IV decitabine

The study met its primary endpoint of equivalence with high confidence: Oral/IV 5-day AUC 98.9% (90% CI 92.7, 105.6)



	All patients (n=133)
Complete remission (CR)	29 (25%)
Marrow CR Marrow CR + Hematologic improvement (HI)	43 (32%) 22 (17%)
Hematologic Improvement (HI)	10 (8%)
Overall response	**82 (62%)**

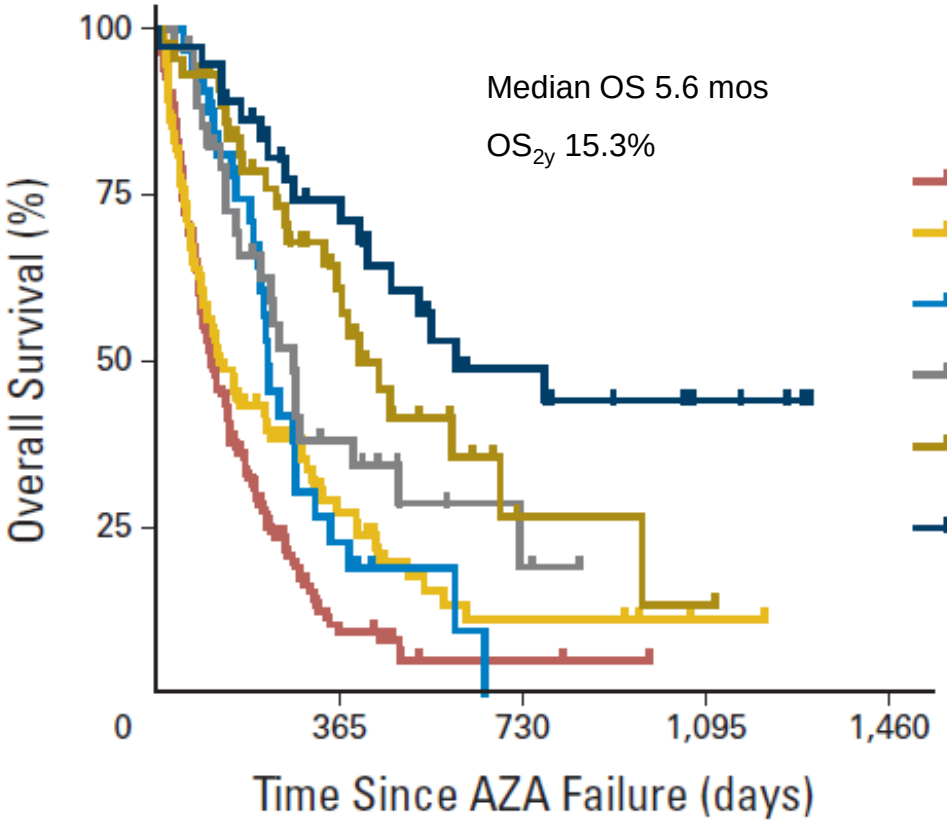
Median no. cycles 9 (range, 4-17); median treatment duration 8.2 mos (range , 3.9-17.7)

- 64/133 (48%) patients had IPSS Intermediate-1 risk MDS

Health Canada approved (2020) for the treatment of adults with IPSS intermediate-1, intermediate-2, and high-risk MDS, including previously treated and untreated, *de novo* and secondary MDS with the following French-American-British subtypes (RA, RARS, RAEB, and CMML)

Garcia-Manero, G. et al. *Lancet Haematol*. 2024;11(1):e15-e26.

Overall Survival According to Salvage Therapy



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 et al. J Clin Oncol 2011

[a] Survival was measured from the date of AZA failure; [b] Low dose chemotherapy (cytarabine, 6-mercaptopurine, hydroxyurea, melphalan); [c] Investigational therapy (epigenetic drugs [DNMTi +/- HDACi, HDACi-based regimens], immunomodulatory drugs [thalidomide, lenalidomide] , nonregistered compounds [triapine, etc]

Systematic review and meta-analysis of front-line intensive chemotherapy in MDS

- MEDLINE, Embase, Scopus and Cochrane databases from each database's inception from 1990 to January 27, 2020
- Studies combining AML and MDS outcomes or relapsed/refractory MDS were excluded
- Main endpoints: (a) overall remission rates (ORR), (b) 30- and 60-days mortality, & (c) 1-year, 2-year and 5-year OS
- Included 13 studies (4 studies were randomized)

Currently AML-like chemotherapy is mainly used as induction therapy prior to allogeneic HSCT

	Total patients (n=1,164)
Median age, y (range)	60.1 (17-88)
Males	58.9%
Abnormal cytogenetics	58.4%
Median % BM blasts (range)	17.8% (4-29%)
Induction regimens	7+3, FLAG, s-HAM, others
ORR	55% (CR 52%)
30-d mortality 60-d mortality	7% 15%
Median OS, mos OS_{1y} OS_{2y} OS_{5y}	11.6 48% 21% 5%

7+3, daunorubicin/idarubicin + cytarabine; AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; d, day; FLAG, fludarabine, cytarabine, G-CSF, MDS, myelodysplastic neoplasm; mos, months; OS, overall survival; s-HAM, sequential high-dose cytarabine and mitoxantrone; y, years.

Benkhadra, R.. et al. *J Clin Oncol.* 2020;38(15 supplement):e19530

Phase 3 VERONA Trial

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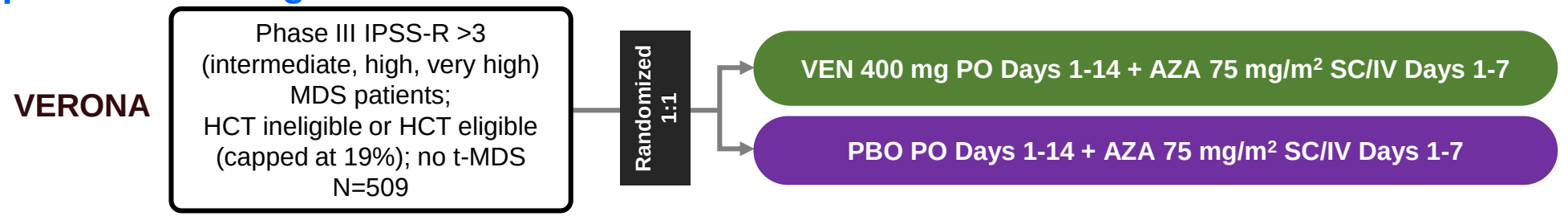
VEN + AZA Efficacy and Safety

VERONA: Phase III, multicentre, randomized, double-blind trial comparing VEN + AZA *versus* PBO + AZA in patients with higher risk MDS



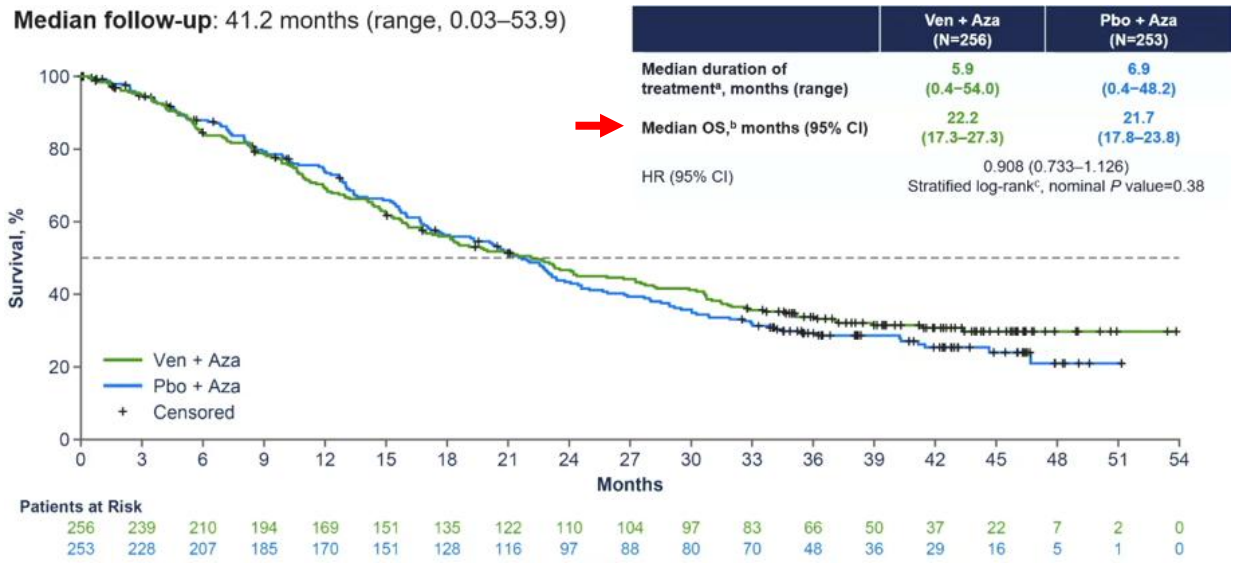
	VEN + AZA (n=256)	PBO + AZA (n=253)	P
Median age, y	72 (31-86)	72 (25-92)	NS
≥65 y, n (%)	203 (79.3)	189 (74.7)	
≥75 y, n (%)	87 (34)	103 (40.7)	
ECOG 0-1, n (%)	237 (92.5)	233 (92.1)	NS
IPSS-R risk group, n (%)			NS
Very high	90 (35.2)	83 (32.8)	
High	96 (37.5)	99 (39.1)	
Intermediate	70 (27.3)	71 (28.1)	
BM blasts, n (%)			NS
<5%	48 (18.8)	48 (19)	
≥5% to <10%	83 (32.4)	93 (36.8)	
≥10% to <20%	125 (48.8)	108 (42.7)	
≥20%	0	4 (1.6)	
Gene mutations, n (%)			NS
TP53	49 (24.5)	38 (18.7)	
ASXL1	60 (30)	68 (33.5)	
RUNX1	29 (14.5)	49 (24.1)	
EZH2	5 (2.5)	13 (6.4)	

	VEN + AZA (n=256)	PBO + AZA (n=253)	P
Median no. of cycles, (range)	6 (1-53)		
Modified OR (%)	76.2	57.7	< 0.001
CR	18	20	
PR	0.4	0	
mCR	57.8	37.5	
mCR with HI	27.3	18.2	
mCR without HI	30.5	19.4	
Treatment discontinuation, n (%)	231 (90.6)	234 (95.1)	NS
HCT	42 (16.5)	20 (8.1)	
Progressive disease	76 (29.8)	110 (44.7)	
Adverse event	51 (20)	37 (15)	
Patient withdrawal	36 (14.1)	41 (16.7)	
AML transformation, n (%)	**39/256 (15)**	**49/248 (20)**	NS
Median time to AML, mos (range)	9.7 (2.2-41)	6.8 (0.7-46)	

AZA, azacitidine; BM, bone marrow; d, days; HCT, hematopoietic cell transplant; IV, intravenous; mos, months; OR, overall response (CR+PR+mCR) according to IWG 2006 criteria; OS, overall survival; PBO, placebo; PO, per oral; SC, subcutaneous; VEN, venetoclax.

Garcia-Manero et al. ASH 2025 (abstract 13272); *Garcia-Manero et al.* SOHO 2025

VERONA: Phase III, multicentre, randomized, double-blind trial comparing VEN + AZA *versus* PBO + AZA in patients with higher risk MDS



	Ven + Aza (N=256)	Pbo + Aza (N=253)
Median duration of treatment[a], months (range)	5.9 (0.4–54.0)	6.9 (0.4–48.2)
Median OS,[b] months (95% CI)	22.2 (17.3–27.3)	21.7 (17.8–23.8)
HR (95% CI)	0.908 (0.733–1.126) Stratified log-rank[c], nominal *P* value=0.38	

- No difference in OS across all subgroups (trend favoring patient <75y, high IPSS-R & increased blasts, i.e. ≥5% to <20%)
- Neutropenia (77% vs 60%); Thrombocytopenia (66% vs 59%); Febrile neutropenia (23% vs 16%); No new safety signals

	VEN + AZA (n=256)	PBO + AZA (n=253)
Death ≤30d after last dose, n (%)	19 (7.5)	21 (8.5)
Subsequent treatment with HCT and other treatment		
Overall HCT, n (%)	43 (16.8)	33 (13)
Median time to HCT, mos (range)	5.6 (2.9-18.1)	6.7 (2.2-33.9)
HCT without intervening therapy, n (%)	39 (15.2)	23 (9.1)
HCT after additional treatment, n (%)	4 (9.3)	10 (30.3)
Venetoclax	0	5 (15.2)
Best response on study prior to HCT		
CR	11 (25.6)	9 (27.3)
mCR	26 (60.5)	11 (33.3)
Stable disease	6 (14)	13 (39.4)
All post-study therapy, n (%)	**73 (28.5)**	**98 (38.7)**
Venetoclax	27 (10.5)	53 (20.9)

Is there a role for VEN + AZA as bridge to allogeneic HCT in patients with MDS with increased blasts?

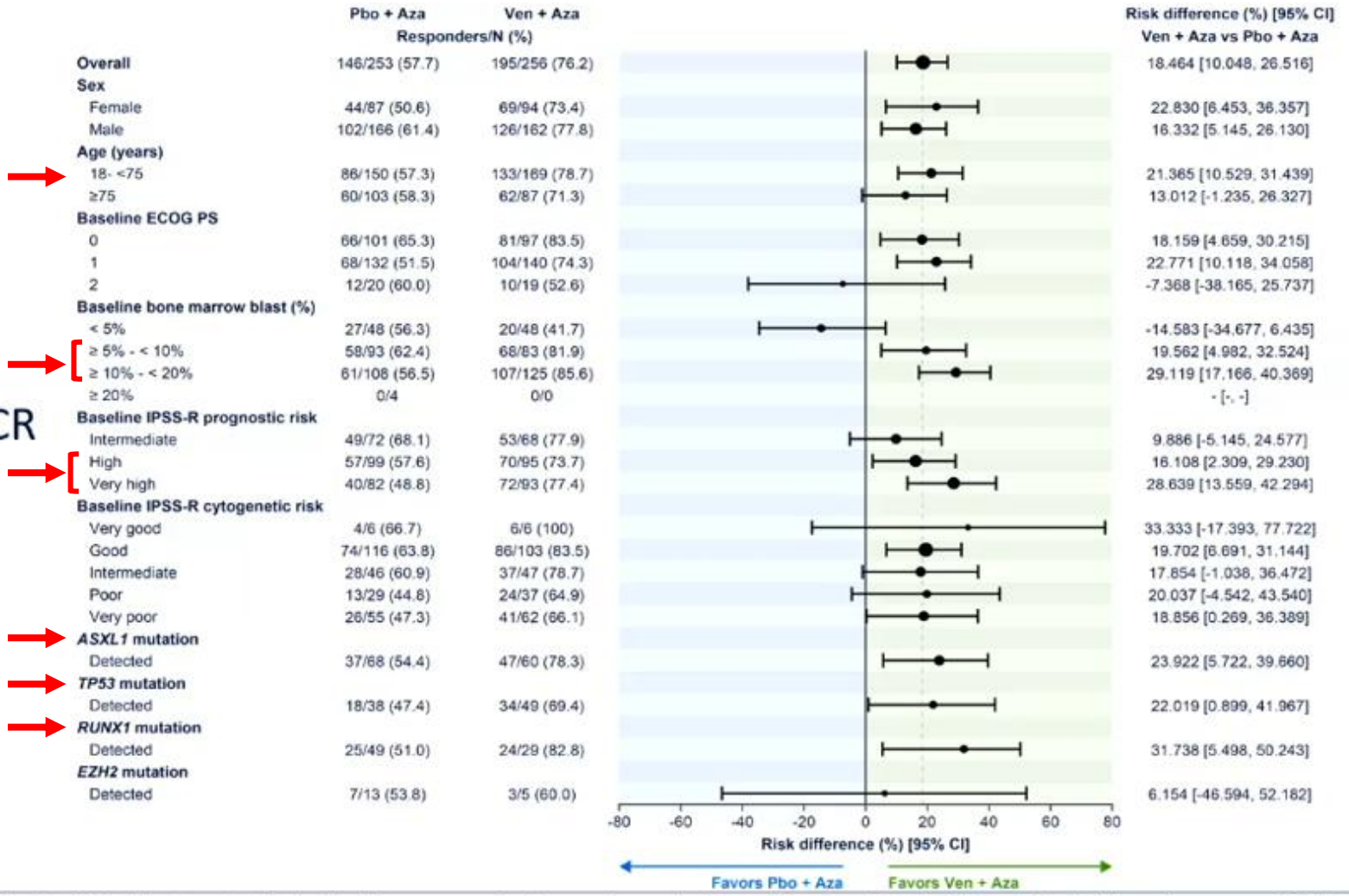
Is there a role for VEN + AZA as bridge to allogeneic HCT in patients with *TP53* mutated MDS?

AZA, azacitidine; d, days; HCT, hematopoietic cell transplant; mos, months; OS, overall survival; PBO, placebo; VEN, venetoclax.

Garcia-Manero et al. ASH 2025 (abstract 13272); *Garcia-Manero et al.* SOHO 2025

VERONA: Phase III, multicentre, randomized, double-blind trial comparing VEN + AZA *versus* PBO + AZA in patients with higher risk MDS

mOR:
CR + PR[b] + mCR



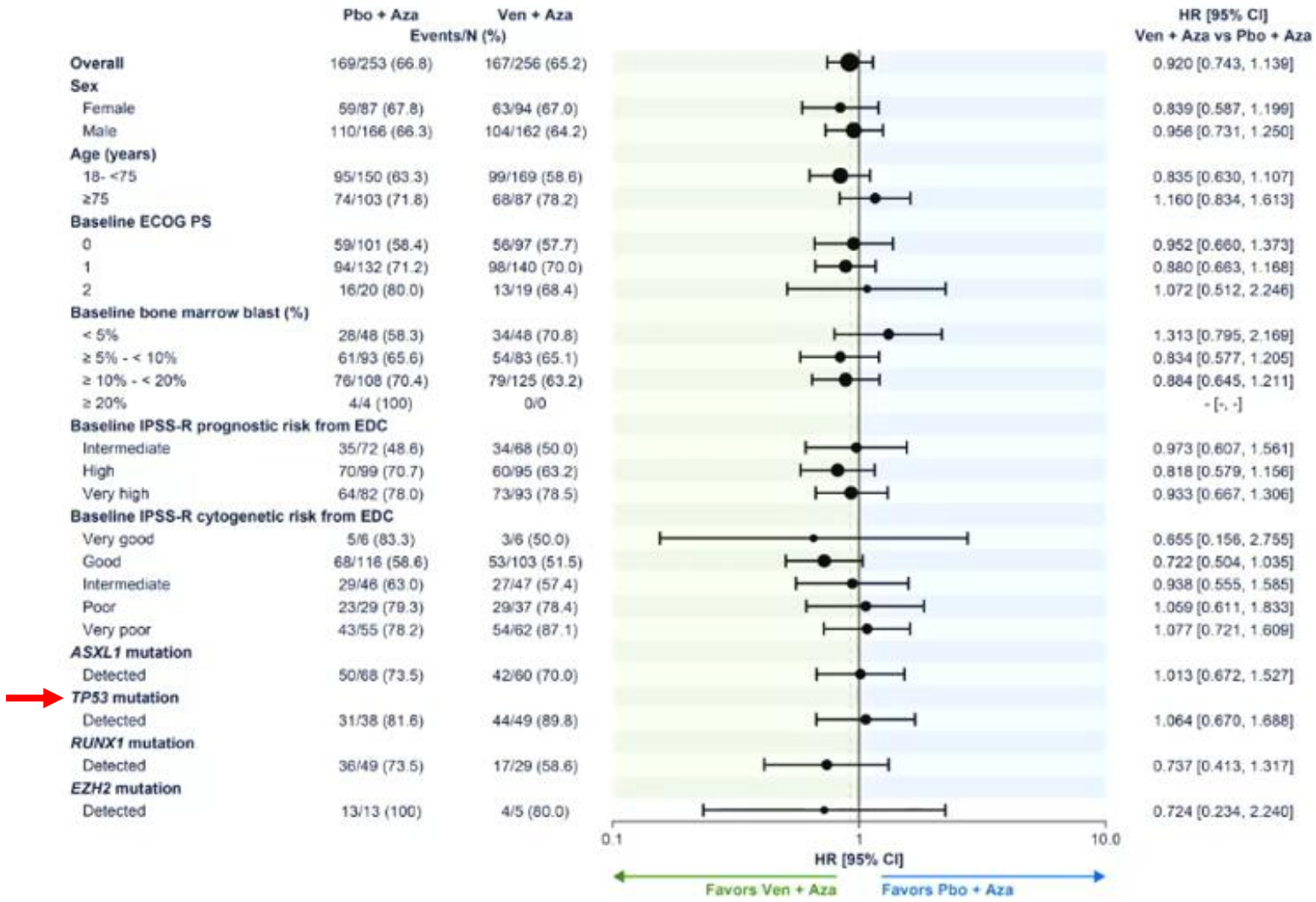
[a]Because the primary endpoint of OS did not meet statistical significance, no ranked secondary endpoints could be formally tested. [b]One PR in the Ven + Aza arm; no PR is the Pbo + Aza arm.

AZA, azacitidine; mOR, modified overall response (CR+PR+mCR) according to IWG 2006 criteria; OS, overall survival; PBO, placebo; VEN, venetoclax.

Garcia-Manero et al. ASH 2025 (abstract 13272); *Garcia-Manero et al.* SOHO 2025

VERONA: Phase III, multicentre, randomized, double-blind trial comparing VEN + AZA *versus* PBO + AZA in patients with higher risk MDS

Overall survival



Is there a role for VEN + AZA as bridge to allogeneic HCT in patients with MDS with increased blasts?

Is there a role for VEN + AZA as bridge to allogeneic HCT in patients with *TP53* mutated MDS?

AZA, azacitidine; EDC, electronic data capture; PBO, placebo; VEN, venetoclax.
Garcia-Manero et al. ASH 2025 (abstract 13272); *Garcia-Manero et al.* SOHO 2025

Issues with the study

- The protocol specified decreasing the dose of the AZA before decreasing dose of the venetoclax
- Was the dose of the AZA was reduced when it should not have been?
- A quarter of the patients had IPSS-R Intermediate (>3-4.5) risk – lower-risk MDS (≤3.5) median OS 5.9y vs higher-risk MDS (>3.5) median OS 1.5y
- 20% of the patients had blasts of 5-9% on the study and may not have benefited from the VEN + AZA combination
- Study was not powered for single agent AZA OS of 22 mos (as real life OS with single AZA was lower at 10-19 mos)
- Off study treatments affecting OS

Why So Many Unsuccessful Trials?

Phase 2 & 3 randomized trials in patients with higher-risk MDS

Agent (study)	Target	N	Population	Randomization	Endpoint	Result
Lenalidomide or **vorinostat** (North American Intergroup S1117; Ph2)	Immunomodulatory drug; HDAC inhibitor	277	Incl CMML; IPSS Intermediate-2 or High (+/- ≥ 5% BM blasts)	1:1:1; lenalidomide + AZA *vs* vorinostat + AZA *vs* AZA	Primary: ORR (CR+PR+HI)	ORR 49% vs 27% vs 38% (*P*=NS)
Pevonedistat (PANTHER; Ph3)	NEDD8 inhibitor	454	Incl CMML-MD + AML 20-30% blasts; IPSS-R Intermediate (>5% BM blasts), High, Very high	1:1; pevonedistat + AZA *vs* AZA alone	Primary: EFS Secondary: OS	EFS 17.7 mos *vs* 15.7 mos (HR 0.968 [95% CI 0.757-1.238]; *P*=0.557)
Eprenetapopt (Ph3)	TP53 reactivator	154	TP53 mutated	1:1; eprenetapopt + AZA *vs* AZA alone	Primary: CR	CR 34.6% *vs* 22.4% (*P*=NS)
Sabatolimab (STIMULUS; Ph2)	TIM3 inhibitor	127	>5% BM blasts; IPSS-R Intermediate, High, Very high	1:1; sabatolimab + AZA/DEC *vs* PBO + AZA/DEC	Primary: CR + PFS Secondary: OS	CR 22% vs 18% (*P*=0.77); PFS 11.1 mos *vs* 8.5 mos (HR 0.75 [95% CI 0.48-1.17]; *P*=0.1022)
Magrolimab (ENHANCE; Ph3)	CD47 monoclonal antibody	539	IPSS-R Intermediate, High, Very high	1:1; magrolimab + AZA *vs* PBO + AZA	Primary: CR + OS	CR 21.3% *vs* 23.6% (*P*=0.5218) OS 15.9 mos vs 18.6 mos (HR 1.203 [95% CI 0.947-1.528]; *P*=0.1299)
Tamibarotene (SELECT-MDS-1; Ph3)	RARα agonist	190/246	↑RARα expression by RT-PCR; IPSS-R Intermediate (>5% BM blasts), High, Very high	2:1; tamibarotene + AZA *vs* PBO + AZA	Primary: CR Secondary: OS	CR 23.81% *vs* 18.75% (*P*=0.2084)
Venetoclax (VERONA; Ph3)	BCL2 inhibitor	509	IPSS-R Intermediate, High, Very high	1:1; VEN + AZA *vs* PBO + AZA	Primary: OS	OS 22.18 mos *vs* 21.68 mos (*P*=0.38)

AZA, azacitidine; BM, bone marrow; CI, confidence interval; CR, complete remission; DEC, decitabine; EFS, event-free survival; HI, hematologic improvement; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; Ph, phase; PR, partial response; VEN, venetoclax.

Sekeres, M. et al. *J Clin Oncol.* 2017;35(24):2745-53; Adès, L. et al. *Blood Adv.* 2022;6(17);5132-45; https://clinicaltrials.gov/study/NCT03745716?tab=results; Zeidan, A. et al. *Lancet Haematol*. 2024;11(1):e38–e50; DeZern, A. et al. *Blood Adv.* 2025;9(16):4090-9; https://clinicaltrials.gov/study/NCT04313881?tab=results; Garcia-Manero, G. et al. ASH 2025

Clinical risk categories do not fully reflect underlying disease biology driving treatment vulnerability

Biology-driven trial design→ Design trials based on shared disease biology rather than risk categories alone (e.g., “AML-like” vs “MDS-like” biology).

TP53-inactivated MDS: distinct biology, poor prognosis, and no **OS benefit despite higher response rates**

TP53-specific strategies → Evaluate *TP53*-inactivated MDS in dedicated trials or stratify by *TP53* status, prioritizing EFS and OS over response rates to assess true clinical benefit.

Signals of excessive toxicity and early discontinuation in early-phase trials are frequently underappreciated before phase 3 testing

Early toxicity as a stop signal → Do not ignore early excessive toxicity or premature discontinuation in phase I–II; these signals should inform phase III feasibility and site selection.

IWG 2006 response criteria may misrepresent true clinical benefit, inflating ORR without meaningful survival impact in HR-MDS

Modern response criteria → IWG 2023 response criteria for HR-MDS focus on **more precise** reporting of patient-centric & clinically meaningful outcomes.

courtesy of Dr. Anna Flavia Patino

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Thank you!

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