P.O.H.O

Pédiatrie Onco Hémato-Ouest

La leucémie aigue à chromosome Philadelphie n'est pas un long fleuve tranquille

- Actualités 2016 -

POHO- 09/12/2016

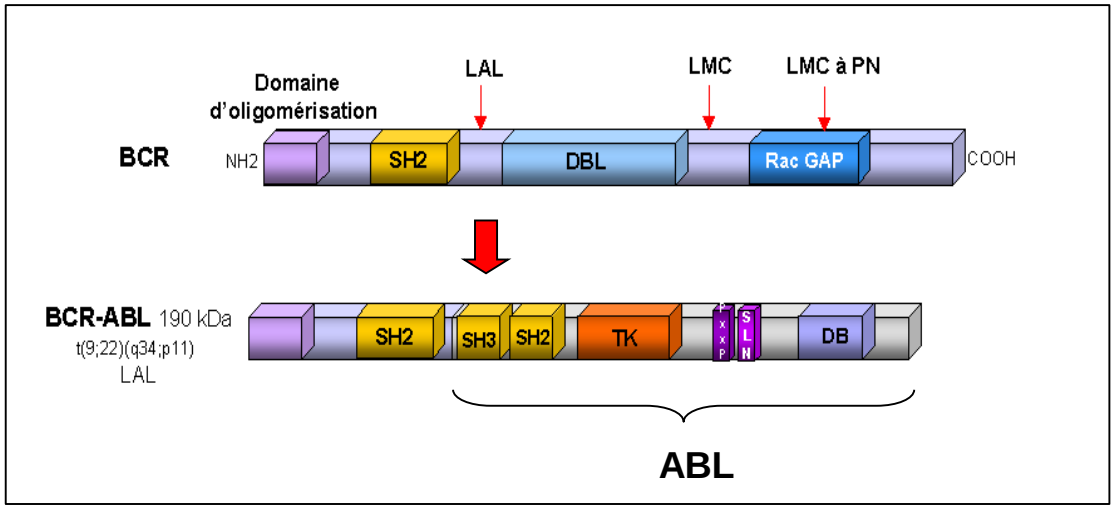
Pr V. Gandemer

CHU Rennes-Université Rennes1

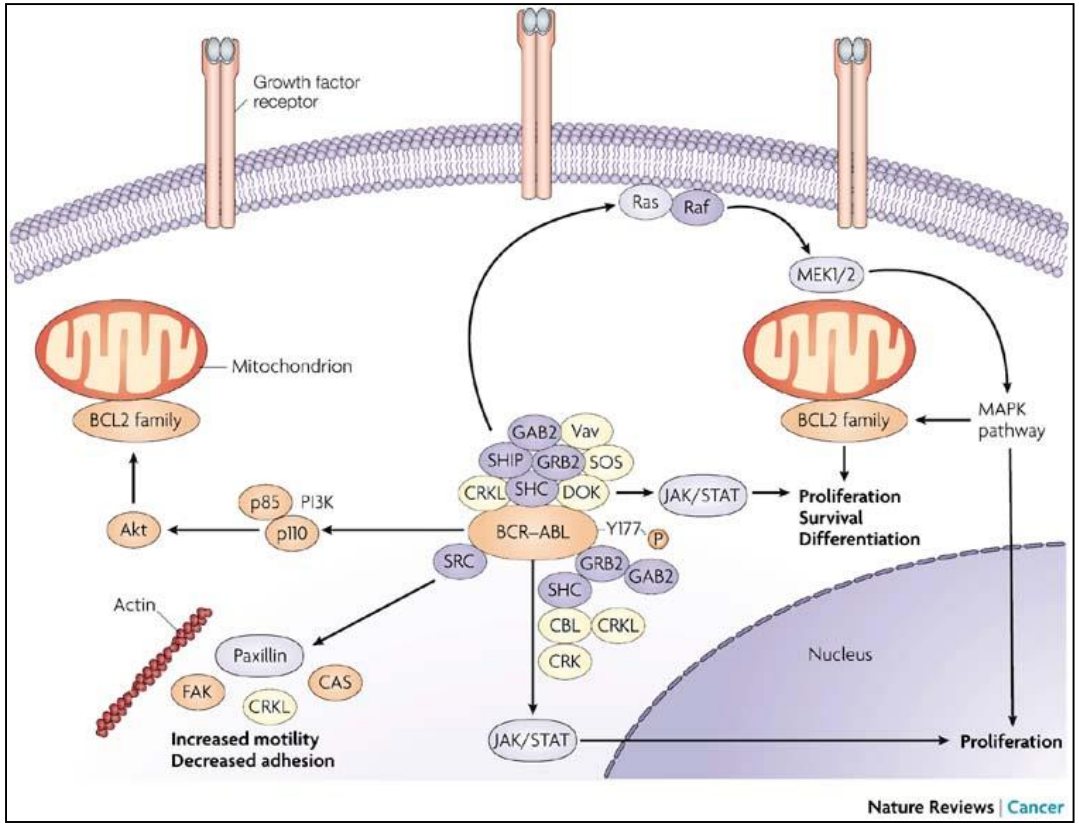
Plan

1. Rappel : la LAL Phi avant l'ère de l'imatinib
2. L'imatinib et les TKI
3. Les protocoles pédiatriques basés sur l'imatinib
    1. EsPhALL
    2. COG
    3. EsPhALL amendé
4. Enjeux 10 ans après
5. Perspectives 2017
6. Conclusion

Le chromosome Philadelphie



activation constitutive du domaine tyrosine kinase de ABL



Les LAL Phi de l'enfant

5 % des LAL de l'enfant (et 25% des LAL de l'adulte)

Caractéristiques:

- **LAL de la lignée B** (pré B ou **commune**) dans 98%
- >60% garçons
- Âge moyen= 8 ans (**60%<10 ans**)
- Leucocytose moyenne= 48.000 (30% >100.000 GB)
- SNC =5-6%

Arico et al., NEJM 2000
Amended EsphALL, 6th Report, 2015

Diagnostic:

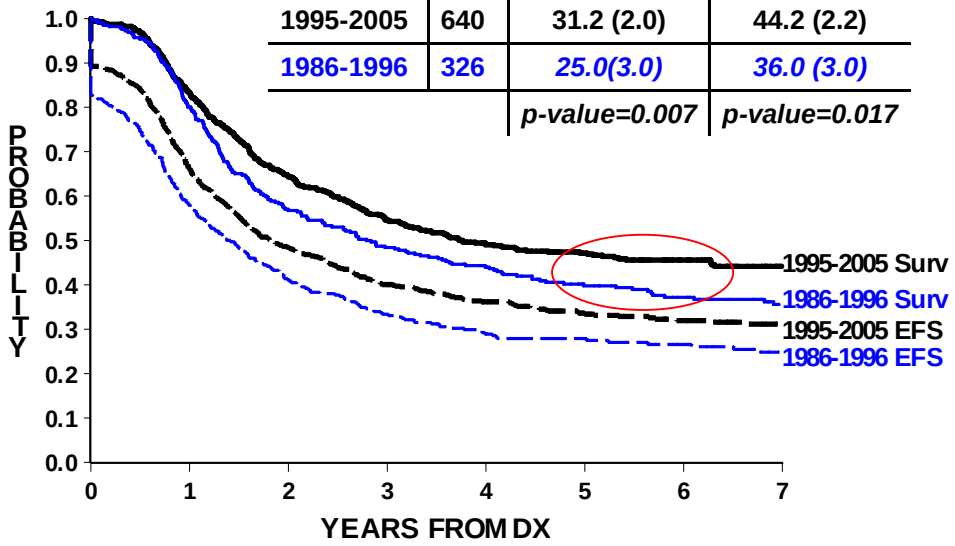
Caryotype standard + techniques moléculaires : FISH , RT-PCR

	Good Risk		*Poor Risk*		*total*	
	N	%	N	%	N	%
On study patients	102	65.8	53	*34.2*	155	*100.0*
Protein detected						
p190	63	*61.8*	40	*75.5*	103	*66.5*
p210	18	*17.6*	1	*1.9*	19	*12.2*
NK	21	*20.6*	12	*22.6*	33^	*21.3*

La LAL Phi avant l'ère de l'Imatinib

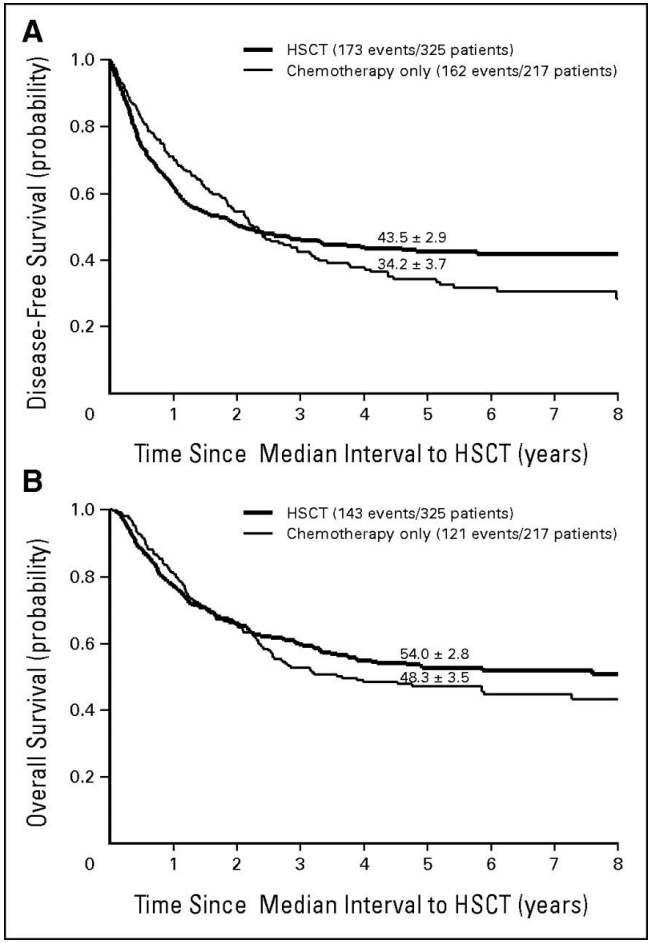
5 ans

	N. pts.	7-year	
		EFS	Survival
1995-2005	640	31.2 (2.0)	44.2 (2.2)
1986-1996	326	*25.0(3.0)*	*36.0 (3.0)*
		p-value=0.007	*p-value=0.017*



International PdL Childhood ALL Study Group

Aricò M et al., JCO 2010



N=542 patients

La LAL Phi avant l'ère de l'Imatinib

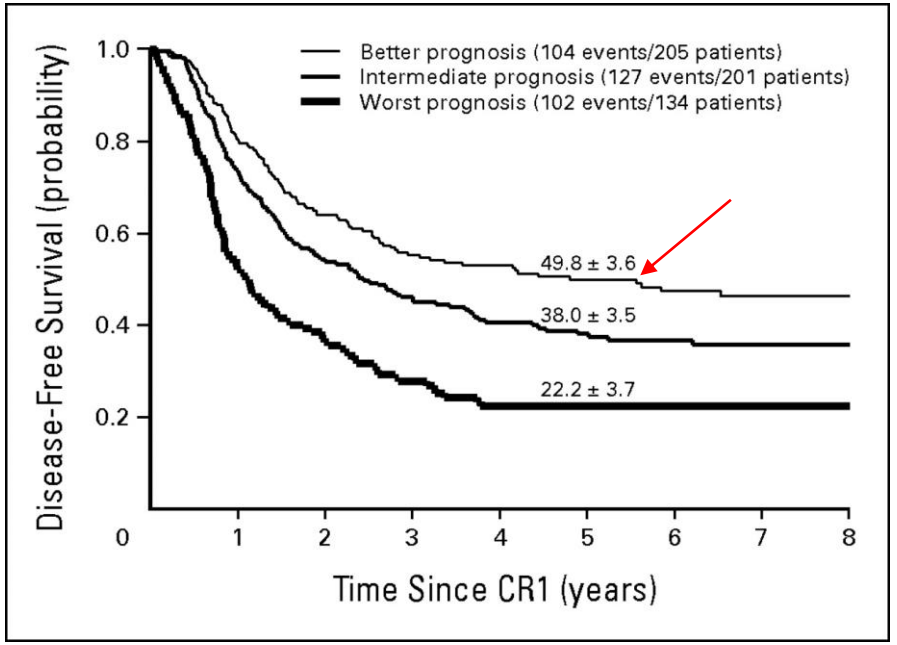
Facteurs pronostiques:

- **Corticosensibilité** :
  - nbre de blastes sur la NFS-pl à J8(<1.000/mm3)

Schrappe et al., Blood 1998

- Âge/ Leucocytes au dg
  - <10 ans / < 50.000 GB/mm3

  (**critères Rome-NCI**)



Reiter et al., Blood 1994
Ribeiro et al., Leukemia 1997
Arico et al., JCO 2010

La LAL Phi avant l'ère de l'Imatinib

Facteurs associés au pc en multivarié:

- Âge
- Leucocytose au dg
- Réponse précoce

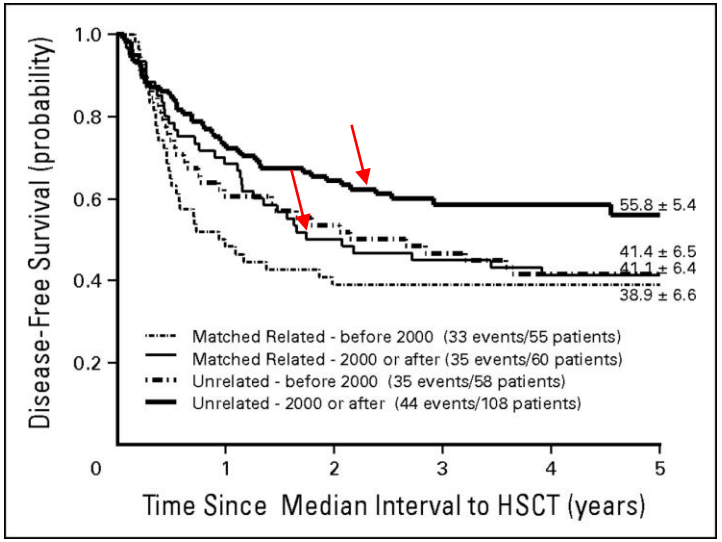
au traitement : cortico et chimioS

Stratification EsPhALL

- Allogreffe

↘Rechutes

↘DC

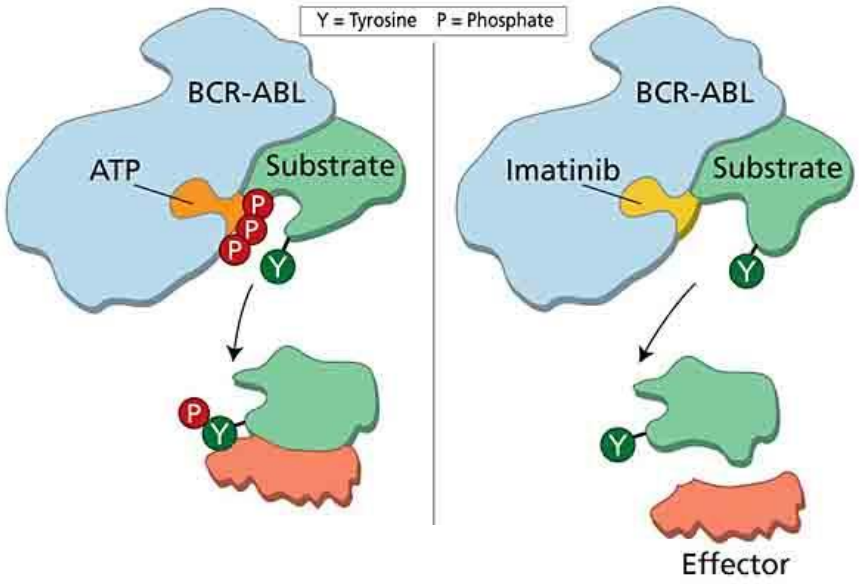


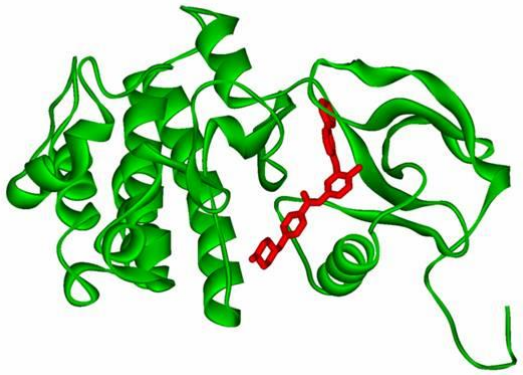
Gandemer et al., BMC Cancer 2009

Arico et al., JCO 2010

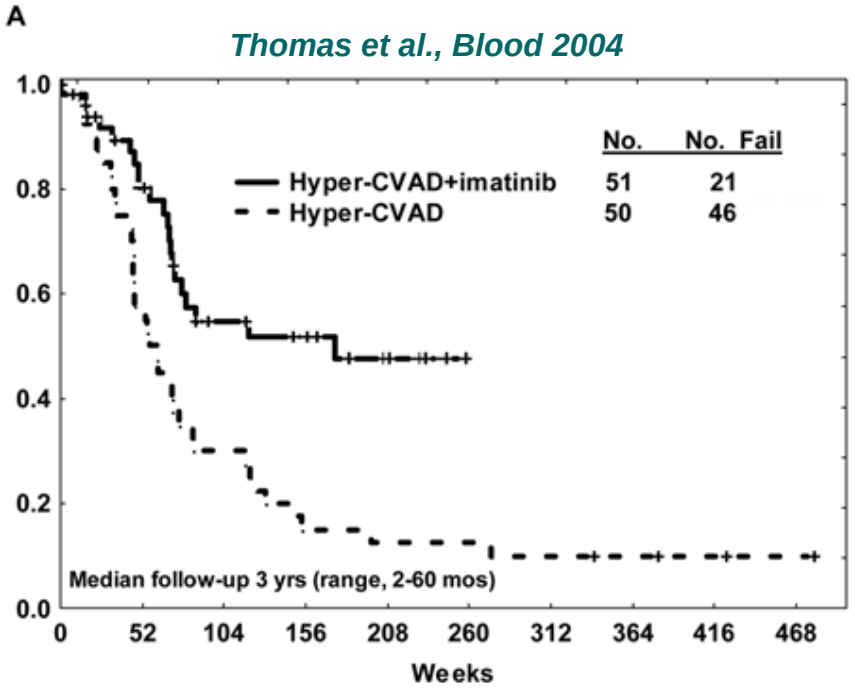
L'imatinib et les inhibiteurs de tyrosine kinase (TKI)

- 1ère thérapie ciblée : Imatinib mesylate (Glivec®)
  - Bloque partiellement le site de liaison à l'ATP de la protéine de fusion BCR/ABL





De 2004 à 2007



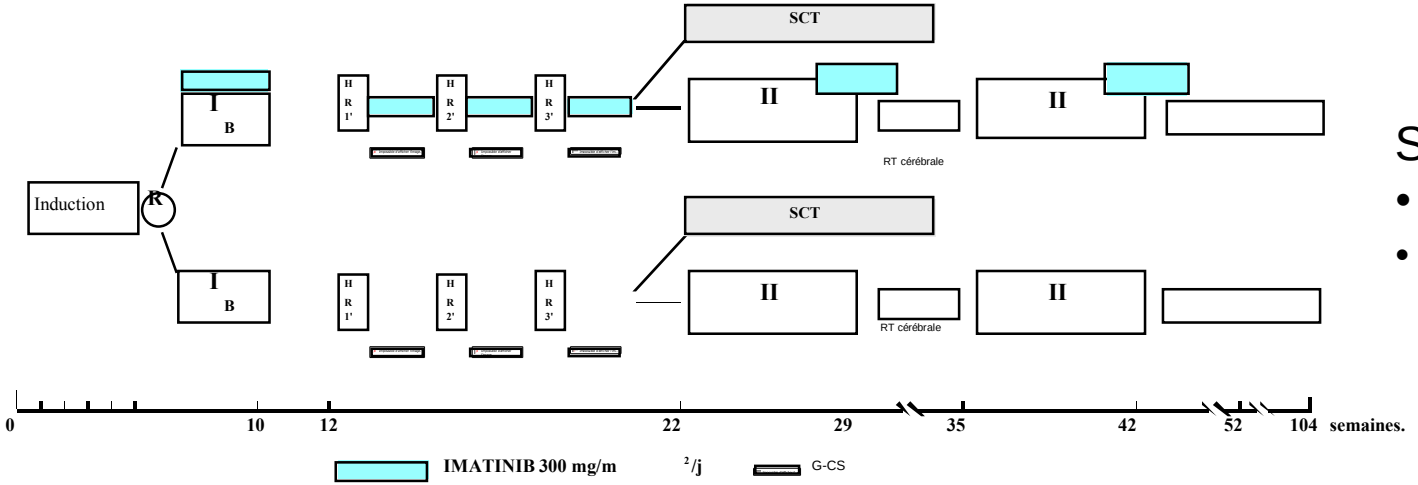
Subtype	Chemo-therapy regimen	Imatinib dosing: Induction	Consolid-ation	Mainte-nance	No.	CR, %	Relapse, %	DFS, % (at y)	Survival, % (at y)
Adults (all)									
Thomas et al[28,29]	Hyper-CVAD	C	C	C	39	92	14	83 (3)	55 (3)
Adults (age < 65 years)									
Yanada et al[31,43]	JALSG ALL202	C	A	C	80	96	26	60 (1) 51 (2)	76 (1) 58 (2)
Lee et al[30]	Modified Linker	C	C	C	20	95	32	62 (2)	59 (2)
Wassmann et al[32]	GMALL Alternating Concurrent	 None None	 A C	 NR NR	 47 45	 NA NA	 NR NR	 52 (2) 61 (2)	 36 (2) 43 (2)
de Labarthe et al[35]	GRAAPH-2003	None	C	NR	45	96	19	51 (1.5)	65 (1.5)

Thomas et al., Hematology 2007

Protocoles basés sur l'imatinib en pédiatrie

- **Quelle est la juste place des TKI chez l'enfant**
  - x2 bons répondeurs /adultes
  - EFS= 50%
  - Recours large à l'allogreffe

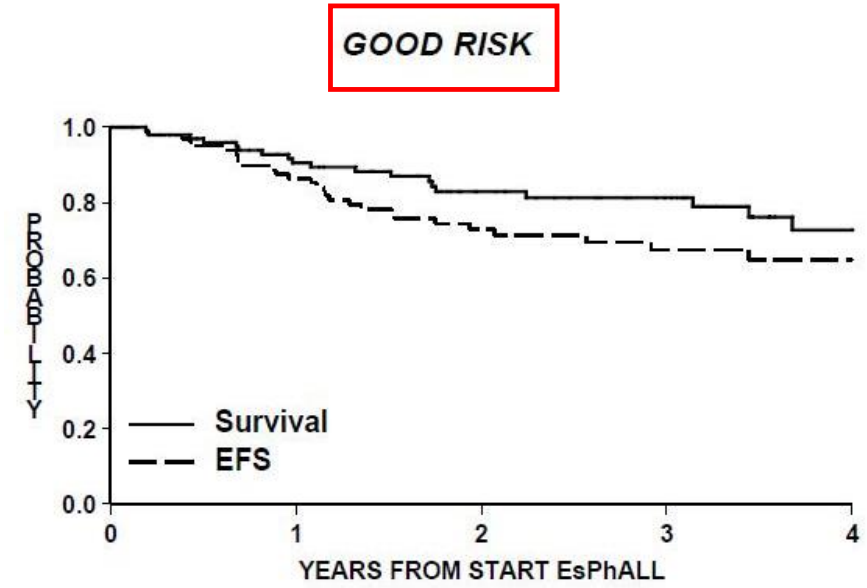
Protocole européen EsPhALL pour les LAL Phi+ de l'enfant (2004-2005)

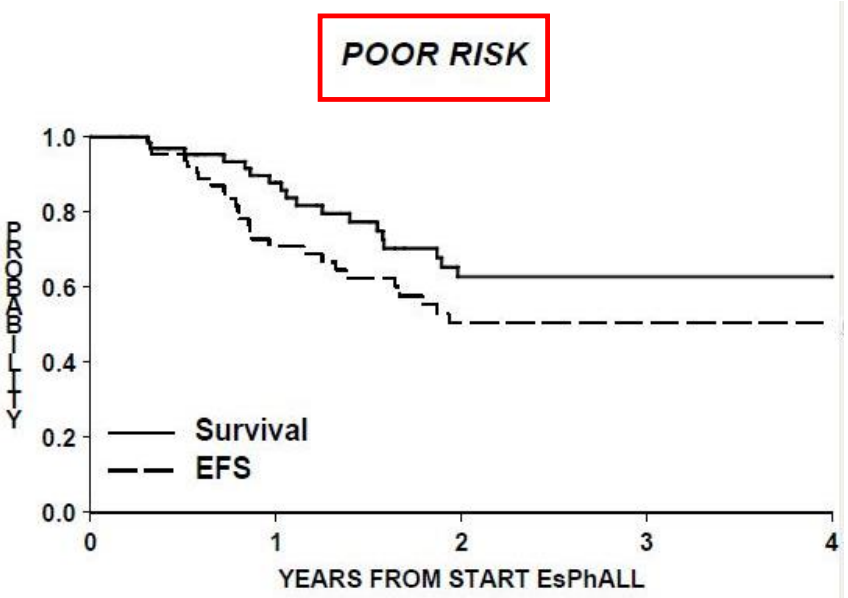


Stratification sur
- CorticoS à J8
- ChimioS à J15 ou J21

AIEOP,BFM-G/CH, BFM-A, COALL,DCOG,EORTC, FRALLE, UKALL,NOPHO, CZECH REPUBLIC

Résultats EsPhALL





	N. pts.	N. events (relapses)	3-year EFS (SE)	N. deaths	3-year Surv (SE)
Good Risk	108	28(11)	67.4 (5.4)	19	81.3 (4.3)

	N. pts.	N. events (relapses)	3-year EFS (SE)	N. deaths	3-year Surv (SE)
Poor Risk	70	26(19)	50.5 (7.2)	18	62.7 (7.2)

99% mis en RC (Ia+Ib):

Rechutes :22% (MO++)

DC en RC: 8%

Bons répondeurs : 61%

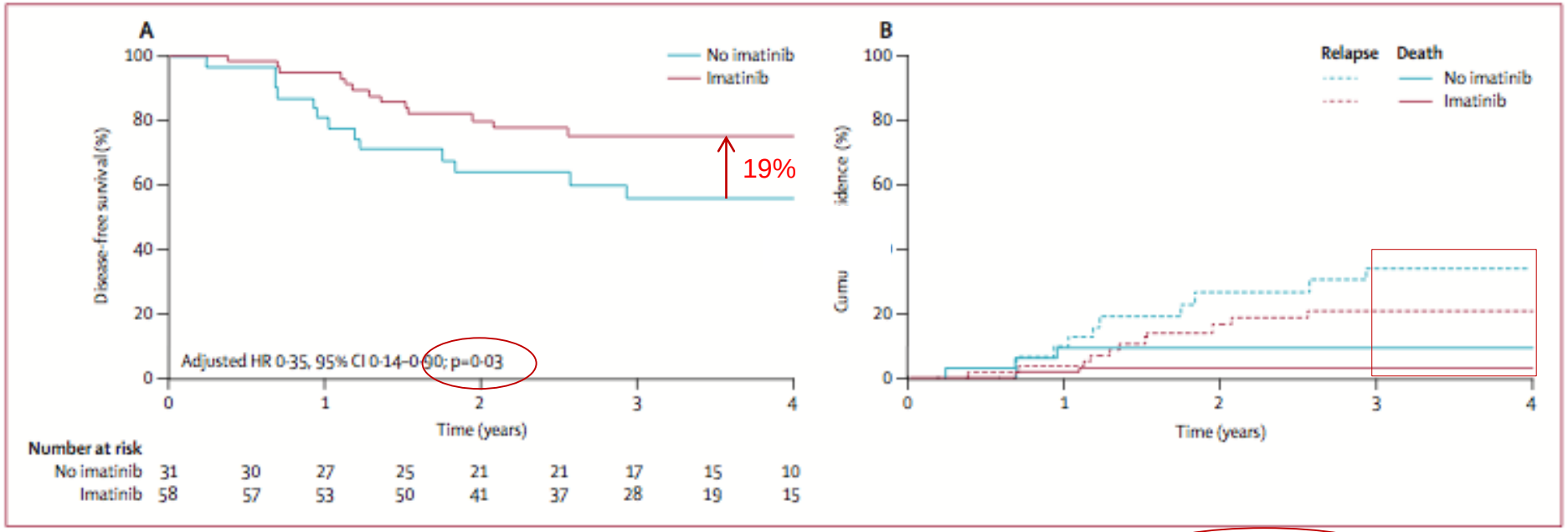


Figure 4: **Disease-free survival curves and cumulative incidence of relapse and of death in continuous complete remission for good-risk patients, analysed as treated**
(A) Disease-free survival. (B) Cumulative incidence of relapse and death continuous complete remission for patients in the good-risk group. One event in a patient in the imatinib group at 6 years after randomisation is omitted (died in continuous complete remission of pulmonary graft-versus-host disease after transplantation).

avec 77% allogreffés en RC1

Biondi A et al., Lancet Oncol 2012

Mais….. le COG AALL0031

Schultz (ASH 2007) : COG AALL0031

- **Dose cumulée d´Imatinib relevante?**

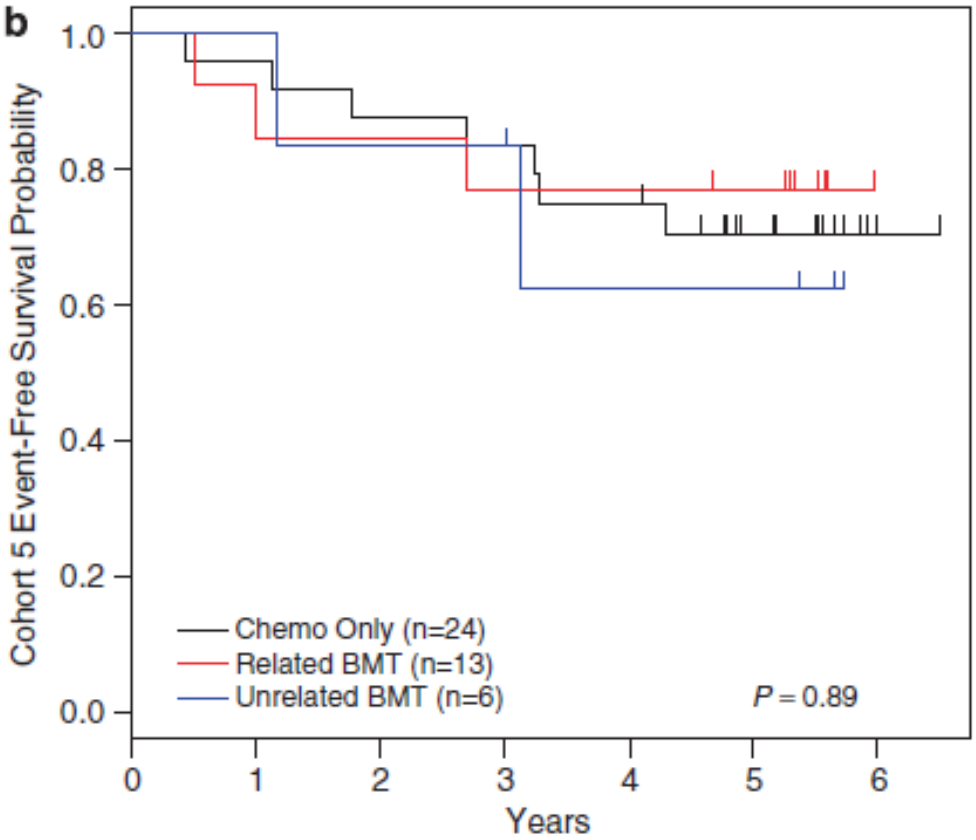
Therapy	Cons 1 (3 wk)	Cons 2 (3 wk)	Reind 1 (3 wk)	Intens 1 (9 wk)	Reind 2 (3 wk)	Intens 2 (9 wk)	Maint 1-4 (8-wk cycles)	Maint 5-12 (8-wk cycles)
Cohort 1				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 2		Imatinib × 3 wk	Imatinib × 3 wk		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 3	Imatinib × 3 wk →				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 4	Imatinib × 3 wk →							Imatinib × 2 wk every 4 wk
Cohort 5	Continuous dosing of imatinib							Imatinib × 2 wk every 4 wk

Therapy given	N	2 year EFS	SE
All cohorts (except M3)	83	60.2%	6.3%
Cohort 1/2 = 42 et 63 j de Glivec	17	42.1%	11.9%
Cohort 5 = 280 j de Glivec	44	80.7%	17.7%

- **Quelle place pour la greffe à l'ère du Glivec®?**

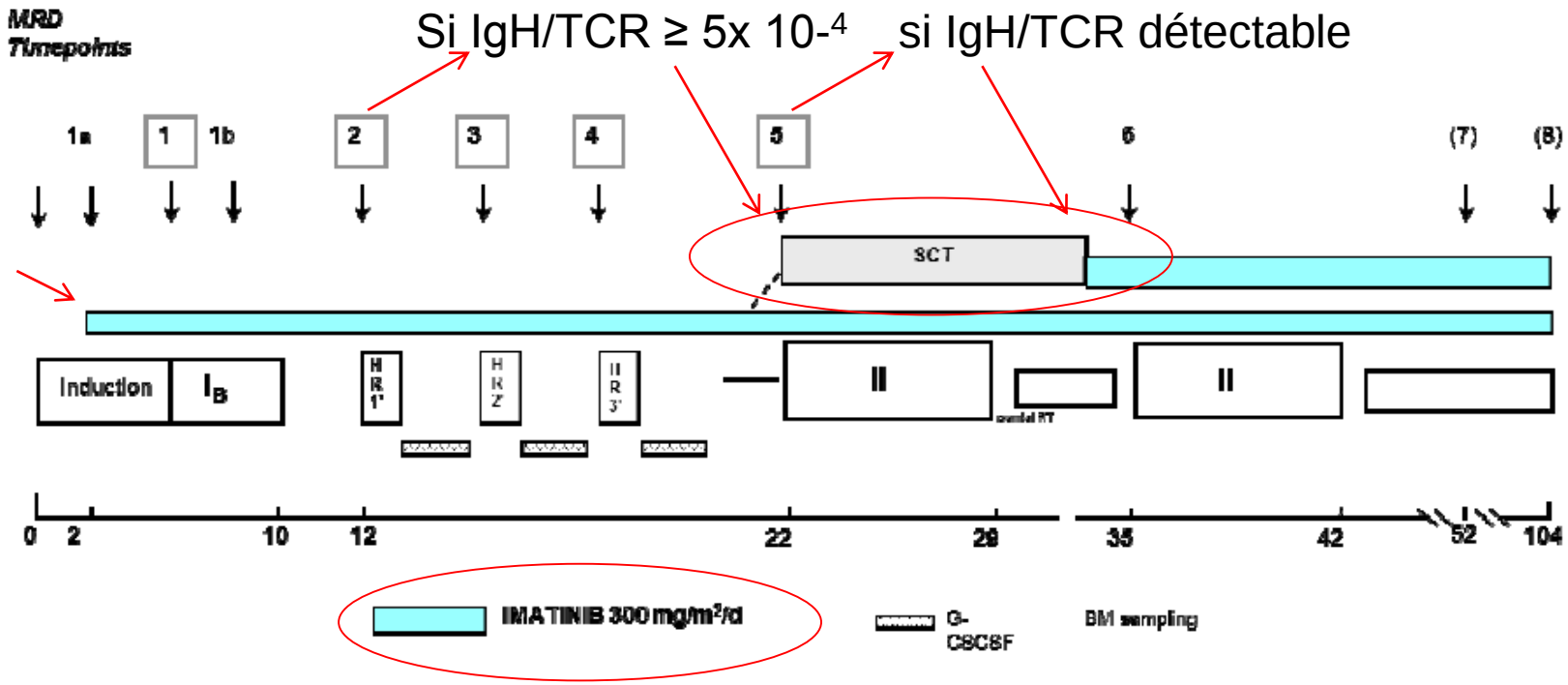
Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group Study AALL0031

KR Schultz[1], A Carroll[2], NA Heerema[3], WP Bowman[4], A Aledo[5], WB Slayton[6], H Sather[7], M Devidas[8], HW Zheng[9], SM Davies[10], PS Gaynon[11], M Trigg[12], R Rutledge[13], D Jorstad[14], N Winick[15], MJ Borowitz[16], SP Hunger[9], WL Carroll[17] and B Camitta[14] from the Children's Oncology Group



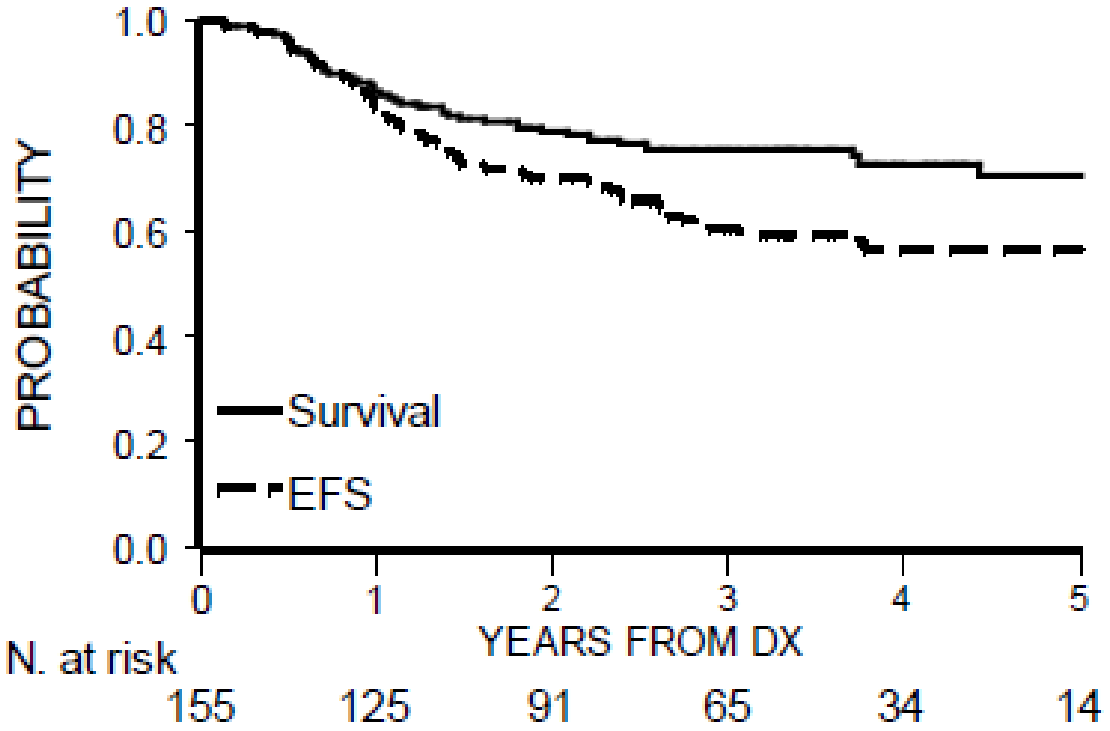
Schultz K et al. Leukemia, 2014

Amended EsPhALL
Outline



À partir de 2010

EsPhALL amendé



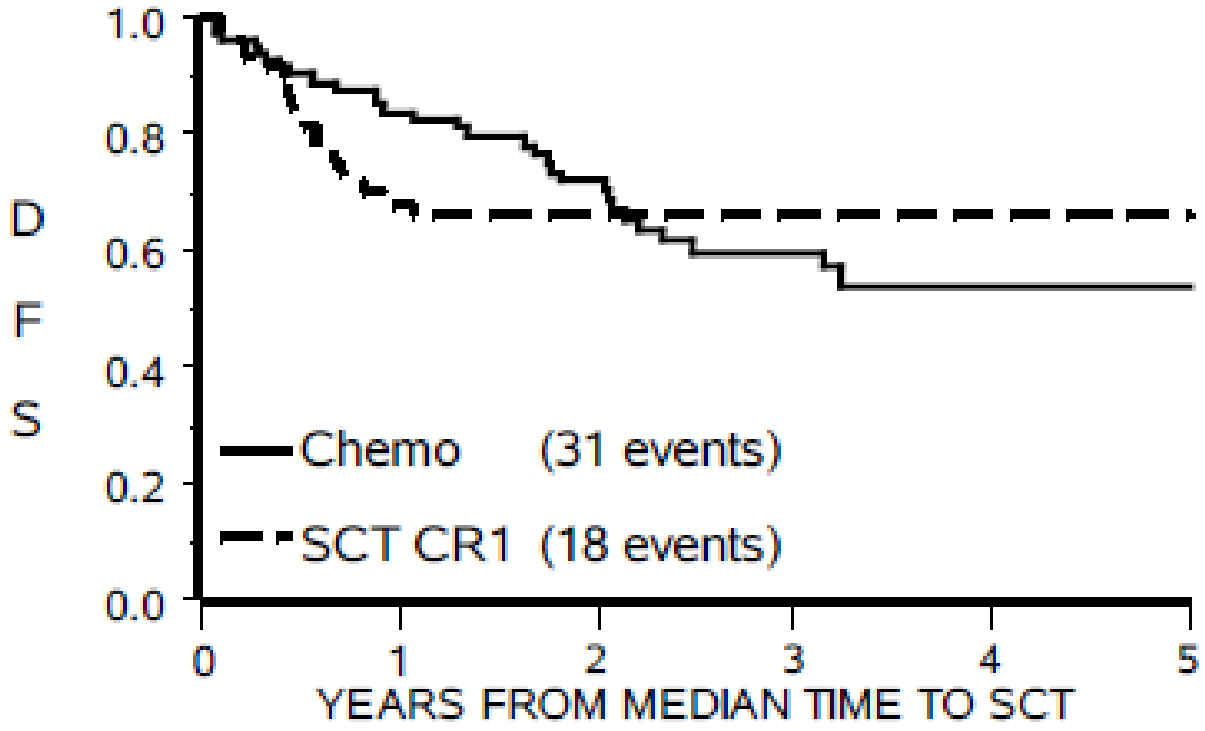
Pas mieux!
Mais…

	N. pts.	N. events (relapses)	EFS (SE) 4-year	EFS (SE) 5-year	N. deaths	Survival (SE) 4-year	Survival (SE) 5-year
Overall	155	58 (33)	56.9 (4.5)	56.9 (4.5)	38	73.1 (4.0)	70.6 (4.5)

'closed' EsPhALL:

	N. pts.	N. events (relapses)	EFS (SE) 4-year	EFS (SE) 5-year	N. deaths	Survival (SE) 4-year	Survival (SE) 5-year
Overall	160	65 (50)	61.0 (3.9)	60.3 (3.9)	48	73.6 (3.5)	71.6 (3.6)

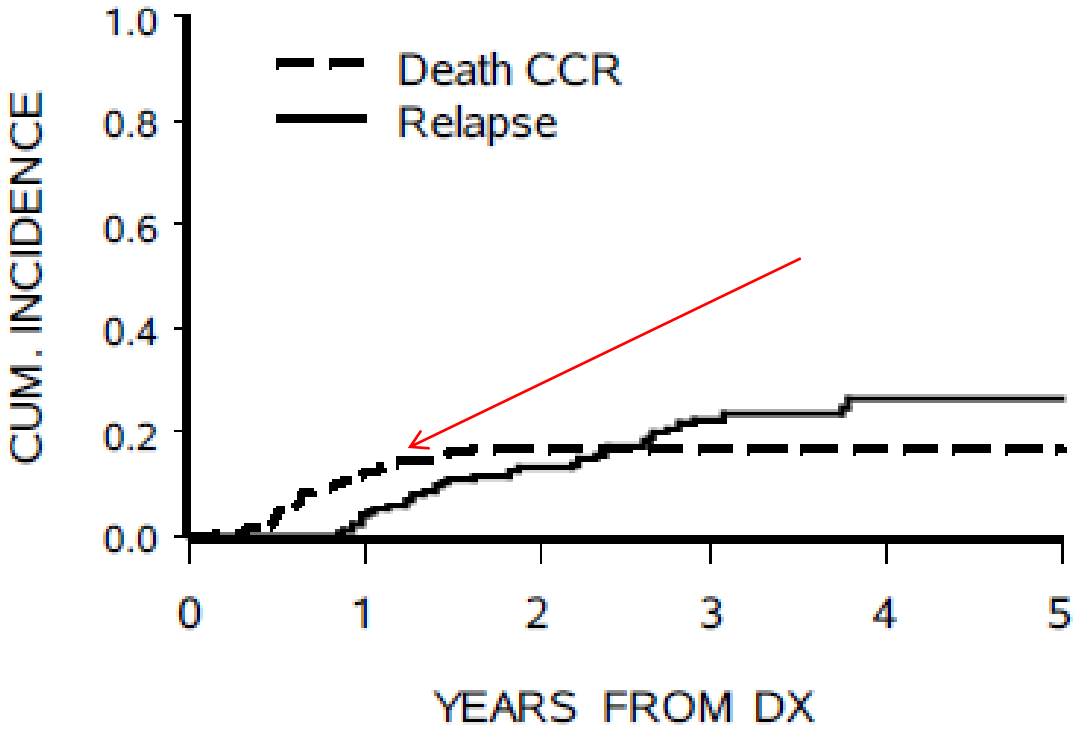
40% de greffés vs ≈80%



Dg-greffe : 5,5 mois (3,8-11,9)

Performed treatment	N. pts.	N. events	N. rel	N. deaths CCR	4-year DFS (SE)	p-value
Chemo	114	31	26	5	54.1 (6.7)	0.0176
SCT CR1	58	18	7	11	66.6 (6.4)	

Décès en RC1 trop nombreux



	N. pts.	N. relapses	C.I. (SE) 4-year	C.I. (SE) 5-year
Overall	154	33	26.3 (4.1)	26.3 (4.1)

	N. pts.	N. deaths CCR	C.I. (SE) 4-year	C.I. (SE) 5-year
Overall	154	26	16.8 (3.1)	16.8 (3.1)

'closed' EsPhALL

	N. pts.	N. relapses	C.I. (SE) 4-year	C.I. (SE) 5-year
Overall	160	50	30.2 (3.7)	30.9 (3.7)

	N. pts.	N. deaths CCR	C.I. (SE) 4-year	C.I. (SE) 5-year
Overall	160	15	8.8 (2.3)	8.8 (2.3)

Enjeux actuels

- **Place et intensité de la chimiothérapie**

- Toxicité excessive incite à diminuer CT
  - **EsPhALL**: MRD IgH/TCR fin Ib : 91% MRD < $5x10^{-4}$ sur n=71
  - **Expérience du GRAALL** : obj =% MMoIR (BCR/ABL<0,1%)

Arm A : VCR/dexa
Arm B: Hyper CVAD +imatinib 400 mgx2/j

EFS 42%vs 32% p =0,13

Table 3. Response to the first 2 treatment cycles

	All patients (n = 268)	Arm A (n = 135)	Arm B (n = 133)	P
Hematologic CR, n (%)	254 (94.8)	133 (98.5)	121 (91.0)	.006
After cycle 1	249	131	118	.009
After cycle 2	5	2	3	.68
Refractory ALL after cycle 2, n (%)	4 (1.5)	1 (0.7)	3 (2.2)	.37
MMolR, n/tested (%)				
After cycle 1	96/217 (44.2)	50/116 (43.1)	46/101 (45.5)	.78
After cycle 2	134/205 (65.4)	74/112 (66.1)	60/93 (64.5)	.88
Molecular CR, n/tested (%)				
After cycle 1	21/217 (9.7)	11/116 (9.5)	10/101 (9.9)	.99
After cycle 2	53/205 (25.8)	32/112 (28.6)	21/93 (22.6)	.34
Induction deaths, n (%)				
Early deaths*	10 (3.7)	1 (0.7)	9 (6.7)	.010
Day 60 mortality†	15 (5.6)	3 (2.2)	12 (9.0)	.017

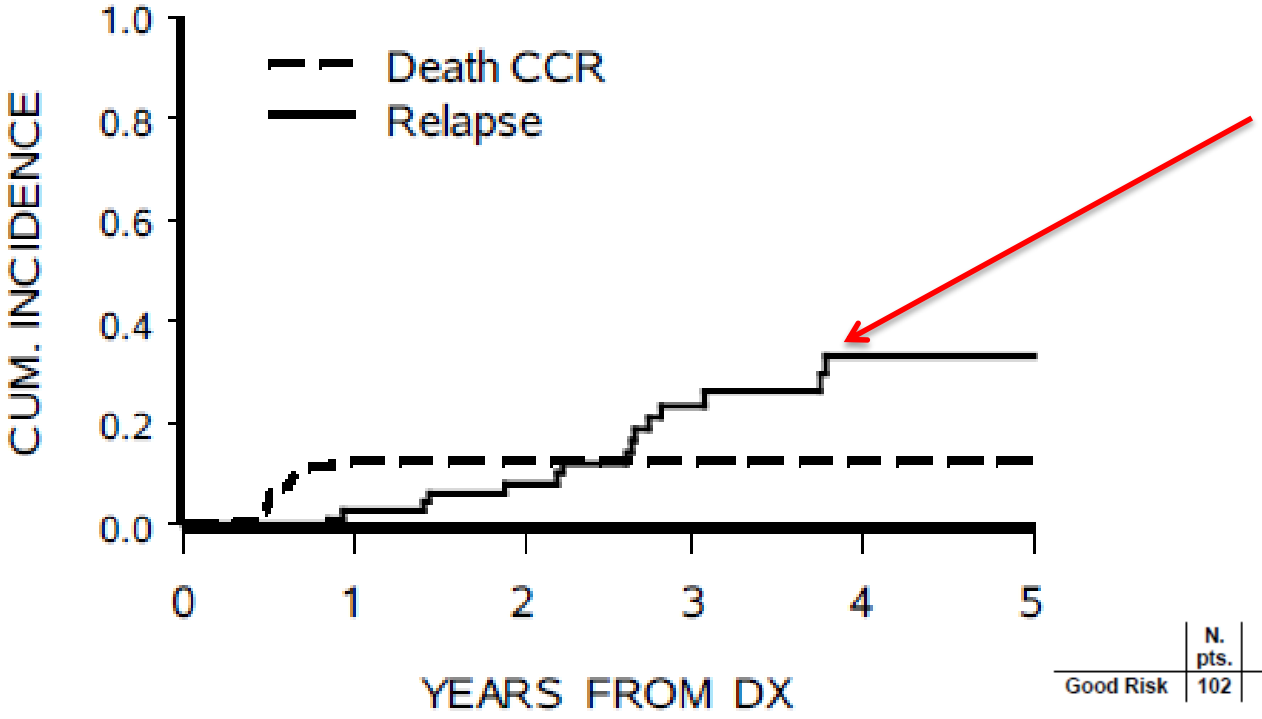
*Early death was defined as death occurring during cycle 1 or 2, before the assessment of hematologic response after cycle 1 or 2.

Chalandon, Y et al. Blood, 2015

Enjeux actuels

- Place et intensité de la chimiothérapie : **pas de plateau**

Bons répondeurs



	N. pts.	N. relapses	C.I. (SE) 4-year	C.I. (SE) 5-year
Good Risk	102	15	33.5 (7.6)	-

	N. pts.	N. deaths CCR	C.I. (SE) 4-year	C.I. (SE) 5-year
Good Risk	102	11	12.8 (3.7)	-

Enjeux actuels

- **Importance chimiothérapie ?**
  - ➢++ intensive dans le COG AALL0031(cohort 5)

	AALL0031	EsPhALL
Duration intensive Rx (End IA until start Maint)	71 weeks (MTX HD, ARAC, Cyclo-Ifo, VP16..)	31 weeks
Total Duration of therapy	127 weeks	104 weeks
Use of SCT		Higher
Imatinib exposure	Much more prolonged	

Enjeux actuels

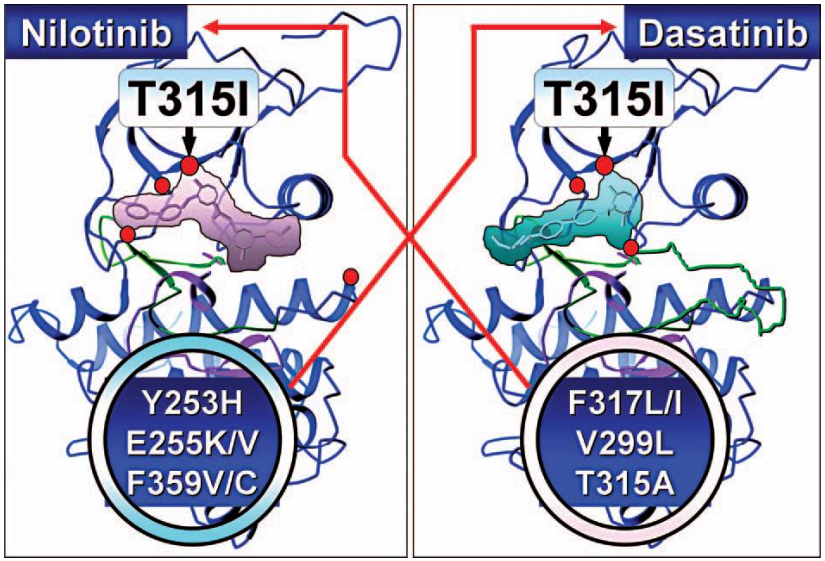
- **Importance chimiothérapie ?**
  - ➢++ intensive dans le COG AALL0031(cohort 5)
- **Changer d'ITK?**
  - Dasatinib? (Sprycel®)
    - + puissant (x 30-50 *in vivo*)
    - peut lier la forme active ou inactive du domaine kinase de ABL

    (+ affin aussi …)
    - Inhibe aussi voie Src
    - Passe la barrière méningée

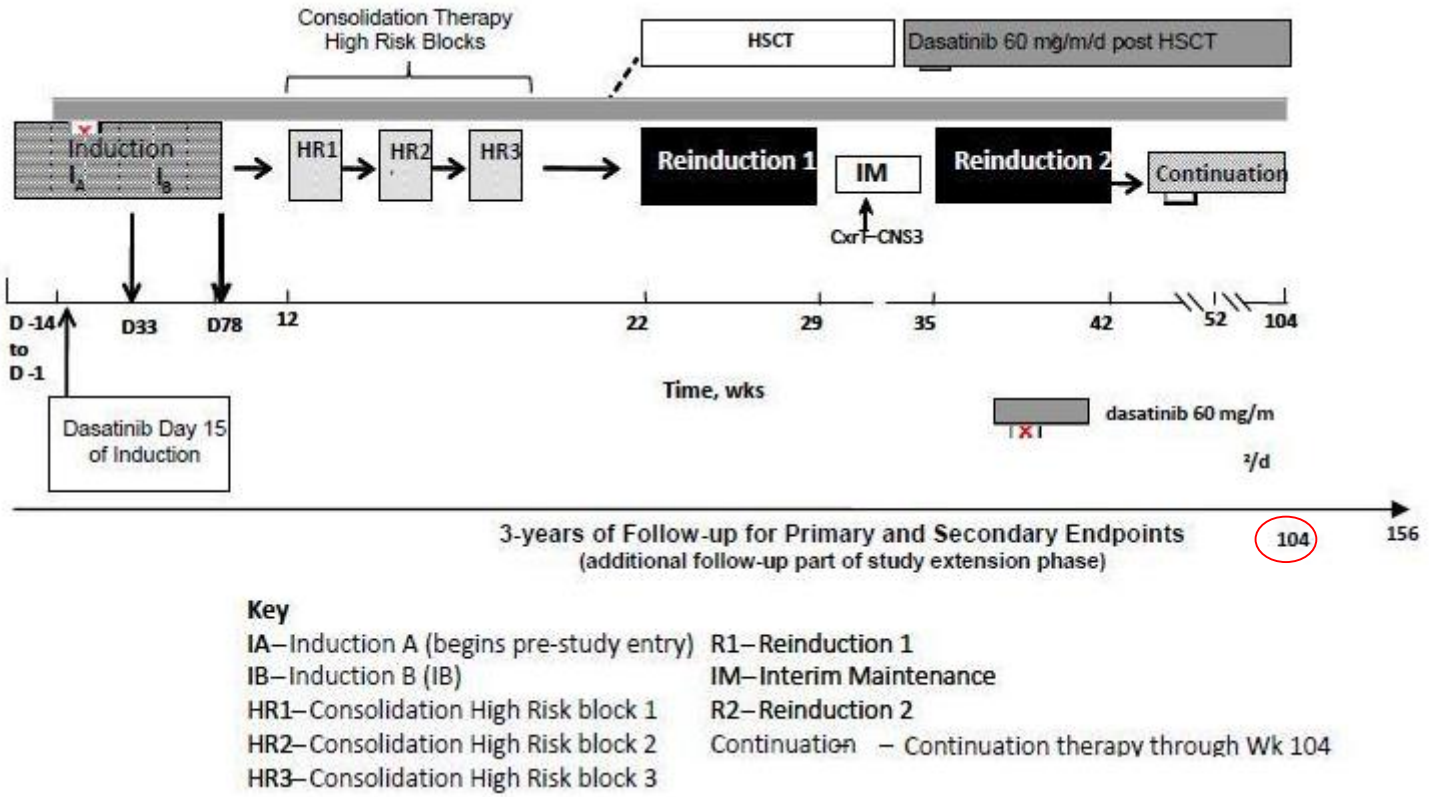
  Et autres

  ➢(COG AALL0622) :

  - toxicité neurologique ++
  - Pas de plateau non plus



Clinical Protocol CA180372
phase II internationale : COG, MRC, AIEOP



Key

IA–Induction A (begins pre-study entry)
IB–Induction B (IB)
HR1–Consolidation High Risk block 1
HR2–Consolidation High Risk block 2
HR3–Consolidation High Risk block 3
R1–Reinduction 1
IM–Interim Maintenance
R2–Reinduction 2
Continuation – Continuation therapy through Wk 104

But : EFS 3 ans >72%

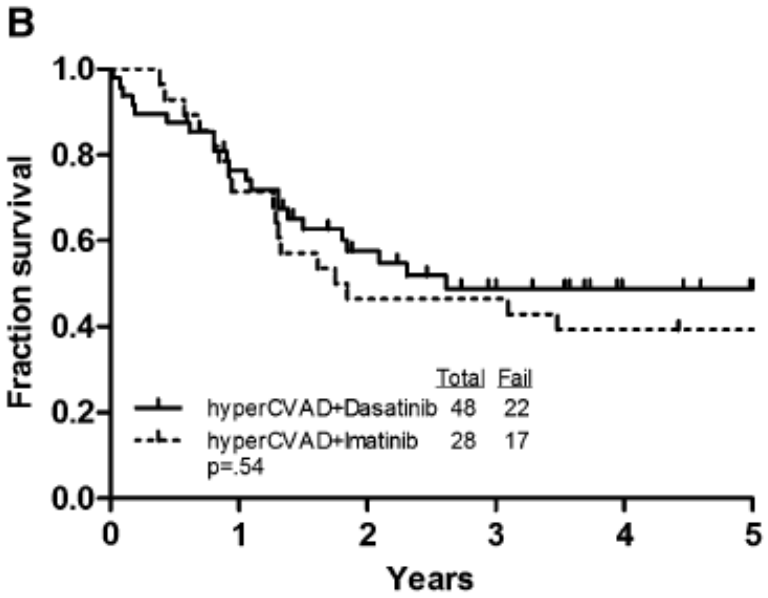
HSCT for patients:
MRD TP2 >5x10-4
MRD TP2< 5x10-4 if still MRD+ after 3rd HR

2012-2014 (75 patients)
MRD à chaque TP: CMF+IgH/TCR+BCR/ABL

→ Résultats?

Enjeux actuels

- **Importance chimiothérapie ?**
  - ➢++ intensive dans le COG AALL0031(cohort 5)
- **Changer d'ITK?**
  - ➢Dasatinib: pas mieux chez adultes



blood®
2013 122: 1214-1221
doi:10.1182/blood-2012-11-466482 originally published online July 8, 2013

Detection of MRD may predict the outcome of patients with Philadelphia chromosome –positive ALL treated with tyrosine kinase inhibitors plus chemotherapy

Farhad Ravandi, Jeffrey L. Jorgensen, Deborah A. Thomas, Susan O'Brien, Rebecca Garris, Stefan Faderl, Xuelin Huang, Sijin Wen, Jan A. Burger, Alessandra Ferrajoli, Partow Kebriaei, Richard E. Champlin, Zeev Estrov, Pramoda Challagundla, Sa A. Wang, Rajyalakshmi Luthra, Jorge E. Cortes and Hagop M. Kantarjian

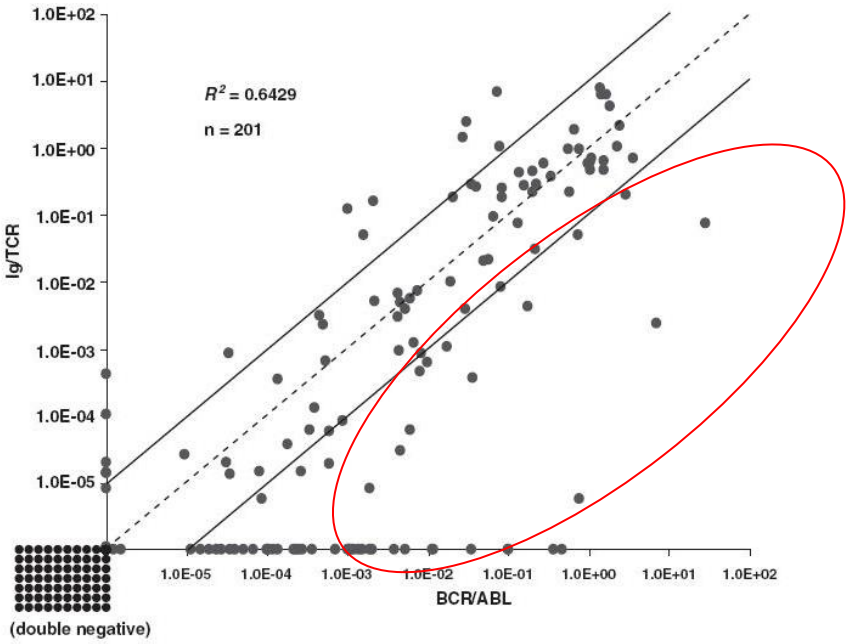
Enjeux actuels

- **Importance chimiothérapie ?**
  - ➢++ intensive dans le COG AALL0031(cohort 5)
- **Changer d'ITK?**
  - ➢Dasatinib: pas mieux
- **Valeur de la MRD/ Greffe en RC1?**

Quelle valeur prédictive de la MRD dans LAL Phi?

- PCR IgH/TCR (EsphALL)
- CMF (COG)
- BCR/ABL ?
  - Corrélation avec IgH/TCR

MRD



Zaliova K et al. Leukemia, 2009
Lee et al., cancer 2009

  - Non ↘ de 3 log =prédictif de la rechute

blood®
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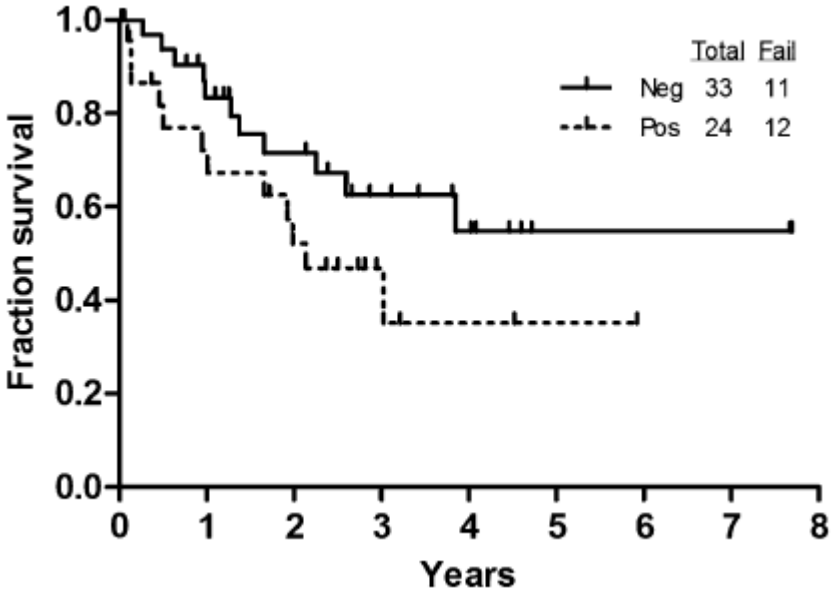
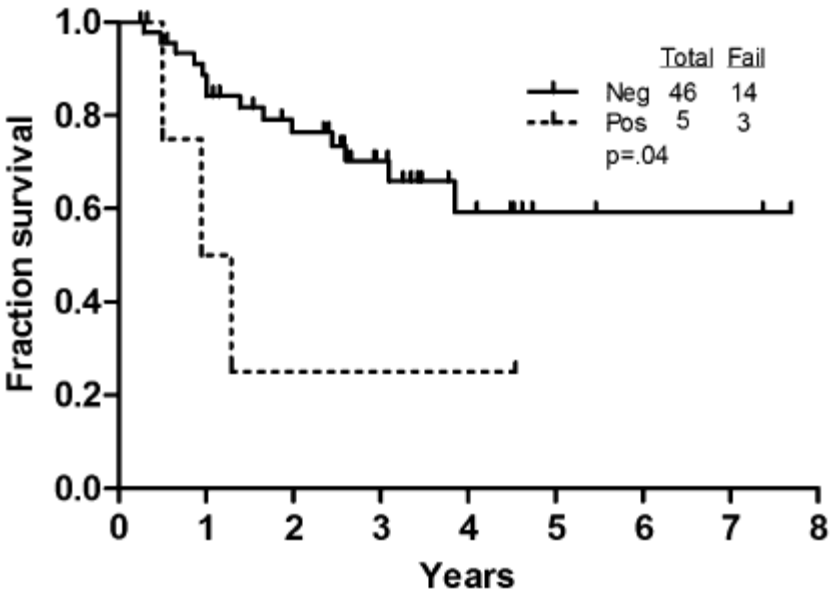
CMF

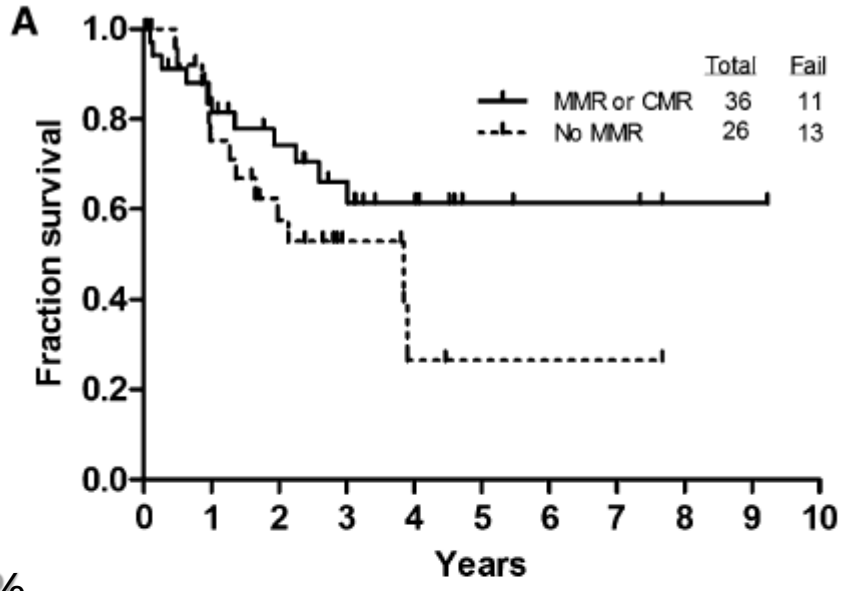


At CR

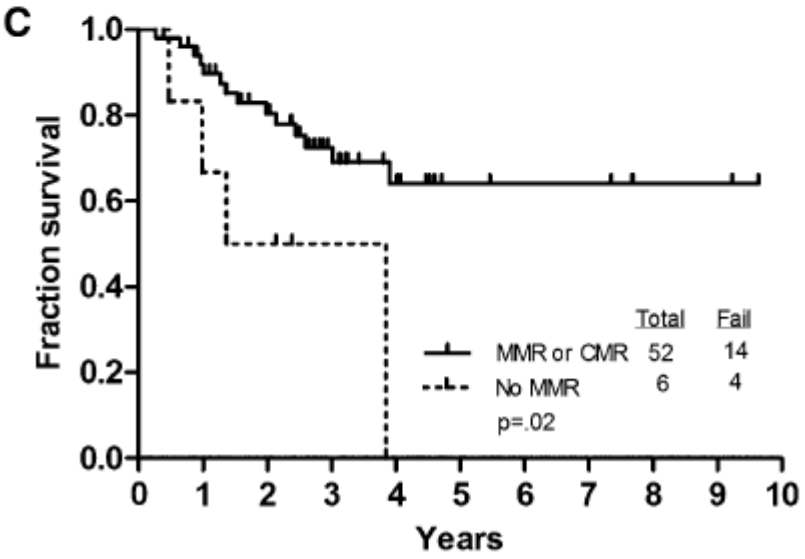


At 3 months

At CR



BCR/ABL<0,1%



At 3 months

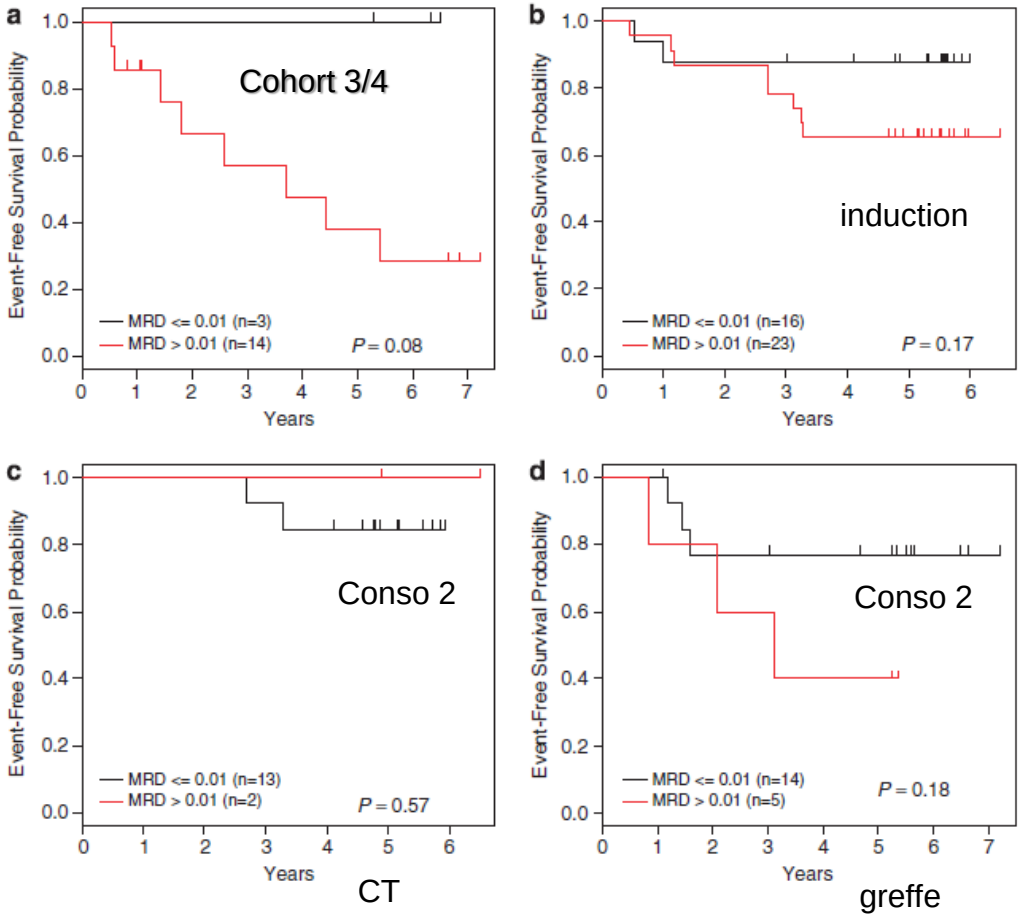
Mais 15 patients /76 (27 échantillons) BCR/ABL>0,1% et neg en CMF :
Cellules BCR/ABL+ pas dans compartiment CD19+

Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group Study AALL0031

KR Schultz[1], A Carroll[2], NA Heerema[3], WP Bowman[4], A Aledo[5], WB Slayton[6], H Sather[7], M Devidas[8], HW Zheng[9], SM Davies[10], PS Gaynon[11], M Trigg[12], R Rutledge[13], D Jorstad[14], N Winick[15], MJ Borowitz[16], SP Hunger[9], WL Carroll[17] and B Camitta[14] from the Children's Oncology Group

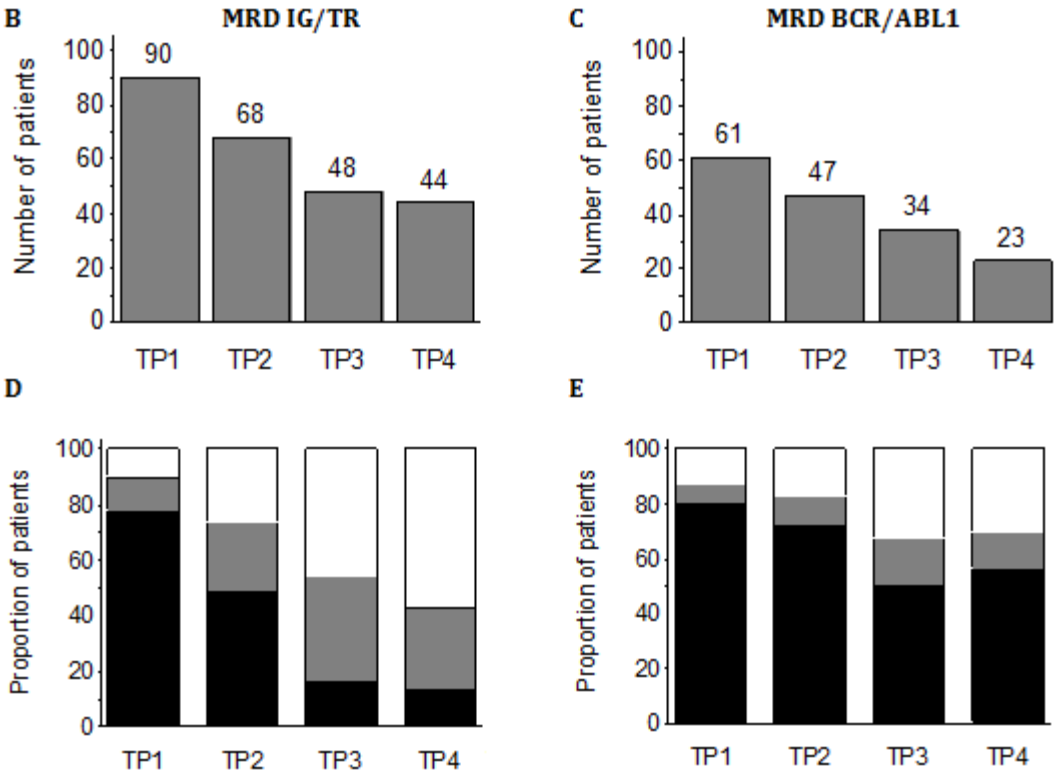
MRD non significative

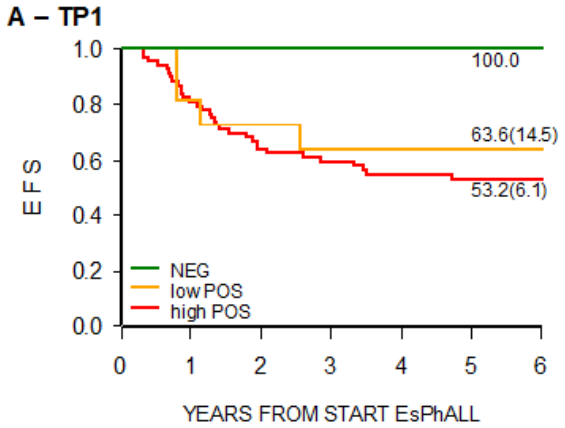
Cohort 5



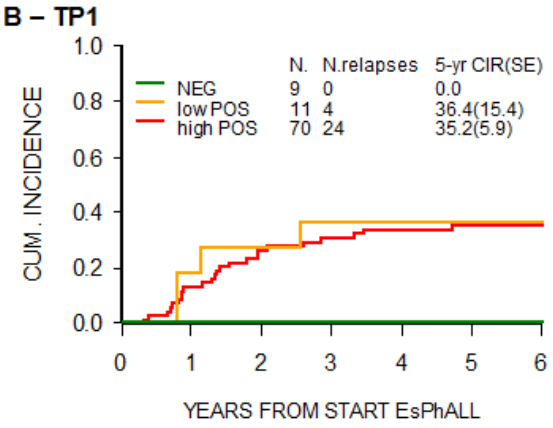
ESphALL (<2010)

MRD negative
low positive <5x10^{-4}
highly positive ≥5x10^{-4}

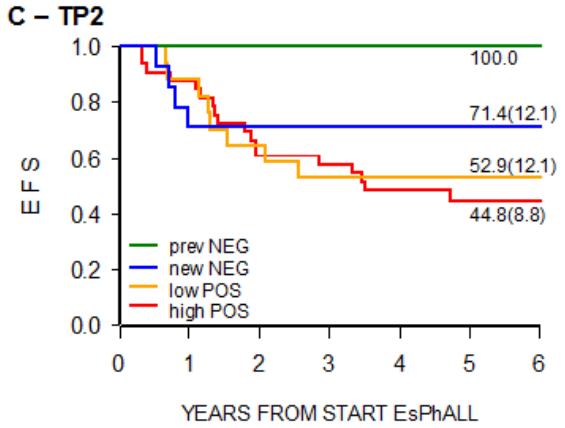


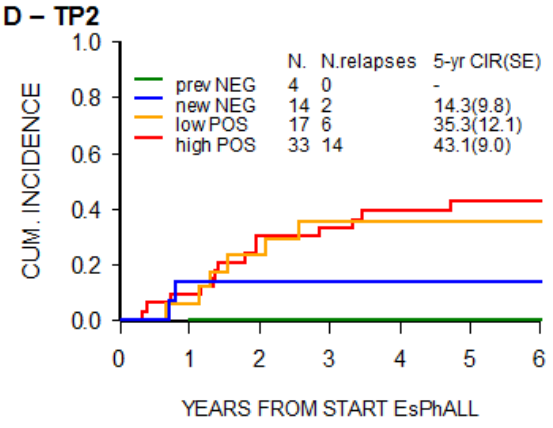


P=0.01



IgH/TCR





Mais dans EsPhALL amendé :

1-Prédiction imparfaite en fin Ia **:**

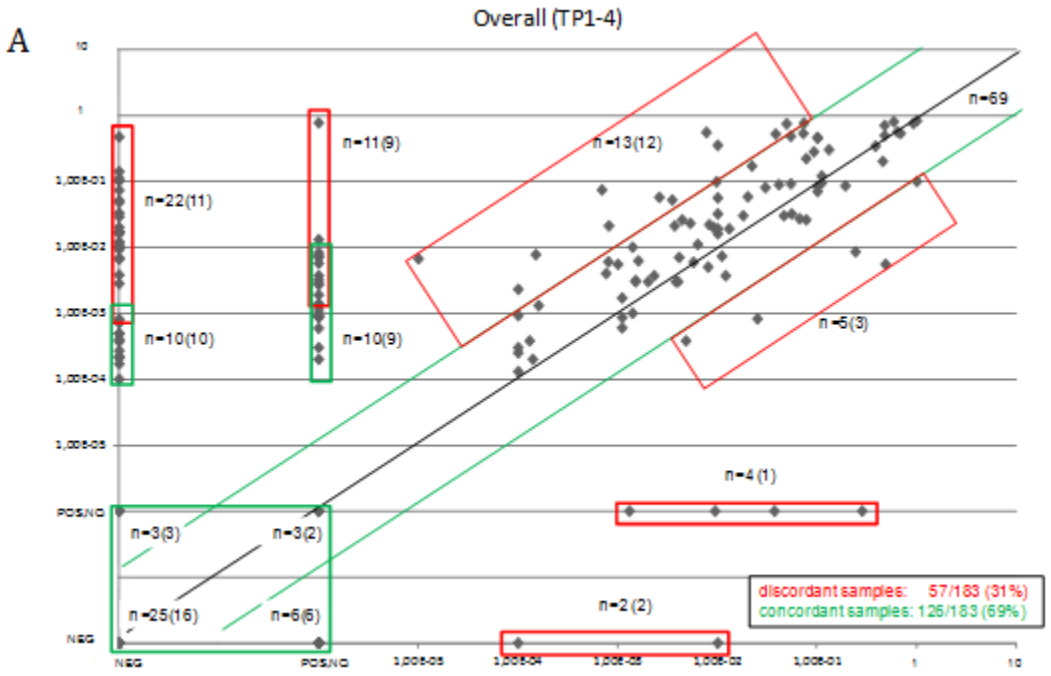
- 20% des MRD<$5x10^{-4}$ rechutent
- 30% des ≥ $5x10^{-4}$ rechutent

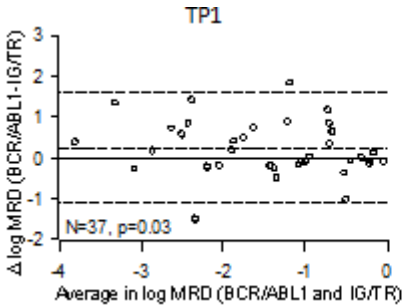
2-MRD en fin Ib plus pertinente

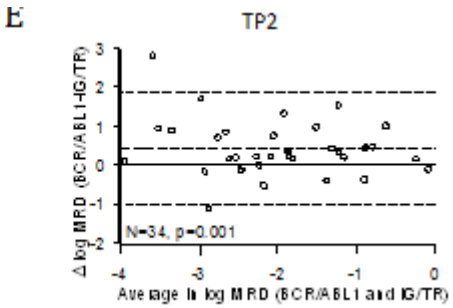
Concordance BCR-ABL/ IgH-TCR: 70%

- Valeur proche TP1 et TP2 mais dissociation ensuite :

Cellule souche BCR/ABL+?



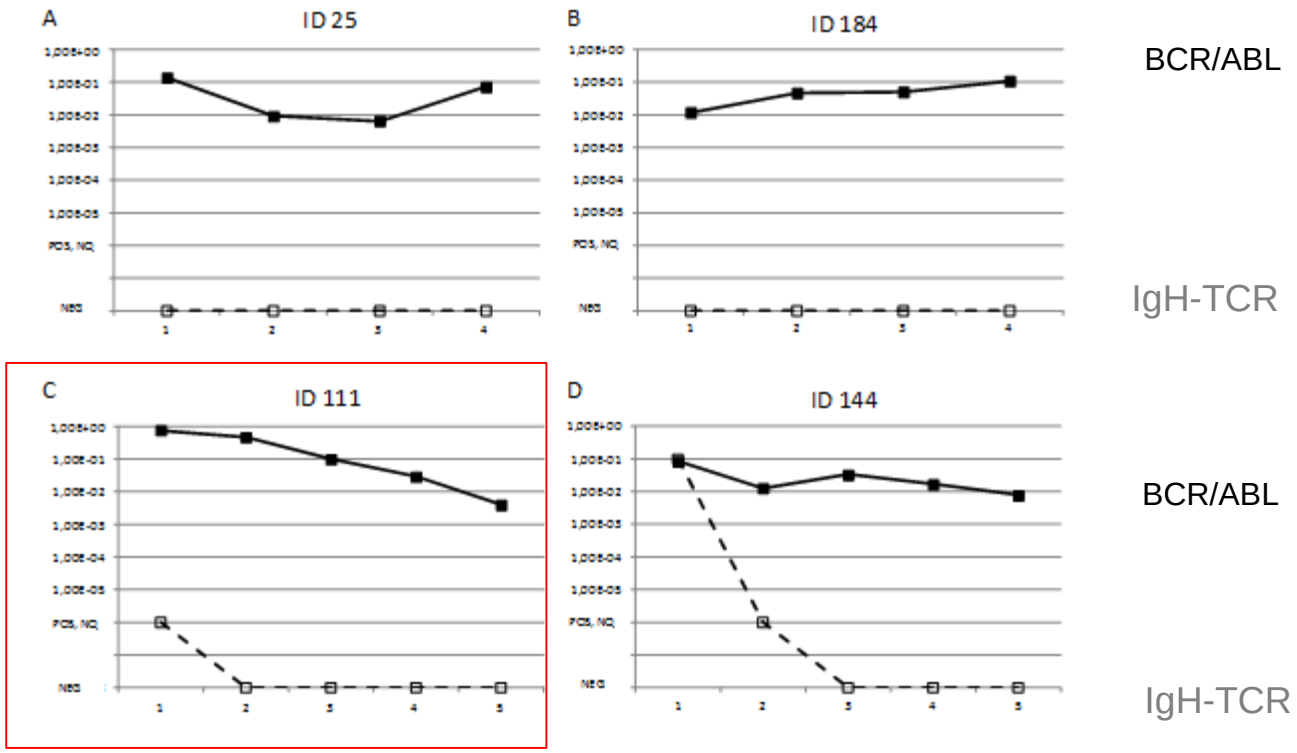




Concordance BCR-ABL/ IgH-TCR 70%

- Valeur proche TP1 et TP2 mais dissociation ensuite :

Cellule souche BCR/ABL+?



Aucun cas inverse

Enjeux actuels

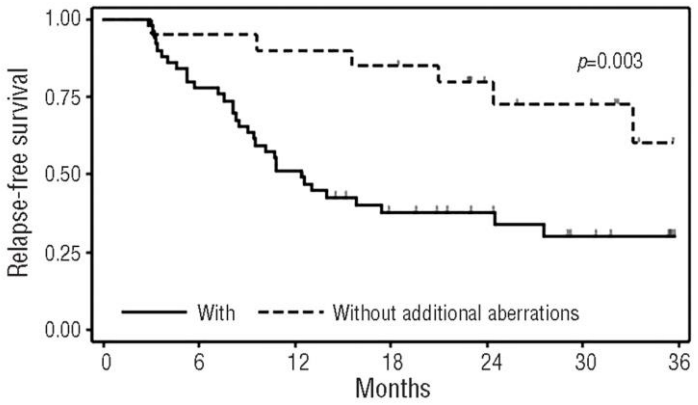
- **Importance chimiothérapie ?**
  - ➢++ intensive dans le COG AALL0031(cohort 5)
- **Changer d'ITK?**
  - ➢Dasatinib: pas mieux
- **Valeur de la MRD/ Greffe en RC1**
  - – IgH/TCR insuffisamment prédictif
  - – BCR/ABL?
- **Phi : groupe cytogénétique hétérogène**
  - – Malgré profil transcriptionnel particulier

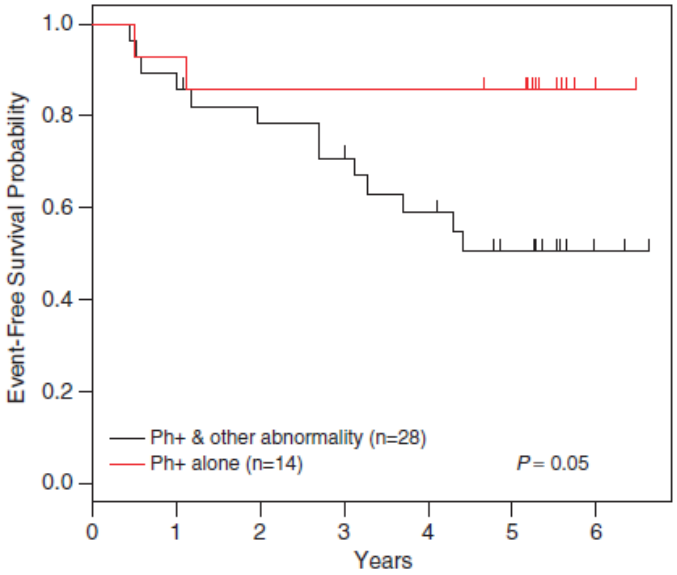
• Attention groupe hétérogène

• Anomalies additionnelles

- – +der 22
- – Abn (9p)
- – 7-
- – Tri 8

Yanada M et al., Haematologica 2008





Schultz et al., Leukemia 2014

Secondary cytogenetic aberrations were present in 44 (64%) patients, the most frequent being +der(22) ($N = 17$), ⩾50 chromosomes ($N = 14$), −7/del(7p) ($N = 10$), abnormal (9p) ($N = 9$) and +8 ($N = 6$). The overall 5-year EFS was 67 ± 7% for

Cohorts 3, 4 et 5

Impact de Ikaros ?

Frequency of deletions in Ph+ ALL (Modified from Charles G. Mullighan, Gene and Development 2008)

Subcategory	Number of cases	Gene deletion frequency (%)		
		IKAROS	PAX5	CDKN2A/B
Ph+ B-ALL[a]	43	84	51	54
Non Ph+ B-ALL	211	11	30	32
T-ALL	50	4	10	72

Mullighan C et al., Nature 2008

Iacobucci I et al., Blood 2009

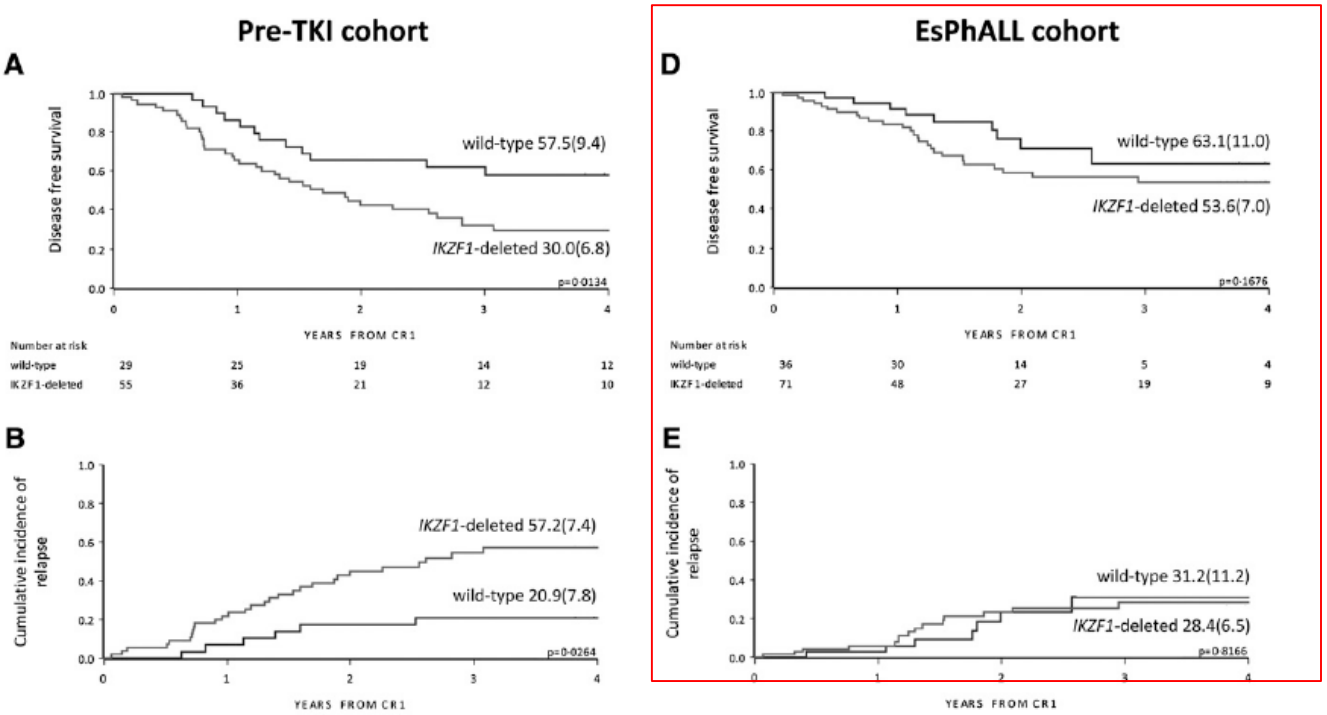
75%, n= 106

Rôle dans sensibilité aux TKI ?

blood®
2014 123: 1691-1698
doi:10.1182/blood-2013-06-509794 originally published online December 23, 2013

IKZF1 status as a prognostic feature in *BCR-ABL1*–positive childhood ALL

Arian van der Veer, Marketa Zaliova, Federica Mottadelli, Paola De Lorenzo, Gertruuy te Kronnie, Christine J. Harrison, Hélène Cavé, Jan Trka, Vaskar Saha, Martin Schrappe, Rob Pieters, Andrea Biondi, Maria Grazia Valsecchi, Martin Stanulla, Monique L. den Boer and Giovanni Cazzaniga

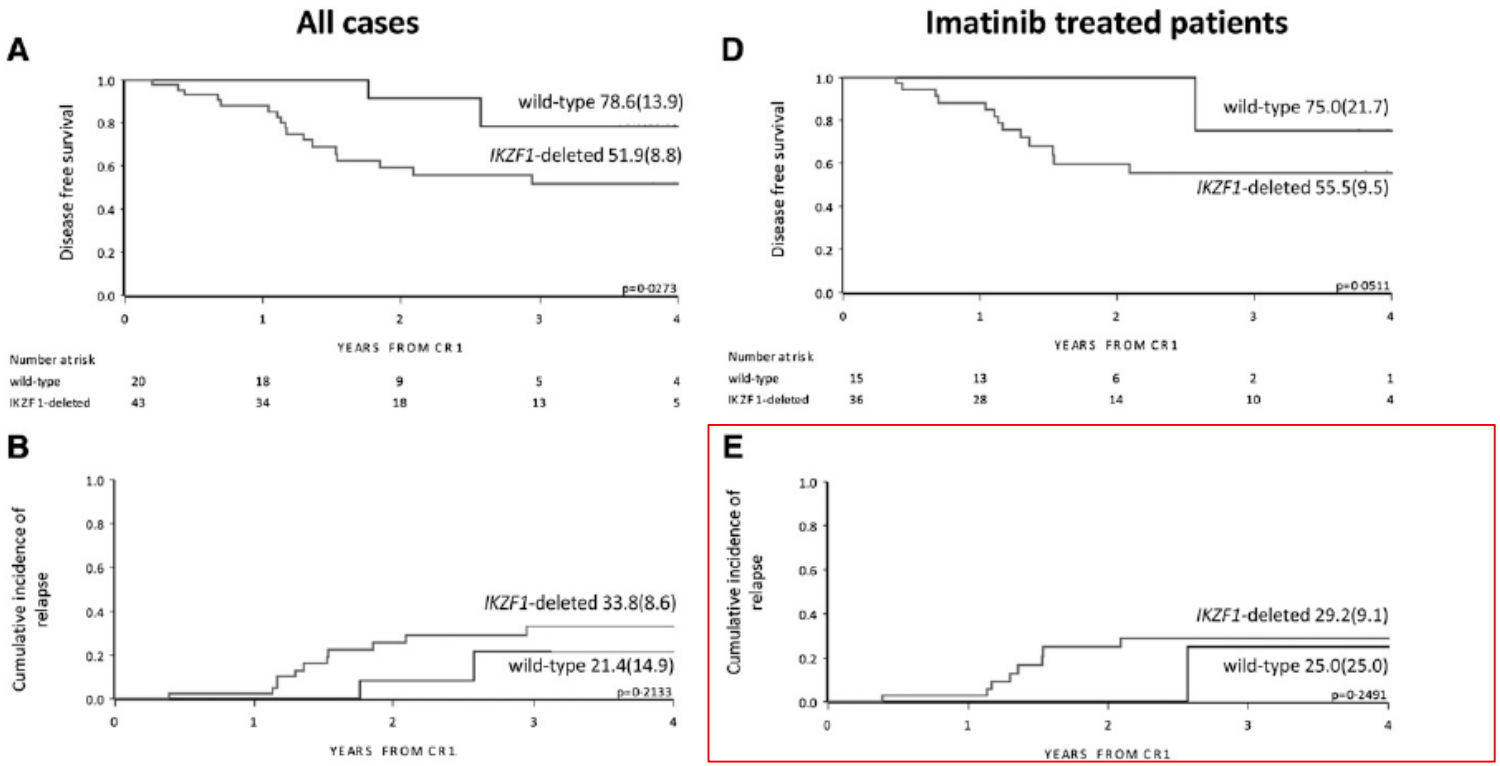


29 WT et 55 délétés

36 WT et 71 délétés

Attention groupe hétérogène

EsphALL bons répondeurs + Imatinib
N=51

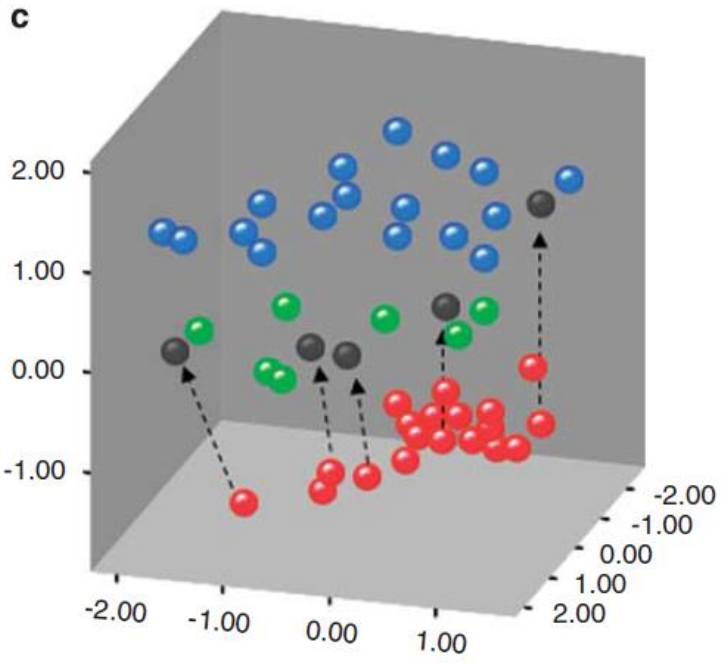


36 délétés et 15 WT

van der Veer A et al., Blood 2014

Attention groupe hétérogène

- signature transcriptionnelle/gènes de la survie



Zuo Z et al., Modern Pathology 2010

Table 2 The list of genes that highly correlate with therapeutic response in adult Ph+ ALL patients

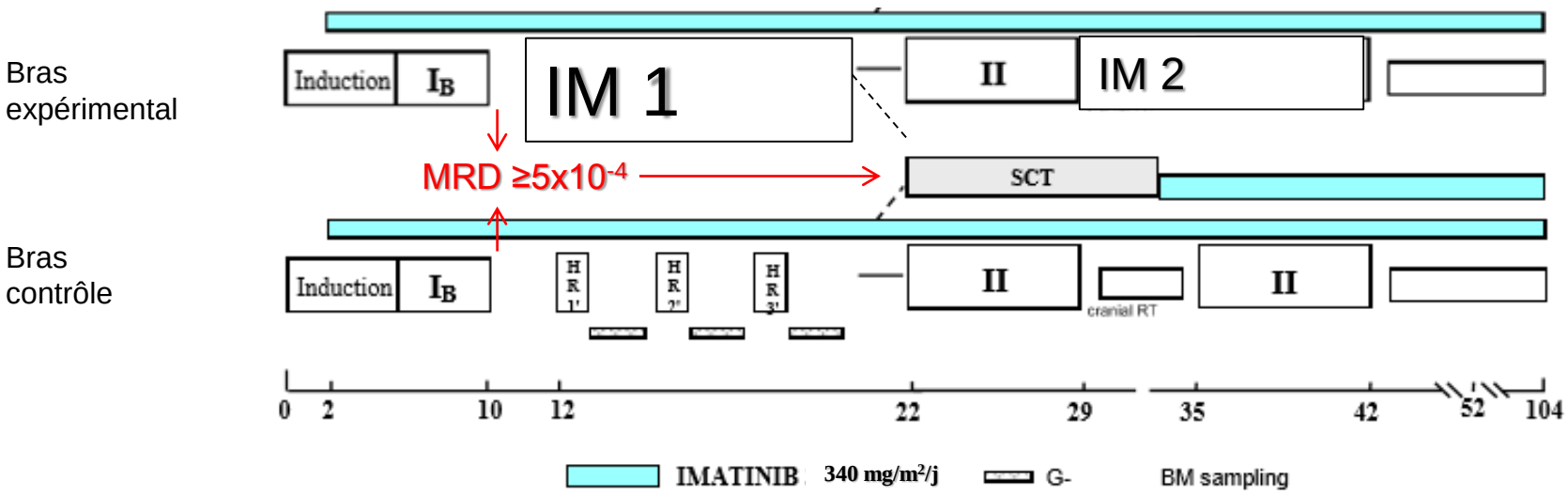
Symbol	*Gene name*	*Group*	*Major pathways*	*Upregulated*	P-*value*
CD69	CD69 molecule	Transmembrane receptor	Cytotoxicity, apoptosis	Group A	0.002
FLT3	fms-related tyrosine kinase 3	Protein kinase receptor	Growth, apoptosis	Group A	0.002
ITPR1	Inositol 1,4,5-triphosphate receptor, type 1	Ion channel, cation transporter	Apoptosis, growth	Group A	0.002
NPM1	Nucleophosmin	Chaperone, transcription regulator	Apoptosis, growth	Group A	0.002
PTGS1	Prostaglandin-endoperoxide synthase 1	Synthase	Apoptosis, drug resistance	Group B	0.029
SLC2A3	Solute carrier family 2, member 3	Carbohydrate transporter	Apoptosis, Hif1a signaling	Group B	0.002
SPRY2	Sprouty homolog 2	Signaling molecule	Growth, migration	Group A	0.002
TCF4	Transcription factor 4	Helix-loop-helix transcription factor	Growth, acute phase response	Group A	0.002
TP53	Tumor protein p53	Transcription factor	Apoptosis, growth	Group A	0.002

Perspectives

- **Essai EsPhALL+COG 2017**

AALL1631 (S Hunger, COG sponsor) début automne 2016

Objectif: diminuer toxicité sans diminuer DFS



NB: RXT pour SNC3 à18gy et phase II: dexa splitée J1-7 puis J15-21
MRD= IgH/TCR (à défaut CMF) mais pas BCR/ABL

Perspectives

- **Essai EsPhALL+COG 2017**

→ **Réponse à intensité de CT**

- **Valeur MRD dans la LAL Phi /DFS pour la stratégie thérapeutique**

→ **compléter étude de l'EsPhALL amendé + phase II CA180372 avec dasatinib**

Perspectives

- **Essai EsPhALL + COG 2017**
- **Valeur MRD dans la LAL Phi /DFS dans stratégie**
- **Affiner facteurs prédictifs de mauvais pronostic à long terme (IKZF1, add…)**

- **↗ indications de greffe en RC1**
- **Nouvelles thérapies ciblées en 1ère ligne :**
  - **anti Jak1/2 : ruxolitinib**
  - **autre ITK actifs sur la voie Src : bosutinib, vandetanib (antiRET)…**
- **Immunothérapie des LAL-B (Bite, CAR-T…)**

Perspectives

- **Essai EsPhALL + COG 2017**
- **Valeur MRD dans la LAL Phi /DFS dans stratégie**
- **Affiner facteurs prédictifs de mauvais pronostic à long terme**
- **ITK en post greffe**
  - **Faisabilité/tolérance**
  - **Préemptif ou préventif (rôle IS anti GVL?)**
  - **Lequel/résistance ?**

Perspectives

- Essai EsPhALL + COG 2017
- Valeur MRD dans la LAL Phi /DFS dans stratégie
- Affiner facteurs prédictifs de mauvais pronostic à long terme
- ITK en post greffe
- Durée d'exposition et effets à long terme

Conclusion

- LAL Phi =un des premiers modèles de **thérapie ciblée** en cancérologie pédiatrie

- L'addition d'ITK a révolutionné cette maladie

  ➔**EFS:** **30%** **< 2000**

  vs **≈ 60%** **en 2015 avec < 50% recours à la greffe**

- Place pour des progrès/échecs et effets secondaires :

  ✓Stratification et bio marqueurs : MRD et autres

  ✓Thérapeutique :

  - intensité de chimiothérapie
  - place de la greffe
  - place de nouveaux agents

  ✓ Effets à long terme (croissance osseuse…)