Université de Paris

Groupe Francophone des Myélodysplasies

Higher risk myelodysplastic syndromes after HMAs

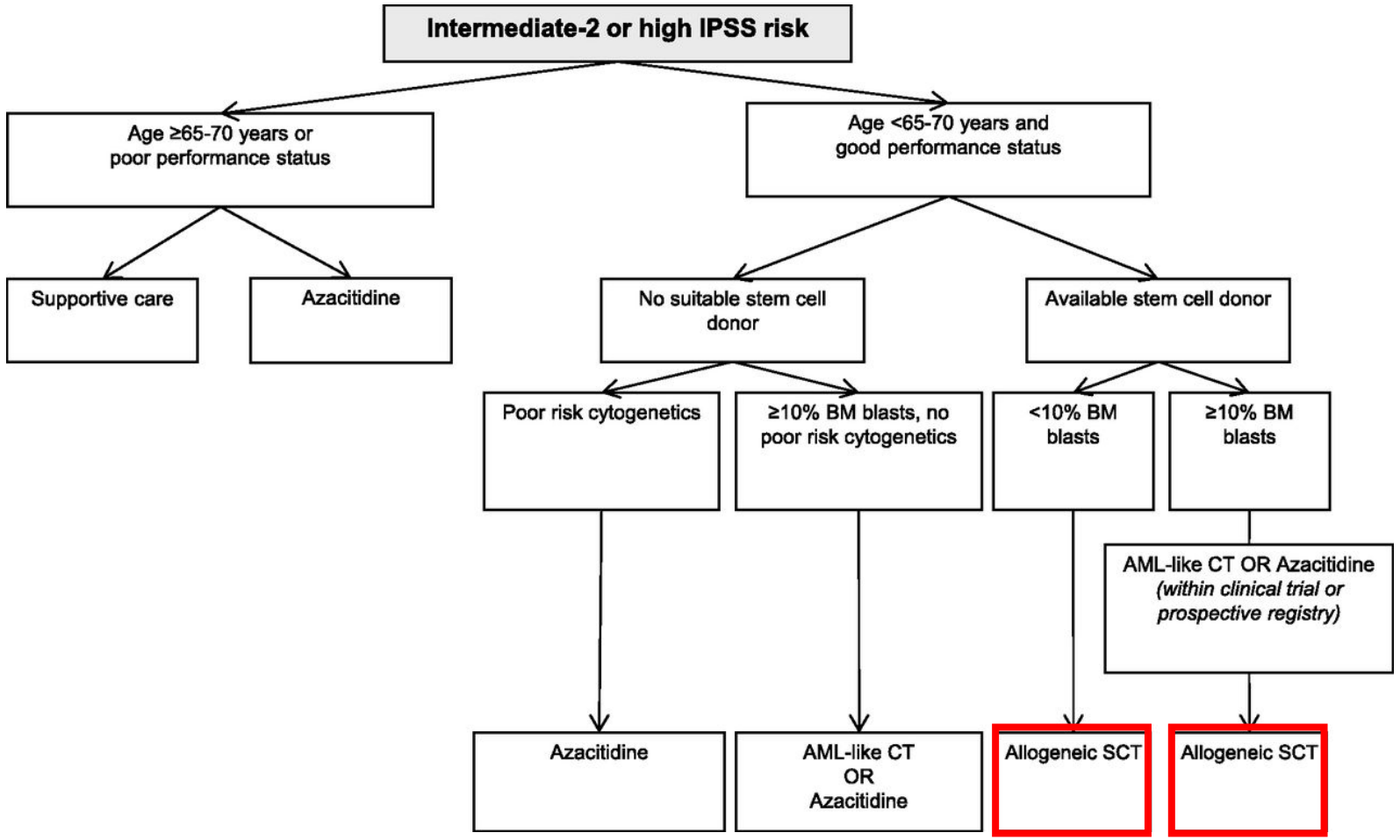
Lionel Adès, MD PhD
Hopital Saint Louis & INSERM U 944
Paris, France

Disclosures

- Research support : Celgene, Novartis, Jazz Pharmaceuticals

- Advisory Board : Celgene, Novartis, Jazz Pharmaceuticals, Takeda, Abbvie, Helsinn, Otzuka, Bristol Myers Squibb, Silent Therapeutics

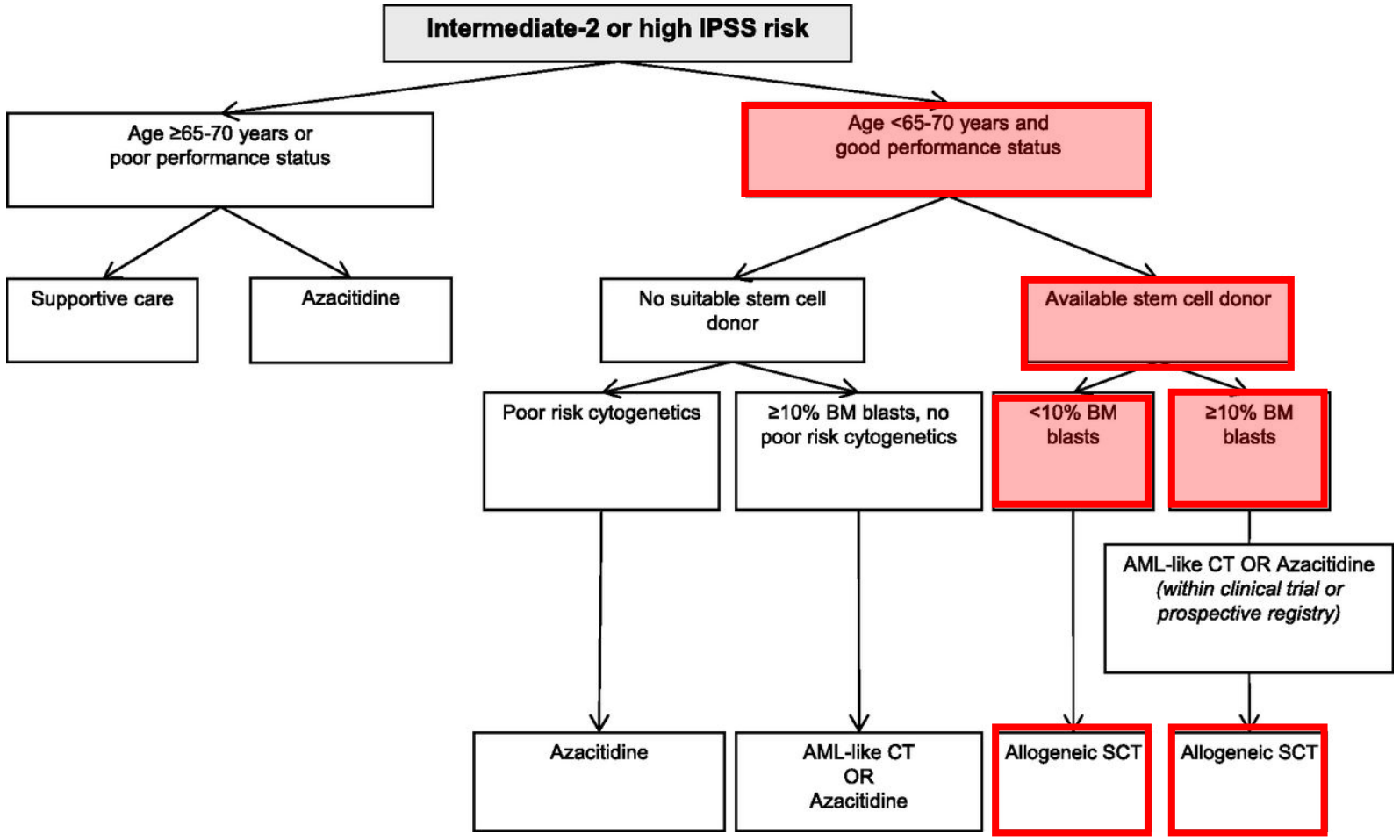
Treatment algorithm for Higher risk MDS



Allogeneic stem cell transplantation remains, the only curative treatment option of higher risk MDS

ELN Recommandations Luca Malcovati et al, Blood 2013

Treatment algorithm for Higher risk MDS

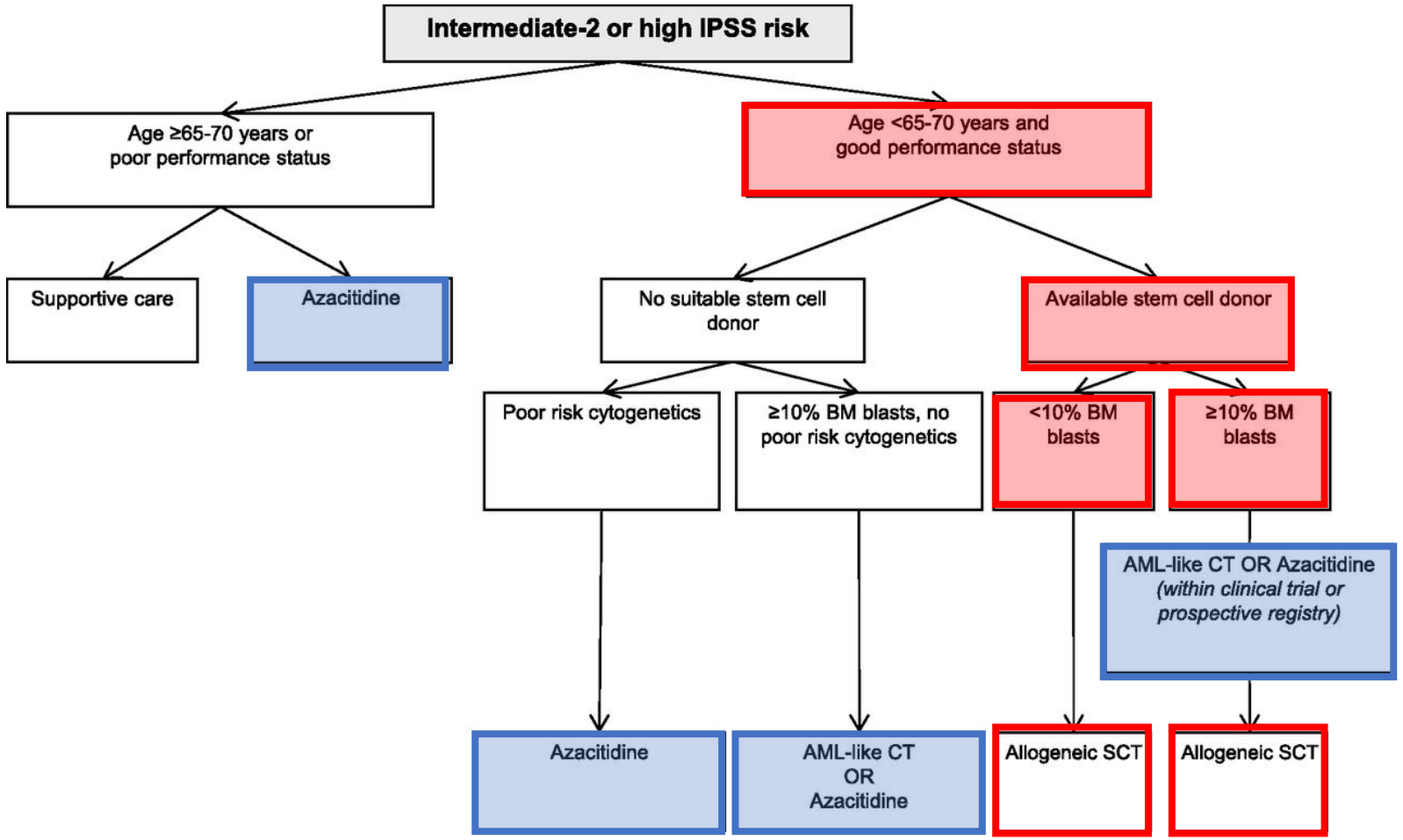


Allogeneic stem cell transplantation remains, the only curative treatment option of higher risk MDS

… when feasible !

ELN Recommandations Luca Malcovati et al, Blood 2013

Treatment algorithm for Higher risk MDS



Allogeneic stem cell transplantation remains, the only curative treatment option of higher risk MDS

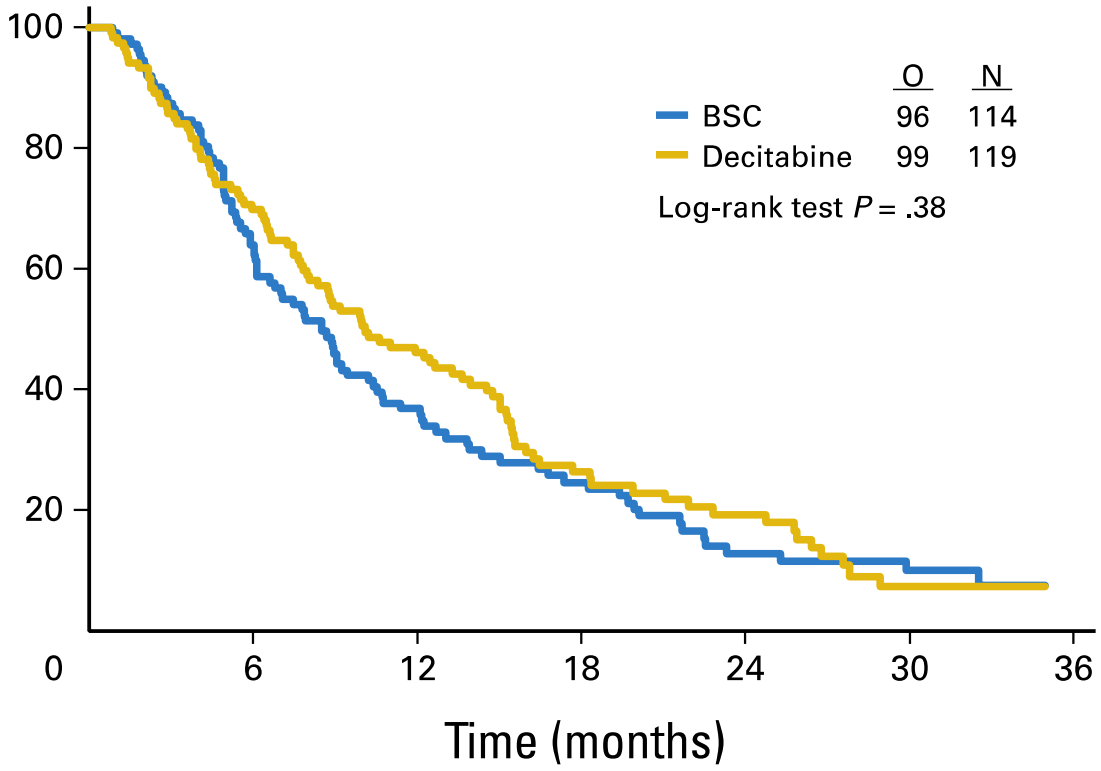
… when feasible !

Currently, hypomethylating agents– azacitidine and decitabine– are the first line treatment in higher risk MDS cases

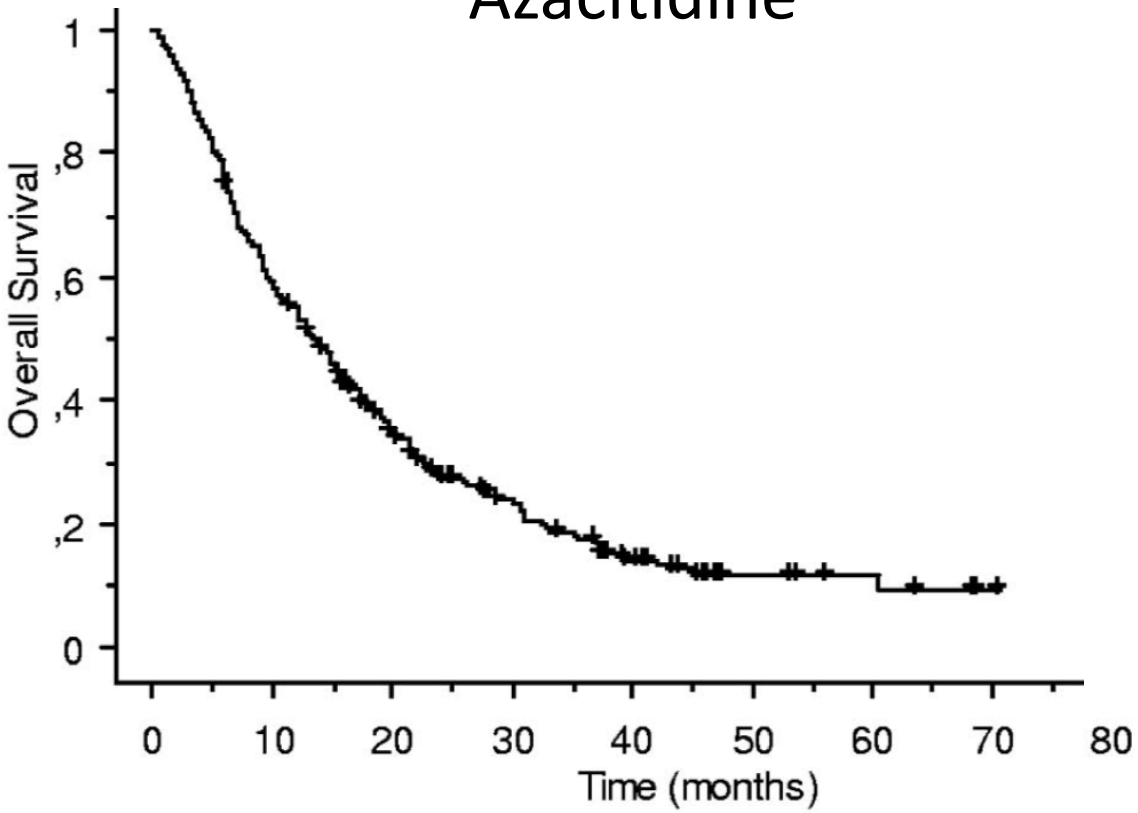
ELN Recommandations Luca Malcovati et al, Blood 2013

…But No long term Survivor with HMA

Decitabine



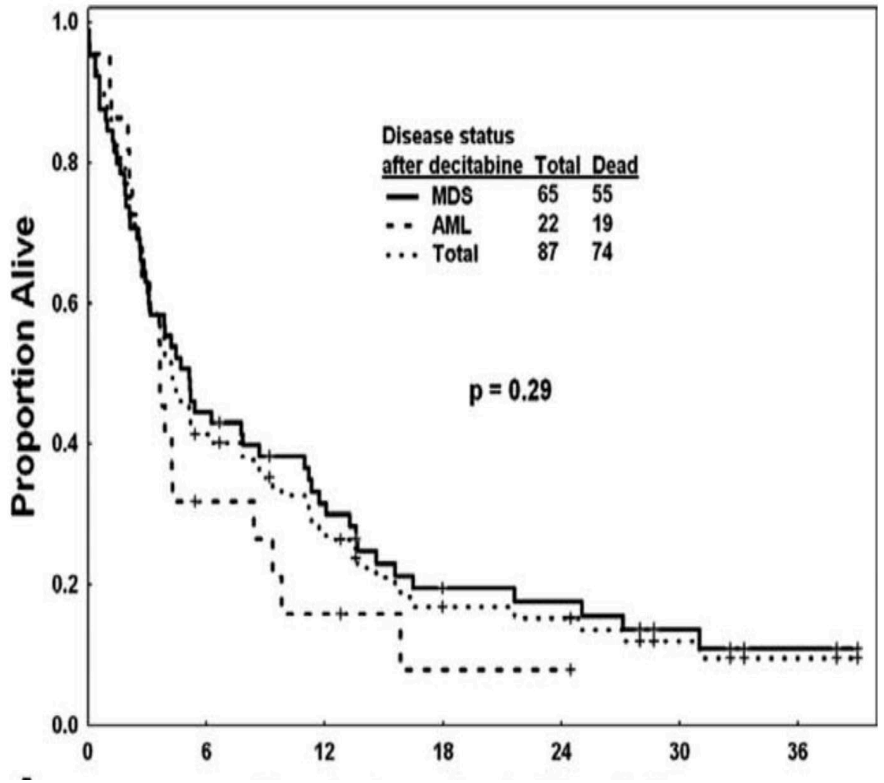
Azacitidine



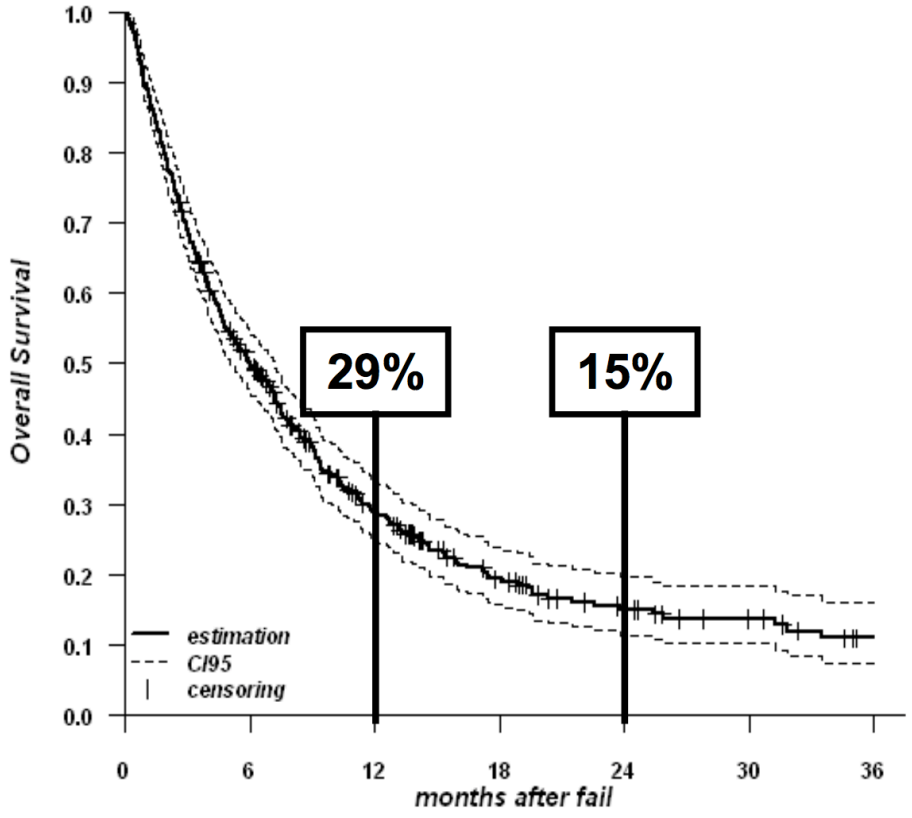
Lübbert el al, JCO 2011
Itzykson, Blood 2012

…And Survival is poor after HMA failure

Decitabine

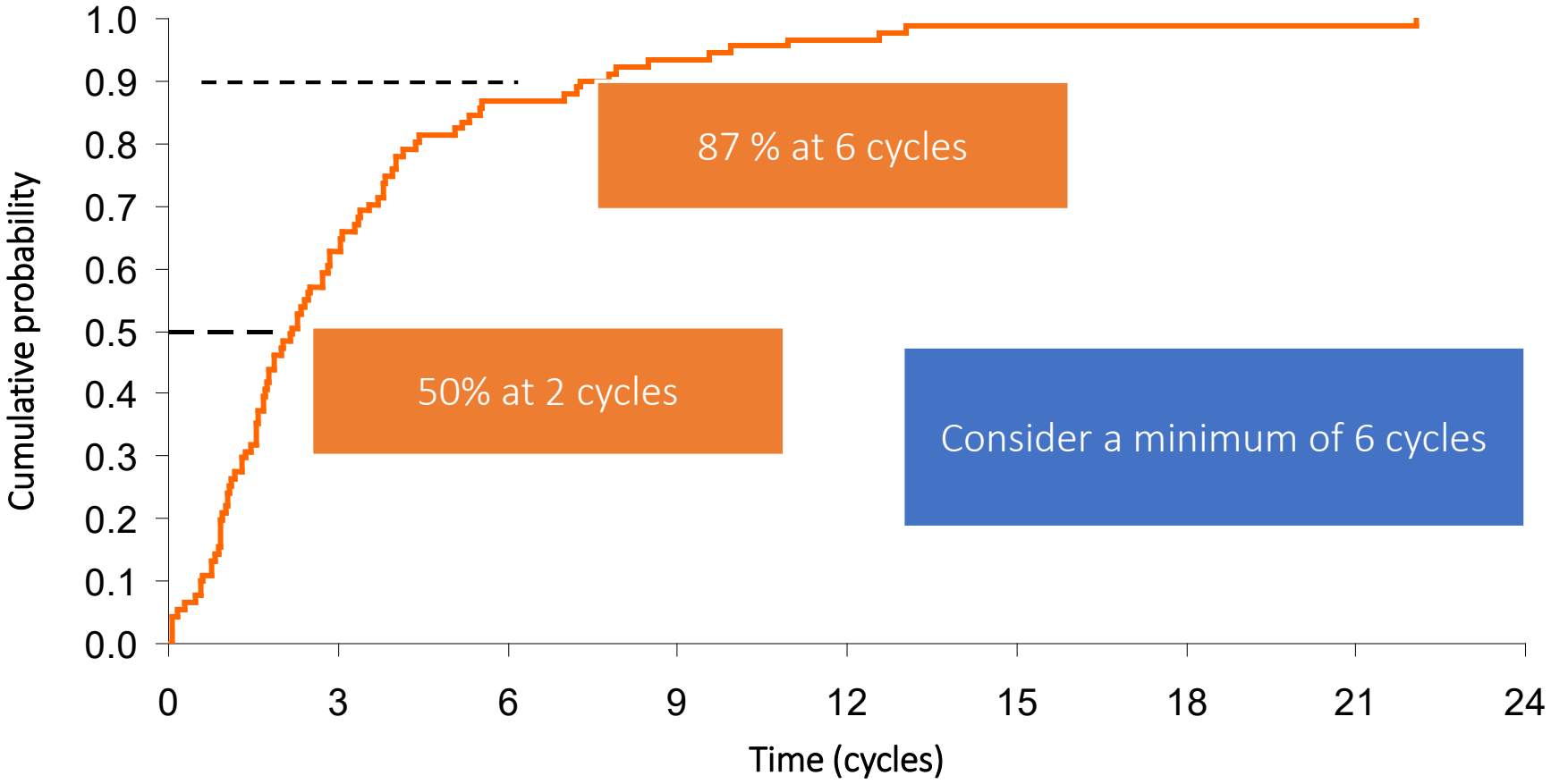


Azacitidine



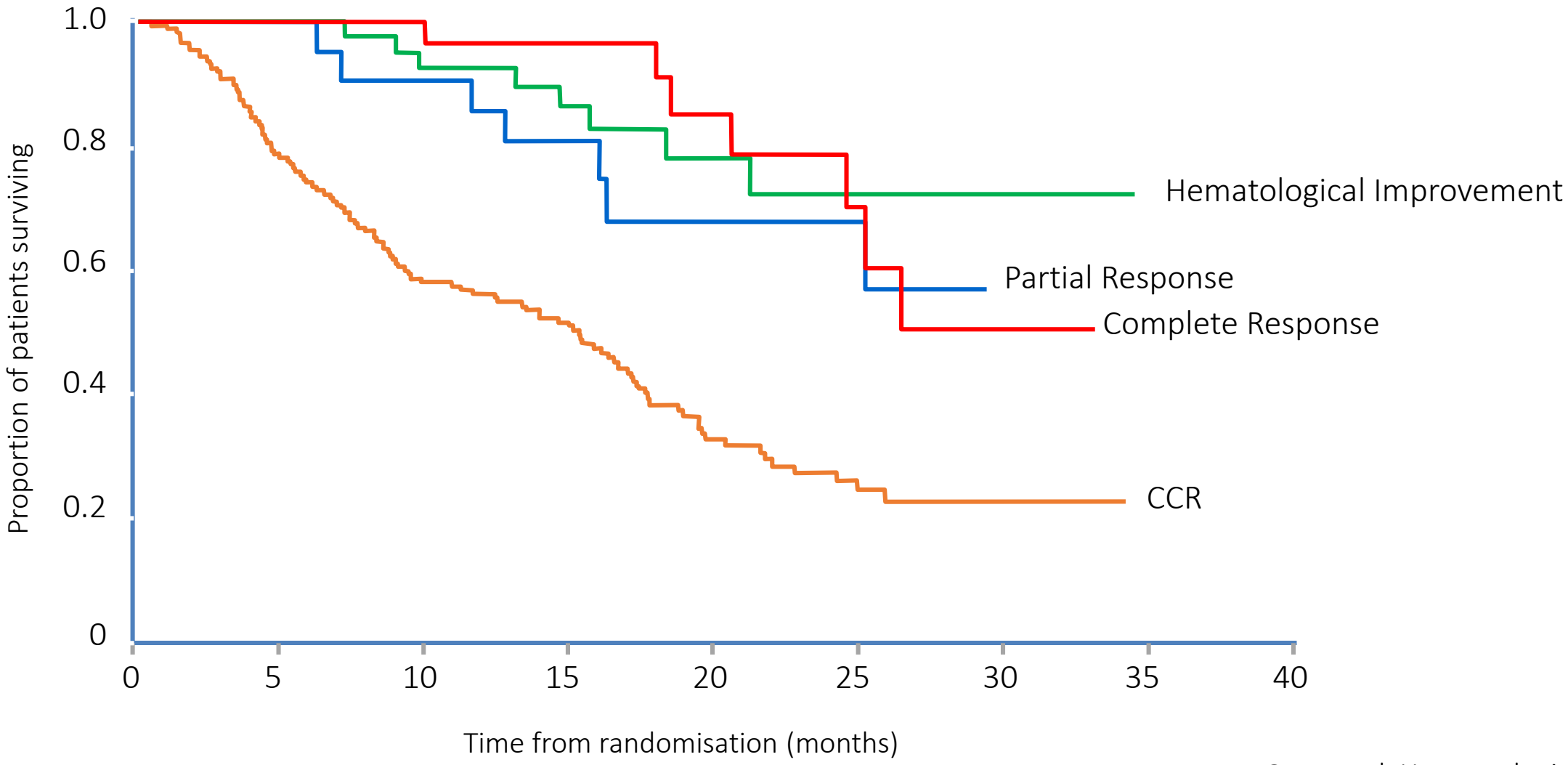
Jabbour el al, Cancer 2010
Prebet et al. JCO 2011

Retain patients on treatment for long enough that response can be assessed



Silverman LR, et al.

Type of response does not influence OS



Gore et al. Haematologica 2013

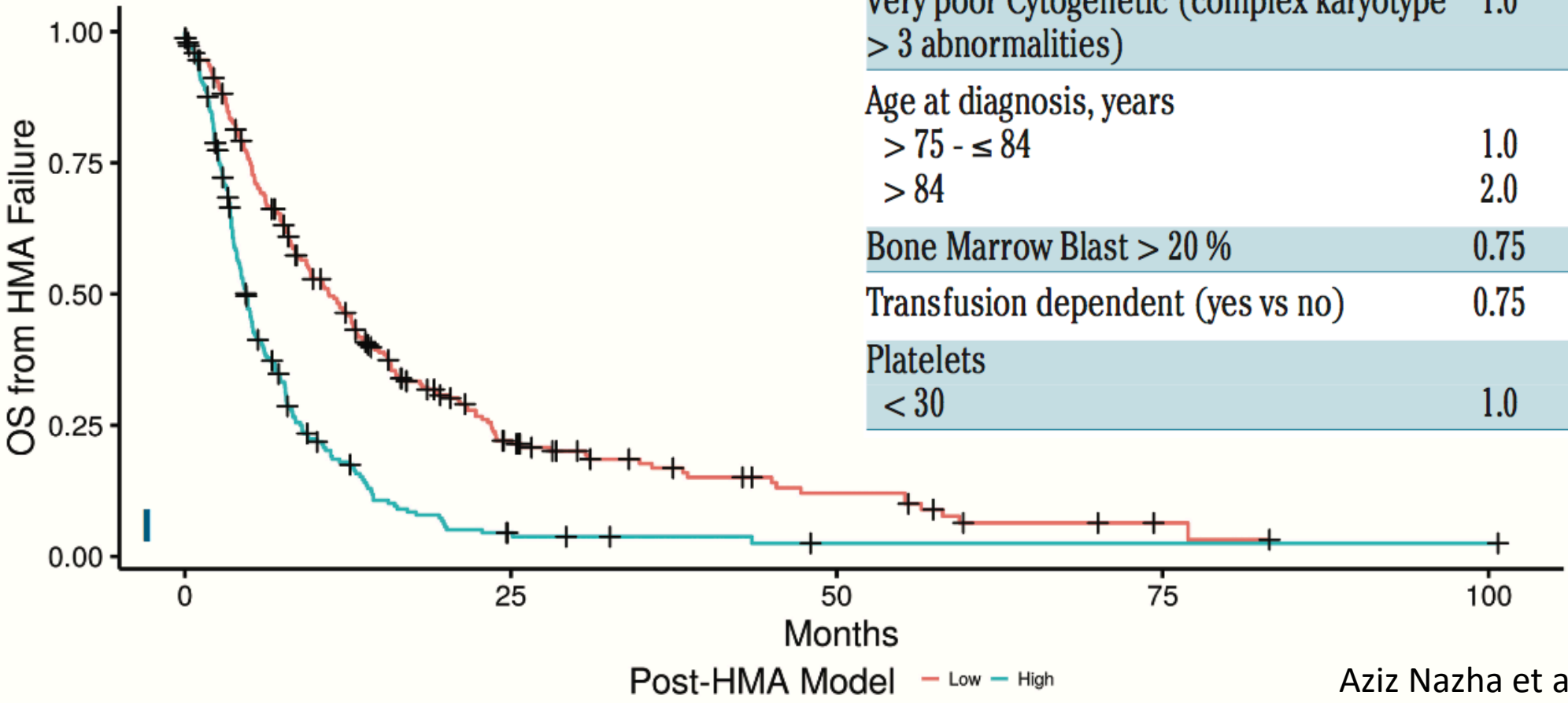
Different types of Failure

Group	Status	Median OS
Primary Failure	Stable disease without HI at C6 Disease Progression	4.6 mo
Secondary failure	Failure after CR/PR/HI	7.4 Mo

Prebet et al. JCO 2011

Prognostic factors at the time of HMA failure

Parameter at HMA failure	Score	Beta	P
ECOG Performance status > 1	1.0	0.56	0.01
Very poor Cytogenetic (complex karyotype > 3 abnormalities)	1.0	0.57	< 0.001
Age at diagnosis, years			
> 75 - ≤ 84	1.0	0.52	< 0.001
> 84	2.0	0.90	< 0.001
Bone Marrow Blast > 20 %	0.75	0.36	0.01
Transfusion dependent (yes vs no)	0.75	0.39	< 0.001
Platelets			
< 30	1.0	0.54	< 0.001



Aziz Nazha et al. Haematologica 2016

Hypomethylating agent failure

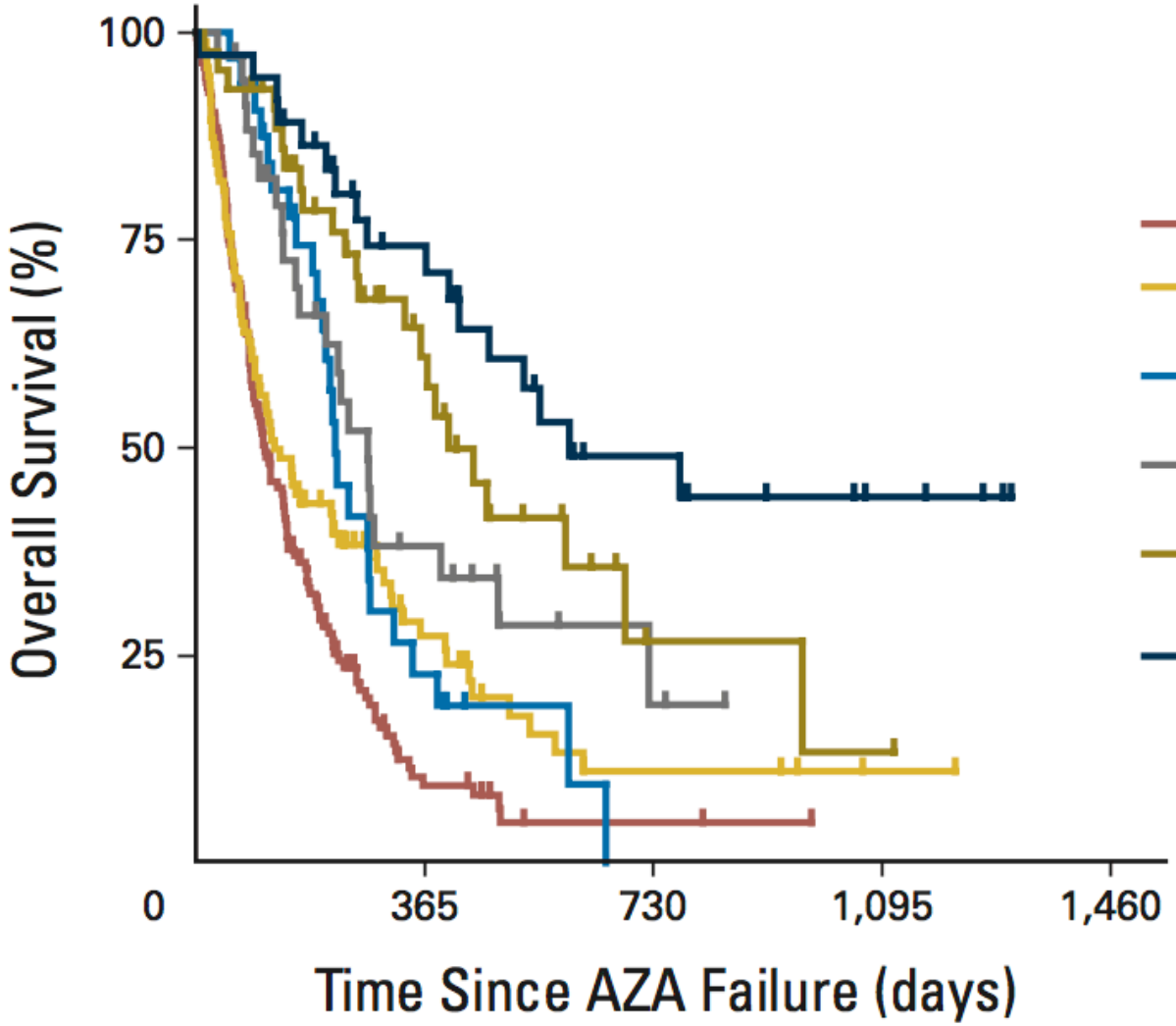
- Despite the use of HMA for more than 15 years
  - timing of evaluations of response
  - and subsequent clear definition of resistance remain unclear

Key Messages

1. Retain patients on treatment for long enough that response can be assessed
2. Type of response does not influence OS
3. Different types of failure (Primary/secondary)
4. Limited therapeutic option for HMA failure

Therapeutic Options (?)

Different Therapeutic Options



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*†

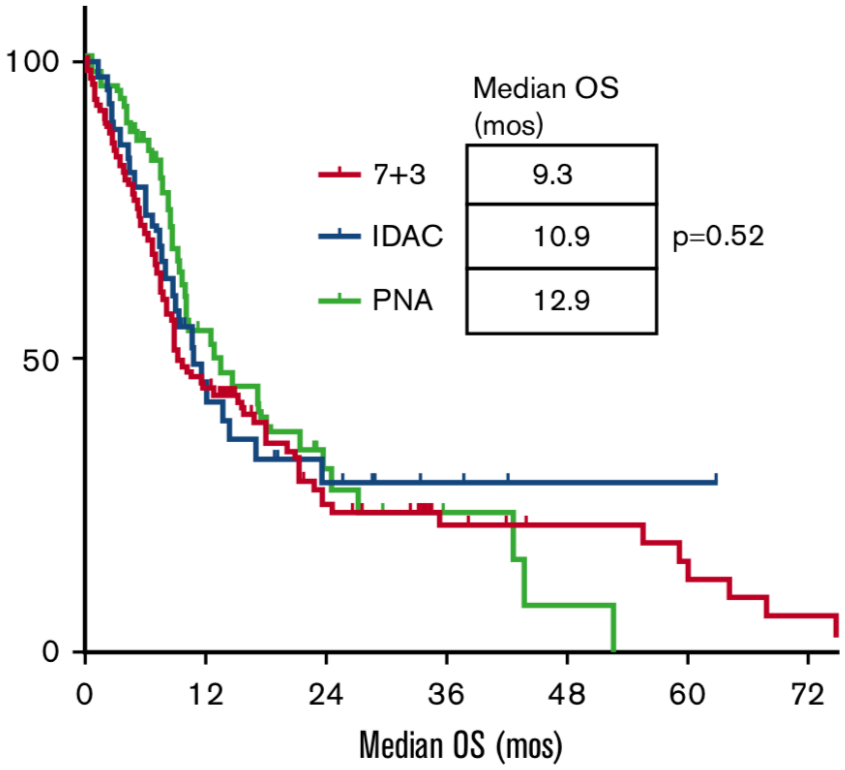
23% of the patients

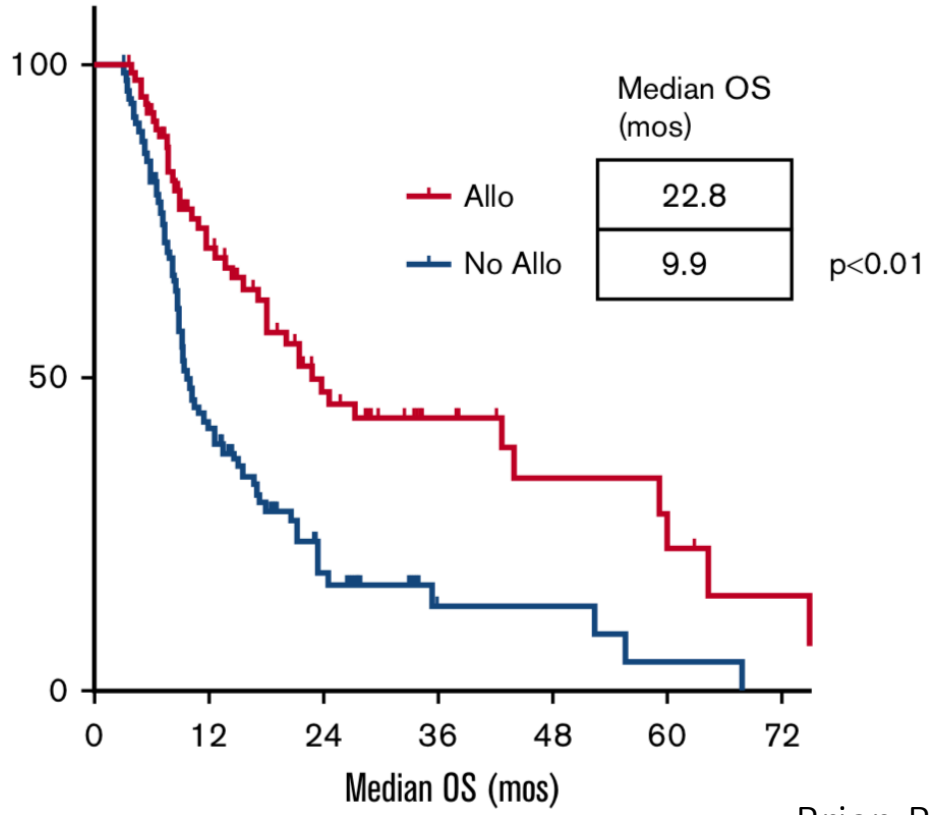
Prebet et al. JCO 2011

Role of Intensive Chemo after HMA failure

307 MDS patients treated intensively following HMA failure

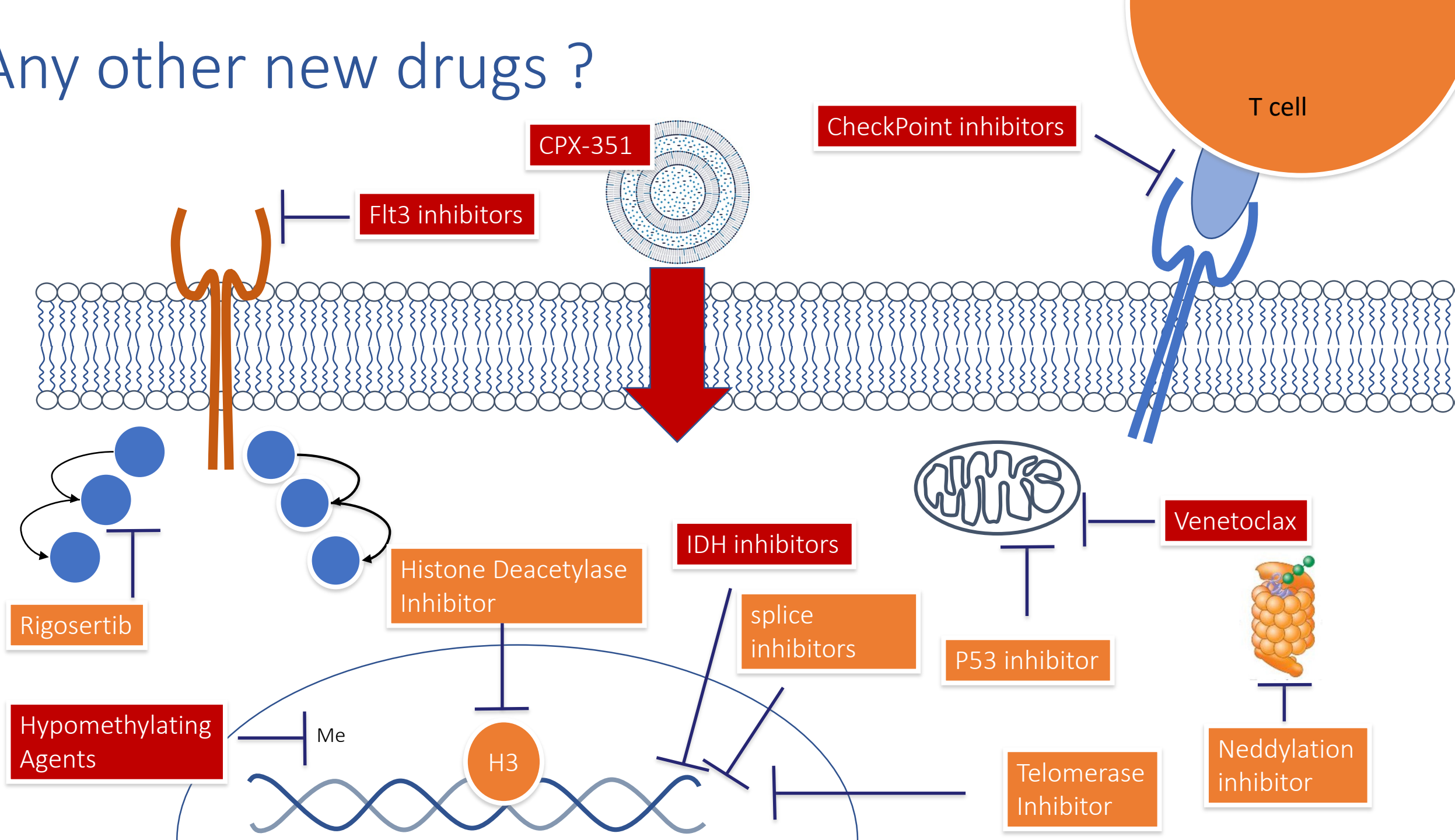
- CR 41%
- 40% of the Reponders were bridged to SCT



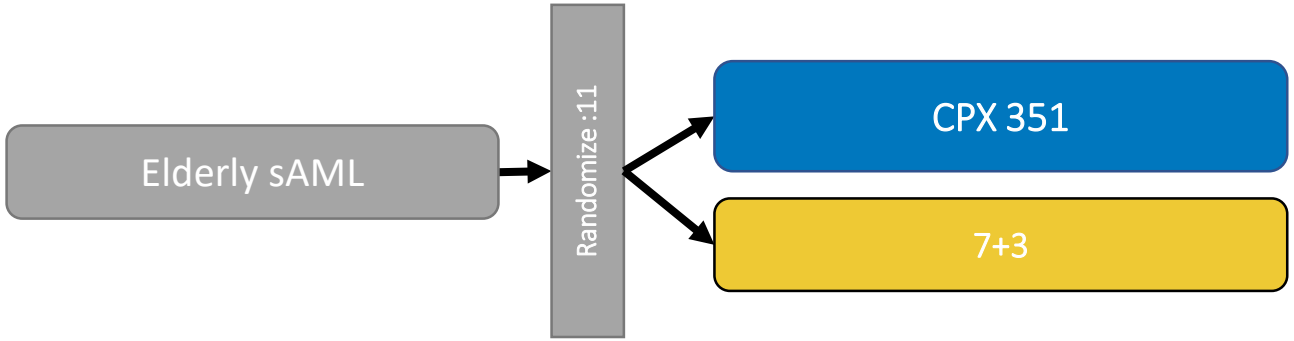


Brian Ball et al. Blood Adv 2018

Any other new drugs ?

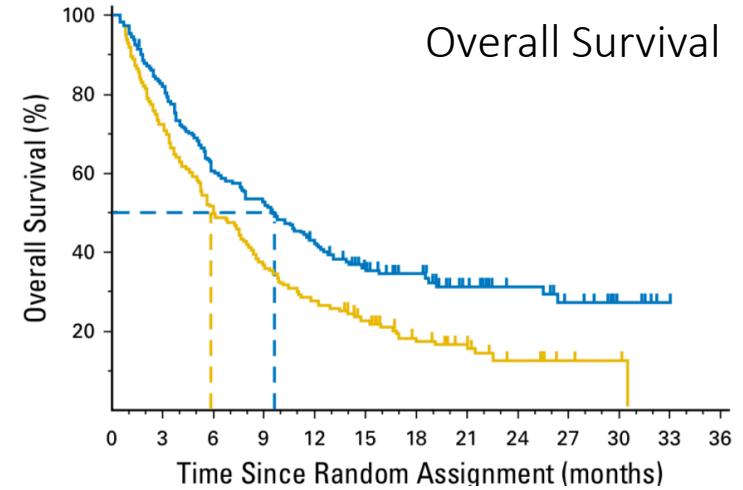


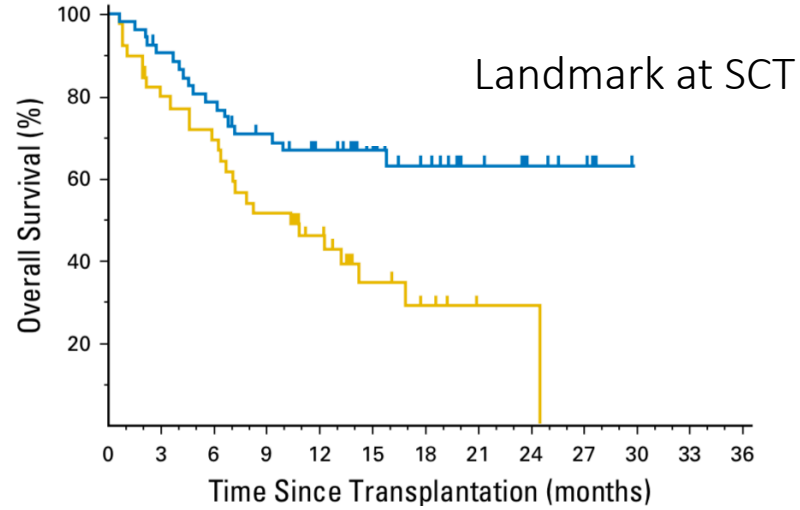
CPX-351 (cytarabine and daunorubicin) Liposome 7+3 in Older Patients With sAML



CPX-351 significantly improves :

- Median overall survival versus 7+3 (9.56 *v* 5.95 months)
- Remission rate (47.7% *v* 33.3%; *P* = .016)
- Outcome after SCT

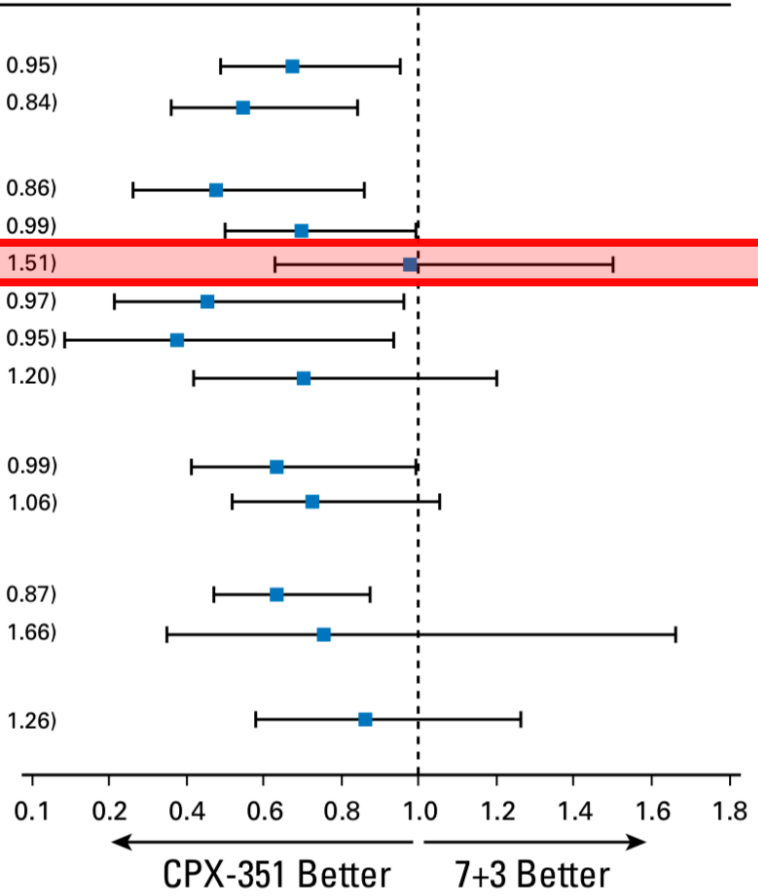




J. Lancet et al. J Clin Oncol 2018

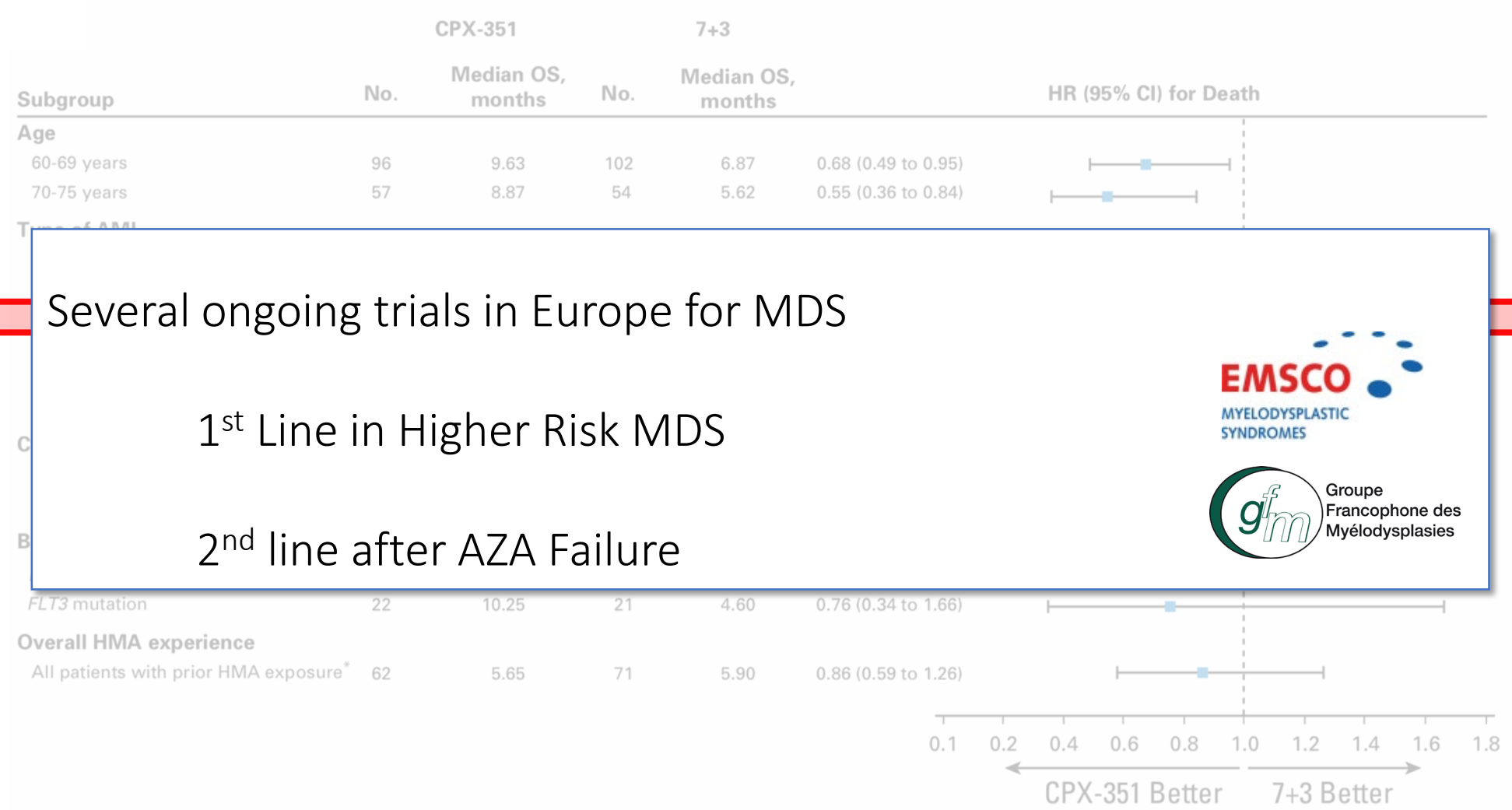
CPX-351 (cytarabine and daunorubicin) Liposome 7+3 in Older Patients With sAML

Subgroup	CPX-351 No.	CPX-351 Median OS, months	7+3 No.	7+3 Median OS, months	HR (95% CI) for Death
Age					
60-69 years	96	9.63	102	6.87	0.68 (0.49 to 0.95)
70-75 years	57	8.87	54	5.62	0.55 (0.36 to 0.84)
Type of AML					
Therapy-related AML	30	12.17	33	5.95	0.48 (0.26 to 0.86)
AML with antecedent MDS or CMML	82	7.38	86	5.95	0.70 (0.50 to 0.99)
MDS with prior HMA exposure	50	5.65	55	7.43	0.98 (0.64 to 1.51)
MDS without prior HMA exposure	21	15.74	19	5.13	0.46 (0.21 to 0.97)
CMML	11	9.33	12	2.28	0.37 (0.14 to 0.95)
De novo AML with MDS karyotype	41	10.09	37	7.36	0.71 (0.42 to 1.20)
Cytogenetic risk at screening					
Favorable/intermediate	71	14.72	63	8.41	0.64 (0.41 to 0.99)
Unfavorable	72	6.60	83	5.16	0.73 (0.51 to 1.06)
Baseline *FLT3* mutation status					
FLT3 wild type	116	9.33	120	5.98	0.64 (0.47 to 0.87)
FLT3 mutation	22	10.25	21	4.60	0.76 (0.34 to 1.66)
Overall HMA experience					
All patients with prior HMA exposure*	62	5.65	71	5.90	0.86 (0.59 to 1.26)



J. Lancet et al. J Clin Oncol 2018

CPX-351 (cytarabine and daunorubicin) Liposome 7+3 in Older Patients With sAML



Several ongoing trials in Europe for MDS

1st Line in Higher Risk MDS

2nd line after AZA Failure

EMSCO MYELODYSPLASTIC SYNDROMES

Groupe Francophone des Myélodysplasies

J. Lancet et al. J Clin Oncol 2018

From an HMA to another one

Group	n	Disease	Response	Survival	Ref
Decitabine after Azacitidine	36	CMML	19%	7.3 mo	Harel *Leuk Res* 2015
Guadecitabine after HMA	56	Int-2/High risk MDS AML post MDS	14%	7.1 mo	Sebert *Hematologica* 2019
	53	Int1, Int2 and High risk MDS	43%	12 mo	Garcia Manero *Lancet Hematol* 2019
ASTX727 *	47	Int1, Int2 and High risk MDS	62%	UK	Garcia Manero *ASH* 2017

* *Combination of oral decitabine cytidine deaminase inhibitor that* enhances its bioavailability.

From an HMA to another one

Group	n	Disease	Response	Survival	Ref
Decitabine after Azacitidine	36	CMML	19%	7.3 mo	Harel *Leuk Res* 2015
Guadecita after HM					rt ogica 9 anero ematol 9
ASTX727 *	47	risk MDS	62%	UK	anero *ASH* 2017

This strategy is usually Associated with :

- modest response
- and Poor OS

Encouraging results (phase 1 and 2 trial) with new epigenetic drugs

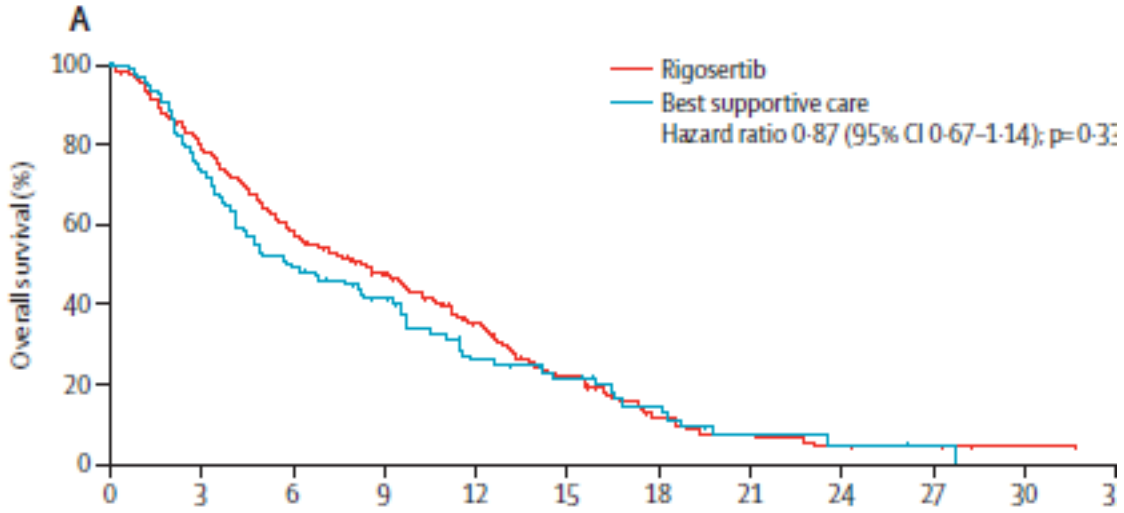
* *Combination of oral decitabine cytidine deaminase inhibitor that* enhances its bioavailability.

Rigosertib

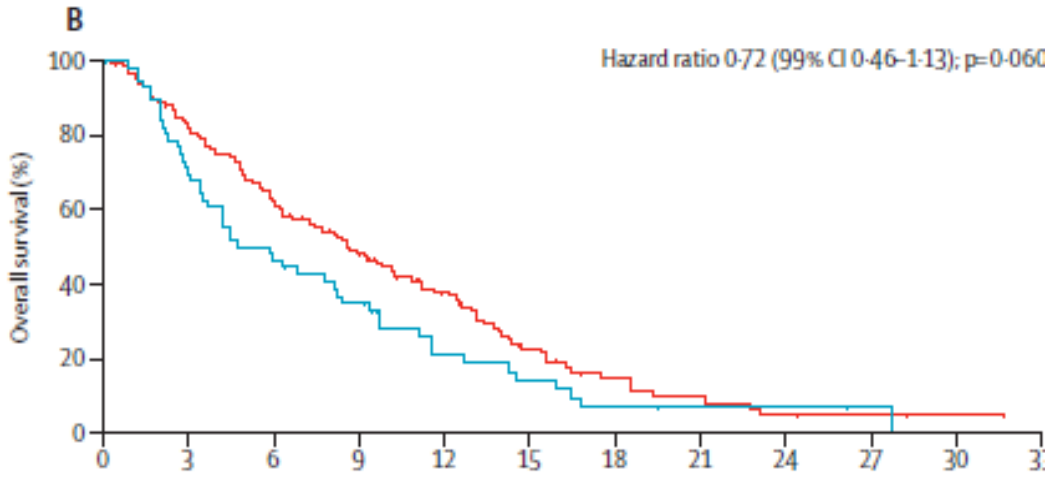
binds to the Ras-binding domain of multiple kinases including RAF, PI3K, …

Phase 3 study: Rigosertib i.v. vs. BSC OS 8.2 vs. 5.8 months (p=NS)

All patients

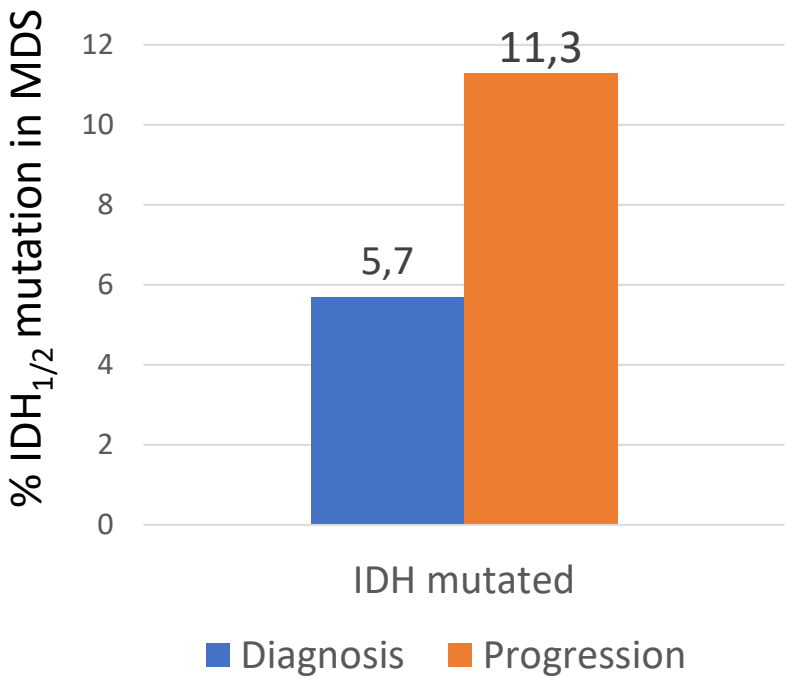


Primary failure

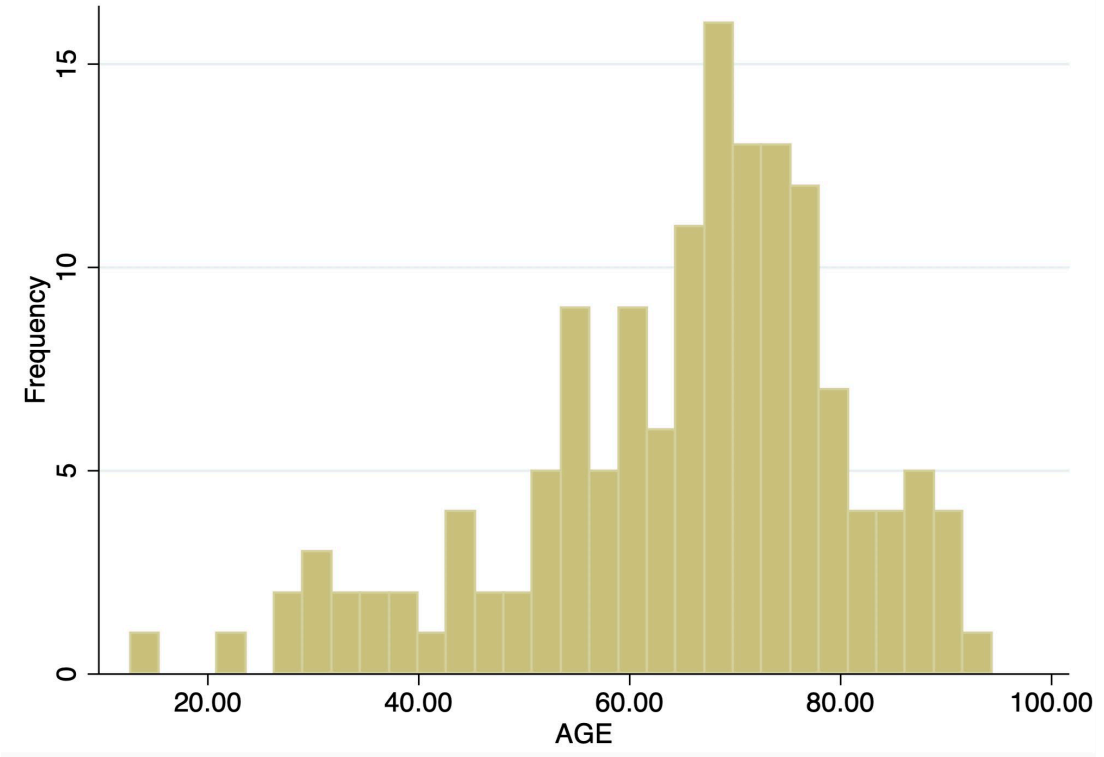


Garcia-Manero et al. Lancet Oncology 2016

Targeting $IDH_{1/2}$ mutations



Acquisition of IDHm at progression : Suggesting the importance of molecular profiling at the time of progression



$IDH_{1/2}$ mutations are more frequent in older patients

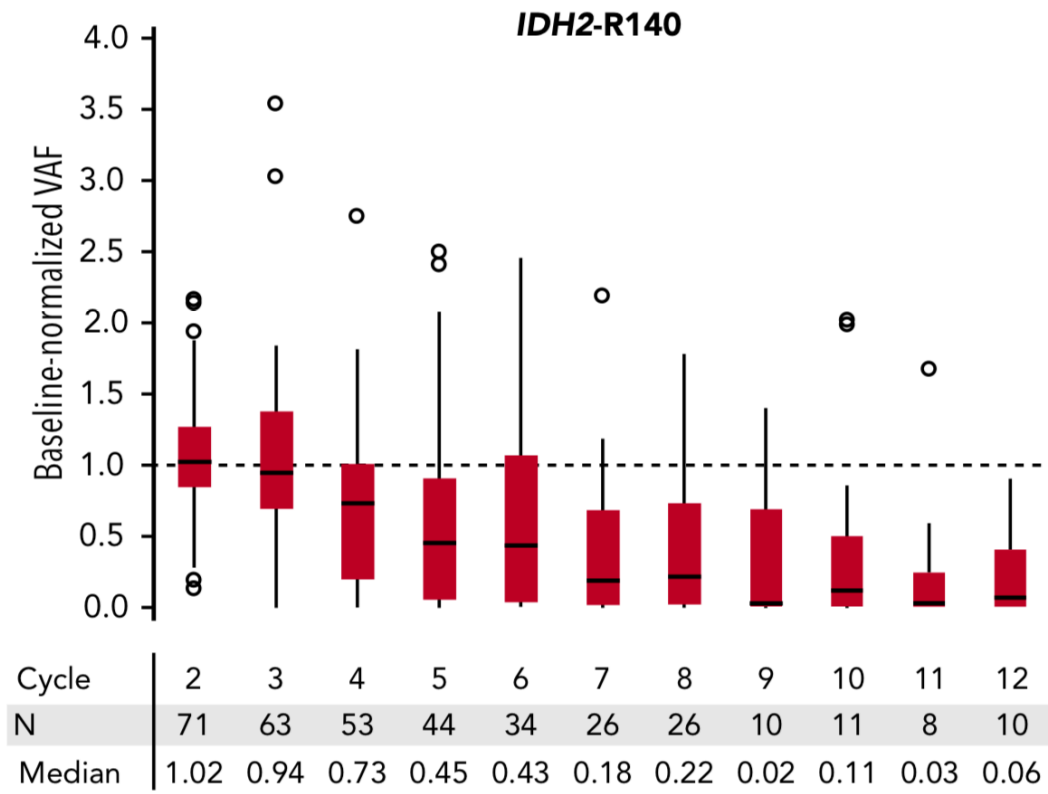
DiNardo et al. Leukemia 2016
Personal Data (E. Clappier)

Enasidenib in IDH2^{m} AML/MDS

R/R AML - single agent

	N=214 All	N=30 MDS
ORR	38.8%	53%
CR/Cri/CRp	29%	40%
Time to Response	1.9 mo	1 mo
Overall Survival	8.8 mo	9 mo
Event Free Survival	4.7 mo	-

Associated with molecular Response



Stein et al. , Blood 2019

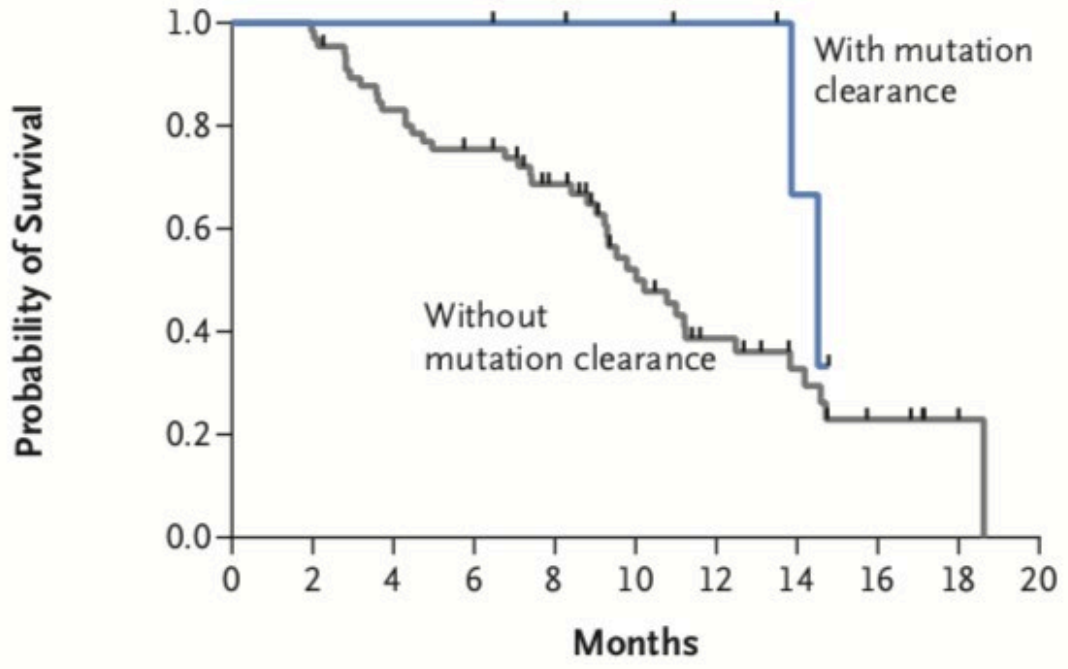
Stein et al. ASH 2016

Ivosidenib 500 mg/d (LAM R/R IDH1m)

R/R AML – Single Agent

	N=125
ORR	41.6%
CR/Cri/CRp	30.4%
Time to Response	1.9 mois
Overall Survival	8.8 mois
Event Free Survival	6 mois

Associated with molecular Response

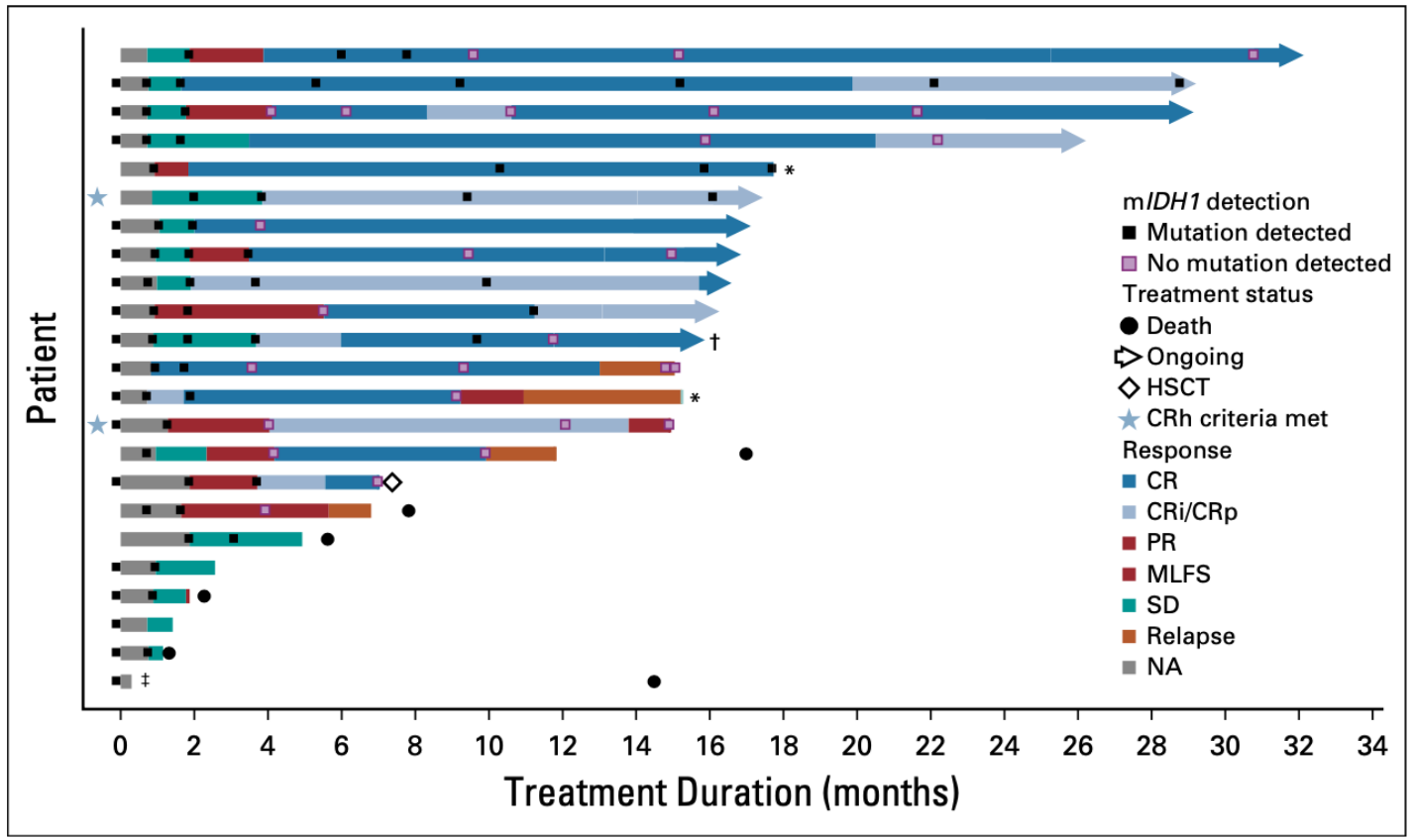


Di Nardo, NEJM 2019

AZA+Ivosidenib in IDH1^{m} AML (n = 23), phase Ib

Response Category	Response
CR + CRh,[a] No. (%) [95% CI]	16 (69.6) [47.1 to 86.8]
Median time to CR/CRh, months (range)	2.8 (0.8-11.5)
Median duration of CR/CRh, months [95% CI]	NE [12.2 to NE]
CR, No. (%) [95% CI]	14 (60.9) [38.5 to 80.3]
Median time to CR, months (range)	3.7 (0.8-15.7)
Median duration of CR, months [95% CI]	NE [9.3 to NE]
CRh,[a] No. (%)	2 (8.7)
ORR,[b] No. (%) [95% CI]	18 (78.3) [56.3 to 92.5]
Median time to response, months (range)	1.8 (0.7-3.8)
Median duration of response, months [95% CI]	NE [10.3 to NE]
Best response,[c] No. (%)	
CR	14 (60.9)
CRi/CRp	2 (8.7)
MLFS	2 (8.7)
SD	4 (17.4)
NA	1 (4.3)

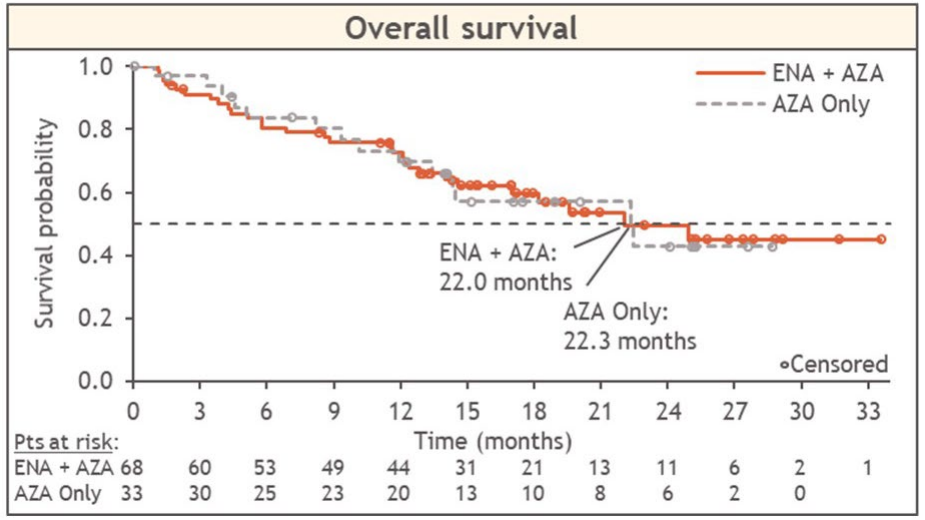
	Mutation Clearance[a]	
Response	BMMCs (n = 21)[b]	PBMCs (n = 23)[b]
CR/CRh	11/16 (68.8)	12/16 (75.0)
CR	10/14 (71.4)	11/14 (78.6)
CRh	1/2 (50.0)	1/2 (50.0)
Non-CR/CRh responders	1/2 (50.0)	1/2 (50.0)
Nonresponders	0/3 (0.0)	0/5 (0.0)

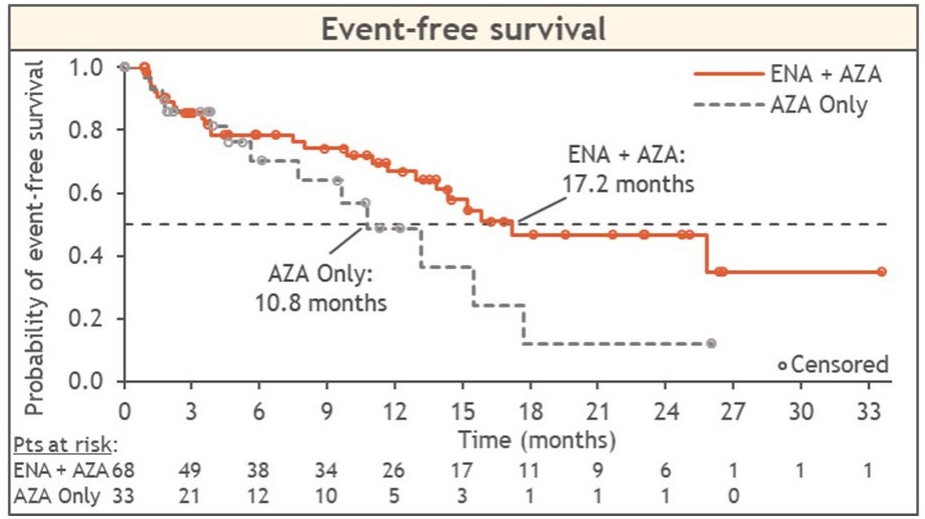


DiNardo C, et al. JCO 2021

AZA vs AZA + enasidenib in IDH2^{m} AML (n = 101)

	ENA + AZA (n=68)	AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**	**14 (42)**
[ORR 95%CI]	**[58, 81]**	**[26, 61]**
***P* value**	**0.0064**	
CR, n (%)	36 (53)	4 (12)
[CR rate 95%CI]	[41, 65]	[3, 28]
P value	0.0001	
CRi/CRp, n (%)	7 (10)	4 (12)
PR, n (%)	3 (4)	4 (12)
MLFS, n (%)	2 (3)	2 (6)
Stable disease, n (%)	13 (19)	13 (39)
Disease progression, n (%)	2 (3)	1 (3)
Not evaluable / Missing, n (%)	5 (7)	5 (15)
Time to first response, months, median (range)	1.9 (0.7-9.0)	2.0 (0.8-5.8)
Time to CR, months, median (range)	5.5 (0.7-19.5)	3.7 (3.0-4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]	12.1 [2.8, 14.6]





DiNardo C, et al. Oral presentation at the ASCO Annual Meeting 2020; abstract 7501.

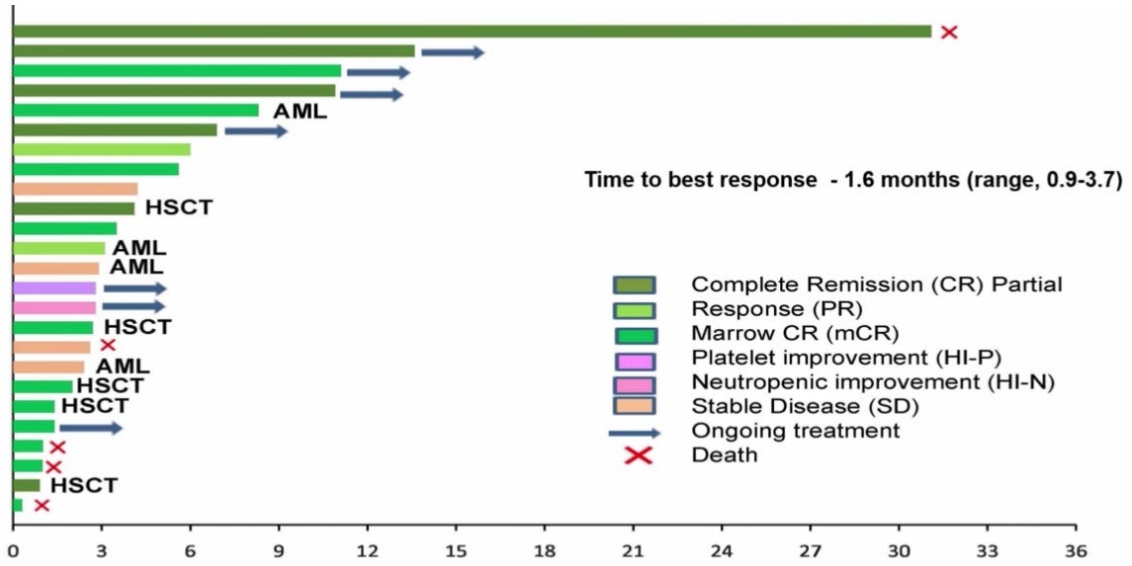
PHASE II STUDY OF THE IDH2-INHIBITOR ENASIDENIB IN PATIENTS WITH HIGH-RISK IDH2-MUTATED MYELODYSPLASTIC SYNDROMES (MDS)

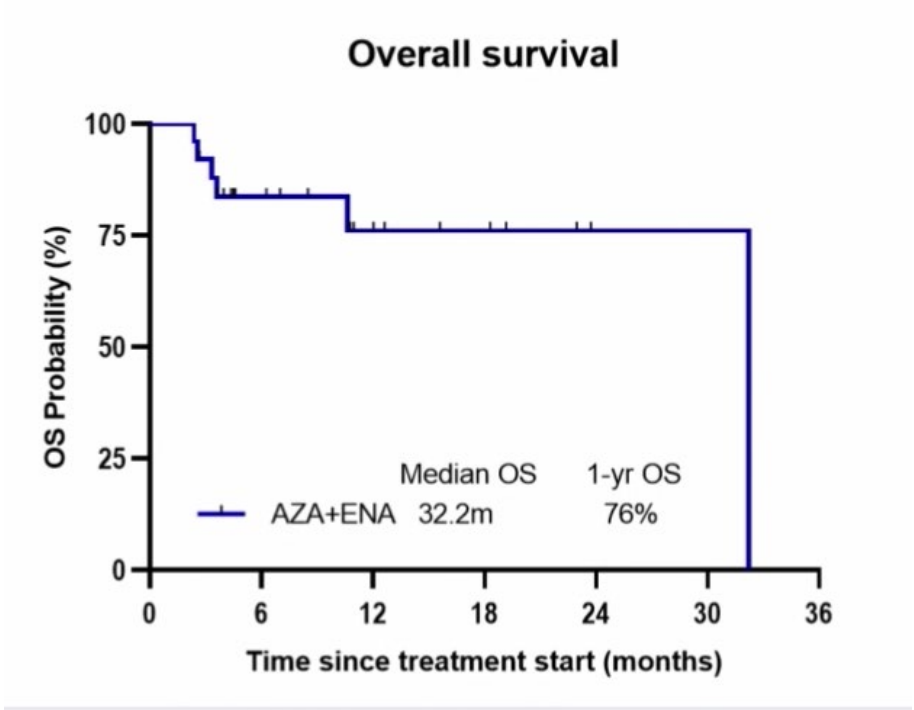
- Preliminary Results from the Phase II Study of the IDH2-Inhibitor **Enasidenib** in Patients with High-Risk IDH2-Mutated Myelodysplastic Syndromes (MDS)

	Response Evaluable (N = 46)	Arm A (Untreated) ENA+AZA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Overall response rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)

Venugopal, EHA 2021

Results Arm A – 1st line: AZA + ENASIDENIB





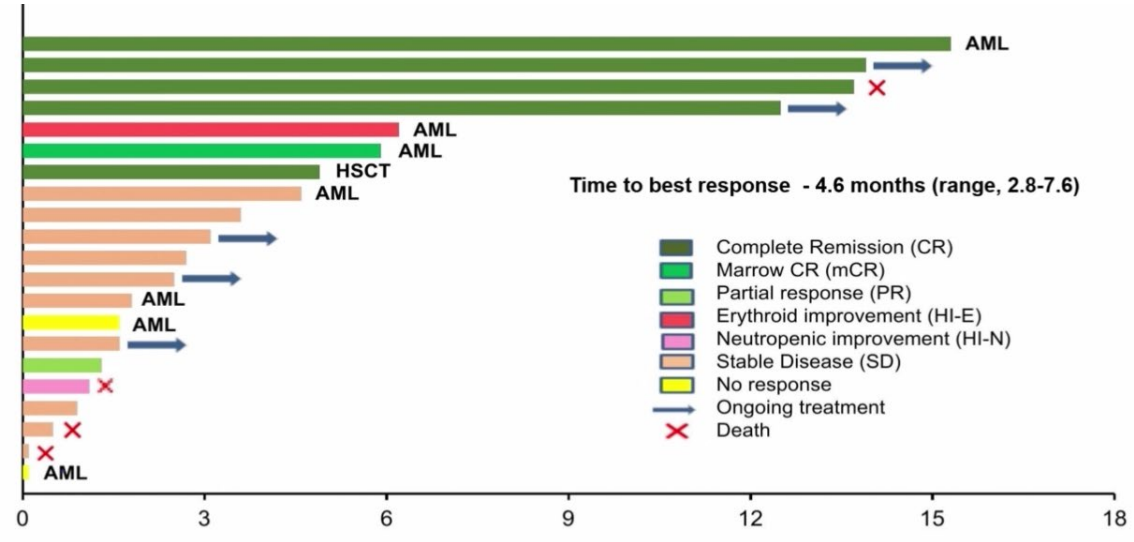
Suivi médian: 10,8 mois

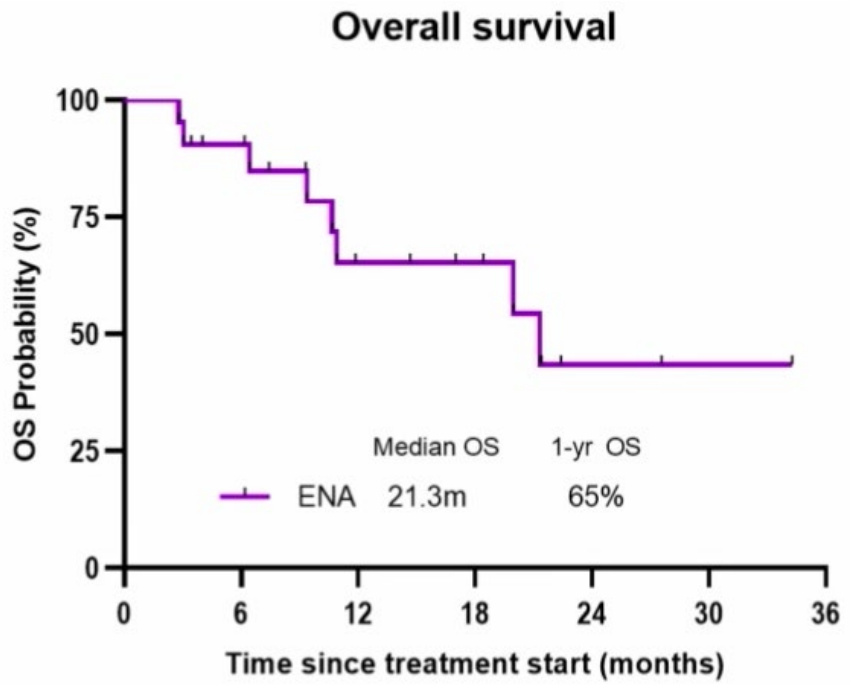
Temps médian jusqu'à la réponse: 1,6 mois

Survie globale médiane: 32,2 mois

Venugopal et al. EHA meeting abs S167

Results ARM B – HAM Failure : ENASIDENIB





- *Suivi médian: 18,4 mois*
- *Temps médian jusqu'à la réponse: 4,6 mois*
- *Survie globale médiane: 21,3 mois*

Venugopal et al. EHA meeting abs S167

IDH_1 & IDH_2 inhibitors in MDS

Groupe Francophone des Myélodysplasies

EMSCO MYELODYSPLASTIC SYNDROMES

IDEAL STUDY	IDIOME STUDY
Enasidenib (AG-221; IDH2 inhibitor)	Ivosidenib (AG-120; IDH1 inhibitor)

Cohort A: Patients with higher risk MDS who failed to achieved any type of response after 6 cycles of AZA, without disease progression (stable disease without hematological improvement-HI)

Cohort B: Patients with untreated higher risk without life threatening cytopenia

Cohort C: Lower risk MDS with anemia resistant to erythropoiesis stimulating agents

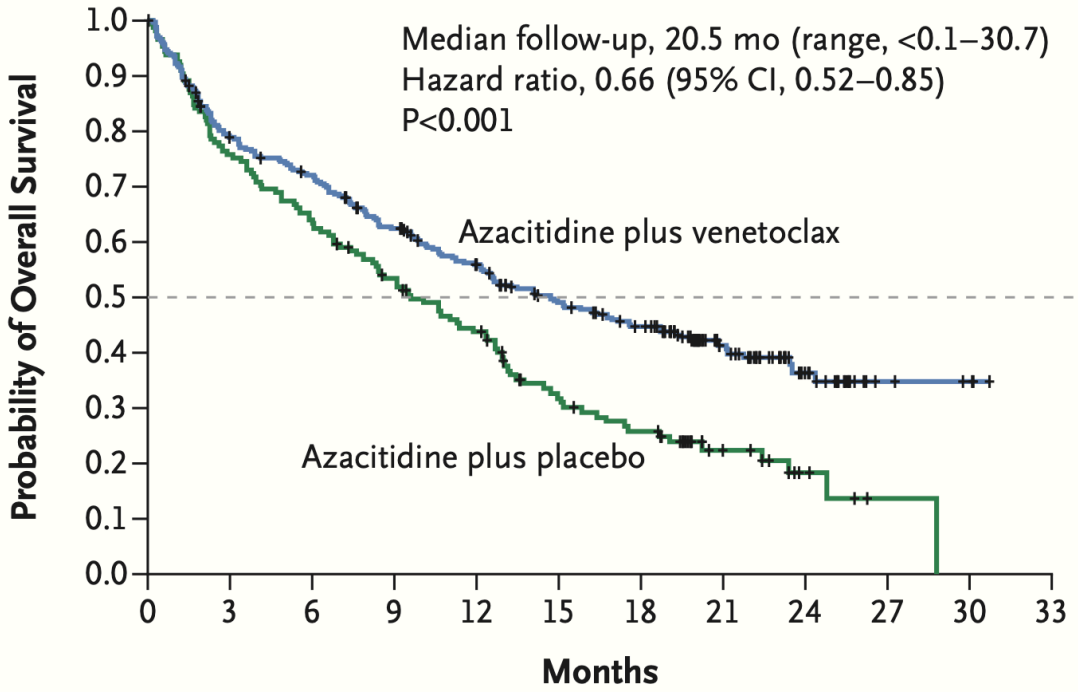
AML : HMA vs venetoclax + HMA (Viale-A)

Table. Patient responses in treatment groups

	AZA+VEN (n=286)	AZA+PBO (n=145)	p-value
CR + CRi rate, % (95% CI)	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<0.001
CR+CRi by initiation of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<0.001
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<0.001
TI, % (95% CI)			
Red blood cells	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<0.001
Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<0.001
CR+CRi rates in molecular subgroups, % (95% CI)			
IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<0.001
FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	0.021
NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	0.012
TP53	55.3 (38.3-71.4)	0	<0.001
Event free survival, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	<0.001

AZA+VEN: Azacitidine+Venetoclax; AZA+PBO: Azacitidine+Placebo; CR:Complete remission; CRi: CR with incomplete count recovery; CRh: CR with partial hematologic recovery; TI: Transfusion independence (defined as ≥56 days with no RBC or platelet transfusion between first and last day of treatment)

OS 14.7 months in the azacitidine–venetoclax group vs 9.6 months

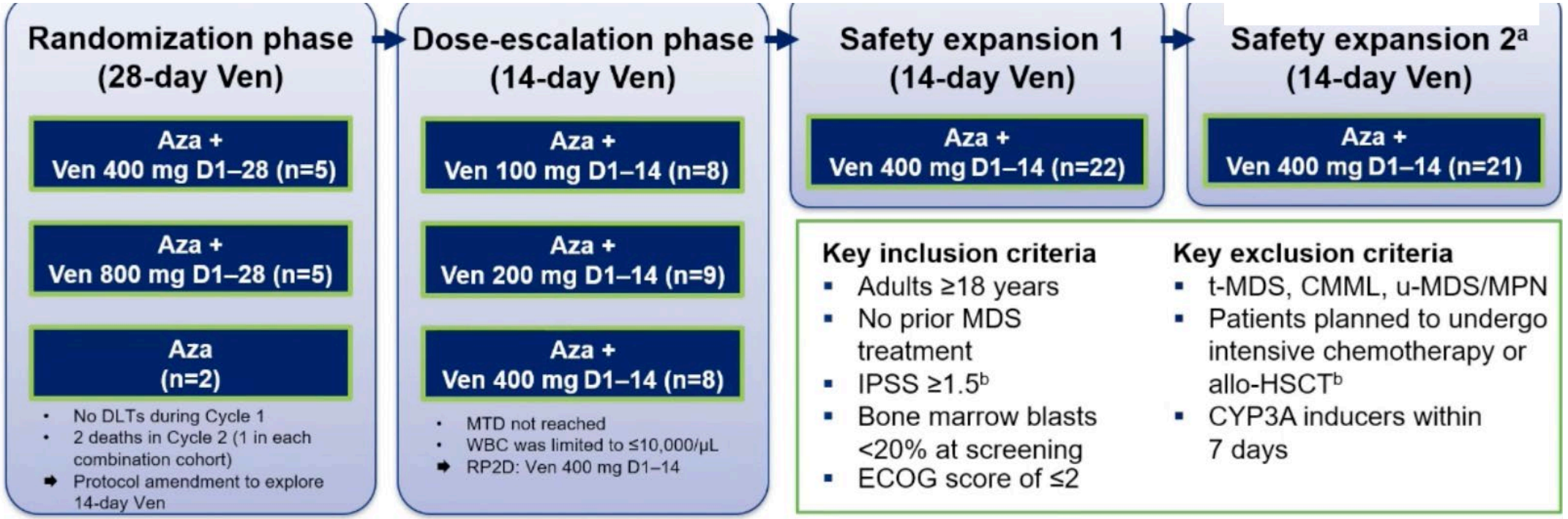


DiNardo C, et al. NEJM 2020

HR MDS 1st line – AZA-Venetoclax

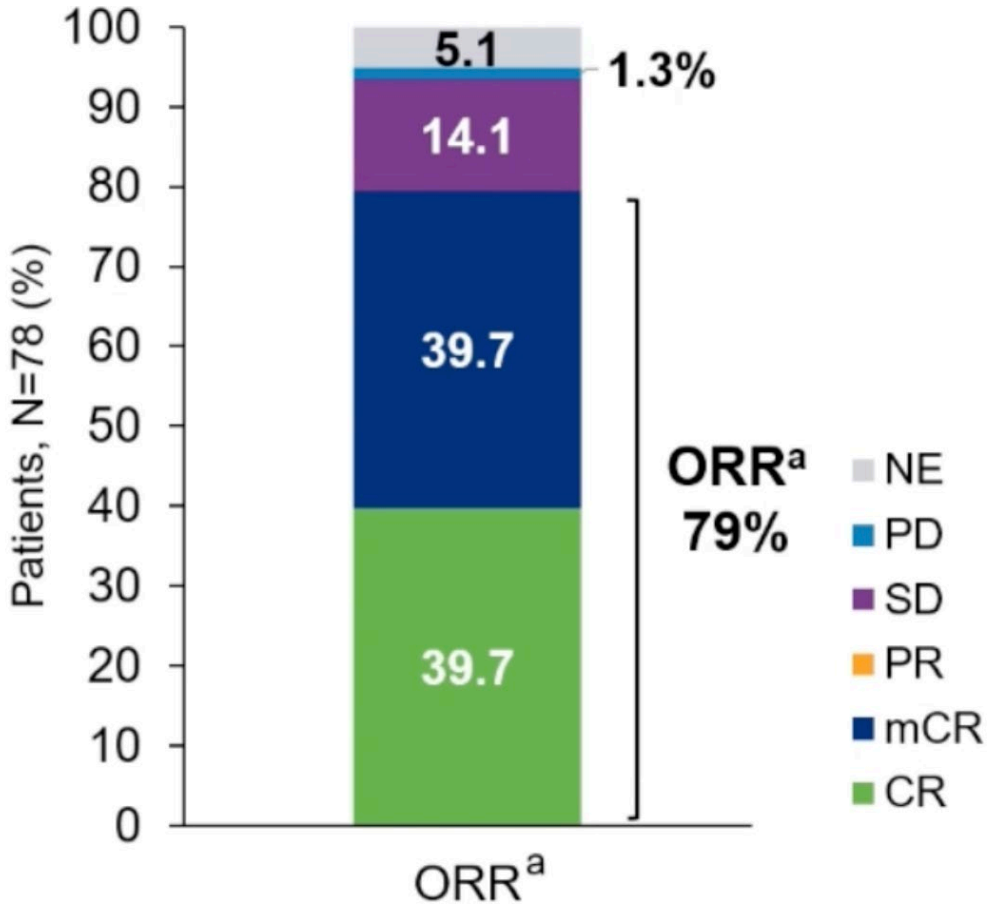
- Phase 1b study evaluating Venetoclax and Azacitidine as a first-line treatment for high-risk MDS.

N=78



Garcia et al. ASH 2020

HR MDS 1st line – AZA-Venetoclax

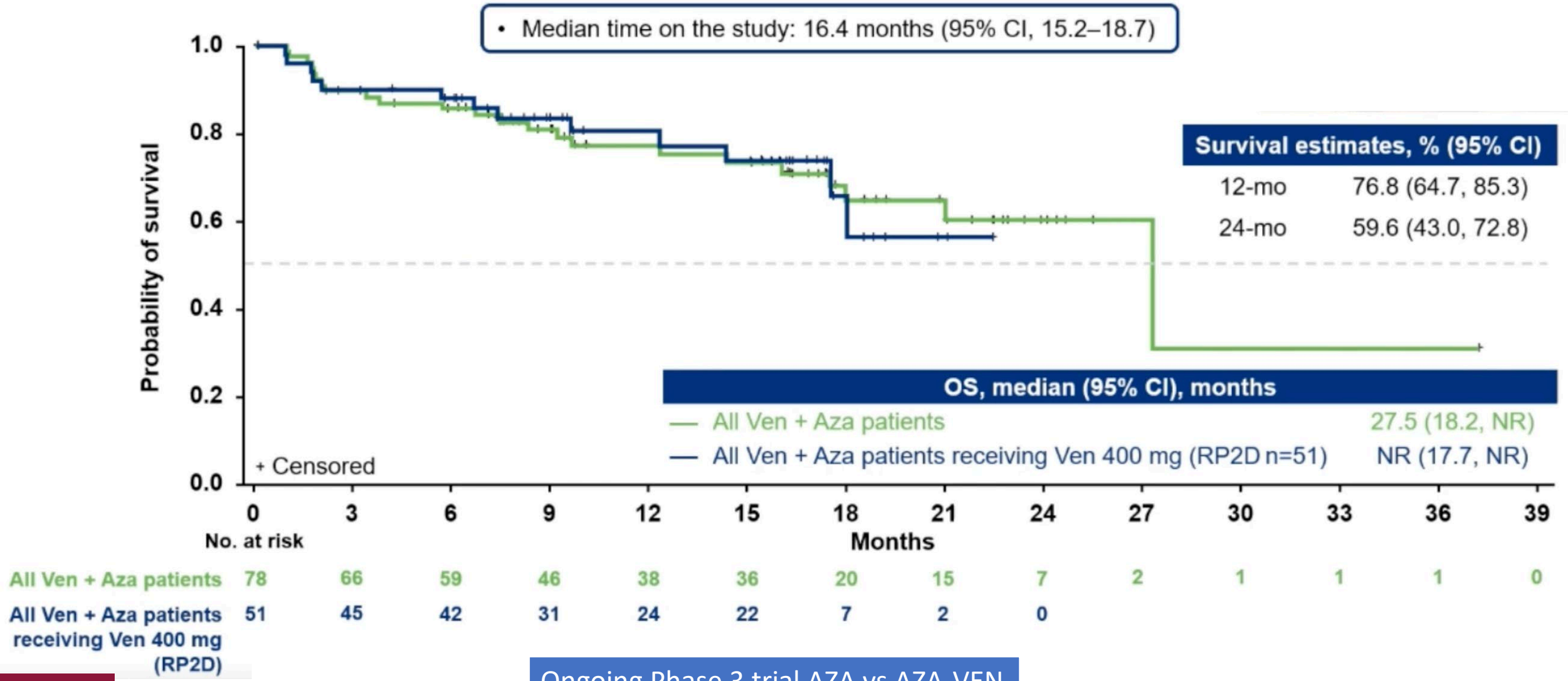


Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

- Overall, 74 patients (95%) required a cycle delay; median time to delay 15.0 days (range 3–99)
- 43 patients (55%) had ≥2 Ven dose interruptions
  - AEs 59 (80%); hematologic toxicity 27 (37%); logistics/scheduling 19 (26%), other 41 (55%)
- A total of 35% of patients required ≥1 Ven dose reduction[e]
  - AEs 6 (21%); starting CYP3A inhibitor 20 (71%); other 7 (25%)
- A total of 33% of patients required ≥1 Aza dose reduction[e]
- 30-day mortality after first dose was 1%

Garcia et al. ASH 2020

HR MDS 1st line – AZA-Venetoclax



Ongoing Phase 3 trial AZA vs AZA-VEN

Garcia et al. ASH 2020

HR MDS 1st line – AZA-Venetoclax – UPDATE EHA 2021

Summary of efficacy	n (% of N=78)
Overall Response Rate (CR + mCR + PR)	62 (80)
CR	31 (40)
mCR	31 (40)
mCR + hematologic improvement[a] n/N (%)	13/31 (42)
Transfusion Independence Rate[b] n/N (%) [95% confidence interval]	20/43 (46.5) [31.2, 62.3]
	Months [95% confidence interval]
Median Overall Survival	28.2 [17.7, not estimable]
Median Overall Survival for CR	28.6 [27.5, not estimable]
Median Duration of Response for CR	13.8 [8.9, not estimable]

[a]Hematologic improvement (HI) includes pts who are eligible for HI evaluations and achieved neutrophil, erythroid, or platelet responses.

[b]For patients who were transfusion-dependent on RBC or platelet at baseline.

CR, complete remission; mCR, marrow complete remission; PR, partial remission

Grade 3/4 TEAEs were experienced by 96% of pts
neutropenia (82%)
febrile neutropenia (49%)
and thrombocytopenia (42%)
The 30-day mortality rate after first dose was 1%.

Median OS of the study population was 28.2 mos (95% CI 17.7, –).
Median OS for 31 pts achieving CR was 28.6 mos (95% CI 27.5, –).
23% of the study population moved on to post-study allogeneic HSCT (incl. BM and peripheral blood stem cell).

WEI et al. EHA 2021

HMA-Ven for Second line treatment (mostly AML)

	#Patients	treatment	Response	OS	OS of responders
Aldoss et al.[90]	90	VEN + AZA (9) VEN + DEC (81)	46%	7,8 mo	16,6 mo
DiNardo et al.[91]	43	VEN + AZA (8) VEN + DEC (23) VEN + LDAC (8) VEN + autre (4)	21%	3,0 mo	4,8 mo
Ram et al.[92]	23	VEN + AZA ou DEC	43%	5,6 mo	10,8 mo
Goldberg et al.[93]	24	VEN + AZA (5) VEN + DEC (1) VEN + LDAC (2)	29%	UK	UK

Checkpoint inhibitor in HMA R/R MDS

- Exposure to azacitidine upregulates PD1/PDL1/CTLA4 expression, opening a new possible therapeutic approach in these diseases
- Basket exploratory phase 2 trial of immune checkpoint inhibitors in Myelodysplastic Syndrome

- Patients with MDS ≥ 18 years
- adequate renal and hepatic function without history of autoimmune disorders

Front-line cohort - 2 different cohorts:
- AZA + nivolumab (3 mg/kg days 6 + 20 every 4-week cycle)
- AZA + ipilimumab (3 mg/kg day 6 every 4-week cycle)

HMA-failure : Two cohorts :
- Nivolumab (3 mg/kg d 1 + 15 every 4-week cycle)
- Ipilimumab (3 mg/kg d 1 every 3-week cycle)

after 6 cycles (or earlier if progression) AZA allowed (resensitization)

Guillermo Garcia-Manero, ASH 2018 #465

Checkpoint inhibitor in HMA R/R MDS

	Nivo	Ipi
Overall response	2/15 (13%)	2/15 (13%)
CR/CRp	0 (0%)	3 (15%)
Clearance of detectable mutations		3 (15%)
Median overall survival (FU 20 months)	8 months	8 months
Event-free survival	7 months	6 months
One-year survival	25%	45%

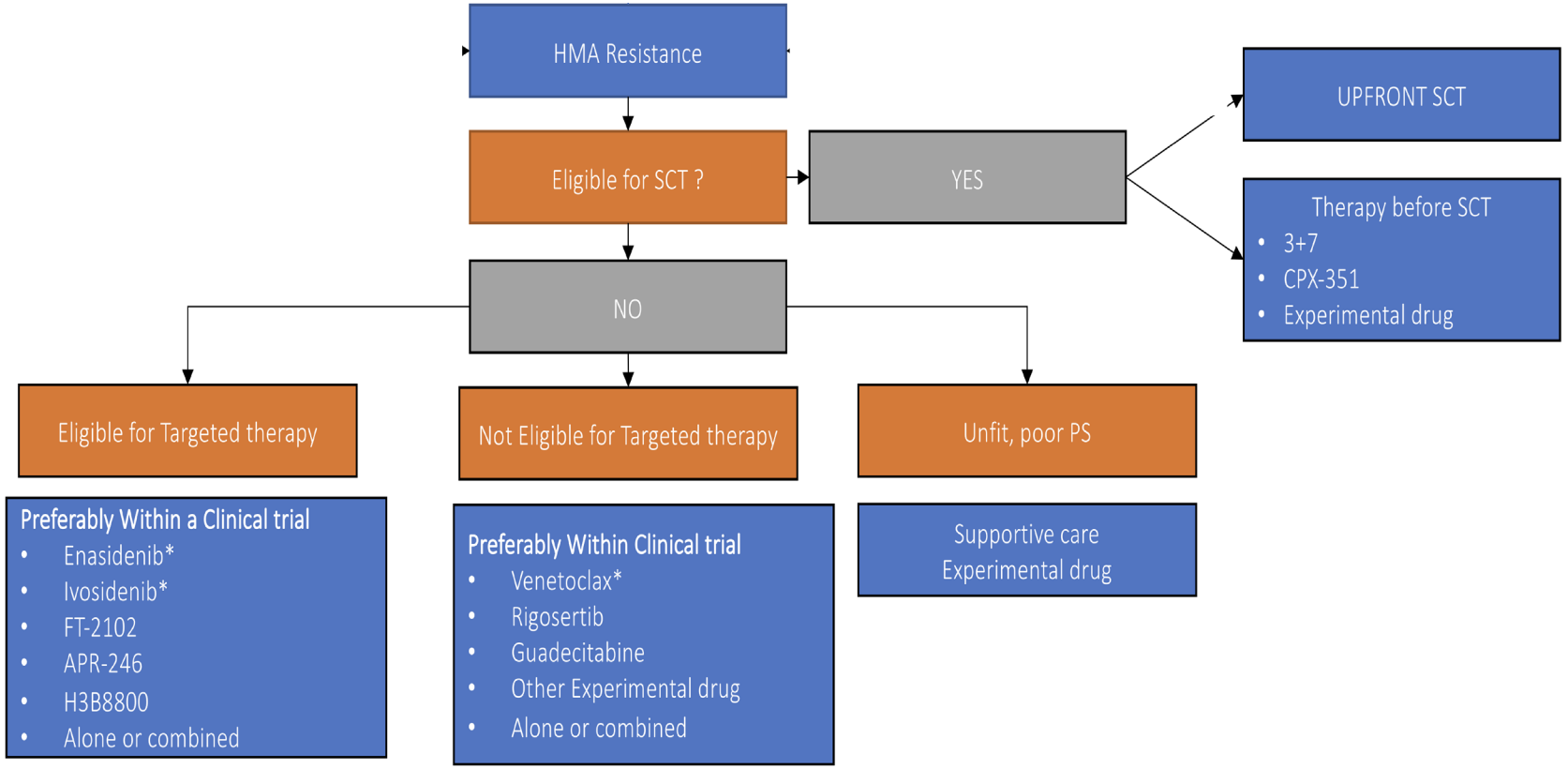
Guillermo Garcia-Manero, ASH 2018 #465

New drugs under investigation in 1st Line therapy

- Magrolimab
- Sabtolimab
- Pevonedistat
- …

- → Any role for HMA failure ?

HMA Resistance



Key Messages

1. Check for SCT eligibility → 3+7/CPX351 before SCT
2. Check for $IDH_{1/2}$ mutation
3. Eligibility for Clinical trial ?
4. Bcl2 inhibitors ?
5. Supportive care

Acknowledgments

- Pierre Fenaux
- Raphael Itzykson
- Marie Sebert
- Ramy Rahmé
- Elsa Miekoutima

- Marie Robin
- Gérard Socié

- Stéphanie Mathis
- Maria-Elena Noguera
- Wendy Cuccuini
- Odile Maarek
- Emmanuelle Clappier

- Jean Soulier
- Hugues de Thé

- Fatiha Chermat

- Uwe Plazbecker
- Silke Gloasguen

université PARIS DIDEROT PARIS 7

Groupe Francophone des Myélodysplasies

EMSCO MYELODYSPLASTIC SYNDROMES