INSTITUT DE RECHERCHE SAINT-LOUIS
Hématologie I Immunologie I Oncologie

THEMA
THE NATIONAL CENTER FOR PRECISION MEDICINE IN LEUKEMIA

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Groupe Francophone des Myélodysplasies

Treatment of HR MDS – Future perspective

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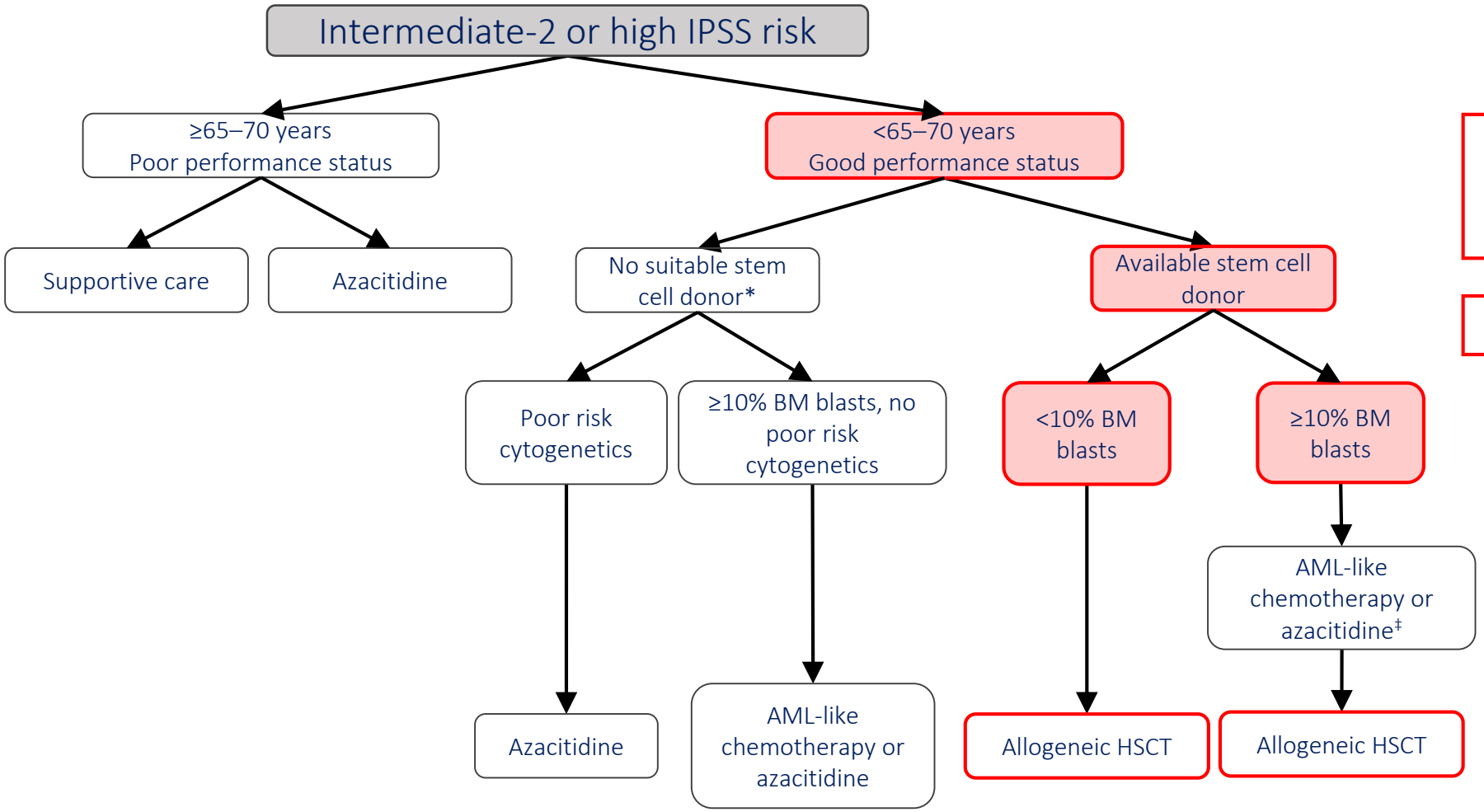
Conflict of interest

Name of Company	Research support	Scientific Advisory Board
BMS/CELGENE	X	X
NOVARTIS		X
TAKEDA		X
ABBVIE	X	X
ROCHE		X
SERVIER	X	

Treatment algorithm for high-risk MDS before 2024

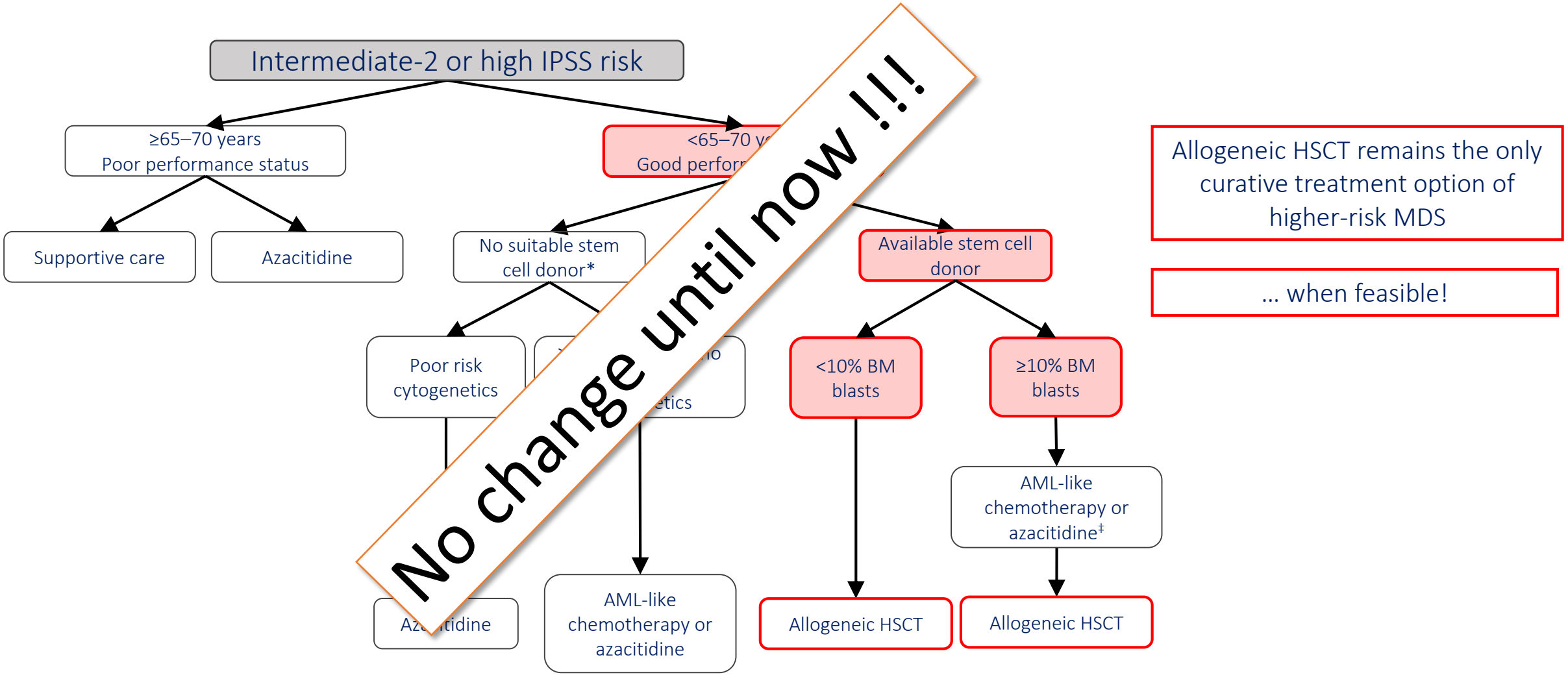


Allogeneic HSCT remains the only curative treatment option of higher-risk MDS

… when feasible!

Malcovati L, et al. Blood 2013;122:2943–64

Treatment algorithm for high-risk MDS in 2024



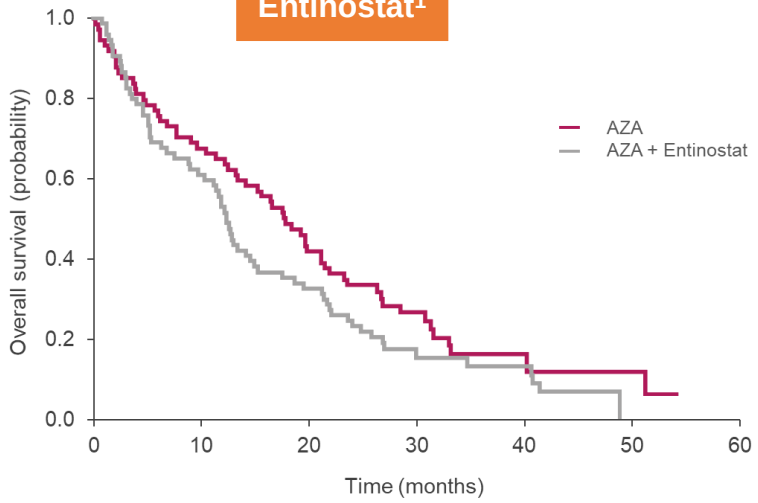
Allogeneic HSCT remains the only curative treatment option of higher-risk MDS

… when feasible!

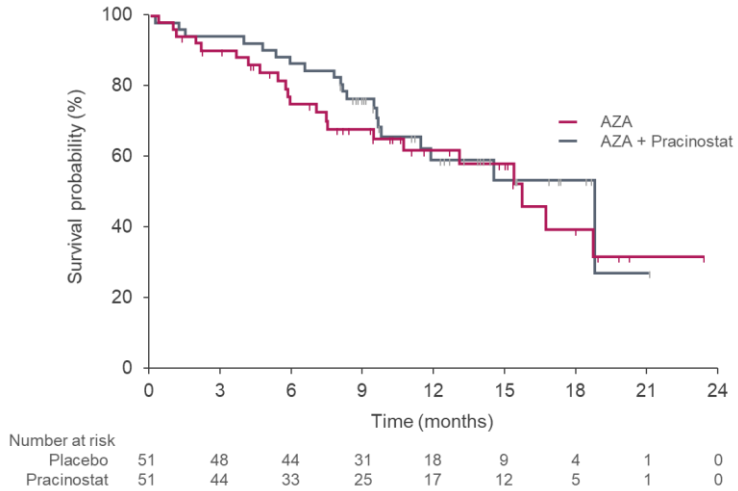
Malcovati L, et al. Blood 2013;122:2943–64

So far, No benefit in randomized studies

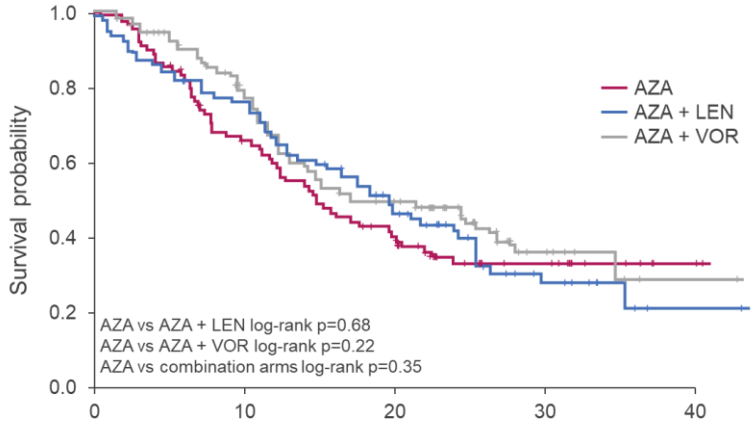
Entinostat[1]



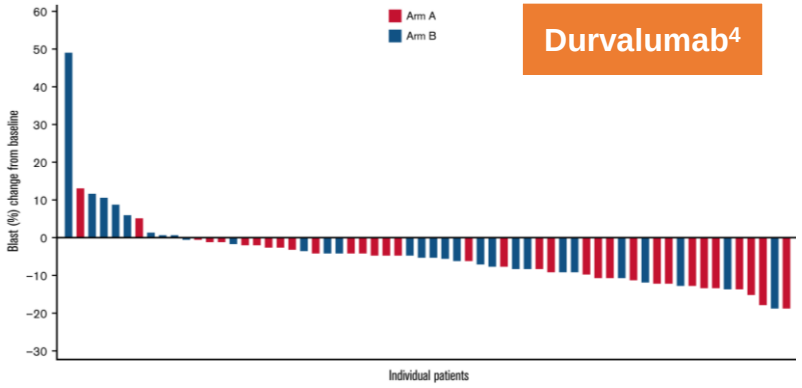
Pracinostat[2]



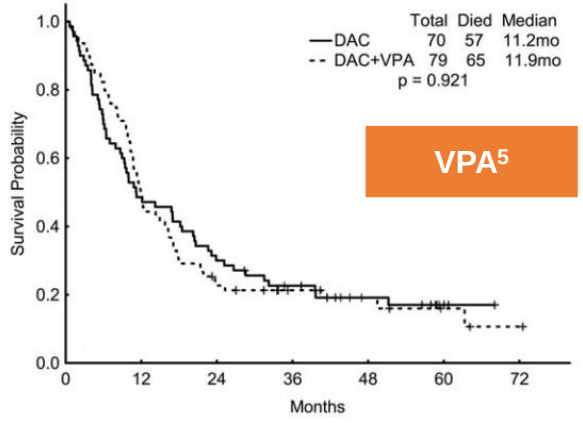
Vorinostat Lenalidomide[3]



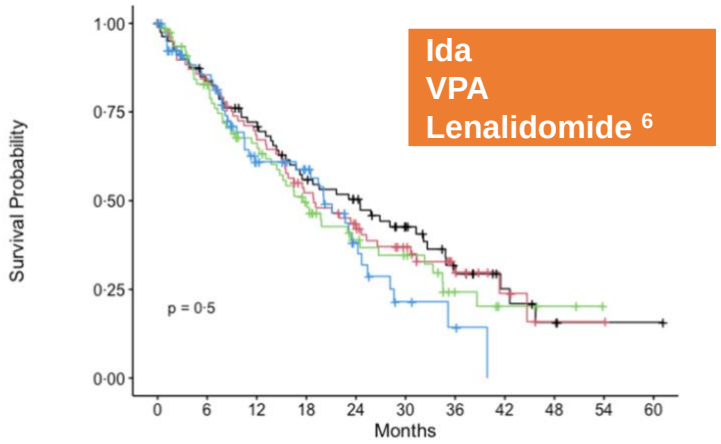
Durvalumab[4]



VPA[5]



Ida VPA Lenalidomide [6]



1. Prébet T, et al. J Clin Oncol 2014;20:1242–8; 2. Garcia-Manero G, et al. Cancer 2017;213:994–1002; Sekeres M, et al. J Clin Oncol 2017;35:2745–53, 4 Zeidan et al Blood Adv 2022, 5 Issa et al. Cancer 2015, 6 Ades et al, BJH 2022

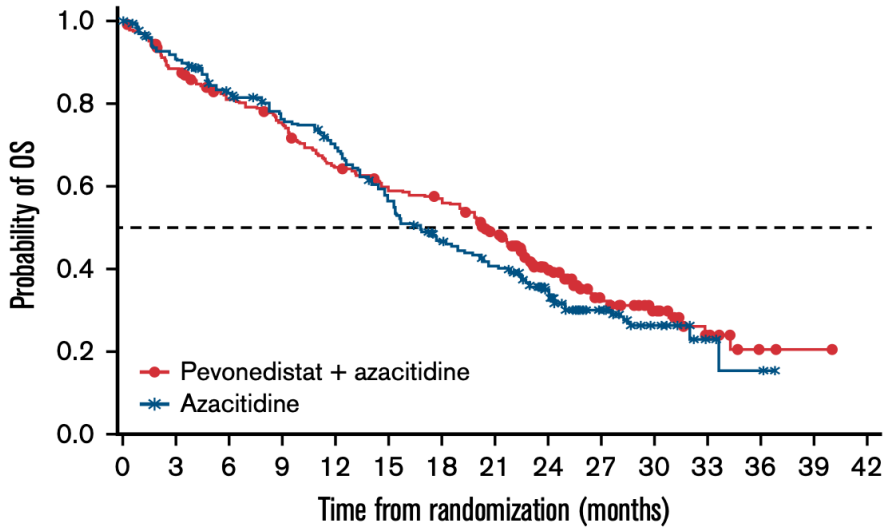
… Even in more recent trials, with «more potent» drugs

Rational selection rather than convenient repurposing

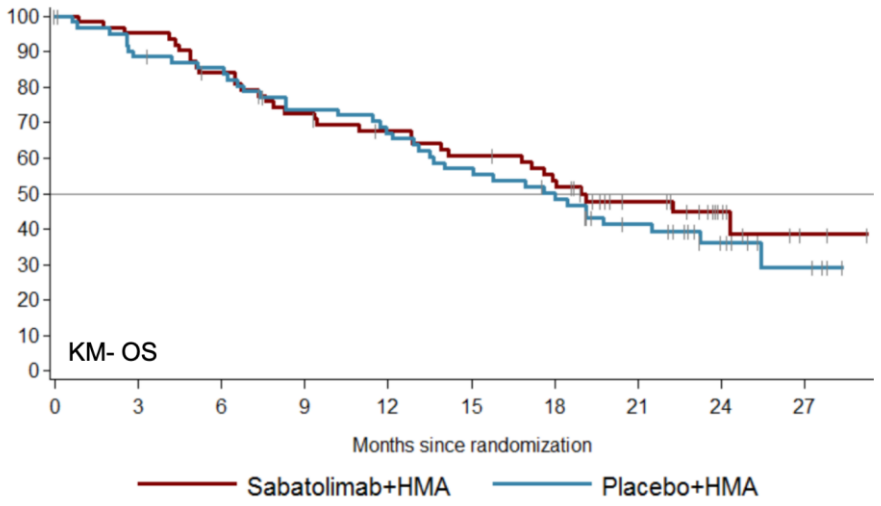
APR 246 [1]

The trial did not meet its primary endpoint, complete remission (CR) rate.
CR: 33.3% versus 22.4% in the AZA alone arm (P=0.13)

Pevonedistat[2]



Sabatolimab[3]

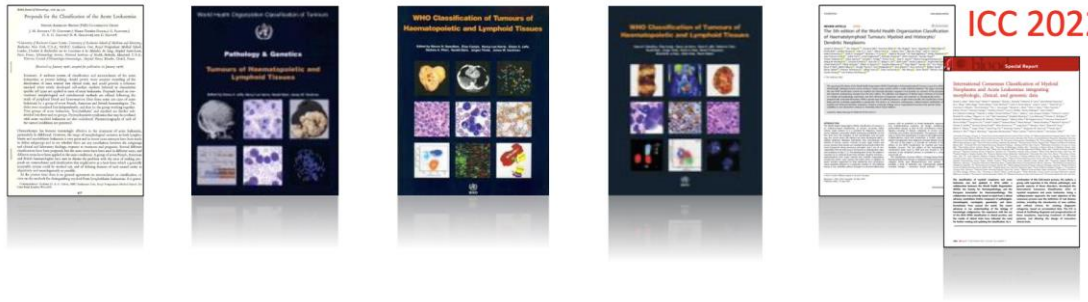


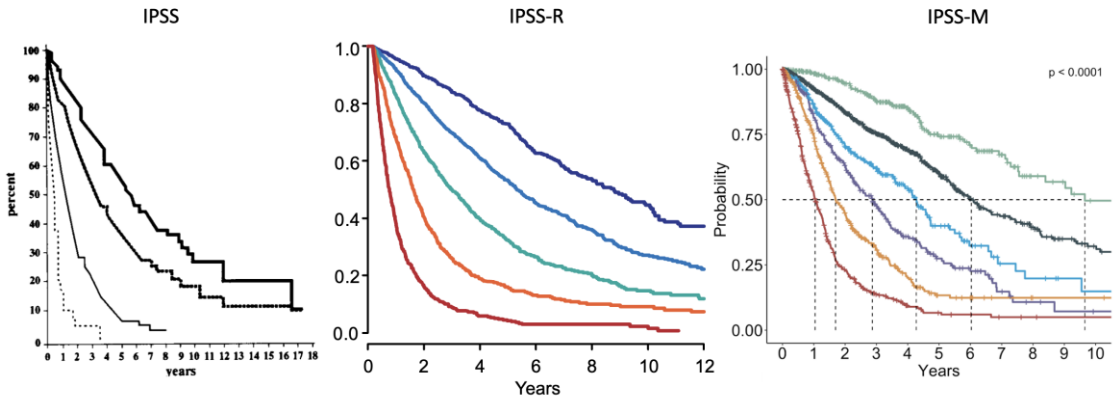
1. Press Release, 3 Adès et al Blood Adv 2022, 3. Zeidan ASH 2022

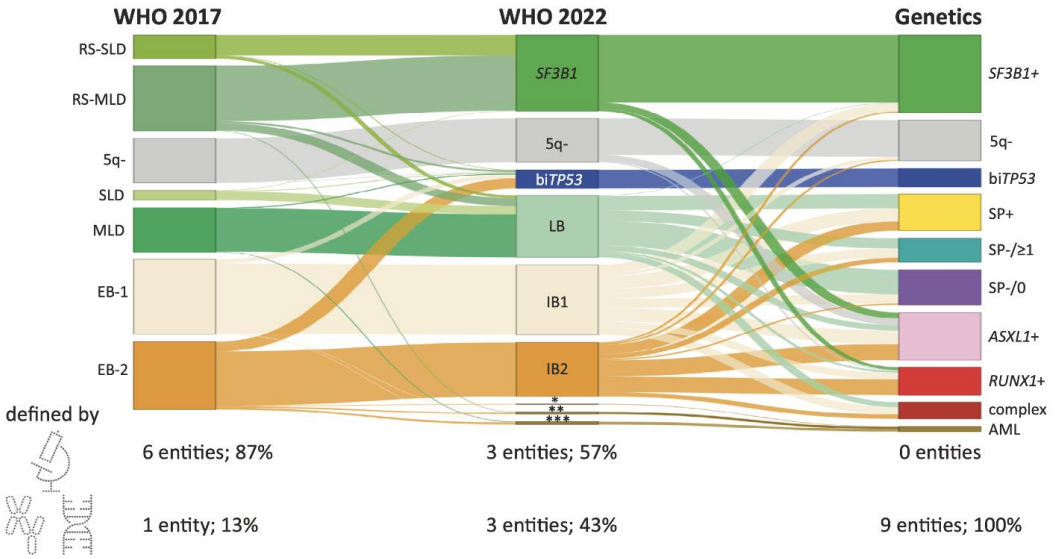
Problem #1
Have a good definition of the disease

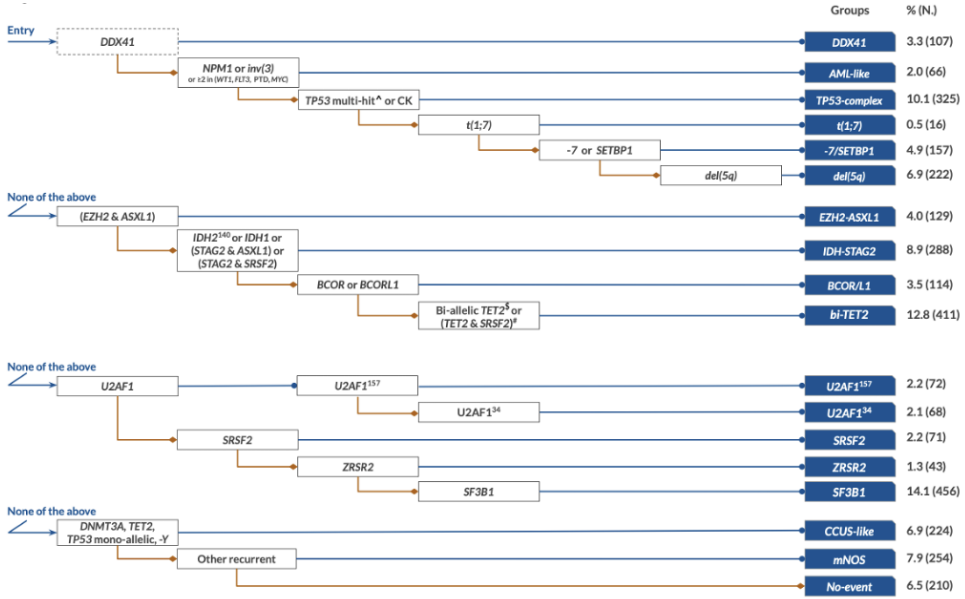
MDS HR : Do we have a definition problem?

FAB 1976 WHO 2001 WHO 2008 WHO 2017 WHO 2022 ICC 2022





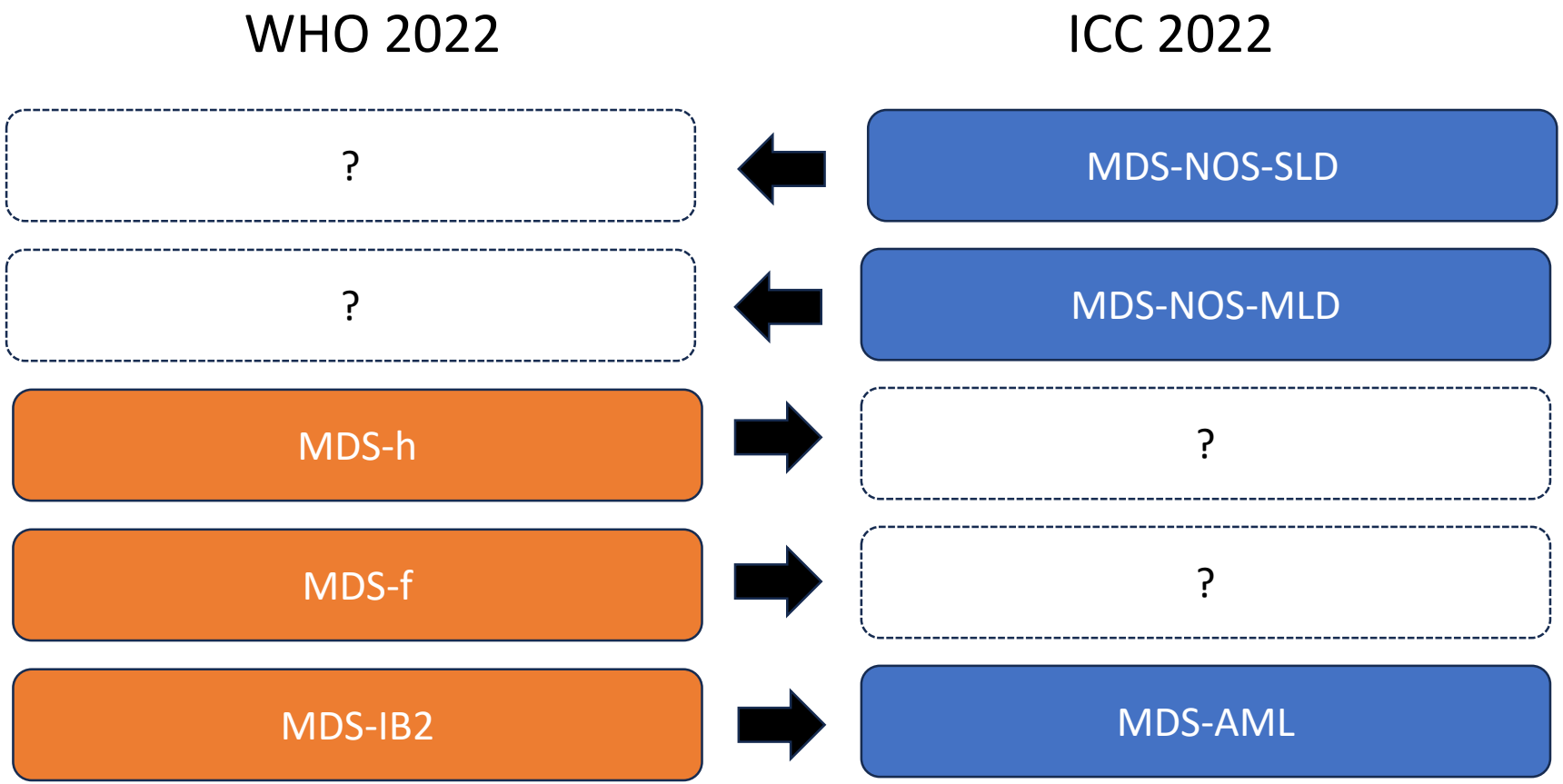




Huber et al, Leukemia 2023

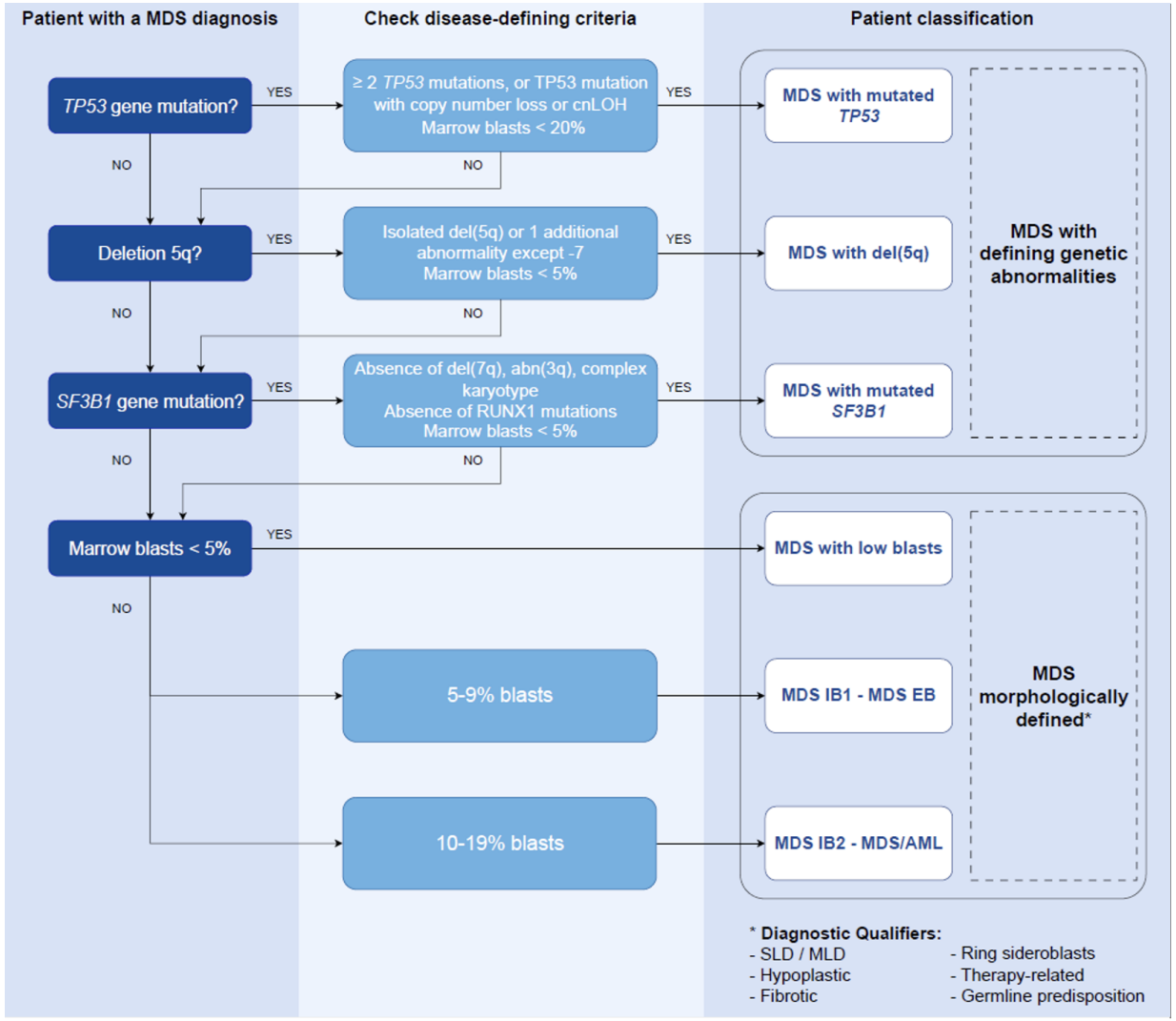
Elsa Bernard et al. ASH 2023

Orphant entities in each classification



How to avoid a confusion of languages ?

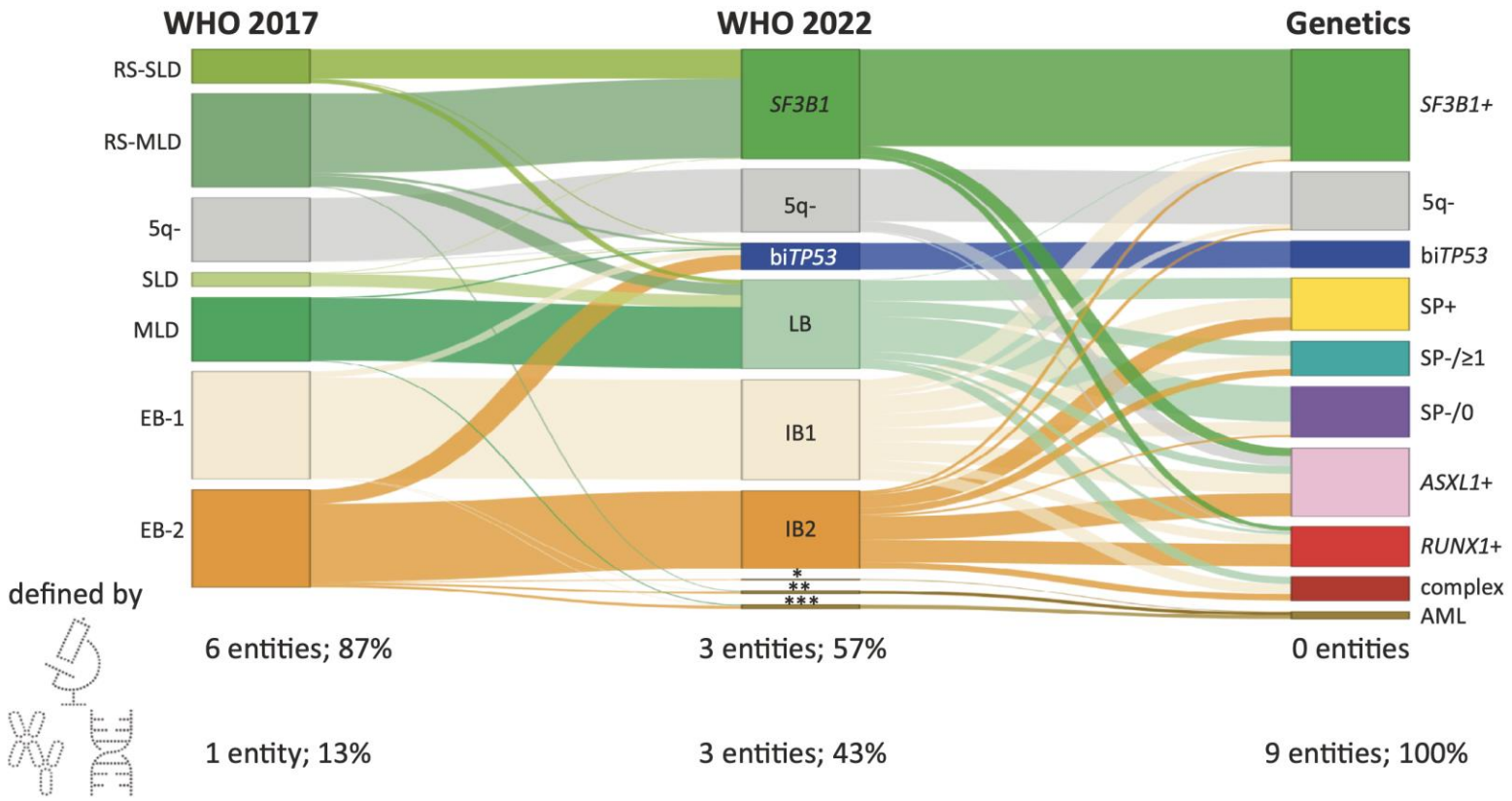
A Delphi consensus process involving 71 experts from 11 countries

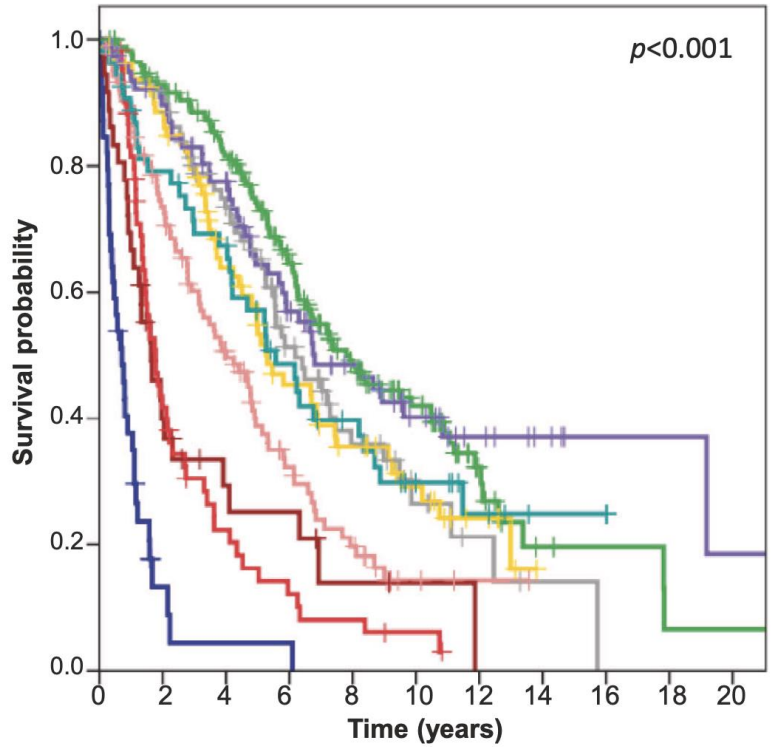


Adapted from Lanino et al. ASH 2023
RS Komrokji, L Lanino, S Ball, JP Bewersdorf et al. Submitted

Towards a molecular definition of MDS?

A first attempt by the MLL : A proposed classification makes the use of blast counting redundant (9 groups)

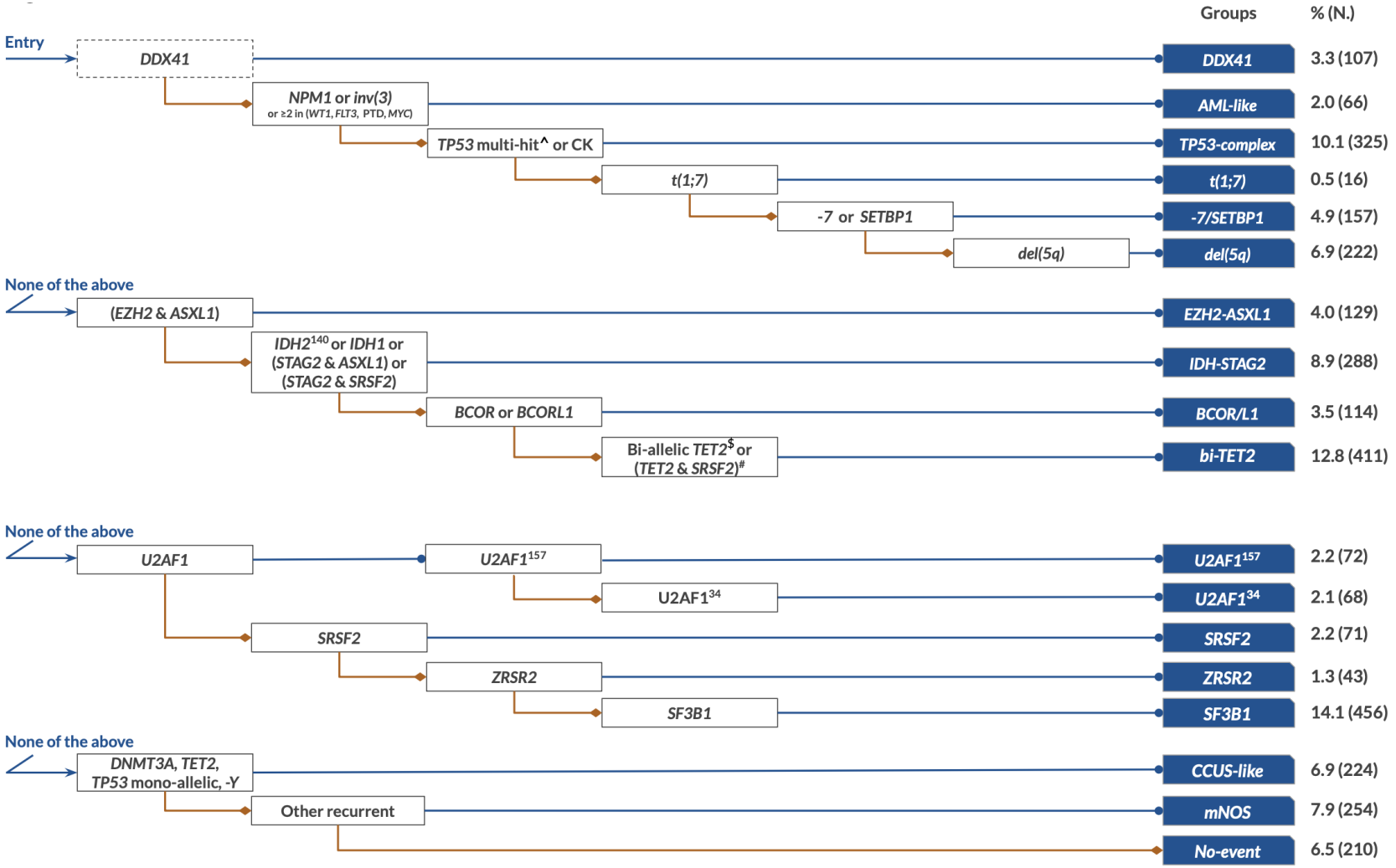




Huber et al, Leukemia 2023

Towards a molecular definition Molecular taxonomy of MDS

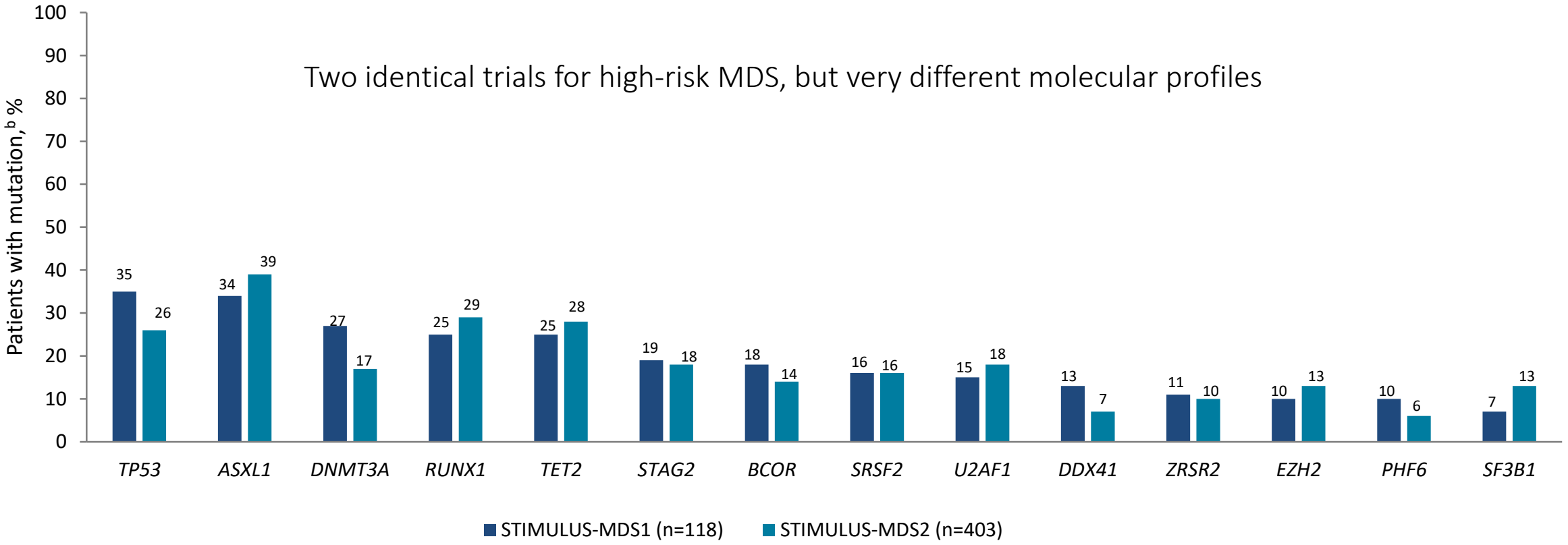
…but how to deal with 18 groups?



Elsa Bernard et al. Blood 2024

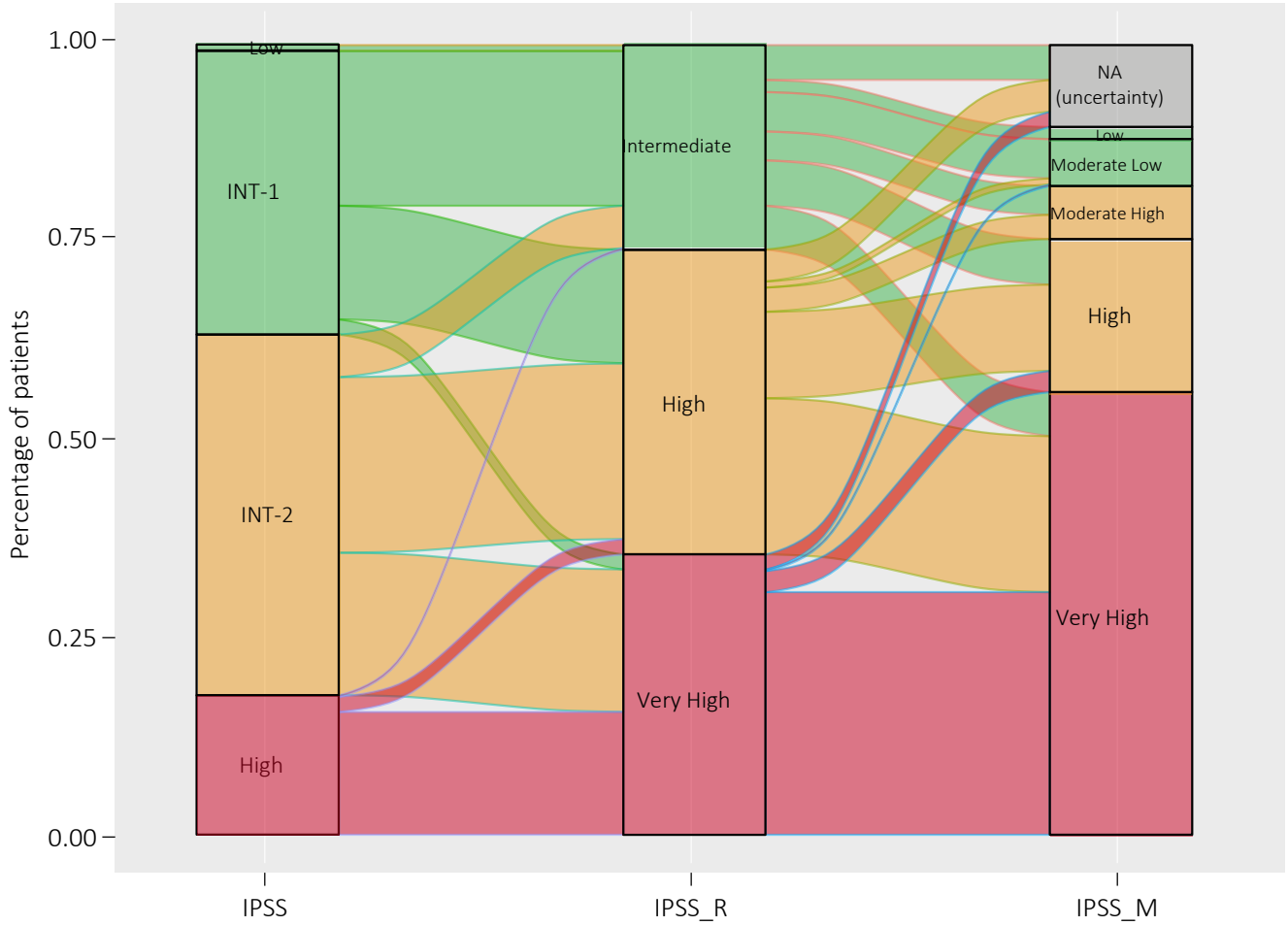
Problem #2
Avoid TP53^{m} patients in clinical trial for HR MDS

Mutation profile: Two consecutive trials STIMULUS-MDS1 and MDS2



Valeria Santini et al. ASH 2022

IPSS, IPSS-R, et IPSS-M : Two consecutive trials STIMULUS-MDS1 & MDS2



- Patients enrolled according to IPSS-R
- Upstaging was observed from IPSS criteria to IPSS-R
- Upstaging was also observed from IPSS-R criteria to IPSS-M
  - 51% of patients with HR IPSS-R were upstaged to vHR IPSS-M

Complete genetic assessment at baseline will improve evaluation in clinical trials and provide useful information for treatment decisions.

Valeria Santini et al. ASH 2022

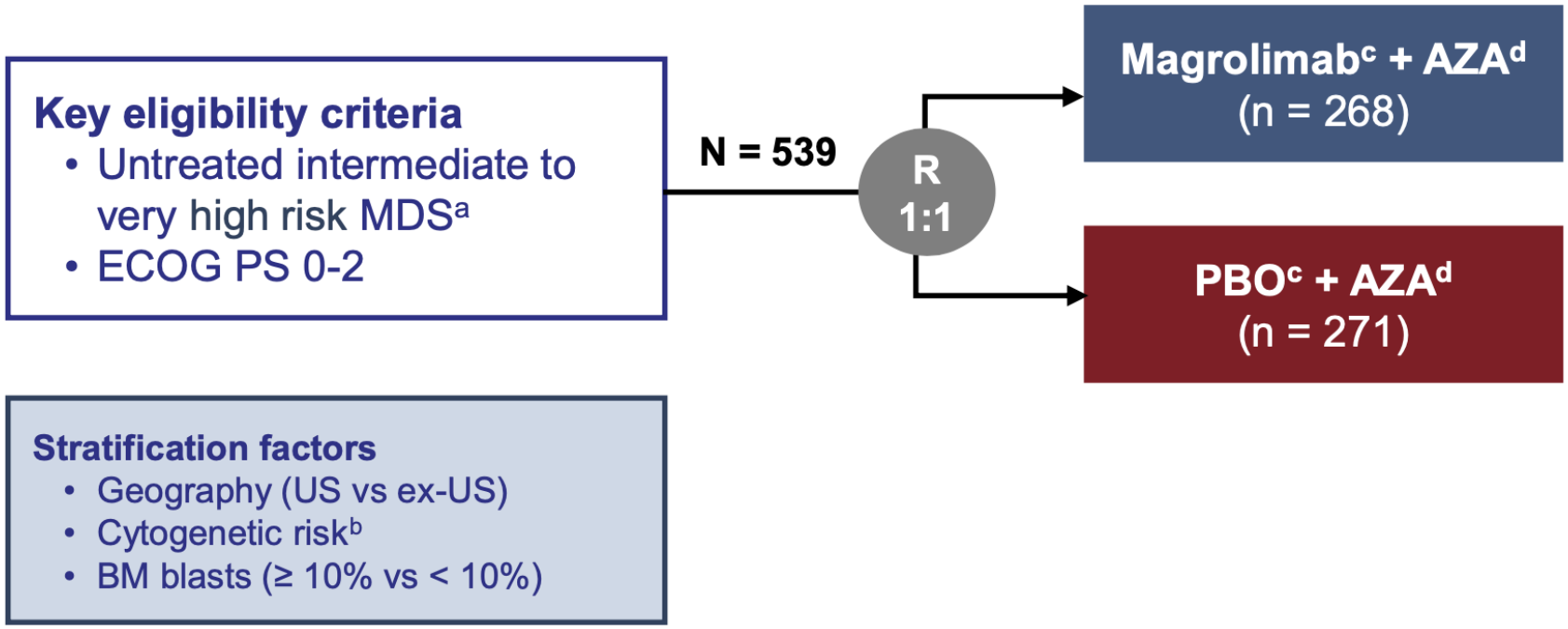
Magrolimab-AZA in HR MDS (Phase Ib)

Outcome	All (N = 95[a])	*TP53*-wt MDS (N = 61)	*TP53*-mut MDS (N = 25)
OR rate, %[b]	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0
Converted to RBC transfusion independence, %[c]	35.1	26.1	46.2
PFS, months, median (95% CI)	11.6 (9.0 to 14.0)	11.8 (8.8 to 16.6)	11.0 (6.3 to 12.8)
OS, months, median (95% CI)	NR (16.3 to NR)	NR (21.3 to NR)	16.3 (10.8 to NR)

CONCLUSION Magrolimab + azacitidine was well tolerated with promising efficacy in patients with untreated higher-risk MDS, including those with *TP53* mutations. A phase III trial of magrolimab/placebo + azacitidine is ongoing (ClinicalTrials.gov identifier: NCT04313881 [ENHANCE]).

David Sallman et al. JCO 2023

The Enhance trial : HMA + Magrolimab or placebo



Dual primary end points:
- CR rate[e]
- OS

Key secondary end points:
- ORR
- Duration of CR
- RBC TI rate
- EFS
- PFS
- CR rate in *TP53m* MDS
- MRD-negative response rate
- Time to transformation to AML
- Safety

ClinicalTrials.gov Identifier: NCT04313881

Patient characteristics (n=539)

Characteristic		Magrolimab + AZA (n = 268)	PBO + AZA (n = 271)
Age, median (range), years		71 (28–87)	69 (19–88)
Male, n (%)		181 (67.5)	177 (65.3)
Geographical region, n (%)	US	175 (65.3)	177 (65.3)
	Ex-US	93 (34.7)	94 (34.7)
Bone marrow blasts,[a] n (%)	≥ 10%	103 (38.4)	106 (39.1)
	< 10%	165 (61.6)	164 (60.5)
Cytogenetic risk status,[a,b] n (%)	Very good/good/intermediate	130 (48.5)	138 (50.9)
	Poor/very poor	123 (45.9)	124 (45.8)
IPSS-R,[c] n (%)	Intermediate	77 (28.7)	65 (24.0)
	High	81 (30.2)	87 (32.1)
	Very high	109 (40.7)	118 (43.5)
TP53 mutation-positive,[d] n/N (%)		79/167 (47.3)	64/178 (36.0)
Eligible for hematopoietic SCT per investigator, n (%)		135 (50.4)	160 (59.0)
RBC transfusion dependent, n (%)		140 (52.2)	125 (46.1)
Therapy-related MDS present, n (%)		53 (19.8)	48 (17.7)

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Reponses

Outcome	Magrolimab + AZA (n = 268)[a]	PBO + AZA (n = 271)[a]
Best response of CR at primary analysis (n = 348),[b] % (95% CI)	**20.5 (14.8–27.2)**	**25.0 (18.7–32.2)**
Odds ratio (95% CI),[c] *P*-value	**0.779 (0.471–1.288)**	
Final analysis (ITT)		
Best response of CR, % (95% CI)	**21.3 (16.5–26.7)**	**23.6 (18.7–29.1)**
Median[d] duration of CR (95% CI),[b,e] months	10.9 (8.9–16.7)	11.1 (8.1–NE)
ORR,[f] % (95% CI)	53.7 (47.6–59.8)	58.7 (52.6–64.6)
CR rate in *TP53m* population, % (95% CI)[g]	17.7 (10.0–27.9)	32.8 (21.6-45.7)
TI rate, % (95% CI)[h]	27.9 (20.6–36.1)	35.2 (26.9-44.2)
Median[d] duration of TI (95% CI),[i] months	11.8 (6.1–17.2)	8.2 (4.9-10.4)
MRD-negative status, % (95% CI)[j]	21.6 (16.9–27.1)	22.5 (17.7–28.0)
Transformed to AML, n (%)	34 (12.7)	43 (15.9)
Median[d] time to transformation (95% CI),[k] months	NE (21.2–NE)	25.5 (25.5–NE)
SCT rate,[l] % (95% CI)	20.9 (16.2–26.3)	35.4 (29.7–41.4)
Median[d] time to SCT (range), months	6.05 (2.66–16.85)	5.85 (2.76–19.12)

- There was no significant difference in CR rate or ORR between treatments
- The CR rate in the *TP53m* population was lower with magrolimab + AZA
- Fewer patients in the magrolimab + AZA arm proceeded to SCT ($P = 0.0001$)

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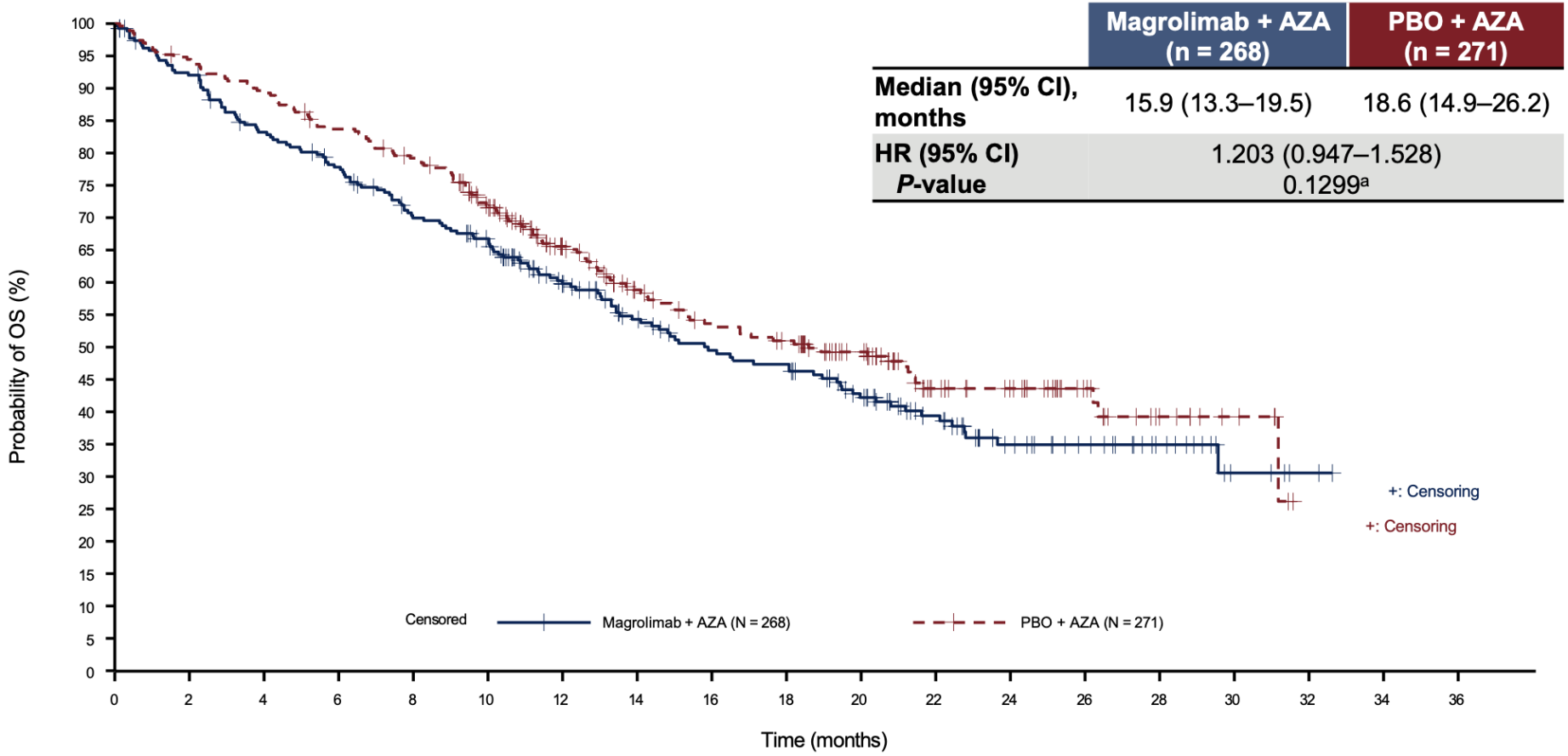
Overall survival of all enrolled patients

	Magrolimab + AZA (n = 268)	PBO + AZA (n = 271)
Median (95% CI), months	15.9 (13.3–19.5)	18.6 (14.9–26.2)
HR (95% CI)	1.203 (0.947–1.528)	
***P*-value**	0.1299[a]	



N at risk (events)

Magrolimab + AZA	288 (0)	242 (21)	216 (44)	200 (58)	176 (78)	163 (86)	126 (102)	105 (113)	92 (122)	88 (126)	70 (135)	50 (139)	32 (144)	21 (144)	15 (144)	5 (145)	2 (145)	0 (145)
PBO + AZA	271 (0)	255 (15)	242 (28)	224 (44)	210 (56)	179 (76)	141 (90)	115 (104)	101 (115)	94 (119)	74 (122)	46 (149)	38 (129)	22 (129)	11 (131)	6 (131)	0 (132)	

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Problem #3
Having realistic endpoints

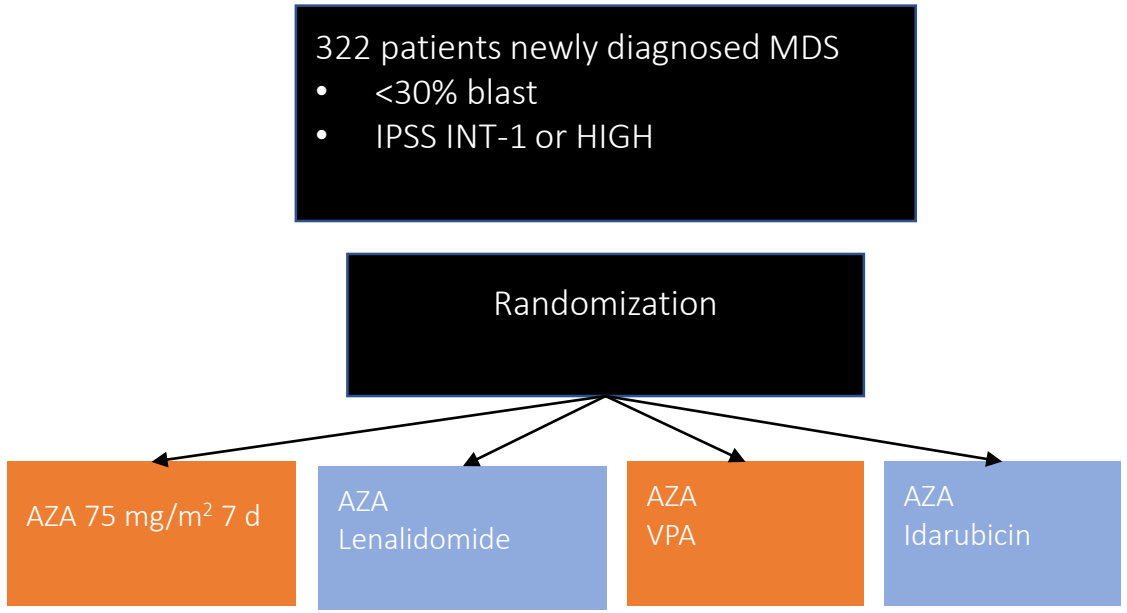
Under powered studies or optimistic endpoints ?

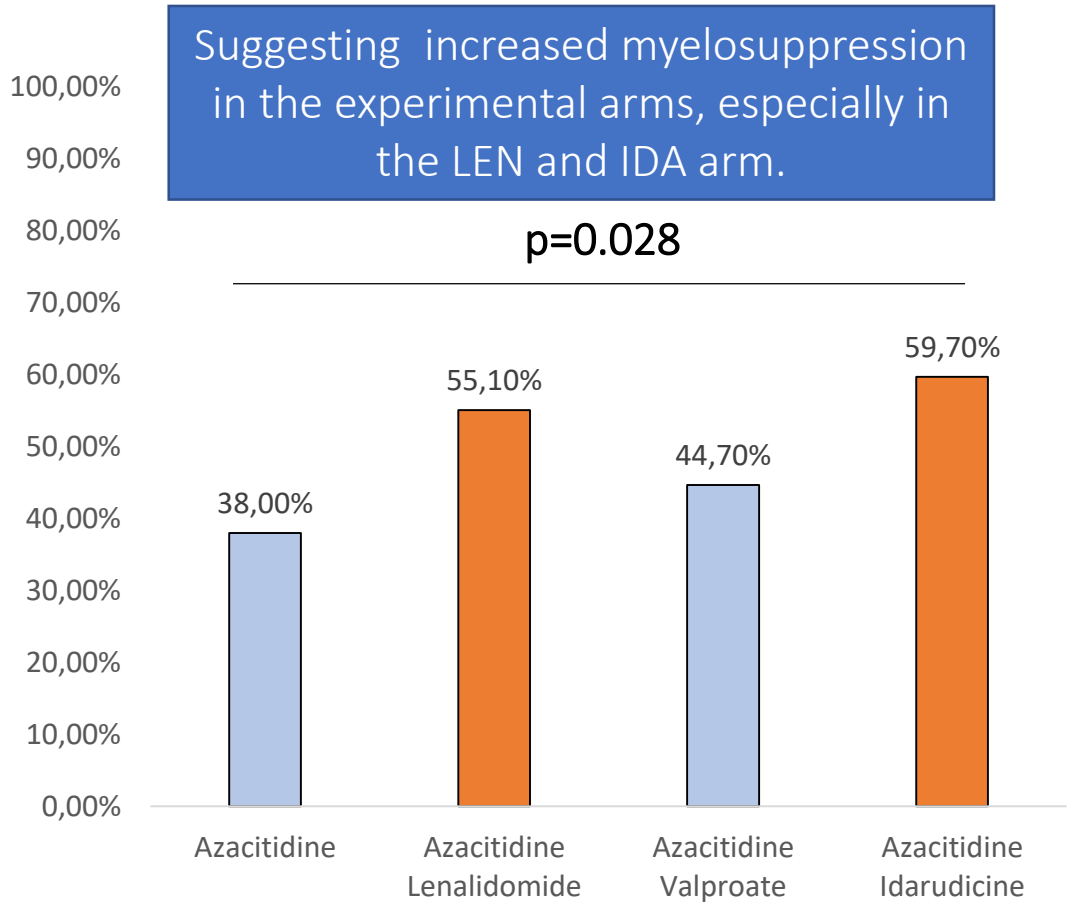
… *Or ineffective drug of course !!*

	Phase	Arm	n	Primary endpoint	Sample size calculation
Panther	3	2	454	EFS	10 → 17 mo
AZA PLUS	2	4	322	CR+PR	30%→45%
US-Intergroup	2	3	277	ORR	35%→55%
APR246 ph3	3	2	154	CR rate	25%→50%
Stimulus MDS-1	2	2	127	CR/PFS	CR : 18%→50% PFS: 12→20mo

Problem #4
Do not underestimate side effects

Toxicities observed in AZA-Plus Trial



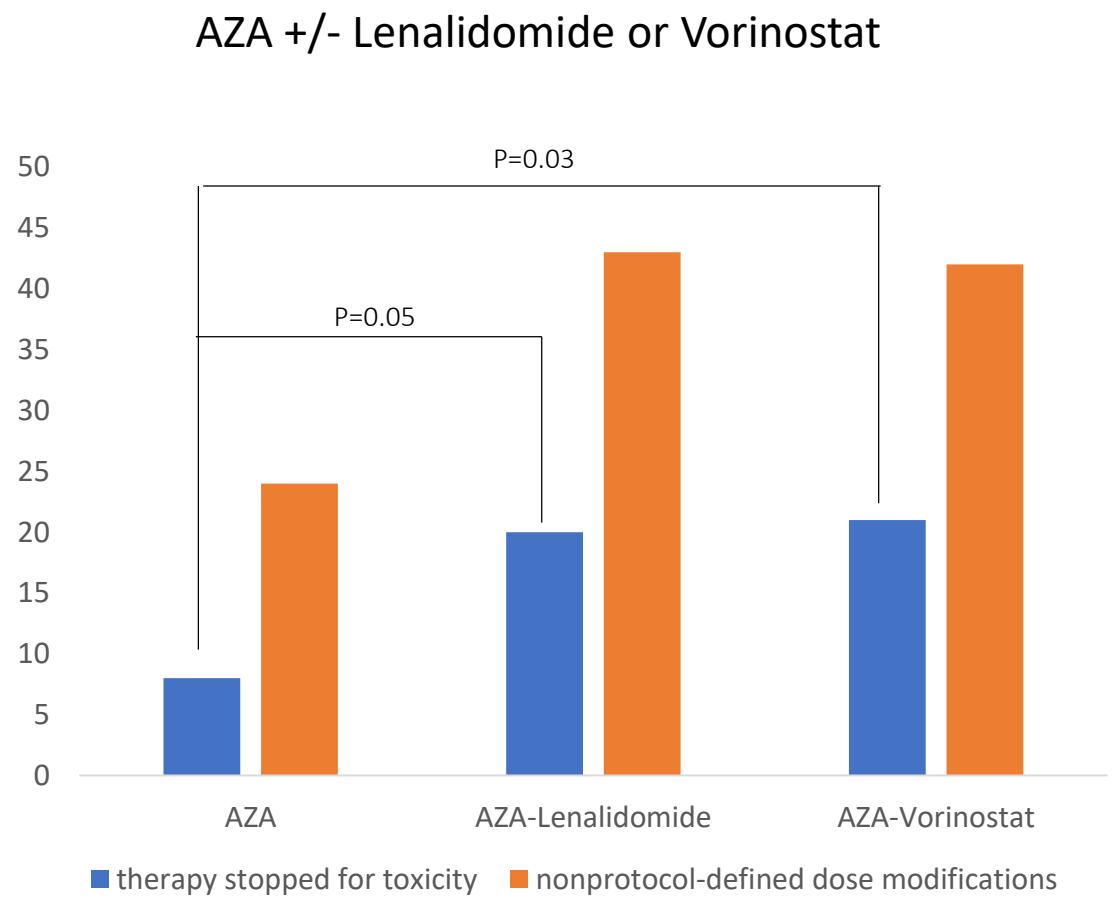


Rates of hospitalization during the first 6 cycles

Adès et al. BJH 2022

Another example of increased toxicities in Randomized trials

where toxicity induced an early discontinuation of treatment in experimental arms



Sekeres et al. J Clin Oncol 2017

Magrolimab-AZA phase 3 trial

Magrolimab + AZA was associated with a higher incidence of fatal TEAEs, grade ≥ 3 and serious TEAEs,

Safety outcome, n (%)[a]	Overall	
	Magrolimab + AZA (n = 263)	PBO + AZA (n = 264)
Grade ≥ 3 TEAE	244 (92.8)	209 (79.2)
Related to any study drug	201 (76.4)	149 (56.4)
Serious TEAE	189 (71.9)	136 (51.5)
Related to any study drug	114 (43.3)	52 (19.7)
TEAE leading to discontinuation of any study drug	63 (24.0)	32 (12.1)
TEAE leading to delay or interruption of any study drug	199 (75.7)	147 (55.7)
TEAE leading to death[a]	40 (15.2)	26 (9.8)

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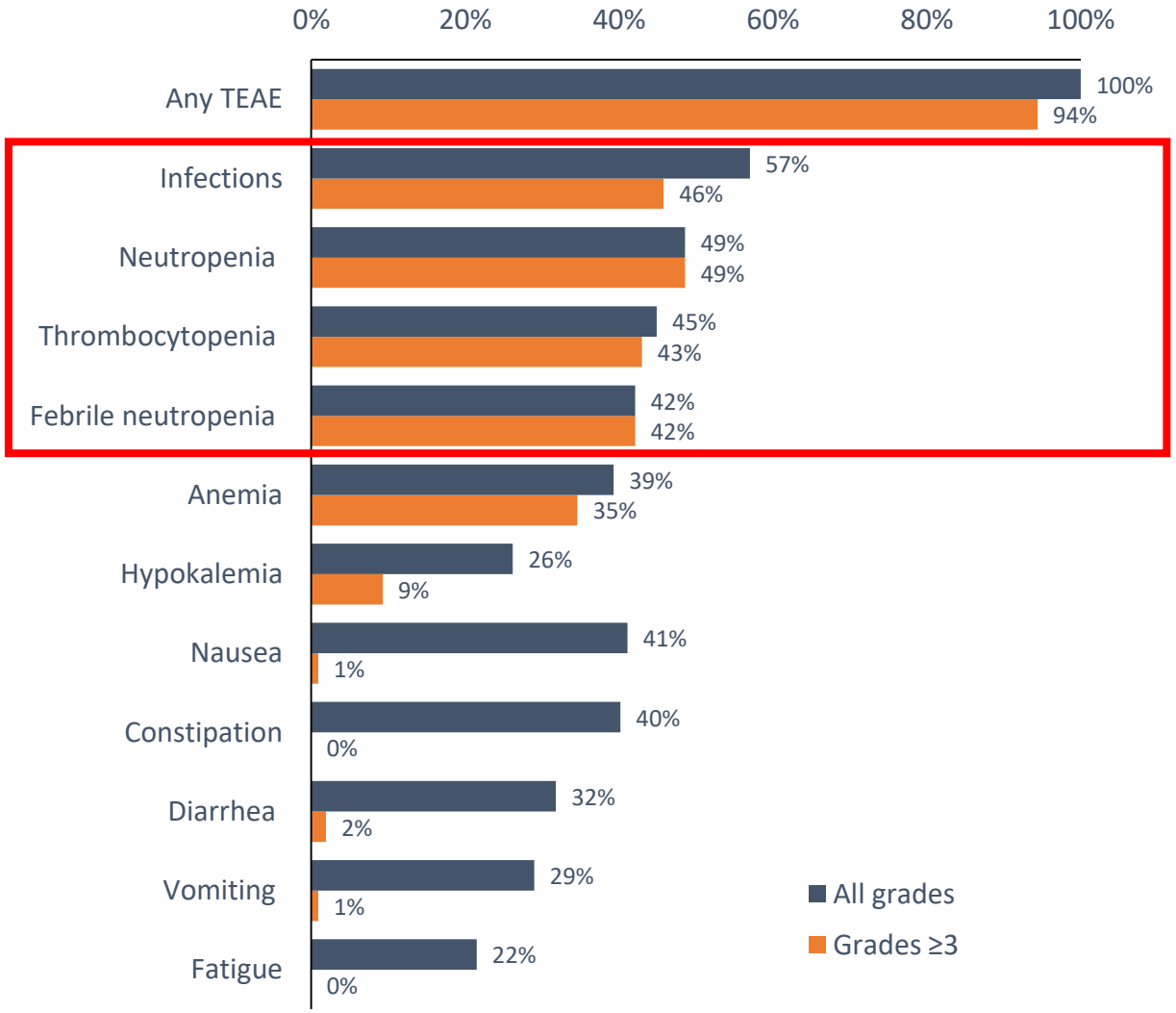
VEN-AZA in MDS: Treatment-Emergent Adverse Events (n=107)

- SAEs occurred in 73 (68.2%) patients:
  - Febrile neutropenia in 39 (36.4%)
  - Infections in 43 (40.2%)

- 59 deaths (55.1%) were reported
  - 23 (21.5%) due to disease progression
  - 17 (15.8%) due to TEAEs
  - 7 (6.5%) due to complications from SCT
  - 6 (5.6%) due to other reasons
  - 6 (5.6%) unknown

- 60-day mortality after the first dose was 6.5%

- 72 (67.3%) patients experienced ≥1 TEAE leading to Ven interruption



Garcia et al. ASH 2023

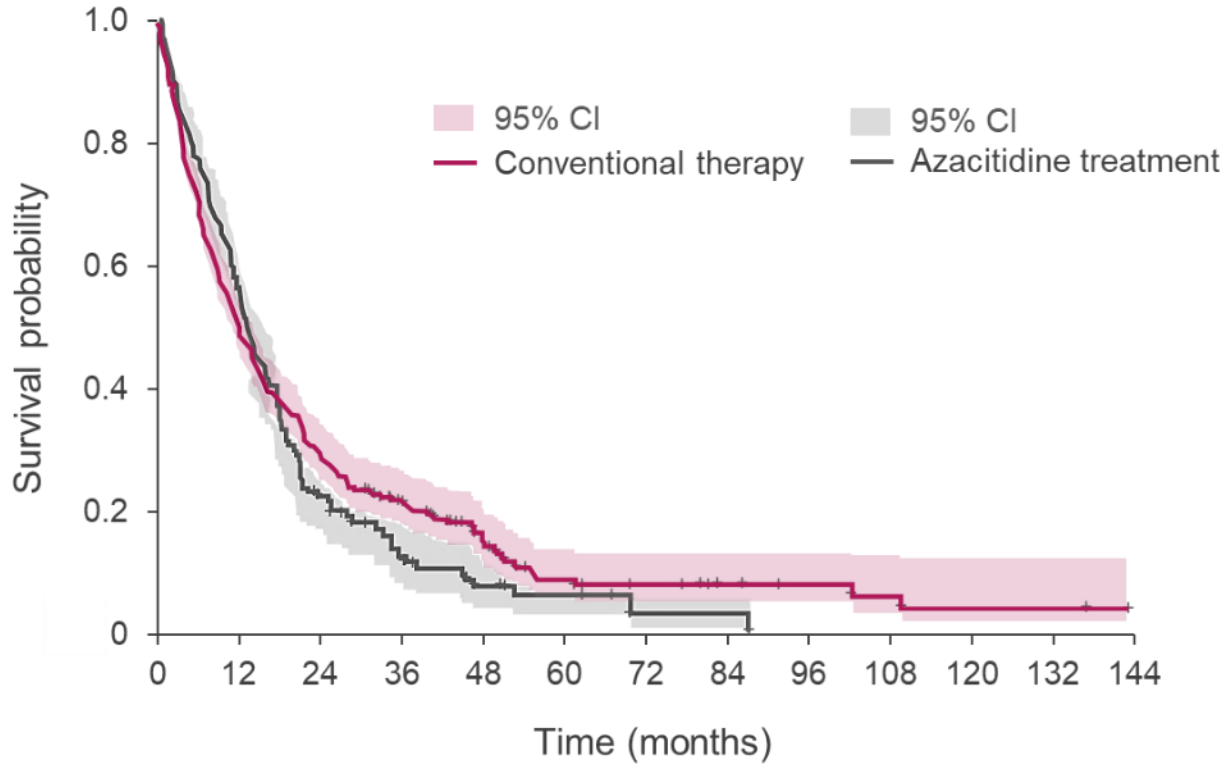
Problem #5
why real life data are so different from clinical trials?

HMAs: Survival from real-world data

- Retrospective study
- Spanish MDS registry from 2000–2013
- Higher-risk MDS (N=821); azacitidine (n=251)

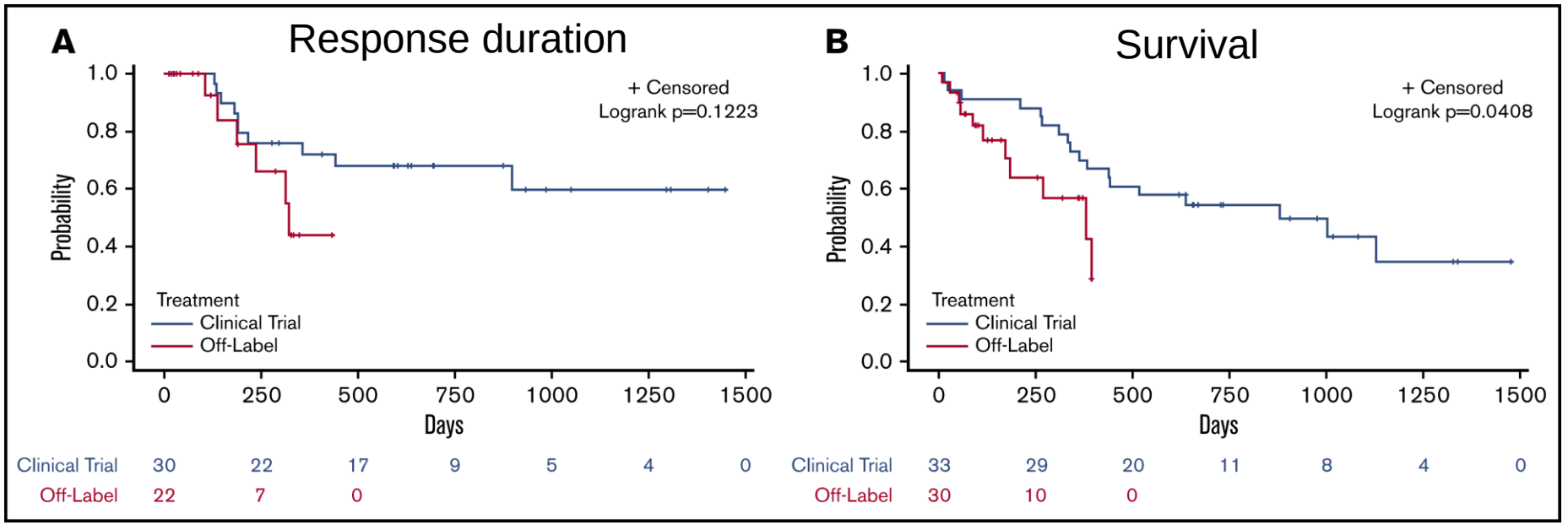
Raised many unsolved questions:

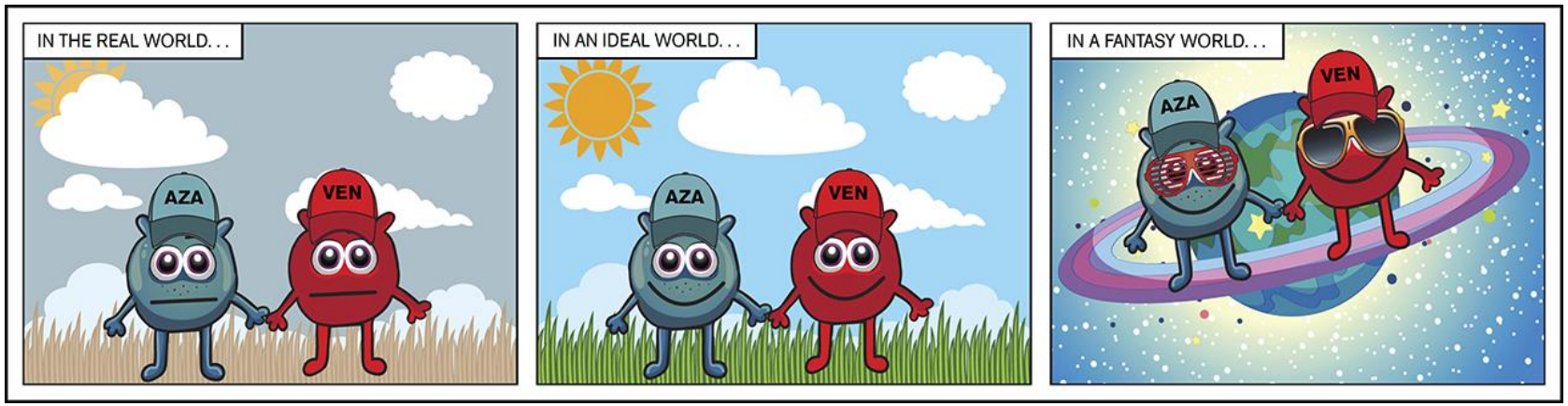
- Is MDS a very heterogenous disease?
- What is the impact on specific subgroups?
- What is the impact of comorbidities?



Bernal T, et al. *Leukemia*. 2015;29(9):1875-1881.

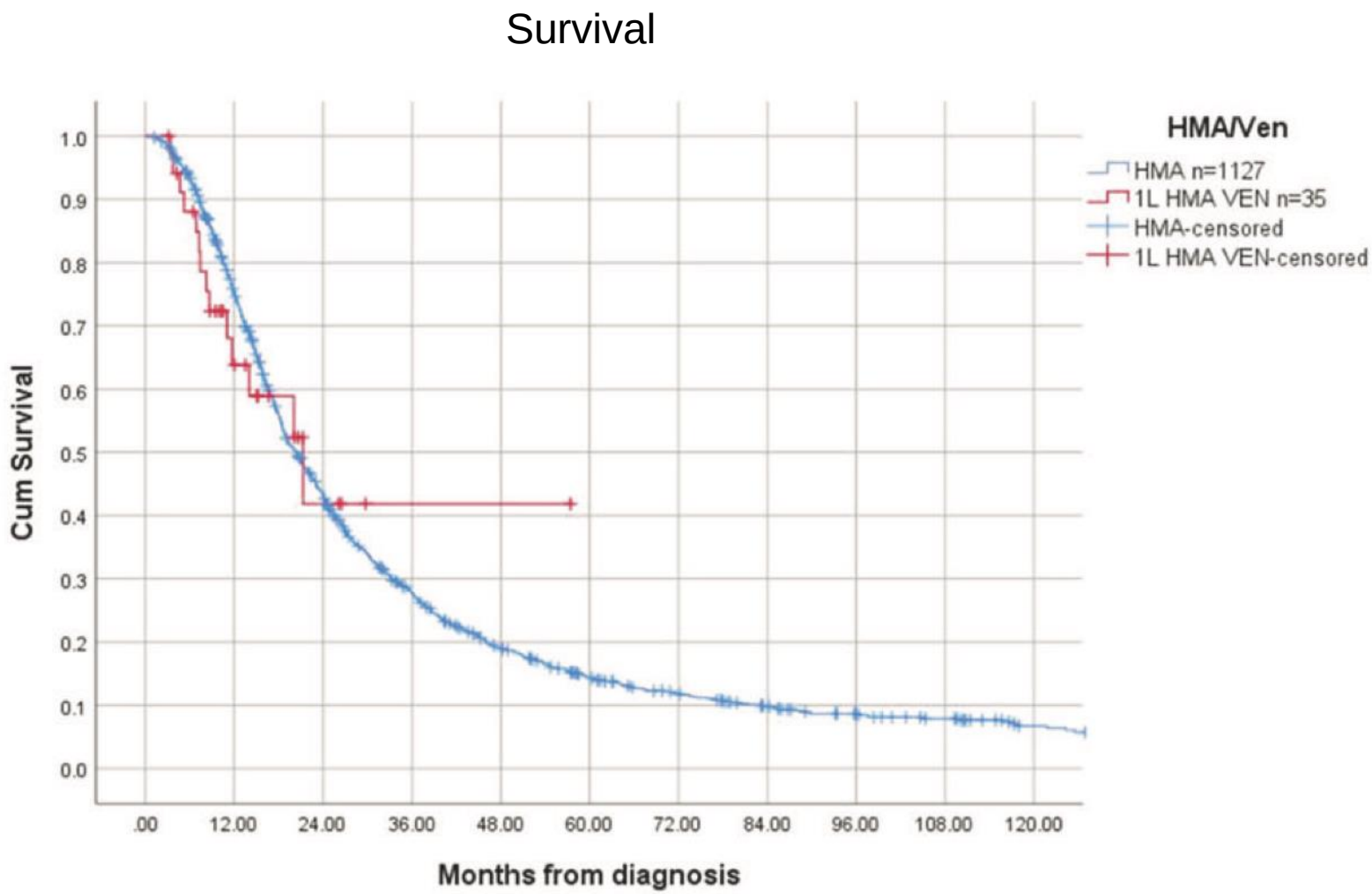
AZA-VEN in AML: clinical trial results may differ in real life





Amanda C. Winters, Blood Adv, 2019

AZA-VEN in MDS



Rami S. Komrokji et al. Blood Cancer J 2022

Problem #6
Who are the best candidate for SCT?

The role of SCT in MDS

- the only potentially curative treatment
- outcome is influenced by multiple factors inherent to the patient, the MDS subtype, and the allo-HCT procedure itself.
- Many unanswered questions including :
  - What type of disease ?
  - Classified according to what ?
  - Which prognosis scoring system ?
  - Any treatement before SCT? After SCT ?
  - Among others….

Problem #7
Academic access to the drugs

Conclusions

- Early phase 2 trials might overestimate the activity of studied drugs in combination.
- Population probably too heterogeneous: IPSS→IPSS-R→IPSS-M
- The « one size fit all » is not anymore the way to go
- Primary endpoint : OS (or EFS?) in randomized trial → Impact on #Patients.
- Reinforce the dialogue between clinic & Science
- International collaborative studies : Clinic & Science
- Don’t overlook toxicty
- **But some great expectation for our patients in the future (comming next)**