Actualités dans les SMD de haut risque

Groupe Francophone des Myélodysplasies

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UNIVERSITÉ PARIS 13

IPSS et IPSS-R

- Higher risk MDS
  - IPSS intermediate-2 or high

  or R-IPSS very high, high and intermediate (> 3.5)
  - Delay disease progression
  - Prolong survival

- Lower risk MDS
  - IPSS low or intermediate-1

  or R-IPSS very low, low , int <4
  - Improve blood cytopenias *(mainly anemia)*
  - Improve quality of life

Traitement des SMD de haut risque

- Allogreffe de moelle
- Chimiothérapie
- Agents Hypométhylants
- Autres (en combinaison avec les hypométhylants)

Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents (HMA)
- Others (mainly in combination with HMA)

Outcome of higher risk MDS according to donor availability: M

Robin, Leukemia, 2014

- 163 patients : 21%no donor; 71% HLA-matched donor (34% sibling and 37% unrelated) and 9% patients HLA mismatched donor
- 117 patients treated by AZA and 40 by CT. marrow blasts < 10% achieved in 68% and 57% for patients without and with donor

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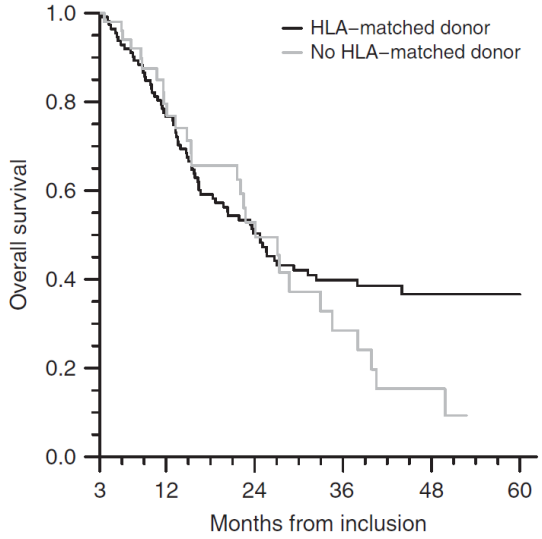
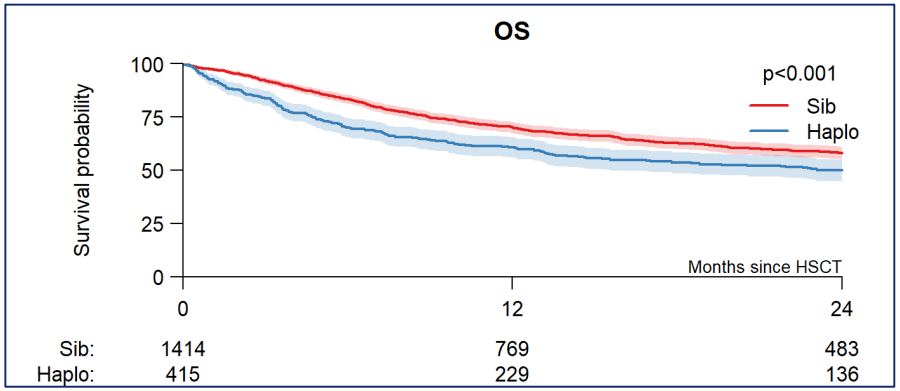
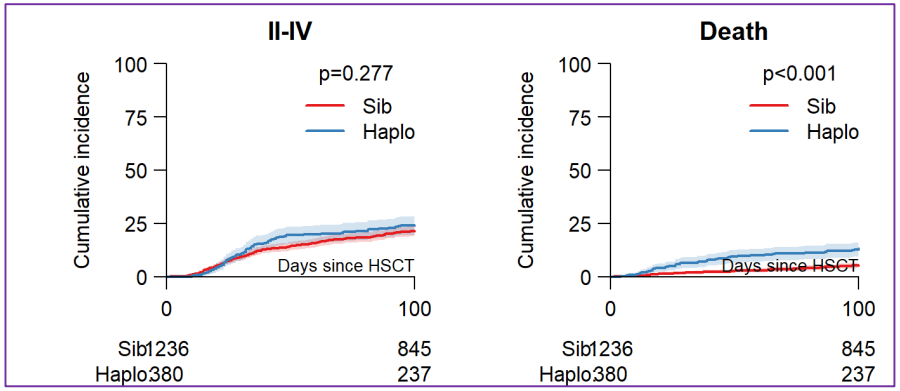
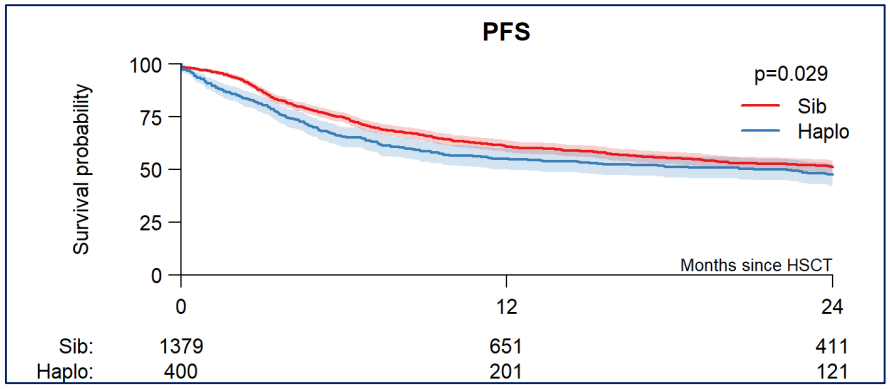


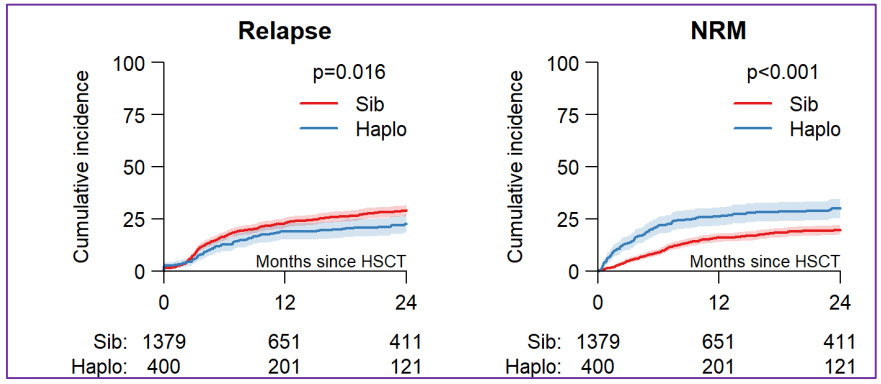
No. at risk:										
HLA–matched donor	112	85	63	50	39	33	23	14	8	5
No matched donor	50	29	21	15	8	6	3	2	0	0

Matched Sibling vs Haplo Donor for MDS 2014-2017 CLWP









Raj K, Eikema DA, et al on behalf of CLWP

Allo SCT: preceded or not by cytoreduction?

Largely based on marrow blast% and karyotype

- marrow blasts <10% : immediate transplant

- marrow blasts > 10%
  - Upfront allo ?
  - Normal karyotype : intensive chemo prior to transplant ?
  - Unfavorable karyotype: HMA (+ others ?) prior to transplant ?

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Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study)

Nicolaus Kröger, MD[1]; Katja Sockel, MD[2]; Christine Wolschke, MD[1]; Wolfgang Bethge, MD[3]; Richard F. Schlenk, MD[4,5]; Dominik Wolf, MD[6,7,8]; Michael Stadler, MD[9]; Guido Kobbe, MD[10]; Gerald Wulf, MD[11]; Gesine Bug, MD[12]; Kerstin Schäfer-Eckart, MD[13]; Christof Scheid, MD[14]; Florian Nolte, MD[15]; Jan Krönke, MD[16]; Matthias Stelljes, MD[17]; Dietrich Beelen, MD[18]; Marion Heinzelmann[1]; Detlef Haase, MD[11]; Hannes Buchner, PhD[19]; Gabriele Bleckert, PhD[19]; Aristoteles Giagounidis, MD[20]; Uwe Platzbecker, MD[2,21]; on behalf of the German MDS Study Group and the German Cooperative Transplant Study Group

Remission status after 5-aza induction, No. (%)	
CR	8 (10)
PR	14 (17)
SD	47 (58)
Others (marrow CR and cytogenetic response)	11 (14)
Disease progression, No. (%)	1 (1)

Traitement avant allogreffe dans les SMD de haut risque

Essai non randomisé

- CPX 351
- AZA+ Venetoclax
- Allogreffe d'emblée

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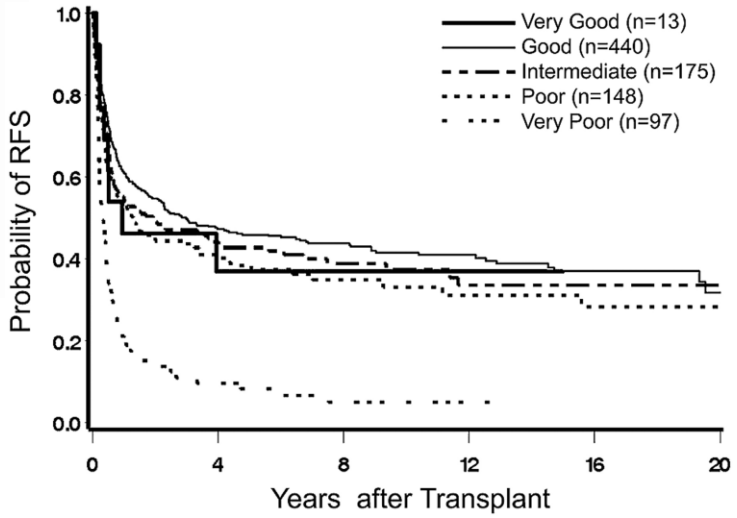
Poor outcome of allo SCT if very poor karyotype and/or TP 53 mutations)

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Survival by 5-group cytogenetic classification.



Deeg H J et al. Blood 2012;120:1398-1408

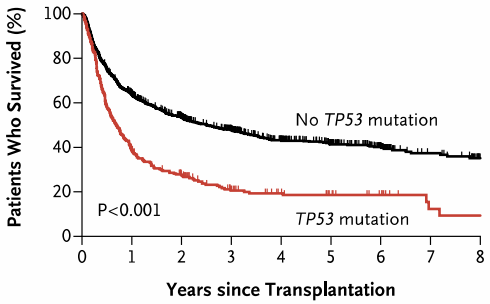
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation

R.C. Lindsley, W. Saber, B.G. Mar, R. Redd, T. Wang, M.D. Haagenson, P.V. Grauman, Z.-H. Hu, S.R. Spellman, S.J. Lee, M.R. Verneris, K. Hsu, K. Fleischhauer, C. Cutler, J.H. Antin, D. Neuberg, and B.L. Ebert

B Overall Survival, According to *TP53* Mutation Status



No. at Risk

No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

Bejar et al. *ASH 2012* abstract *#311*

Etude DACORAL(GFM- ASTX 727 post allo)

"Preventive" Post-transplant ASTX 727 in very high risk MDS patients: a phase II prospective study

(M Robin)

Inclusion criteria
Patients aged from 18 to 70 years
MDS according to WHO with a very complex cytogenetic (according to IPSS-R) or TP 53 gene mutation

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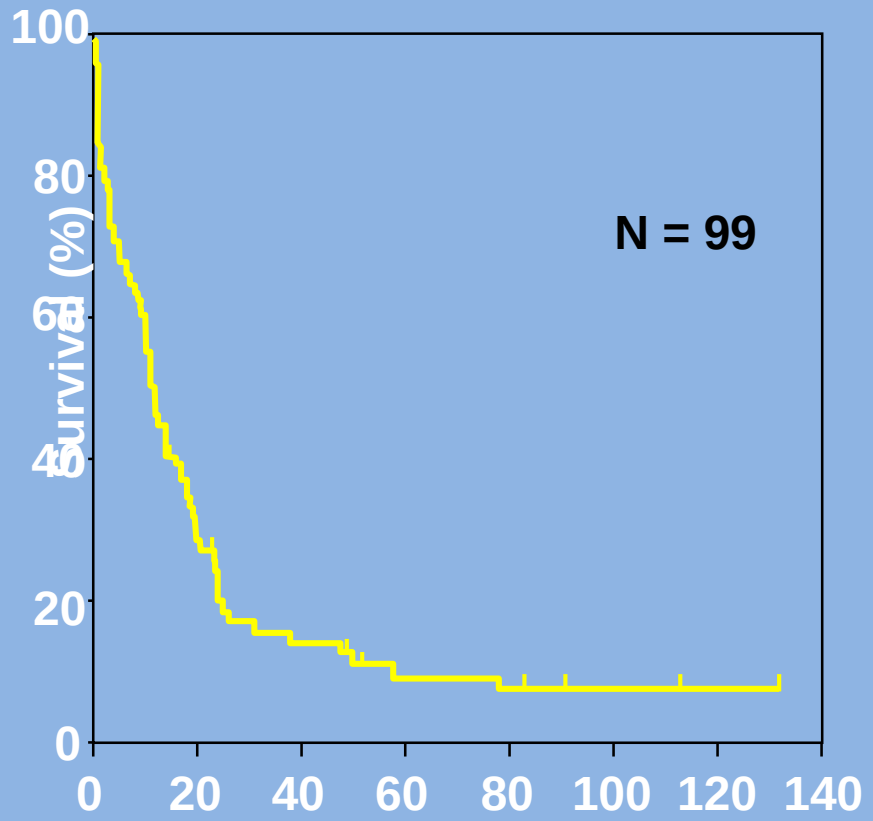
- ASTX 727 (decitabine + cedazuridine) started on day 40
- Immunosuppression stopped on day 70
- DLI started on day 100

Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (mainly in combination with HMA)

Survival with Anthracycline-AraC Chemotherapy



- CR in 45 to 60% patients
- Very low CR if complex karyotype
- Median CR duration 1 year

Wattel E. et al.

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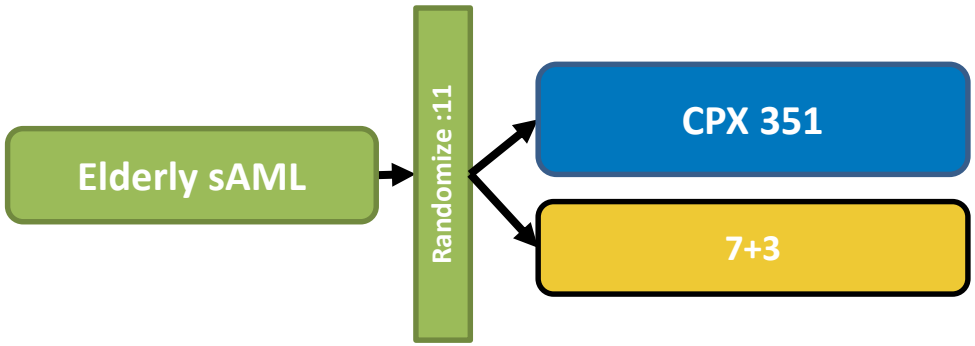
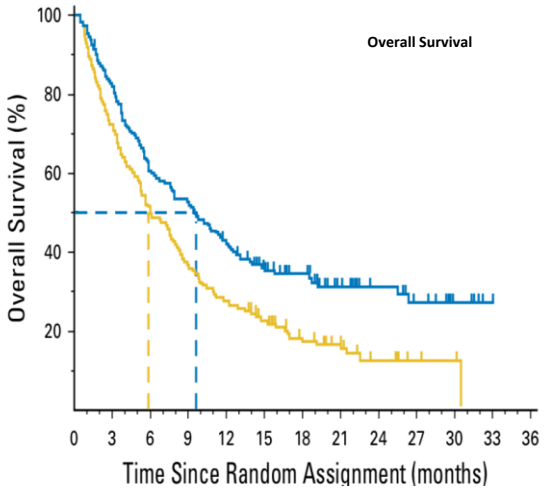
***Br J Haematology*. 1997;98:983-991.**

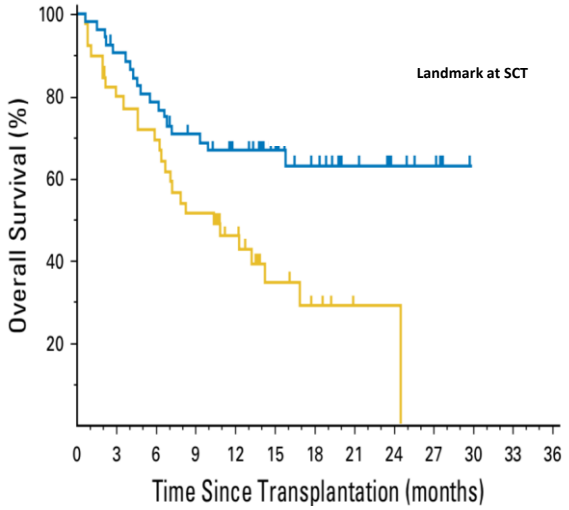
CPX-351 (cytarabine and daunorubicin) Liposome 7+3 in Older Patients With sAML



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

Subanalysis of Patients with sAMLRAEB-t Enrolled in a Phase 3 Study of CPX-351 Versus Conventional 7+3 Cytarabine and Daunorubicin

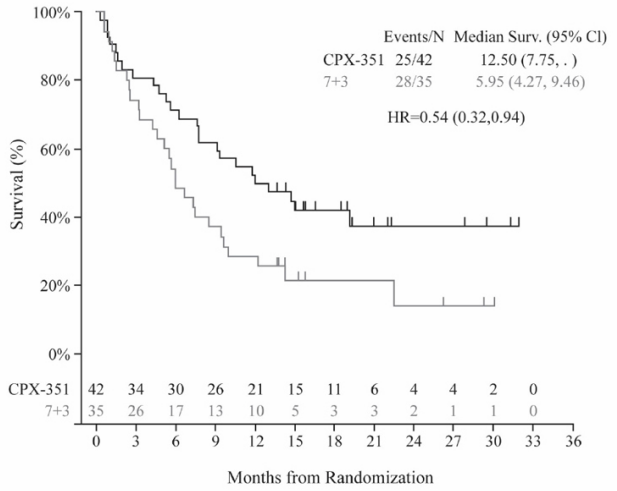
Tara L. Lin et al ASH 2017

Table: Baseline Characteristics of Patients with RAEB-t AML

Characteristic, n (%)	CPX-351 (n = 42)	7+3 (n = 35)
Age		
60-69 years	26 (62)	21 (60)
70-75 years	16 (38)	14 (40)
Male sex	25 (60)	25 (71)
ECOG performance status		
0	14 (33)	10 (29)
1	23 (55)	19 (54)
2	5 (12)	6 (17)
AML type		
de novo AML with MDS karyotype	11 (26)	3 (9)
History of MDS with prior HMA treatment	16 (38)	14 (40)
History of MDS without prior HMA treatment	3 (7)	5 (14)
History of CMML	5 (12)	4 (11)
Therapy-related AML	7 (17)	9 (26)
Karyotype	n = 41	n = 31
Adverse	19 (46)	11 (36)
Non-adverse	22 (54)	20 (65)
White blood cell count	n = 42	n = 35
$<20\times10^9$/L	38 (91)	32 (91)
$\geq20\times10^9$/L	4 (10)	3 (9)
Platelet count	n = 42	n = 35
$\leq50\times10^9$/L	24 (57)	22 (63)
$>50\times10^9$/L	18 (43)	13 (37)
FLT3 mutation[a]	n = 36	n = 30
Positive	3 (8)	3 (10)
Negative	33 (92)	27 (90)

RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; HMA, hypomethylating agents; CMML, chronic myelomonocytic leukemia; *FLT3*, FMS-like tyrosine kinase 3.
[a]Included internal tandem duplications and kinase domain mutations.

Figure: OS by treatment arm in patients with RAEB-t AML



OS, overall survival; RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio.

CPX 351dans les SMD de haut risque

(P Péterlin)

- N=20
- 50% RC
- 15% RCi
- 20 % RC médullaire
- 15% d'échecs

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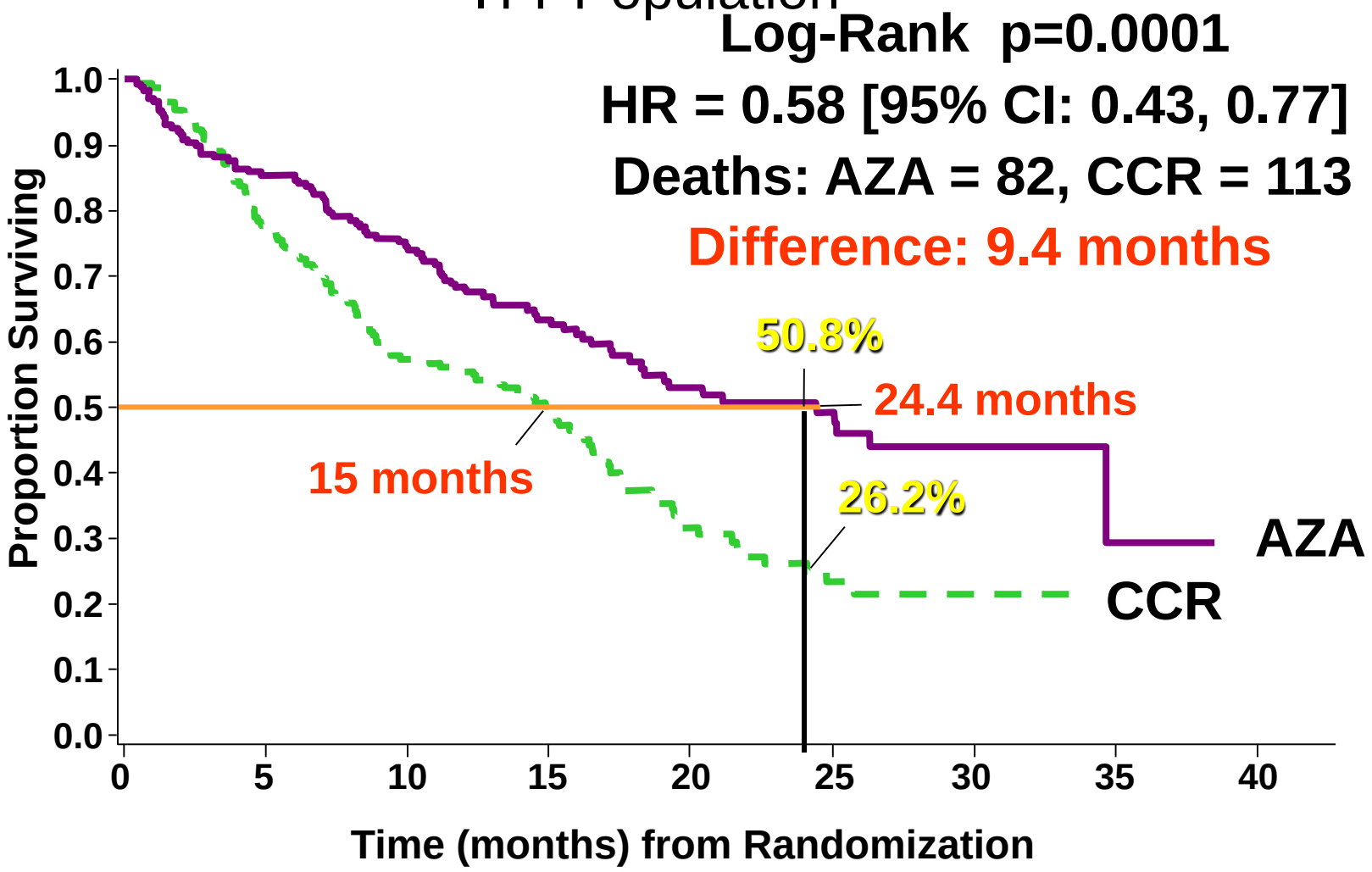
Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (mainly in combination with HMA)

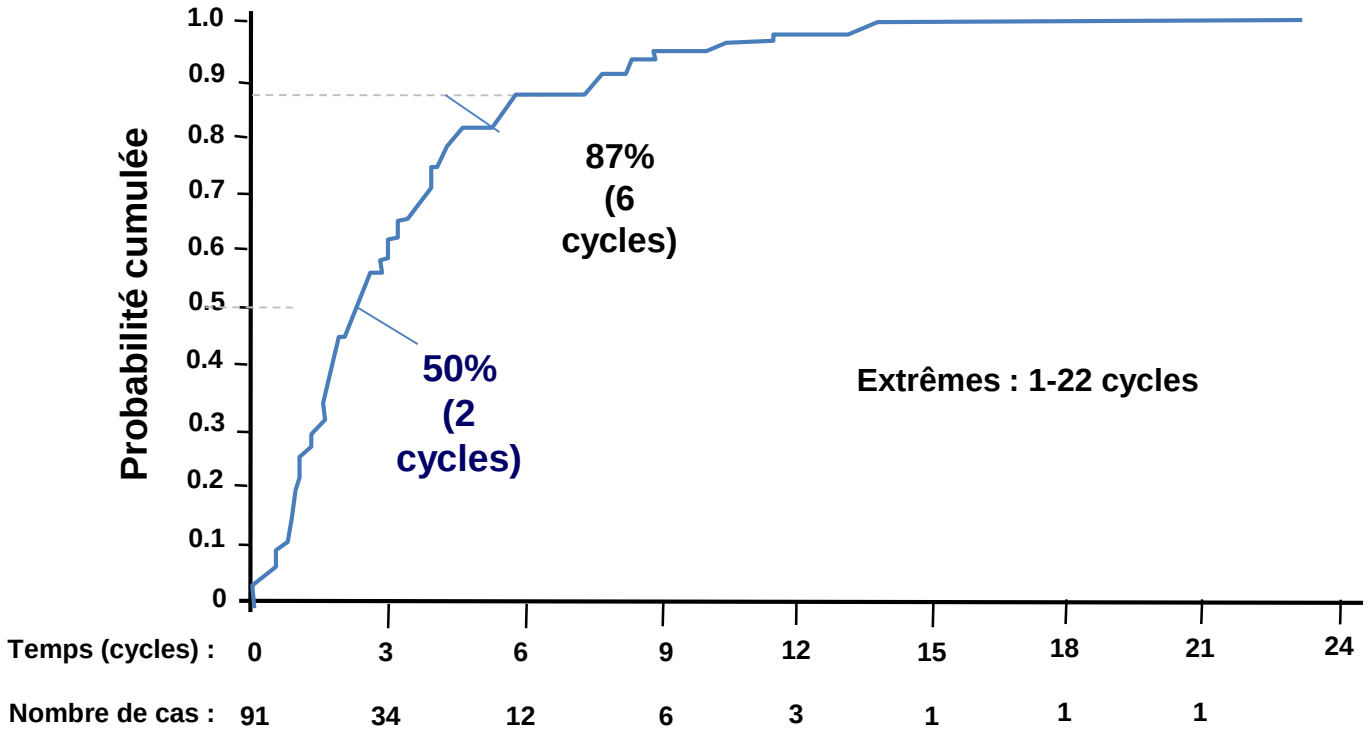
AZA 001:Overall Survival: Azacitidine vs CCR

ITT Population



AZA 001:Azacitidina actua de manera lenta

- response after 2 to more than 6 cycles
- Continuing treatment improves responses in 48% of the cases



Abs 227 – CO – L R SILVERMAN et al.

AZA 001 trial:Secondary Endpoints: IWG (2000) CR,PR and HI

Response	AZA N=179 (%)
Overall (CR+PR)	29
CR	17
PR	12
IWG HI	
Major+Minor	49

TO THE EDITOR:

Long-term survival of older patients with MDS treated with HMA therapy without subsequent stem cell transplantation

Amer M. Zeidan,[1,2] Maximilian Stahl,[1,2] Xin Hu,[2] Rong Wang,[2,3] Scott F. Huntington,[1,2] Nikolai A. Podoltsev,[1,2] Steven D. Gore,[1,2] Xiaomei Ma,[2,3] and Amy J. Davidoff[2,4]

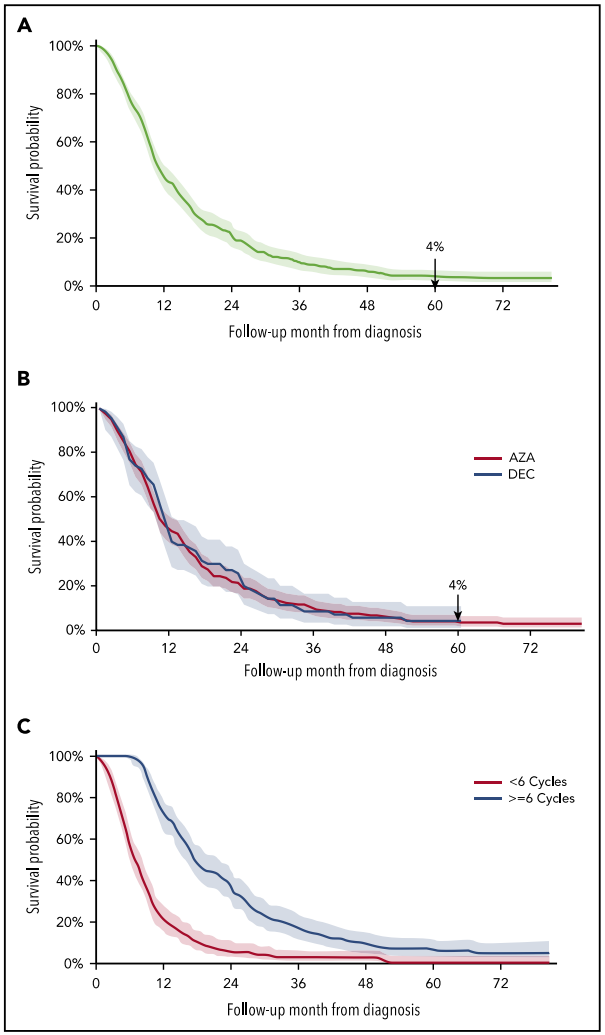
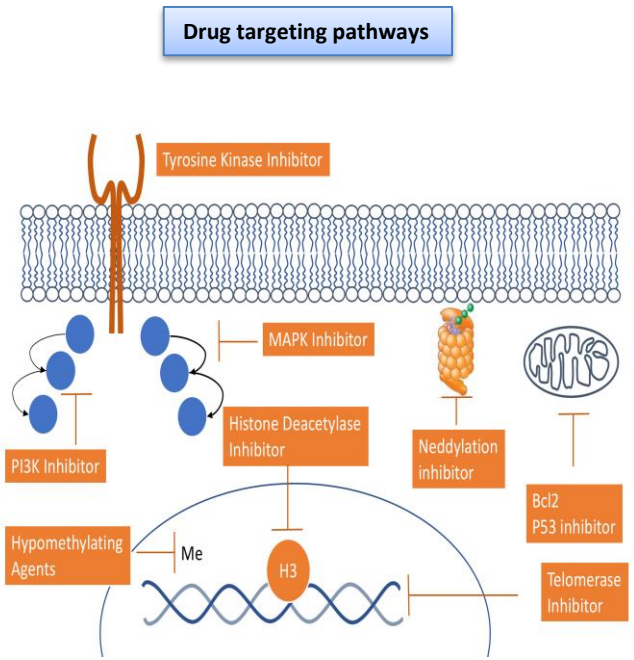


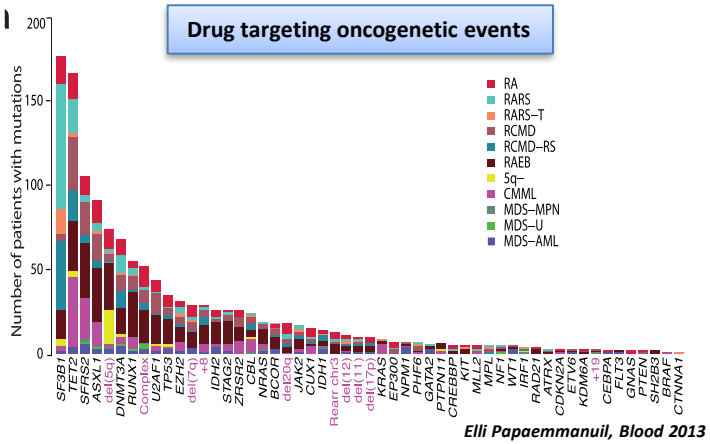
Figure 1. Kaplan-Meier survival curves. (A) RAEB patients (N = 336). (B) RAEB patients (N = 336) stratified by type of HMA used (azacitidine [AZA], N = 266 vs decitabine [DEC], N = 70). (C) RAEB patients (N = 336) stratified by those receiving ≥6 cycles (N = 159) or <6 cycles (N = 177) of the HMA.

Treatment of high risk MDS

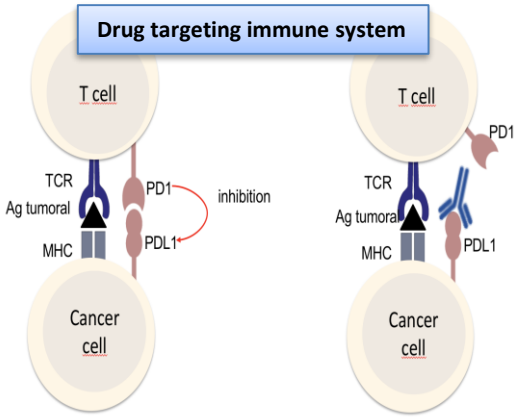
- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (mainly in combination with HMA)

Three different types of Drugs



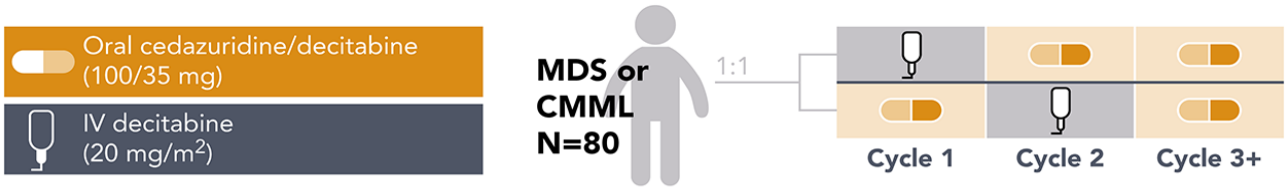


Elli Papaemmanuil, Blood 2013

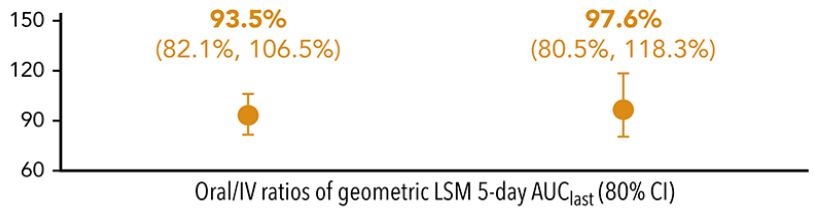


Phase 2 study of ASTX 727:* Study design and pharmacokinetics

Randomized cross-over study of oral ASTX272* in patients with IPSS intermediate-1/2- or HR-MDS or CMML



Systemic exposure



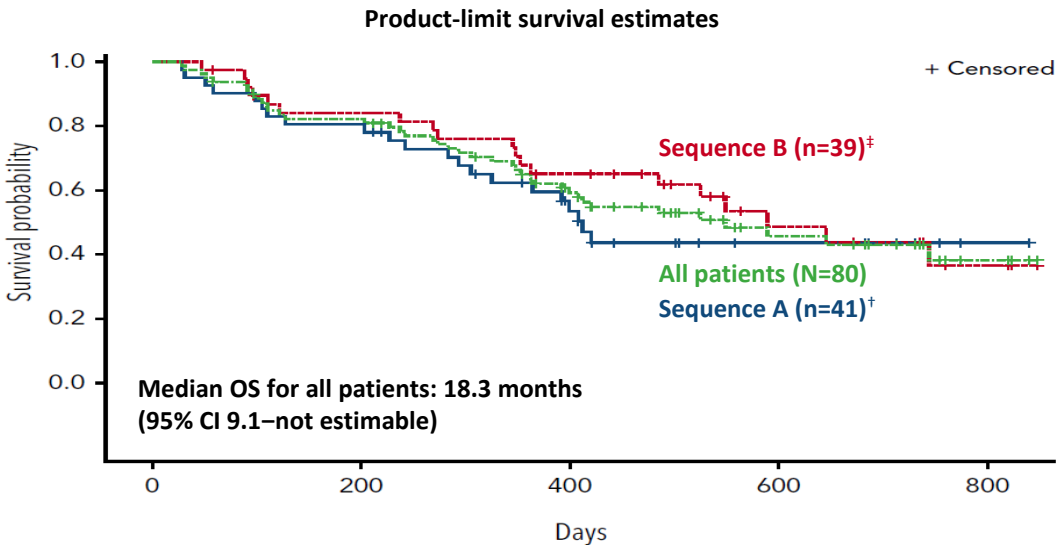
DNA demethylation: ≤1% defference

* Oral cedazuridine/decitabine.

Garcia-Manero G, *et al. Blood* 2020; **136**:674–683

Phase 2 study of ASTX272:* Survival

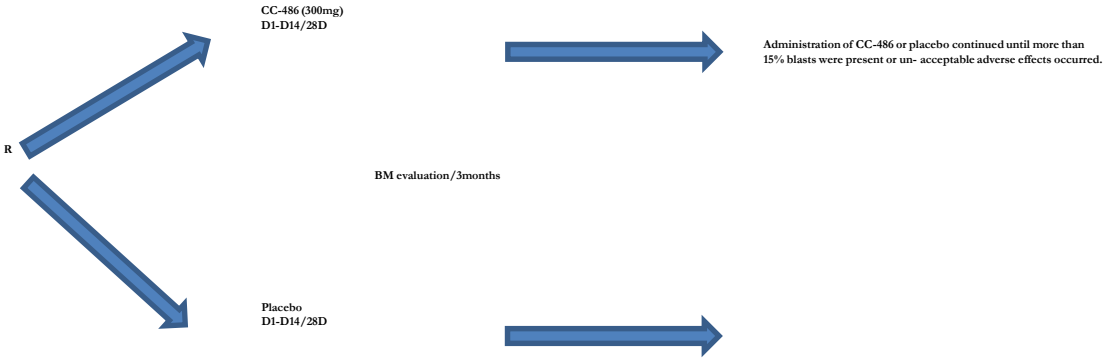
Randomized cross-over study of oral ASTX272* in patients with IPSS intermediate-1/2- or HR-MDS or CMML



Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

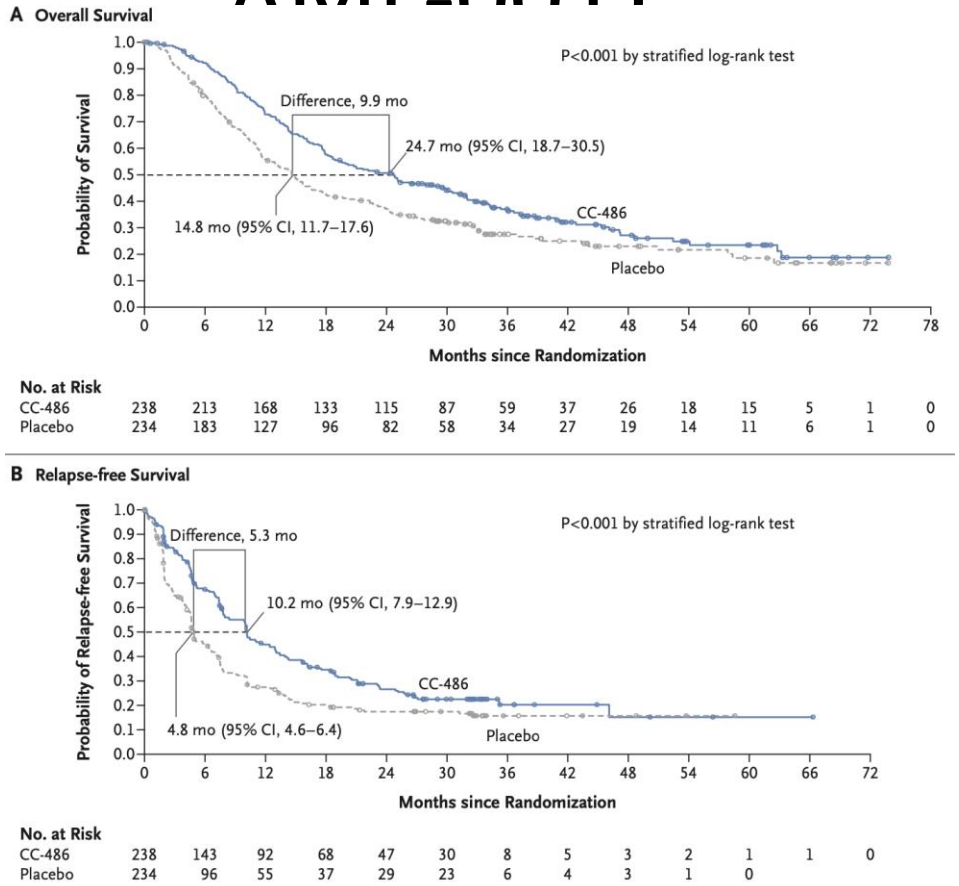
A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

- De Novo or secondary AML
- > 55 years old
- Intermediate or poor risk cytogenetic
- AML in CR/Cri within 4 months
- All patients had to have undergone induction chemotherapy, with or without consolidation therapy
- Non eligible for HSCT



Wei et al. NEJM Dec2020

AML maintenance (QUAZAR AML-001)



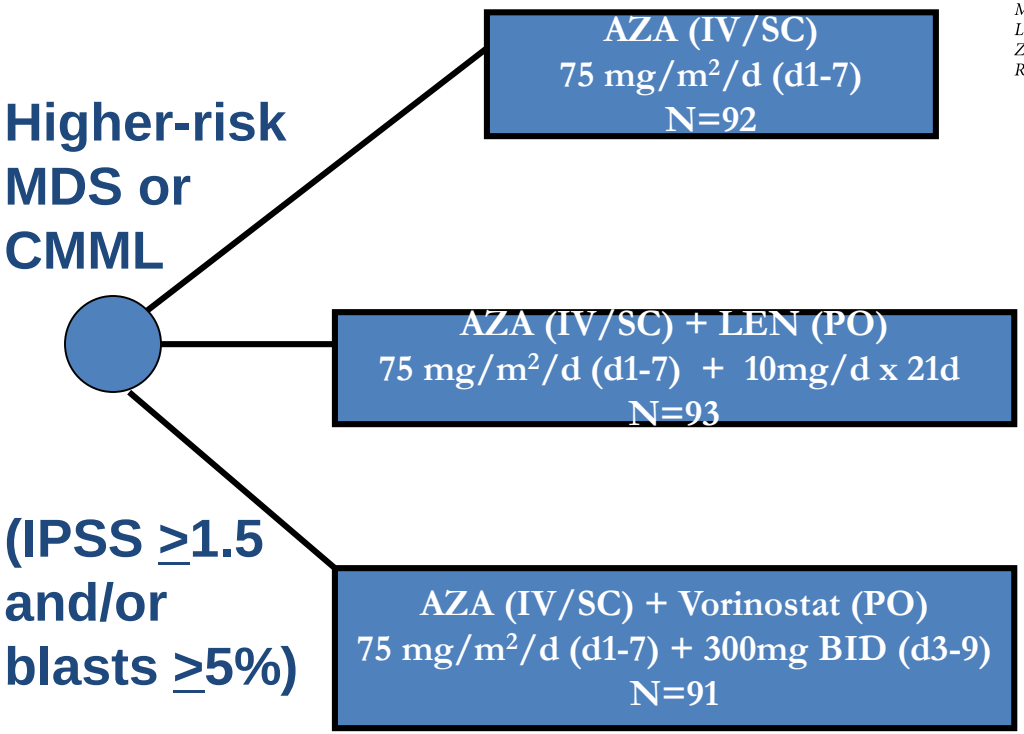
Wei et al. NEJM Dec2020

VOLUME 35 · NUMBER 24 · AUGUST 20, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Study of Azacitidine Alone or in Combination With Lenalidomide or With Vorinostat in Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia: North American Intergroup Study SWOG S1117

Mikkael A. Sekeres, Megan Othus, Alan F. List, Olatoyosi Odenike, Richard M. Stone, Steven D. Gore, Mark R. Litzow, Rena Buckstein, Min Fang, Diane Roulston, Clara D. Bloomfield, Anna Moseley, Aziz Nazha, Yanming Zhang, Mario R. Velasco, Rakesh Gaur, Ehab Atallah, Eyal C. Attar, Elina K. Cook, Alyssa H. Cull, Michael J. Rauh, Frederick R. Appelbaum, and Harry P. Erba



Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 276

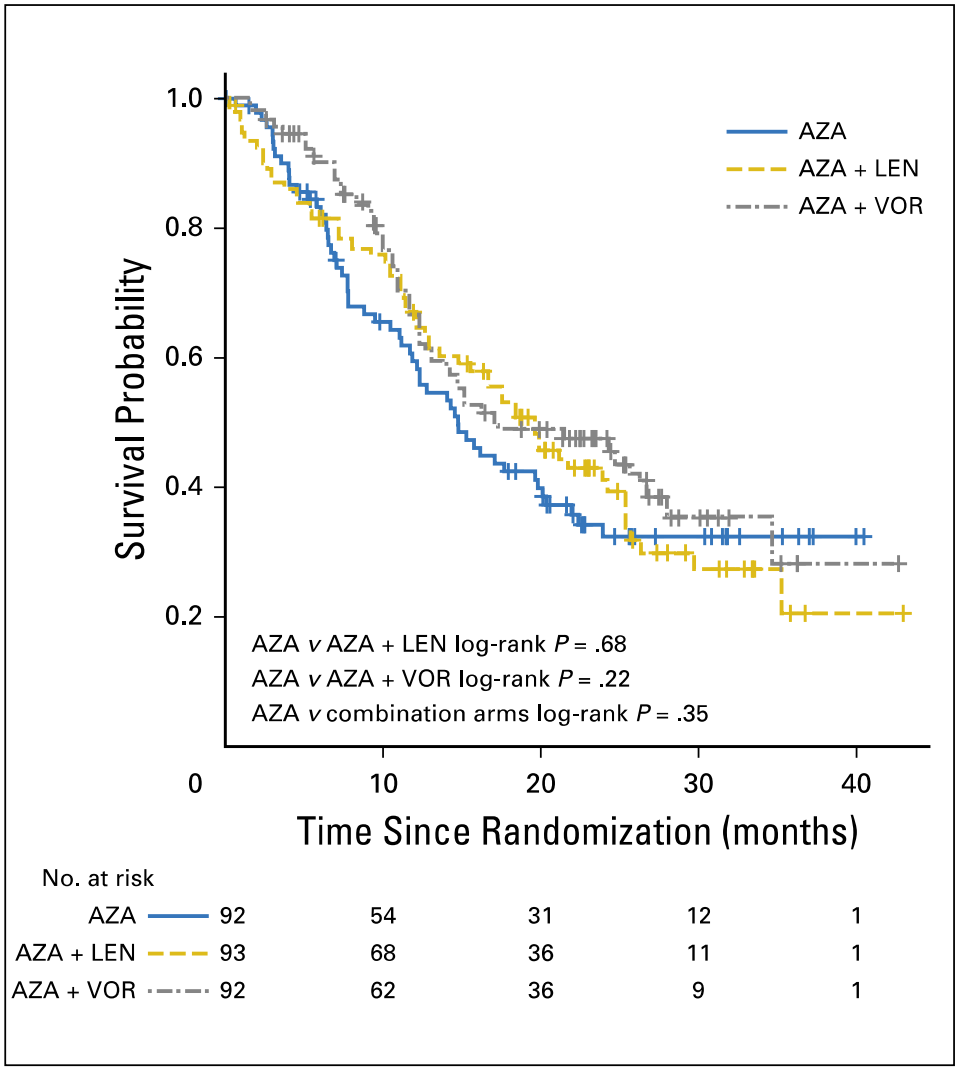
Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

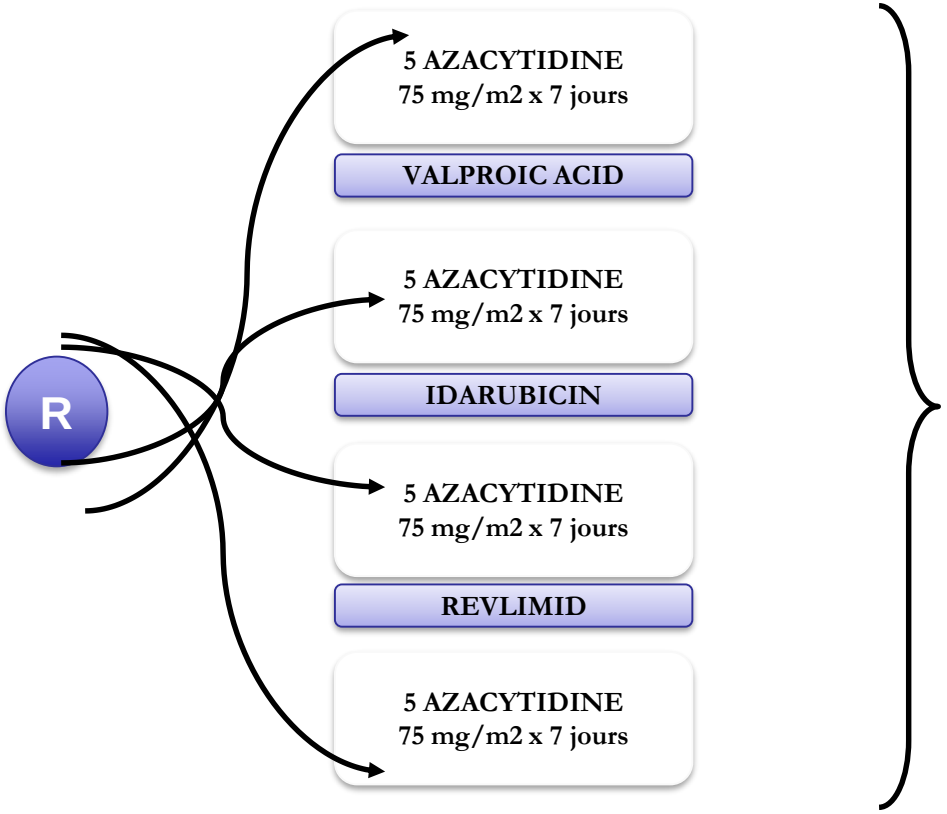
03/2012 – 06/2014

Sekeres et al. JCO ,2017


1.0
0.8
0.6
0.4
0.2
0
Survival Probability
AZA
AZA + LEN
AZA + VOR
AZA v AZA + LEN log-rank P = .68
AZA v AZA + VOR log-rank P = .22
AZA v combination arms log-rank P = .35
10
20
30
40
Time Since Randomization (months)
No. at risk
AZA 92 54 31 12 1
AZA + LEN 93 68 36 11 1
AZA + VOR 92 62 36 9 1

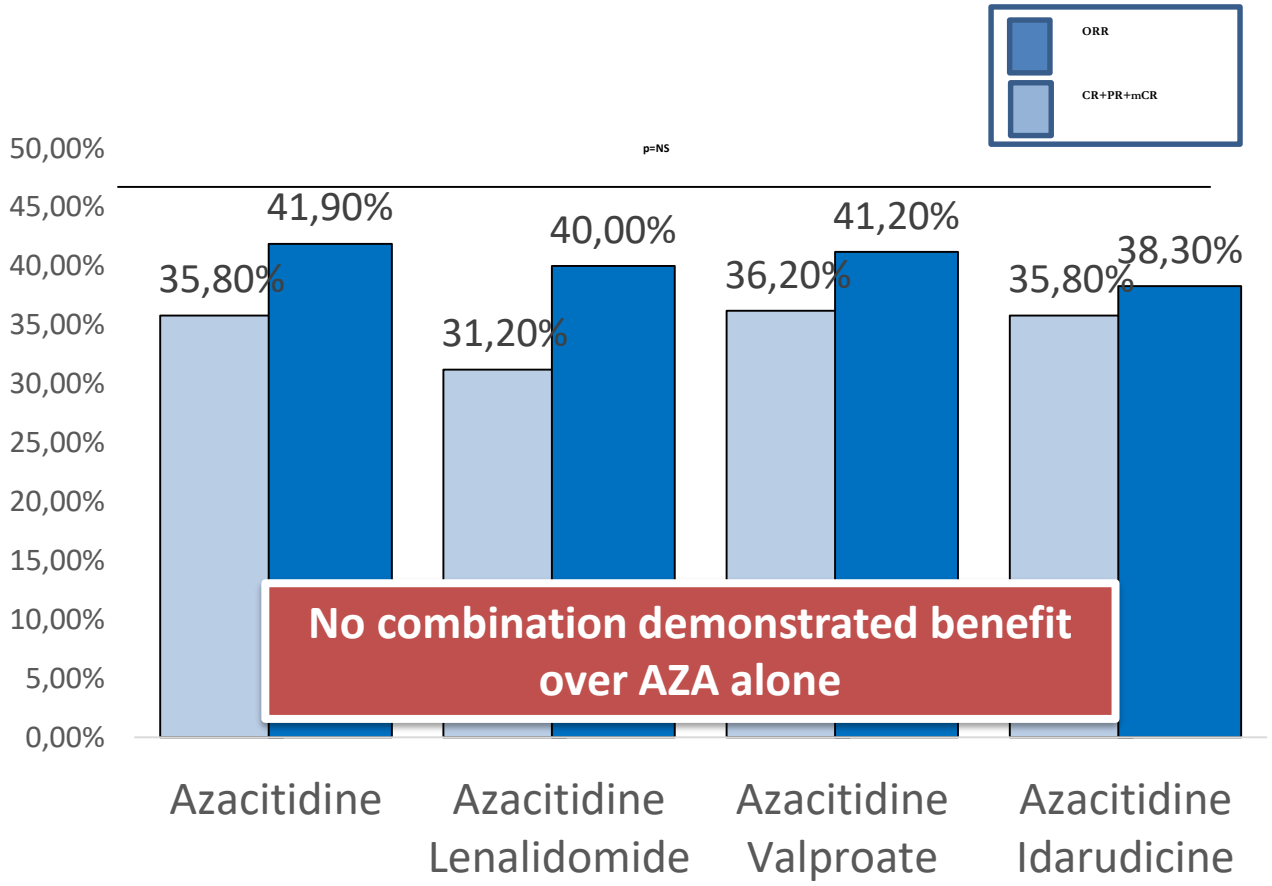
High risk MDS 1st line

AZA PLUS trial «pick the winner»

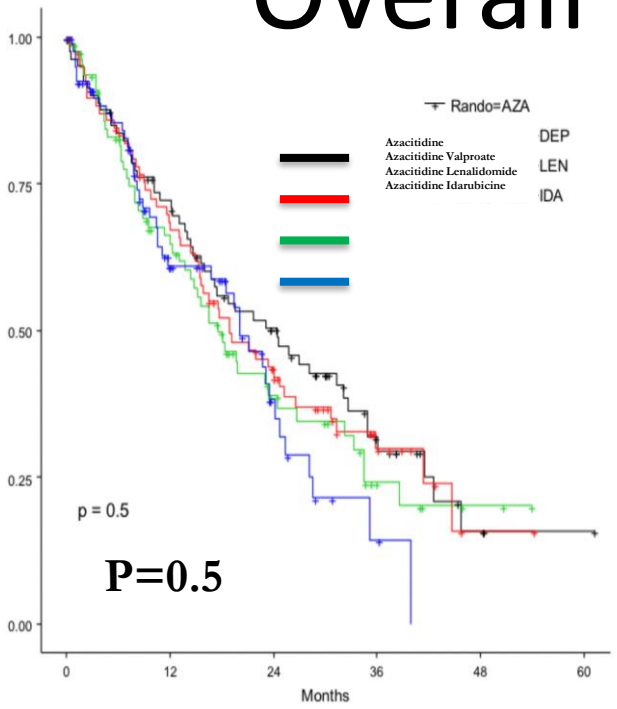


Groupe Francophone des Myélodysplasies

Overall Response rate at 6 cycles



Overall Survival



Factors associated with poorer OS

- **Presence of circulating blasts (p=0.003)**
- **High IPSS (p<0.0001)**

		AZA alone	AZA-VPA	AZA-LEN	AZA-IDA
Median (months)	**OS**	24.5	18.9	17.5	20.1

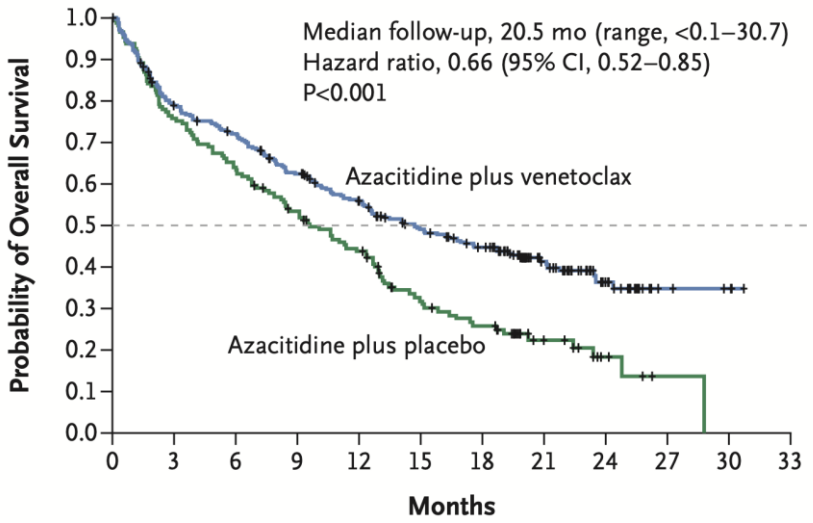
AML : HMA vs venetoclax + HMA (Viale-A)

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

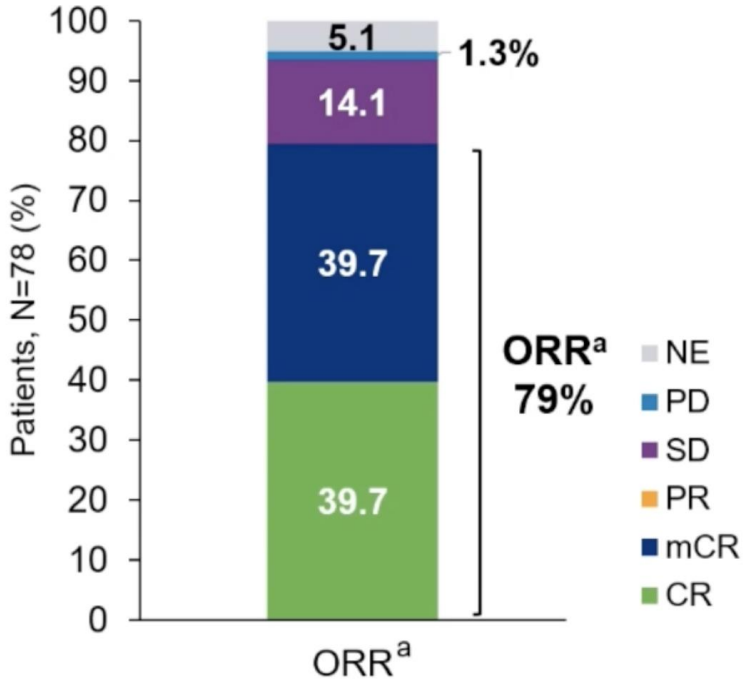
AZA+VEN: Azacitidine+Venetoclax; AZA+PBO: Azacitidine+Placebo; CR:Complete remission; CRi: CR with incomplete count recovery; CRh: CR with partial hematologic recovery; TI: Transfusion independence (defined as ≥56 days with no RBC or platelet transfusion between first and last day of treatment)

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

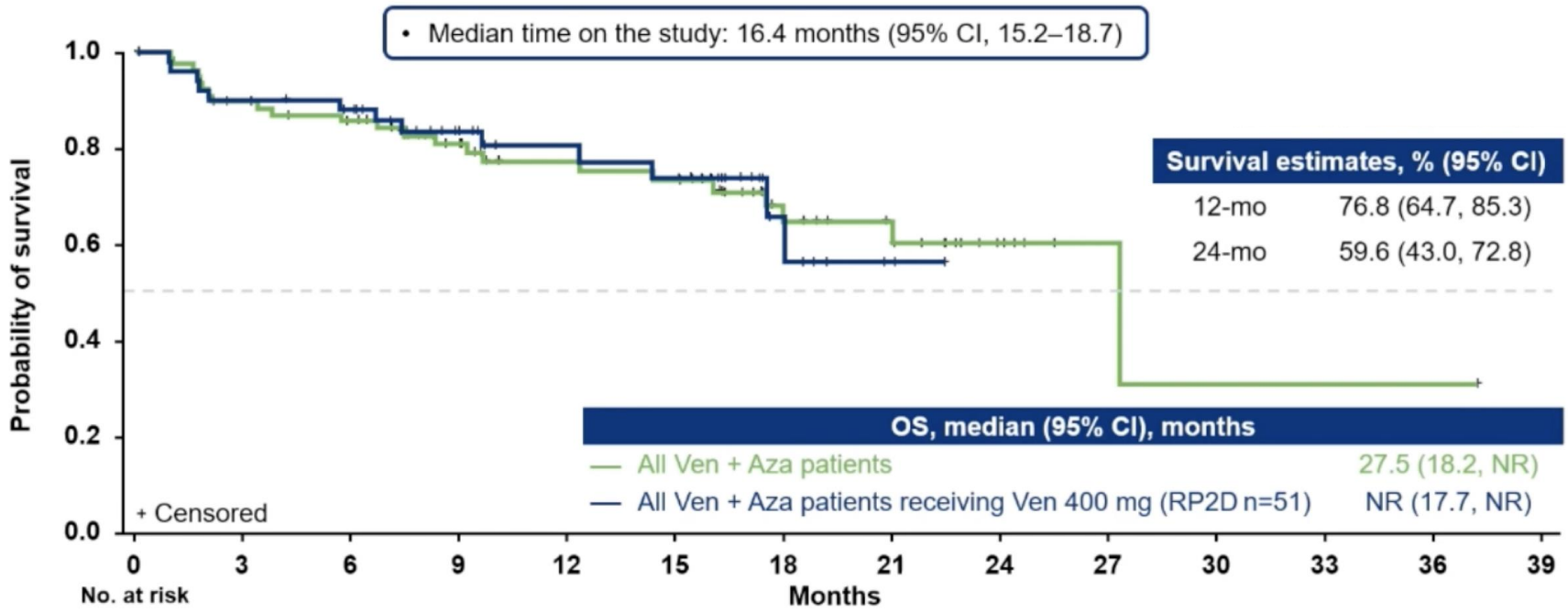


Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

- 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

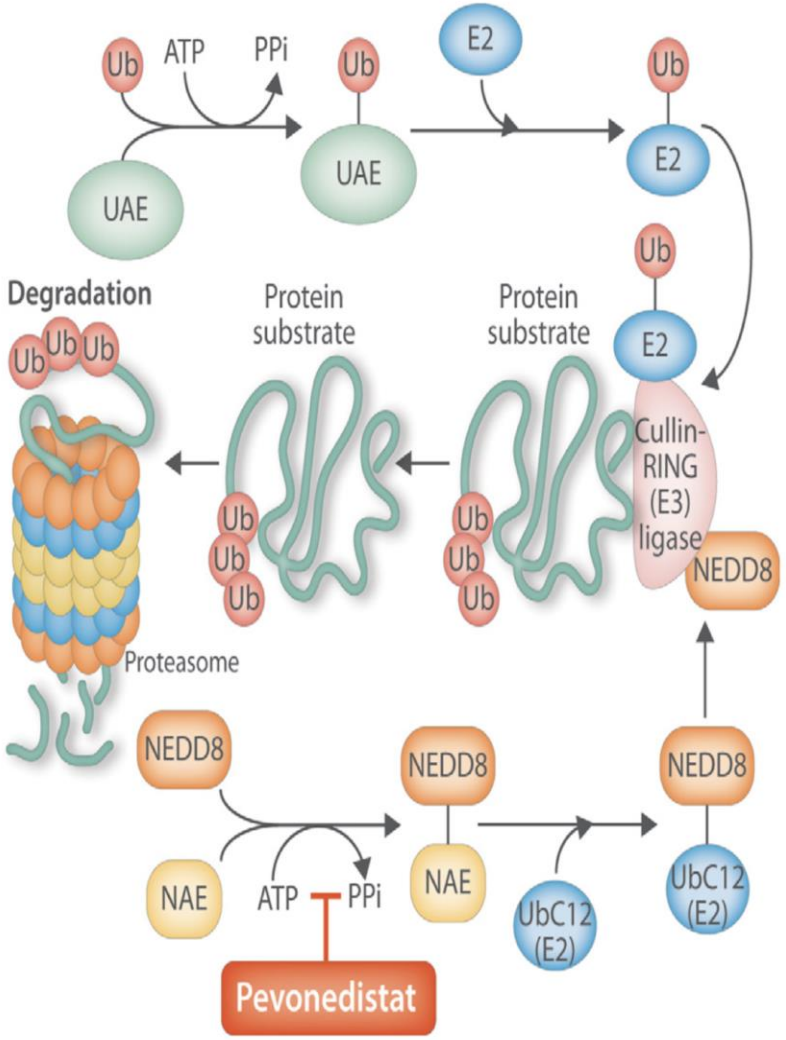
HR MDS 1st line – AZA-Venetoclax



García et al. ASH 2020

Pevonedistat

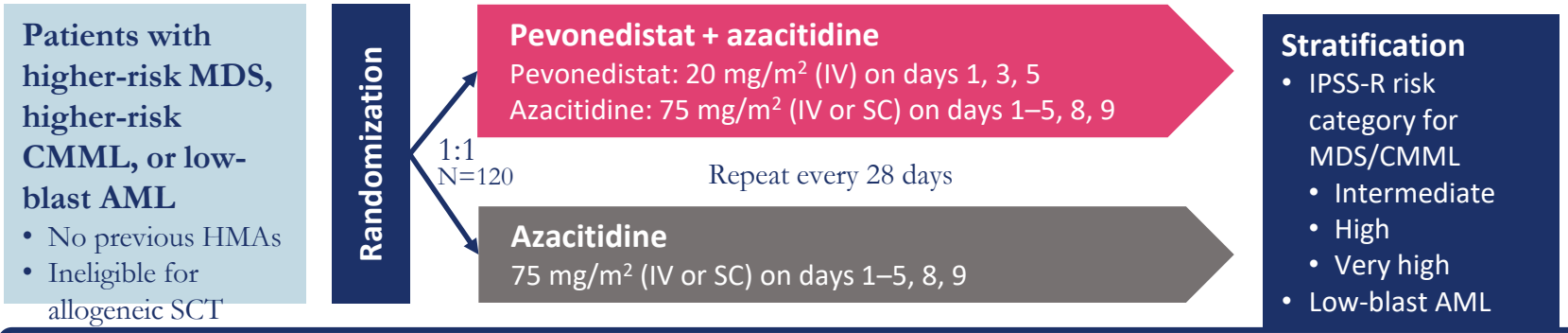
Pevonedistat inhibits the NEDD8-activating enzyme, with key effects on the ubiquitination pathway



Amir T. Fathi , Blood 2018

Role of Pevonedistat

NCT02610777: Phase II, randomized, open-label, global, multicenter study [proof of concept]



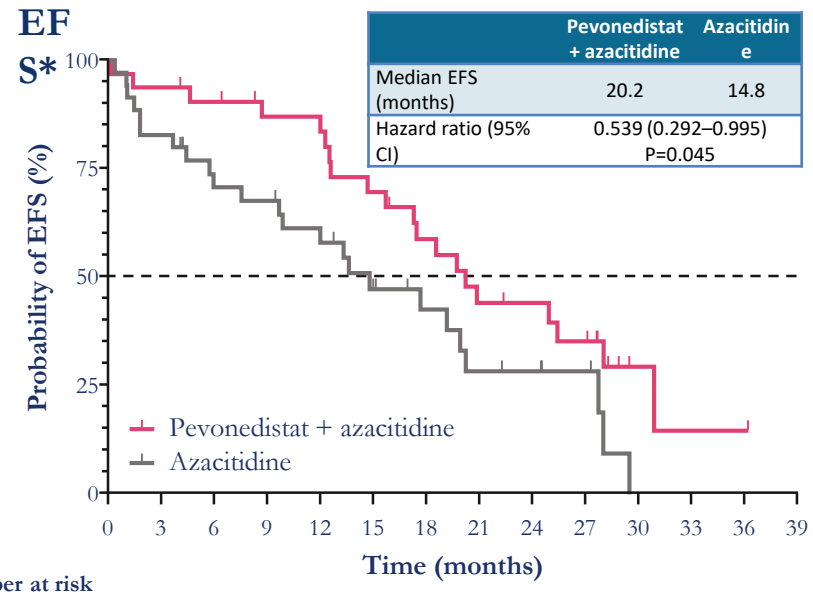
Study endpoints

- **EFS** (defined as time to death or transformation to AML in higher-risk MDS/CMML or death in low-blast AML): The study was powered on EFS as the original primary endpoint
- **OS**: Original secondary endpoint, changed to primary endpoint based on regulatory feedback after enrollment
- **ORR**: Secondary endpoint

EFS, event-free survival; HMA, hypomethylating agent; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; ORR, objective response rate; OS: overall survival; SC, subcutaneous; SCT, stem cell transplant.

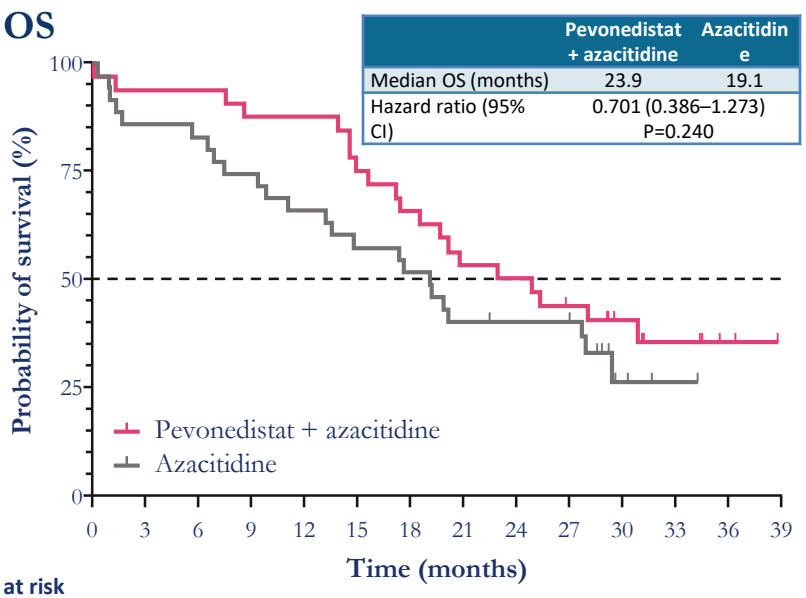
Adès et al. , ASCO 2020

EFS and OS: Higher-risk MDS



	Pevonedistat + azacitidine	Azacitidine
Median EFS (months)	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	

Number at risk														
Pevonedistat + azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	12	9	6	5	4	0	0	0	0



	Pevonedistat + azacitidine	Azacitidine
Median OS (months)	23.9	19.1
Hazard ratio (95% CI)	0.701 (0.386–1.273) P=0.240	

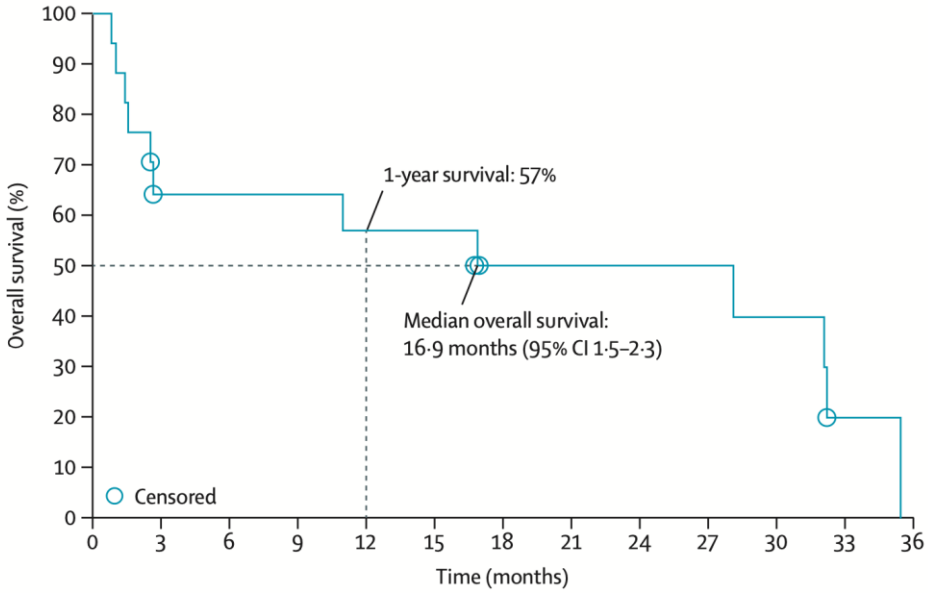
Number at risk														
Pevonedistat + azacitidine	32	30	30	28	28	24	21	17	16	13	8	5	2	0
Azacitidine	35	30	29	26	23	20	18	14	13	13	3	1	0	0

***EFS defined as time to death or transformation to AML in higher-risk MDS.**

Adès et al. , ASCO 2020

Enasidenib in patients with mutant IDH2 myelodysplastic syndromes

- **17 MDS IDH2m patients**
  - **3 patients had relapsed after SCT**
  - **13 had previously received HMA.**
- **overall response 53%**
- **median duration of response of 9·2 months**
- **Six (46%) of 13 patients previously treated with HMA responded.**



Stein, Lancet Haematology 2020

IDH_1 & IDH_2 inhibitors in MDS

Groupe Francophone des Myélodysplasies

EMSCO MYELODYSPLASTIC SYNDROMES

IDEAL STUDY

Enasidenib (AG-221; IDH2 inhibitor)

IDIOME STUDY

Ivosidenib (AG-120; IDH1 inhibitor)

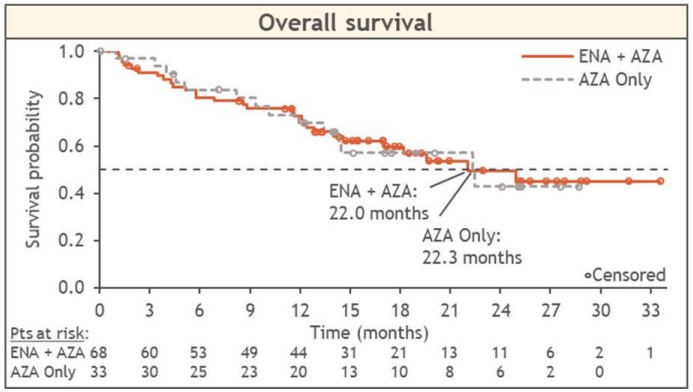
Cohort A: Patients with higher risk MDS who failed to achieved any type of response after 6 cycles of AZA, without disease progression (stable disease without hematological improvement-HI)

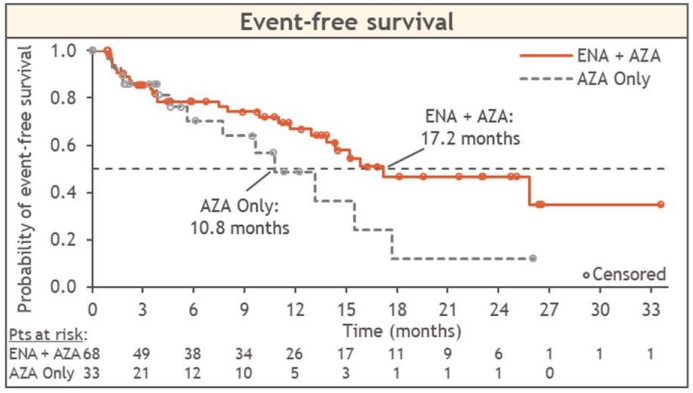
Cohort B: Patients with untreated higher risk without life threatening cytopenia

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

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]



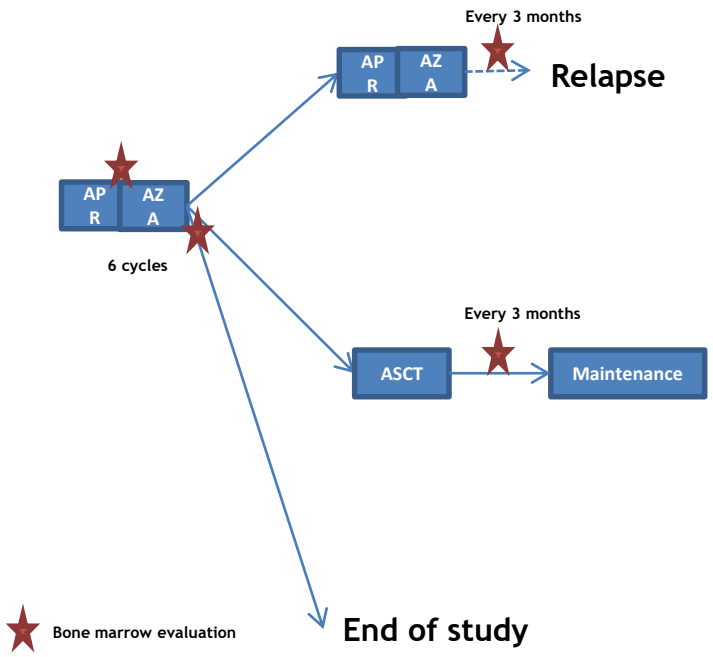


DiNardo C, et al. Oral presentation at the ASCO Annual Meeting 2020; abstract 7501.

Phase II AZA + APR 246 in MDS/AML

GFM-APR (Cluzeau, JCO 2021)

MDS int, high and very high IPSS-R and AML (including with > 30% marrow blasts) with TP 53 mutation



- APR-246 4500mg/d IV over 6 hours days 1-4
- AZA 75mg/m² SC daily days 4-10
- 28 day cycles
- *Maintenance treatment after Allogeneic SCT for 12 months:*
  - *Azacitidine 36mg/m² SC daily days 4-8*
  - *APR-246 3700mg/d IV over 6 hours days 1-4*

Groupe Francophone des Myélodysplasies

French experience with APR-AZA

53 patients enrolled between Sept 2018 and July 2019

	Global cohort n=53	MDS n=34	AML n=19
Median age (range)	73 (44-87)	74 (46-87)	73 (48-94)
M/F	28/25	9/25	8/11
WHO 2016 classification			
MDS	65%	100%	*
Intermediate IPSS-R	6%	9%	*
High IPSS-R	6%	9%	*
Very High IPSS-R	53%	82%	*
AML	35%	*	100%
20-30% blasts	24%	*	68%
> 30% blasts	11%	*	32%
Cytogenetic risk			
Complex karyotype	87%	83%	88%
Monosomal karyotype	70%	50%	23%
Including del 5q	57%	33%	65%

Cluzeau, et al. JCO 2021

Response

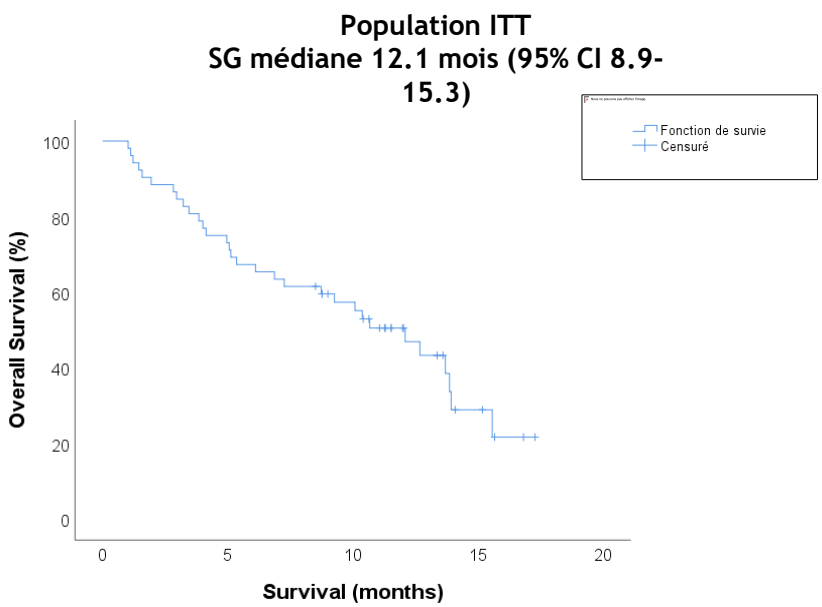
in the 44 patients enrolled before June 2019

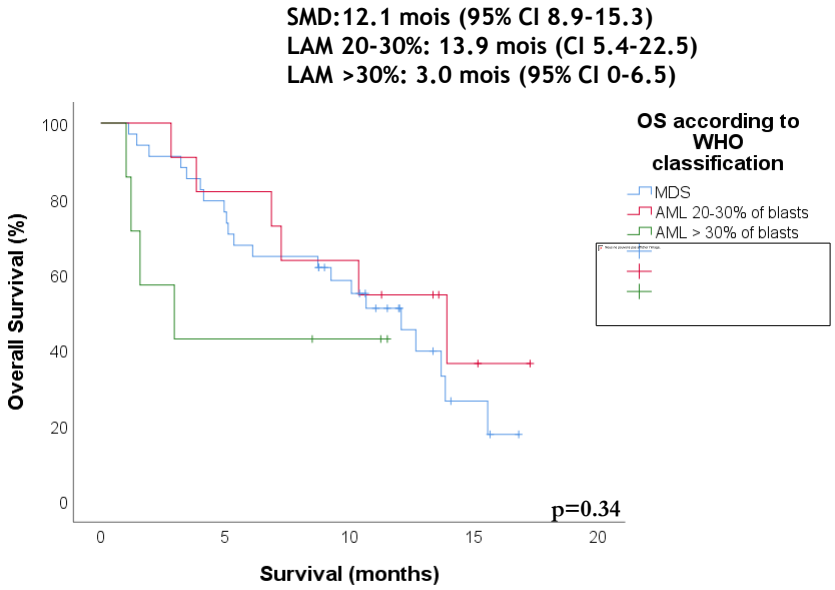
Intention to treat	n=44		
Time of evaluation	*Best Response*	*After C3*	*After C6*
ORR	**55%**	**51%**	**51%**
CR	39%	25%	39%
mCR/MLFS	7%	12%	7%
PR	0%	7%	0%
SD with HI	9%	7%	5%

Intention to treat	MDS n=27	AML20-30 n=12	AML>30 n=5
ORR	**67%**	**50%**	**40%**
CR	59%	33%	0%
mCR/MLFS	4%	0%	20%
PR	0%	0%	0%
SD with HI	4%	17%	20%

Cluzeau, et al. JCO 2021

Overall survival





Suivi médian: 9.7 mois

Cluzeau, et al. JCO 2021

Leukemia (2019) 33:379–389
https://doi.org/10.1038/s41375-018-0312-9

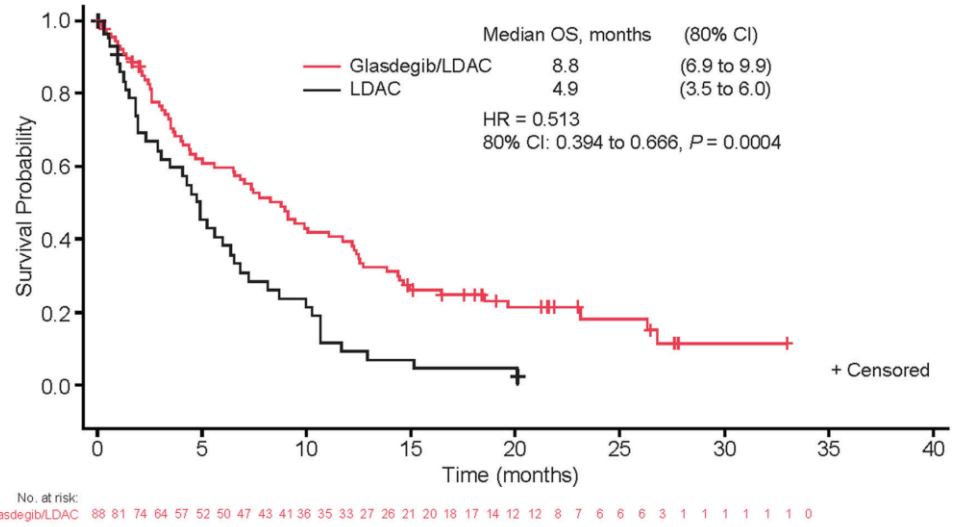
ARTICLE

Acute myeloid leukemia

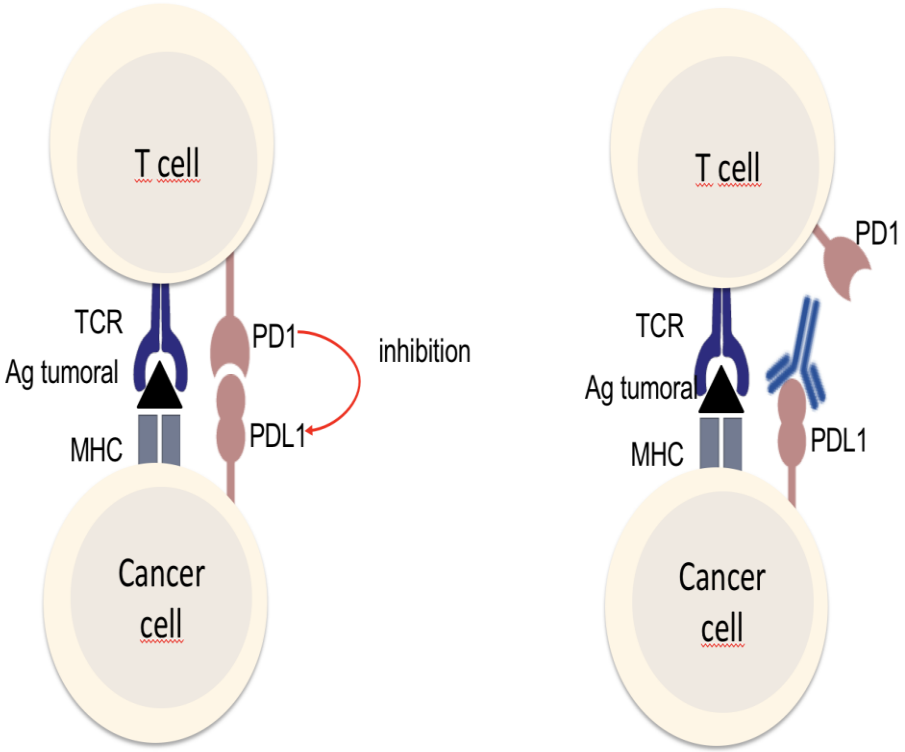
Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome

Jorge E. Cortes[1] · Florian H. Heidel[2,14] · Andrzej Hellmann[3] · Walter Fiedler[4] · B. Douglas Smith[5] · Tadeusz Robak[6] · Pau Montesinos[7,8] · Daniel A. Pollyea[9] · Pierre DesJardins[10] · Oliver Ottmann[11] · Weidong Wendy Ma[12] · M. Naveed Shaik[12] · A. Douglas Laird[12] · Mirjana Zeremski[12] · Ashleigh O'Connell[12] · Geoffrey Chan[12] · Michael Heuser[13]

- 88 and 44 patients were randomized to glasdegib/LDAC and LDAC
- Median OS 8.8 months with glasdegib/LDAC and 4.9 months with LDAC (P = 0.0004). 17.0% and 2.3% achieved CR (P < 0.05).



Immunotherapies



AZA+ checkpoint inhibitor

Guillermo Garcia-Manero, #465

	First Line		2nd Line	
	AZA + Nivo	**AZA + Ipi**	**Nivo**	**Ipi**
Overall response	15/20 (75%)	15/21 (71%)	2/15 (13%)	2/15 (13%)
CR/CRp	10/20 (50%)	8/21 (38%)	0 (0%)	3 (15%)
Clearance of detectable mutations	4 (20%)	3 (14%)		3 (15%)
Median overall survival (FU 20 months)	12 months	not reached	8 months	8 months
Event-free survival	10 months	not reached	7 months	6 months
One-year survival	50%	68%	25%	45%

nt

Magrolimab+AZA in HR MDS & AML

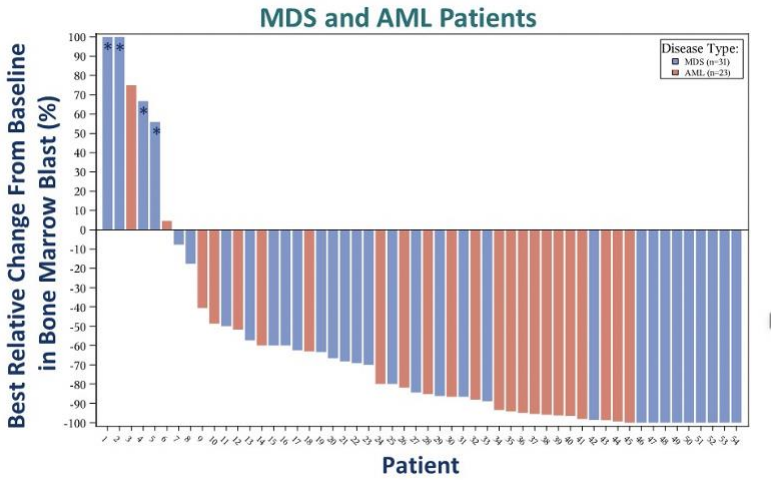
MDS

AML

Magrolimab is a CD47 Ab : First in class Macrophage Immune Chekpoint inhibitor

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

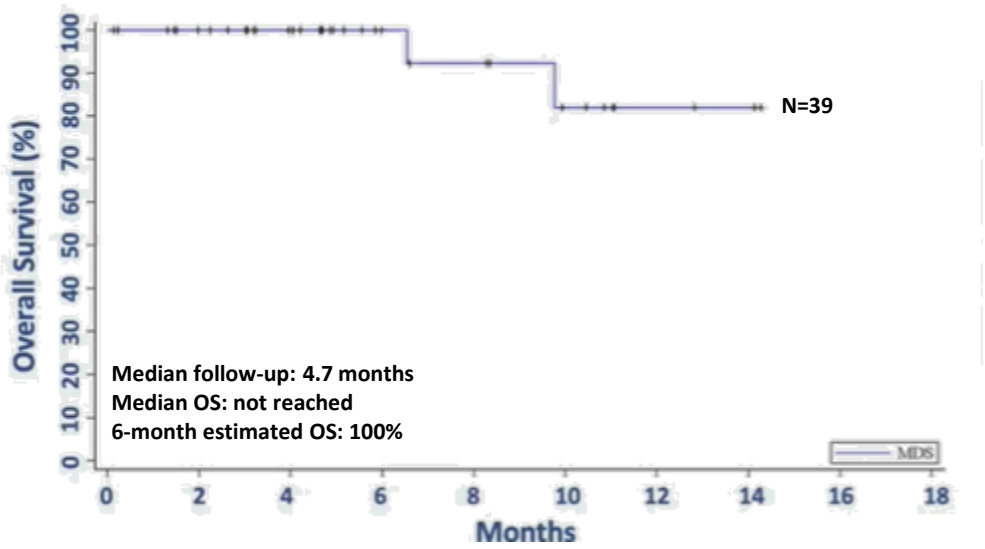
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Université de Paris

Presented By David Sallman at Asco 2020

Magrolimab (anti-CD47 antibody) + azacitidine: OS

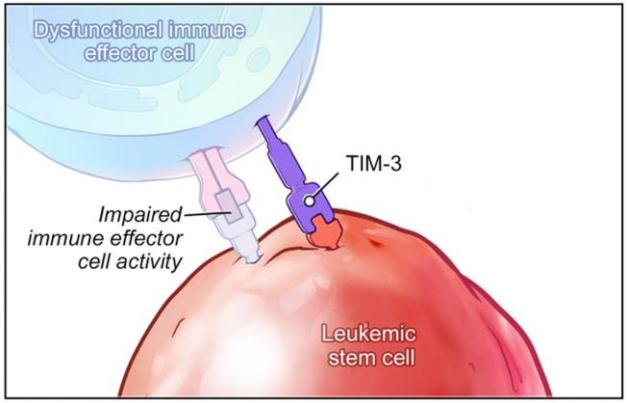
Phase 1b study of magrolimab + azacitidine in patients with higher-risk MDS

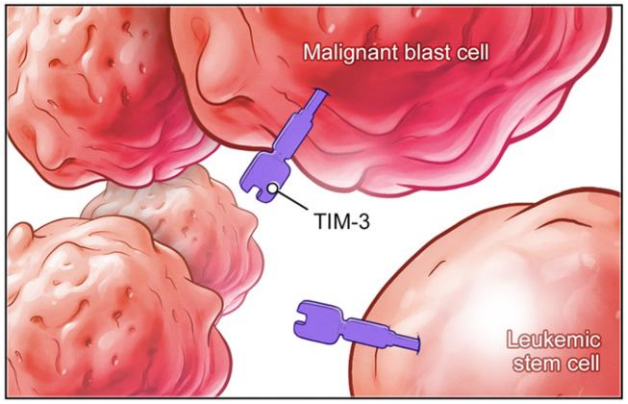


Sallman DA, *et al.* EHA 2020; Oral presentation S187.

TIM-3 is an inhibitory receptor and leukemic stem cell target

- TIM-3 is an inhibitory receptor expressed on macrophages/monocytes, NK cells, dendritic cells, and T cells and is involved in regulating innate and adaptive immune responses[1,2]
- TIM-3 is expressed on myeloid cells and also on leukemic stem cells and blasts, but not on normal hematopoietic stem cells,[3,4] making it a promising target in MDS/AML[4-6]



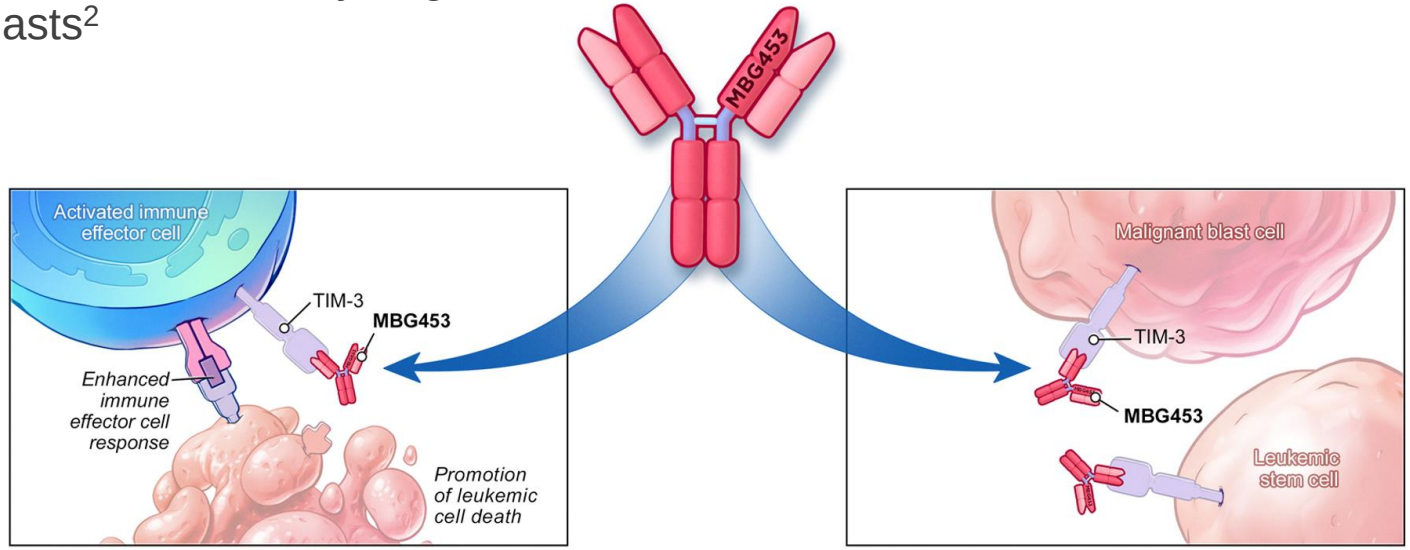


AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264; 2. Das M, et al. *Immunol Rev.* 2017;276:97–111; 3. Kikushige Y and Miyamoto T. *Int J Hematol.* 2013;98:627–633; 4. Kikushige Y, et al. *Cell Stem Cell.* 2010;7:708–717; 5. Ngiow SF. *Cancer Res* 2011;71:3540–3551; 6. Sakuishi K, et al. *Trends Immunol.* 2011;32:345–349.

Strong rationale for MBG453 blockade of TIM-3 in MDS/AML

- MBG453 is a high-affinity, humanized, IgG4 anti-TIM-3 monoclonal antibody that enhances immune cell-mediated killing of AML cells in vitro[1,2]
- MBG453 simultaneously targets immune effector cells as well as leukemic stem cells and blasts[2]



HR-MDS, high-risk MDS; IgG, immunoglobulin G.

1. Sabatos-Peyton C. AACR 2016. Oral presentation; 2. Borate U, et al. ASH 2019. Oral presentation.

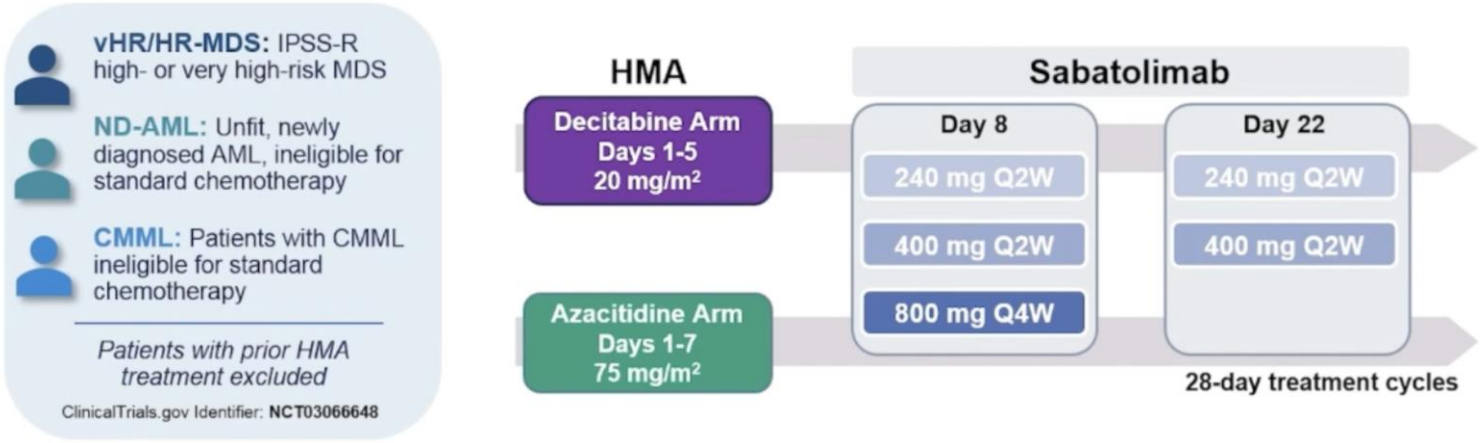
Sabatolimab+HMA (MBG453)

MDS

AML

Sabatolimab (MBG453) is an antibody targeting TIM-3, an inhibitory receptor that regulates adaptive and innate immune responses.
TIM-3 is expressed on

- immune cells
- as well as leukemic stem cells (LSCs) and blasts,
- but not normal hematopoietic stem cells



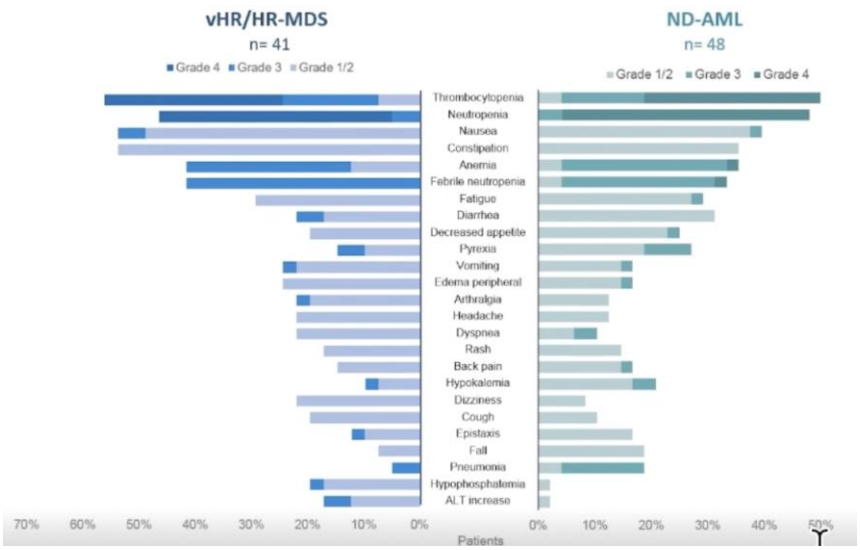
Université de Paris

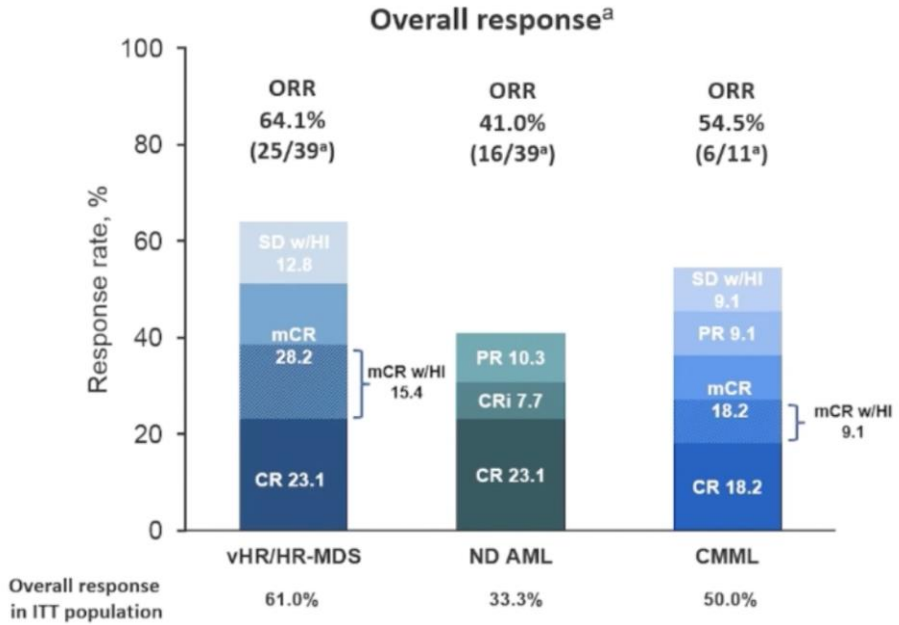
Presented By Andrew Brunner at ASH2020

Sabatolimab + HMA (MBG453)

MDS

AML





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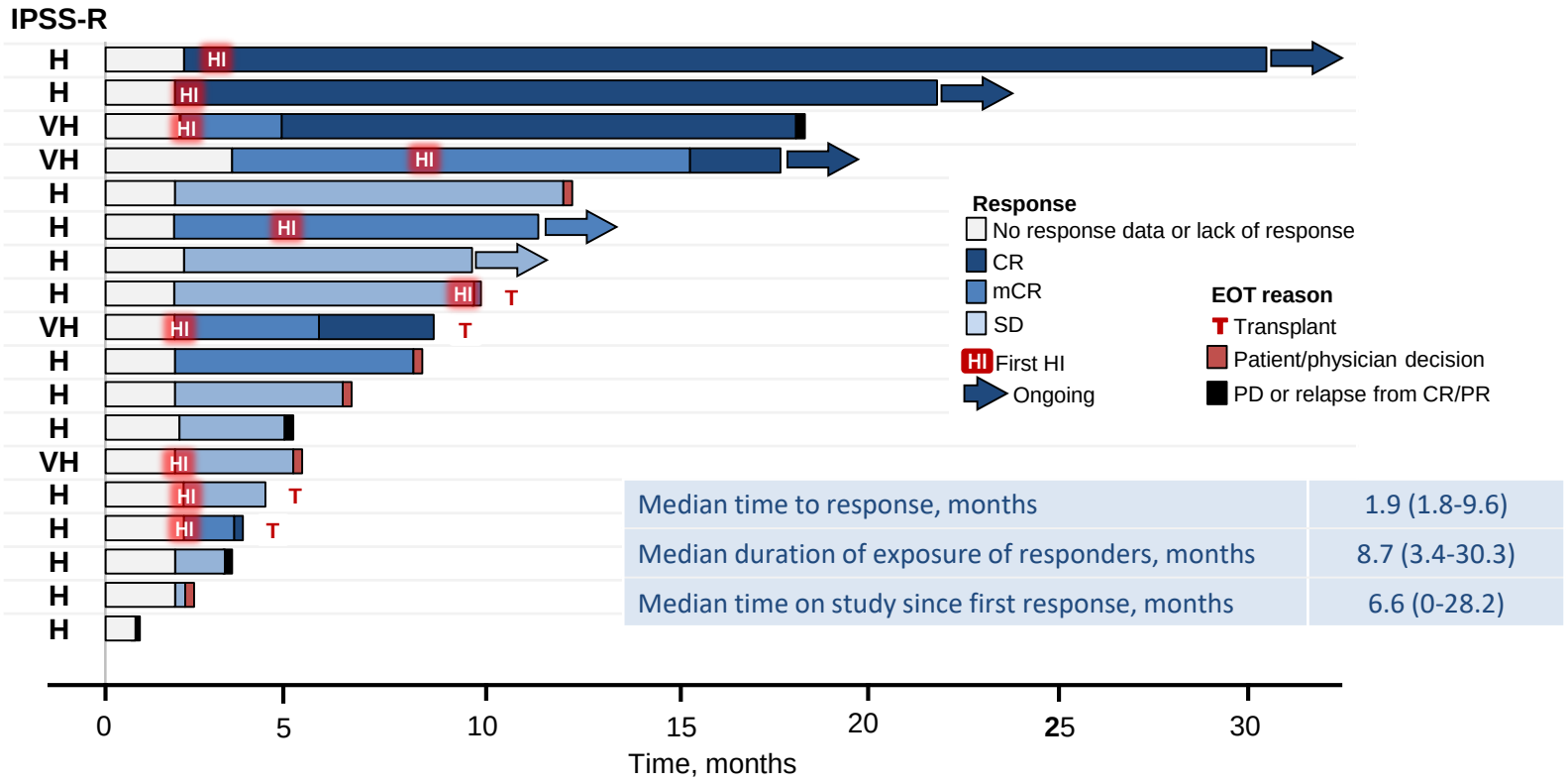
Presented By Andrew Brunner at ASH2020

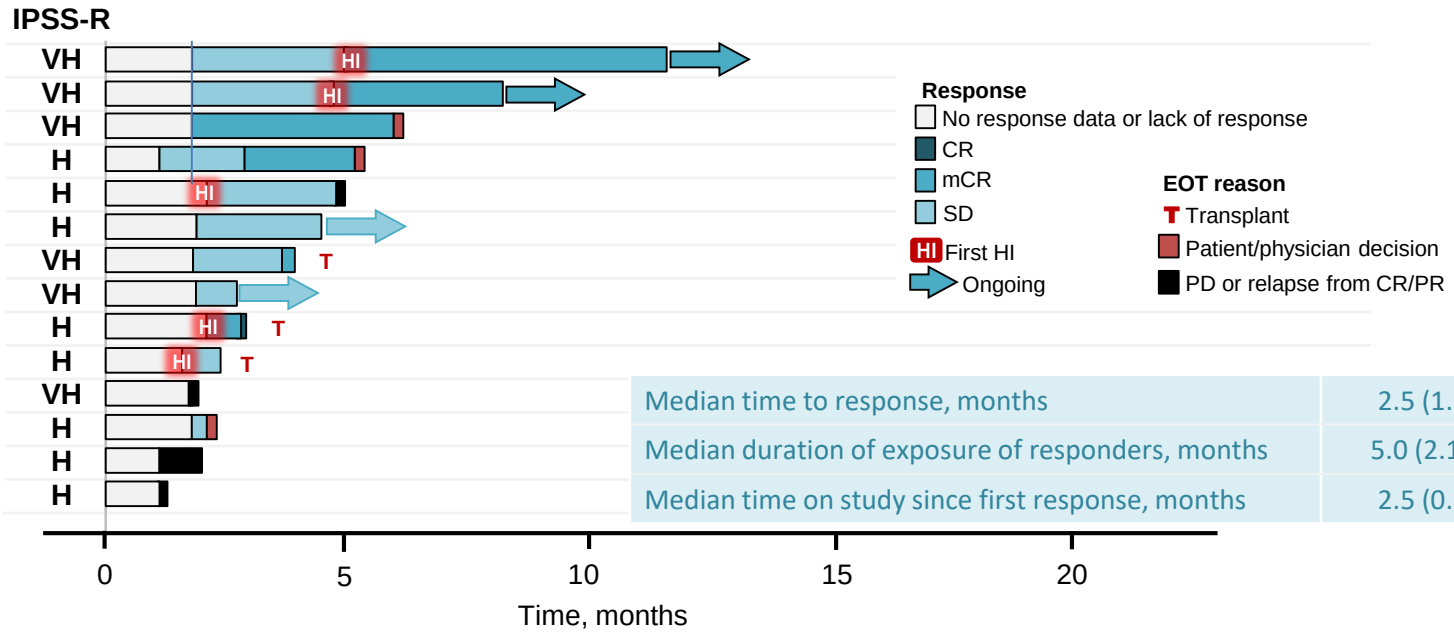
Emerging durability of MBG453 + decitabine in HR-MDS



Median time to response, months	1.9 (1.8-9.6)
Median duration of exposure of responders, months	8.7 (3.4-30.3)
Median time on study since first response, months	6.6 (0-28.2)

EOT, end of treatment; PD, progressive disease.

Initial durability of MBG453 + azacitidine in HR-MDS



Median time to response, months	2.5 (1.7-5.1)
Median duration of exposure of responders, months	5.0 (2.1-11.8)
Median time on study since first response, months	2.5 (0.2-6.7)

Département d'hématologie et inmunologie des Hôpitaux St Louis, R Debré, Avicenne APHP et Université de Paris

Hôpital St Louis

- 7 services d'hématologie (H Dombret, N Boissel, G Socié, B Arnulf, E Oksenhendler, P Fenaux, C Thiéblemont)
- Service de réanimation (E Azoulay)
- Service de pneumologie (A Tazi)

Hôpital Robert Debré

- Service de pédiatrie hématologique (A Baruchel)
- Unité de traitement de la drépanocytose (M Benkerrou)

Hôpital Avicenne

- Service d'hématologie (C Gardin)

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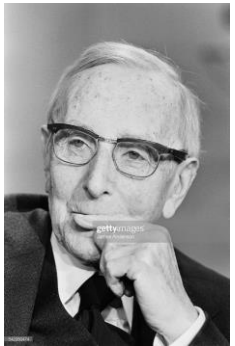

Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS (35 centers in France and Belgium
  + Switzerland)

- Website: www. gfmgroup.org

- Online registry of French MDS cases

- Close cooperation with:
  - a patient support group
  - the International MDS Foundation
  - the European Leukemia Net

Groupe Francophone des Myélodysplasies

Essais cliniques du GFM

- SMD de haut risque
  - Première ligne
  - Deuxième (ou plus) ligne
  - Allogreffe
  - LMMC
  - SMD avec mutation TP 53

- SMD de faible risque
  - Première ligne
  - Deuxième (ou plus) ligne

Groupe Francophone des Myélodysplasies

Essais cliniques du GFM

- SMD de haut risque
  - Première ligne
  - Deuxième (ou plus) ligne
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  - LMMC
  - SMD avec mutation TP 53

- SMD de faible risque
  - Première ligne
  - Deuxième (ou plus) ligne

Associations AZA + ?? (L Adès)

- SMD de haut risque
- essai de phase 2 randomisé . 3 contre 2 ?
- Coopération internationale ?

Chimio intensive

- CPX 351 en première ligne dans les SMD de haut risque (P Péterlin) *

Essais cliniques du GFM

- SMD de haut risque
  - Première ligne
  - Deuxième (ou plus) ligne
  - Allogreffe
  - LMMC
  - SMD avec mutation TP 53

Groupe Francophone des Myélodysplasies

- SMD de faible risque
  - Première ligne
  - Deuxième (ou plus) ligne

Inhibiteurs d'IDH1 et IDH 2

- **IDEAL STUDY**– A single-arm phase II multicenter study of IDH2 (AG 221) inhibitor in patients with IDH2 mutated myelodysplastic syndrome (L Adès) *

- **IDIOME STUDY** – Etude de phase II multicentrique non-randomisée de l'inhibiteur d'IDH1 (AG-120) chez les patients avec le syndrome myélodysplasique avec mutation IDH1 (M Sébert) *

Chimiothérapie en seconde ligne des SMD de haut risque

BST 003 (prodrogue d'AraC) (MA Hospital)

Essais cliniques du GFM (juin 2021)

- SMD de haut risque
  - Première ligne
  - Deuxième (ou plus) ligne
  - Allogreffe
  - LMMC
  - SMD avec mutation TP 53

- SMD de faible risque
  - Première ligne
  - Deuxième (ou plus) ligne

Allogeneic HSCT in lower risk MDS: A prospective multicenter phase II study based on donor availability on behalf of the GFM & SFGM-TC (M Robin) *

- ✓ Classical IPSS intermediate 1 or low myelodysplastic syndrome
- ✓ Intermediate or higher risk revised IPSS
- ✓ Failure to a previous treatment or ineligibility for an approved treatment or central thrombocytopenia (20 G/L) requiring platelet transfusions or symptomatic neutropenia < 0.5 G/L.
- ✓ Patient aged > 45 and < 70 years
- ✓ For whom a transplantation from a matched donor is considered
- ✓ Irrespective of donor availability
- ✓ Performance status lower than 3 (WHO 0, 1, or 2)

Etude DACORAL(GFM- ASTX 727 post allo) "Preventive" Post-transplant ASTX 727 in very high risk MDS patients: a phase II prospective study

(M Robin)

Inclusion criteria
Patients aged from 18 to 70 years
MDS according to WHO with a very complex cytogenetic (according to IPSS-R) or TP 53 gene mutation

Groupe Francophone des Myélodysplasies

- ASTX 727 (decitabine + cedazuridine) started on day 40
- Immunosuppression stopped on day 70
- DLI started on day 100

Venetoclax + AZA + DLI dans les SMD en rechute post allogreffe

(T Cluzeau,M Robin)

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- Venetoclax à dose réduite seul
- Puis AZA+ Venetoclax+ DLI

Approche pregreffe dans les SMD de haut risque ?

- Traitement prégreffe ?
- Étude non randomisée, peut être à partir du registre du GFM ?

Essais cliniques du GFM

- SMD de haut risque
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  - Deuxième (ou plus) ligne
  - Allogreffe
  - LMMC
  - SMD avec mutation TP 53

Groupe Francophone des Myélodysplasies

- SMD de faible risque
  - Première ligne
  - Deuxième (ou plus) ligne

Essais LMMC (R Itzykson)

- LMMC évolutives

- AZA +
  - VEN (essai AVENHIR)
  - Magrolimab (essai Monomagro)

SMD /LAM avec mutation TP 53 (T Cluzeau)

- AZA+ATO (SMD)
- AZA+ATO+ VEN(LAM)