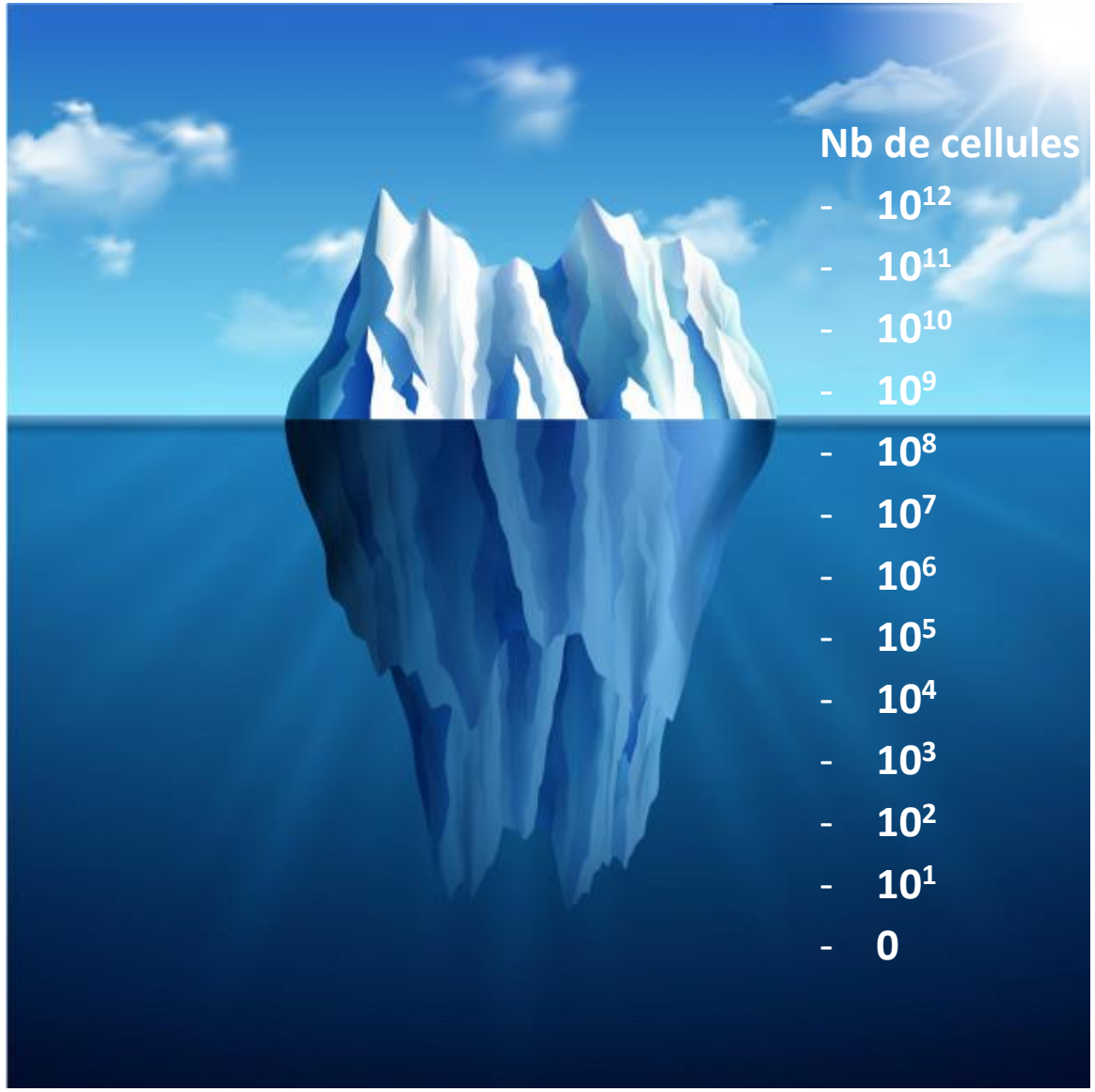
Cours DES Hématologie
28/01/2022

Suivi de la maladie résiduelle des LAL Ph+

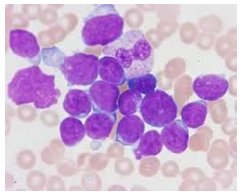
LAL Ph-like

GRAALL
LALA GOELAMS SAKK

L’évaluation de la maladie résiduelle



Examen cytologique sensibilité 1-5%



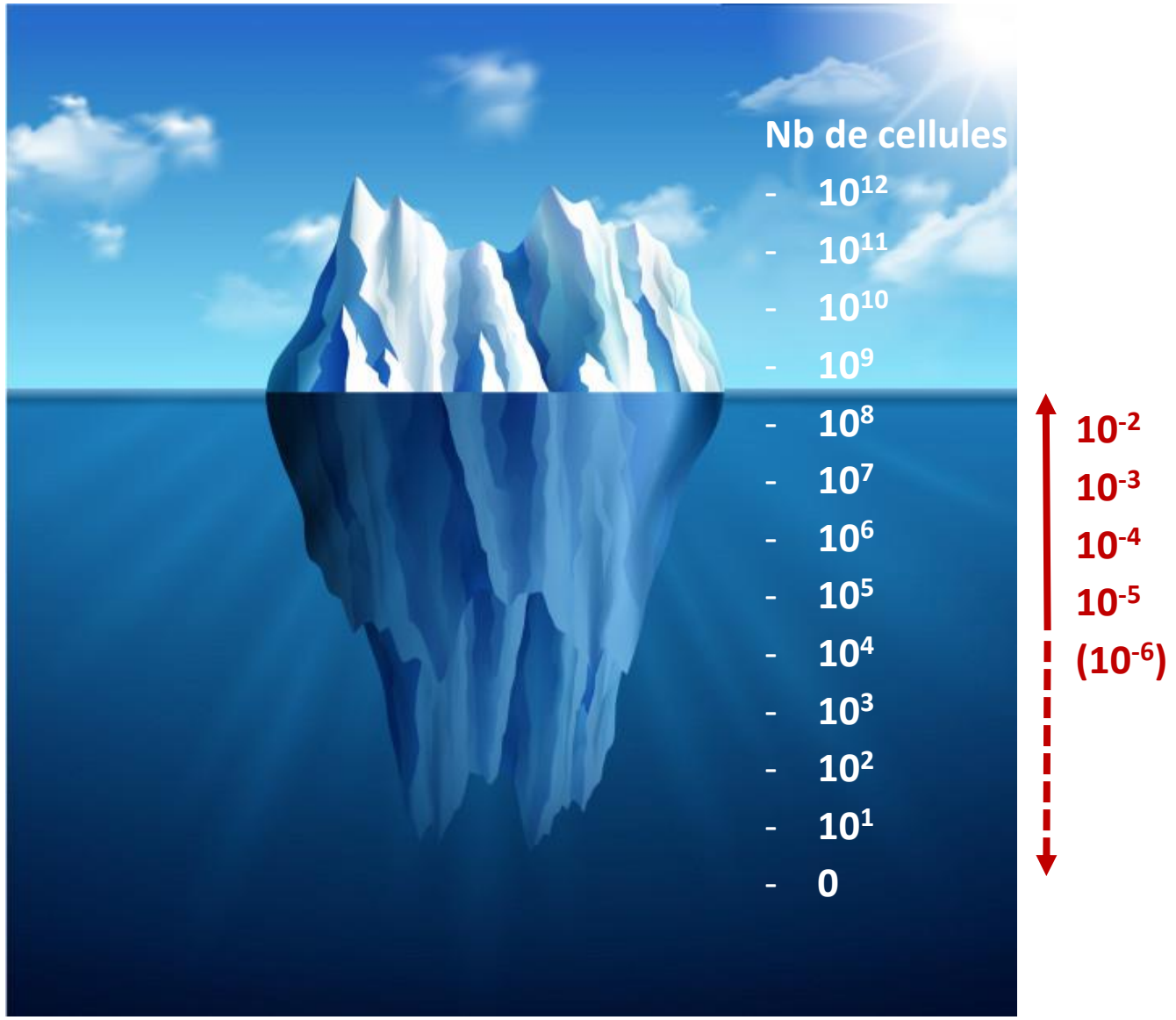
10^{-2}
10^{-3}
10^{-4}
10^{-5}
(10^{-6})

Maladie résiduelle

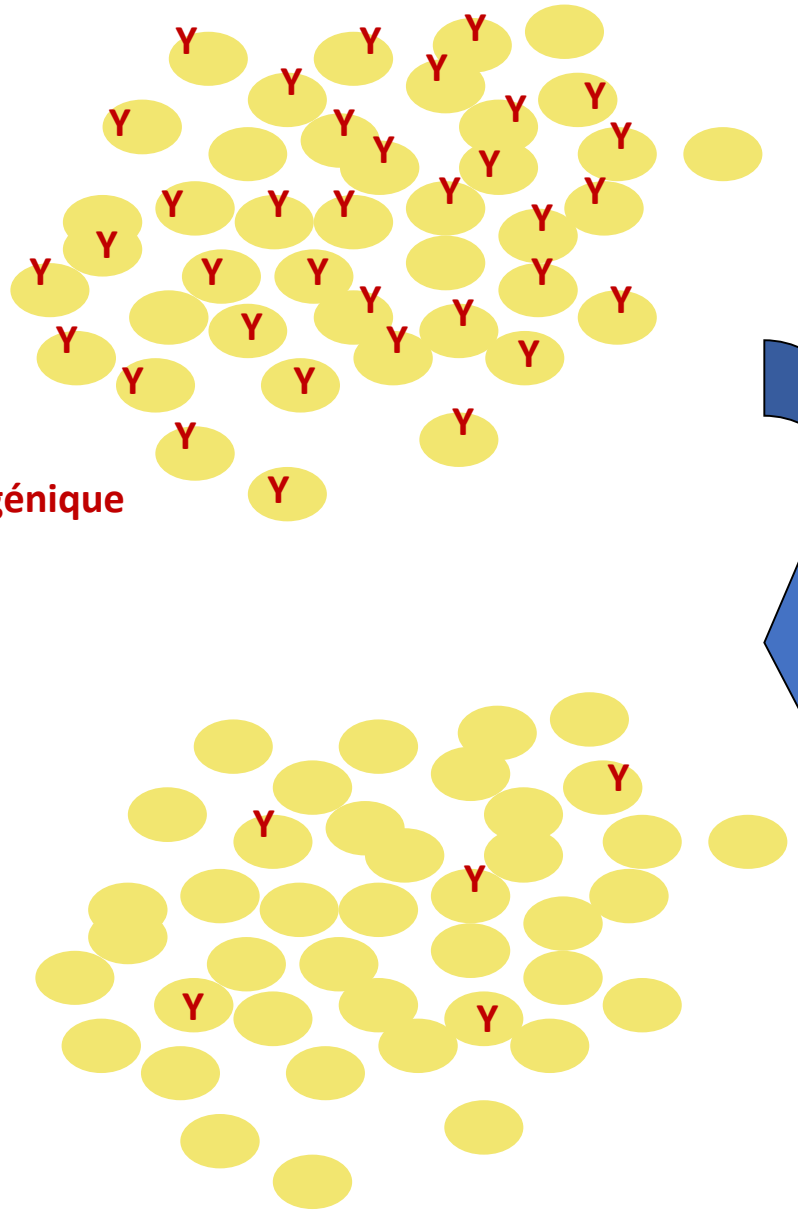
MRD « ~~négative~~ » = **indétectable**

L’évaluation de la maladie résiduelle

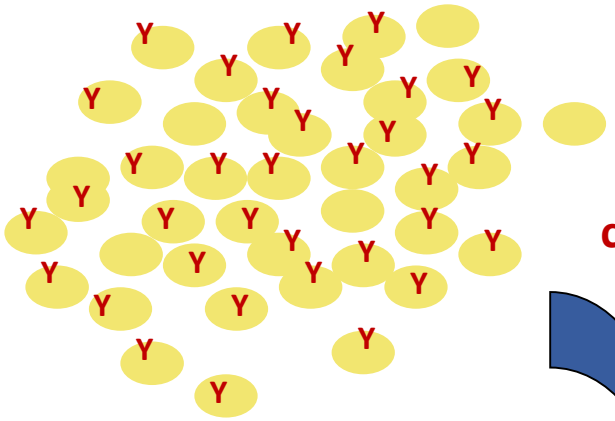
- Comment ?
- Pourquoi ?



Marqueurs moléculaires oncogéniques



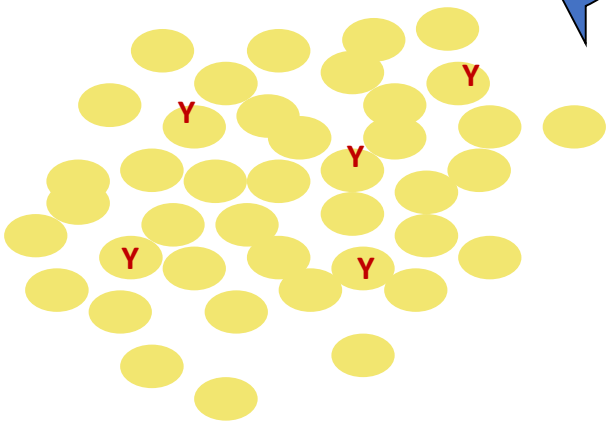
Marqueurs moléculaires oncogéniques



Y = marqueur oncogénique

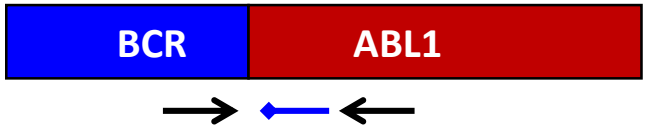
Diagnostic
=
cellules leucémiques +++

Traitement

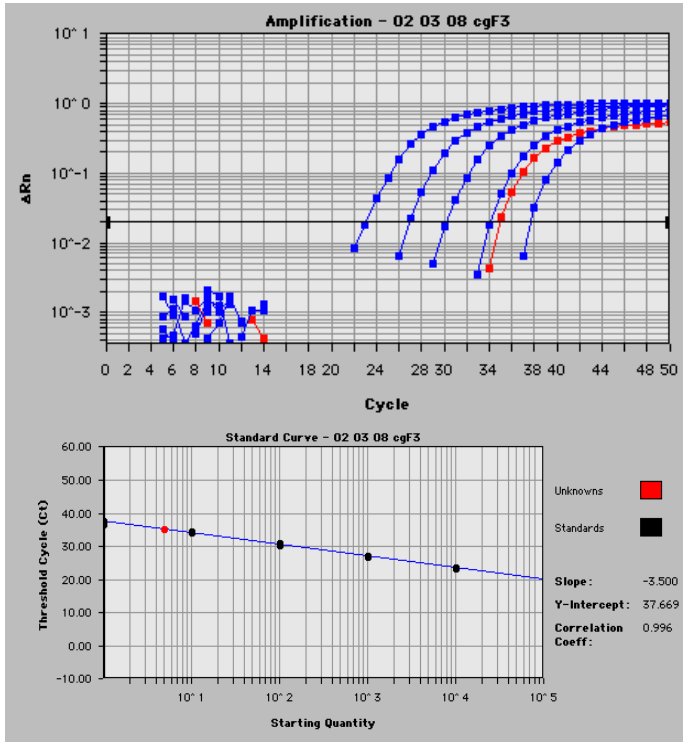


Rémission complète
=
cellules normales
+/-
cellules leucémiques résiduelles <5%

L'exemple du transcrit BCR-ABL1



amorce BCR sonde amorce ABL1



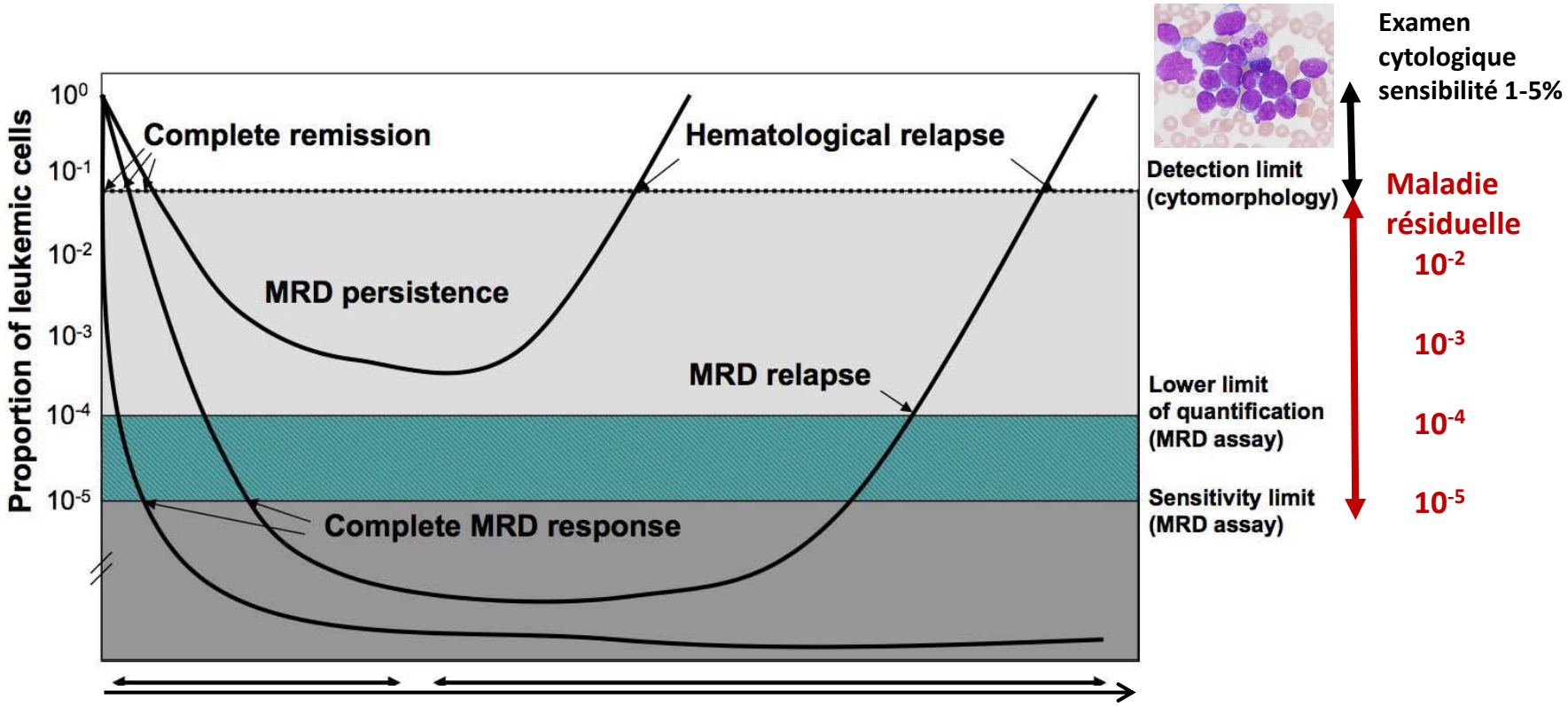
RT-qPCR

Normalisation sur un « gène de ménage » (ABL1 par exemple)

Résultat = nb copies BCR-ABL1/nb copies ABL1 *100

Maladie résiduelle

Pourquoi ?

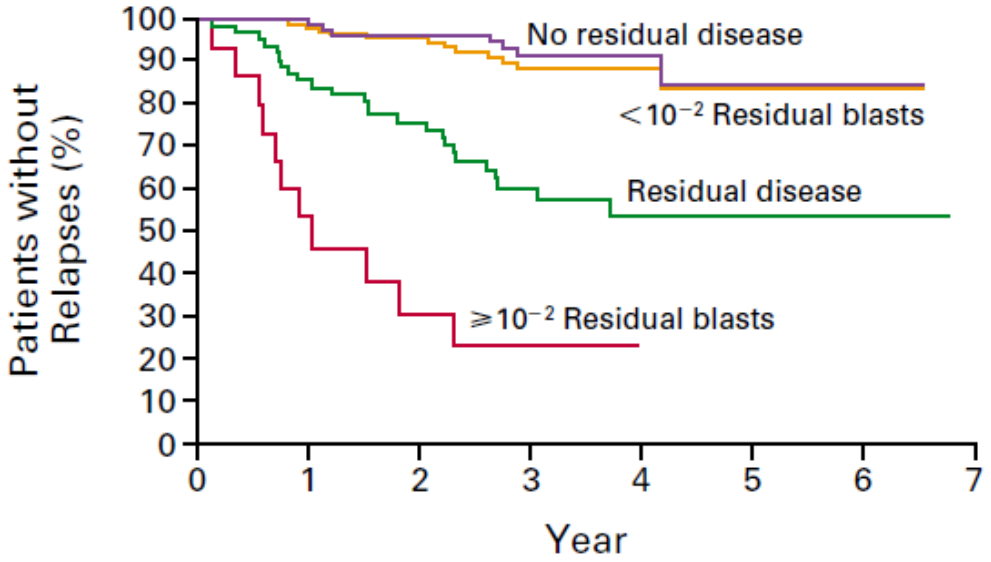


-> Evaluer la réponse au traitement pour adapter la suite de la prise en charge +++

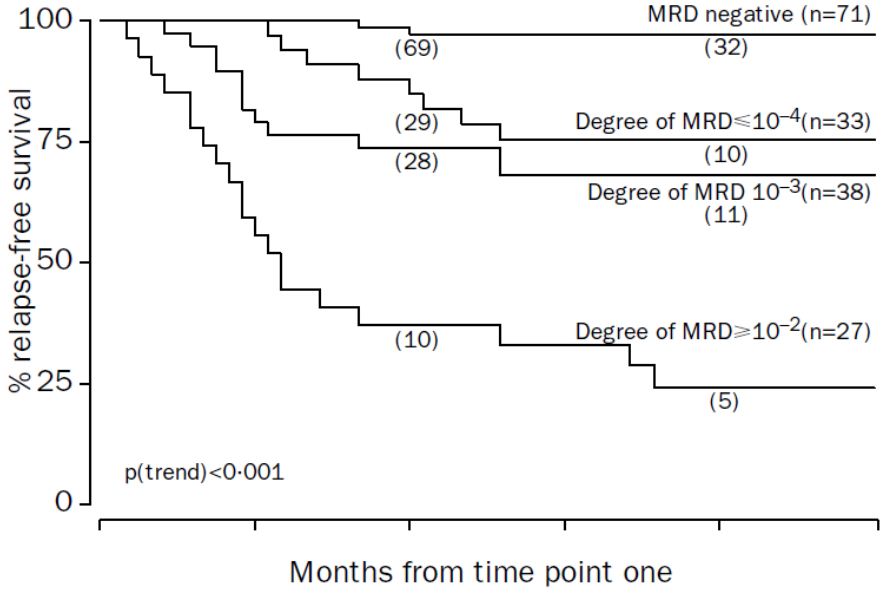
Maladie résiduelle

Pourquoi ?

L'expérience des LAL pédiatriques



Cavé H et al., NEJM 1998



Van Dongen JJ et al., Lancet 1998

-> La maladie résiduelle après les première cures est corrélée au risque de rechute

Maladie résiduelle

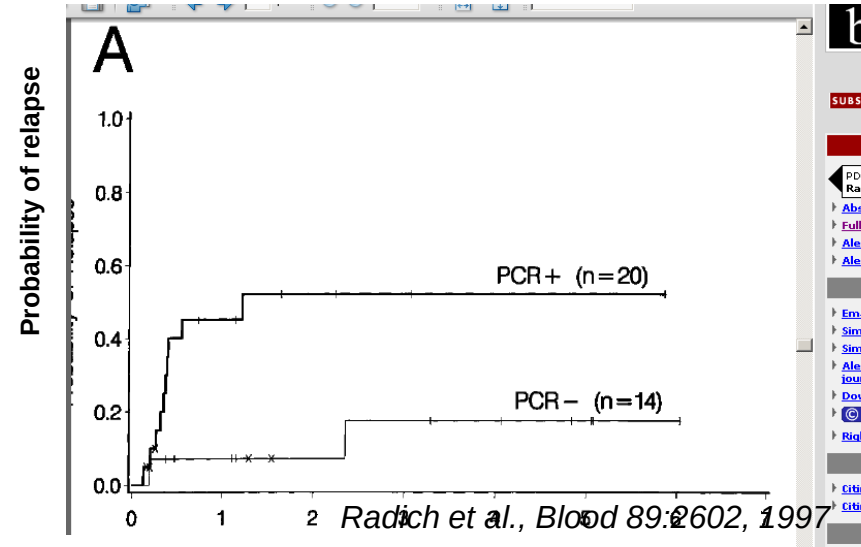
Pourquoi ?

Etudes moléculaires de la réponse au traitement des LAL Ph+

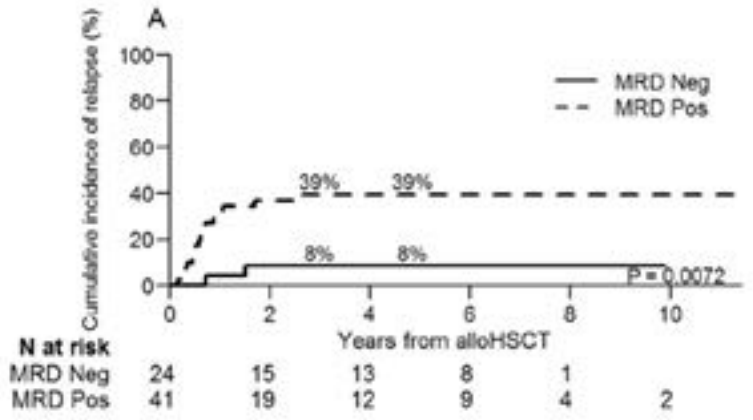
- Apprécier la qualité de la RC
  - Indication d'autogreffe de CSH (GRAAPH-2014)
  - Pronostique de la rechute post Allo-SCT

- Identifier les patients à risque de rechute hématologique
  - Sous ITK
    - Changement d'ITK
  - post Allo-SCT
    - Maintenance avec ITK
    - ↕ ciclosporine, DLI

- Objectif I[aire] ou II[aire] des essais thérapeutiques (GRAAPH-2014)



Radich et al., Blood 89:2602, 1997



Lussana F et al. Biol Blood Marrow Transplant. 2016, 22:1983-87

But…

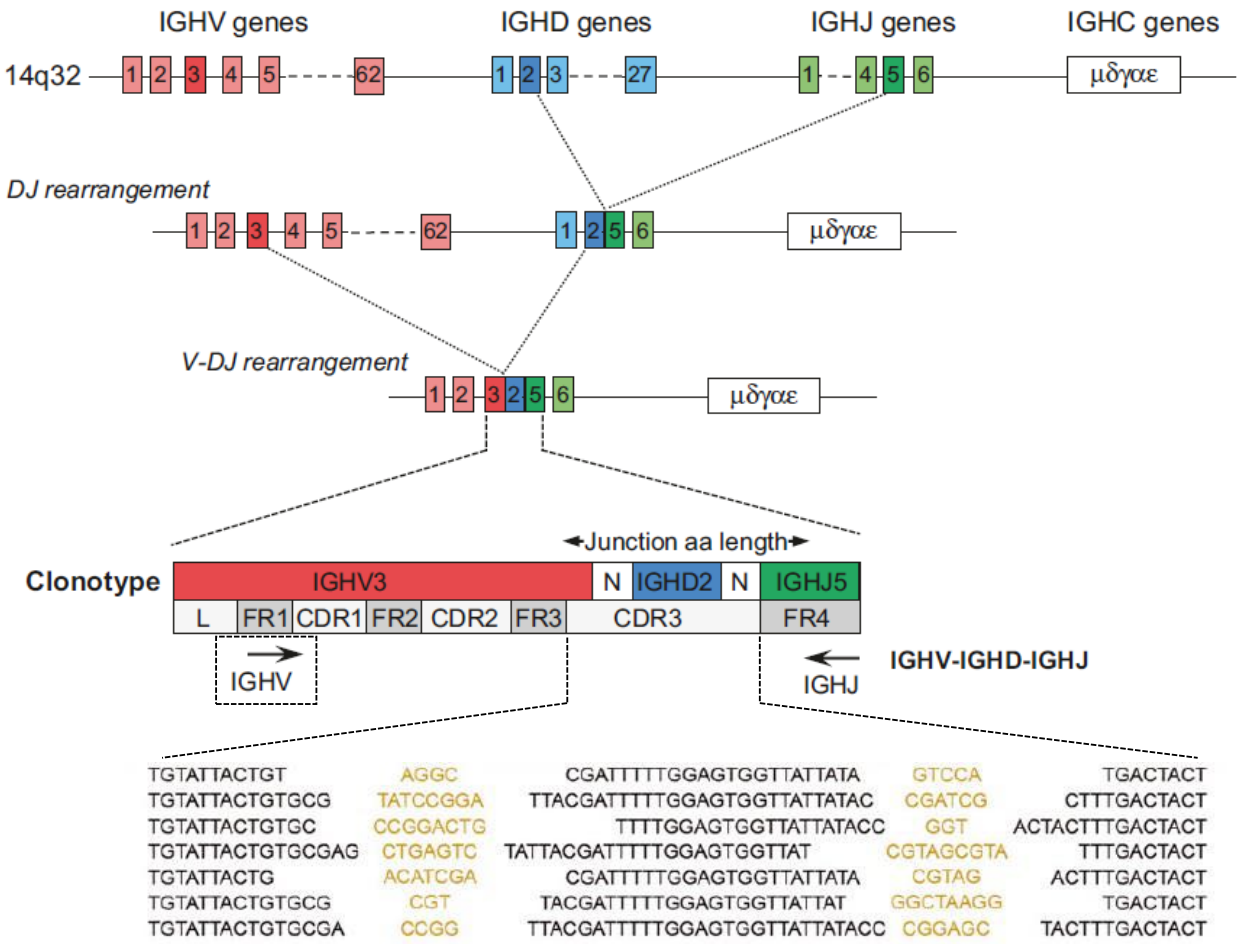
- Few studies demonstrating the prognostic value of BCR-ABL1 MRD in Ph+ ALL
- Anecdotical observations of persistent BCR-ABL1 in patients in continuous remission
- Studies in children Ph+ ALL compared BCR-ABL1 and Ig/TCR MRD

Questions

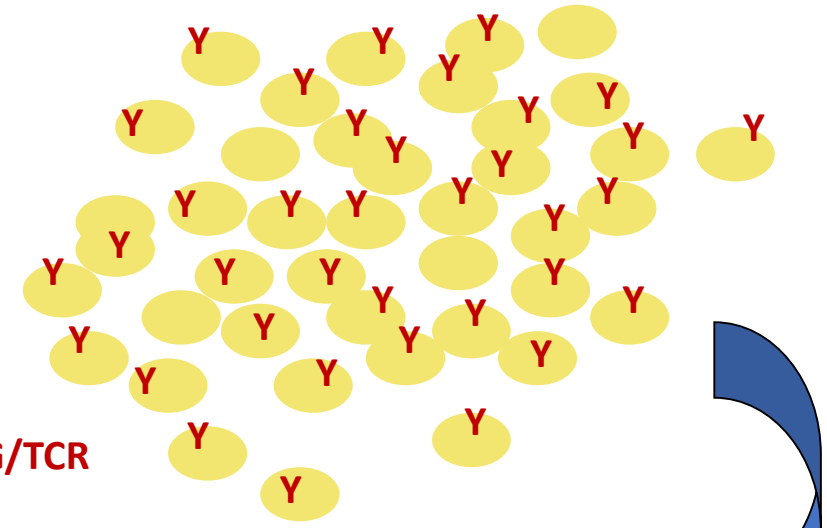
- Significance of residual BCR-ABL1 in adult Ph+ ALL ?
- Prognostic value of Ig/TCR MRD in adult Ph+ ALL ?

Marqueurs de clonalité lymphoïde

= Réarrangements génomiques des gènes codant les chaînes des immunoglobulines ou du récepteur T à l'antigène (IG/TCR)



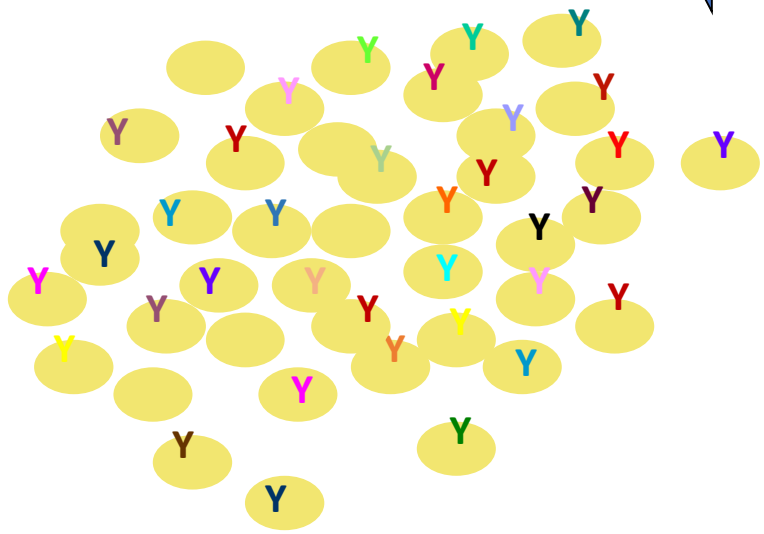
Marqueurs de clonalité lymphoïde



Y = réarrangement IG/TCR clono-spécifique

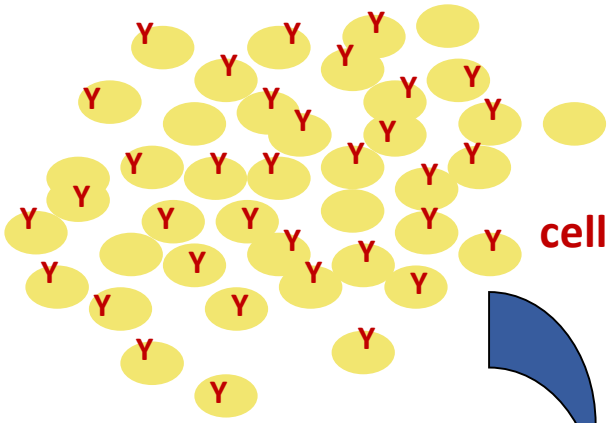
Diagnostic
=
cellules leucémiques +++

Traitement



Rémission complète
=
cellules normales
+/-
cellules leucémiques résiduelles <5%

Marqueurs de clonalité lymphoïde



Diagnostic
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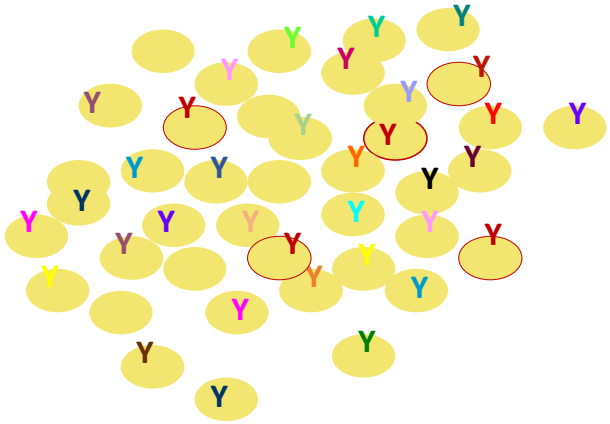
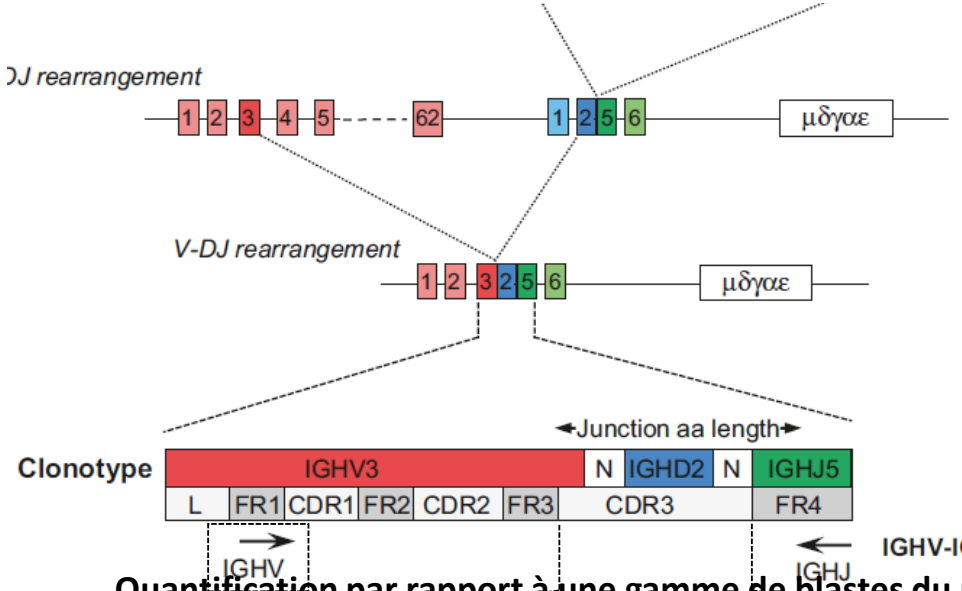
Y = réarrangement IG/TCR clono-spécifique

Traitement



Rémission complète
=
cellules normales
+/-
cellules leucémiques résiduelles <5%

1- Identification des réarrangements clono-spécifiques par PCR + séquençage (NGS)



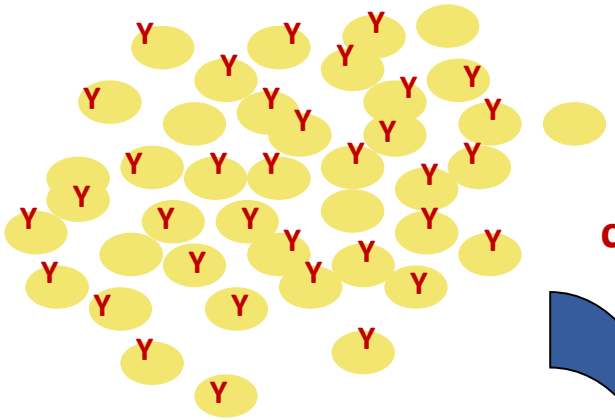
Quantification par rapport à une gamme de blastes du patient: de 10 000 à 1 blastes/100 000 cellules normales, soit 10^{-1} à 10^{-5}

TGTATTACTGT AGGC CGATTTTTGGAGTGGTTATTATA GTCCA TGACTACT
TGTATTACTGTGCG TATCCGGA TTACGATTTTTGGAGTGGTTATTATAC CGATCG CTTTGACTACT
TGTATTACTGTGC CCGGACTG TTTTGGAGTGGTTATTATACC GGT ACTACTTTGACTACT
TGTATTACTGTGCGAG GTGACTG TATTACGATTTTTGGAGTGGTTAT CGTACGGTA TTTGACTACT
TGTATTACTG ACATCGA CGATTTTTGGAGTGGTTATTATA CGTAG ACTTTGACTACT
TGTATTACTGTGCG CGT TACGATTTTTGGAGTGGTTATTAT GGCTAAGG TGACTACT
TGTATTACTGTGCGA CGGA TTACGATTTTTGGAGTGGTTATTATACTAC AAGC TACTTTGACTACT

1 copie d'ADN réarrangé = 1 blaste

Résultat ≈ taux de blastes résiduels

Marqueurs moléculaires oncogéniques



Y = marqueur oncogénique

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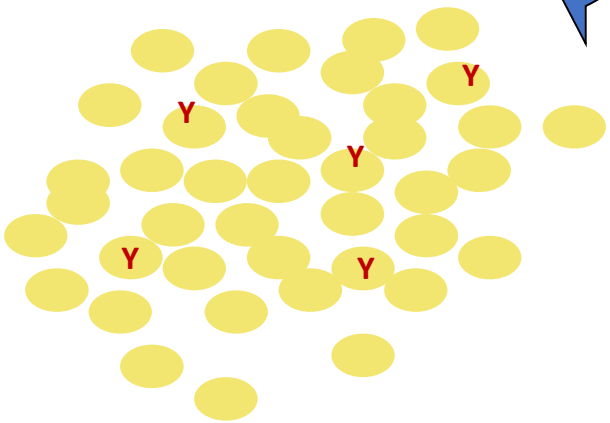
Traitement



Rémission complète
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cellules normales
+/-
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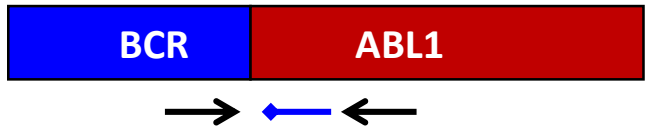
L'exemple du transcrit BCR-ABL1



amorce BCR sonde amorce ABL1

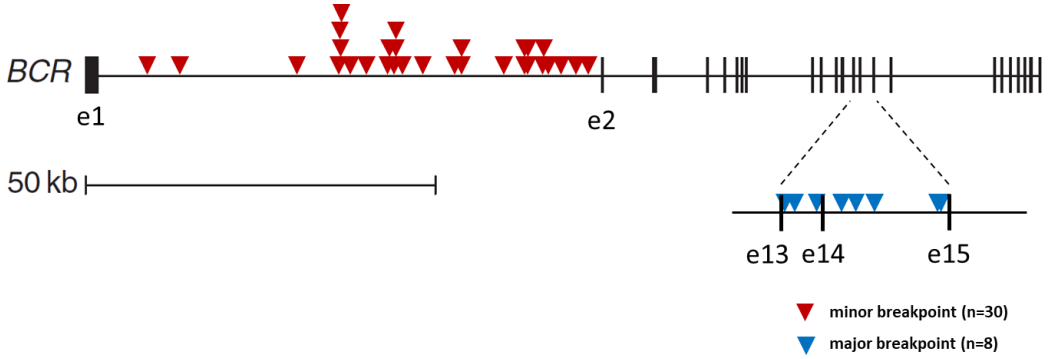
Taux de transcrit ≠ Taux de cellules résiduelles

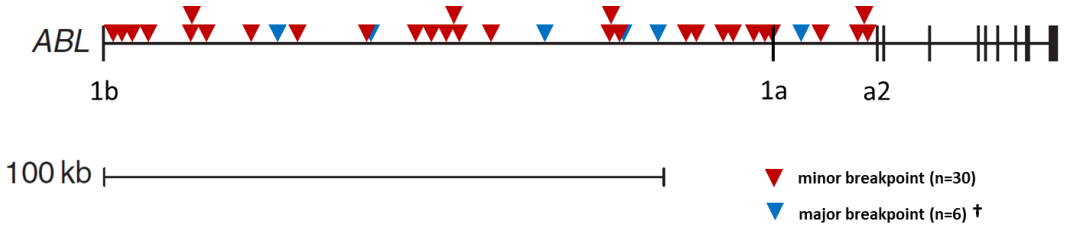
Taux de transcrit dépend du niveau d'expression

Normalisation sur un « gène de ménage » (ABL1 par exemple)

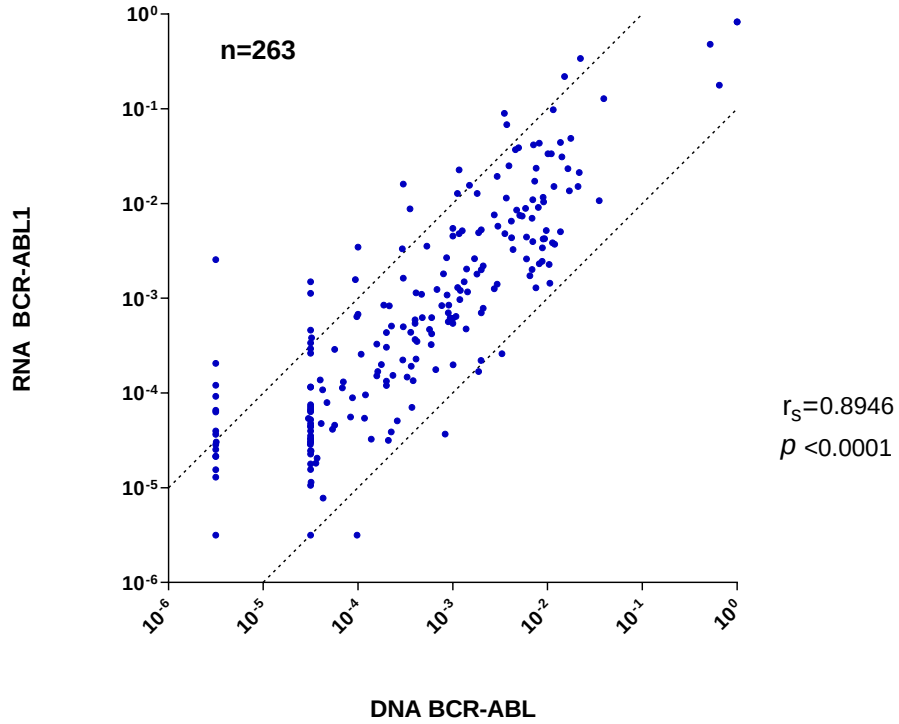
Résultat = nb copies BCR-ABL1/nb copies ABL1 *100

Genomic BCR-ABL1 MRD demonstrates good and poor correlation with BCR-ABL transcript and Ig/TCR MRD, respectively

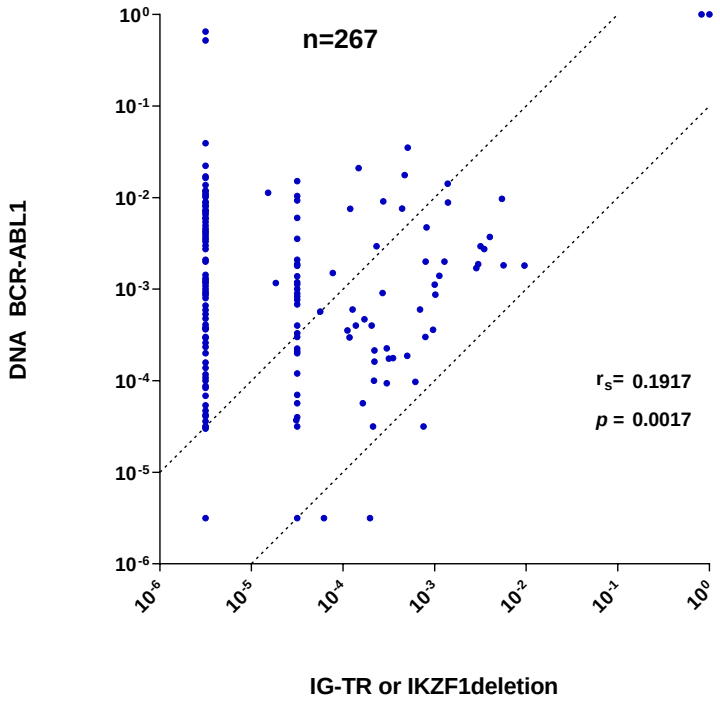




BM&PB global DNA and RNA BCR-ABL1 comparison

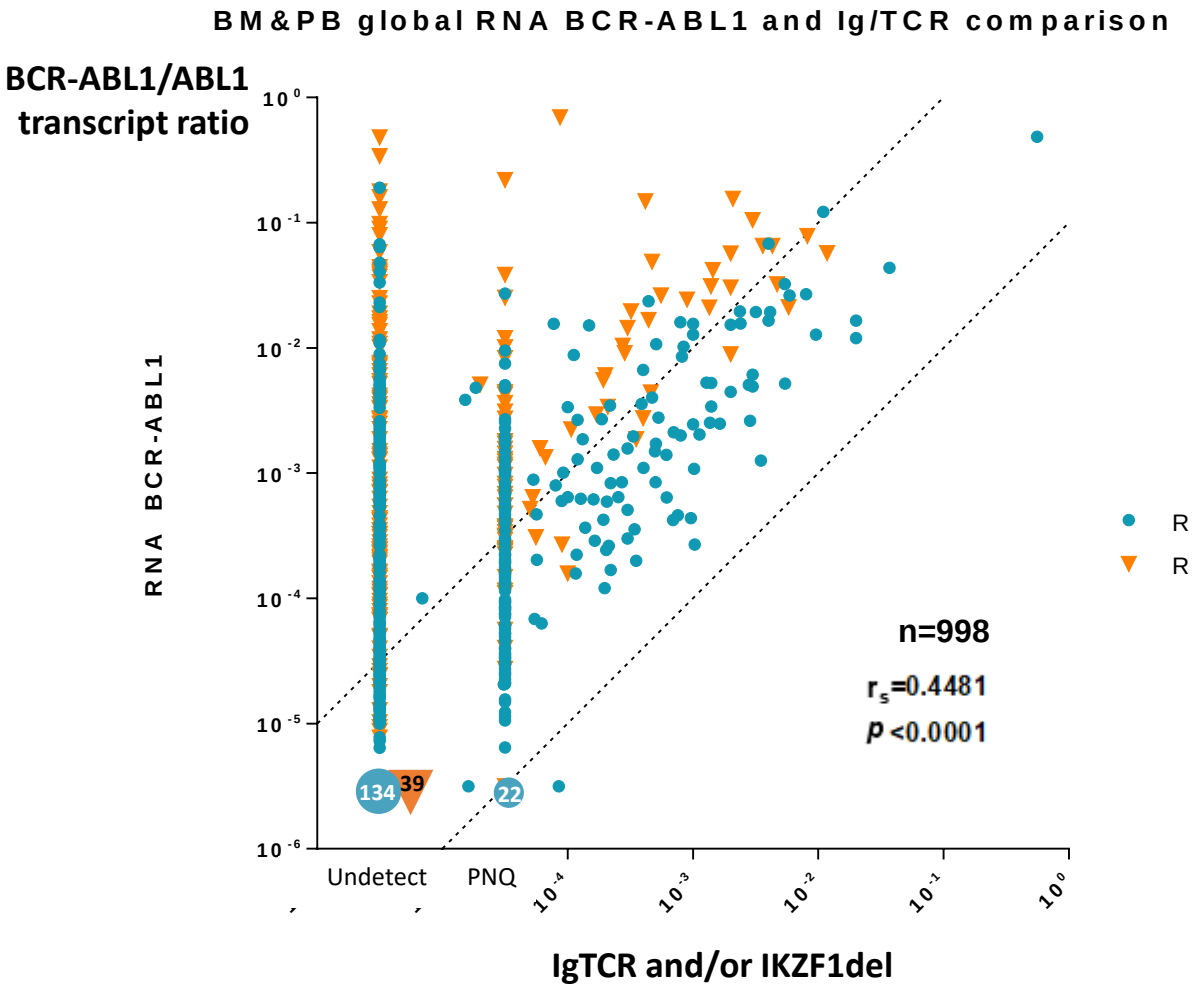


***BM&PB global DNA BCR-ABL1 and Ig/TCR comparison**



Combined IG/TCR and BCR-ABL1 MRD monitoring in *de novo* adult Ph+ ALL reveals frequent discordant results

Paired-analyses of follow-up samples in n= 156 patients

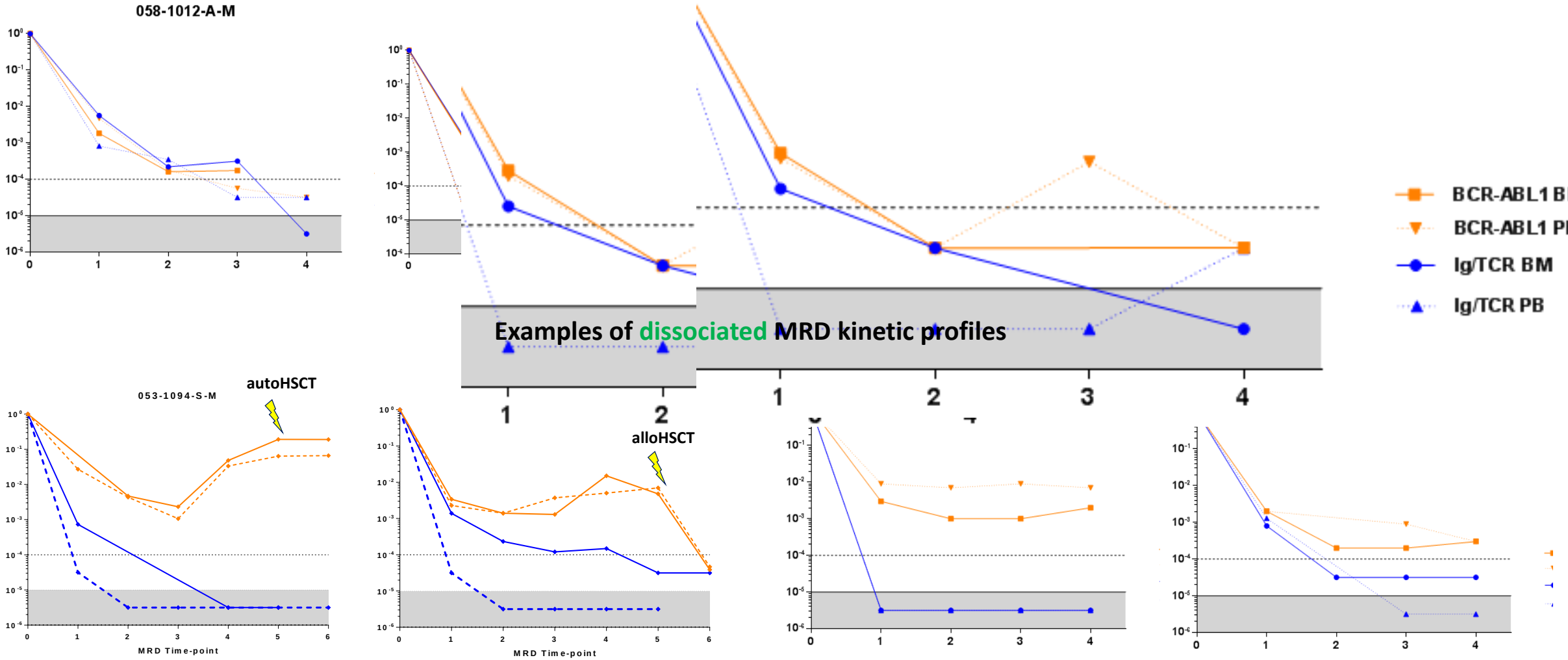


MRD TP1-5 (before HSCT)
876 samples: 385 BM and 491 PB

Poor correlation with frequent positive/high BCR-ABL1 transcript while negative/low Ig/TCR levels

Paired BCR-ABL1 and IG-TR MRD follow-up identifies patients with residual BCR-ABL1 clonal hematopoiesis

N.B. BCR-ABL1 quantification performed on DNA

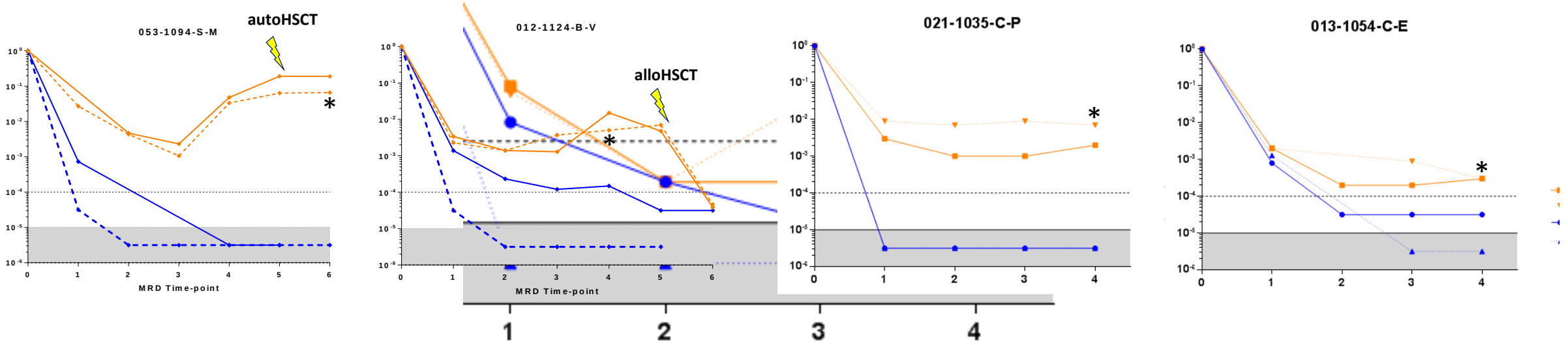


Examples of dissociated MRD kinetic profiles

Paired BCR-ABL1 and IG-TR MRD follow-up identifies patients with residual BCR-ABL1 clonal hematopoiesis

N.B. BCR-ABL1 quantification performed on DNA

Examples of dissociated MRD kinetic profiles



* Cell sorting of blood samples and BCR-ABL1 quantification in T and B lymphocytes and monocytes cell fractions

	BCR-ABL1/ABL1 transcripts	BCR-ABL1 status
T cells	0%	Negative
B cells	Not evaluable	Undetermined
Monocytes	21%	Positive

	BCR-ABL1/ABL1 transcripts	BCR-ABL1 status
T cells	0.22%	Positive
B cells	Not evaluable	Undetermined
Monocytes	0.82%	Positive

	BCR-ABL1/ABL1 transcripts	BCR-ABL1 status
T cells	0%	Negative
B cells	52%	Positive
Monocytes	0%	Negative

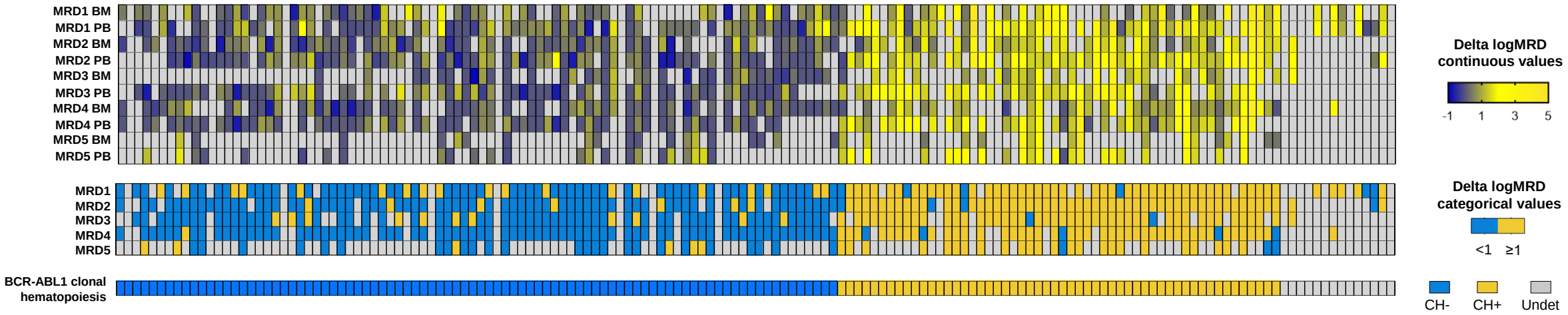
	BCR-ABL1/ABL1 transcripts	BCR-ABL1 status
T cells	0.40%	Positive
B cells	0%	Negative
Monocytes	0%	Negative

54/140 (39%) pts in GRAAPH-2014 were defined as having residual BCR-ABL1 clonal hematopoiesis (CH+)

Paired-analyses of follow-up samples in n= 156 patients

MRD TP1-5 (before HSCT)
876 samples: 385 BM and 491 PB

-> Patients with residual CH defined as having ≥ 1 log difference observed on ≥ 3 MRD timepoints



-> 140/156 patients could be classified : **54/140 (39%) CH+**

16 undetermined: 9 early withdrawal (≤ 2 MRD TP) and 7 insufficient data

Baseline characteristics associated with BCR-ABL1 clonal hematopoiesis

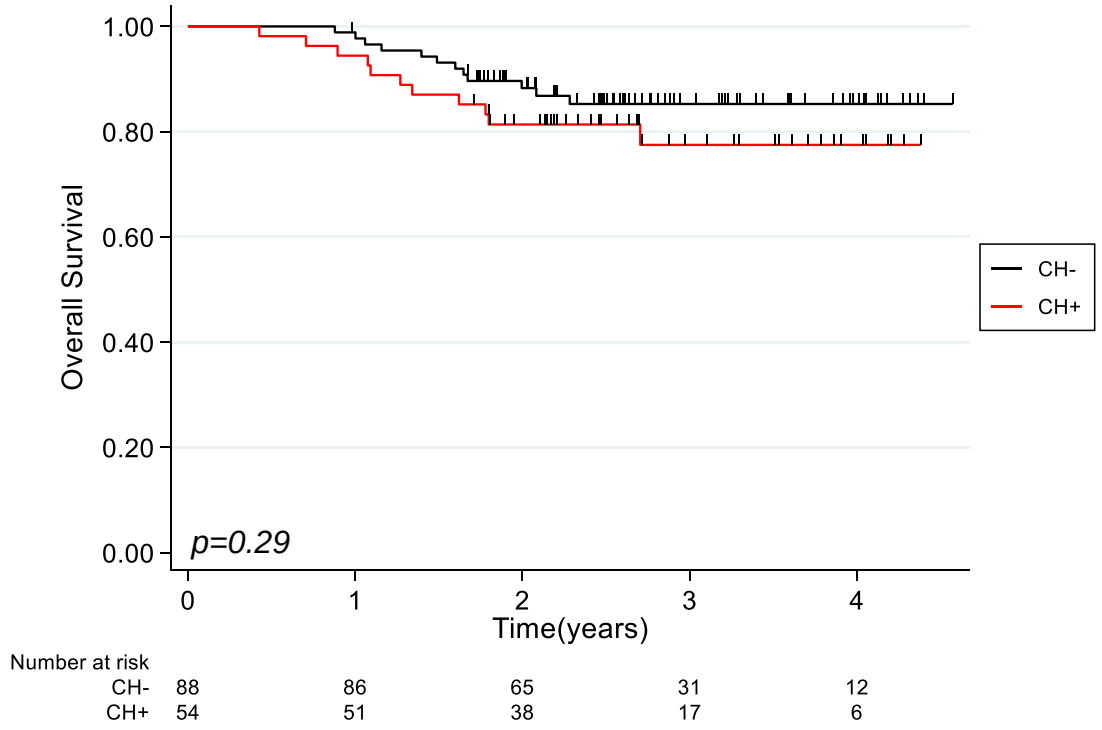
Characteristic	CH+	CH-	Total	*p value*
Patients No.	54 (39%)	86 (61%)	140 (100%)	
Clinical subsets analyzed				
Male/female, No.	31/23 (57%)	44/42 (51%)	75/65 (54%)	*0.49*
Median age, years (range)	46.8 (18.1-59.9)	47.1 (19.0-59.6)	47.1 (18.1-59.9)	*0.94*
Median WBC count, G/L (range)	25.8 (1.8-188.3)	15.7 (1.0-279.1)	18.6 (1.0-279.1)	*0.08*
PB granulocytes neutrophils, G/L (range)	4.2 (0.6-55.4)	2.1 (0.0-15.2)	2.4 (0.0-55.4)	***0.0003*** ***
PB lymphocytes, G/L (range)	3.0 (0.6-12.6)	3.0 (0.7-33.4)	3.0 (0.6-33.4)	*0.90*
PB monocytes, G/L (range)	0.2 (0.0-11.5)	0.1 (0.0-16.4)	0.2 (0.0-16.4)	*0.05*
PB blast, G/L (range)	10.1 (0.0-158.8)	6.9 (0.0-254.0)	8.1 (0.0-254.0)	*0.49*
BM blasts % (range)	84.0 (20.0-98.0)	90.0 (1.0-100.0)	88.0 (1.0-100.0)	***0.03*** *
Karyotype	47	75	122	
t(9;22) with ACA	27 (57%)	56 (75%)	83 (68%)	*0.07*
Co-existence t(9;22) with and w/o ACA	11 (23%)	7 (9%)	18 (15%)	***0.04*** *
BCR-ABL1 transcript Ψ				***0.0002*** ***
e1a2	29 (54%)	72 (84%)	99 (71%)	
b2a2 and/or b3a2	25 (46%)	14 (16%)	38 (27%)	
IKZF1 deletion	54	85	139	
Intragenic deletion	25 (46%)	53 (62%)	78 (56%)	*0.08*
Dominant negative isoform (Δ4-7)	14 (26%)	31 (36%)	45 (32%)	*0.26*

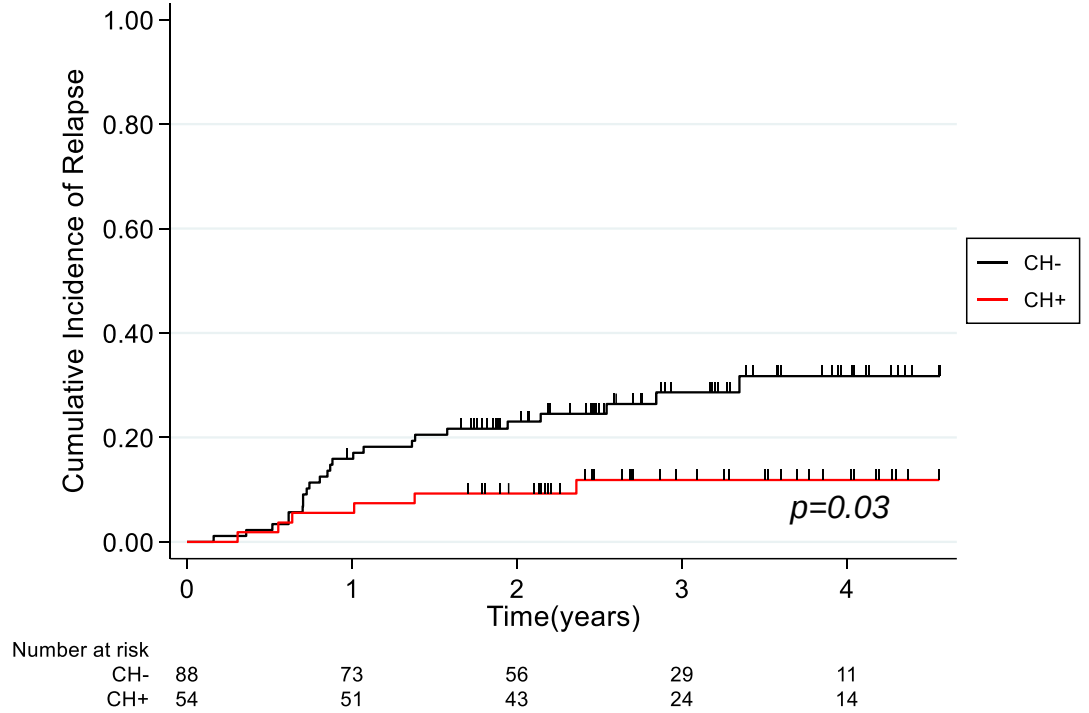
Mild myeloid hyperplasia features

- **Higher PB granulocytes**
- **Fewer BM blasts**

Enrichment in Major breakpoints, but minor breakpoint still found in ~50% of CH+ patients

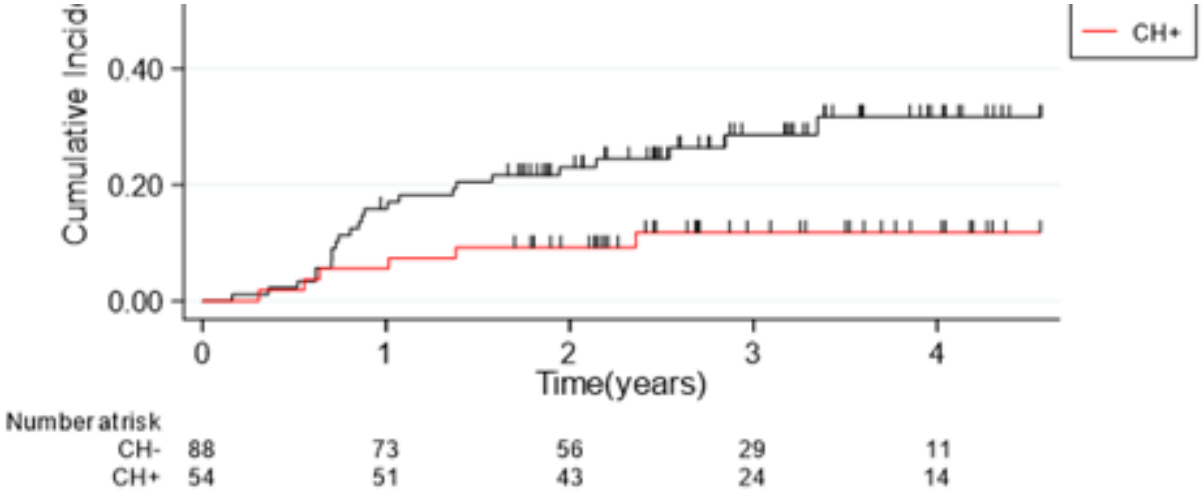
Clonal hematopoiesis is not associated with an adverse outcome for patients treated in the GRAAPH-2014 trial



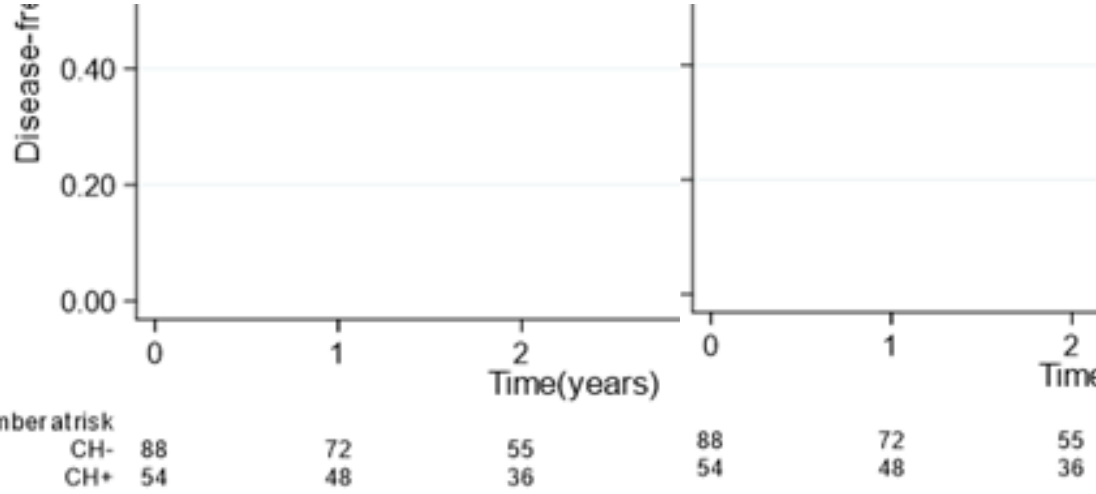


Allo-SCT may not benefit to CH+ patients

CH-

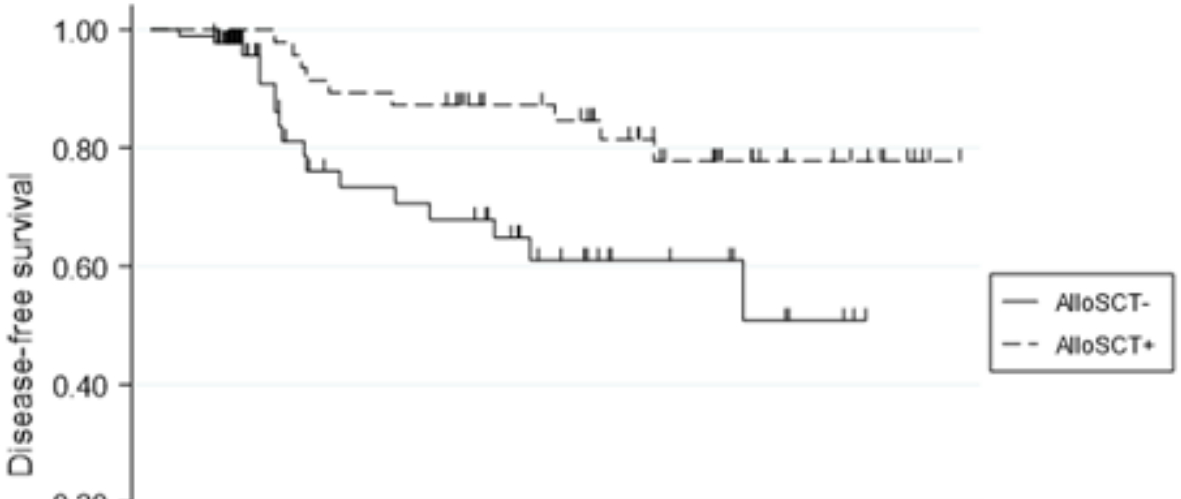


CH+



C

SHR 0.40, 95% CI [0.17-0.91], p=0.03



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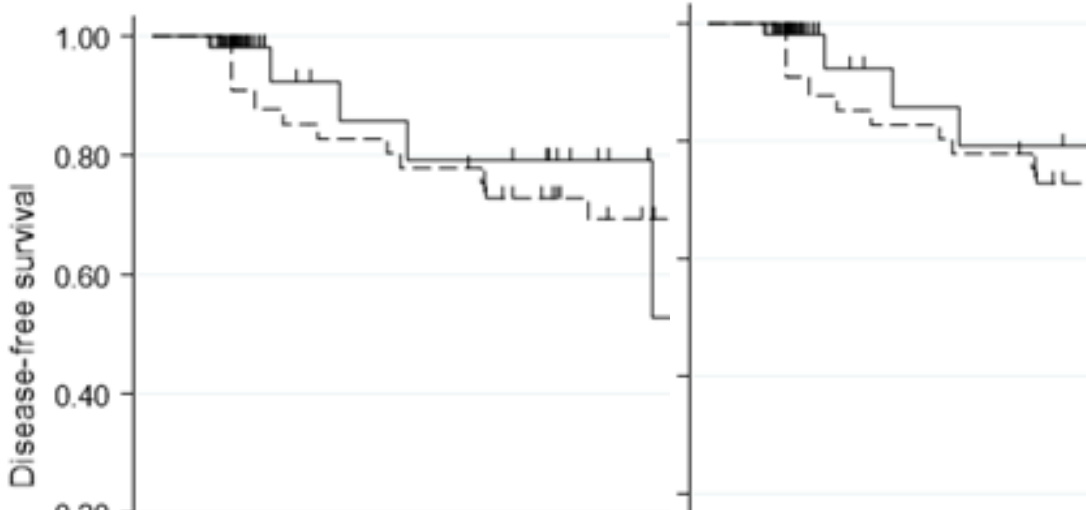
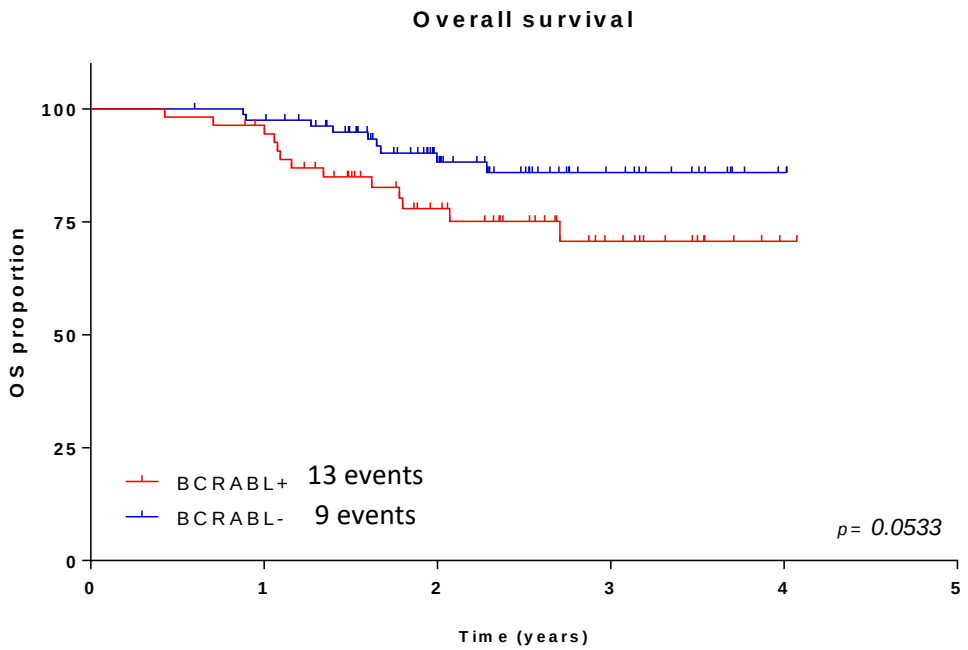


Protocol endpoint : Outcome after the end of 4 cycles according to MRD

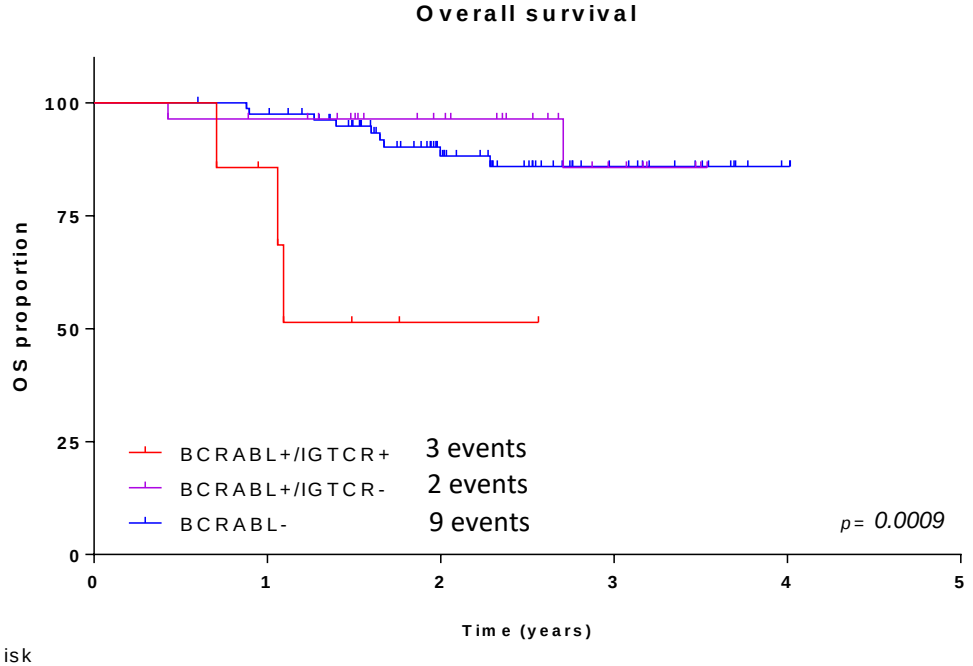
MRD4 BCR-ABL1 ≥0.01%



No. at Risk					
BCRABL+	55	51	30	13	1
BCRABL-	81	78	45	17	2

IGTCR MRD

MRD4 BCR-ABL1 ≥0.01% and IgTCR ≥10-4



No. at Risk					
BCRABL+/IGTCR+	7	5	1	0	0
BCRABL+/IGTCR-	28	26	17	6	0
BCRABL-	81	78	45	17	2

- **IGTCR MRD refines the BCRABL MRD-positive group to predict adverse outcome**

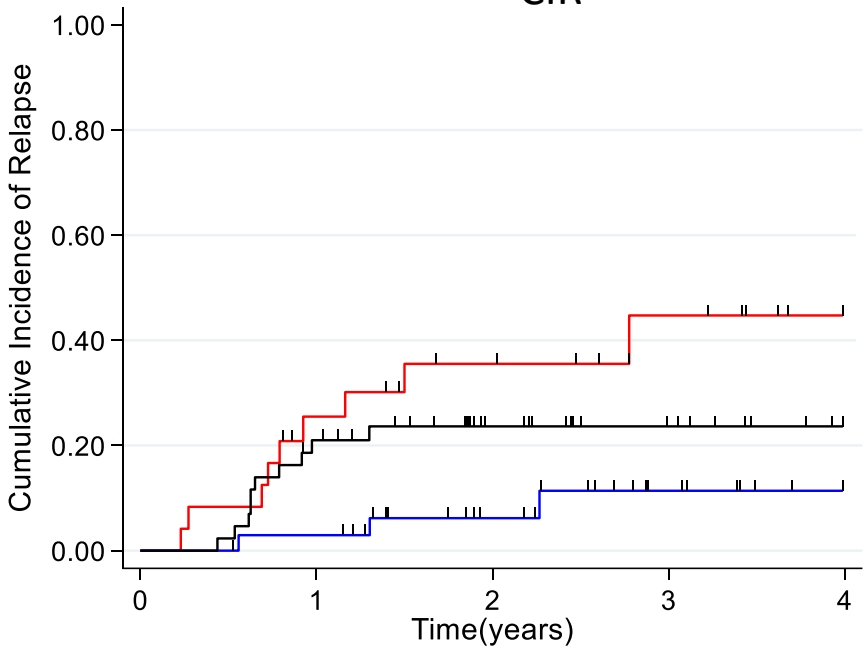
IG/TCR MRD at TP2 allows to identify two distinct groups of patients among those BCR-ABL1 positive

BCR-ABL1 >= 0.01% and Ig/TCR >= 10-4

BCR-ABL1 >= 0.01% and Ig/TCR < 10-4

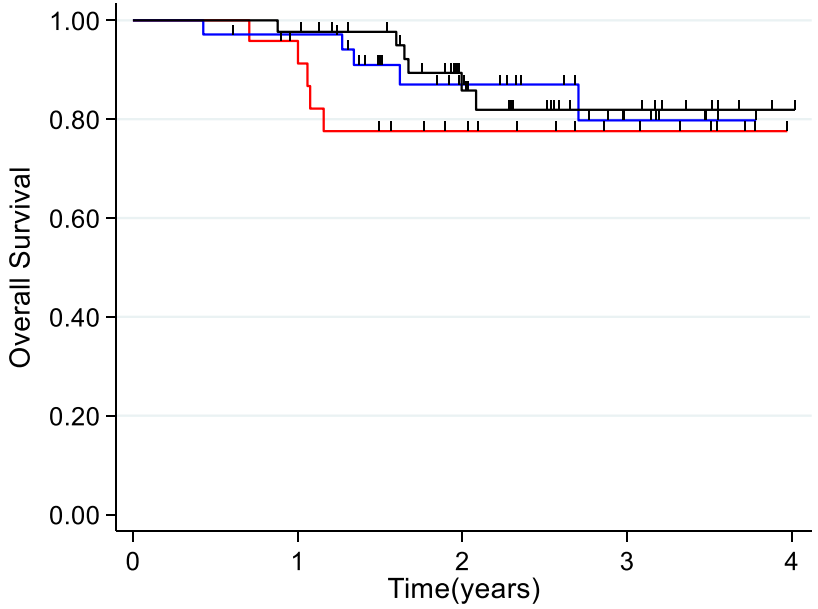
BCR-ABL1 < 0.01%

CIR



Number at risk					
IgTCR+/RM4-	24	16	11	6	0
IgTCR-/RM4-	35	33	20	10	0
IgTCR-/RM4+	43	33	18	8	0

OS



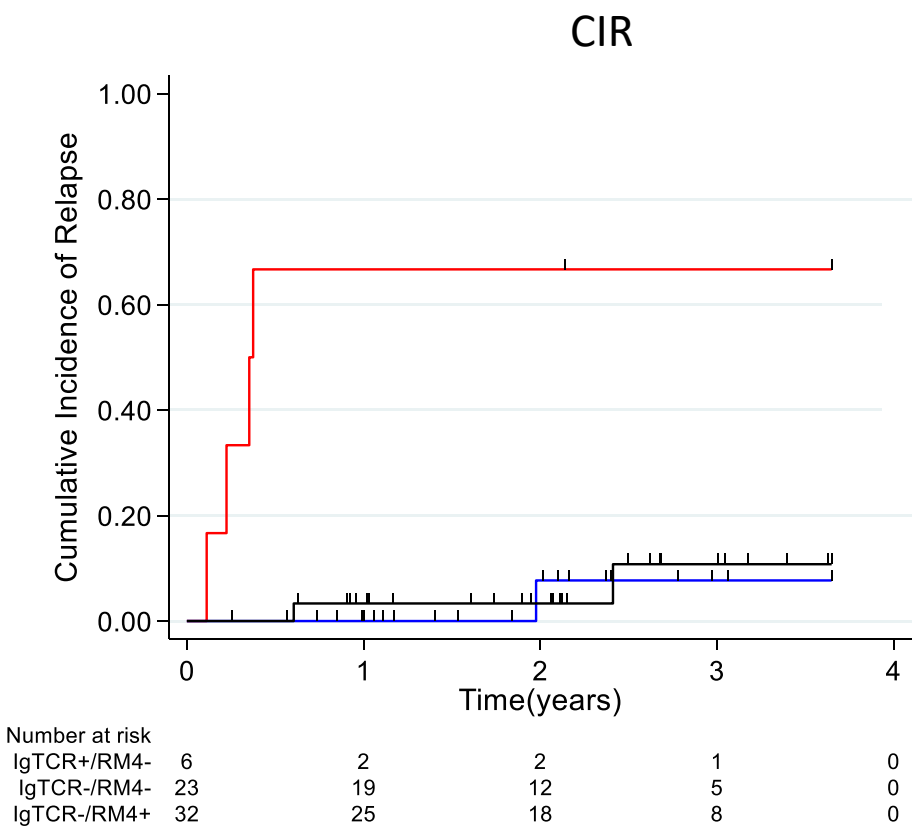
Number at risk					
IgTCR+/RM4-	24	21	13	7	0
IgTCR-/RM4-	35	33	19	7	0
IgTCR-/RM4+	43	42	24	9	1

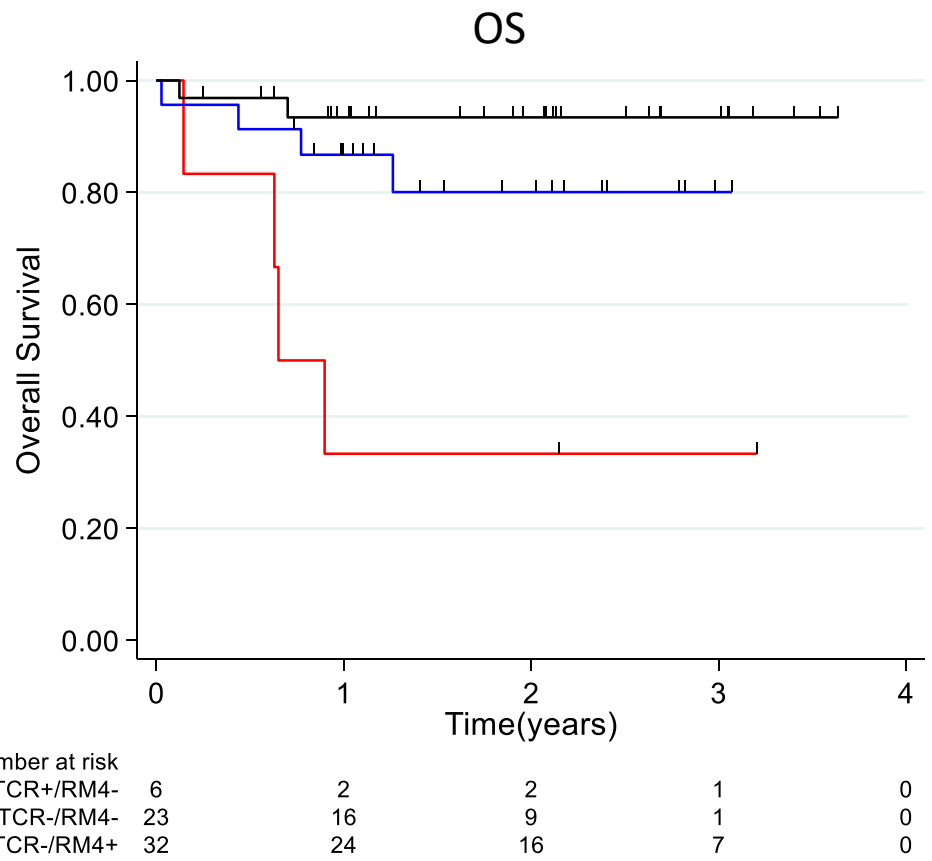
Pre-alloSCT IG/TCR MRD identifies patients at very high risk of relapse

BCR-ABL1 >= 0.01% and Ig/TCR >= 10-4

BCR-ABL1 >= 0.01% and Ig/TCR < 10-4

BCR-ABL1 < 0.01%



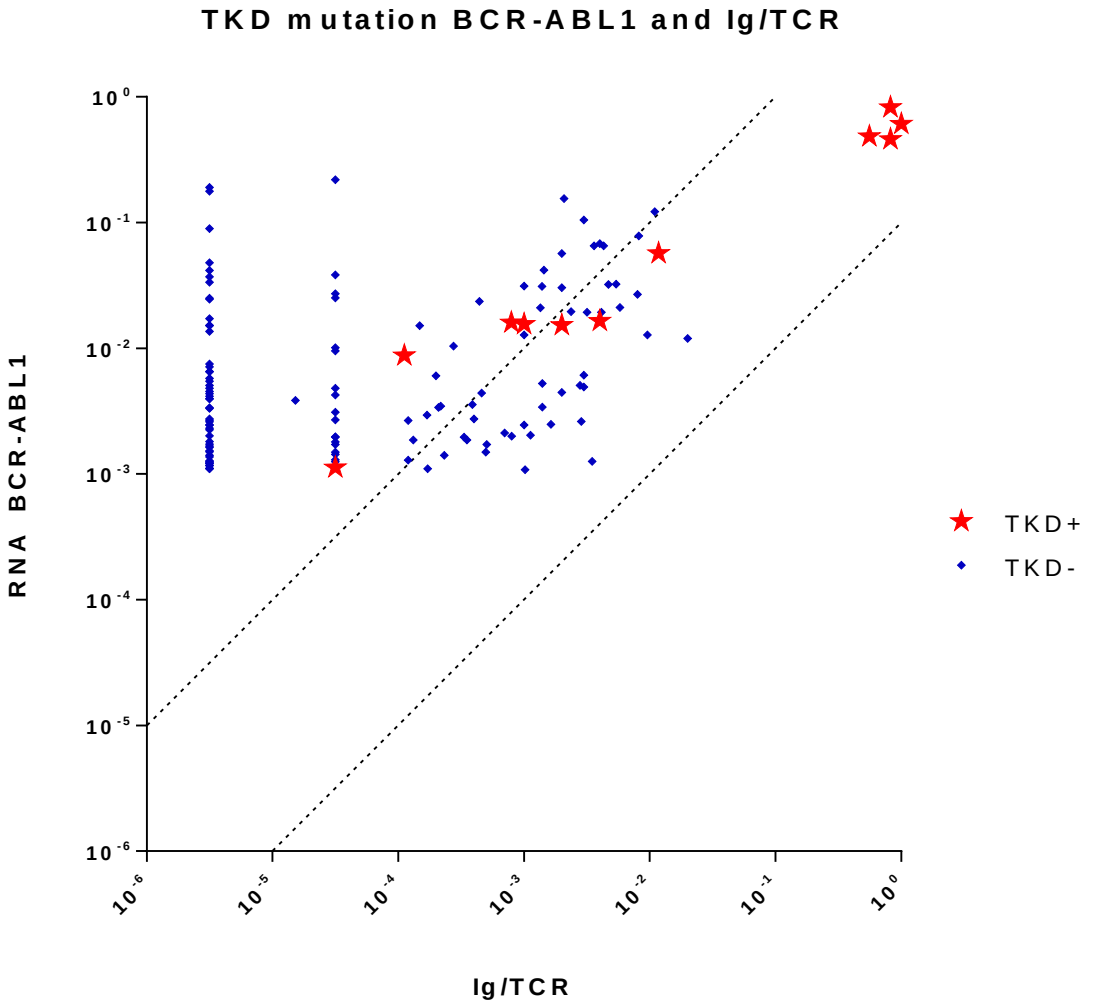


*MRD assessed <45d before HSCT

IgTCR MRD and TKD mutation acquisition

	TKD+	TKD-
IgTCR+	11	76
IgTCR-	0	55
IgTCR ND	3	65

p = 0.006



TKD mutation screening:

- **211 screens (166 BM / 44 PB when BM not available)**
  - **14 mutations**
  - **Only in association with positive Ig/TCR MRD (with PNQ or ND)**
  - ***No PB positivity in case of BM negativity***

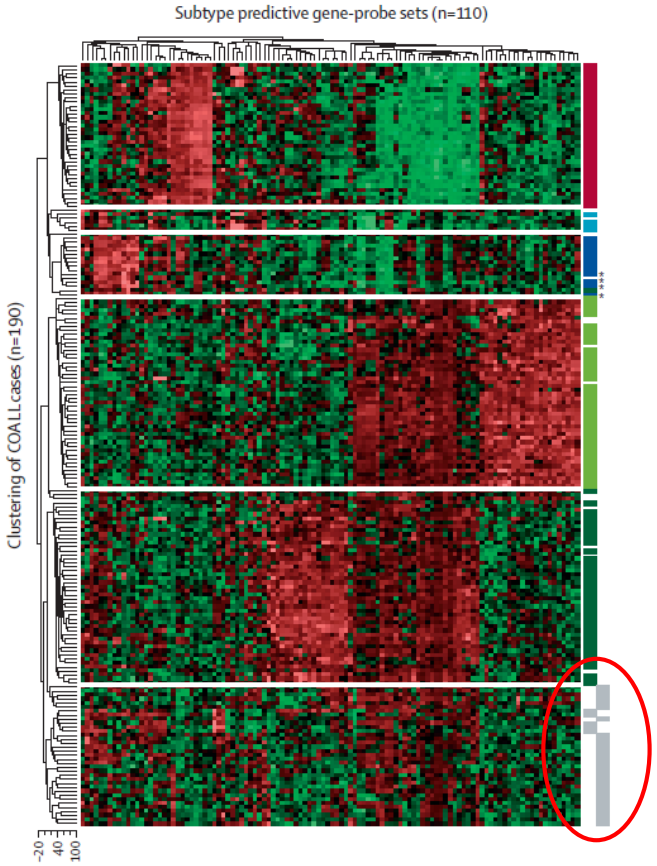
Findings :

- **TKD mutations can only be found in follow-up samples pour residual lymphoblasts (MRD IG/TCR positive)**
- **No mutation has been found in patients with only BCR-ABL1 clonal hematopoiesis**
- **Ig/TCR MRD can guide and rationalize TKD mutational screening**

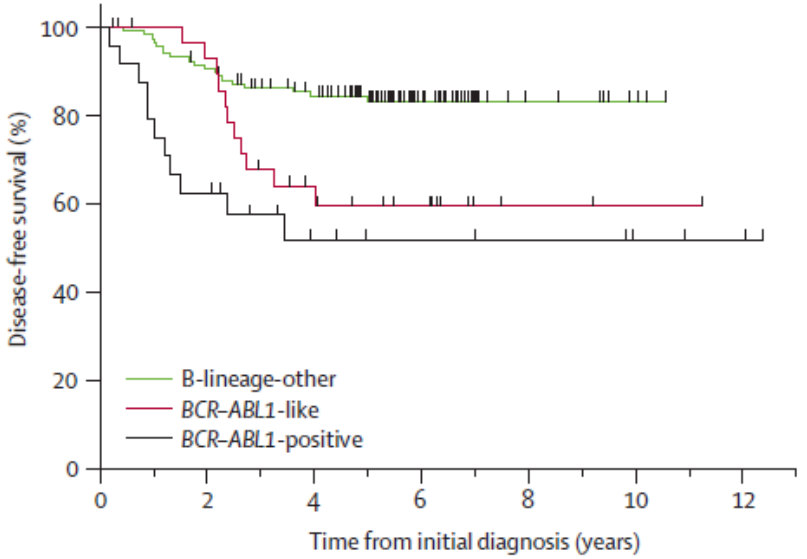
Conclusions

- Ig/TCR MRD revealed residual BCR-ABL1 clonal hematopoiesis in ~ 40% of adult Ph+ ALL
- BCR-ABL1 clonal hematopoiesis is not associated with a higher risk of relapse in the GRAAPH-2014 protocol
- Strong impact on interpretation of BCR-ABL1 follow-up results
- IG/TCR MRD may be a better predictor of outcome
- Long-term follow-up will be necessary to inform optimal clinical management in those patients

LAL Ph-like (*BCR-ABL1*-like) : un groupe de mauvais pronostic



Den Boer, Lancet Oncology 2009

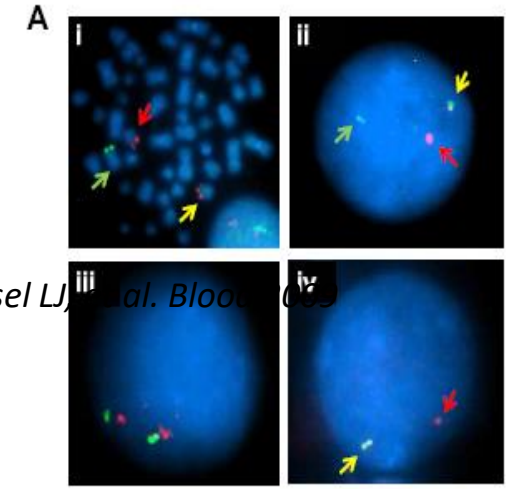


ProB signature
Frequent *IKZF1* deletions (40-90%)

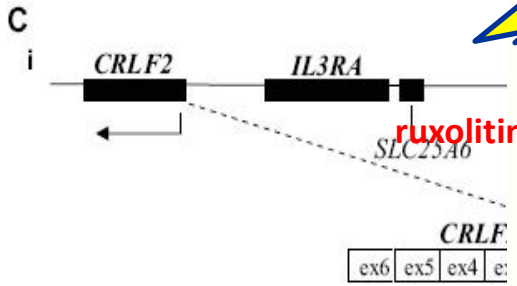
Den Boer, Lancet Oncology 2009
Harvey, Blood 2010

Altérations génétiques ciblant l'axe CRLF2-IL7R-JAK2-STAT5

Translocations *IGH@*-CRLF2
t(X;14)(p22;q32) ou
t(Y;14)(p11;q32)

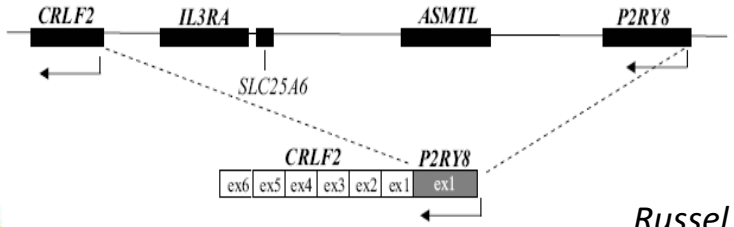


Russel LJ, et al. Blood 2009



Mullighan CG, et al. Proc Natl Acad Sci 2009

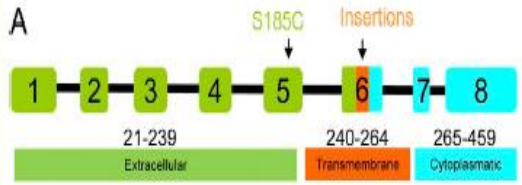
Délétion interstitielle PAR1
fusion *P2RY8-CRLF2*



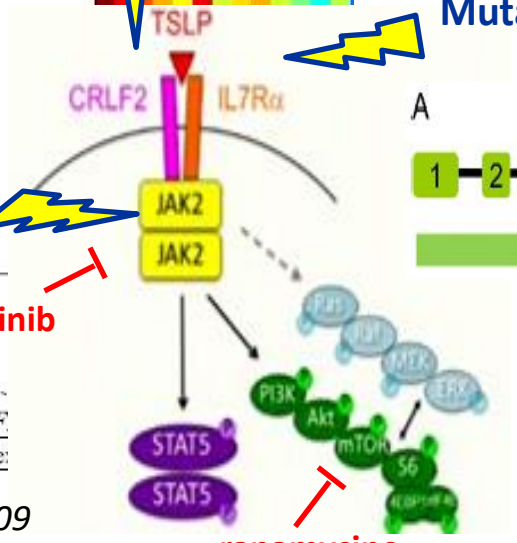
Russel LJ, et al. Blood 2009
Yoda A, et al. Proc Natl Acad Sci 2010

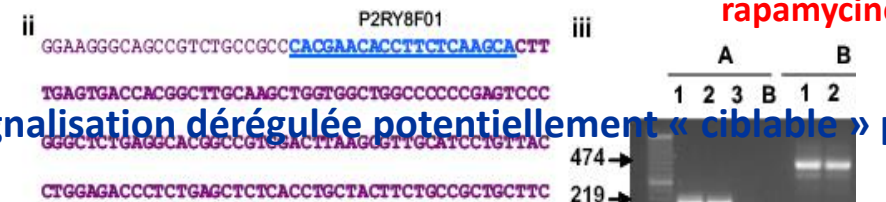
Dérégulation CRLF2

Mutations IL7R



Shochat, J Exp Med 2011



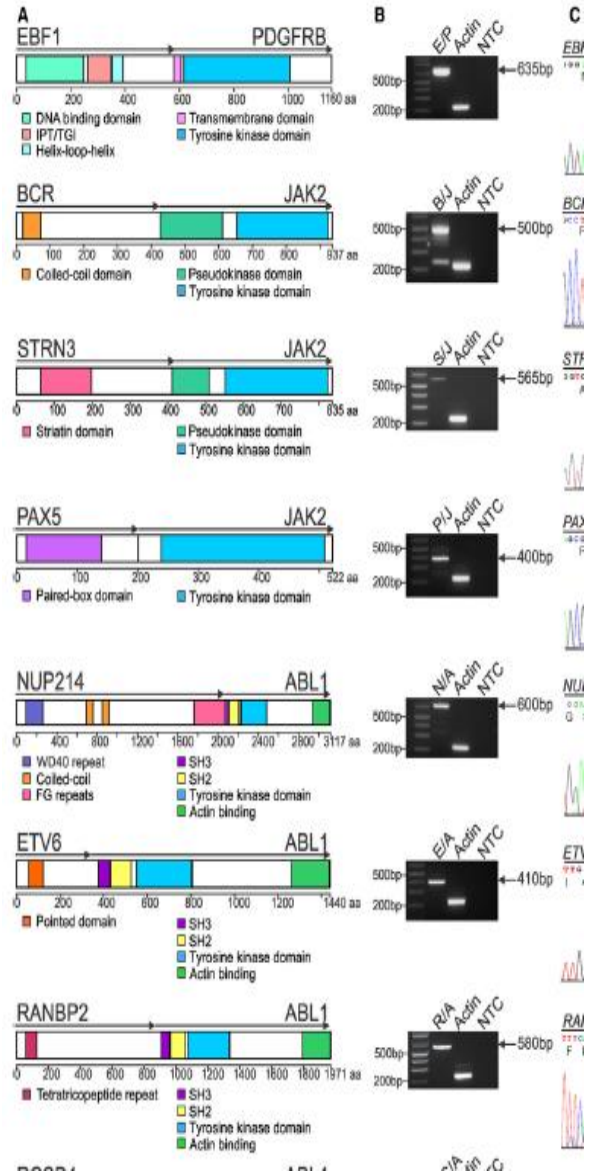


➢ **Signalisation dérégulée potentiellement « ciblable » par des inhibiteurs de JAK, PI3kinase, mTOR**

Fusions impliquant des kinases: partenaires variés +++

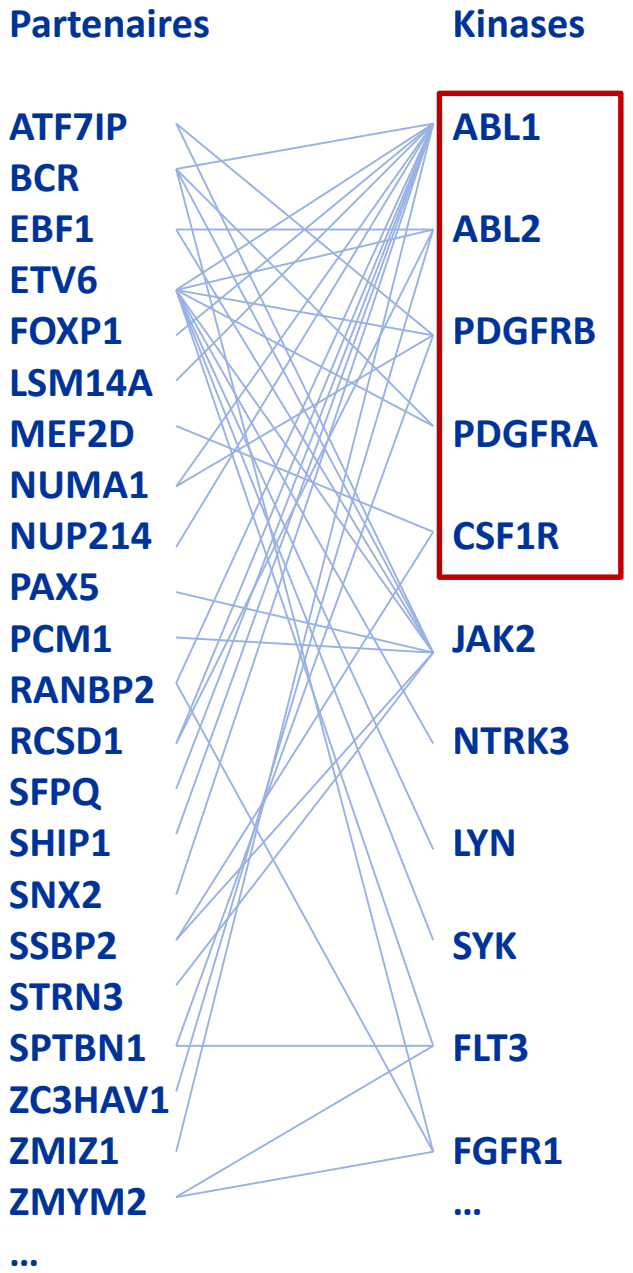
Partenaires	Kinases
ATF7IP	ABL1
BCR	ABL2
EBF1	PDGFRB
ETV6	PDGFRA
FOXP1	CSF1R
LSM14A	JAK2
MEF2D	NTRK3
NUMA1	LYN
NUP214	SYK
PAX5	FLT3
PCM1	FGFR1
RANBP2	…
RCSD1	
SFPQ	
SHIP1	
SNX2	
SSBP2	
STRN3	
SPTBN1	
ZC3HAV1	
ZMIZ1	
ZMYM2	
…	

Peeters P et al., Blood 1997
Reiter A et al., Cancer Res 2005
De Braekeleer E et al., Leukemia 2007
Poitras JL et al., Chromosomes & Cancer 2008
Hidalgo-Curtis C et al., Genes, Chrom & Cancer 2008
Soler G et al., Leukemia 2008
Ernst E et al., British Journal of Haematology 2011
Kakadia PM et al., Leukemia 2011
Kobayashi K et al., British J of Haematology 2014
Lilljebjorn U et al., Leukemia 2014
Roberts KG, et al. N Engl J Med
Kawamura M et al., Genes, Chrom & Cancer 2015
Yano M et al., British J of Haematology 2015
…



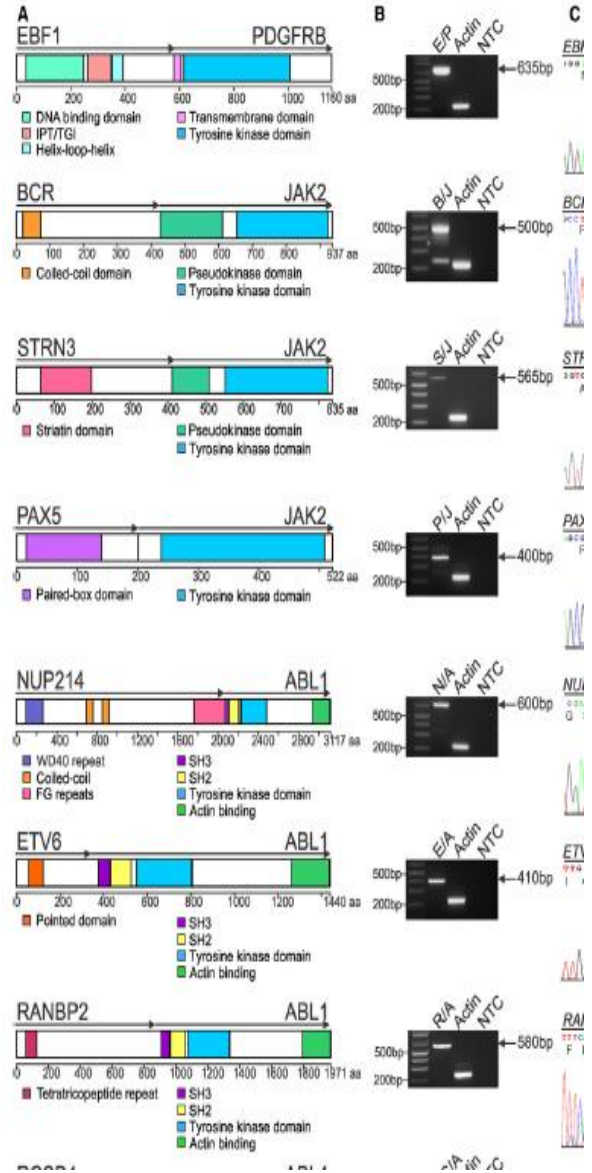
Roberts KG, et al. Cancer Cell 2012

Fusions impliquant des kinases: partenaires variés +++



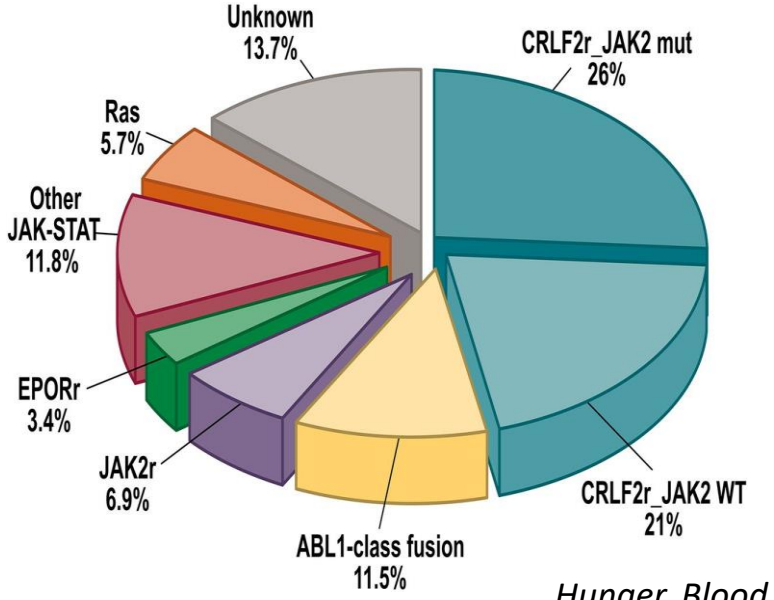
Kinases de classe ABL
-> sensibilité aux inhibiteurs de type imatinib

Peeters P et al., Blood 1997
Reiter A et al., Cancer Res 2005
De Braekeleer E et al., Leukemia 2007
Poitras JL et al., Chromosomes & Cancer 2008
Hidalgo-Curtis C et al., Genes, Chrom & Cancer 2008
Soler G et al., Leukemia 2008
Ernst E et al., British Journal of Haematology 2011
Kakadia PM et al., Leukemia 2011
Kobayashi K et al., British J of Haematology 2014
Lilljebjorn U et al., Leukemia 2014
Roberts KG, et al. N Engl J Med
Kawamura M et al., Genes, Chrom & Cancer 2015
Yano M et al., British J of Haematology 2015
…

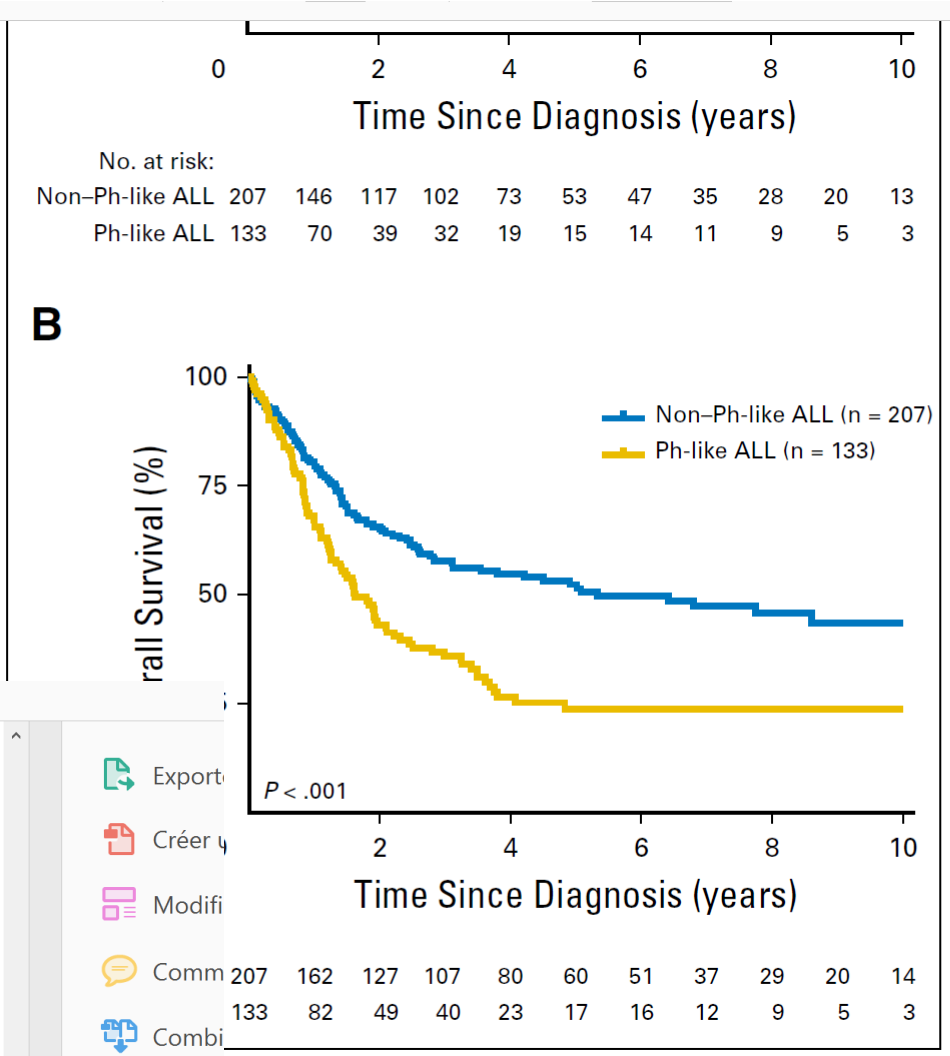


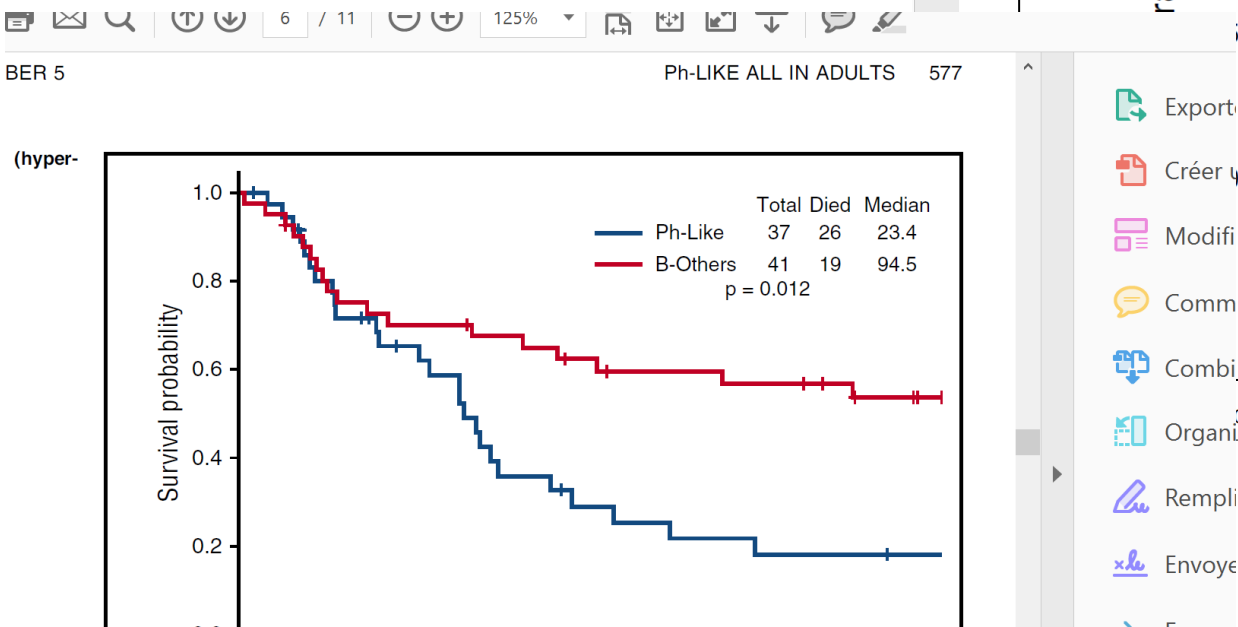
Roberts KG, et al. Cancer Cell 2012

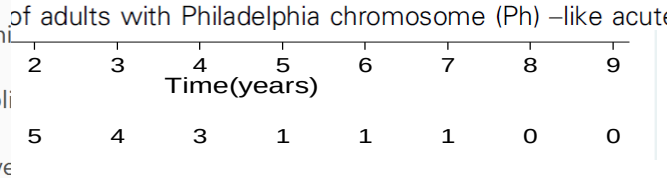
Pronostic des LAL Ph-like chez l'adulte



Hunger, Blood 201







GRAALL, unpublished data

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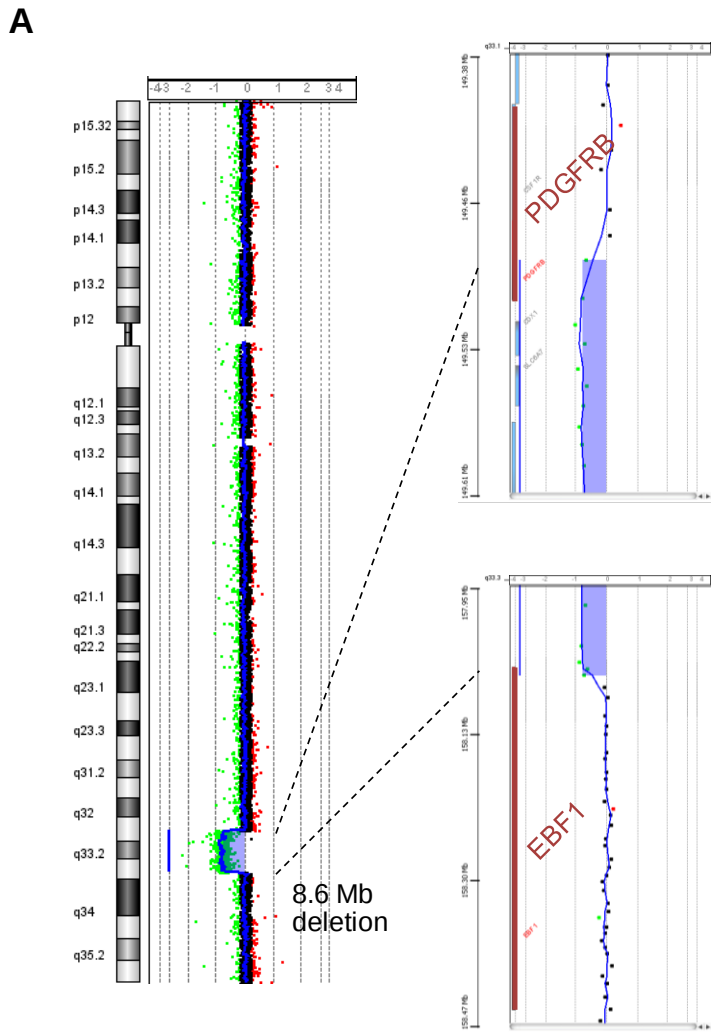
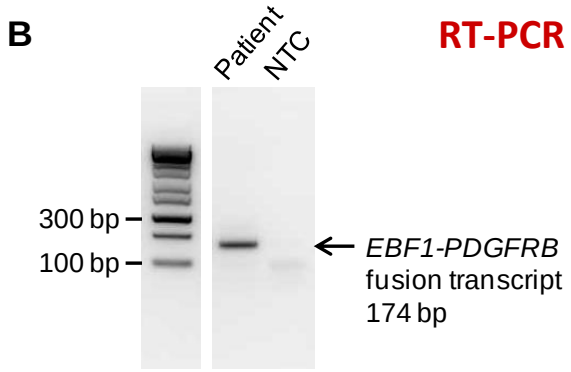
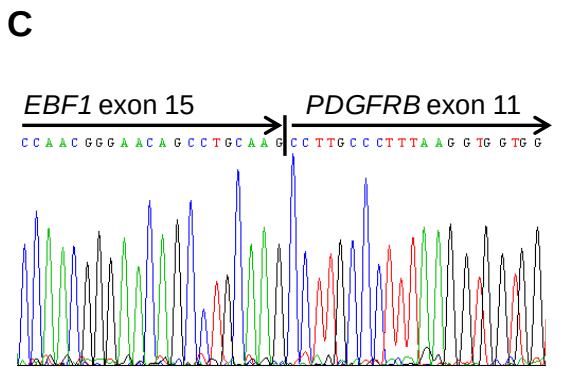
Case report: Successful TKI therapy in a refractory BCP-ALL with *EBF1-PDGFRB* rearrangement

Array-CGH





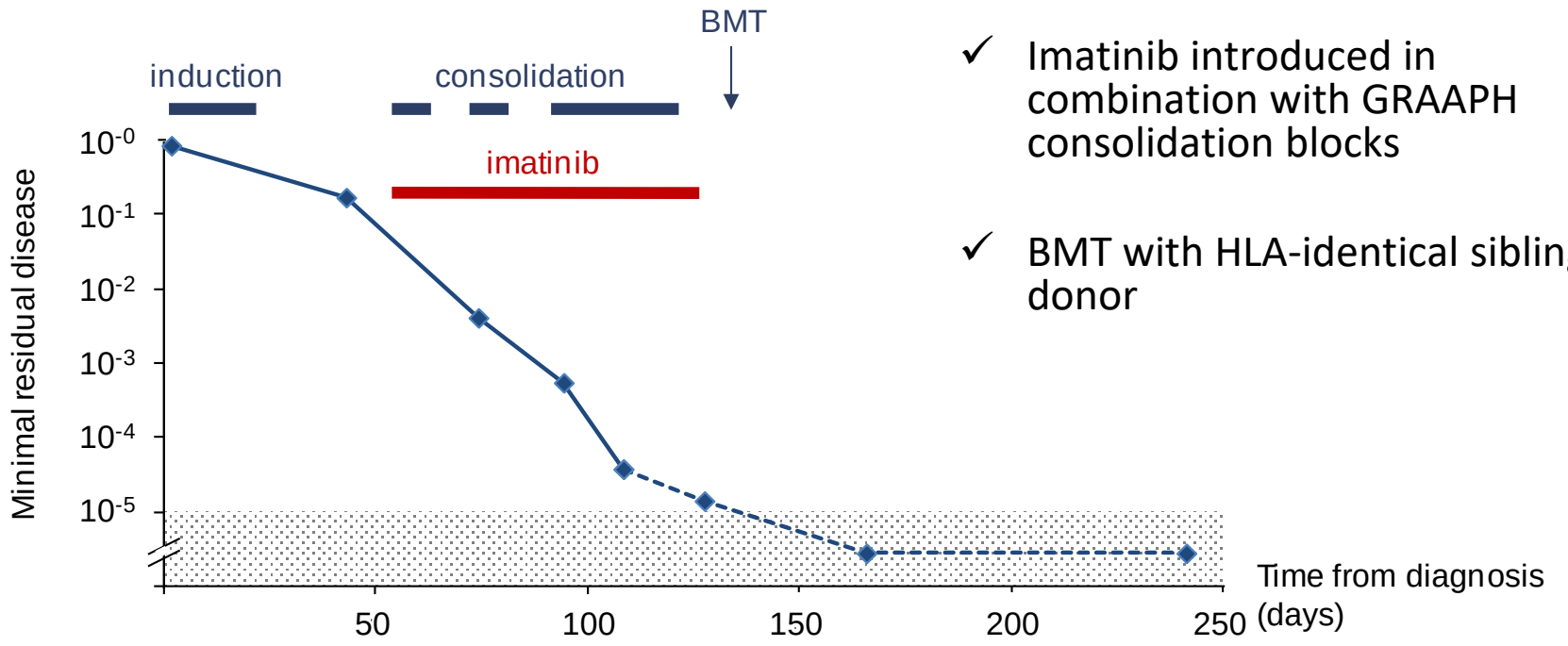


Fusion transcript sequence

Lengliné, Haematologica 2013

Case report: Successful TKI therapy in a refractory BCP-ALL with *EBF1-PDGFRB* rearrangement

MRD follow-up

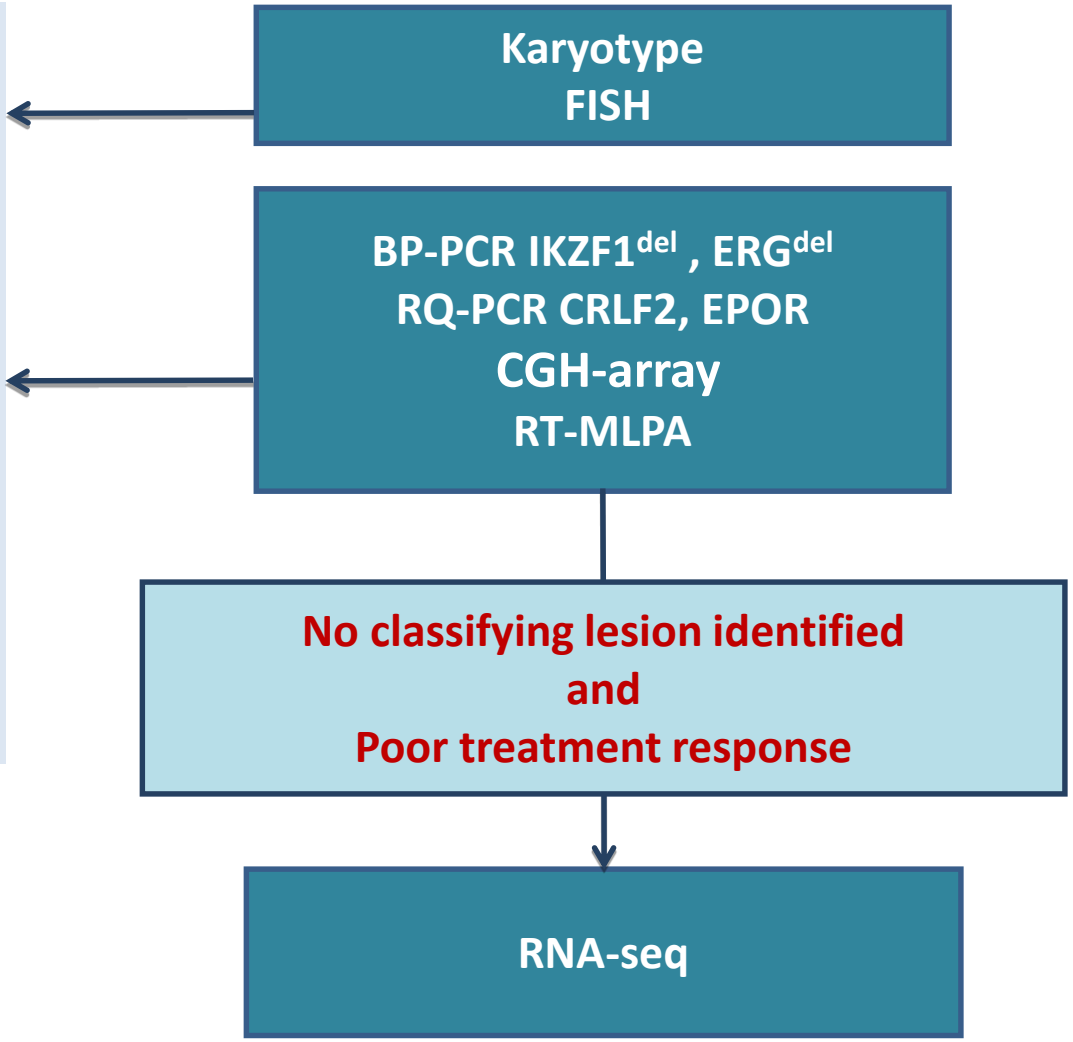


- ✓ Imatinib introduced in combination with GRAAPH consolidation blocks
- ✓ BMT with HLA-identical sibling donor

Lengliné, Haematologica 2013

Stratégie de diagnostic prospectif centralisé des altérations génétiques Ph-like pour une prise en charge thérapeutique précoce

BCR-ABL1
High hyperdiploidy
Low hypodiploidy
MLL fusions
iAMP21
ERGdel (DUX4)
CRLF2 deregulation
EPOR deregulation
TCF3-PBX1
ETV6-RUNX1
TCF3-HLF
ABL1 fusions
JAK2 fusions
PDGFRB fusions
PAX5 fusions
ZNF384 fusions



JE DONNE TU CHERCHES ILS GUÉRISSENT
JOURNÉES NATIONALES CONTRE LA LEUCÉMIE

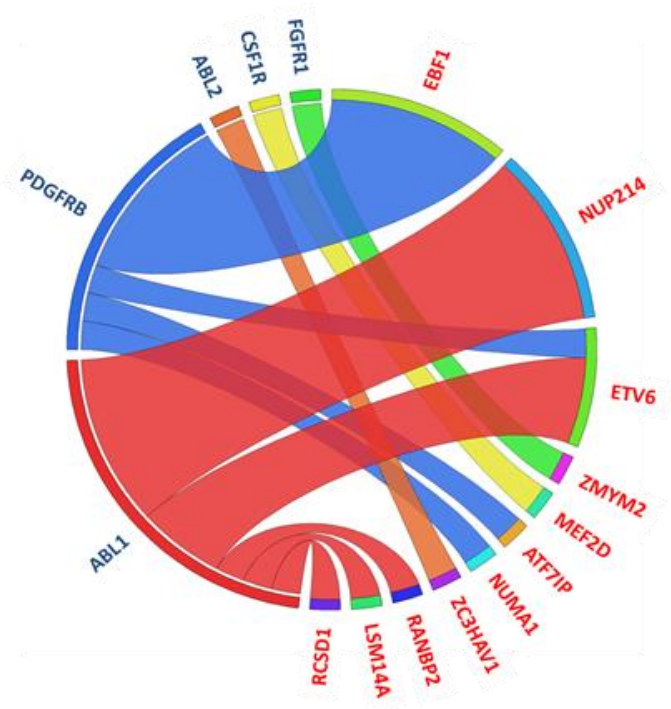
GRAALL
LALA GOELAMS SAKK

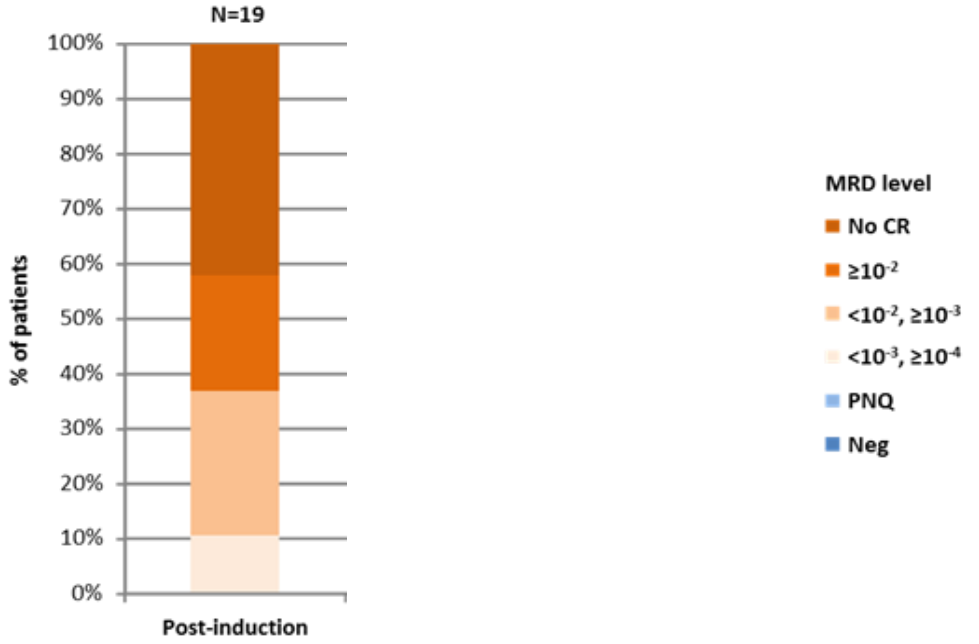
RNA-seq analysis for « B-other » ALL cases

Search for fusion genes

Efficacy of Tyrosine Kinase Inhibitors therapy in patients with Philadelphia-like Acute Lymphoblastic Leukemia harboring ABL-class fusions

Retrospective study on 24 patients
Treated with TKI firstline (n=19) or at relapse (n=5)





Tanensi et al. , Blood 2019

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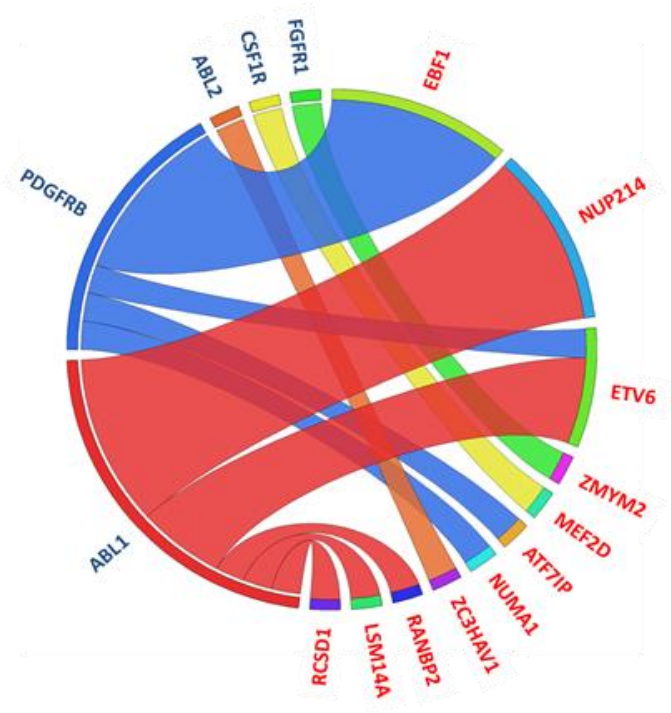

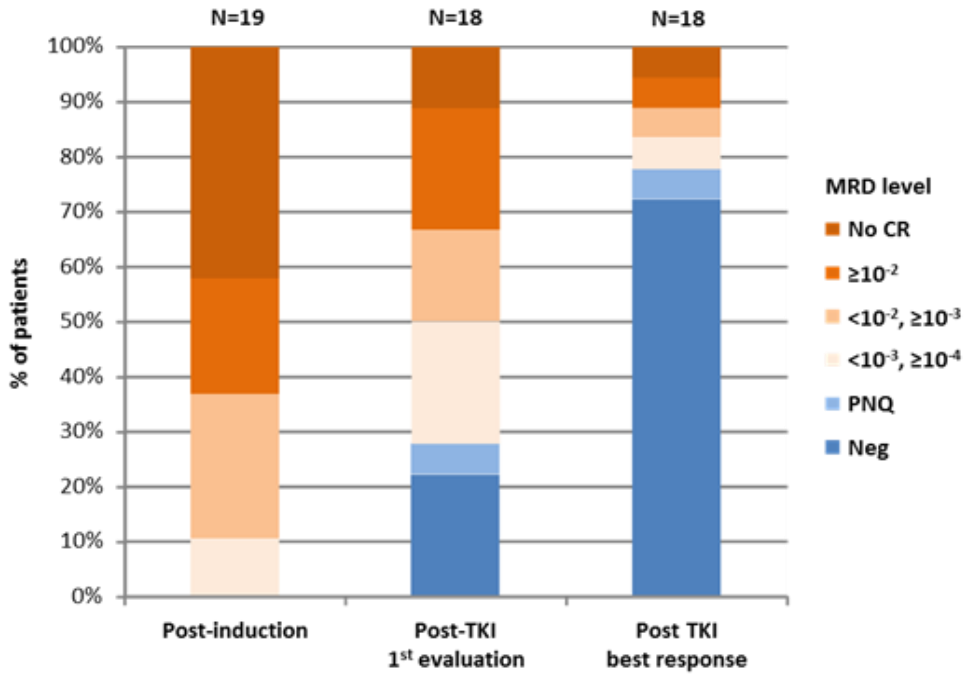

Tanensi et al. , Blood 2019

Efficacy of Tyrosine Kinase Inhibitors therapy in patients with Philadelphia-like Acute Lymphoblastic Leukemia harboring ABL-class fusions

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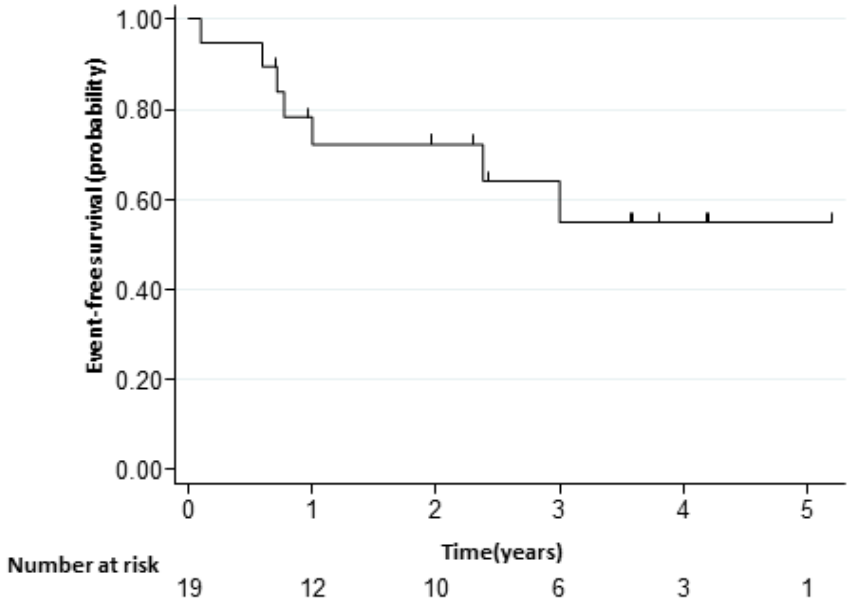
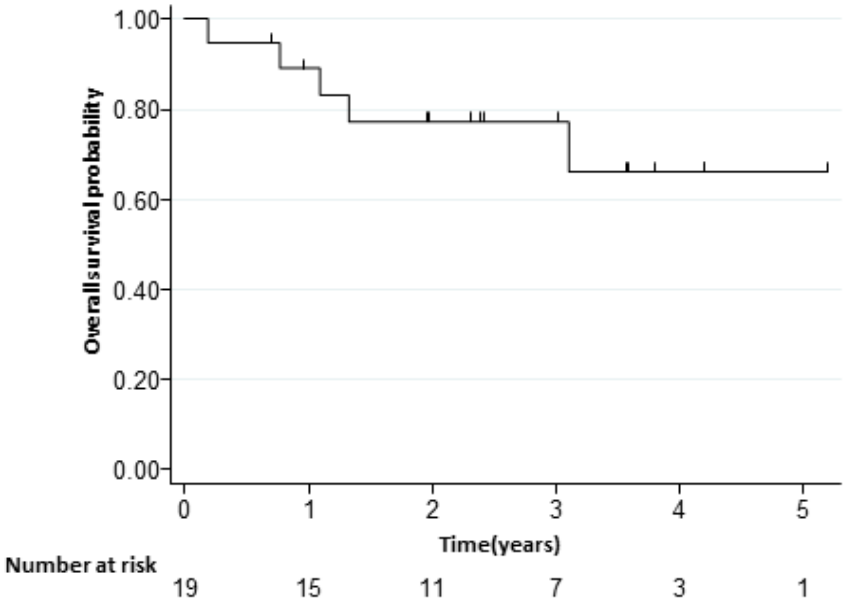


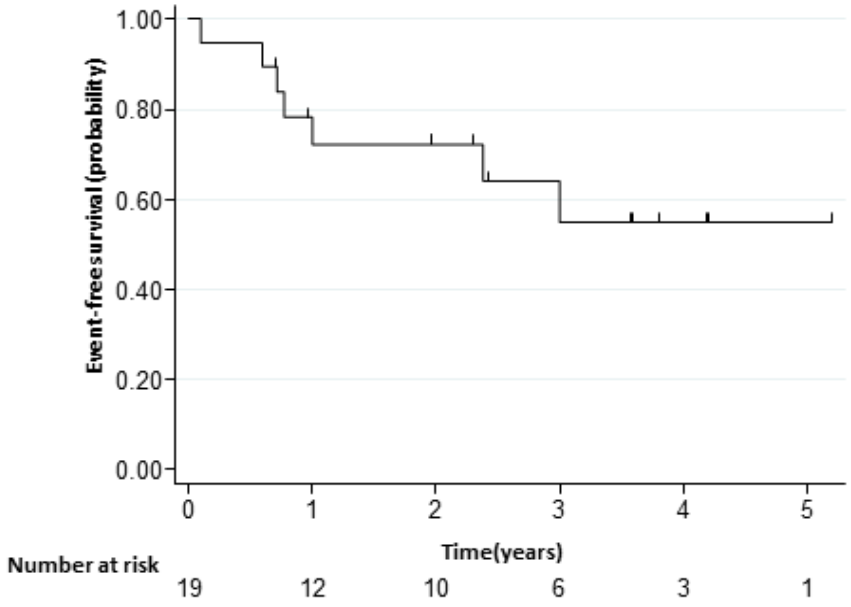


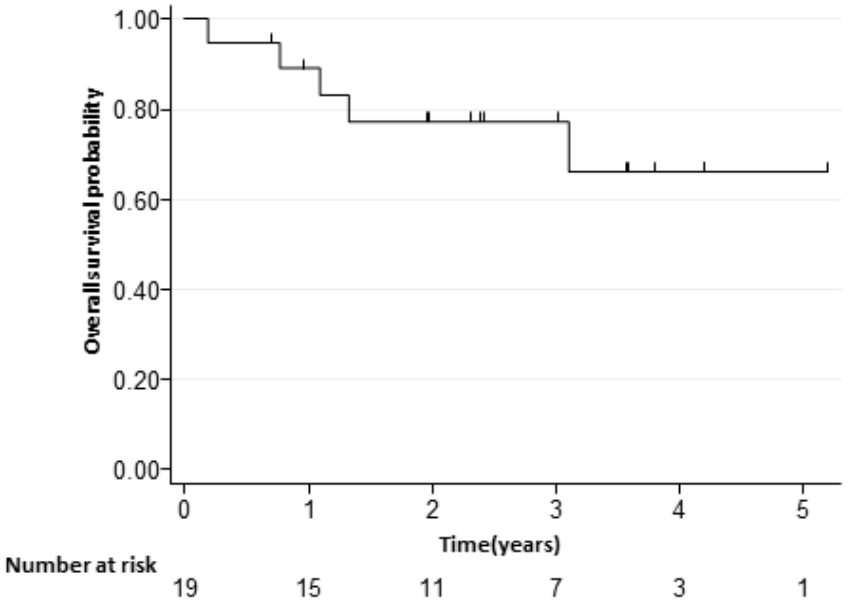
3-years OS 77%

Tanensi et al. , Blood 2019

Efficacy of Tyrosine Kinase Inhibitors therapy in patients with Philadelphia-like Acute Lymphoblastic Leukemia harboring ABL-class fusions

Retrospective study on 24 patients
Treated with TKI firstline (n=19) or at relapse (n=5)





3-years OS 77%

-> Recommendation for the treatment of patients with Ph-like ALL ABL-class in the GRAALL 2014 trial: Imatinib 600 mg in association with chemo

GRAALL
LALA GOELAMS SAKK

Tanensi et al. , Blood 2019

Conclusions

- Ph-like represents a rare subtype in children and adult ALL with poor outcome

- Identification of Ph-like alterations is challenging and may require RNA-seq

- A minority of Ph-like ALL is related to ABL class fusions which are targetable by TKI

    -> Centralized molecular diagnosis

    -> Addition of TKI to chemotherapy backbone at 1st line in case of ABL-class fusion

    -> Currently no kinase inhibitor with validated efficacy in other cases

Has Ph-like ALL Superseded Ph+ ALL as the Least Favorable Subtype?

Thai Hoa Tran [a, b], Sarah K. Tasian [c, d, *]

[a] Division of Pediatric Hematology-Oncology, Charles-Bruneau Cancer Center, CHU Sainte-Justine, Montreal, QC, Canada
[b] Department of Pediatrics, University of Montreal, Montreal, QC, Canada
[c] Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[d] Department of Pediatrics and Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Table 1
Current landscape of Ph-like ALL kinase rearrangements, therapeutic targets, and clinical trials.

Ph-like genetic subgroups	3′ kinase genes	5′ fusion partner genes	Kinase inhibitors	Clinical trials
JAK/STAT pathway alterations	*CRLF2*	*CSF2RA, IGH, P2RY8*	ruxolitinib	NCT02420717 (MDACC)
	JAK2	*ATF7IP, BCR, EBF1, ETV6, GOLGA5, HMBOX1, OFD1, PAX5, PCM1, PPFIBP1, RFX3, SMU1, SNX29, SSBP2, STRN3, TERF2, TPR, USP25, ZBTB46, ZNF274, ZNF340*	ruxolitinib	NCT02723994 (COG AALL1521)
	EPOR	*IGH, IGK, IGL, LAIR1, THADA*	ruxolitinib	NCT03117751 (SJCRH Total XVII)
	TSLP	*IQGAP2*	ruxolitinib	NCT03571321 (University of Chicago)
	IL2RB	*MYH9*	ruxolitinib	
ABL class alterations	*ABL1*	*CENPC, ETV6, FOXP1, LSM14A, NUP153, NUP214, RANBP2, RCSD1, SFPQ, SHIP1, SNX1, SNX2, SPTNA1, ZMIZ1*	dasatinib, imatinib, others	NCT01406756 (COG AALL1131)
	ABL2	*PAG1, RCSD1, ZC3HAV1*	dasatinib, imatinib	NCT02143414 (SWOG S1318)
	CSF1R	*MEF2D, SSBP2, TBL1XR1*	dasatinib, imatinib	NCT02420717 (MDACC)
	PDGFRA	*FIP1L1*	dasatinib, imatinib	NCT03007147 (COG AALL1631)
	PDGFRB	*ATF7IP, EBF1, ETV6, NUMA1, SNX29, SSBP2, TERF2, TNIP1, ZEB2, ZMYND8, ZNF608*	dasatinib, imatinib	NCT03117751 (SJCRH Total XVII)
	LYN	*GATAD2A, NCOR1*	dasatinib, imatinib	
Other kinases	*NTRK3*	*ETV6*	entrectinib larotrectinib	NCT03066661 NCT03834961
	PTK2B	*KDM6A, STAG2, TMEM2*	FAK inhibitors	
	FGFR1	*BCR*	ponatinib	
	FLT3	*ZMYM2*	FLT3 inhibitors	
	TYK2	*MYB, SMARCA4, ZNF340*	JAK1/3 inhibitor	
	BLNK	*DNTT*		
	CBL	*KANK1*		
	DGKH	*ZFAND3*		

Acknowledgements

Philippe Rousselot
Yves Chalandon
Véronique Lhéritier
Hervé Dombret
Nicolas Boissel

And all GRAALL investigators

Hematology laboratory
Saint-Louis hospital

Rathana Kim
Jean-Michel Cayuela
Marie Passet
Jean Soulier