Innovations thérapeutiques en myélodysplasies

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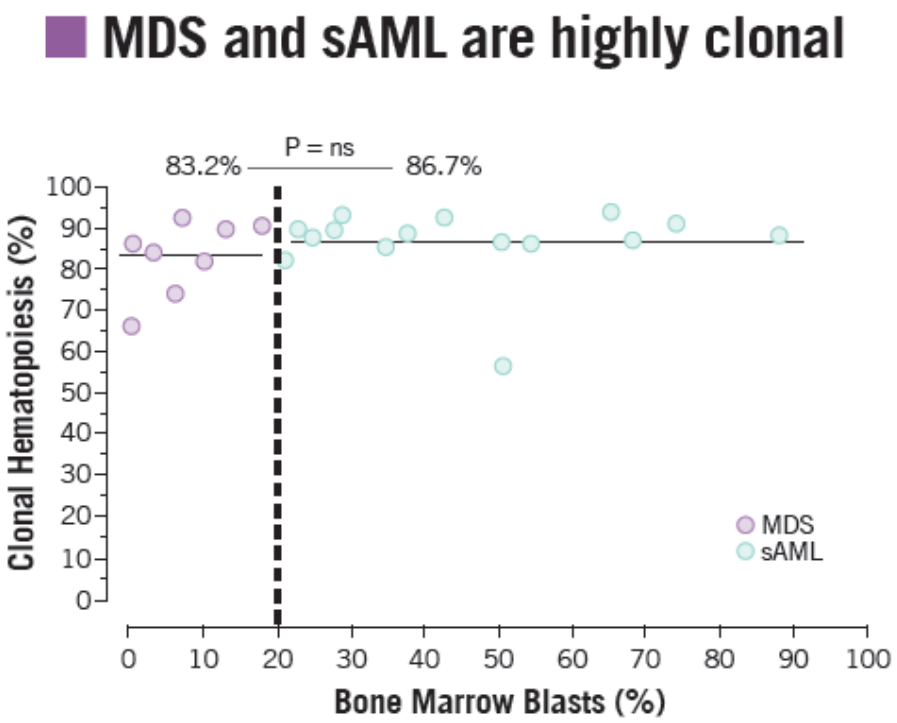
Plan

- Physiopathologie des MDS: concepts actuels
- L'évaluation pronostique
- MDS de bas risque
- MDS de haut risque

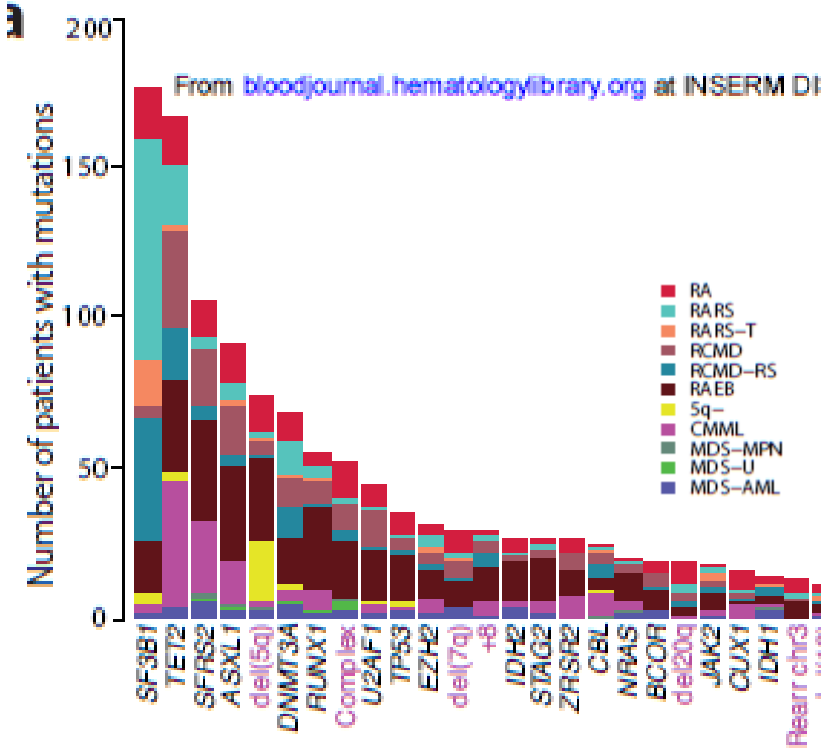
Physiopathologie des MDS: Concepts actuels

Mutations et MDS

- 4 groupes de mutations
  - Kinases
  - Facteurs transcriptionnels
  - Epigenetiques
  - Spliceosome



Ebert et al MDS 2013



Papaemmanuil Blood 2013

Mutations et MDS

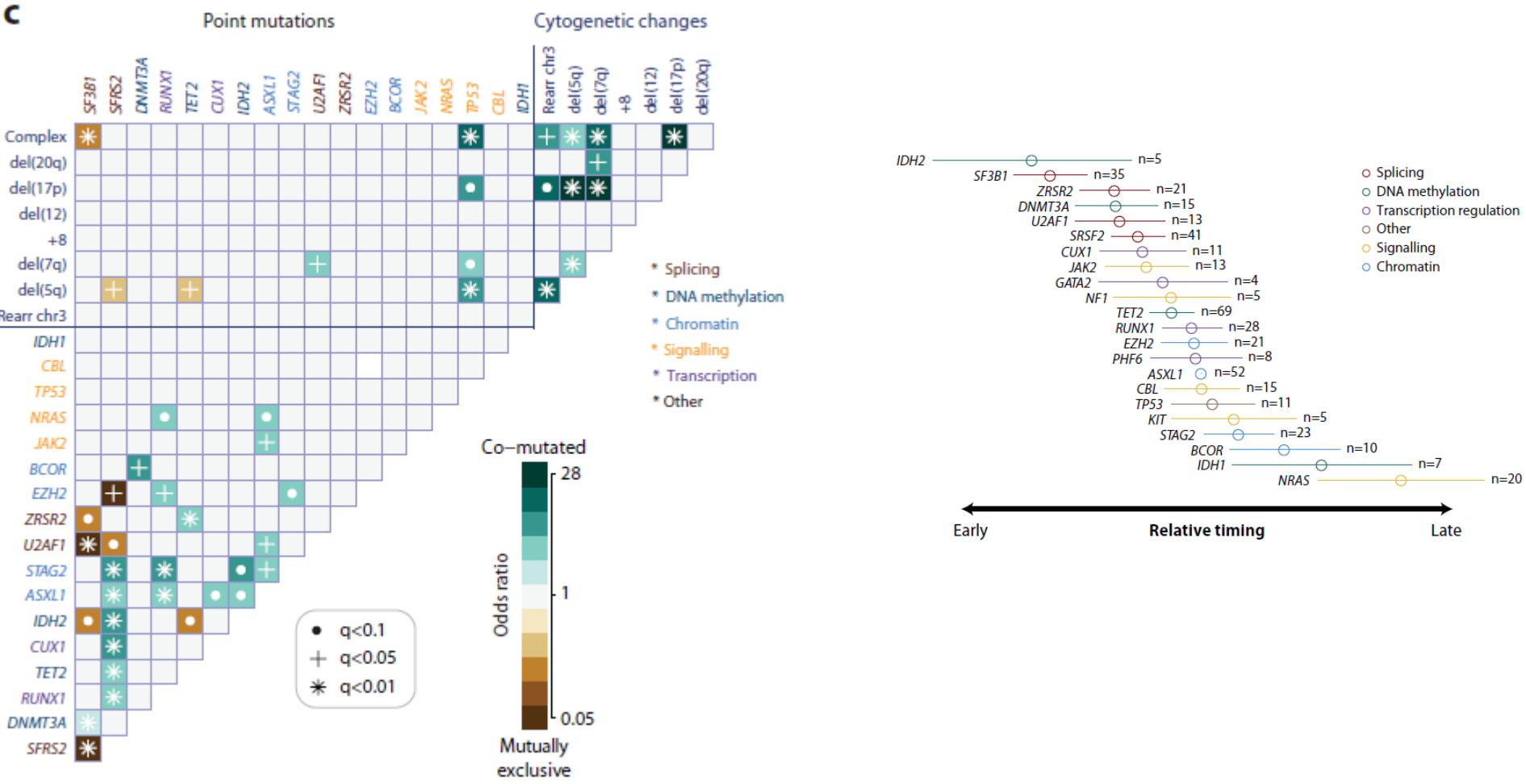
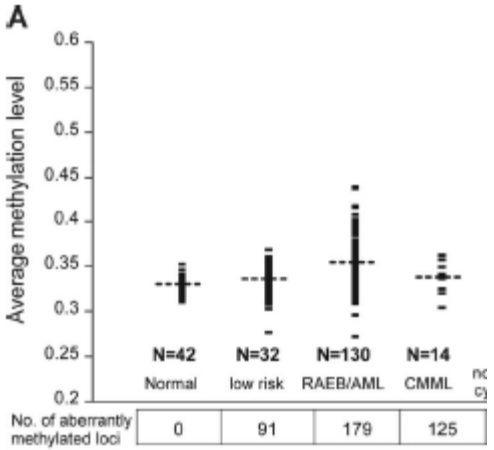


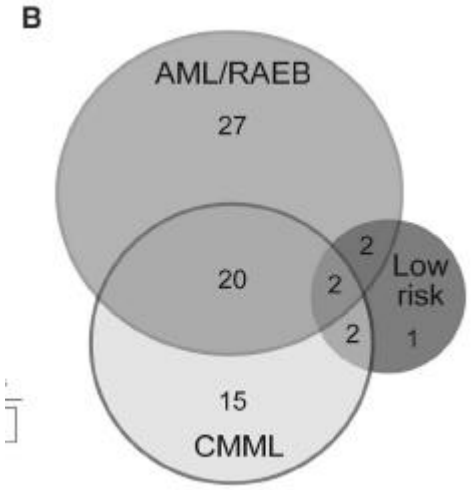
Figure 2

Papaemmanuil Blood 2013

Impact de l'épigénétique

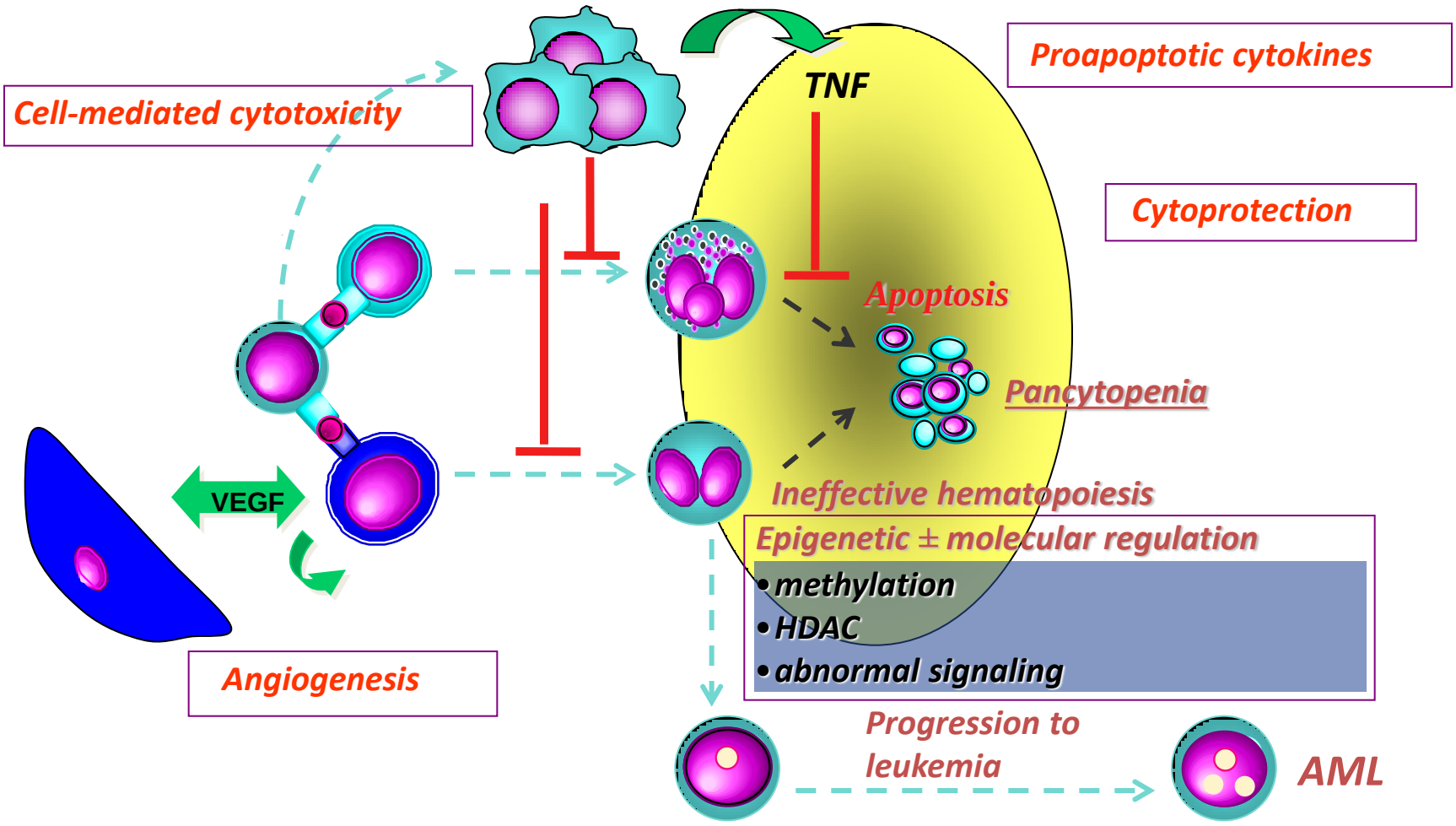
- Rôles des régulateurs épigénétiques
  - TET2/ IDH / ASXL1
- La méthylation de l'ADN croit avec la progression
- Rôle complémentaire aux mutations





Jiang Blood 2009

Rôle du micro environnement



Evaluation pronostique et MDS

Révision 2012 de l'IPSS

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

	Score
Very low (19%)	< 2
Low (38%)	2-3
Intermediate (20%)	3,5-4,5
High (13%)	5-6
Very High (10%)	> 6

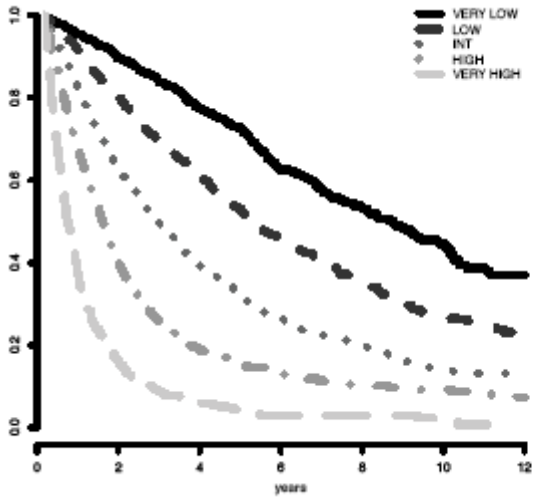


Figure 3. Survival based on IPSS-R prognostic risk-based categories. Survival

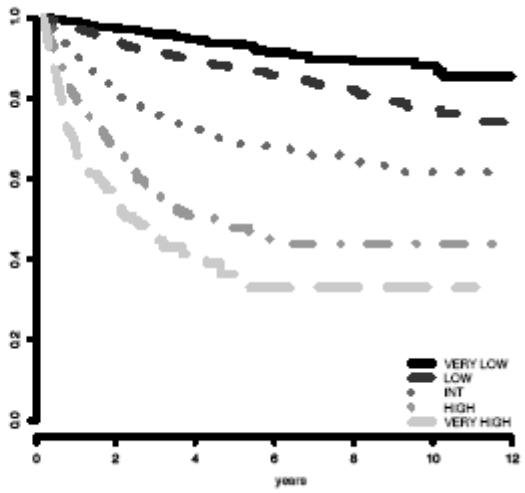


Figure 4. AML evolution based on IPSS-R prognostic risk-based categories.

Greenberg Blood 2012

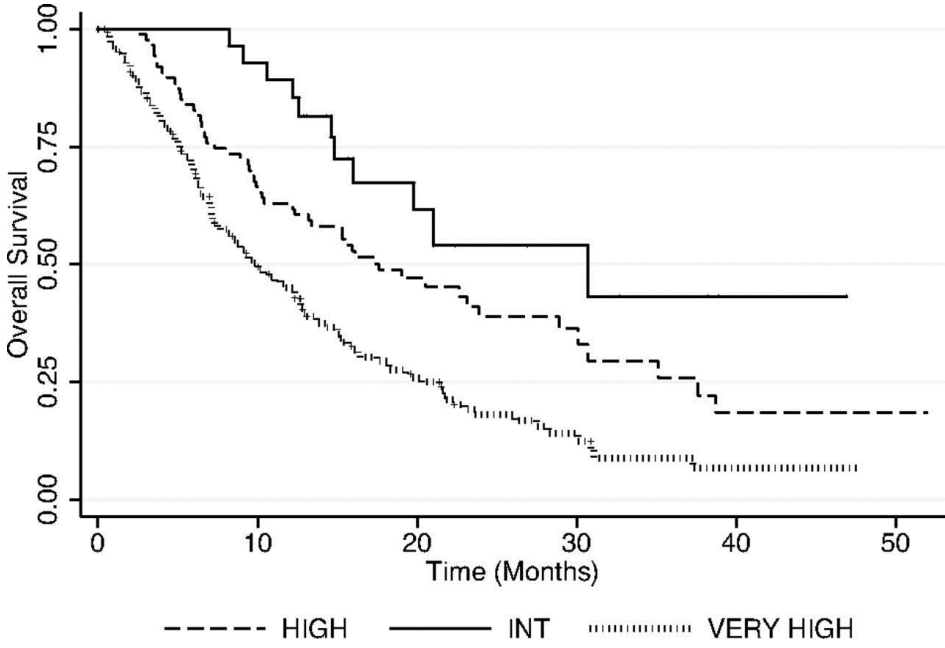
« Revised IPSS »

mds foundation
the myelodysplastic syndromes foundation, inc.

Courtesy Peter Greenberg

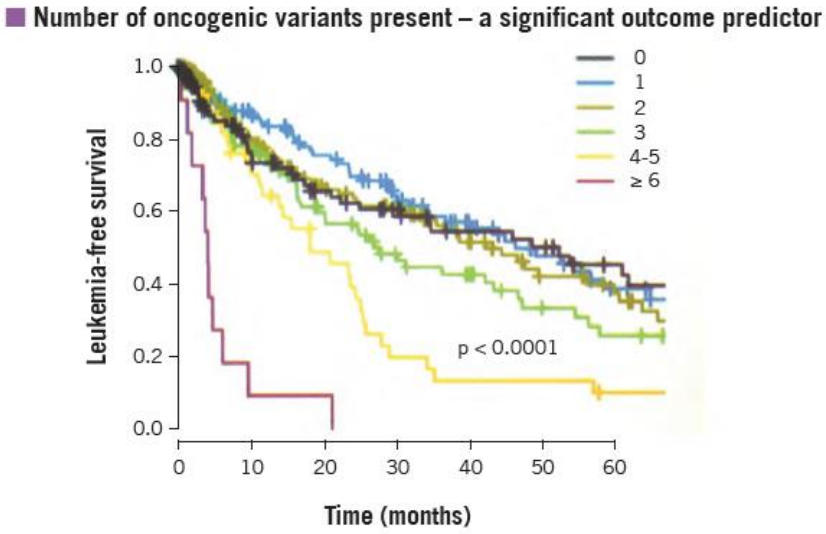
Survie pour les patients traités

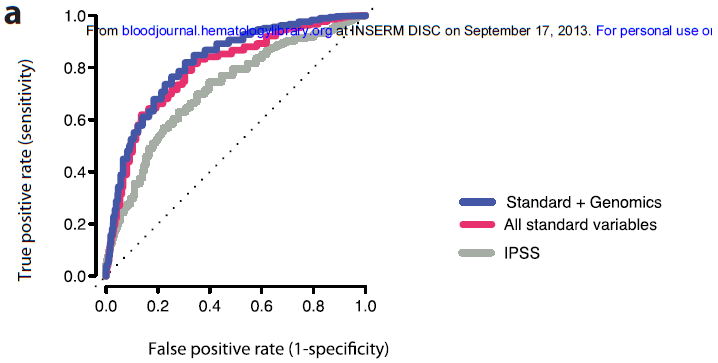
- R IPSS discriminant sous
  - AZA (Lamarque Blood 2012, Zeidan MDS ASCO 2013)
  - LEN (MDS 2013)
  - Allo (MDS 2013)



Quel impact clinique des mutations?

- Aide au diagnostic ? ➔ Rarement…
- Aide au pronostic?
  - Rôle pronostic
    - Association TET2 réponse AZA mais pas d'association OS
    - Association P53 survie AZA mais pas d'association réponse !
  - Eléments discordants sur l'apport des mutations à un modèle « classique » (Ebert/Bejar vs PapaEmmanuelli MDS 2013)
- Cibles thérapeutiques?
  - Spliceosome inhibitors et EZH2 inhibitors (AACR 2013)

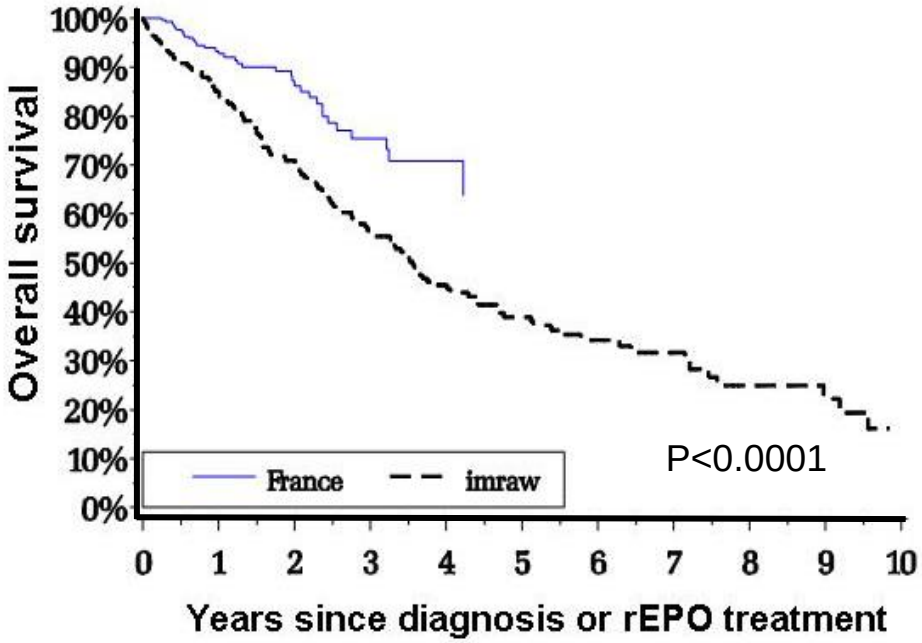


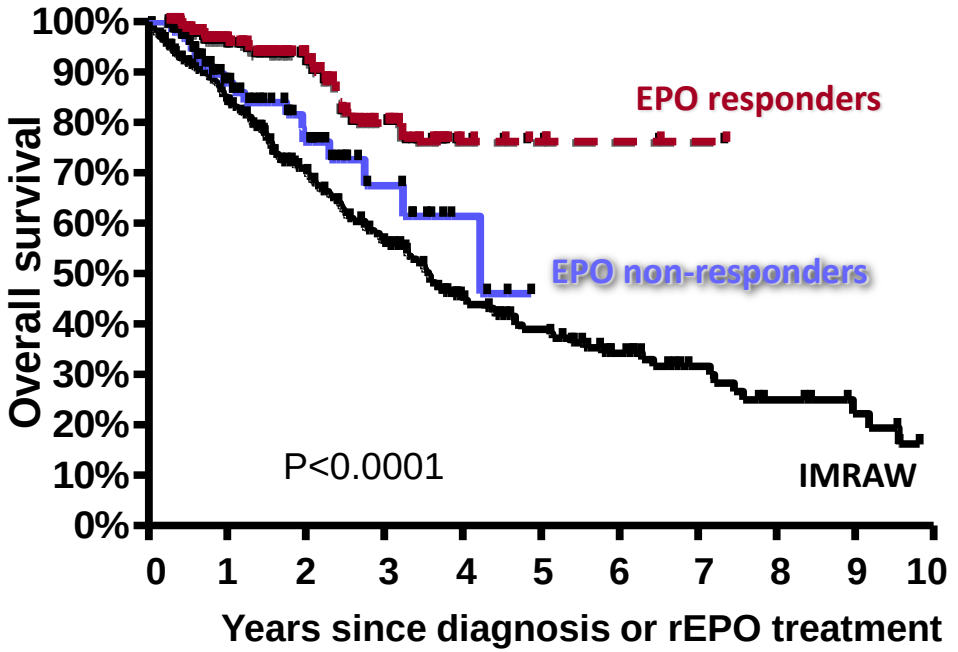


Papaemmanuil Blood2013

MDS de bas risque

EPO treated versus IMRAW cohort : Overall Survival





Park S, et al. BLOOD 2008

Predictive factors of response to ESA
n=419 patients

	response rate %	p value
EPO <200	69%	0,0001
EPO >200	42%	
Transfusion requirement	51%	0,0001
No transfusion	76%	
IPSS score		
low (38%)	68%	0,0003
int-1 (41%)	64%	
int-2 (9%)	38%	_
high (1.5%)	33%	_

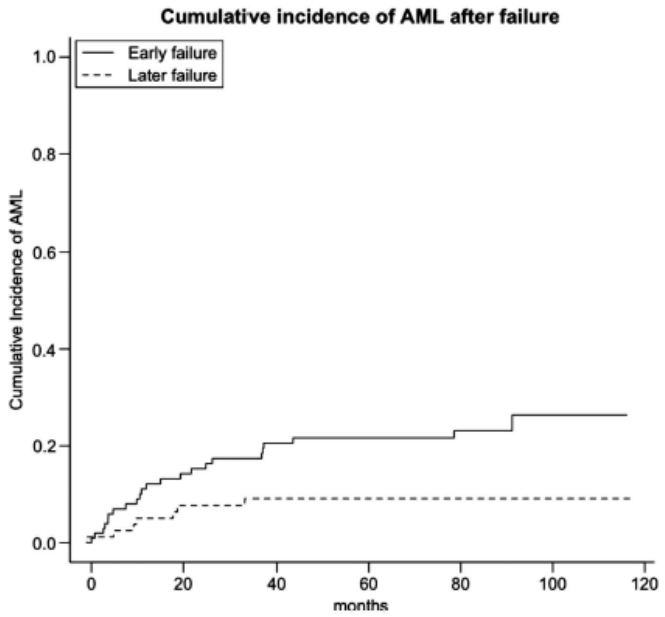
Park ,Kelaidi, Blood, 2008

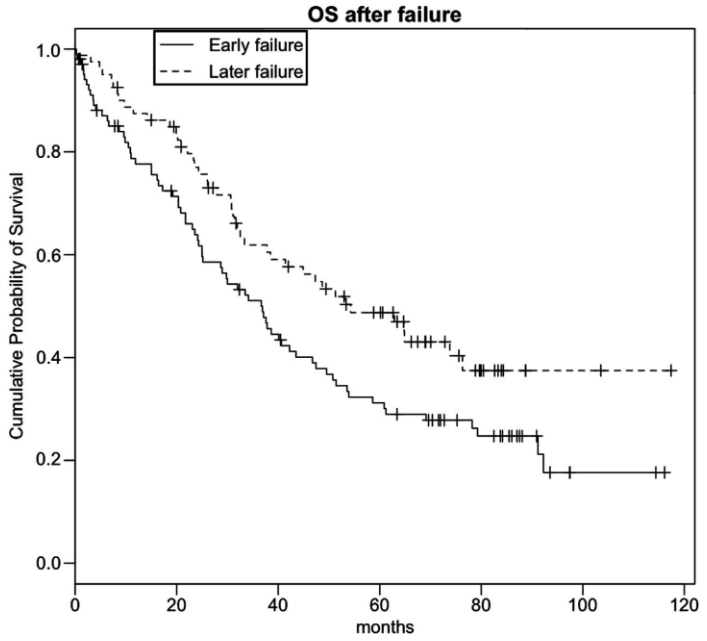
ESAs are the first line treatment

- ESA are not approved in EU for the treatment of low risk MDS
- 2 registration ongoing studies
  - EPO alfa vs BSC
  - Darbepoietin vs BSC
- “intensive” frontline Darbepo
  - Phase 2 trial (Kelaidi, Ann Hematol. 2013;92(5):633)
  - 99 patients
  - IWG 2006 HIe rate: 56 % at 24 weeks
  - Addition of G-CSF rescued 22 % of non-responders
  - Response predicted by EPO levels (100 U/ml)
  - Significant impact on QoL and exercise functionning

Outcome after ESA failure

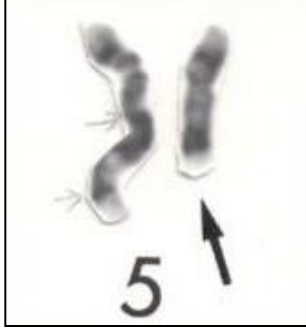
- Retrospective analysis of 186 non del5q IPSS lower-risk patients who failed ESA treatment
  - Early failure (primary or relapse <6 months)
  - Late failure (relapse >6 months)

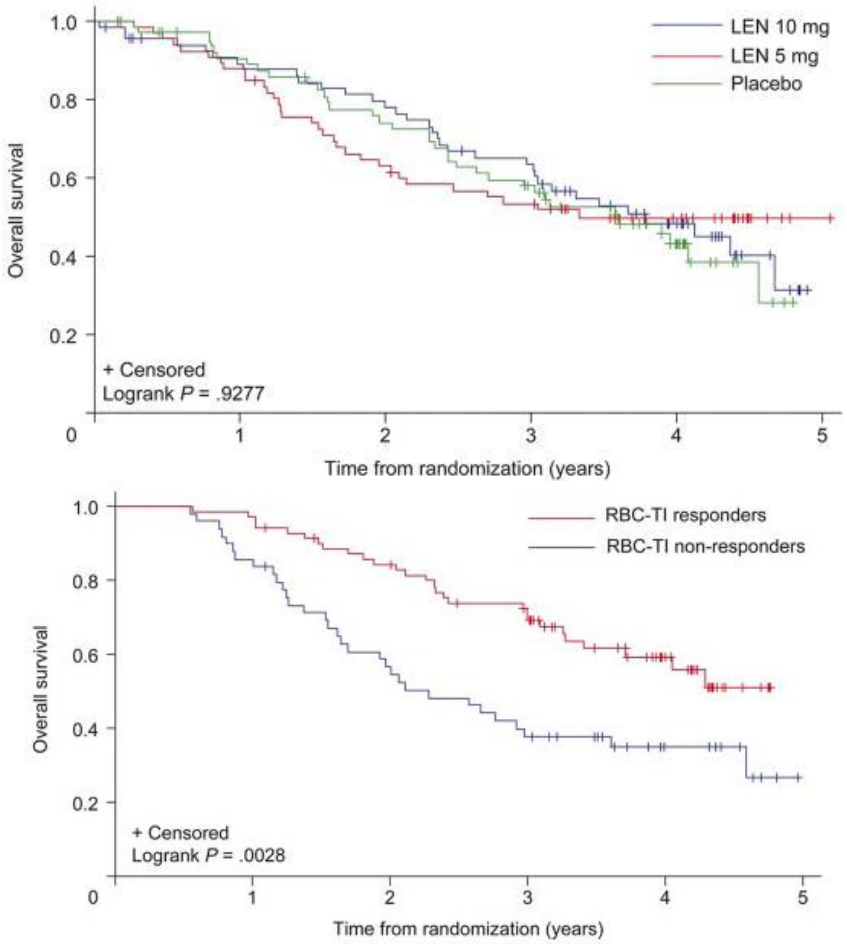




Kelaidi et al. Leukemia 2013

MDS 5q: LENALIDOMIDE





- Actualité…
  - Rôle des mutations de P53 (Jadersten Blood 2011)
  - Place du Cereblon dans l'immunomodulation et la cytotoxicité ?

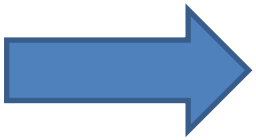
Fenaux Blood 2011

Lopez Girona Leukemia 2012

MDS non 5q: LEN échec EPO

- Efficacité dans les MDS non 5q- inférieure…
- Groupe favorable (Maciewzki Blood 2012)= trisomy 8, caryotype normaux
- Taux de réponse= 25%-30% durée de réponse = 18-24 mois
- Synergie avec l'EPO= taux de réponse 50-55%

Komroji Blood 2012
Sibon BJH 2012
Toma ASCO 2013



Données confirmée par étude GFM-LEN-EPO

GFM LEN EPO :Inclusion criteria

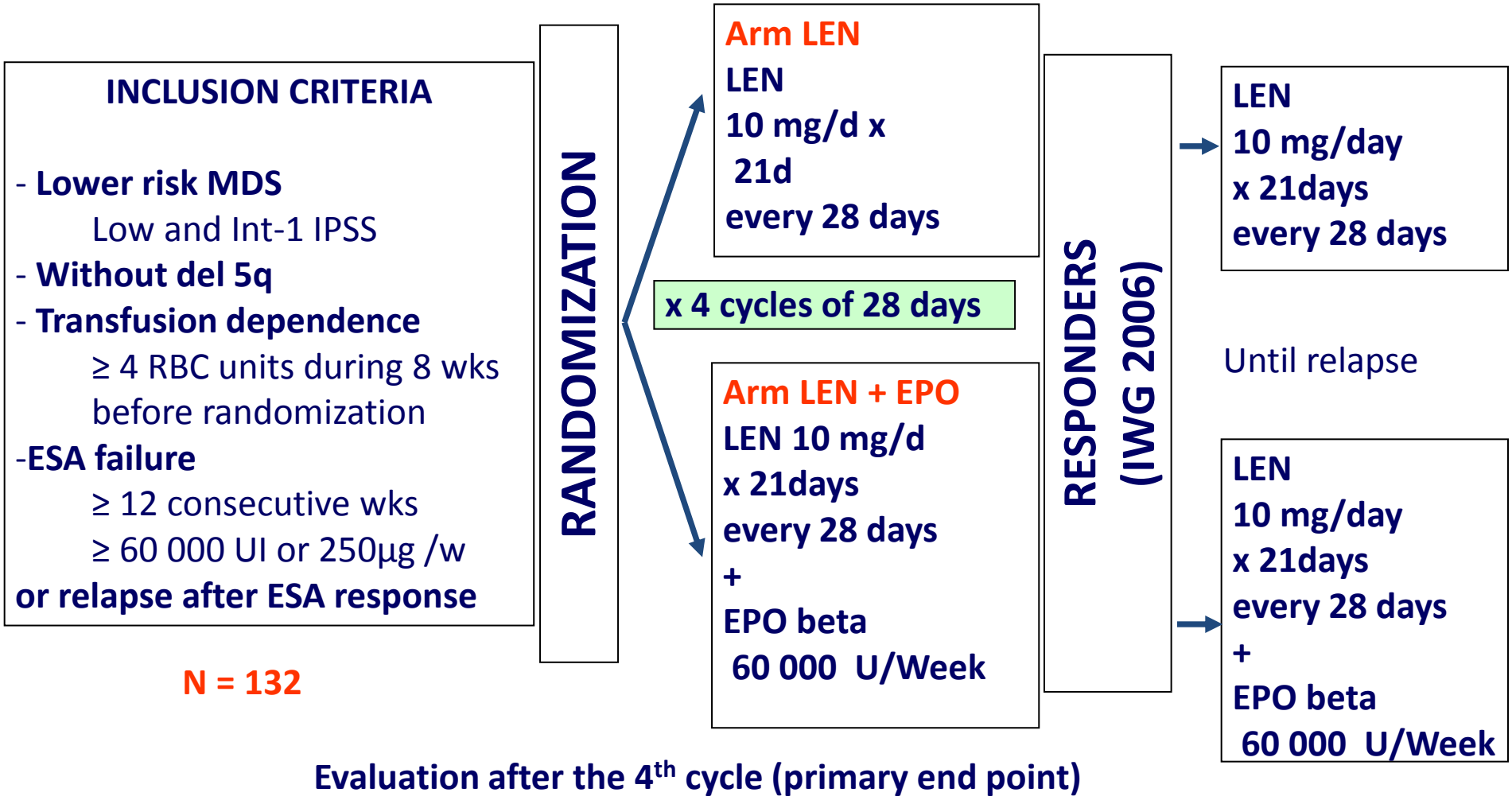
MDS defined as

- RCMD, RA with or without ring sideroblasts
- RAEB 1, or CMML 1, if WBC < 13 G /L
- with a low or int-1 IPSS score

AND

- primary or secondary resistance to
  - epoetin alpha/ beta (> 60000 U/w) or
  - darbepoetin (> 300ug/w)
  - administered for at least 12 weeks
- requirement of RBC transfusions

Study design

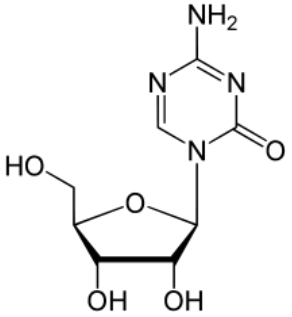


Evaluation after the 4th cycle (primary end point)

HI-E (primary endpoint) and RBC-TI in the ITT population (n=129)

	LEN + EPO N = 65	LEN N = 64	
HI-E	40 %	23.4 %	RR1.7; p= 0.043
RBC-TI	24.6 %	14.1 %	RR1.7; p= 0.13

AZA échec EPO



- Les agents déméthylants permettent des réponses érythroides
  - Lyons 2009= 30- 40% de patients transfusion independants

- Etude rétrospective italienne (Musto Hematologica 2011)= MDS bas risque
  - Réponse 40%
  - OS= 15 mois

- Etude prospective française (GFM AZA EPO)
  - AZA 75mg/m2/j 5J +/- EPO 60 000u/w
  - 98 patients MDS bas risque, échec EPO, transfusés
  - Réponse 34%, Taux d'indépendance transfusionnelle 17 %! , pas de bénéfice EPO
  - OS =18 mois

Gardin ASCO 2012

Oral Azacitidine

- Formulation orale de l'azacitidine
- Biodisponibilité très variable (6% ➔ 20%)
- Phase I
  - Cycle 1 AZA sous cutanée puis cycle 2+ AZA orale J1-J7
  - DLT= diarrhées, dose recommandée 480 mg/j
  - 41 patients, MDS en majorité + 8 AML
  - ORR (CR+ HI)= 35% si pré traités, 73% si naif de traitement , 0% si AML
  - Cinétiques de démethylation comparables S.C. et P.O

Garcia Manero Blood 2011

Chélateurs ferriques

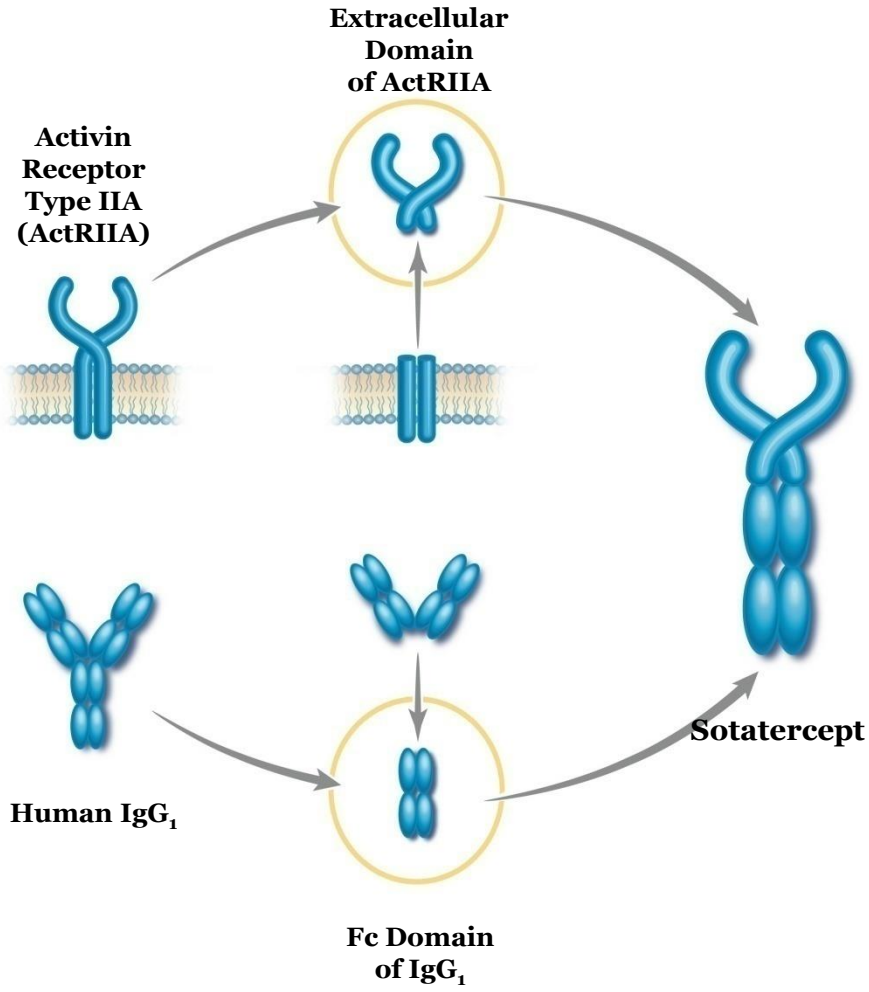
- 227 patients MDS bas risque transfusés
- traités par Deferasirox (EPIC study) sans autres traitements
- 22% de réponse érythroïde durée moyenne 80J
- Confirmé par une étude Nord américaine

➔ Développement en monothérapie et combinaison (EPO/ AZA)

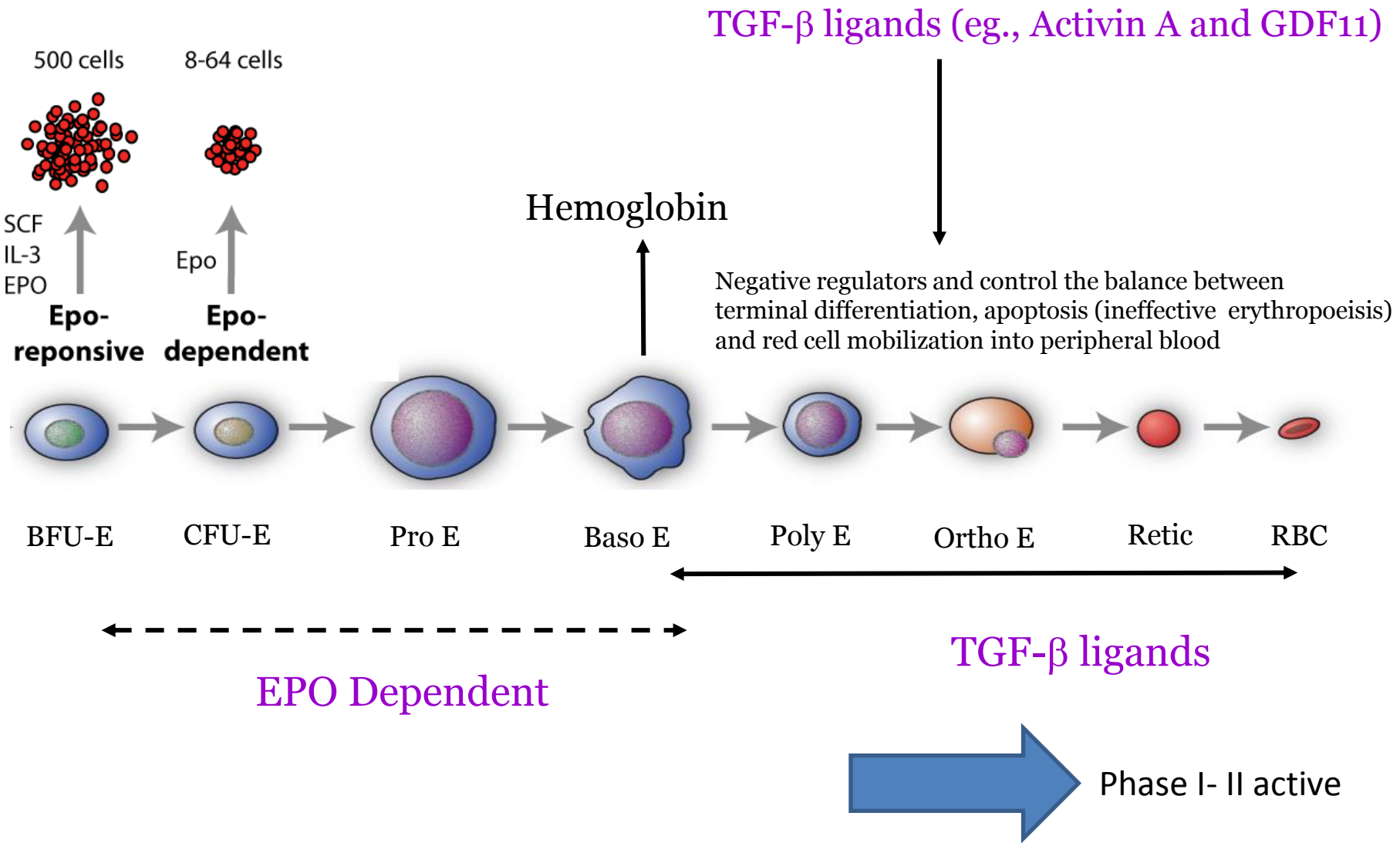
Gatterman hematologica 2012 / List JCO 2012

SOTATERCEPT

- Recombinant Trap protein
- Cible l'activine (TGF Beta)
- DLT chez le sujet sain= Augmentation de l'hémoglobine!
- Autres AE= HTA et diminution FSH



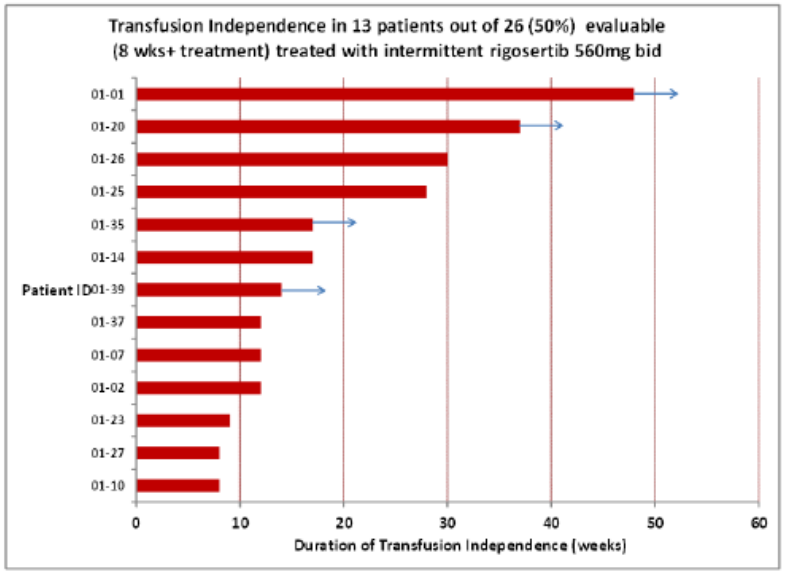
mécanisme d'action



Rigosertib oral

- Rigosertib = PLK /PI3K inhibitor
- Phase II MDS low risk
- 43 pts, 22 préalablement EPO et ou LEN/AZA

Transfusion Independence in 50% of 26 Evaluable Patients



Raza ASCO 2013

MDS bas risque: Au total

- Première ligne de traitement
  - Gestion des cytopénies/ Qualité de vie
  - Optimisation des réponses (associations)
- Deuxième ligne de traitement
  - Survie « courte » des échecs précoces EPO (progression ***et*** cytopénies) → attitudes agressives

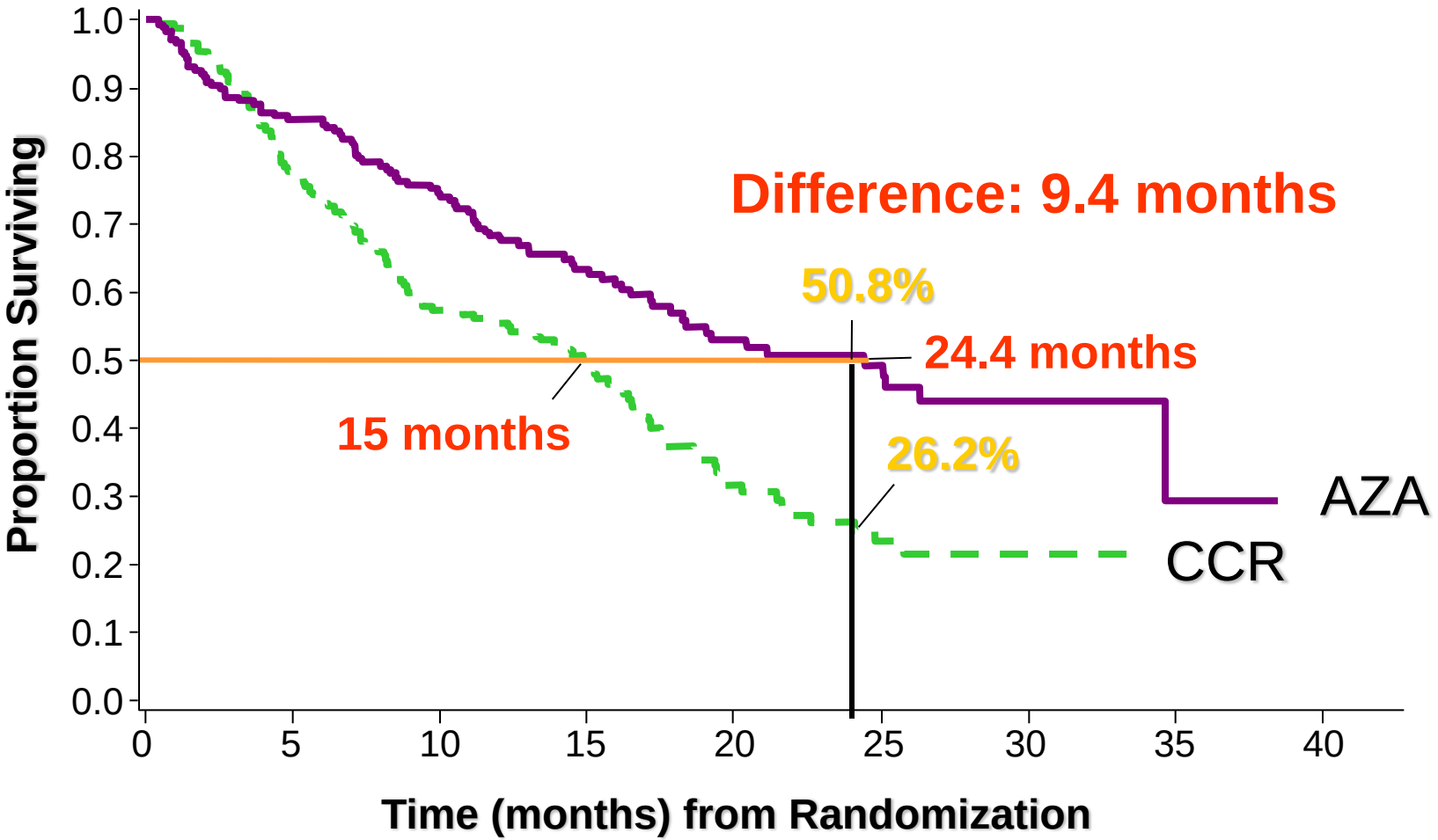
Myélodysplasies de haut risque

Agents déméthylants

	5-azacytidine (Silverman, JCO 2001 et 2006)	Decitabine (Kantarjian Cancer 2006)
Étude	Randomisée vs SC	Randomisée vs SC
Nombre de patients	99	89
Réponses:		
- CR + PR	11%	22 (25%)
- HI	36%	NA
Response duration	15 months	9 months
Time to AML transf.	21 months	11 months
Survie	20 months	NA

AZA 001 study: Overall Survival analysis

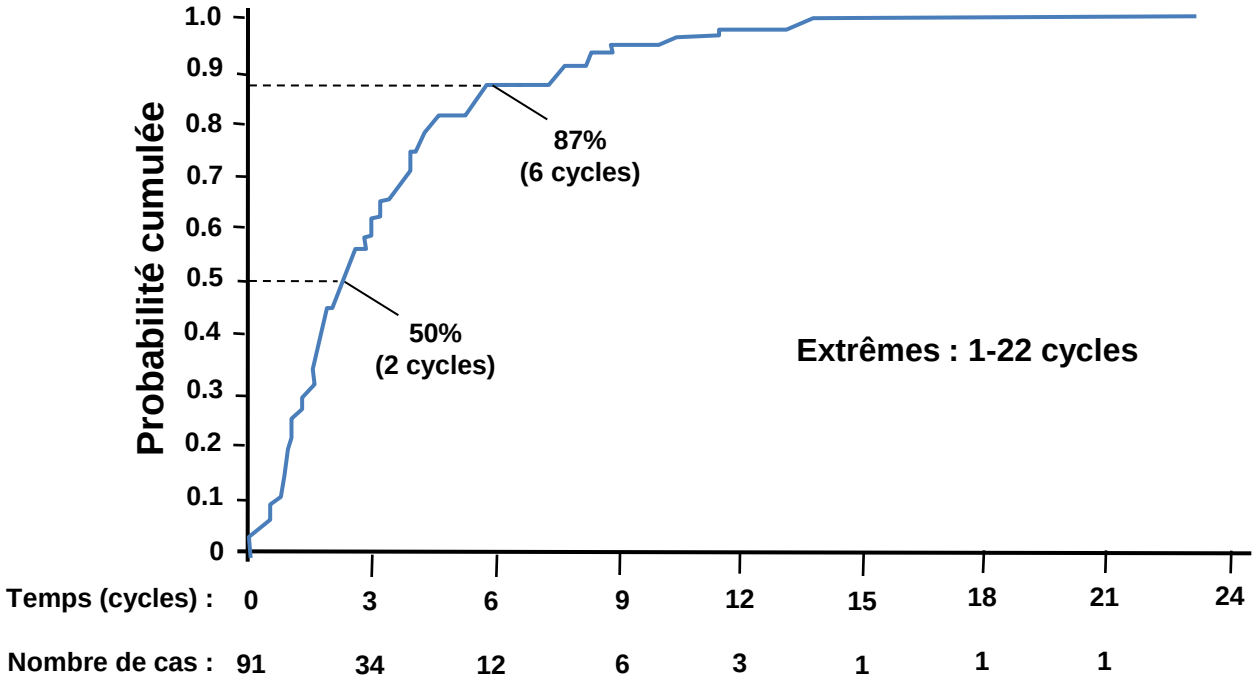
Azacitidine vs CCR ITT Population



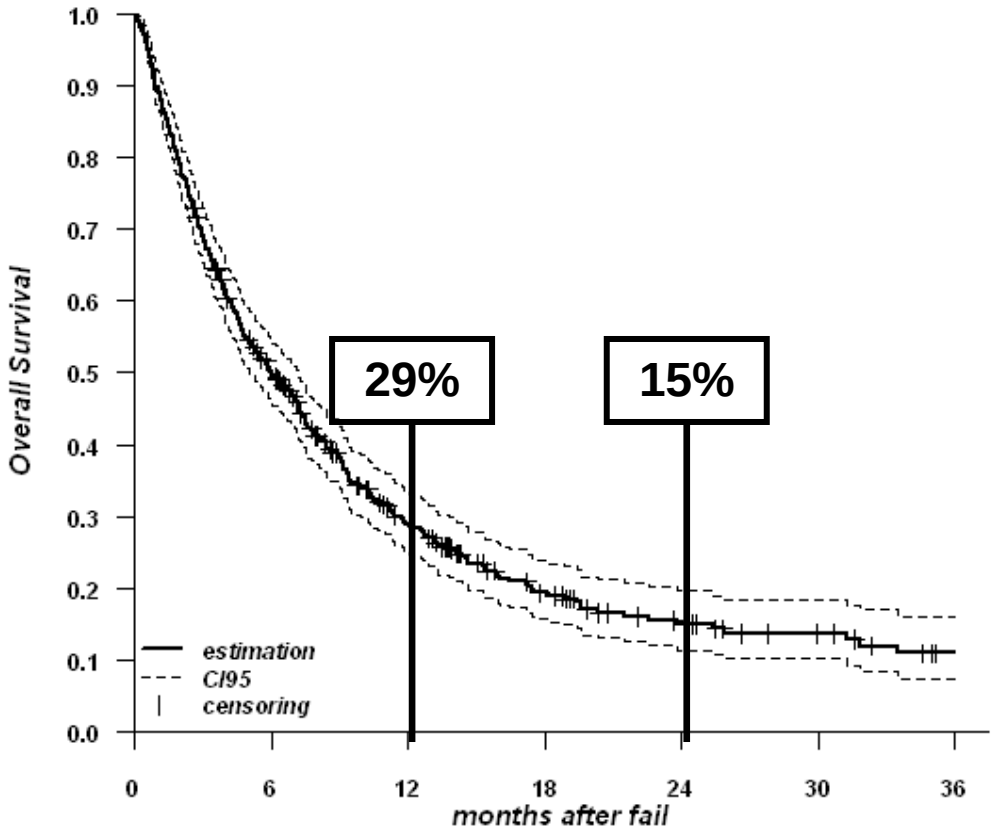
Fenaux Lanc Oncol 2009

Importance de la durée de traitement par déméthylant

- Etude AZA 001: taux de réponse de 51% (IWG 2000)
- Le nombre médian de cycles reçus varie entre 11,5 et 16,5
- Le délai médian pour passer d'une RP/HI à une RC est de 3,2 mois



Survie des Echecs d'AZA



Prebet JCO 2011
Prebet BJH 2012

1ère ligne: Approches actuelles….

- Combinaison AZA + …
  - HDAC inhibiteur
  - Revlimid (Sekeres JCO 2012) + GFM
  - Idarubicin (GFM)
  - TNF inhibitor (Raza BJH 2009)
  - Chélateurs du fer, …
- Autres approches
  - AZA intensif (GFM)

E1905 study

- Phase II randomized study in MDS and AML
  - Arm A= Azacitidine alone 50mg/m^2/d **10 days**
  - Arm B= AZA 10 days + Entinostat day 3 and day 10
  - 6 cycles planned, extension up to 24 cycles for responders
- Primary objective
  - To determine the rate of Hematologic trilineage response (TR= CR+PR+ tri lineage HI)
  - Aim= doubling of TR rate/CALGB9221 (15%➔30%)

Prebet JCO 2013 in press

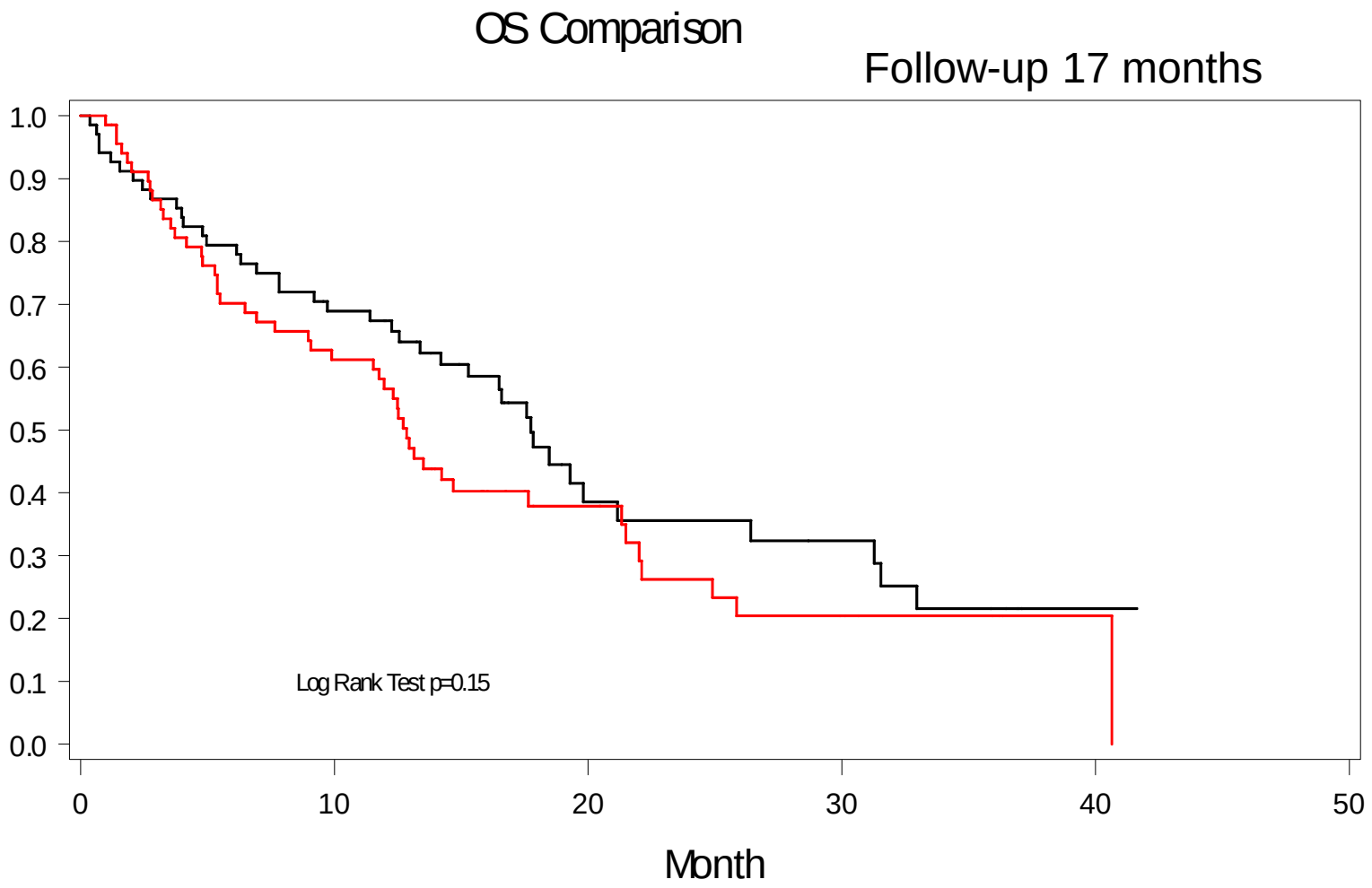
Response evaluation (IWG 2000)

	Arm A AZA alone	Arm B AZA+ Entinostat
Complete Remission	12%	7%
Partial Remission	9%	7%
Trilineage HI	10%	10%
HI not trilineage	12%	19%
No response	57%	56%

Response evaluation (IWG 2000)

	Arm A AZA alone	Arm B AZA+ Entinostat
Complete Remission	Trilineage Response: 31%	Trilineage Response: 24%
Partial Remission		
Trilineage HI		
HI not trilineage	12%	19%
No response	57%	56%

Overall survival analysis



AZA+ LENALIDOMIDE

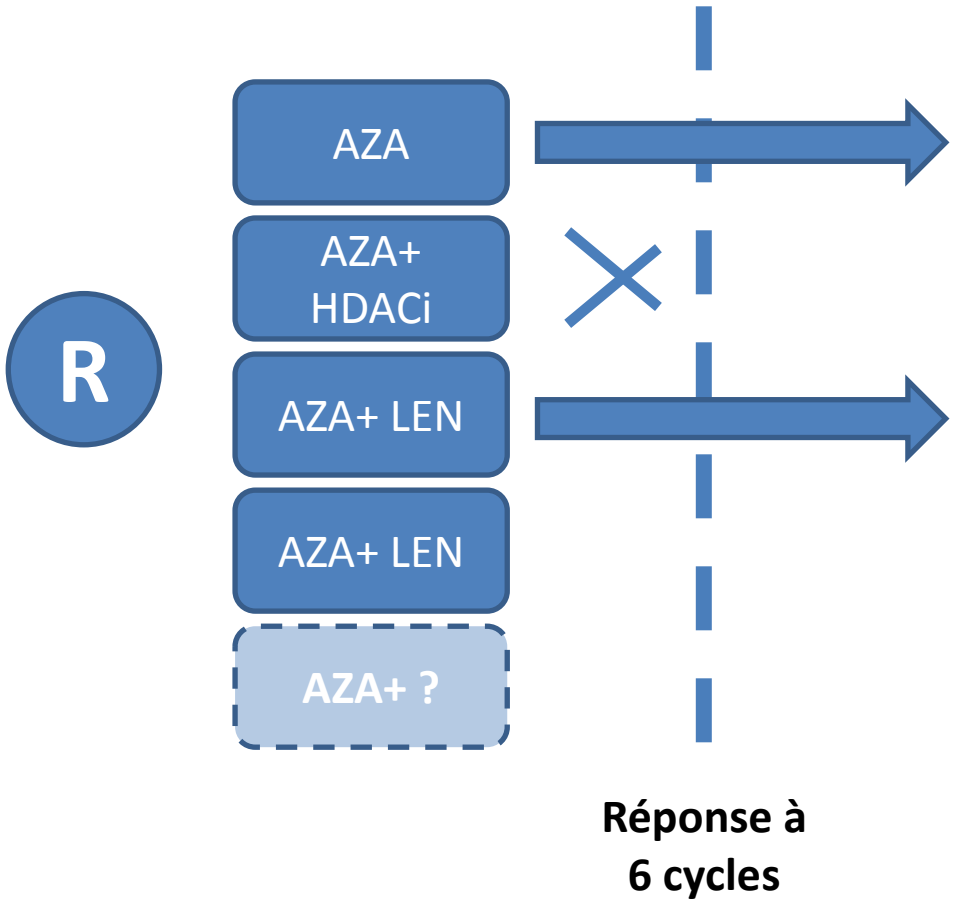
- Combinaison concomitante ou séquentielle phase I/II
- Majoration de la toxicité hématologique
- Biomarqueur= Mutations de type 3 (TET2, DNMT3a, IDH) favorables?

Characteristic	N (% or Range)
Overall Response Rate	26/36 (72)
Complete Response (CR)	16 (44)
Hematologic Improvement (HI)	10 (28)
HI – erythroid	3 (30%)
HI – platelet	3 (30%)
HI – neutrophil	4 (40%)
Median Time to Initial Response (Months)	3.7 (1.4-7.4)
Median CR Duration (Months)	17+ (3-39+)
Median Overall Survival (Months, n=36)	13.6 (3-55)
Median Overall Survival Among CR Patients (Months, n=16)	37+ (7-55+)

Sekeres Blood 2012
Platzberger ASH 2011
Adès ASH 2011

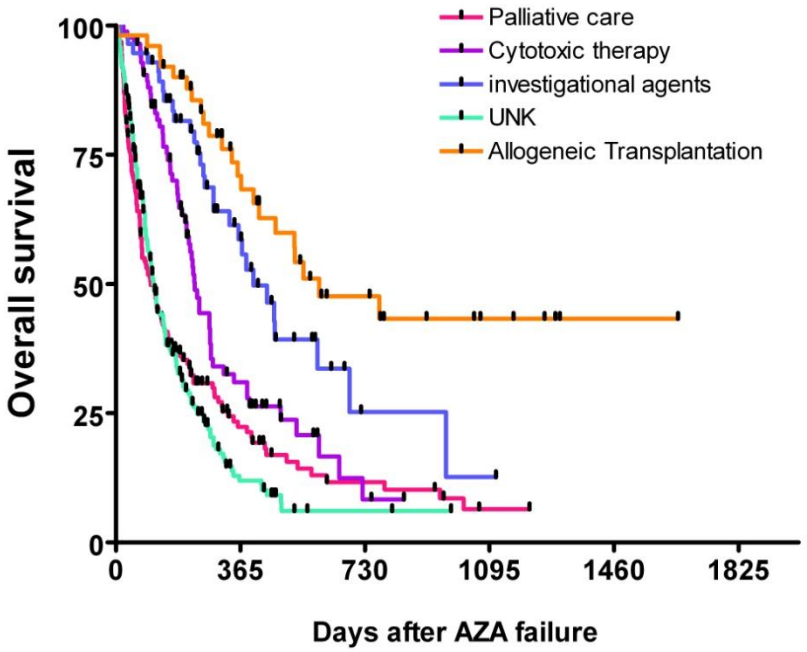
« Pick the winner »

- Protocole GFM … et protocole intergroup US



Comparaison en phase III

Effect of treatment options after AZA failure (n=350)



Type of salvage	N=	ORR[1]	Median OS (months)
Unknown	215	NA	3.6
Supportive Care	160	NA	3.3
Cytotoxic therapy	84	1/25 and 5/33[2]	7.6
Investigational therapy	56	4/39	13.2
Allogeneic Transplantation	50	17/25	18.3

*

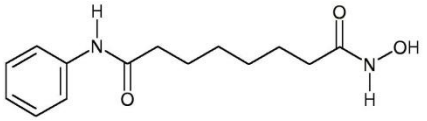
**

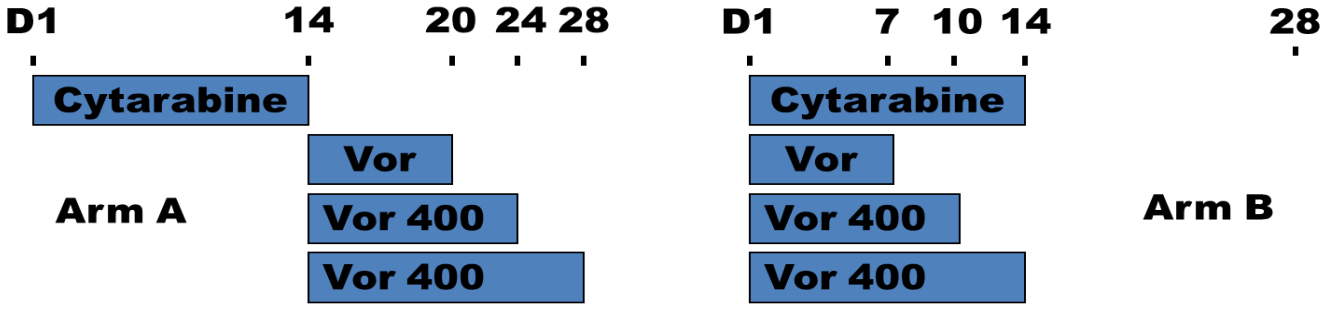
1: Overall response rate

2: intensive chemotherapy

Prebet JCO 2011

GFM VOR 2007

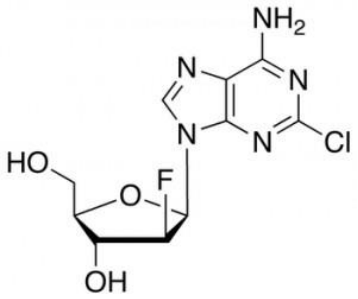




- 42 patients included, 40 patients treated
- Tox: fatigue / GI / thrombocytopenia
- Overall response rate 15% (2CRi, 2 HI, 2 marrow CR)
- Median duration of response 3 months (2-6+)
- Median overall survival 7.3 months
- 2/24 responses in arm A (10%) *vs* 4/16 in arm B (25%, including the 2 CRi)

Prebet Leuk res 2013

CLOFARABINE

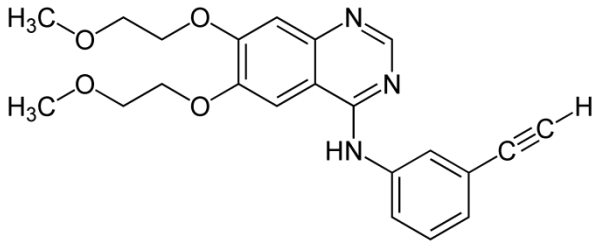


- Nucleosidic analogue IV and oral
- Clinical activity in ALL and AML
- For MDS patients…
  - Clinical activity **BUT** high toxicities at conventional doses

- GFM experience for AZA failure (Phase I):
  - Clofarabine low dose 5-10 mg/m2 D1 to D5 or 1D/2 D1-D10
  - 27 patients treated, DLT: cytopenias and infections
  - 7/25 (28%) responders after 1 cycle

Faderl et al JCO 2011
Braun et al ASH 2011

ERLOTINIB



- EGFR inhibitor
- Off target activity in MDS through STAT signalling
- Phase I-II GFM
  - 29 patients AZA failure
  - no DLT in phase I , Phase II recommended dose 150mg/d
  - 3/22 (13%) responders

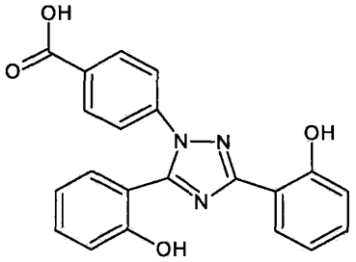
Bohrer Blood 2008
Komroji et al Blood 2012
Thepot, Laisney ASH 2012

LENALIDOMIDE POST AZA

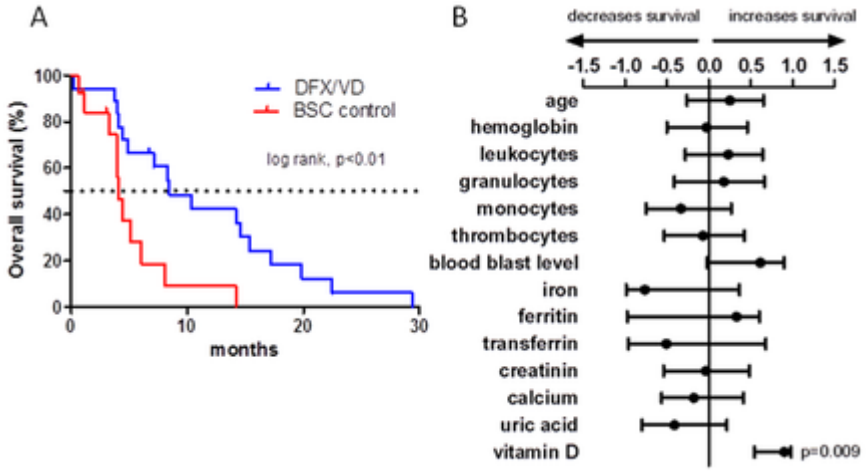
Patient #	demographics	Disease status before AZA	Cytogenetics	IPSS before AZA	AZA treatment[$]	AZA Failure	LEN schedule and response[$]	LEN duration and failure	Overall Survival (months)
1	M, 63y	RAEB-2, EPO resistant	Deletion 11	Int-2	75*7d, HI	12 cycles, PD	5*21d, NR	2 cycles, TOX	20
2	M, 78y	RARS, EPO resistant	Trisomy 8	Int-1	75*5d, HI	10 cycles, PD	5*21d, HI	6 cycles, loss of HI	22+
3	F, 72y	RA, EPO resistant	Deletion 5q complex K.	Int-1	75*7d, NR	7 cycles, SD	5*21d, CR	10 cycles ongoing	16+
4	M, 49y	RARS, EPO resistant	Deletion Y	Int-1	75*5d, NR	6 cycles, SD	10*21d, NR	6 cycles, SD	17[&]
5	F, 71y	RARS, EPO resistant	Normal	Int-1	75*5d, NR	6 cycles, SD	5*21d, NR	1 cycle, SD	4
6	M, 78y	RARS, EPO resistant	Deletion 20q	Int-1	75*5d, NR	9 cycles, SD	5*21d, NR	3 cycles, SD	22
7	F, 62y	AML (RAEB-T), relapsed after Allogeneic HSCT	Deletion 5q	NA	75*7d + DLI, PR	6 cycles, PD	10*21d, CR	3 cycles, PD	7
8	M, 77y	RAEB-2, EPO resistant	Deletion 5q complex K.	Int-2	75*7d, HI	12 cycles, PD	10*21d, NR	2 cycles, TOX	5+
9	F, 69y	RAEB-2, EPO resistant	Deletion 5q, complex K.	Int-2	75*7d, NR	8 cycles, SD	10*21d, CR	12 cycles, ongoing	14+
10	F, 71y	RAEB-2, EPO resistant	Deletion 5q Inversion 3	High	75*5d, CR	5 cycles, PD	10*21d, NR	3 cycles, SD	5

Prebet leukemia Lymphoma 2012

DEFERASIROX+ vitamine D?

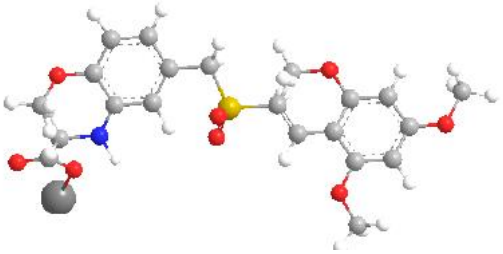


- 17 pts (vs 13 BSC)
- AML-MRC or sec AML previously treated with AZA
- No objective response
- OS 10 ms vs 4 ms (BSC)



Paubelle PLosOne 2013

RIGOSERTIB

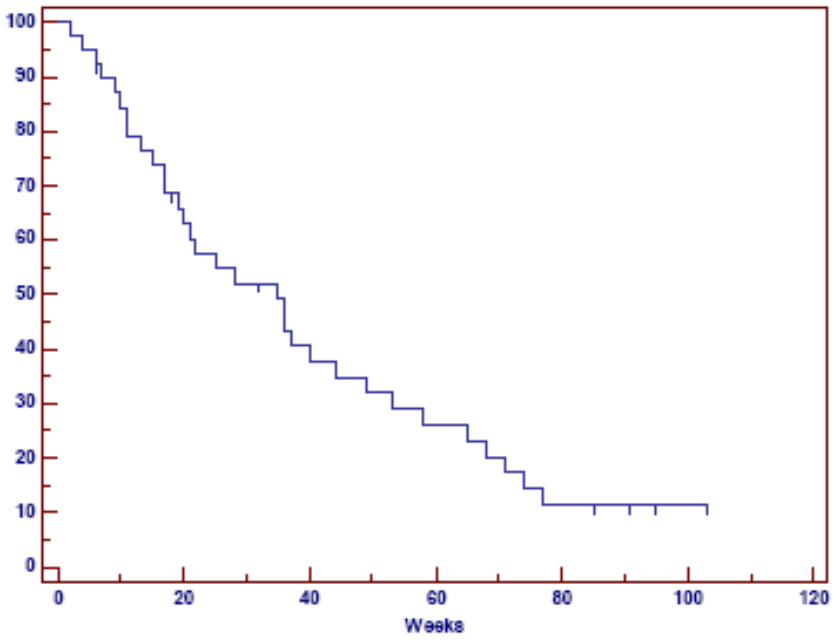


- Multi Hit Kinase inhibitor
  - Not binding in ATP pocket
  - PLK-1 pathway inhibitor
  - PI3 Kinase inhibitor

- Inhibits activation of anti apoptoptic proteins such as MCL-1

RIGOSERTIB
Clinical data phase I-II

- IV and oral formulation
- High risk MDS AZA failur
  - ORR**= 23% (9/39)
  - OS= 9 months
- Toxicity
  - Urinary symptoms



Greenberg ASH 2011

ADD-ON CONCEPT

- Bénéfice de survie pour les patients AZA en maladie stable à 6 cycles
- Traitement jusqu'à progression sous peine de rechute…
  - Persistance d'un pool de LSC sous AZA

Gore Hematologica 2013
Wille Blood 2012

ADD-ON CONCEPT

- Bénéfice de survie pour les patients AZA en maladie stable à 6 cycles
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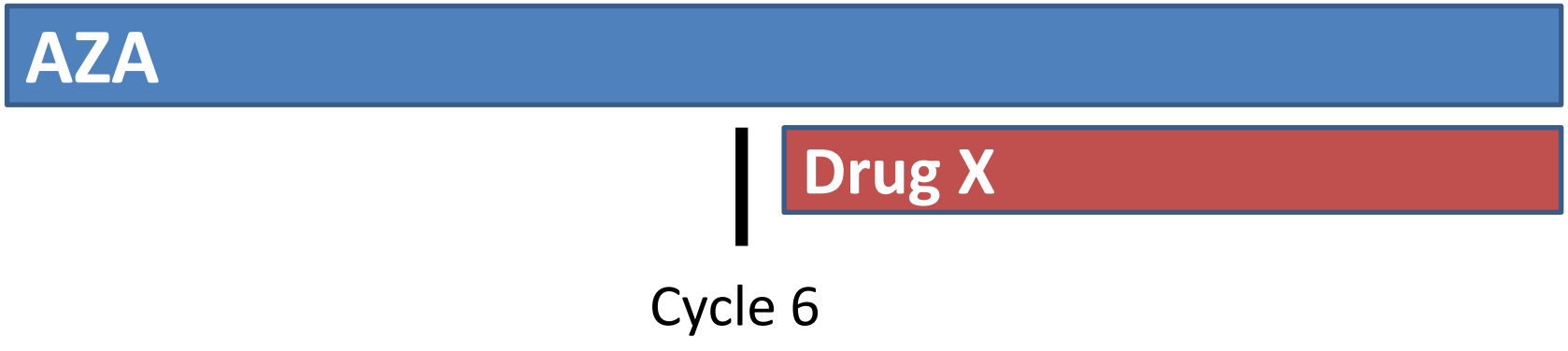
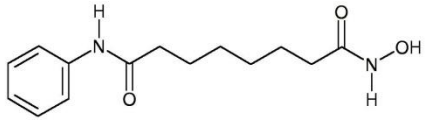
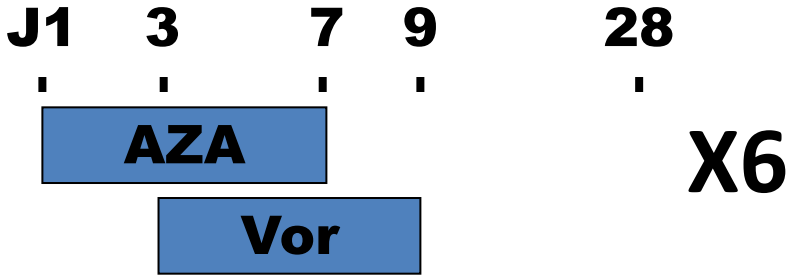
  - Persistance d'un pool de LSC sous AZA



GFM VOR ADD ON



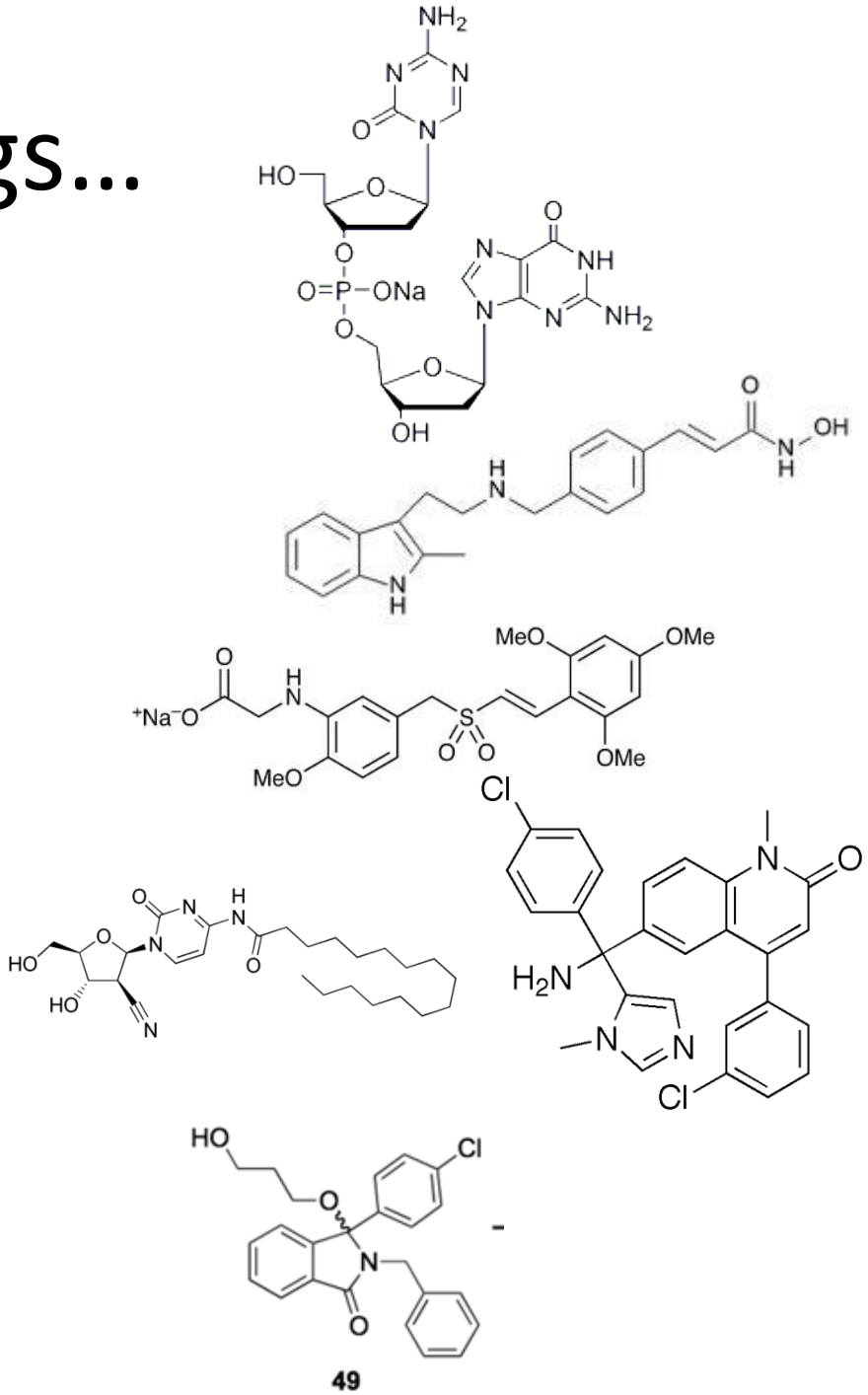
- Pts with AZA failure w/o BM progression
- **<u>Phase II trial:</u>** Addition de Vorinostat 300mg bid J3-9
- 6 cycles of treatment
- 12 pts included



Prebet on behalf og GFM

Lot's of other drugs…

- New epidrugs
  - SGI 110
  - 3rd generation HDACi
- TK inhibitors
  - Rigosertib/volasertib
  - PI3K/AKT targeting
- Sapacitabine
- RAS/RAF pathway inhibitors (back to FTI?)
- P53 inhibitors



MDS haut risque: Au total

- Première ligne
  - HMA= un standard perfectible
  - Place des associations+++ mais attention aux tox
- Deuxième ligne
  - Survie globale courte, pas de standard
  - Développement de nouvelle drogues +++ mais évaluation difficile

Conclusions

- Changement de paradigme au cours des dernières années (AMM AZA et LEN),

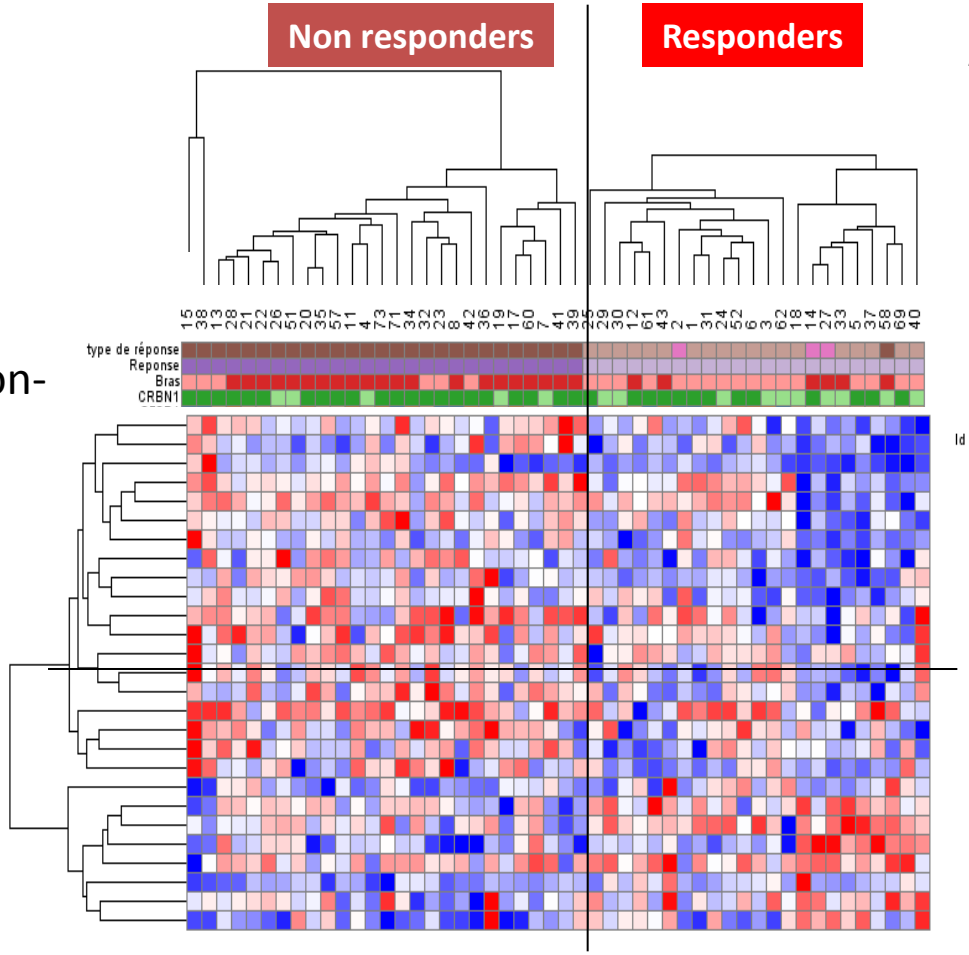
- Les myélodysplasies représentent un nouveau champs d'investigation clinique
  - 1ère ligne= combinaisons EPO/ AZA
  - 2ème ligne= nouvelles drogues

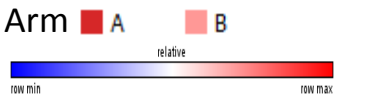
A predictive gene expression signature of response to LEN

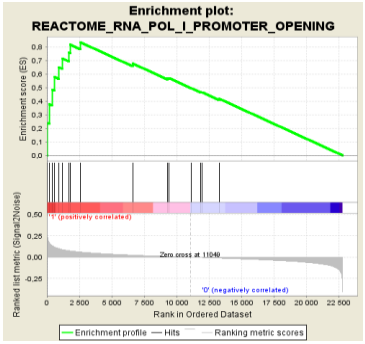
50 patients at diagnosis
- LEN arm: 27 pts
- LEN+ EPO arm : 23 pts

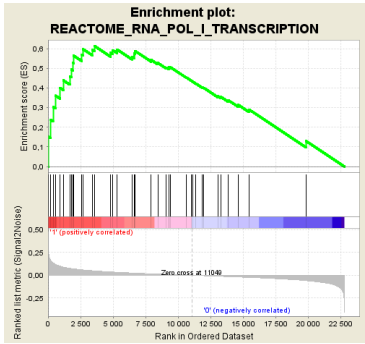
Comparison:
23 responders *vs*. 27 Non-resp

Anova test







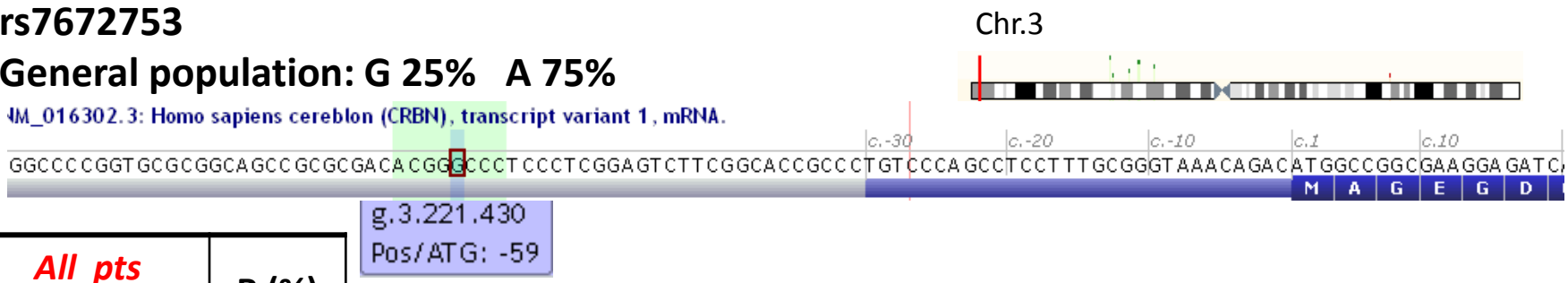


- 8 genes upregulated
- 19 genes down-regulated
- functions : transcription, epigenetics, signaling, DNA repair

Cereblon gene polymorphism as a marker of response to LEN+/- EPO

rs7672753

General population: G 25% A 75%



All pts (n=90)	R (%)
A polym	33
G polym	59

***P*=0.019**

Patients with G polymorphism had a significantly higher HI-E rate than patients with A polymorphism

OR 3.1 (CI95%: 1.2-8.2]

LEN alone (n=44)	R (%)
A polym	17
G polym	47

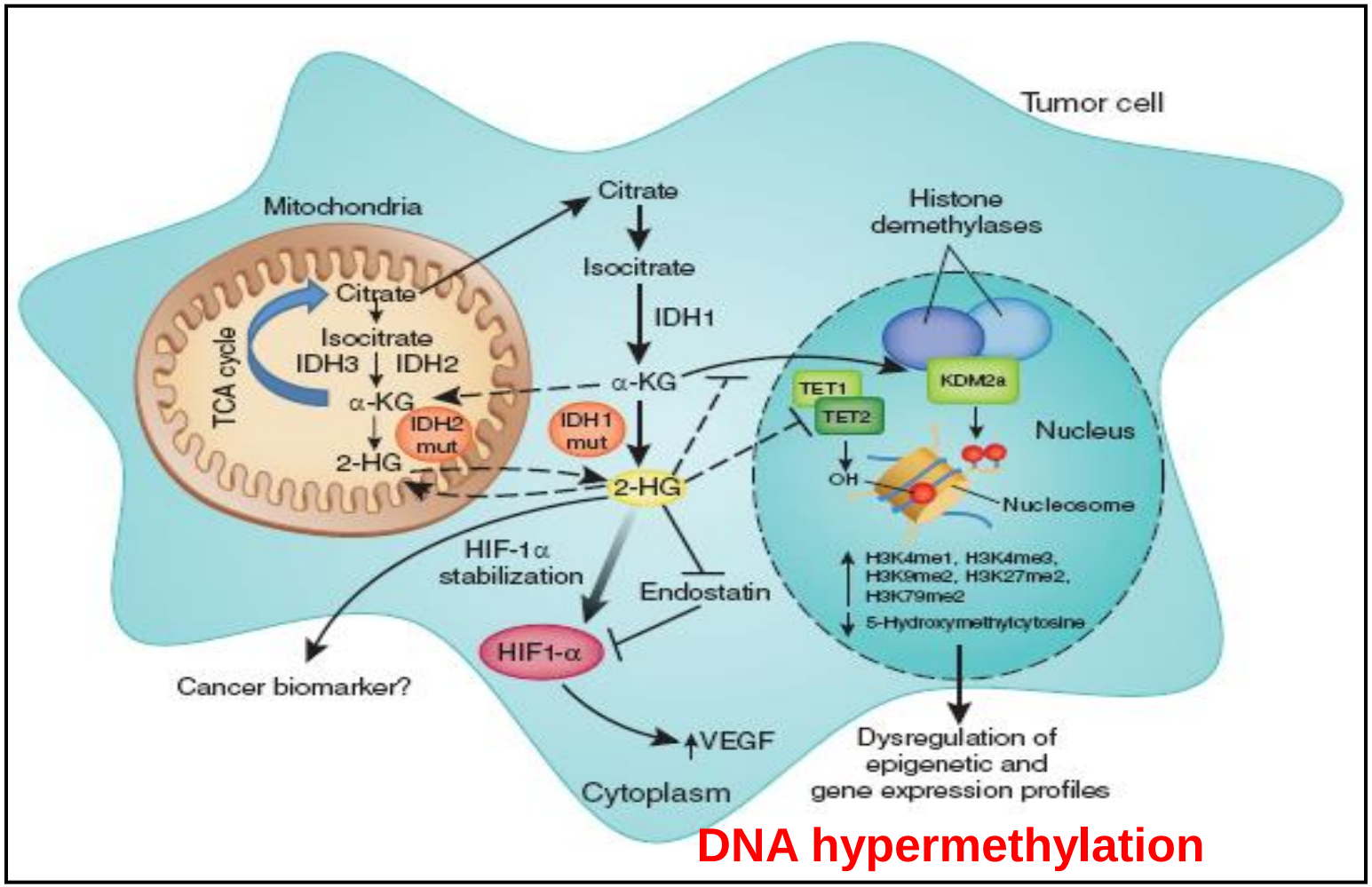
***P*=0.037**

LEN+EPO (n=46)	R (%)
A polym	47
G polym	71

***P*=0.124**

Less impact of CRBN G polymorphism in LEN+ EPO arm

Régulation de la méthylation de l'ADN



Prensner et al; Nature 2011

RAS/RAF pathway inhibition

- Farnesyltransferase inhibitor tipifarnib
  - 82 IPSS Int-1, Int-2, or High risk MDS
  - Responses 26/82 (31.7%; 7 CR, 4 CRp, 2 PR, 13 HI)
  - median OS 11.7 months, median TTL 19.0 months
- MEK inhibitor in RAS mutated patients
  - CMML
  - Phase I GSK oral drug
  - Toxicité Hémato, ophtalmo et cardiaque

Fenaux Blood 2006