Prise en Charge des LAM

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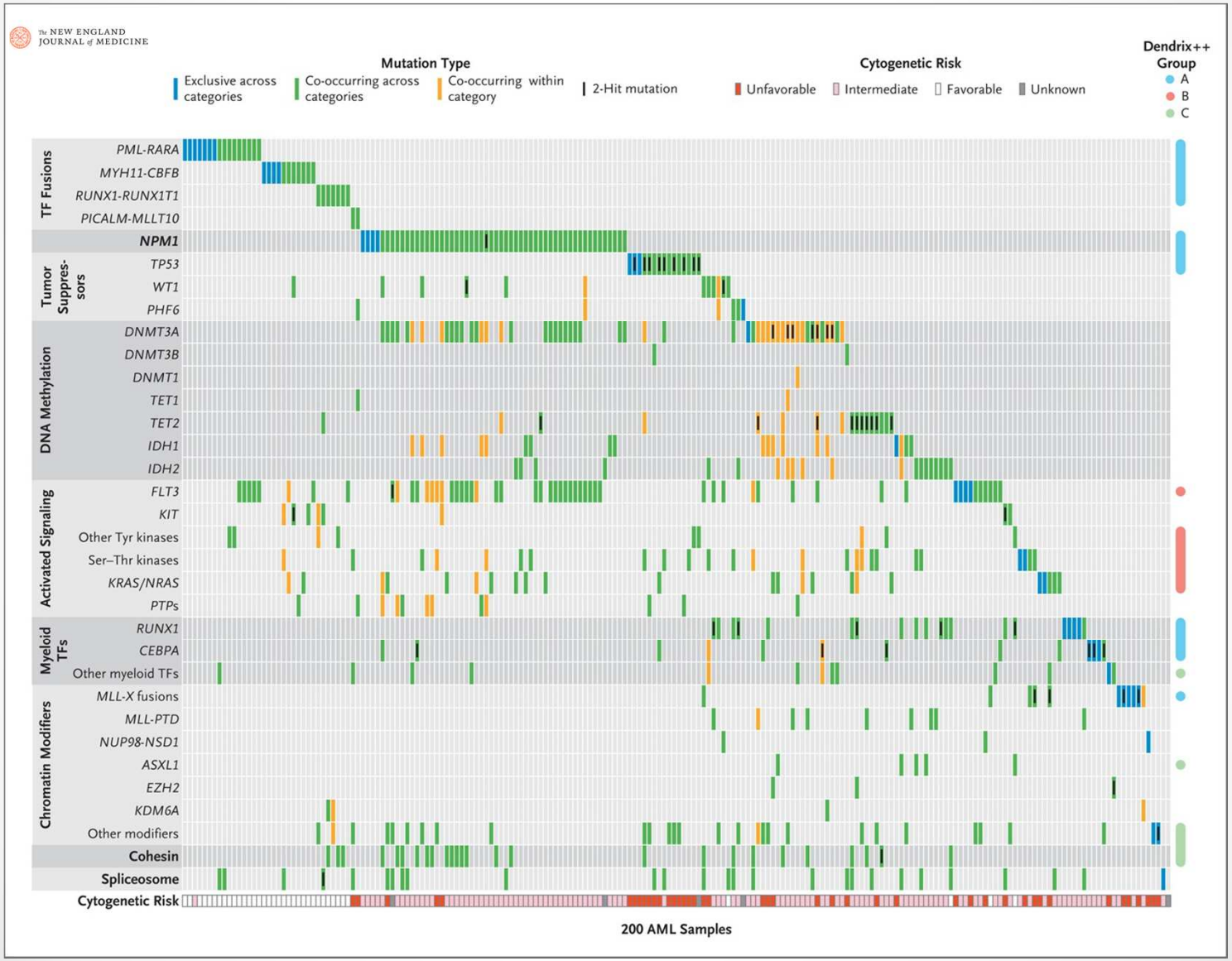
Inventaire 2013



The Cancer Genome Atlas Research Network. N Engl J Med 2013;368:2059-2074

Et toujours le même traitement …

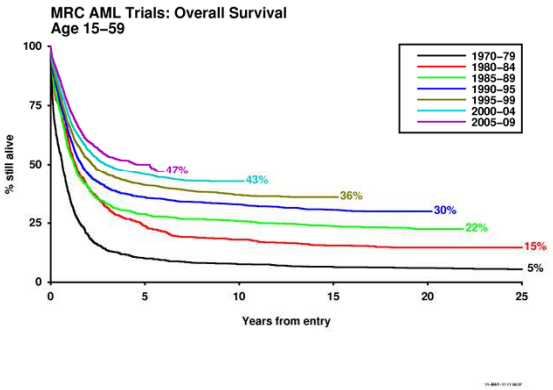
Actualités

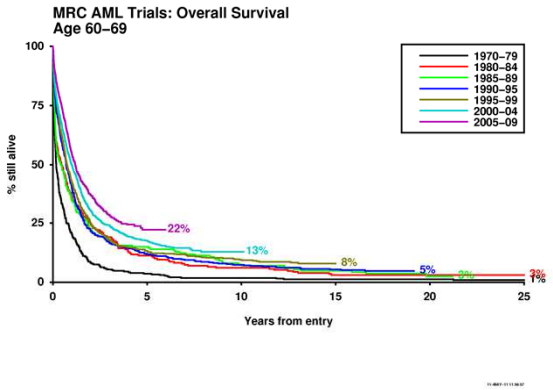
- Intensification des doses de chimiothérapie
- Nouvelles approches de greffe allogénique et d'immunothérapie
- Promesses de traitements ciblés…

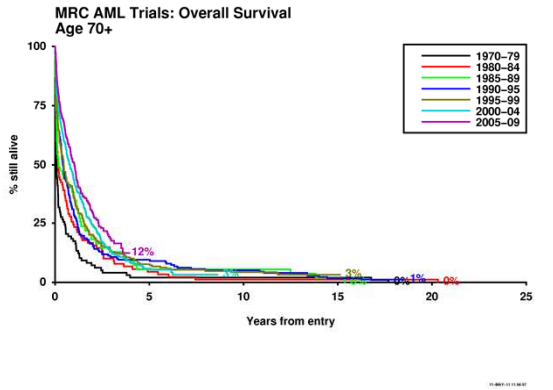
Intensification des doses

- Réservée aux patients capable de le tolérer
- Le traitement doit être considéré dans son ensemble (induction + consolidations)
- L'intensification des doses pourrait ne bénéficier qu'aux groupes de risque suffisamment favorables

Effet de l'âge





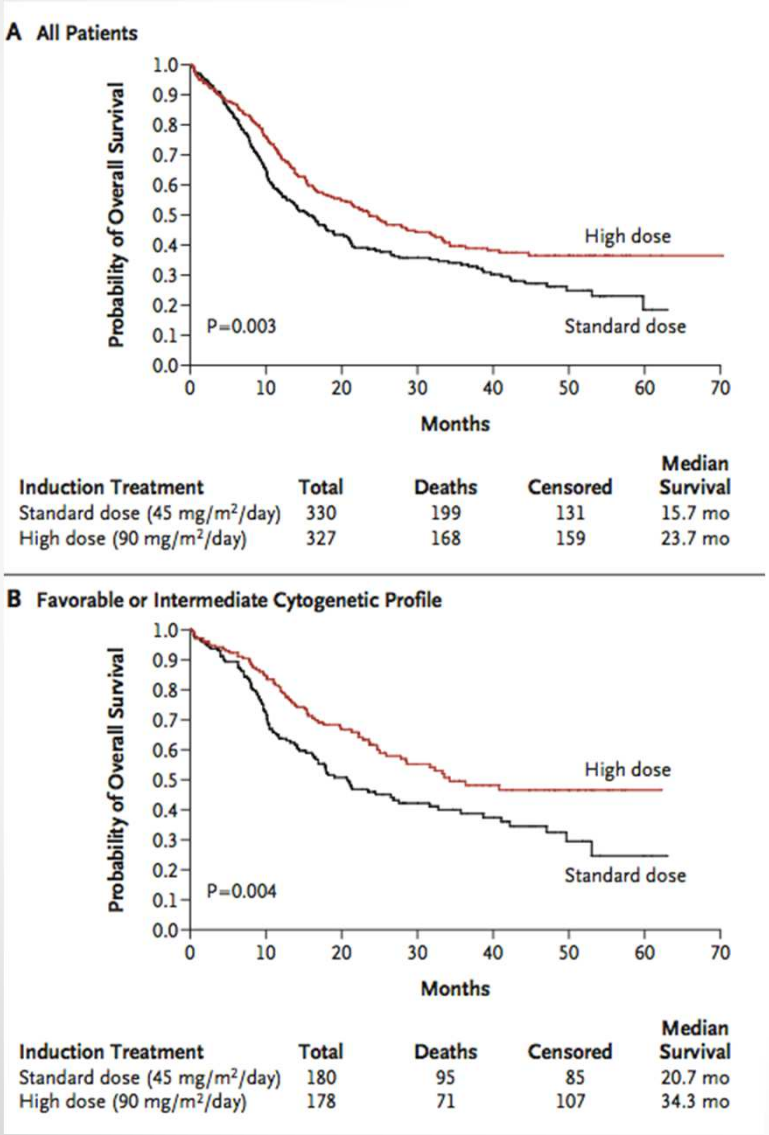


- *Doses sub-optimales*
- **Fond génétique différent**

Adultes jeunes

- *Essais ayant démontré un avantage significatif en survie, et pas seulement dans des sous-groupes de patients.*
  - **HD-DNR en induction**
    - *ECOG-1900 (Fernandez et al. NEJM 2009)*
  - **HD-AraC en consolidation**
    - *CALGB (Mayer et al. NEJM 1994)*
  - **ATRA**
    - *AMLSG 07-04 (Schlenk et al. ASH 2011 #80)*

HD-DNR – 90 mg



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo

Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	180	95	85	20.7 mo
High dose (90 mg/m²/day)	178	71	107	34.3 mo

- ECOG trial.
- 657 patients aged 60 years or less (median, 48 years).
- Primary or therapy-related AML.

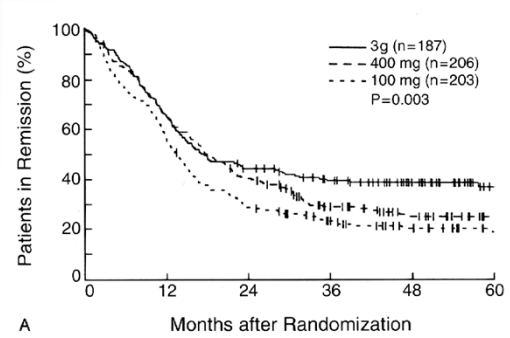
- *Dauno 90mg vs Dauno 45mg*
- Autologous or allogeneic HSCT, according to AML risk.

- Higher CR rate.
- No delayed hematopietic recovery.
- Prolonged OS.
- No benefit in adverse-risk AML.
- No benefit over 50 years of age.
- No benefit in *FLT3* or *MLL* ITD

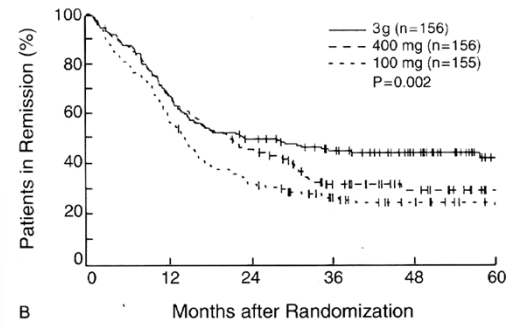
HF. Fernandez et al. N Engl J Med 2009;361:1249-59.

HD-AraC – 3g

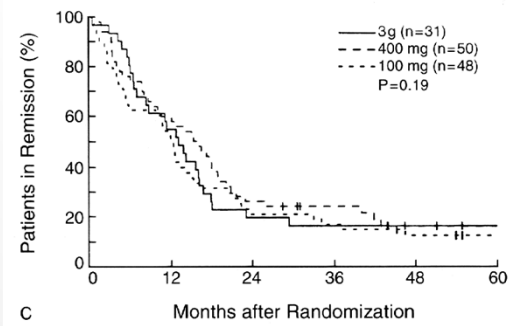
All patients



Age ≤ 60y



Age > 60y



- CALGB trial.
- 657 CR1 patients aged 16 years or more.

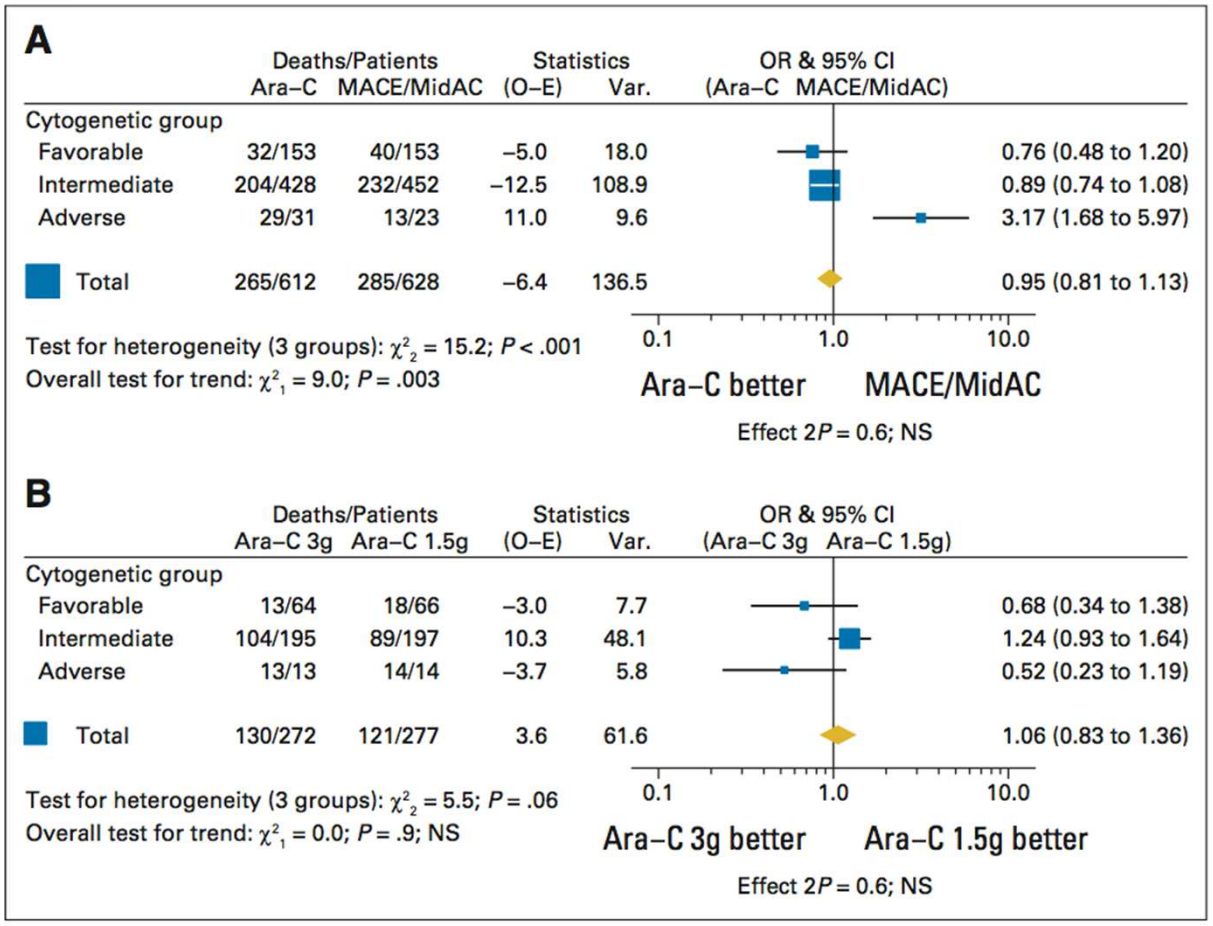
- *AraC:*
  - *100 mg/sqm CIV for 5d*
  - *400 mg/sqm CIV for 5d*
  - *3 g/sqm/12h D1/3/5*

- Prolonged DFS and OS
  - Coming from patients aged ≤ 60y

RJ. Mayer et al., NEJM 1994

HD-AraC
MRC AML15

- MACE/MidAC *versus* AraC 3g *versus* AraC 1.5g



5-year OS:

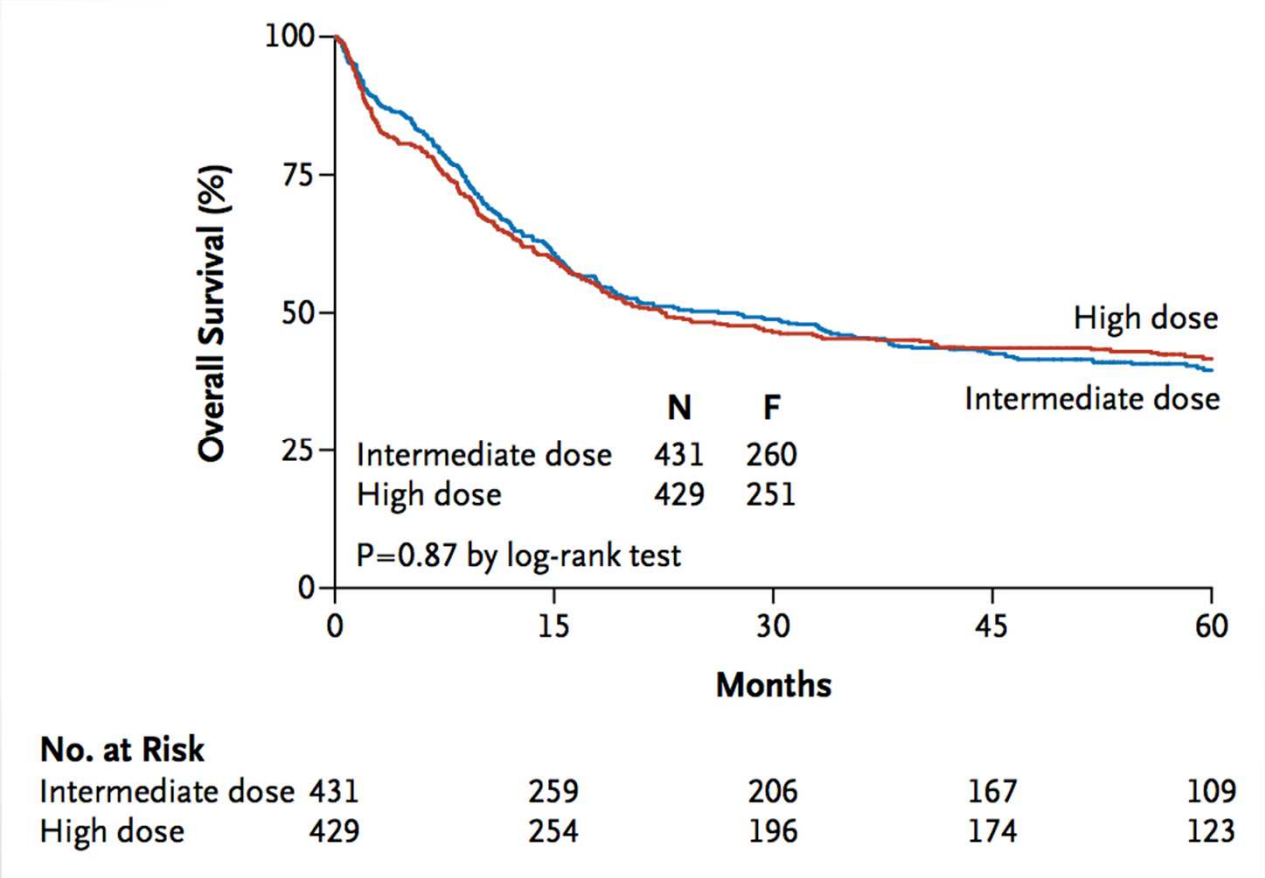
54% vs 52%

52% vs 54%

Burnett et al. JCO 2013

HD-AraC
HOVON-SAKK 42

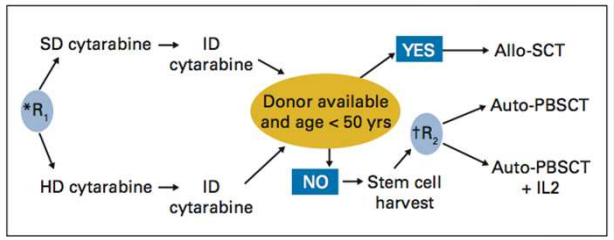
- Intermediate: 200 mg x 7 ➔ 1000 mg/12h x 6d
- High: 1000 mg/12h x 5d ➔ 2000 mg/12h x 4d (1/2/4/6)



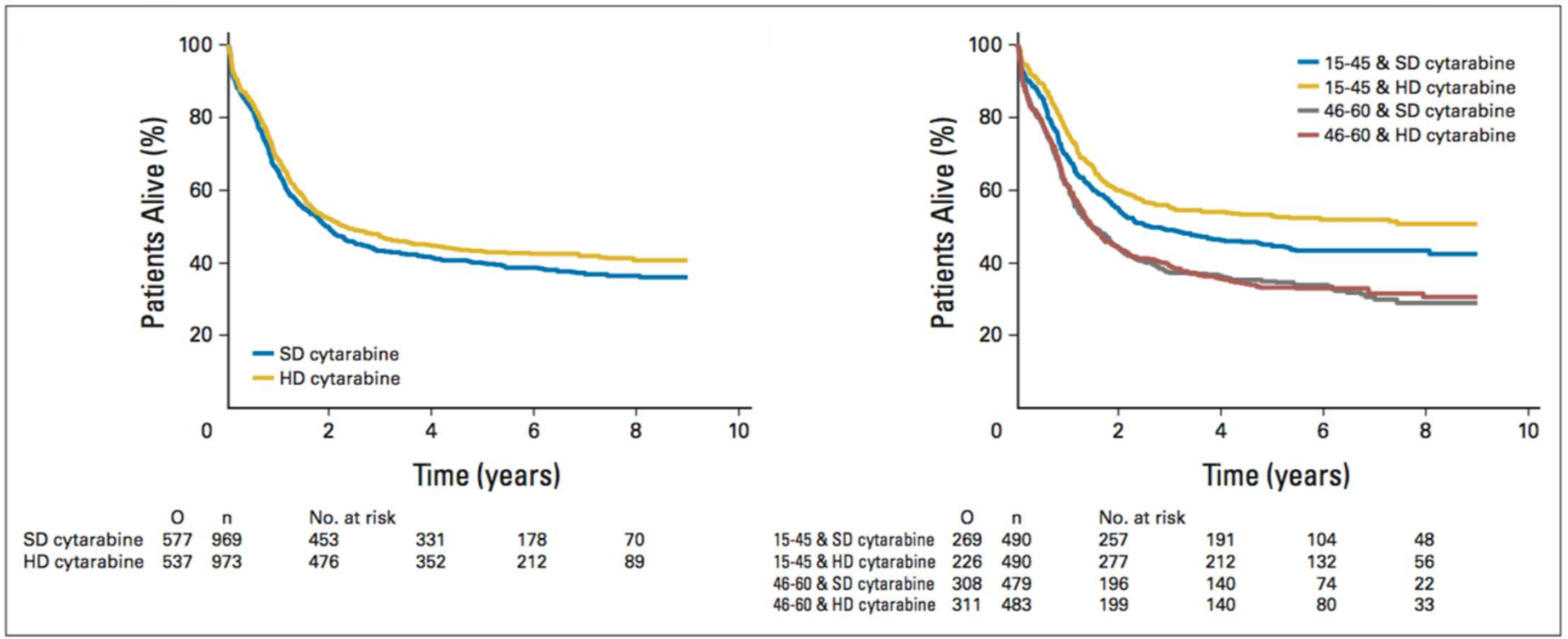
Löwenberg et al. NEJM 2011

HD-AraC
EORTC-GIMEMA AML-12

- SD: 100 mg x 10 ➔ 500 mg/12h x 6d
- HD: 3000 mg/12h x 4d (1/3/5/7) ➔ 500 mg/12h x 6d

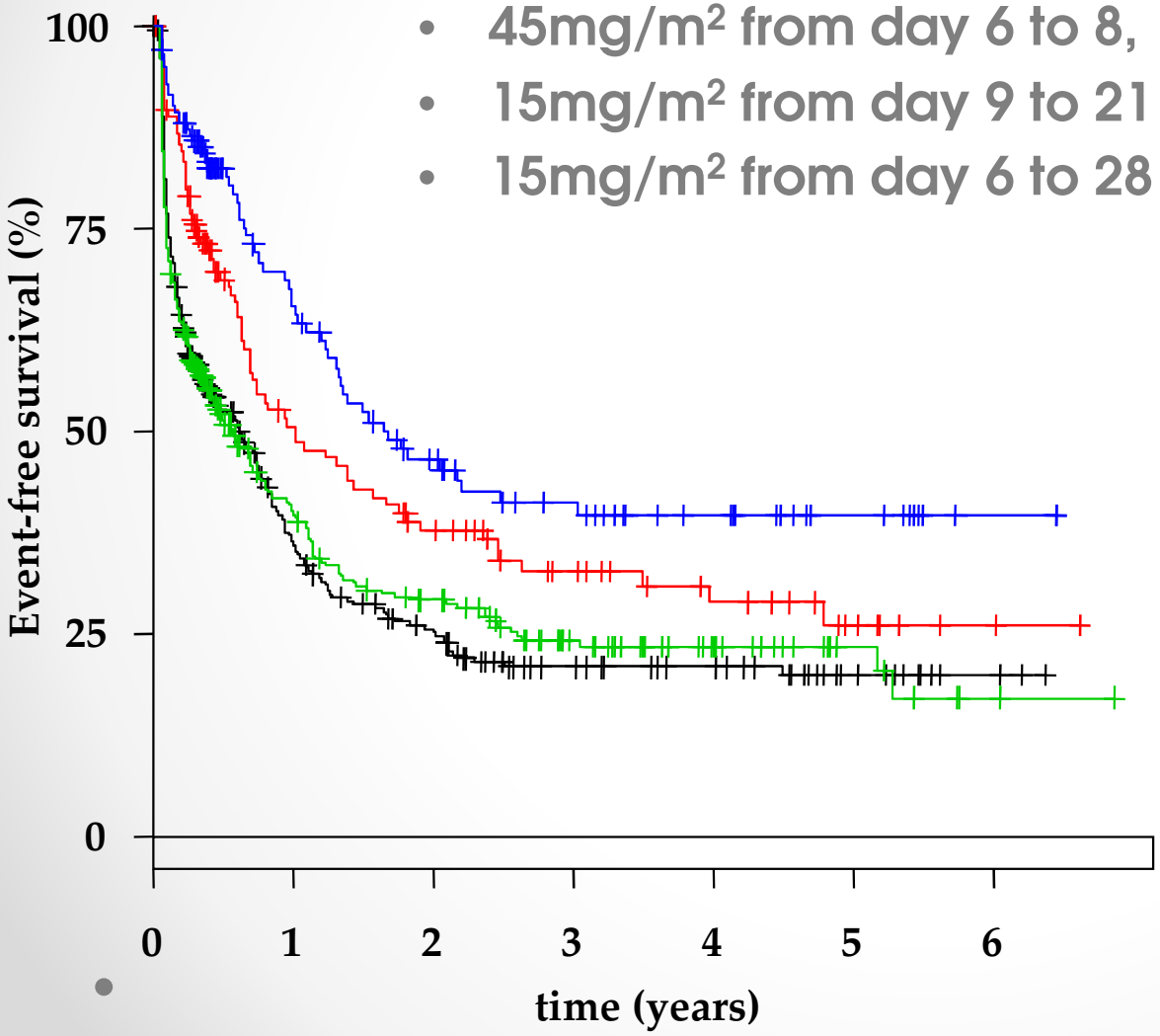


Willemze et al. JCO 2014



ATRA
AMLSG 07-04

- 45mg/m² from day 6 to 8,
- 15mg/m² from day 9 to 21
- 15mg/m² from day 6 to 28 during HiDAC cycles .



NPM1-mut ATRA n=143

p=0.03

NPM1-mut n=146

NPM1-wt n=370

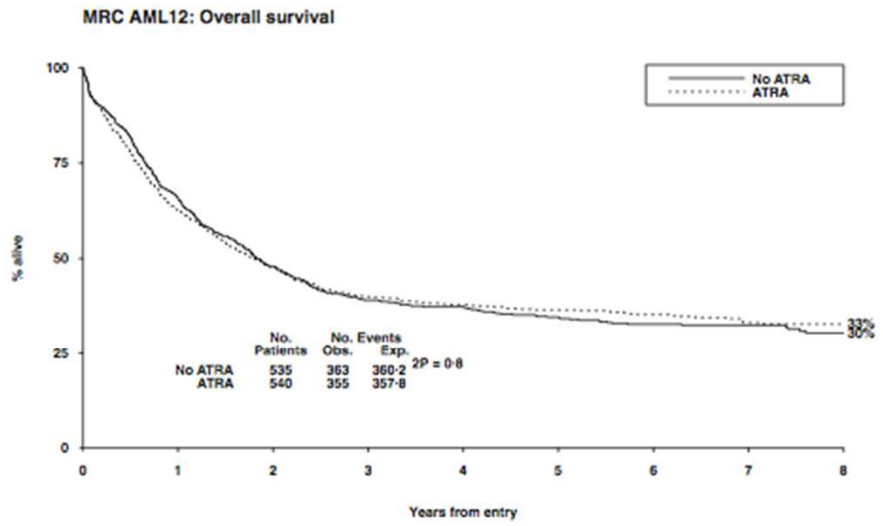
p=0.78

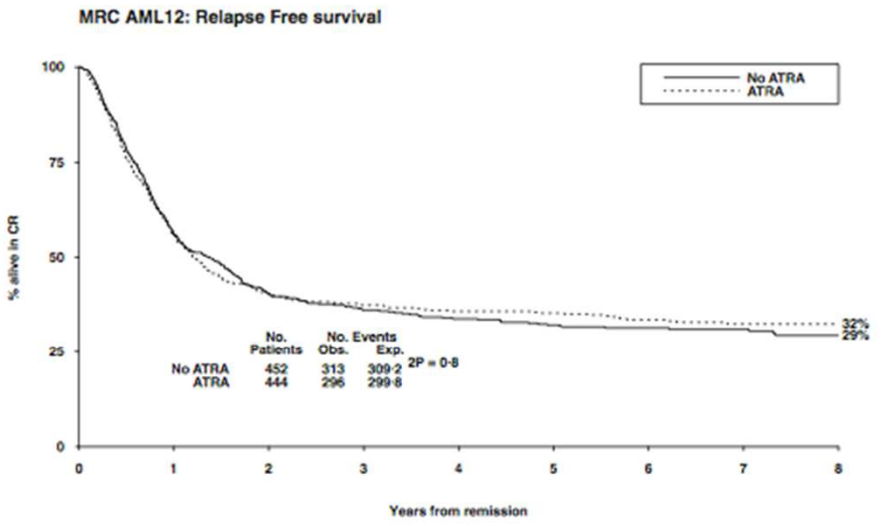
NPM1-wt ATRA n=359

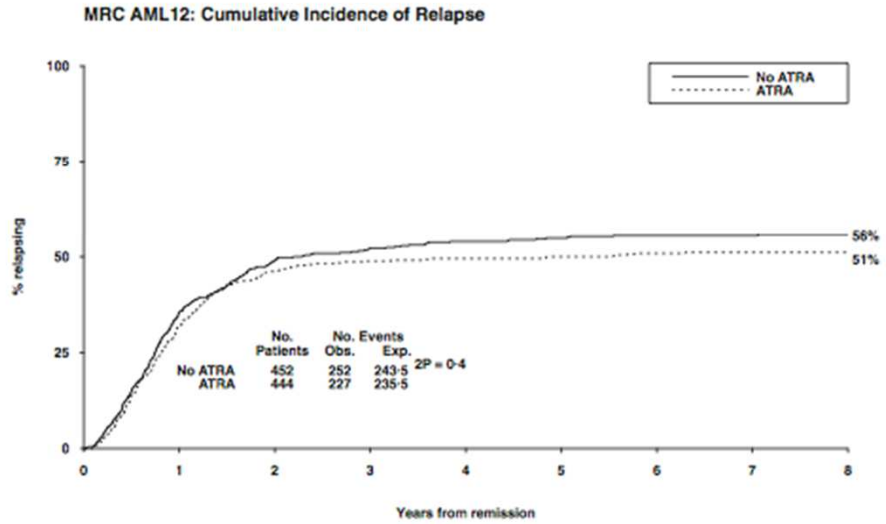
Schlenk et al. ASH 20111

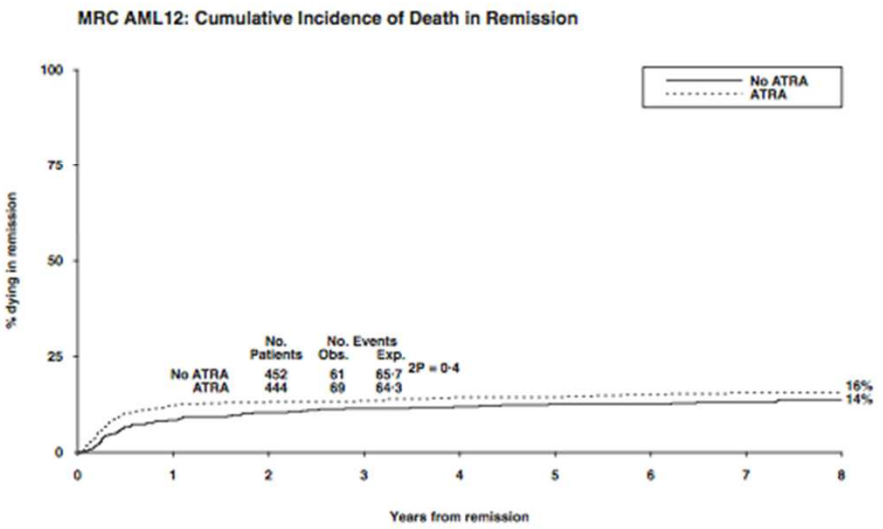
ATRA
MRC AML12

Burnett et al. Blood 2010

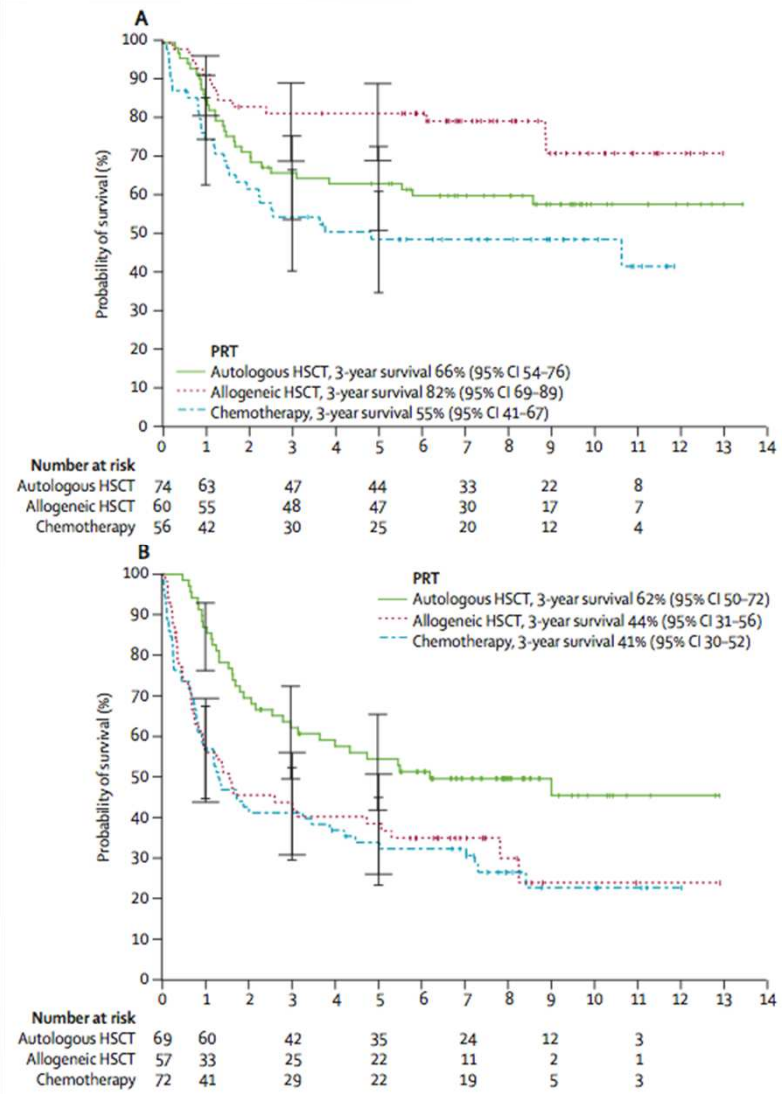








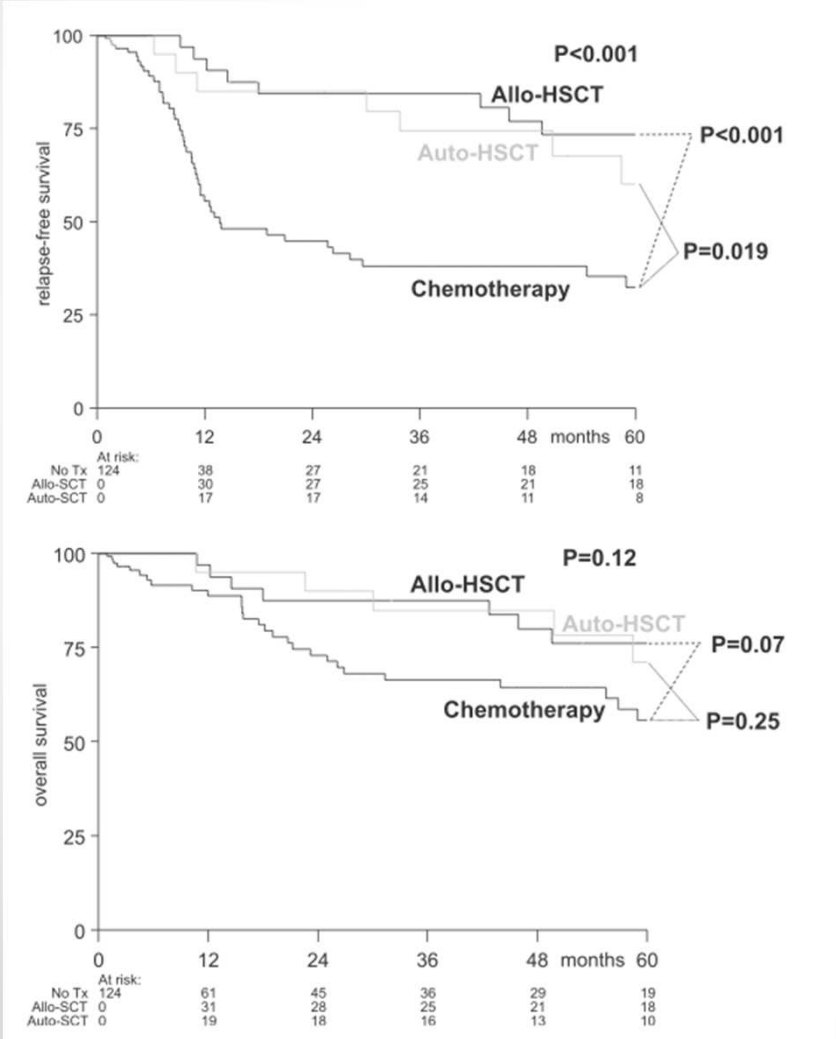
Autogreffe
SAL AML96



- 586 patients 15-60y (*RUNX1-RUNXT1* excluded)
- PRT score:
  - Age, CD34+ blasts %, *FLT3-ITD* ratio, cytogenetics, and secondary AML
  - Validated in the more recent AML2003 trial.
- Treatment impact
  - *favorable PRT, Allo > Auto*
  - *intermediate PRT, Auto>Allo*
- No validation cohort

M. Pfirrmann et al. Lancet Oncol. 2012

Autogreffe
double mutant CEBPA



- HOVON-SAKK + AMLSG
  - 7 trials
  - 124 patients with CEBPAdm

- 32 allo
- 20 auto
- 72 chemo

Schlenk et al. Blood. 2013

Commom standard arm

- *Double induction (Day 1, Day 22)*
  - *seconde course may start earlier if blast >25% or blast percentage reduction <50% at day 15.*
- *Three HD-AraC consolidation cycles (CALGB-like)*

AraC 100mg/m²/d day 1-7	DNR 60mg/m² day 3, 4, 5
AraC 100mg/m²/d day 1-7	DNR 60mg/m² day 3, 4, 5

AraC 3g/m² q 12 h day 1, 3, 5

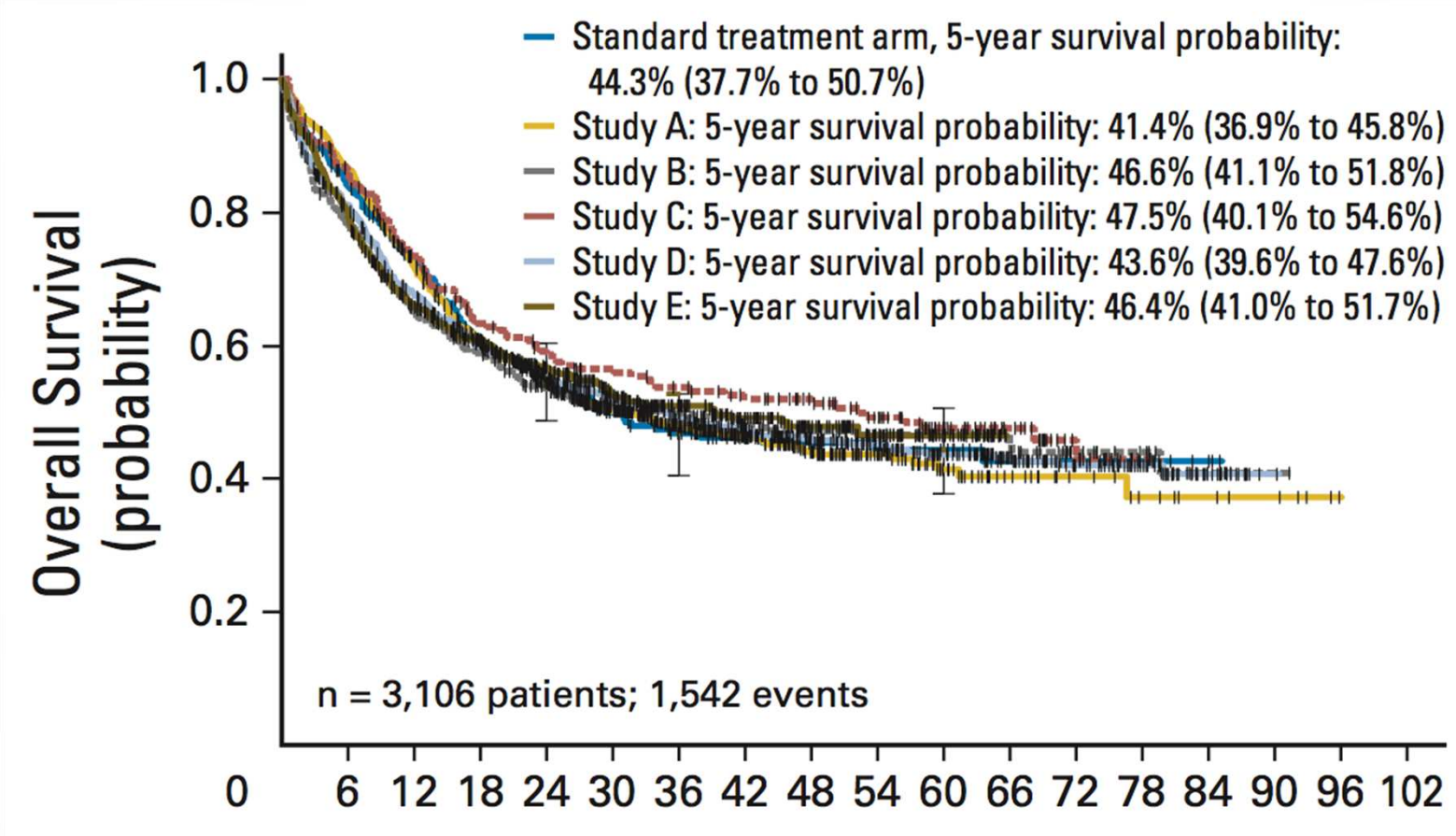
AraC 3g/m² q 12 h day 1, 3, 5

AraC 3g/m² q 12 h day 1, 3, 5

Büchner, Pfirrmann et al

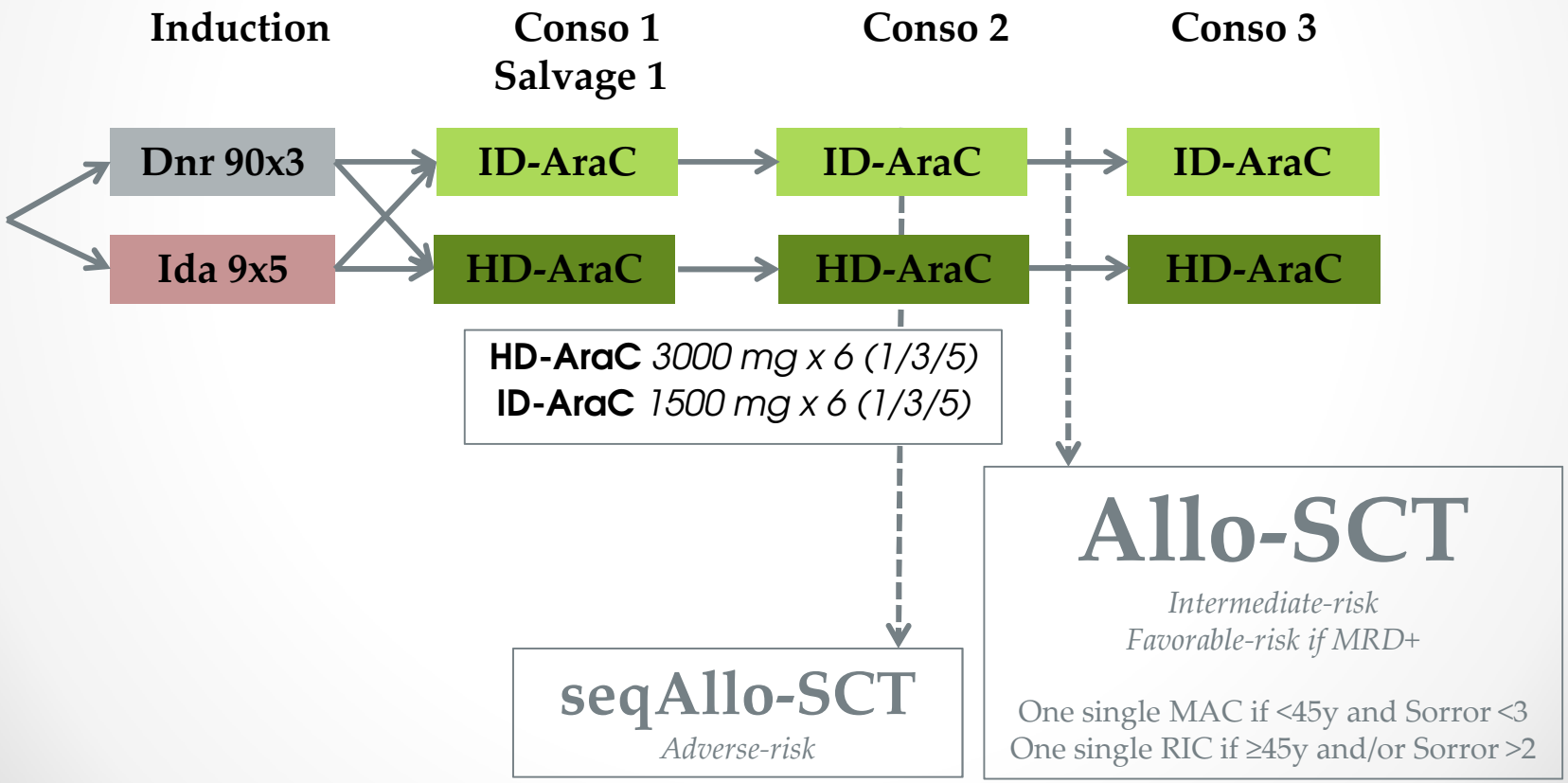
Commom standard arm

- *Five German cooperative groups*



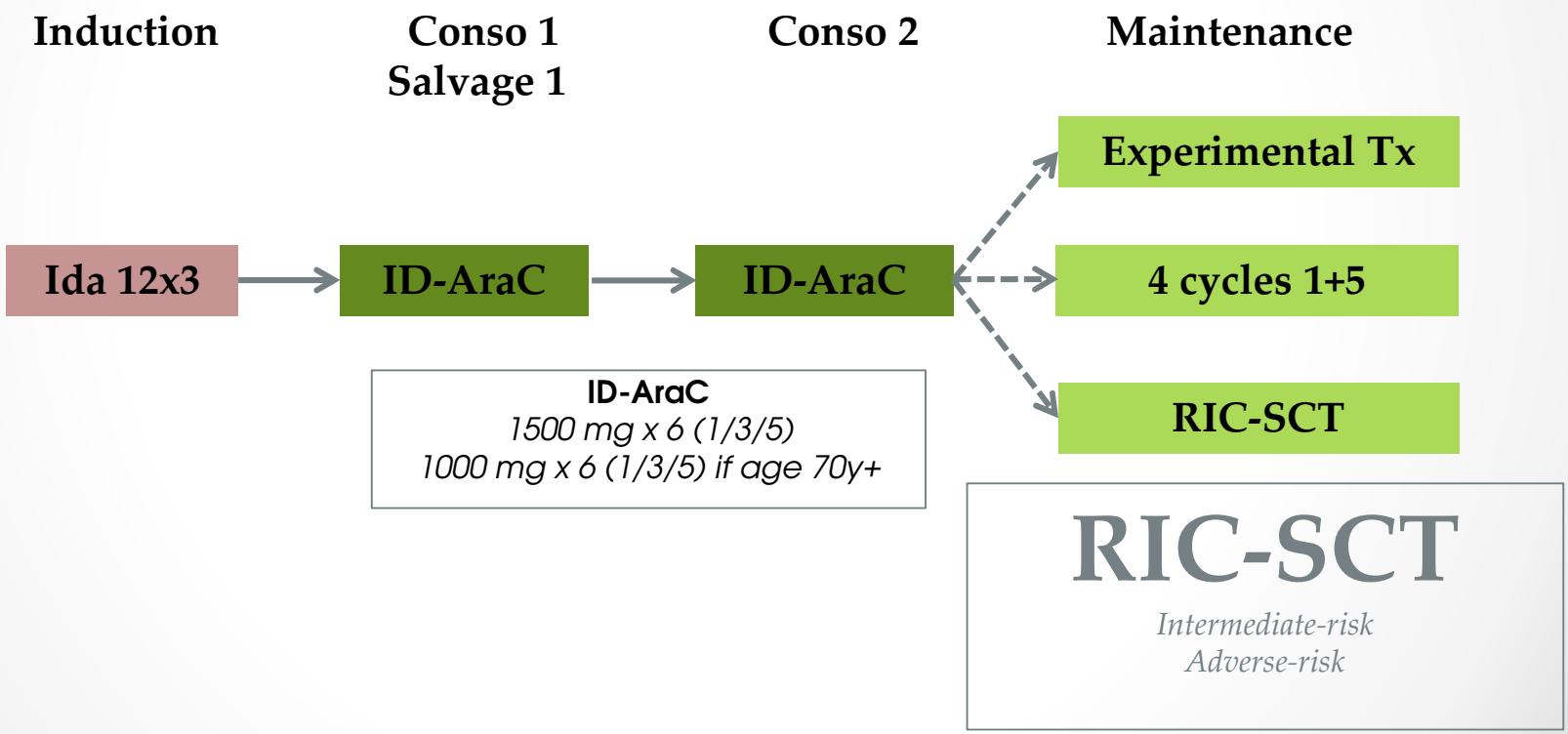
Büchner et al., JCO 2012

Backbone InterGroup (BIG)
ALFA-GOELAMS



Backbone ALFA

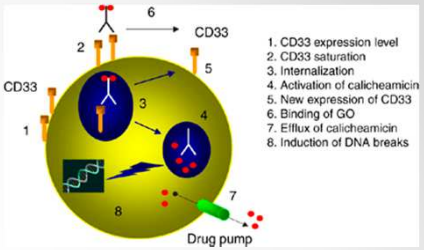
Age 60+



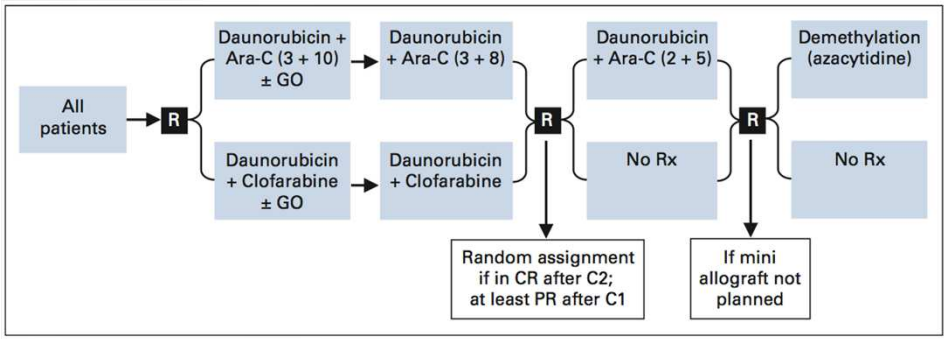
Adultes plus âgés

- *Essais ayant démontré un avantage significatif en survie, et pas seulement dans des sous-groupes de patients.*
  - **GO en induction**
    - *NCRI AML16 (Burnett et al. JCO 2012)*
  - **GO en induction/consolidation**
    - *ALFA-0701 (Castaigne et al. Lancet 2012)*
  - **ATRA**
    - *AMLSG 07-04 (Schlenk et al. Leukemia 2004)*

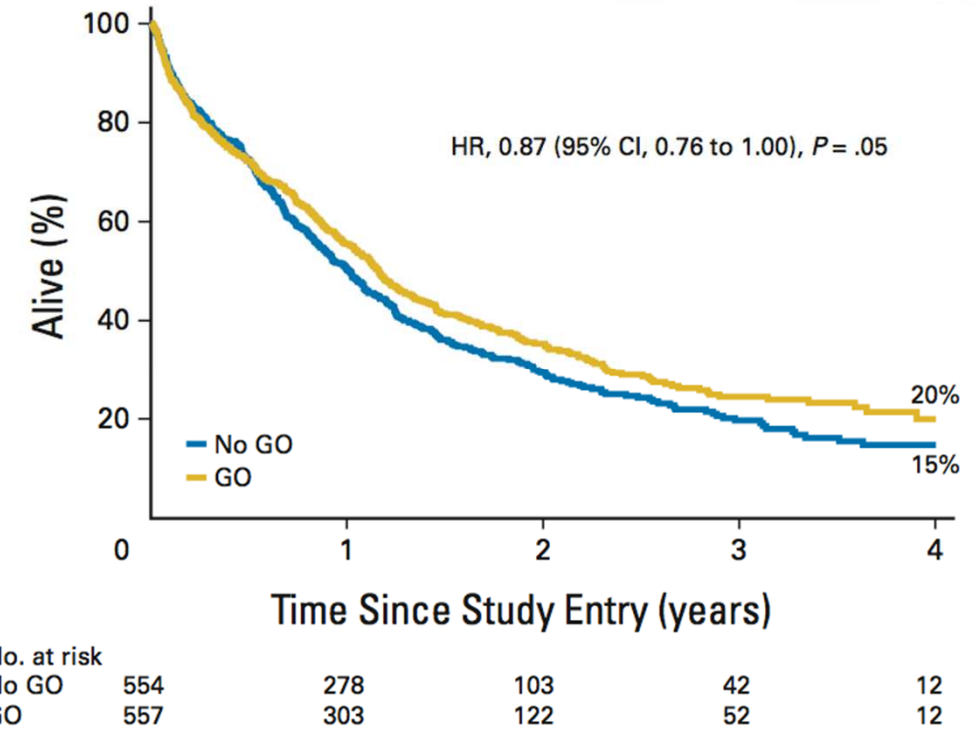
GO
NCRI AML16-I



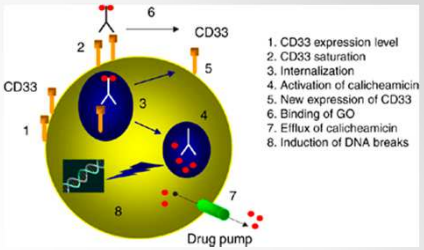
- *N= 1,115 patients*
- *Median age, 67 years (60+)*



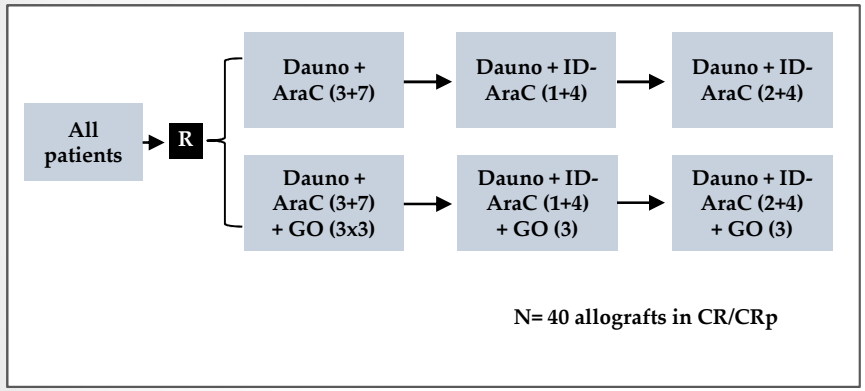
Burnett et al. JCO 2012



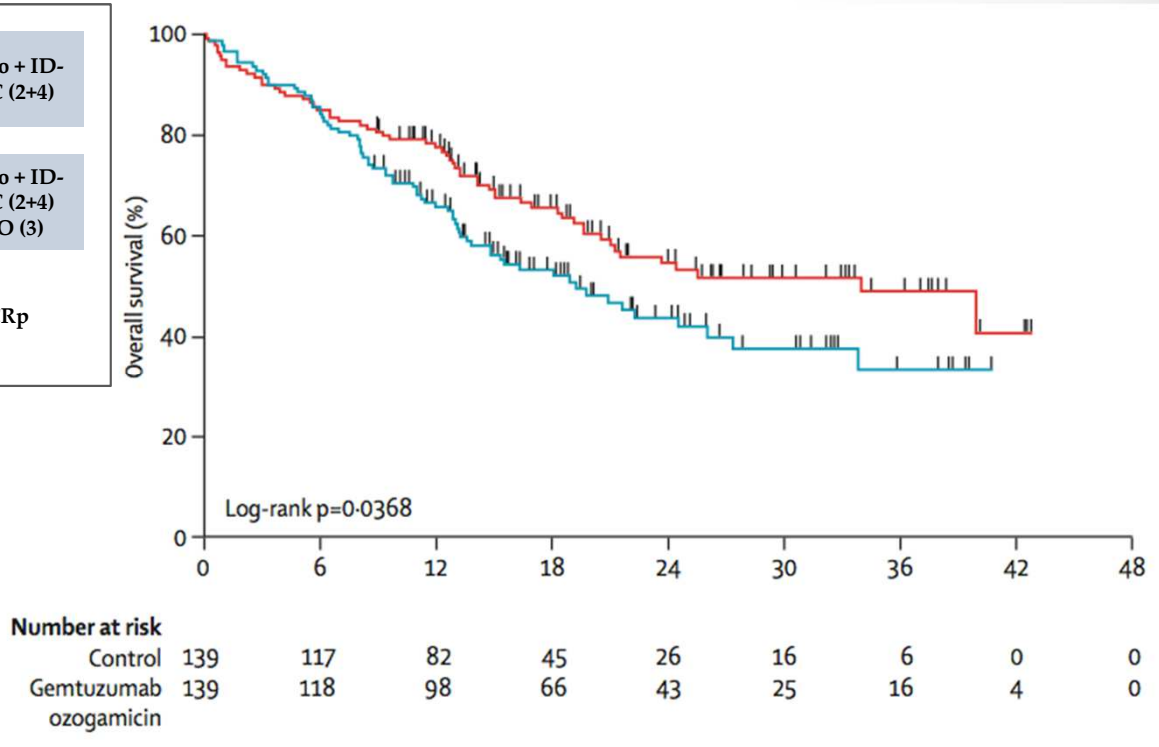
GO
ALFA-0701



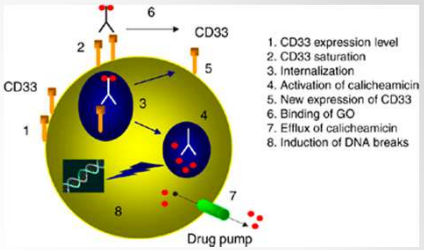
- *N= 278 patients*
- *Median age, 62 years (50-70)*



Castaigne et al. Lancet 2012



GO
Meta-analyse



- *N= 3,325 patients*

Meta–Analysis of Trials of GO in induction
Overall Survival

Trial	Events/Patients GO	Events/Patients No GO	Statistics (O–E)	Statistics Var.	O.R. & CI* (GO : No GO)
3mg/m2 single dose:					
MRC AML15	326/548	348/551	–14·7	168·3	0.92 (0.75, 1.12)
NCRI AML16	447/559	466/554	–31·1	226·8	0.87 (0.73, 1.03)
Subtotal:	**773/1107**	**814/1105**	**–45·7**	**395·1**	**0.89 (0.81, 0.98) 2P = 0·02**
Test for heterogeneity between trials: χ^2_1 = 0·2; P = 0·6; NS					
3mg/m2 fractionated:					
ALFA 0701	59/139	72/139	–11·8	32·1	0.69 (0.44, 1.09)
Subtotal:	**59/139**	**72/139**	**–11·8**	**32·1**	**0.69 (0.49, 0.98) 2P = 0·04**
6mg/m2 dose:					
GOELAMS AML2006 IR	41/119	54/119	–7·0	23·7	0.75 (0.44, 1.27)
SWOG 0106	151/295	144/300	8·0	73·6	1.11 (0.83, 1.50)
Subtotal:	**192/414**	**198/419**	**1·0**	**97·3**	**1.01 (0.83, 1.23) 2P = 0·9; NS**
Test for heterogeneity between trials: χ^2_1 = 2·9; P = 0·09					
Total:	**1024/1660**	**1084/1663**	**–56·6**	**524·5**	**0.90 (0.82, 0.98)**

*95% CI for total and subtotals, 99% CI for individual trials

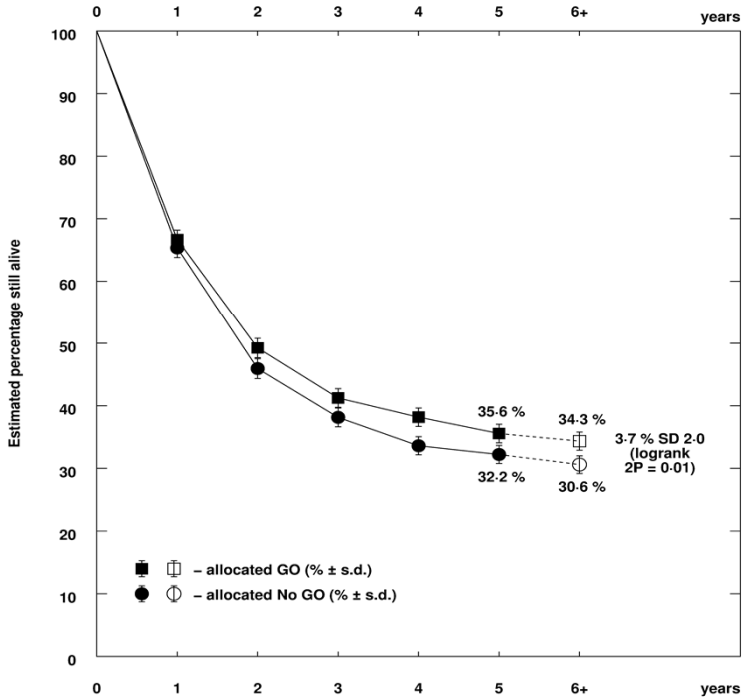
0·0 0·5 1·0 1·5 2·0
GO better | No GO better

Test for heterogeneity (5 trials): χ^2_4 = 6·7; P = 0·2; NS
Test for heterogeneity between subtotals: χ^2_2 = 3·6; P = 0·2; NS
Effect 2P = 0·01

Overall Survival

Annual event rates:

	years 1–5	years 6+
GO	26·7 % SD 0·8	3·5 % SD 0·8
No GO	29·5 % SD 0·9	5·2 % SD 1·0

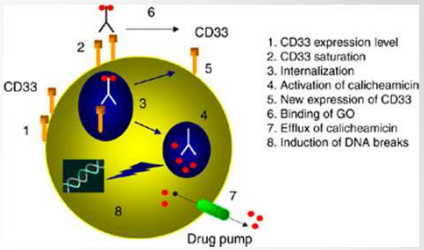


Deaths/person–years:

All patients						
GO	543/1341	275/907	121/673	40/492	25/353	20/576
No GO	571/1340	305/864	113/616	55/444	13/320	27/517

Hills et al. Lancet Oncol (revision)

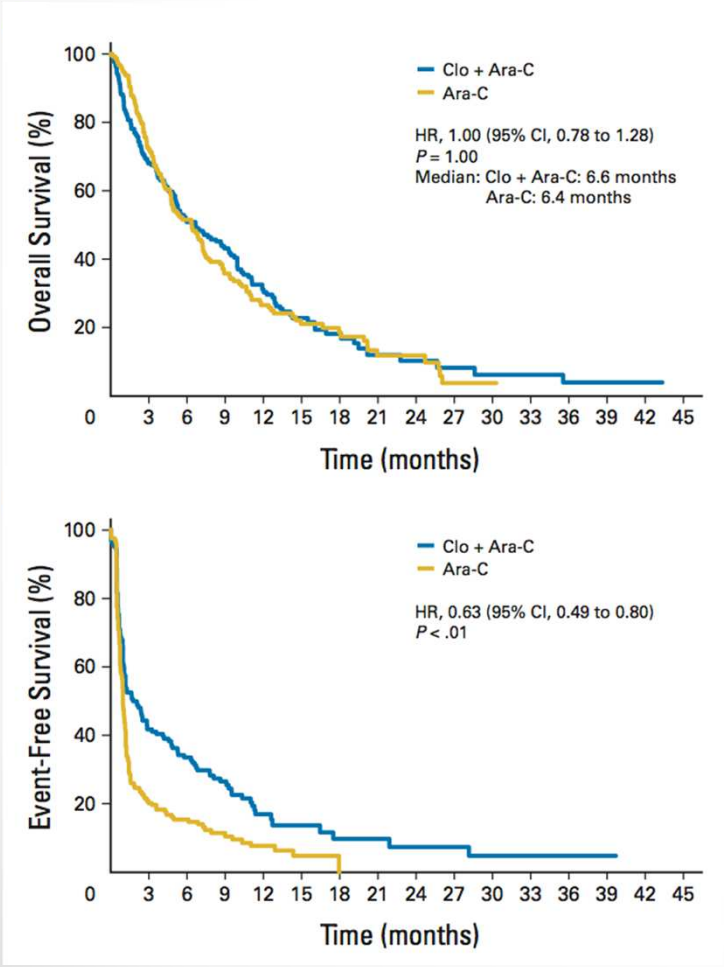
GO
Observations



- Toxicités :
  - Hépatique
  - Plaquettaire
- Sous-groupes cytogénétiques et moléculaires
  - Effet important dans les LAM-CBF
  - Effet important dans les LAM *NPM1*+ et *FLT3*-ITD+
  - Pas d'effet dans les LAM à caryotype défavorable
- Niveau d'expression de l'antigène CD33
  - Pas établi
  - Effet important si > 70% blastes positifs ?

Clofarabine

- Essai CLASSIC I



Ara-C
1 g/m2
for 5 days

±

Clofarabine/Placebo
40 mg/m2
for 5 days

Faderl et al. JCO 2012

Sujets âgés (unfit)

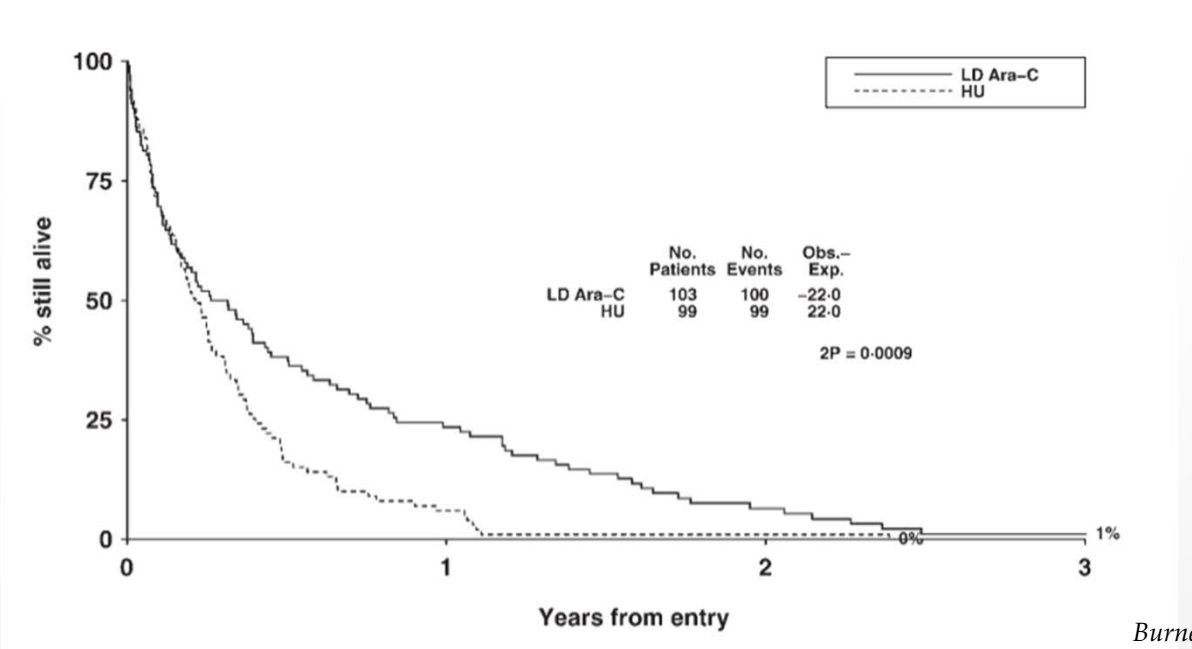
- *Essais ayant démontré un avantage significatif en survie, et pas seulement dans des sous-groupes de patients.*

  - **LD-AraC**
    - *NCRI AML16 (Burnett et al. Cancer 2007)*
  - **Decitabine**
    - *ALFA-0701 (Kantarjian et al. JCO 2012)*
  - **Azacitidine ?**
    - *AZA AML001 (Dombret et al. EHA 2014)*

LD-AraC
NCRI AML14

Response

Variable	Ara-C, %	HU, %	OR (95% CI)*	*P*
No. of patients with data available	102	99		
Response				
Induction death	26	26	1.01 (0.54–1.89)	1.0
Resistant disease	56	73	0.48 (0.27–0.86)	.01
CR	18	1	0.15 (0.06–0.37)	.00006



Burnett, Cancer 2007

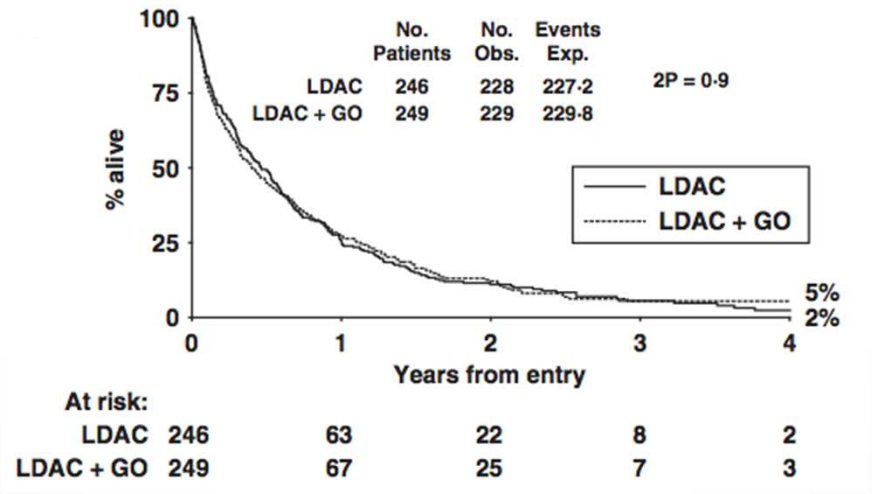
Pick-a-Winner-1 study

Control arm	Study arm	Drug	Short-term endpoint (CR or OS)	Long-term endpoint (OS)
LD-AraC	LD-AraC + tipifarnib	*Farnesyl-transferase inh.*		
LD-AraC	LD-AraC + ATO	*Arsenic trioxide*		
LD-AraC	LD-AraC + mylotarg	*Anti-CD33 immunoconjugate*	*Higher response rate*	*Similar OS*
LD-AraC	LD-clofarabine	*Nucleoside analogue*	*Higher response rate*	*Similar OS*

PaW-1 – GO

Table 3. Response and 12-month outcome

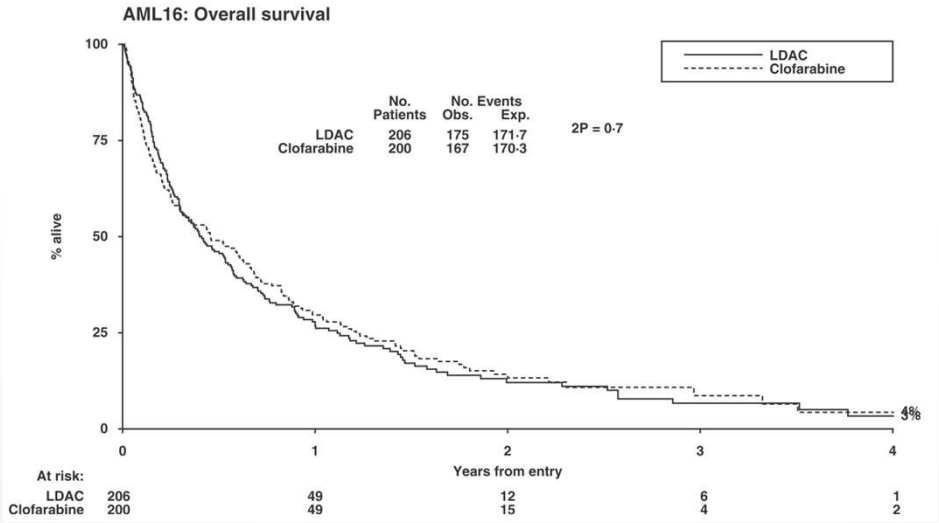
	CR	*CRi*	*ORR (CR + CRi)*	*30-day mortality*	*8-week mortality*	*12-month overall survival*	*12-month relapse-free survival*	*12-month survival from CR*
LDAC	11%	6%	17%	16%	27%	25%	40%	62%
LDAC + GO	21%	9%	30%	18%	29%	27%	31%	55%
OR/HR & 95% CI	0.46 (0.29–0.75)		0.48 (0.32–0.73)			0.99 (0.83–1.16)	1.11 (0.73–1.67)	1.31 (0.86–2.01)
P-value	0.002		0.006			0.9	0.6	0.2



Burnett, Leukemia 2013

PaW-1 – Clofarabine

	LDAC	Clo	HR/OR (95% CI)	*P* value
CR	12%	22%	0.47 (0.28-0.79)	.005
CRi	8%	16%		
ORR (CR + CRi)	19%	38%	0.41 (0.26-0.62)	<.0001
Resistant disease	67%	44%	0.39 (0.27-0.58)	<.0001
Induction death	13%	18%	1.42 (0.83-2.44)	.2
30-d mortality	13%	18%		
60-d mortality	26%	32%		
2-y survival	12%	13%	0.96 (0.78-1.19)	.7
2-y RFS	8%	20%	0.76 (0.49-1.19)	.2
2-y survival from CR	44%	26%	1.19 (0.74-1.91)	.5
2-y survival from relapse	8%	0%	1.91 (1.10-3.31)	.02
2-y survival for non-CR	4%	3%	1.37 (1.06-1.76)	.02



Burnett, Blood 2013

Low-Intensity-1 study

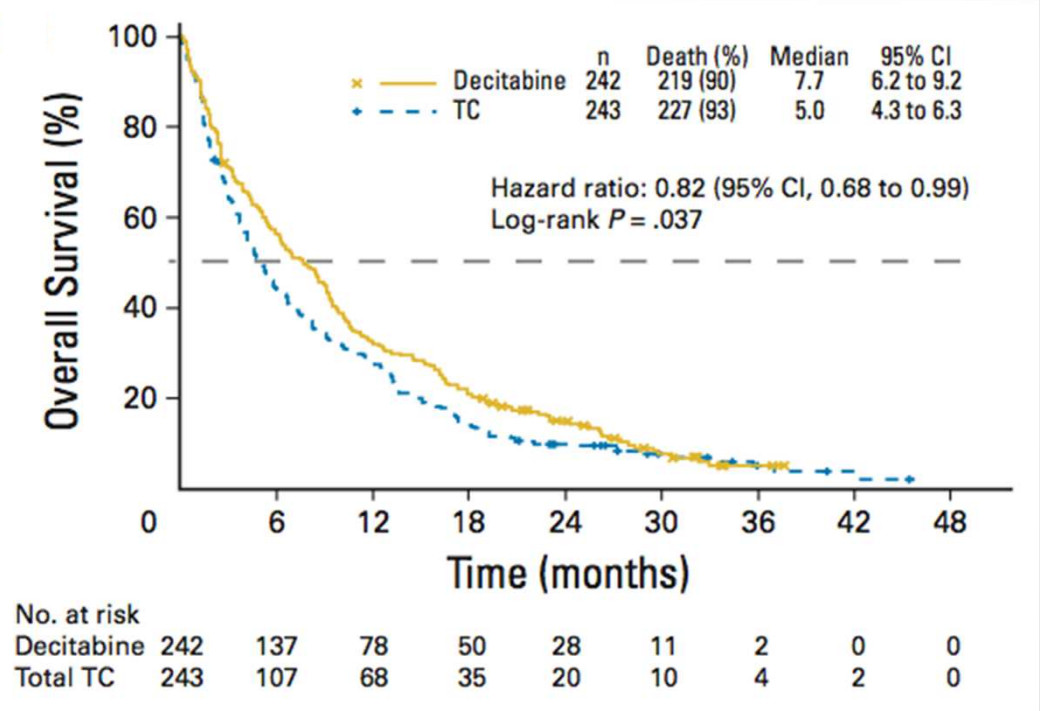
Control arm	Study arm	Drug	Short-term endpoint (CR or OS)	Long-term endpoint (OS)
LD-AraC	Sapacitabine	*Nucleoside analogue*		
LD-AraC	Vosaroxin	*Quinolone derivative*		
LD-AraC	LD-AraC + vosaroxin	*Quinolone derivative*	*Higher response rate, but more early deaths*	
LD-AraC	LD-AraC + quizartinib	*TKI (anti-FLT3)*	*ongoing*	
LD-AraC	LD-AraC + ganetespib	*Hsp90 inhibitor*	*ongoing*	
LD-AraC	LD-AraC + tosedostat	*Metalloenzyme inhibitor*	*ongoing*	
LD-AraC	LD-AraC + selinexor	*Nuclear export inhibitor*	*ongoing*	
LD-AraC	LD-AraC + PLKA-937	*Polo-like Kinase inhibitor*	*awaiting*	

Decitabine

- Essai DACO-016

Table 2. Treatment Response (2009 clinical cutoff)

	TC							
	Supportive Care (n = 28)		Cytarabine (n = 215)		Total TC (n = 243)		Decitabine (n = 242)	
Response	No.	%	No.	%	No.	%	No.	%
CR	1	3.6	17	7.9	18	7.4	38	15.7
CRi	1	3.6	6	2.8	7	2.9	24	9.9
CRp	0	0	1	0.5	1	0.4	5	2.1
CR + CRp	1	3.6	18	8.4	19	7.8*	43	17.8*
Partial remission	1	3.6	8	3.7	9	3.7	6	2.5
Stable disease	3	10.7	52	24.2	55	22.6	67	27.7
Progressive disease	10	35.7	69	32.1	79	32.5	50	20.7
Not evaluable	12	42.9	63	29.3	75	30.9	57	23.6

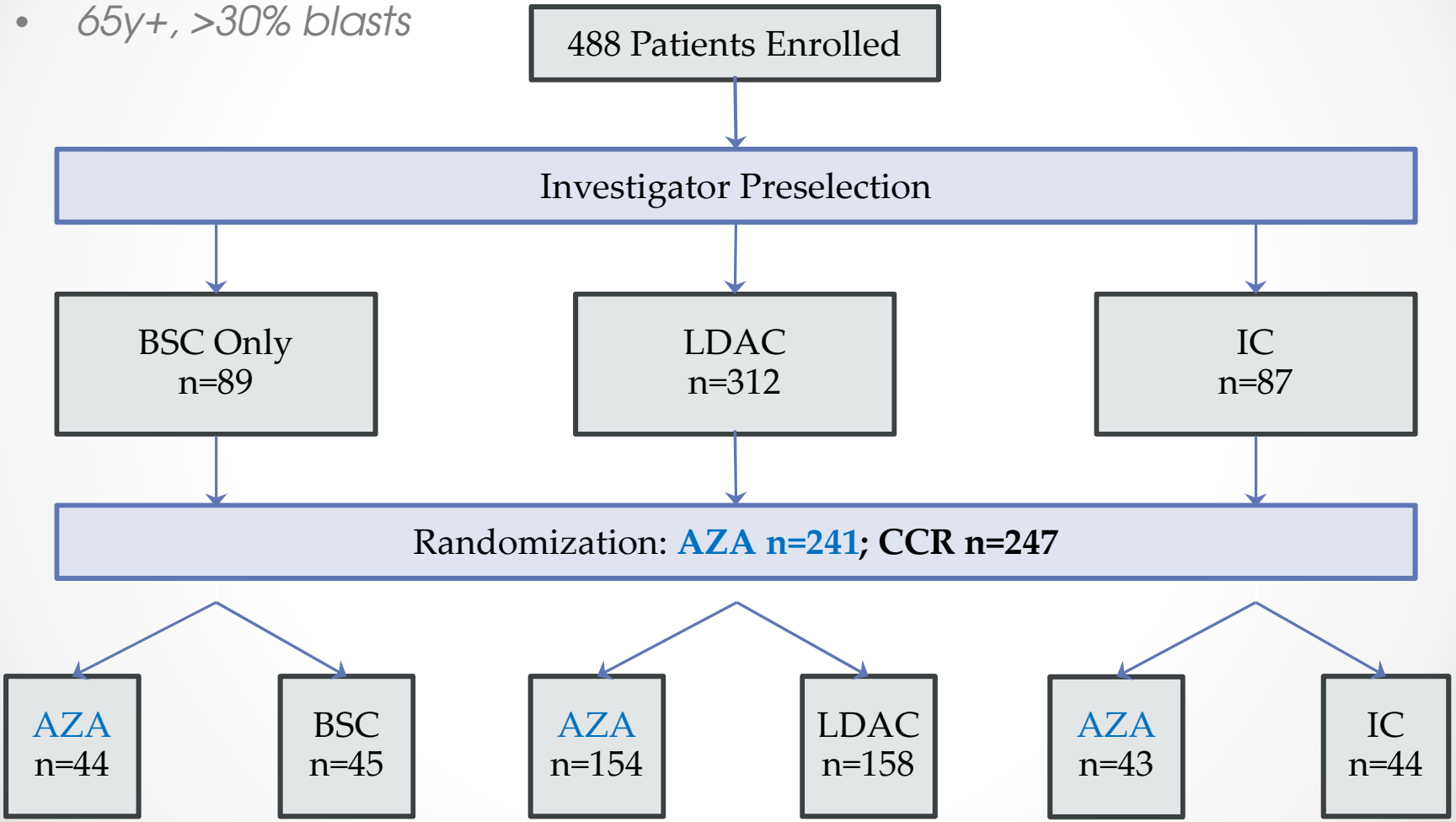


Kantarjian, JCO 2012

Azacitidine

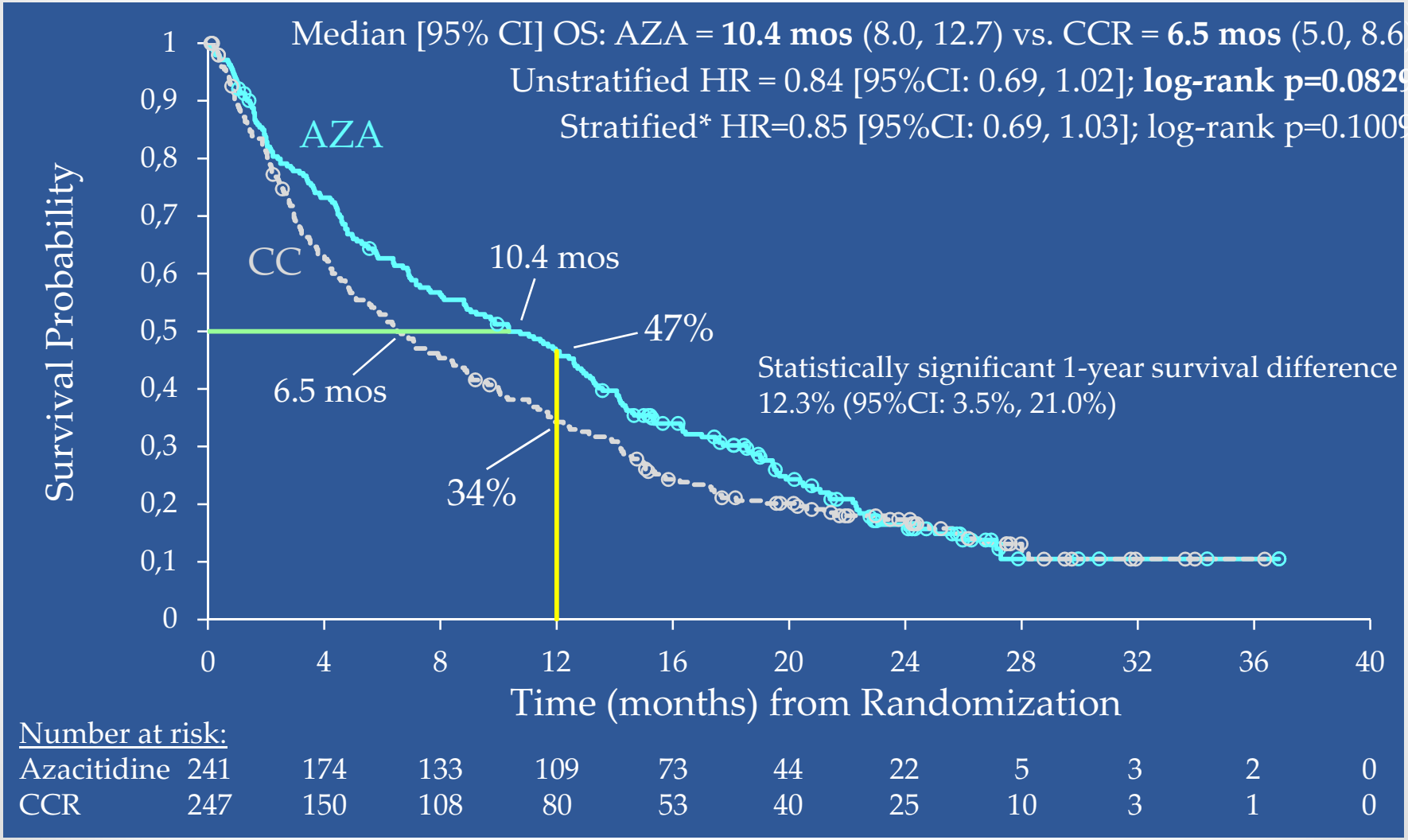
AZA AML001

- *65y+, >30% blasts*



Dombret et al. EHA 2014

AZA AML001



= Censored

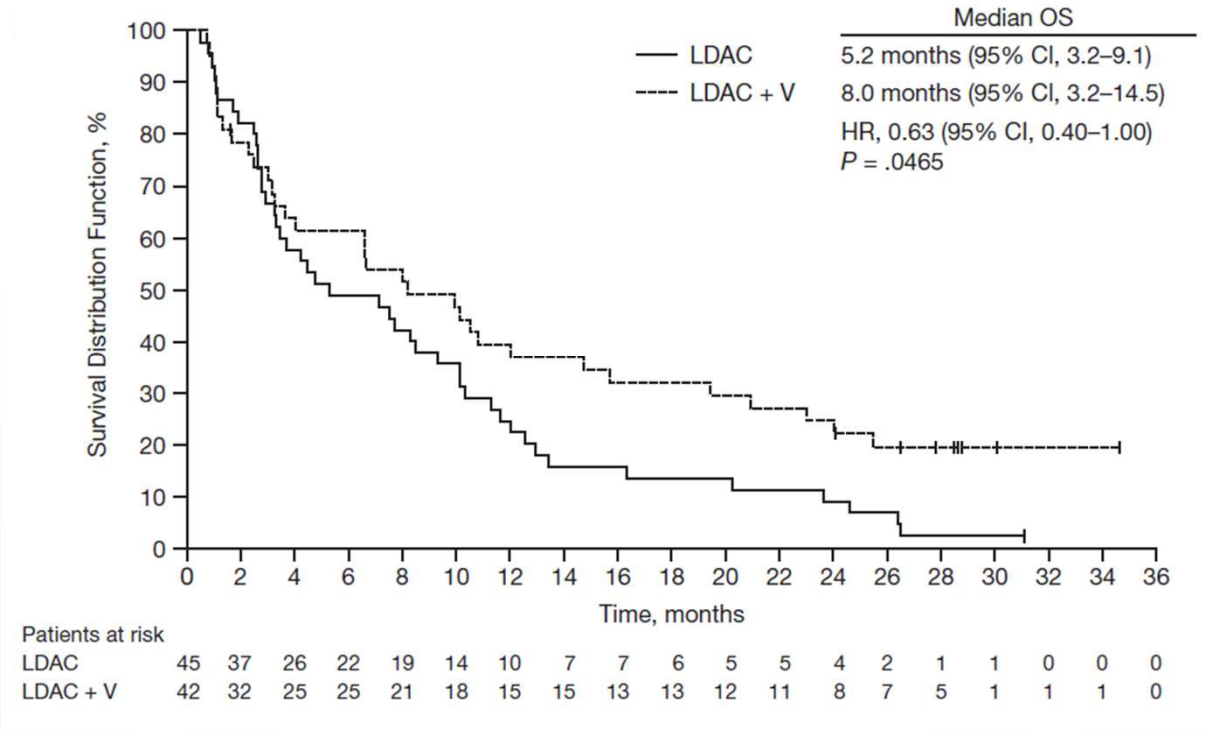
*Stratified by preselected CCR, ECOG PS, and cytogenetic risk

Dombret et al. EHA 2014

Volasertib

- *Polo-like kinase inhibitor (Plk-1/5)*
  - *entry into mitosis regulation*
  - *centrosome maturation*
  - *assembly of the bipolar spindle*
  - *sister chromatid separation*

Also a BRD4 inh.



Döhner et al. (submitted)

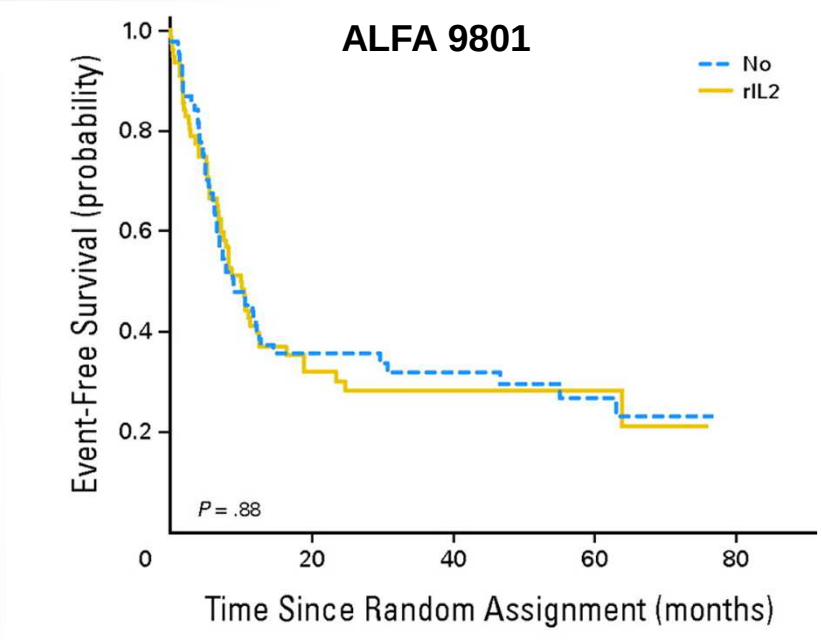
Immunothérapie ?

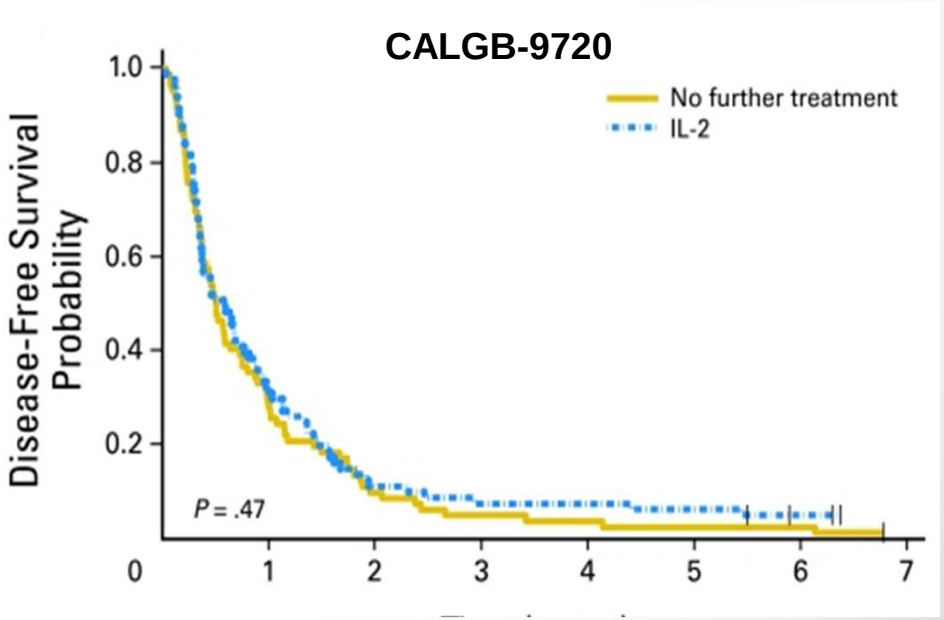
- *Approches d'immunothérapie dans les LAM, développées en maintenance ou en traitement de rechute.*

  - **Immunomodulation**
    - *Cytokines*
    - *Anticorps*
  - **Anticorps monoclonaux**
    - *Conjugés*
    - *Bispécifiques*
  - **Immunothérapie adoptive**
  - **Vaccination**

IL-2

- *IL-2 maintenance: two negative studies*
  - *ALFA-9801*
  - *CALGB-9720*

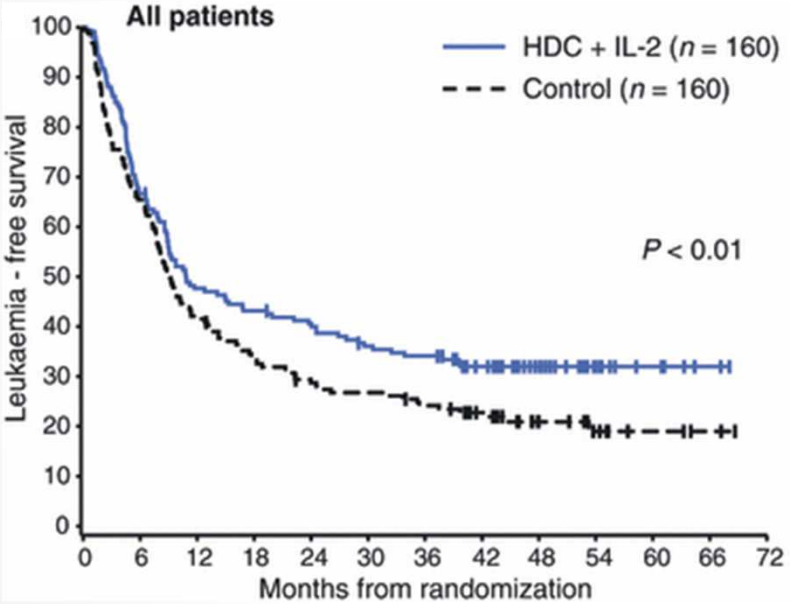


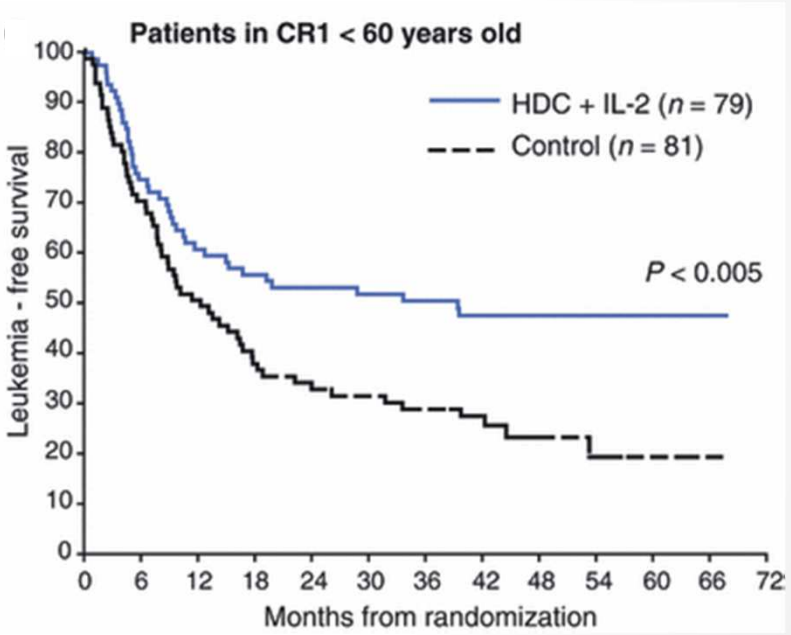


Baer et al. JCO 2008
Pautas et al. JCO 2010

Histamine dihydrochloride

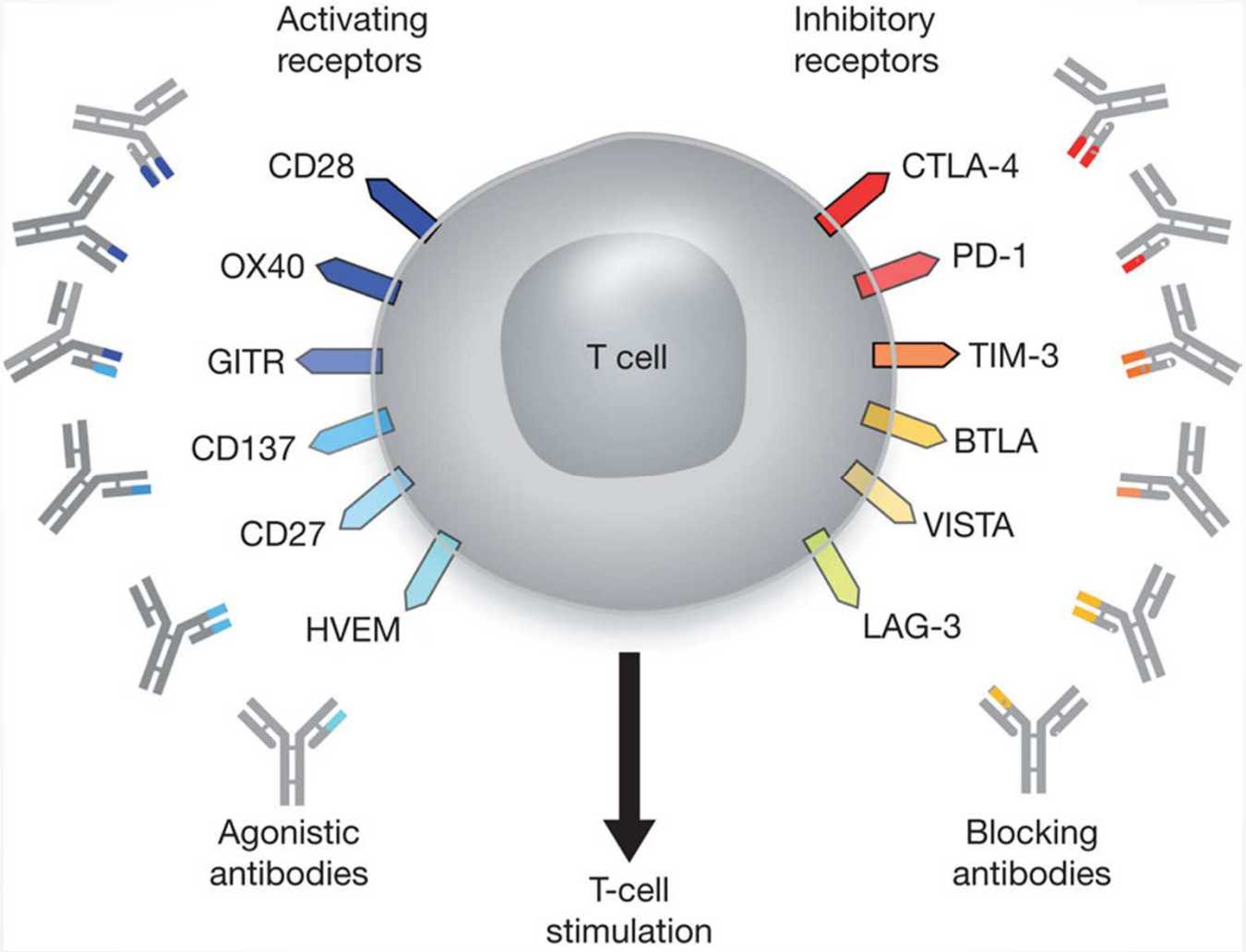
- *Ceplene®*





Brune et al. Blood 2006

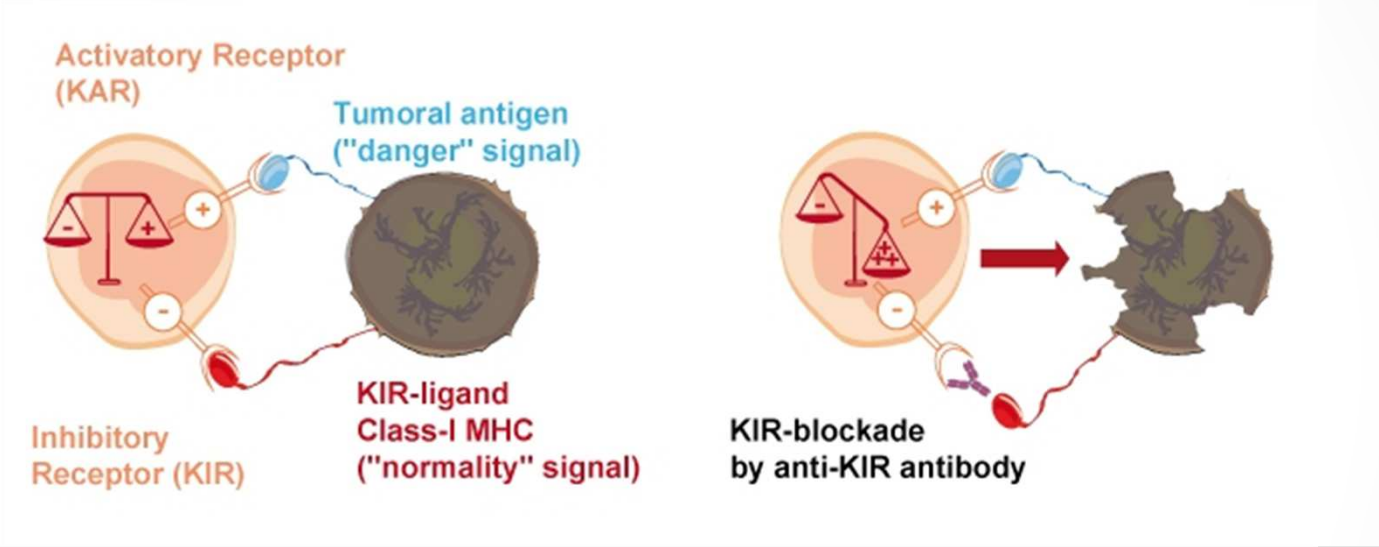
T-cell modulation



Mellman, Nature 2011

NK-cell modulation

Lirilumab (anti-KIR)



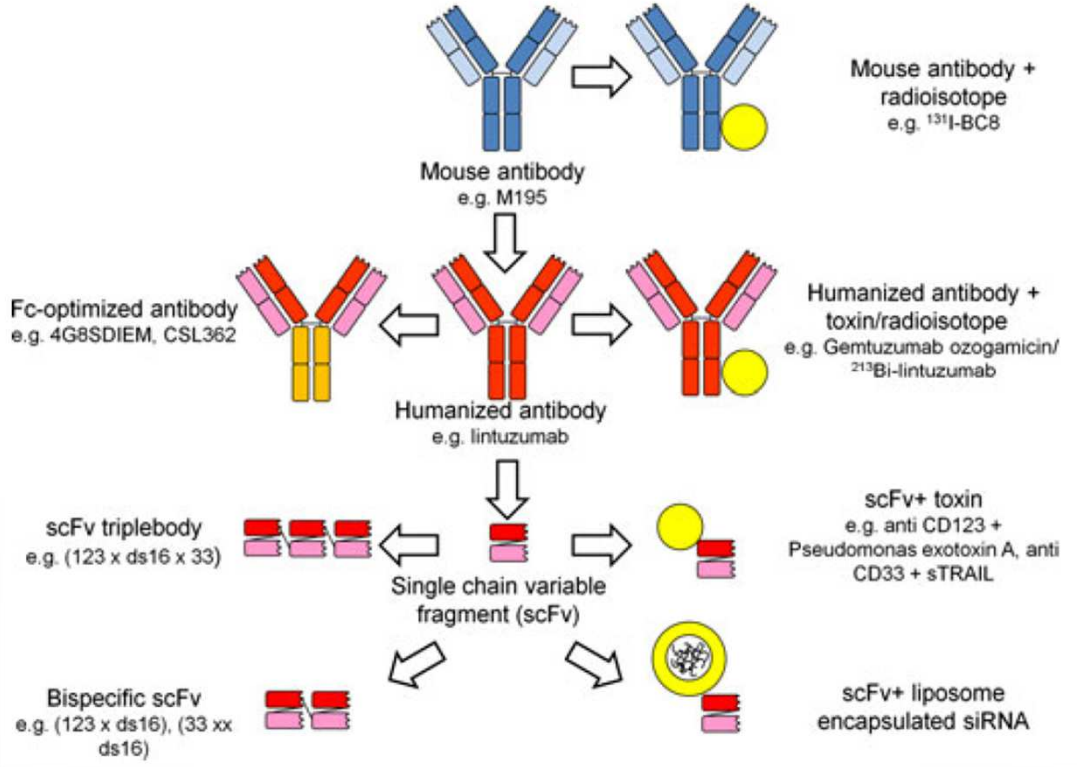
	High dose (1 or 3mg/kg)	Low dose (<1mg/kg)	Log rank test p-value
Median age	73 (63-76)	71 (61-79)	-
Median RFS	21.1 m	9.5 m	P=0.079
Median PFS	12.6 m	2.3 m	P=0.076
Median OS	29.7 m	11.8 m	P=0.034

Phase 3 ongoing

Vey, Blood 2012

Monoclonal Abs & more

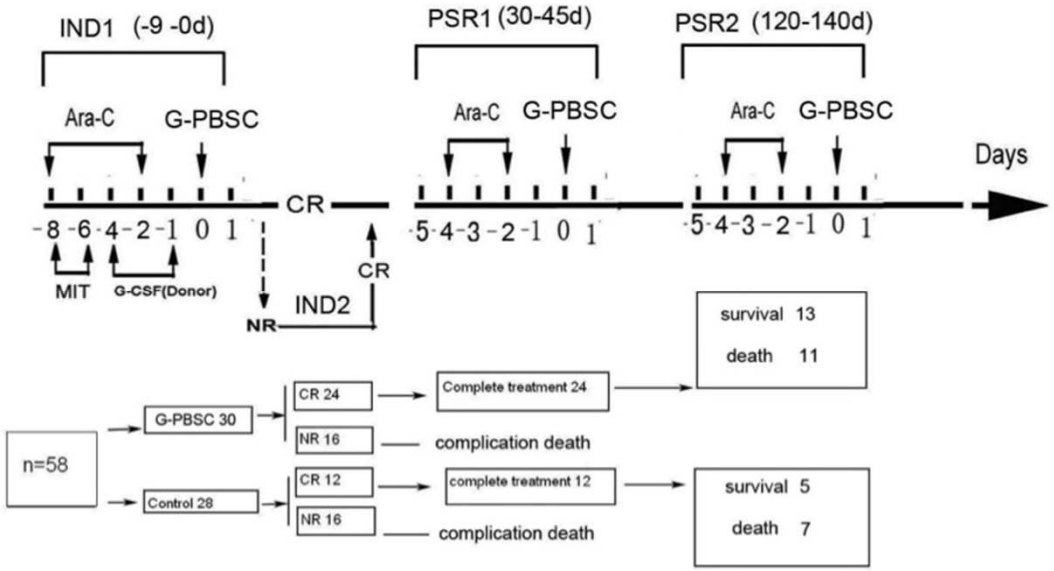
- *Against CD33, CD123… CD47, CD67, CD66, CD45*

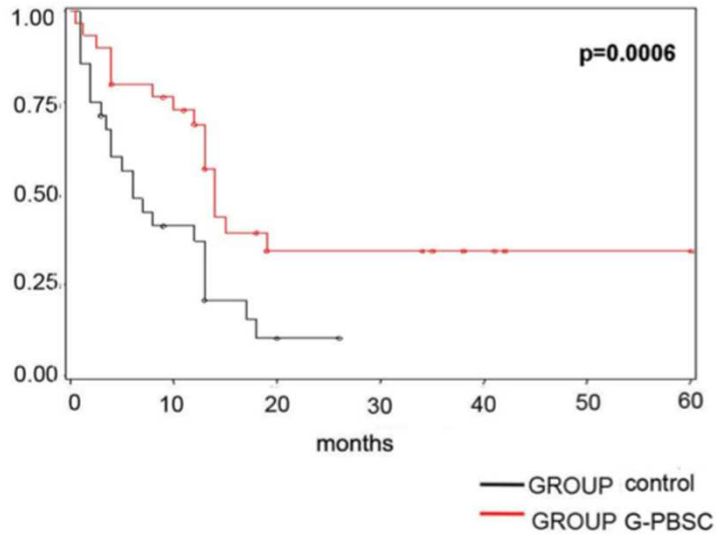


  - *BiTE, using CD3*
  - *BiKE, using CD16*

Adoptive immunotherapy

- *N= 30 pts received mistached G-PBSC from related donors (4 or 5/10 HLA loci) during induction and consolidation*





- *Role of donors with HLA-C^{Lys80} ?*

Guo, Blood 2011

Conclusions

- *Des progrès ont été accomplis du fait de l'augmentation des doses, rendue possible par de meilleurs soins de support (anti-infectieux).*

- *La limite semble atteinte, rendant nécessaire de nouvelles approches ciblées:*
  - *Ciblage thérapeutique*
  - *Ciblage immunologique*