

Traitement des SMD de haut risque

Pierre FENAUX,
Hopital Avicenne, Paris 13 University
Groupe Francophone des Myélodysplasies

Province du Québec, 11/09



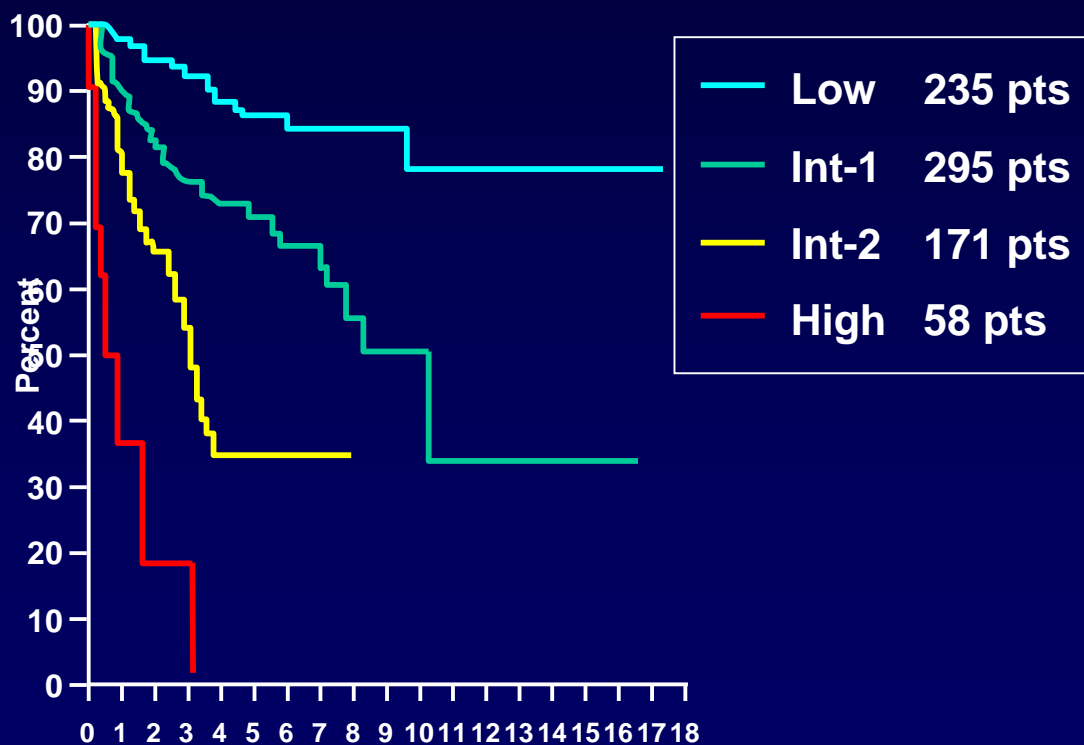
SMD: « haut » vs « faible » Risque

- **Haut risque**
 - IPSS intermediaire-2 ou élevé

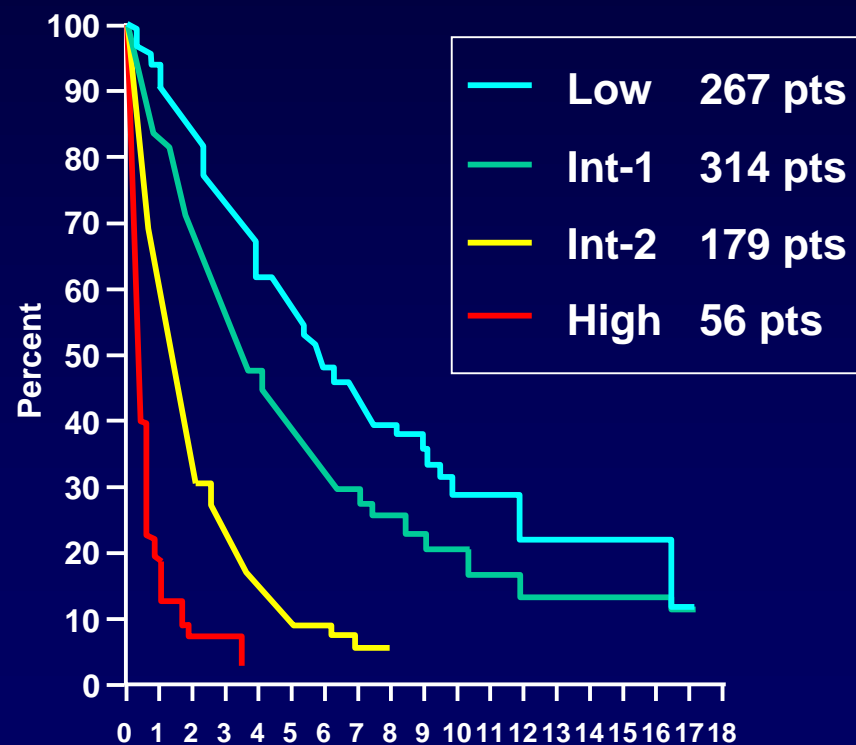
- **Faible risque**
 - IPSS faible ou intermediaire-1

IPSS

AML Evolution



Survival



SMD: Objectifs du Traitement

- **Ralentir la progression (en LAM)**
- **Prolonger la survie**
- **Améliorer les cytopénies sanguines**
- **Améliorer la qualité de vie**

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Traitement des SMD de haut risque

- **Allogreffe**
- **Chimiothérapie (intensive ou non)**
- **Agents Hypométhylants**
- **autres**

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Allo SCT: chemotherapy or hypomethylating agents before transplant (II)?

Treatment before allo based on marrow blasts, karyotype and type of transplant :

- Marrow blasts $<10\%$ (classical allo) and $< 5\%$ (non myelo ablative allo): **immediate transplant**
- increased marrow blasts
 - Normal karyotype: **intensive chemo prior to transplant**
 - Unfavorable karyotype: **hypomethylating agent prior to transplant**

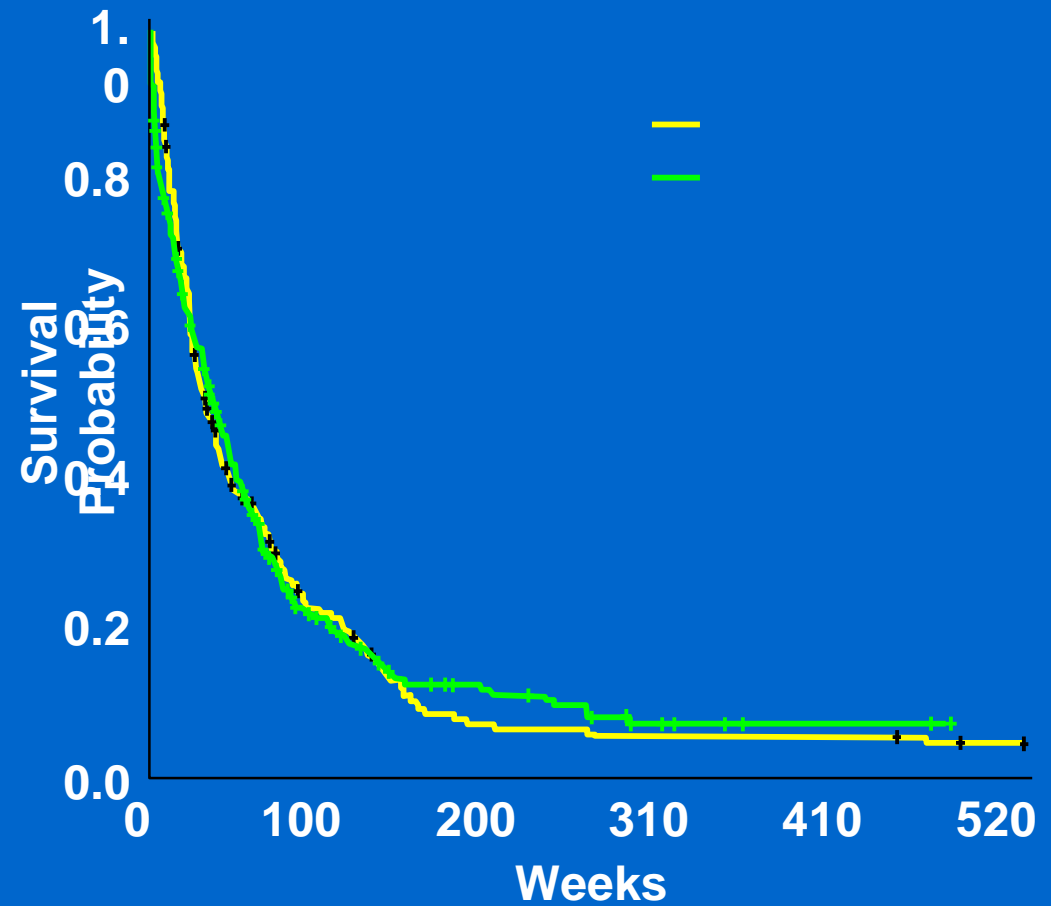
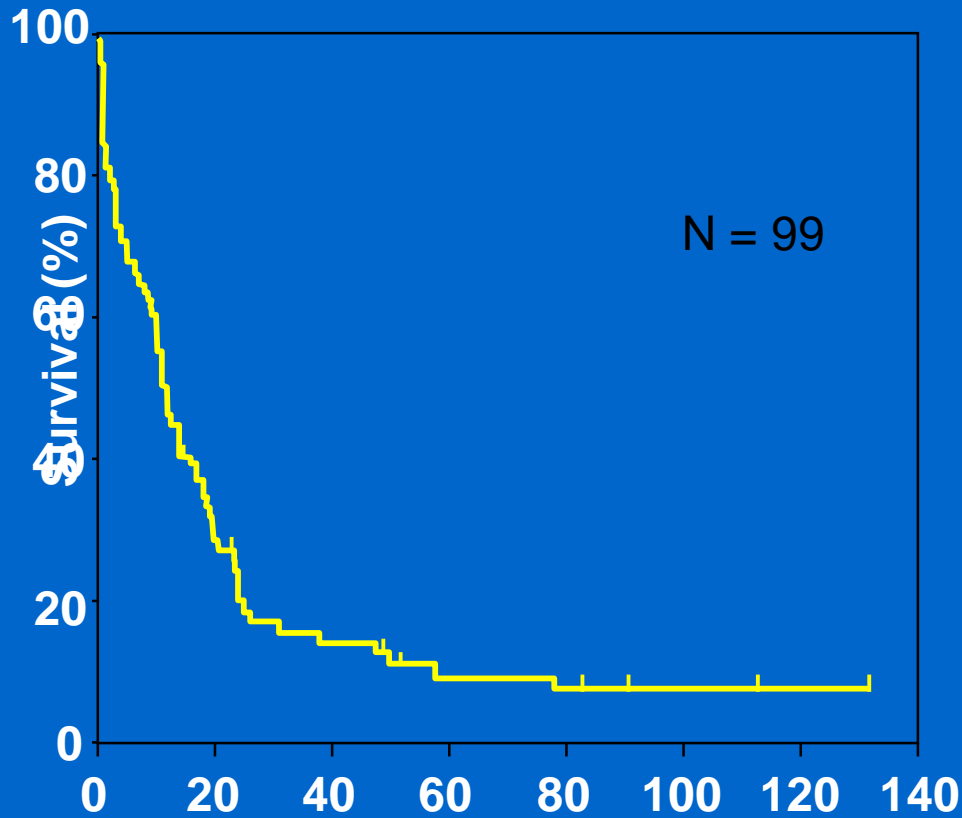
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Intensive chemotherapy

- **Mainly anthracycline-AraC (like in AML)**
- **Generally restricted to patients <65 y**
- **CR rates: 40-60%**
- **Short CR (median 1 y)**
- **response only in the absence of unfavorable karyotype**

Survival with Anthracycline-AraC Chemotherapy



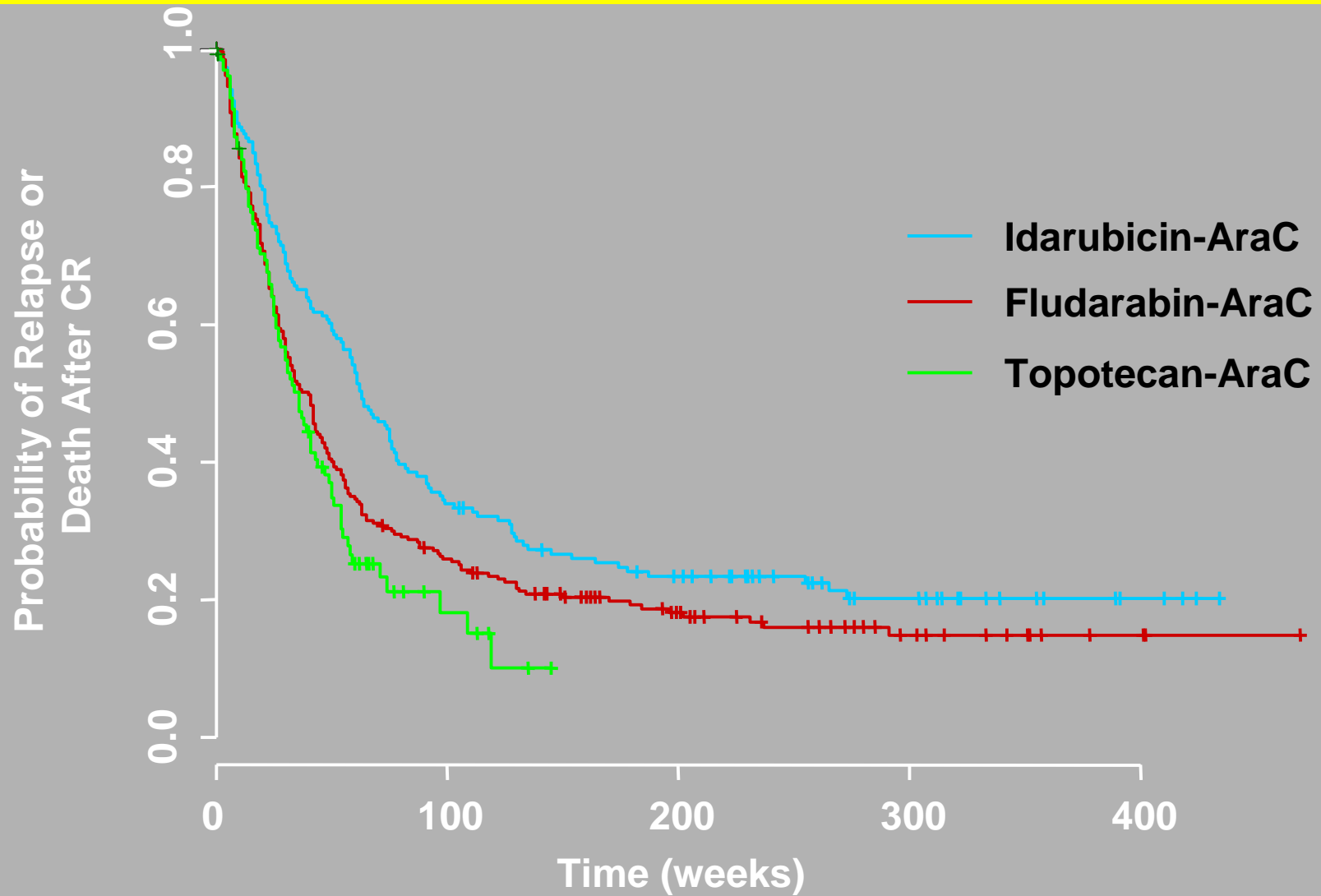
Wattel E. et al.



With Permission of E Estey, MD

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

Intensive Chemotherapy (MDAnderson Experience)



Autologous SCT in MDS achieving CR with chemotherapy

(S Ducastelle, Haematologica, 2005)

- 53 patients autografted in first CR (1992-2001)
- Median follow up 74 months
- 13 % TRM
- **38 (72 %) relapses**, after 2.5 to 37 m
- **OS 38 %, EFS 21 % at 2 years**
- Prognostic factors
 - . Gender
 - . Cytogenetics
 - . t MDS
- **8 long survivors (50+ to 119+ m) :**



Clofarabine in MDS:

Response	PO (n = 24)	IV-15 (n = 20)	IV-30 (n = 16)
Overall Response	12 (48%)	10 (50%)	6 (33%)
Complete response	7 (28%)	7 (35%)	4 (25%)
Hematologic improvement	2 (8%)	3 (15%)	2 (13%)
Grade \geq 3 Adverse Events	PO (n = 25)	IV-15 (n = 20)	IV-30 (n = 16)
Edema	0	5%	25%
Increased ALT/AST	24%/16%	0/0	13%/6%
Hyperbilirubinemia	12%	5%	13%
Acute Renal Failure	8%	10%	19%
6-Week Mortality	0	2 (10%)	2 (13%)

very low dose clofarabine in MDS resistant to Azacytidine

(T Braun, C Gardin)

- Patients without response after 6 cycles of Azacytidine or in relapse
- Escalating doses
- *Presented at ASH 2011*

MDS :low dose chemotherapy: LD AraC

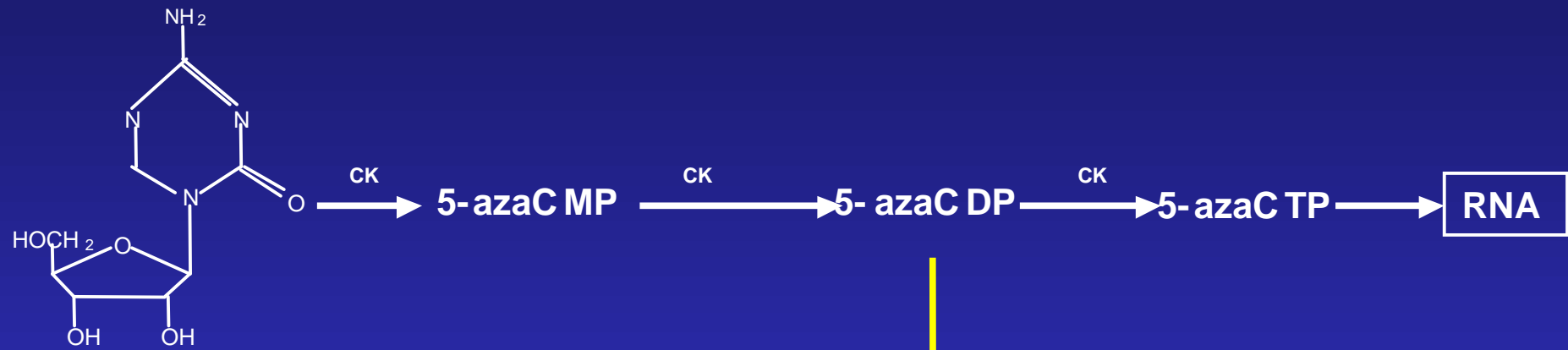
- **LD AraC : 20mg/m²/d**
- **15% RC, 20% RP, 20% HI**
- **Fairly myelotoxic (10% toxic deaths)**
- **response only in the absence of unfavorable karyotype**
- **Better survival than BSC in AML in the elderly (UK-MRC results)**

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Irreversible inactivation of DNA methyltransferase enzyme by azanucleosides after their incorporation into replicating DNA

5-azacytidine (5-azaCR, Vidaza)



5-aza-2'-deoxycytidine (5-azaCdR, Decitabine)

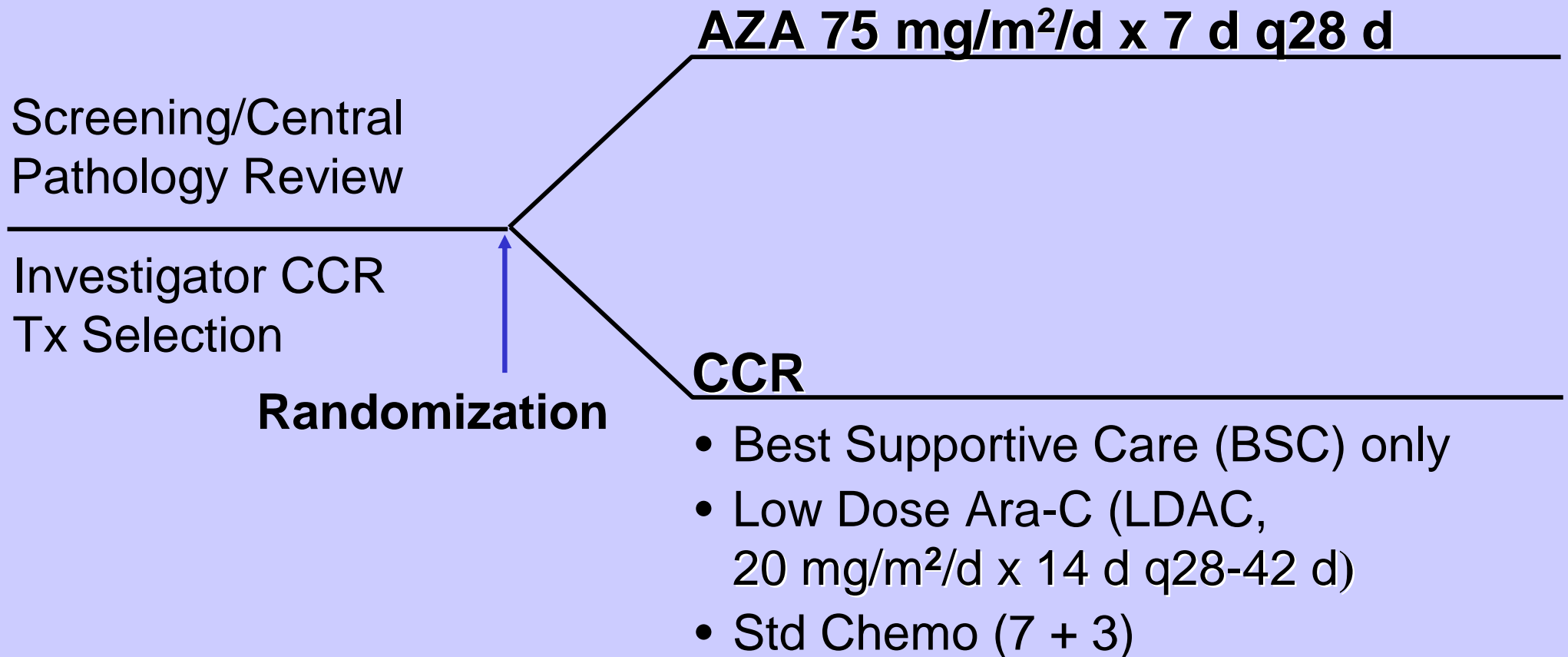


ca. 10 % conversion by ribonucleotide reductase

CK, cytidine kinase
dCK, deoxycytidine kinase

Azacitidine Survival Study

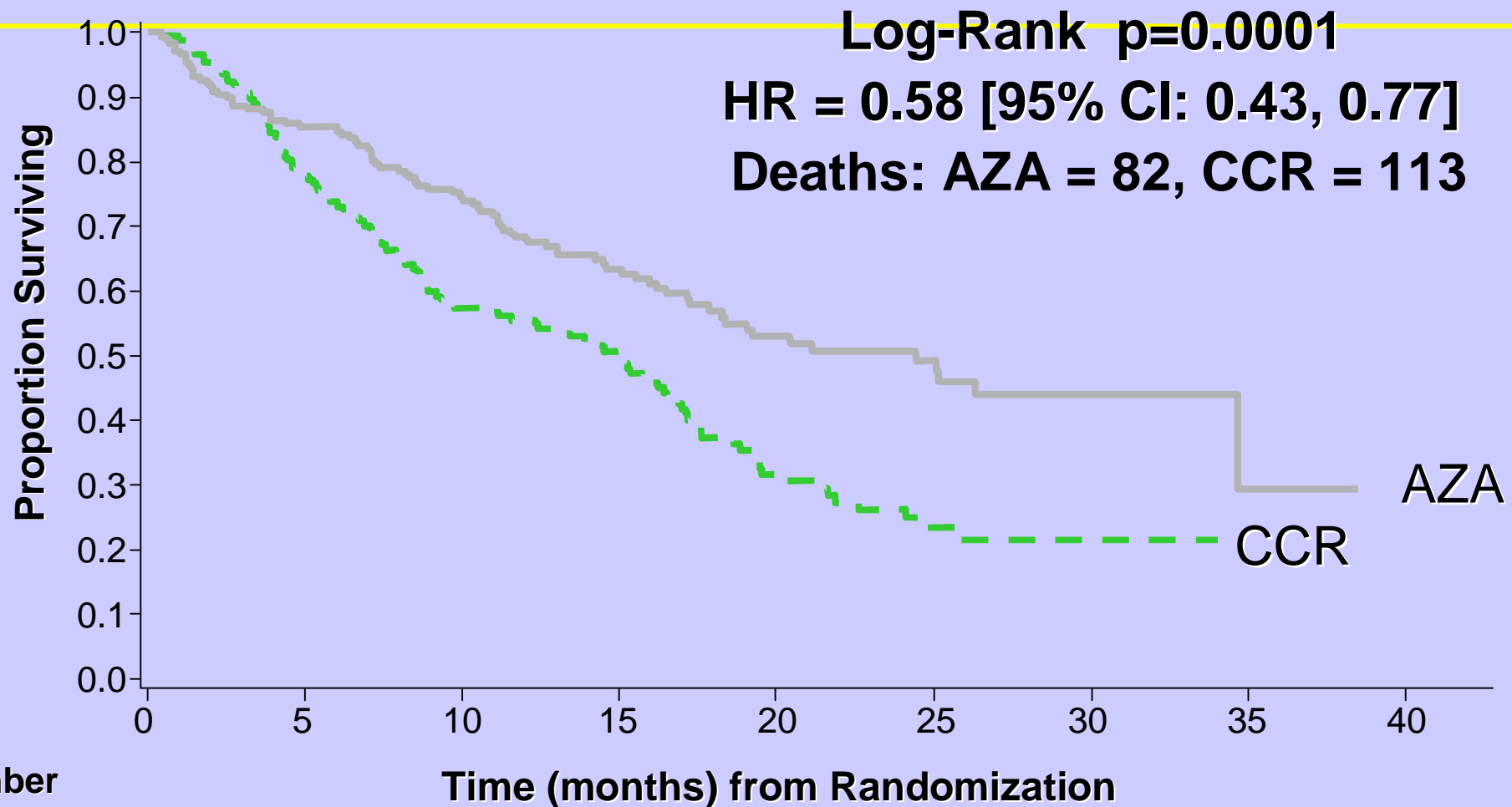
(Lancet Oncol, in press)



BSC was included with each arm

Tx continued until unacceptable toxicity or AML transformation or disease progression

Overall Survival: Azacitidine vs CCR ITT Population (358 patients)



Number
at risk

AZA	179	152	130	85	52	30	10	1
CCR	179	132	95	69	32	14	5	0

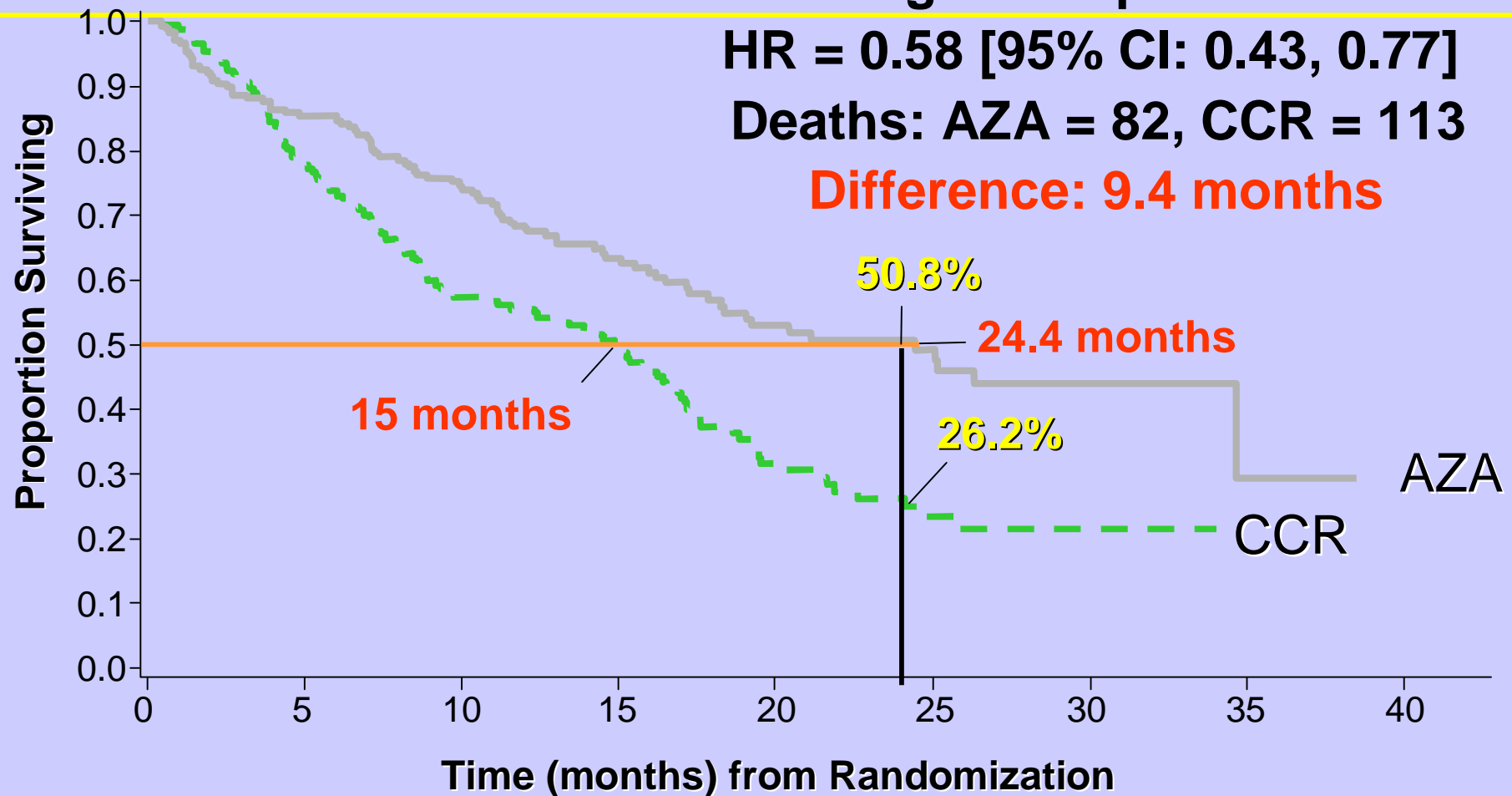
Overall Survival: Azacitidine vs CCR ITT Population

Log-Rank $p=0.0001$

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: AZA = 82, CCR = 113

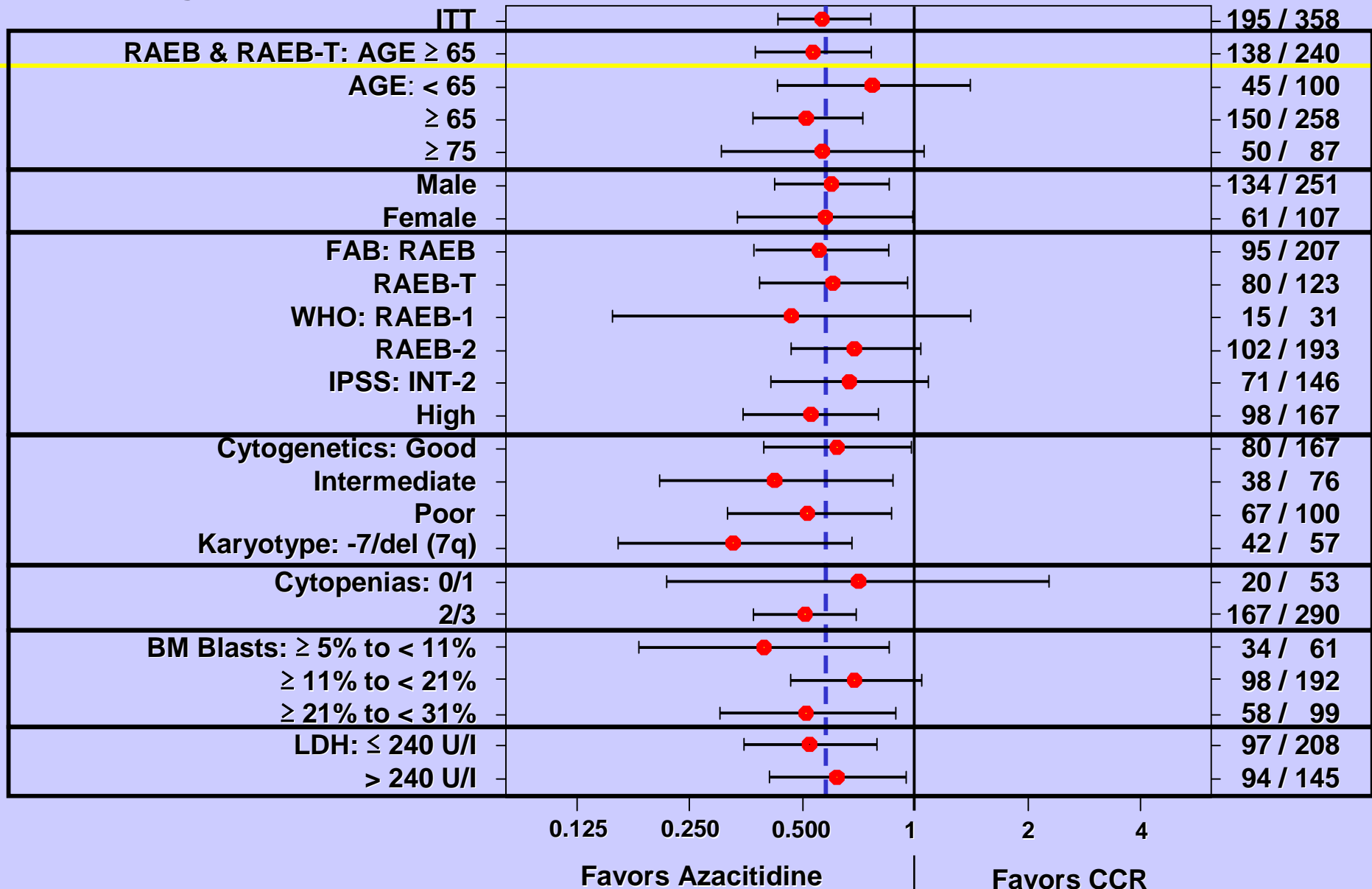
Difference: 9.4 months



Hazard Ratio and 95% CI for Overall Survival

ITT Subgroups

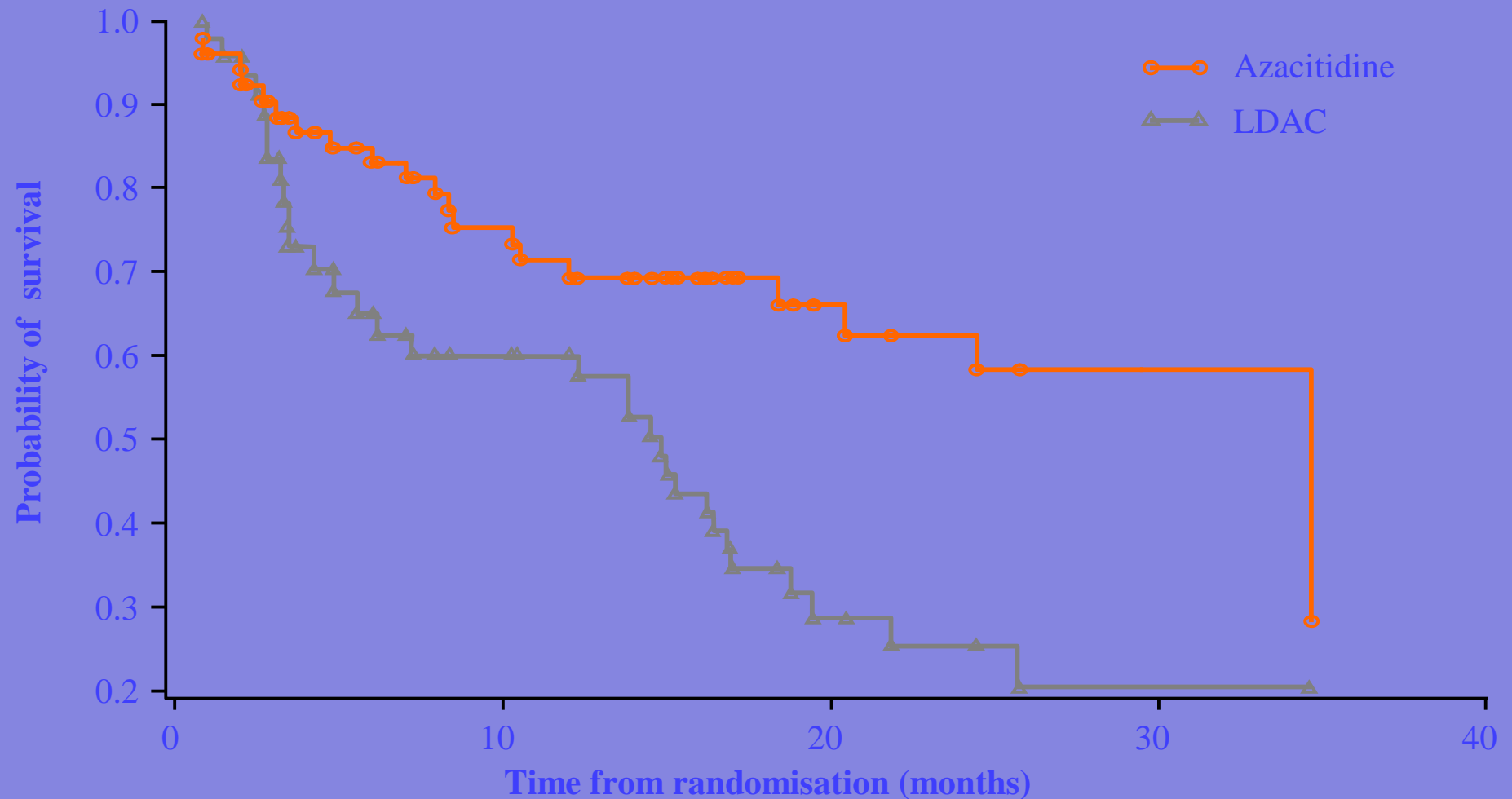
Total - Event / N



Additional Analysis: Median OS by Investigator Selection

Treatment	Differences				
	K-M OS Time mos	K-M OS Time mos	Hazard Ratio	Log-rank P	
AZA (N=117) vs BSC (N=105)	21.1	11.5	9.6	0.56	0.002
AZA (N=45) vs LDAC (N=49)	24.5	15.3	9.2	0.58	0.015
AZA (N=17) vs Stand Chemo (N=25)	25.1	15.7	9.4	0.87	0.75

AZA-001: OS – azacitidine versus LDAC (Brit J Haematol 2009)



AZA 001 trial: azacytidine vs LD AraC ((Brit J Haematol 2009))

	AZA	LD araC	
n	45	49	
Median n° cycles	9	4.5	
Median OS	24.5	15.3	P<0.001
OS fav karyotype	NR	19	HR=0.46
OS unfav karyo	24.5	2.9	HR=0.07
CR+PR	31%	12%	P=0.046
HI	53%	25%	P=0.006
Transf indep	45%	13%	P=0.01
Severe infections/pt year	0.44	1	P=0.017
Median days in hospital/pt year	18	27	P<10 ⁻⁴

Secondary Endpoints

- **Time to AML**
 - 26.1 mos with AZA vs 12.4 with CCR, $p=0.004$
- **RBC Transfusion Independence**
 - 45% with AZA vs 11% with CCR, $p<0.0001$
- **Infections Requiring IV Antimicrobials**
 - Reduced by 33% with AZA vs CCR

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

AZA

N=179

Response

(%)

Overall (CR+PR)

29

CR

17

PR

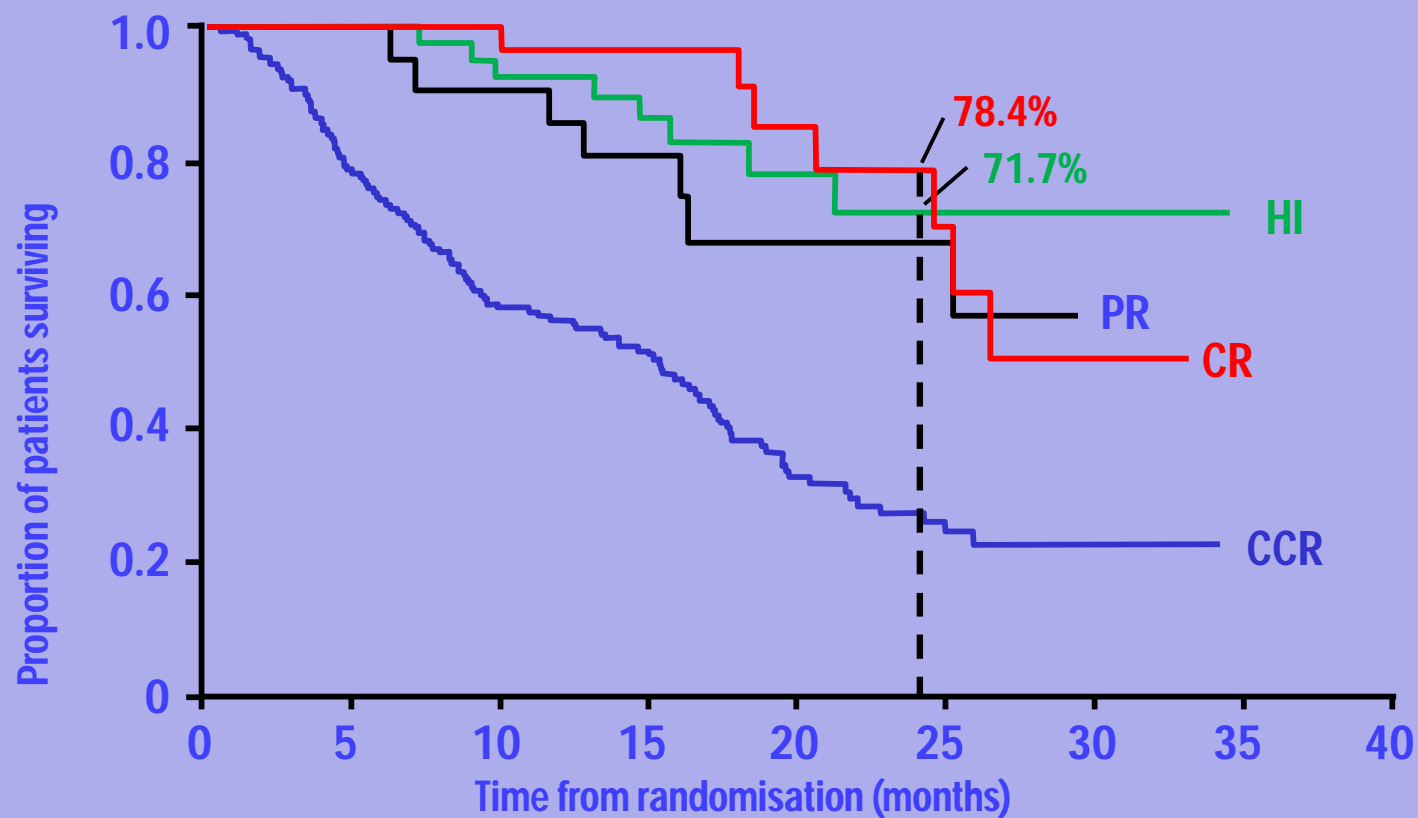
12

IWG HI

Major+Minor

49

AZA-001: 2-year OS with azacitidine by best response (IWG 2000)

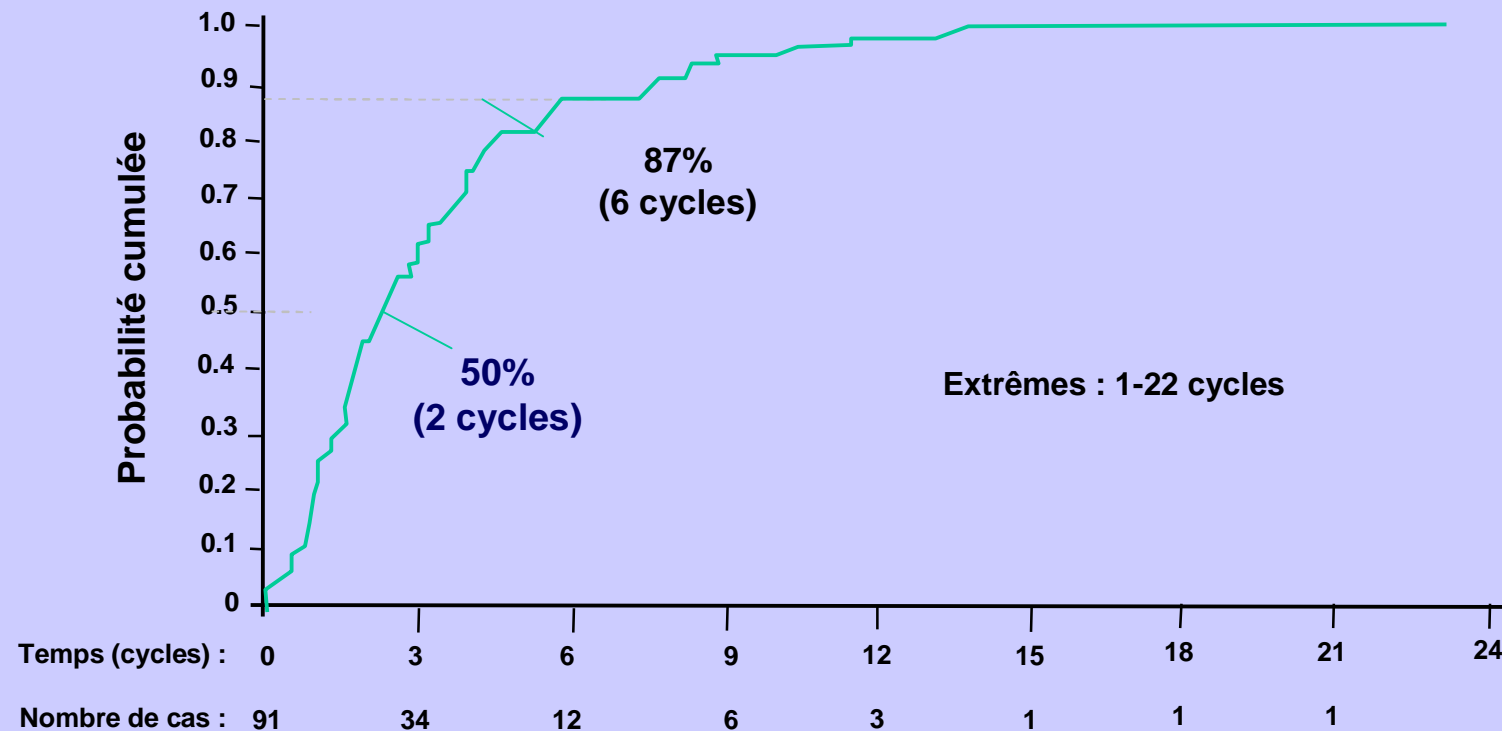


IWG = International Working Group; HI = haematological improvement
PR = partial response; CR = complete response

Adapted from List AF, et al. Oral presentation at
ASCO 2008, Chicago, IL [abstract 7006]

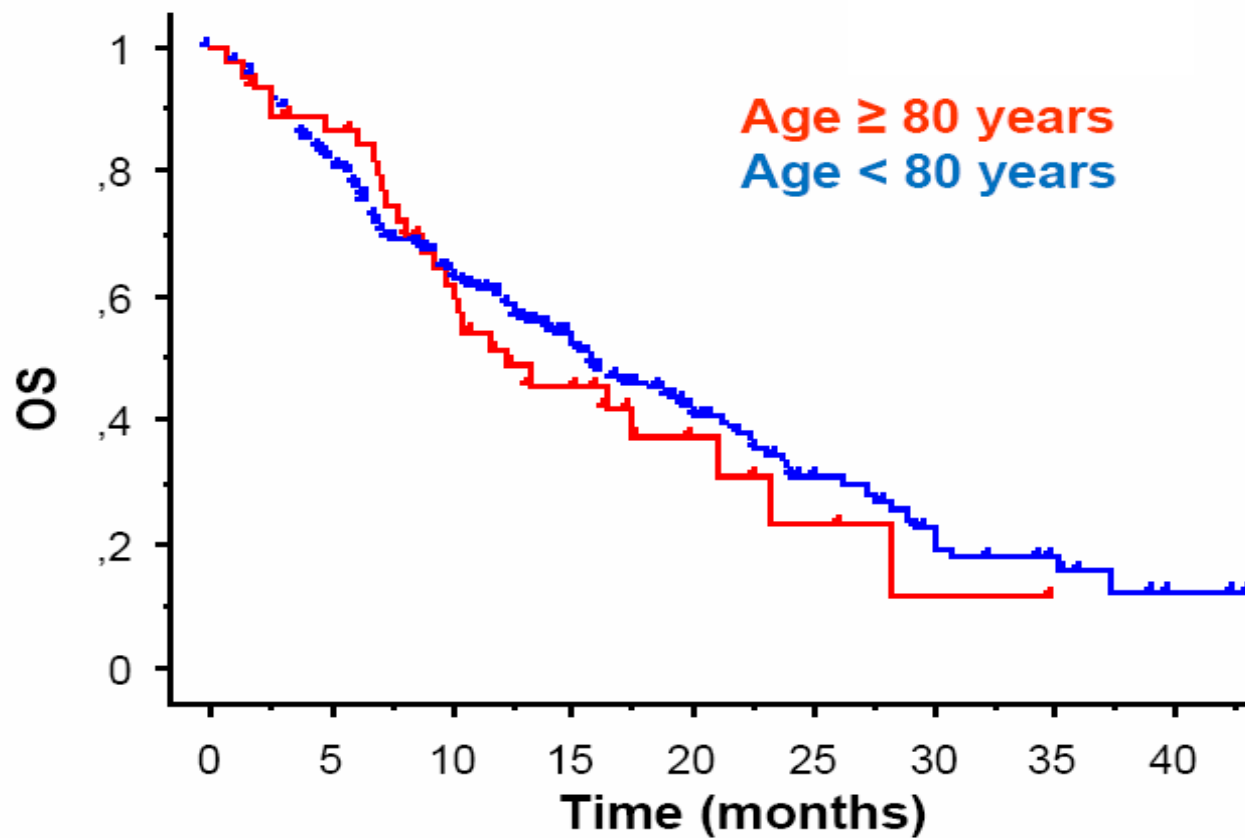
Prolonged treatment with Azacytidine improves responses in MDS

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



French ATU : Survival based on age

OS did not differ from pts <80 years (p=0.6) (Itzykson, Blood, 2011)



Median OS was 12.1 months

1 year-OS was of 50.0%

2-year-OS was of 23.2%

Azacitidine is approved in EU

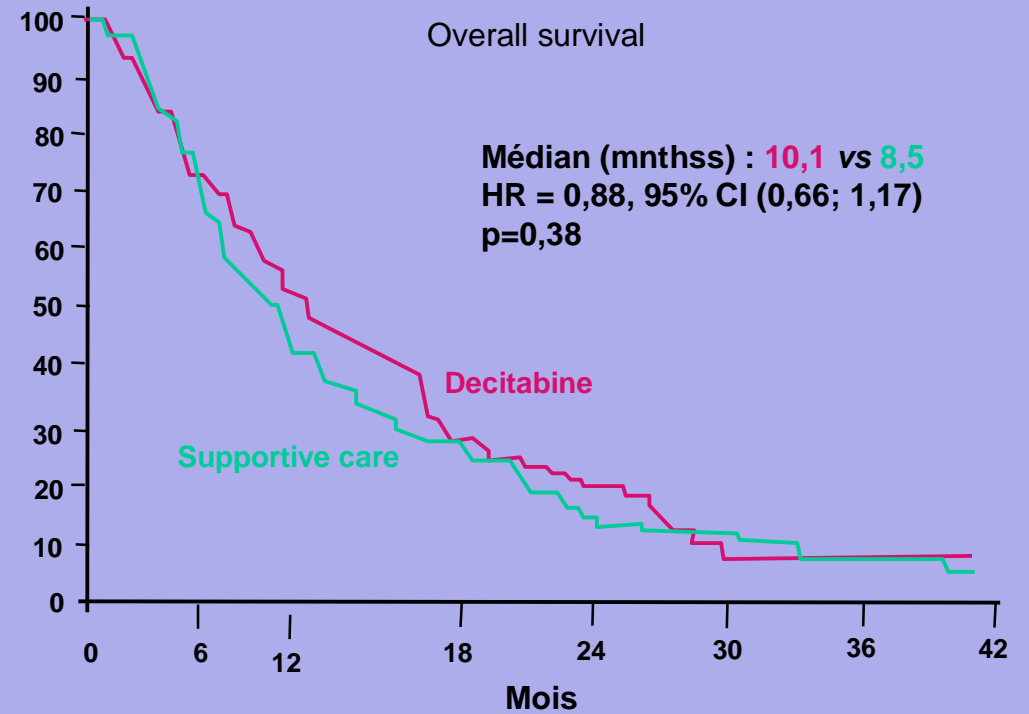
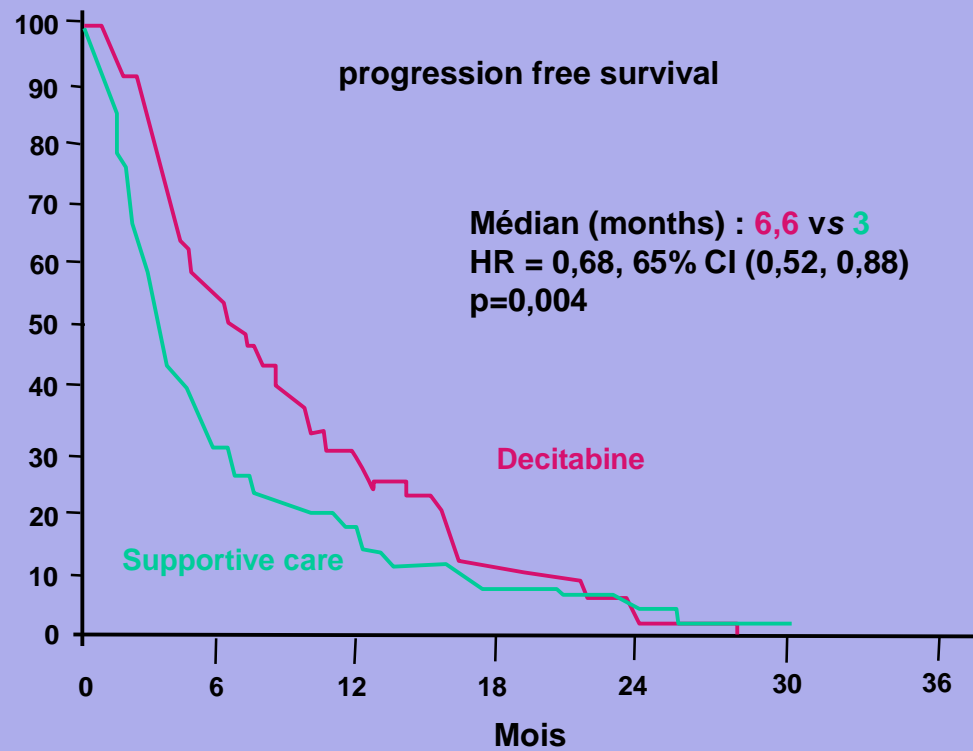
- Azacitidine is indicated for adults who are not eligible for haematopoietic stem cell transplantation with
 - intermediate-2 or high-risk MDS according to the International Prognostic Scoring System
 - AML with 20–30% blasts and multi-lineage dysplasia (WHO classification)
 - CMML with 10–29% marrow blasts without myeloproliferative disorder
- The recommended dosing regimen for azacitidine is 75mg/m² q.d. for 7 days q.28d
- It is recommended that patients are treated for a minimum of 6 cycles
 - treatment should be continued as long as the patient continues to benefit or until disease progression

EORTC Decitabine Phase III study

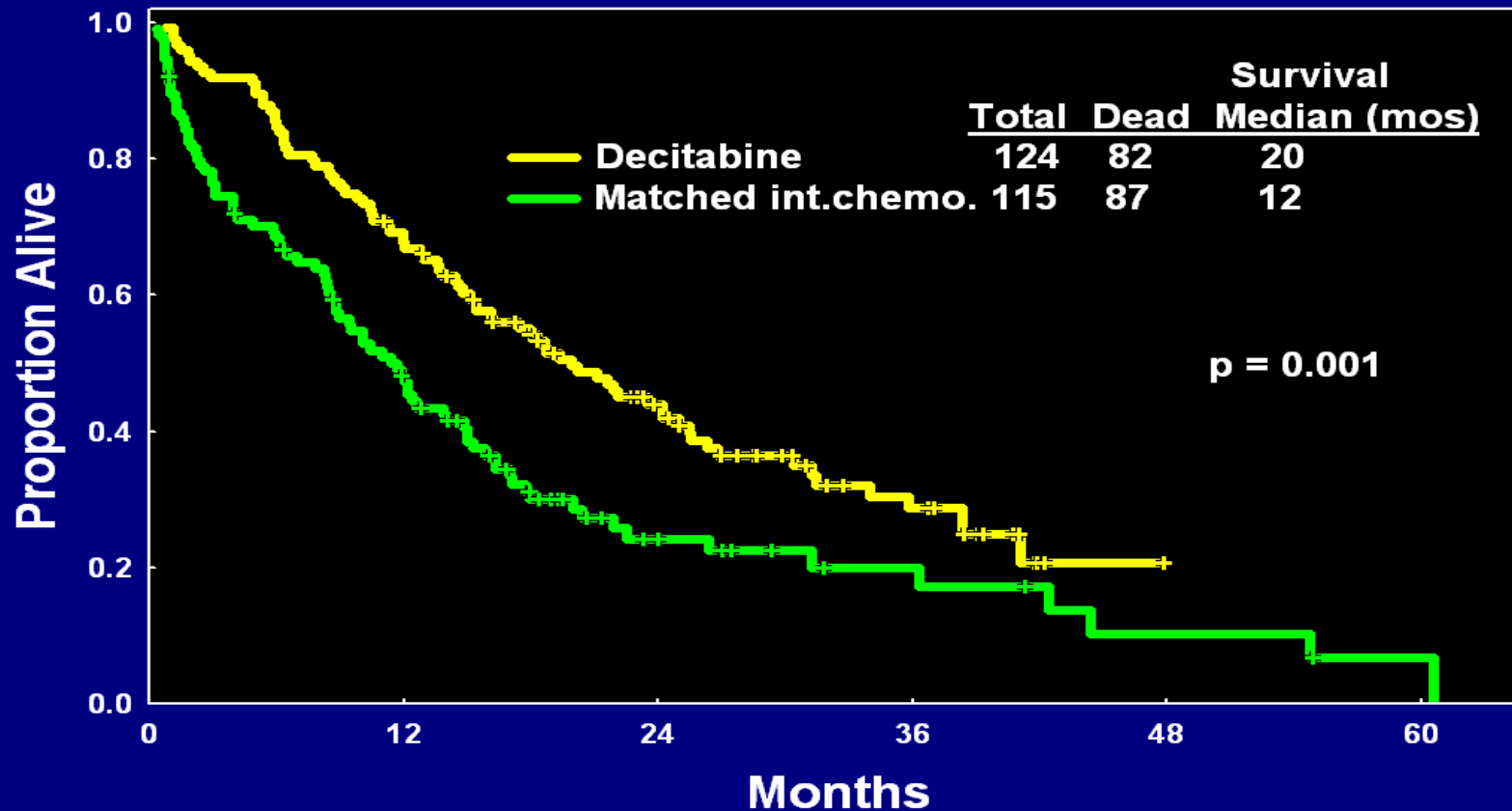
(Wijermans et al, ASH 2008 n° 228)

**“Low-dose intravenous decitabine vs best
supportive care in MDS with
11–30% blasts”**

Improvement in progression free survival, but not survival



Survival with Decitabine vs. Intensive Chemotherapy in Higher Risk MDS (Matched Group)



Kantarjian et al. Cancer (2007) 109 : 1133-1137

Traitement symptomatique et hypométhylants

- **Transfusion CGR et CP pendant les premiers cycles**
- **+++ prévention et traitement des infections (levofloxacine- Posaconazole)**
- **Effets secondaires locaux d'azacitidine**

Perspectives with hypomethylating agents

- **Alternative schedules**
- **As maintenance treatment after chemotherapy (or allo SCT)**
- **Prior to allogeneic SCT**
- **In combination to other agents (mainly HDACi)**
- **In other situations**
 - **CMML**
 - **MDS and AML post MPD**
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 - **In lower risk MDS**

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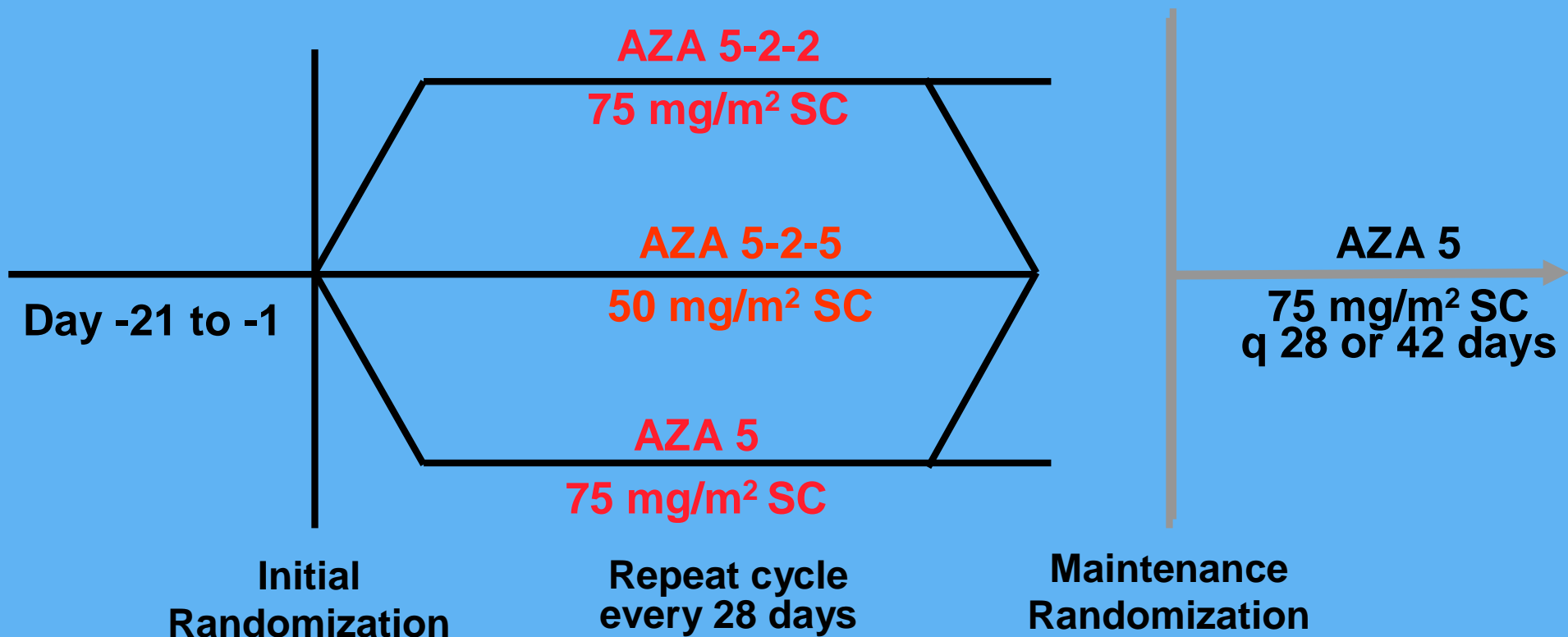
Alternative regimens of AZA

(Lyons ,JCO, 2009)

Phase II, prospective, multicenter,
randomized, open-label, 3-arm trial

Screening

Cycle 1-6



Intensified regimen of Azacitidine in higher MDS patients (L Ades)

- AZA 75 mg/m²/d 5 days every second week

Phase I d'administration prolongée d'Azacitidine orale

- **Phase I antérieure** : 1^{er} cycle administré en sous-cutané, puis escalade de dose jusqu'à 480mg/j 7j/cycle (DMT) : bonne tolérance, activité clinique Garcia-Manero, ASH 2009
- Nouvelle Phase I oligocentrique
- **Objectif** : explorer des schémas d'administration prolongée pour induire une hypométhylation continue
- Inclusion
 - SMD, LMMC, LAM non éligibles à d'autres traitements
 - Hb < 9 g/dL et/ou Plaquettes < 50 G/L
 - Naïfs d'agents hypométhylants
- Escalade de dose
 - 200 mg x2/jour 14 ou 21 jours
 - 300 mg x1/jour 14 ou 21 jours
- Correspond à 36-58% de l'exposition du schéma SC

PK. Garcia-Manero *et al.*, ASH 2010 # 603

Phase I d'administration prolongée d'Azacitidine orale

- 6 patients par cohorte (total 24 patients)
- Médiane 4-6 cycles
- Effets secondaires grade 3/4
 - Nausées/vomissements grade 3 : **1/24**
 - Fatigue grade 3 : **1/24**
- Dose maximale tolérée non atteinte
- Réponse pour les 15 SMD
 - Taux de réponse global **67% dont 2/15 RC et 7/10 indépendance transfusionnelle**
- Réponses non évaluées dans LAM

PK. Garcia-Manero *et al.*, ASH 2010 # 603

Alternative protocols of decitabine?

Decitabine 20mg/m²/jx5 IV

Dose (4 w cycles)	Nb CR(IWG 2006) /Total (%)
20 mg/m ² /j x 5 d IV	33 (39)*
10 mg/m ² x2/j x 5 dSC	3 (21)
10 mg/m ² /j x 10 d IV	4 (24)

* Statistically significant

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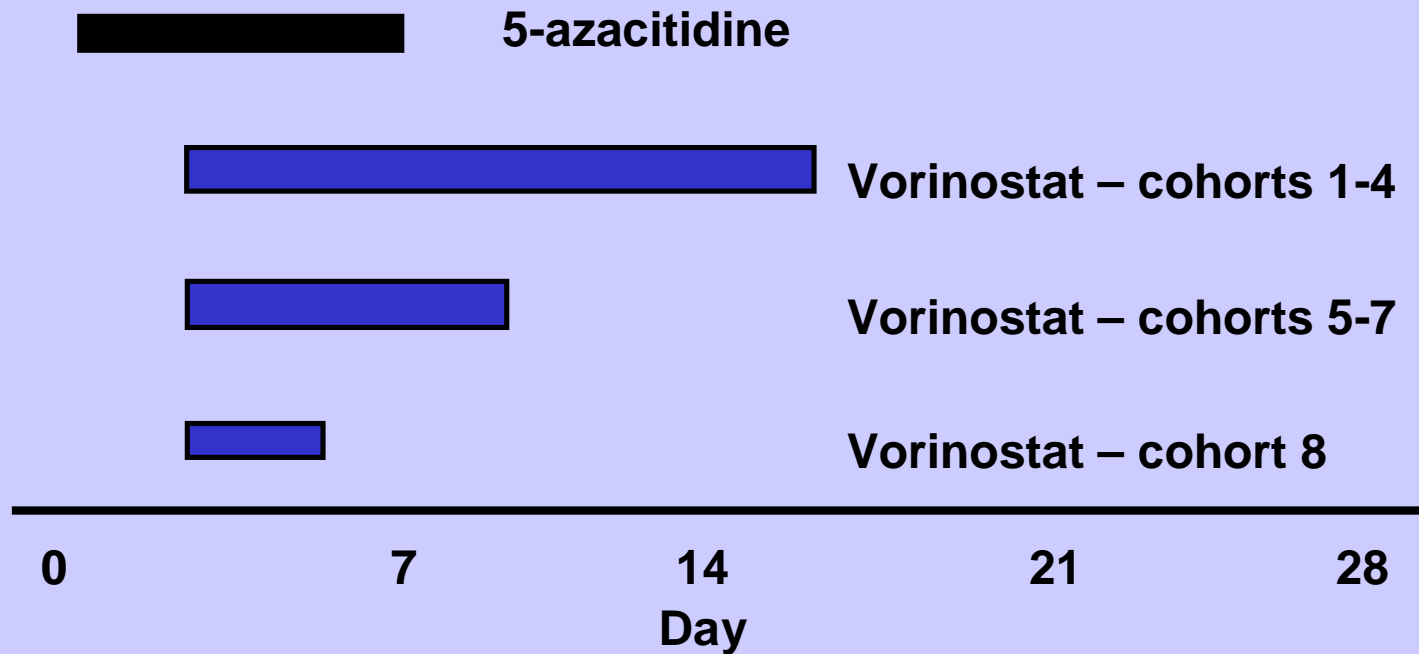
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Histone deacetylase (HDAC) inhibitors

Short-chain fatty acids (SCFA)	Butyrate derivatives, Valproic acid
Hydroxamic acids	Trichostatin A , Vorinostat , Pyroxamide, LAQ824, LBH 589
Epoxyketone-containing cyclic tetrapeptides	Trapoxins
Non-epoxyketone-containing cyclic tetrapeptides	FK228, Apicidin
Benzamides	MGCD-0103, MS-275 , CI-994

A Phase I/II study of vorinostat in combination with 5-azacitidine in patients with MDS



This represents 1 cycle. Cycles repeated every 28 days for a minimum of 4 cycles

Silverman et al. J Clin Oncol 26: 2008 (May 20 Suppl; abs 7000)

Azacitidine and Vorinostat in MDS / AML – NYCC 6898

Response

Enrolled	28
Evaluable for response	22
Overall Response*	18 (82%)+
CR	9 (41%)
CRi	3 (14%)
CR+CRi	12 (55%)
PR	5 (05%)
HI	5 (23%)
Stable	2 (09%)
NR	2 (09%)
Too Early	1
IE for response	3
Withdrew prior to Rx/Ineligible	2
Transfusion Independence (n = 13)	11 (84%)

*IWG 2000 MDS
 IWG 2006 MDS
 IWG AML

+Response Confirmed
 by NCI Audit

Decitabine With or Without Valproic Acid in Patients With MDS and AML

Eligibility criteria:

- MDS by FAB of any age
- AML age > 60
- No good-risk AML
- No prior high-dose chemotherapy
- No prior decitabine > 1 cycle or azacitidine > 2 cycles

R
A
N
D
O
M
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E

Decitabine 20 mg/m² IV/1 h daily days 1-5 q 4 weeks

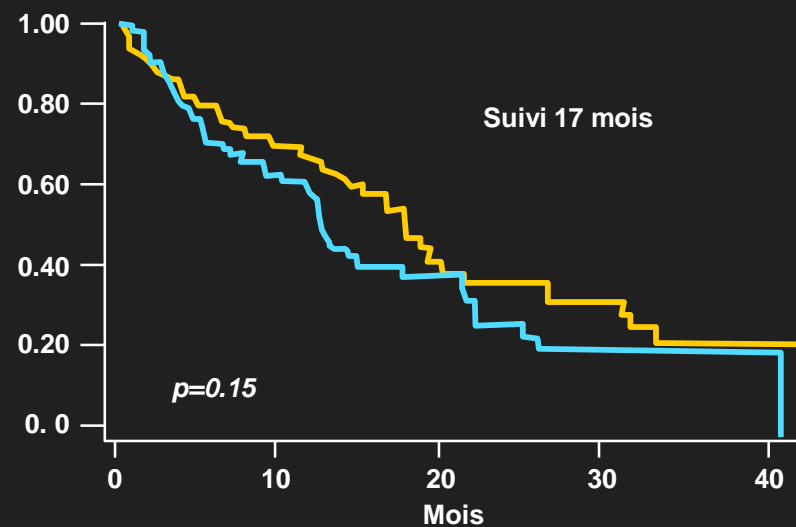
**Decitabine 20 mg/m² IV/1 h daily days 1-5 q 4 weeks
Valproic acid 50 mg/kg/day p.o. days 1-7 q 4 weeks**

Ensayo fase II de AZA ± Entinostat

Respuesta (IWG 2000)

	Bras A AZA seule	Bras B AZA + Entinostat
RC	12%	7%
RP	9%	7%
HI (3 lineas)	10%	10%
HI (1 o 2 lineas)	12%	19%
Ausencia de respuesta	57%	56%

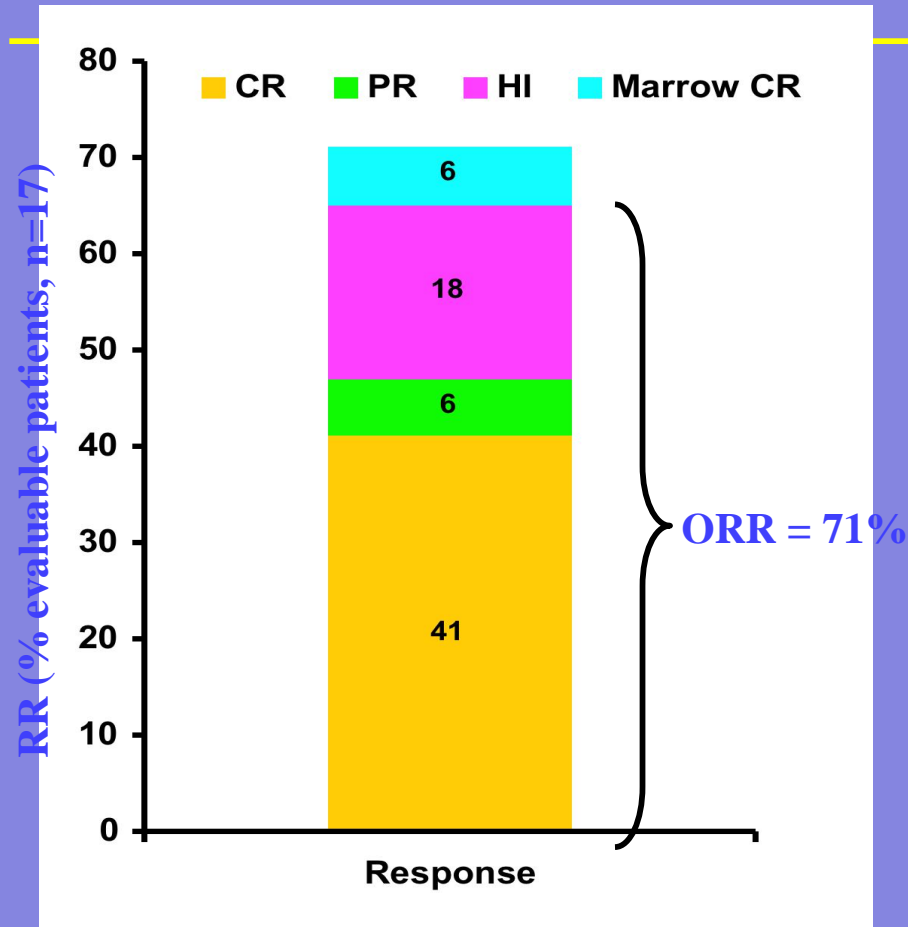
Supervivencia Global



Traitement	Total	Décès	Censure	Médiane SG (mois)
Azacitidine	68	40	28	17.7
Azacitidine+Entinostat	68	47	21	12.8

T. Prebet *et al.*, ASH 2010, # 601 & # 4013

Azacitidine plus lenalidomide in patients with higher-risk MDS: efficacy



Cohort	Grade 3–4 toxicity	Maximum response
1	1	2 CR, 1 progression
2	2	1 CR, 1 PR, 1 HI
3	0	2 CR, 1 SD
4	2	2 CR, 1 SD
5	2	1 HI, 1 SD, 1 progression
6	2	1 HI, 1 BM CR, 1 not evaluable

- These early results suggest superior efficacy versus monotherapy in patients with higher-risk MDS

RR = response rate; ORR = overall RR; SD = stable disease

Sekeres MA, et al. Oral presentation at ASH 2008
Blood 2008;112:[abstract 221]

« Pick a winner approach » with AZA



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Agents hypométhylants dans les LMMC : Résultats du GFM



- **Etude de Phase II de décitabine :**

- LMMC «défavorables» (GB < 13 G/L : IPSS int-2/élevé ; GB > 13 G/L : critères de gravité selon Wattel *et al. Blood* 1996)

- Décitabine 20 mg/m²/J 5 jours/28 jours au moins 3 cycles

- 41 patients inclus, 39 évaluable (médiane 9 cycles)

- **Taux de réponse globale : 39%**

- (RC : 10%, RP : 0%, réponse médullaire : 21%, HI : 8%)

- **Survie globale à 2 ans : 60%** (contre médiane de survie à 20 mois avec HU dans l'essai Wattel *Blood* 1996)

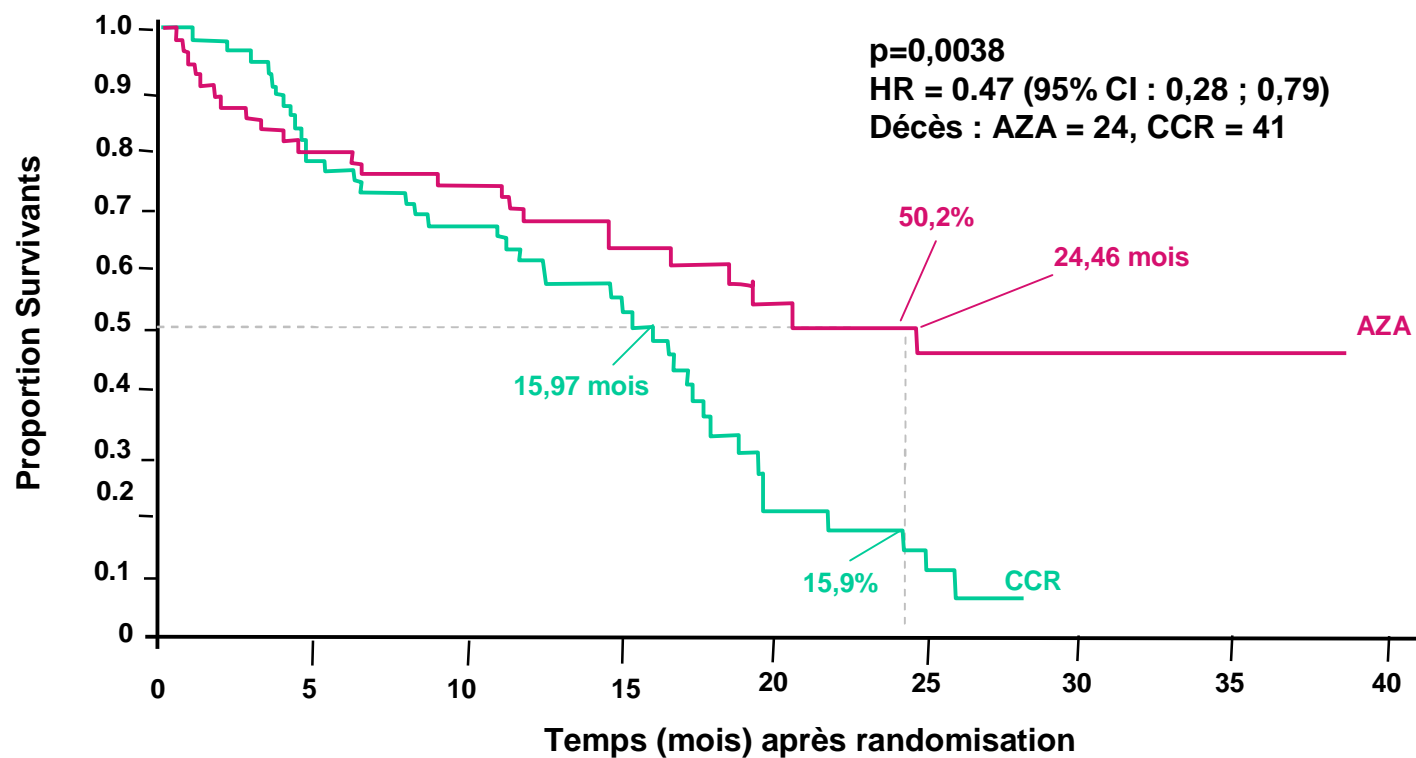
- expression faible de c-jun et cmyb associées à une meilleure survie

T. Braun *et al.*, *Blood*, 2010 -

AZA in MDS/AML post MPD (S Thépot, Blood, 2101)

- **53 patients with MDS or AML post myeloproliferative disorder**
- **52% responses, with reversal to features of MPD (polycythemia, thrombocythemia)in 40% of responses**

Azacytidine in patients with 20 to 30% blasts (JCO, in press)



at risk

AZA as first line treatment in AML (S Thépot, ASH 2009)



Groupe
Francophone des
Myélodysplasies

- N=138 patients, median age 73
- ATU program
- Factors associated with better survival
 - non complex karyotype
 - WBC <10 G/l
 - But not % marrow blasts

PRESENTED AT ASH 2009

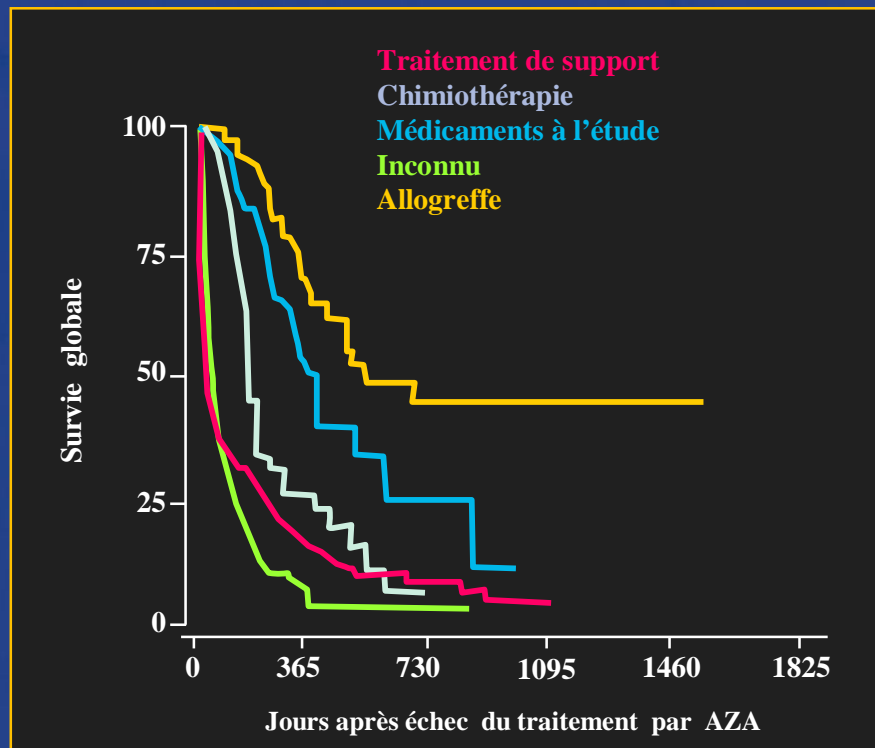
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Le pronostic des SMD et LAM secondaires après l'échec du traitement par Azacitidine est très défavorable



Survie globale selon le traitement reçu après l'échec de l'Azacitidine (n=350)



Type de soins	N =	ORR	OS médiane (mois)
Inconnu	215	NA	3.6
Soins de support	160	NA	3.3
Chimiothérapie	84	1/25 et 5/33	7.6
Médicaments à l'étude	56	4/39	13.2
Allogreffe	50	17/25	18.3

*
**

T. Prébet *et al.*, JCO, 2011

Traitement de seconde ligne dans les SMD de haut risque

- Clofarabine faible dose (C Gardin, T Braun)
- Erlotinib (S Boehrer)
- On 01910. Na (Onconova)

Higher risk MDS with del 5q

- Higher risk MDS (or AML) with del 5q based on increased marrow blast % and/or cytogenetic abn in addition to del 5q

- Complex karyotypes in MDS: 40% have del 5q, associated with very poor prognosis

(Giagounidis, Leukemia, 2005; Haase, Blood, 2008)

Treatment of higher risk MDS with complex karyotypes including del 5q: GFM experience

- Intensive chemotherapy alone : <20% CR
(Gardin, Blood 2007)
- Azacytidine alone :
 - median survival 11 months in AZA 001 study
 - 17% responses (Itzykson, ASH 2008)

LENALIDOMIDE ALONE IN HIGHER RISK MDS WITH DEL

5q

(Ades L, Blood , 2009)

- **N=47**
- Overall Response rate : 28%
- **Hematological response**
 - 7 RC
 - 2 mCR
 - 4 HI-E
- **Cytogenetic response : :4 complete, 3 partial**
- **Median CR duration 11.5 m**

Prognostic factors of CR achievement

		n	CR	%
cytogenetic s	isolated del 5q	9	6	67%
	Single additional abn	11	1	9%
	>1	27	0	0%



Treatment of higher risk MDS (and AML) with complex karyotypes including del 5q: GFM perspectives (L Ades)

- Patients « fit » for intensive chemotherapy: **DNR+ AraC+ REV**

Presented at ASH 2010

- Patients « unfit » for intensive chemotherapy: **AZA+ REV**



Groupe Francophone des Myélodysplasies



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