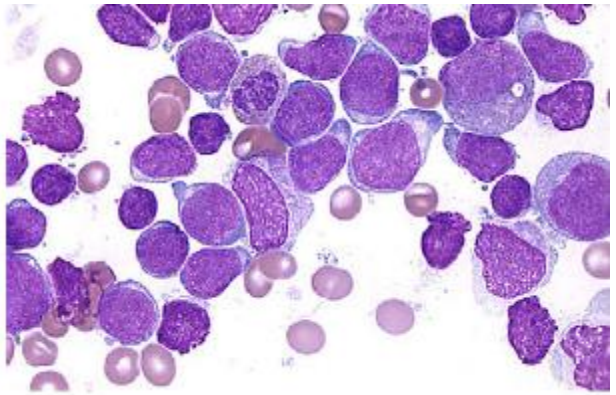
LAL Ph+ aspects cliniques et thérapeutiques
DES: 28.01.2022



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SFGM-TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

GRAALL LALA GOELAMS SAKK

SAKK WE BRING PROGRESS TO CANCER CARE

SWISS CANCER CENTER LEMAN

HUG Hôpitaux Universitaires Genève

DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Incite					X	X	X
BMS						X	X
Pfizer						X	X
Abbvie						X	X
MSD						X	X
Roche						X	X
Novartis						X	X
Gilead							X
Amgen						X	X
Jazz						X	X
AstraZeneca					X	X	X

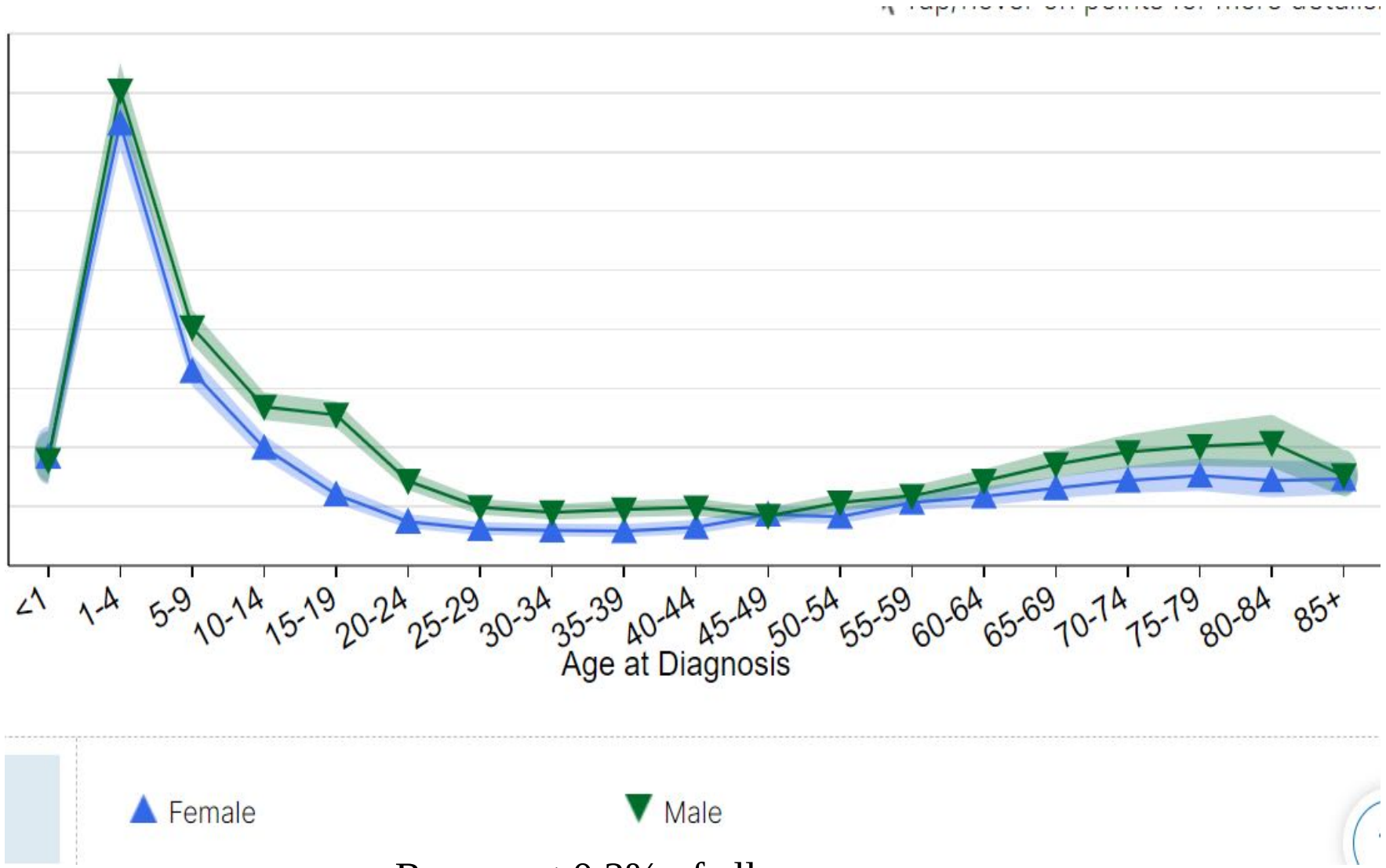
Objectifs d'apprentissage

- **Définir une LAL et plus particulièrement une LAL Ph+**
- **Connaître l'épidémiologie des LAL/LAL Ph+**
- **Connaître les différentes méthodes diagnostiques employées**
- **Etre capable de décrire les stratégies thérapeutique de prise en charge des patients souffrants de LAL Ph+ en 1ère ligne et en rechute**
- **Connaître les méthodes de suivi de la maladie et de diagnostic précoce de la rechute**

LAL Ph+ plan

- **Epidémiologie et facteurs prédisposant aux LAL/LAL Ph+**
- **Présentation clinique**
- **Diagnostic**
- **Facteurs pronostics**
- **Devenir avant l'ère des inhibiteurs de tyrosine kinase**
- **Stratégies thérapeutiques de 1ère ligne: - jeune adulte**
  - adulte âgé
- **Prise en charge de la rechute**
- **Impact de la MRD**

Age-specific annual incidence of ALL (US SEER data 2014-2018)



Represent 0.3% of all cancers
Incidence 1.6/100’000/yr
Median age at diagnosis 17 yr

Predisposing factors of ALL

Genetic susceptibility

- Congenital syndromes: Down's syndrome, Fanconi anaemia, Ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome
- Inherited gene variants: *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A* or *CDKN2B*, *PIP4K2A*, *ETV6*
- Constitutional Robertsonian translocation between chromosomes 15 and 21, rob(15;21)(q10;q10)
- Single nucleotide polymorphisms: rs12402181 in miR-3117 and rs62571442 in miR-3689d2

Environmental factors

- Pesticide exposure
- Ionising radiation
- Childhood infections

F Malard, M Mohty Lancet 2020:395

LAL Ph+ plan

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Clinical presentation

- **Classical triad of symptoms related to BM failure: fatigue, bruising+bleeding, fever with infection**
- **Headache and cranial or other nerve palsy in 5-10% due to CNS invasion**
- **Enlargement of superficial lymph nodes, liver and/or spleen**
- **Hyperleucocytosis and blasts > 100 G/L →rarely leukostasis syndrome or catastrophic early bleeding**

Staging procedures

Medical history	Co-morbid diseases Occupational risk factors Allergic reactions Drugs
Physical examination	General, performance status Head, neck, oral cavity Thorax (lungs, heart, blood pressure) Abdomen (liver, spleen) Extremities and neurological Superficial lymph nodes Skin Body temperature Optical fundus Haemorrhages/infections
Laboratory	Full blood counts with differential, Liver and kidney functions, serum LDH, electrolytes, serum albumin Immunoglobulin level determination Glucose, clotting test, blood group HLA typing, Serology for viral hepatitis type B and C, HIV
Instrumental	Electrocardiogram, chest X-ray
Invasive procedures	Bone marrow aspirate/biopsy Lumbar puncture

R Bassan Crit Rev Onc Hem 2004:50

LAL Ph+ plan

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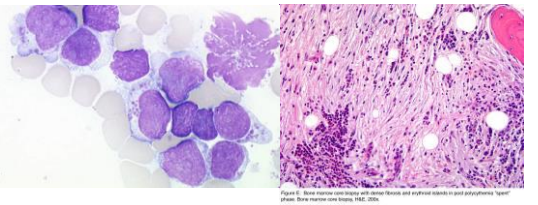
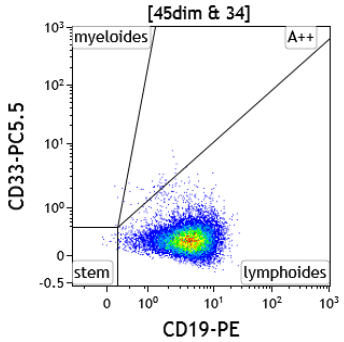
Specific hematological procedures for diagnosis

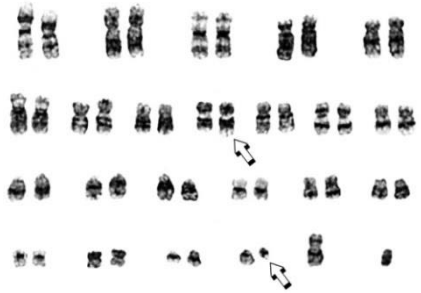
- Bone marrow cytology and biopsy for cytology and histology

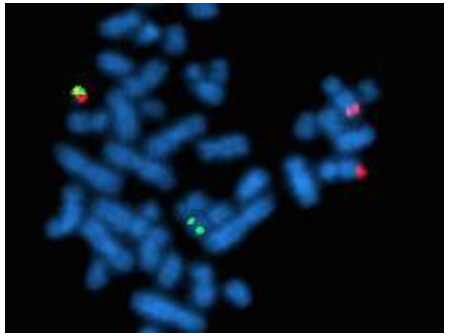


- Flow cytometry

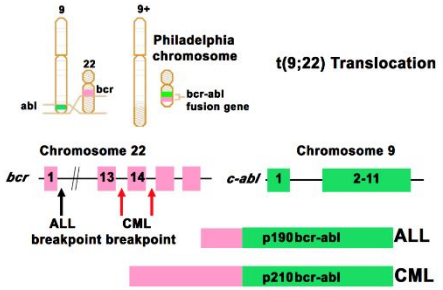


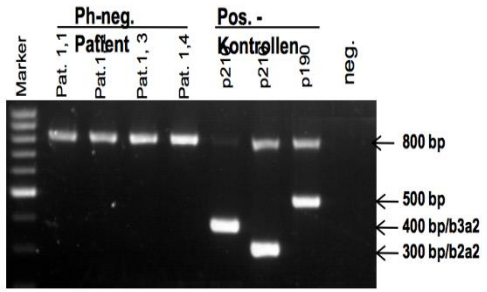
- Conventional cytogenetics + FISH

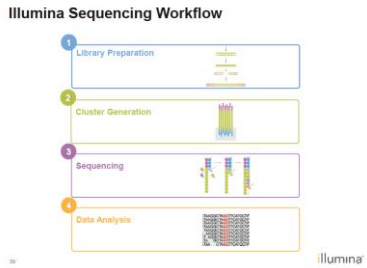




- Molecular biology by PCR/NGS, mainly BCR-ABL and Ig/TCR for measurable residual disease (MRD) evaluation during the course of the treatment



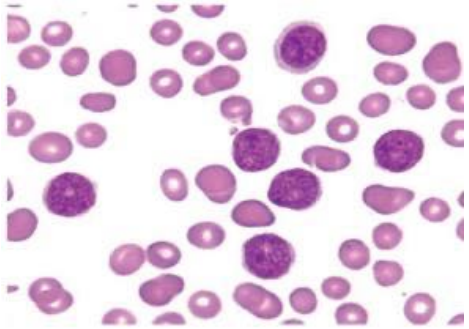
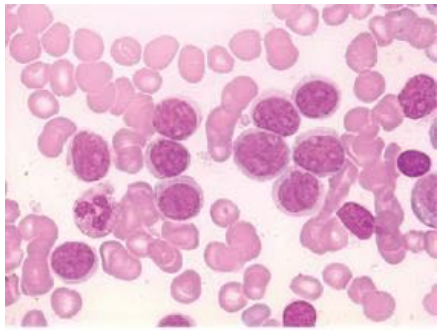
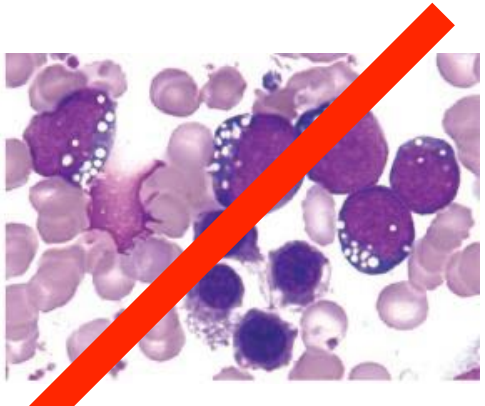




Diagnostic

classification FAB 1976 **WHO 2016**

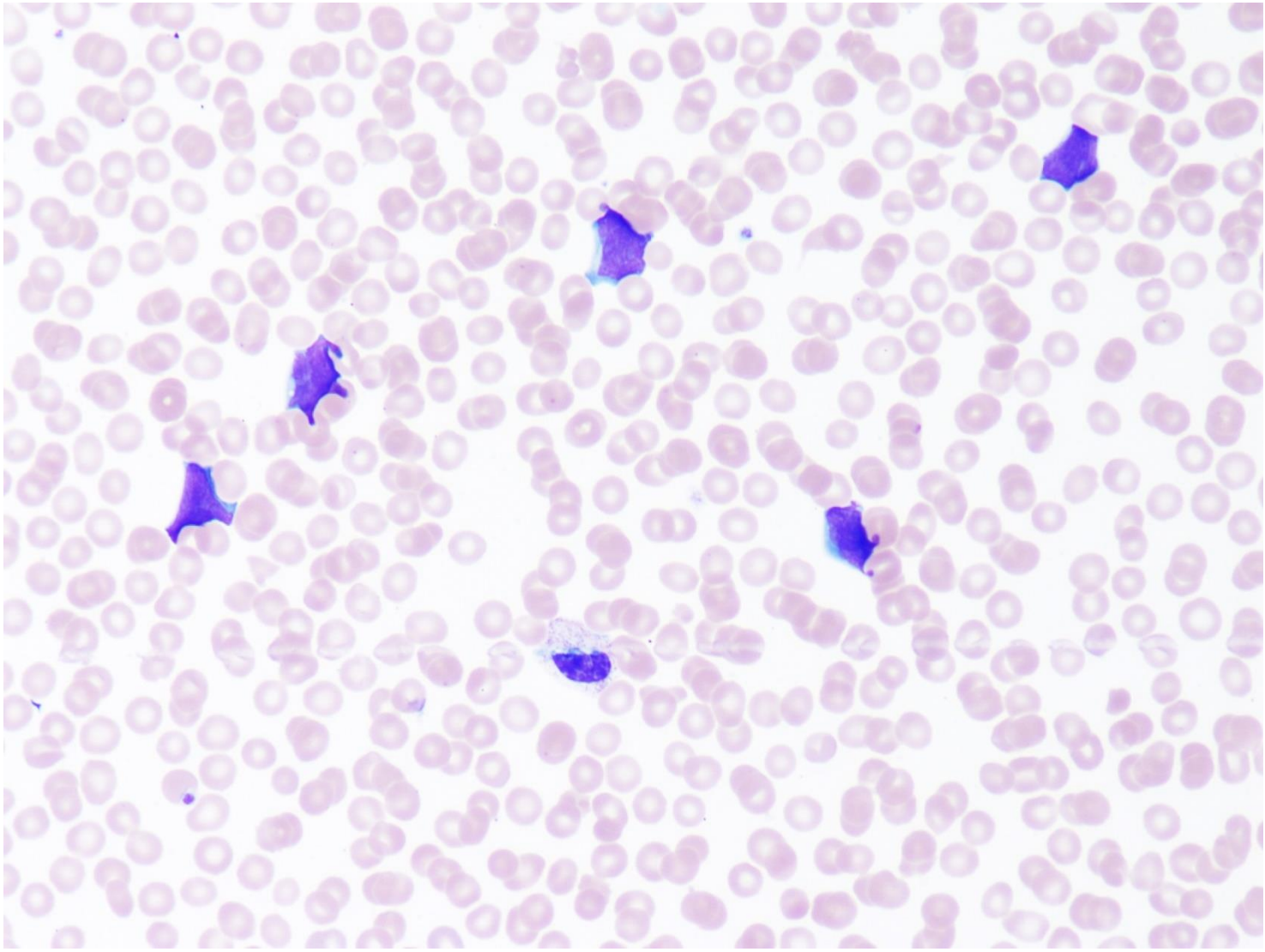
- Définition : >20-25% de lymphoblastes médullaires (protocoles)
- Atteinte extramédullaire fréquente : ganglions, rate, foie, testicules et surtout SNC!
- Par convention on utilise le terme de lymphome lymphoblastique si infiltration nulle ou minime de la moelle
- Exclusion du Burkitt t(8;14) avec infiltration médullaire (ex : LAL3)

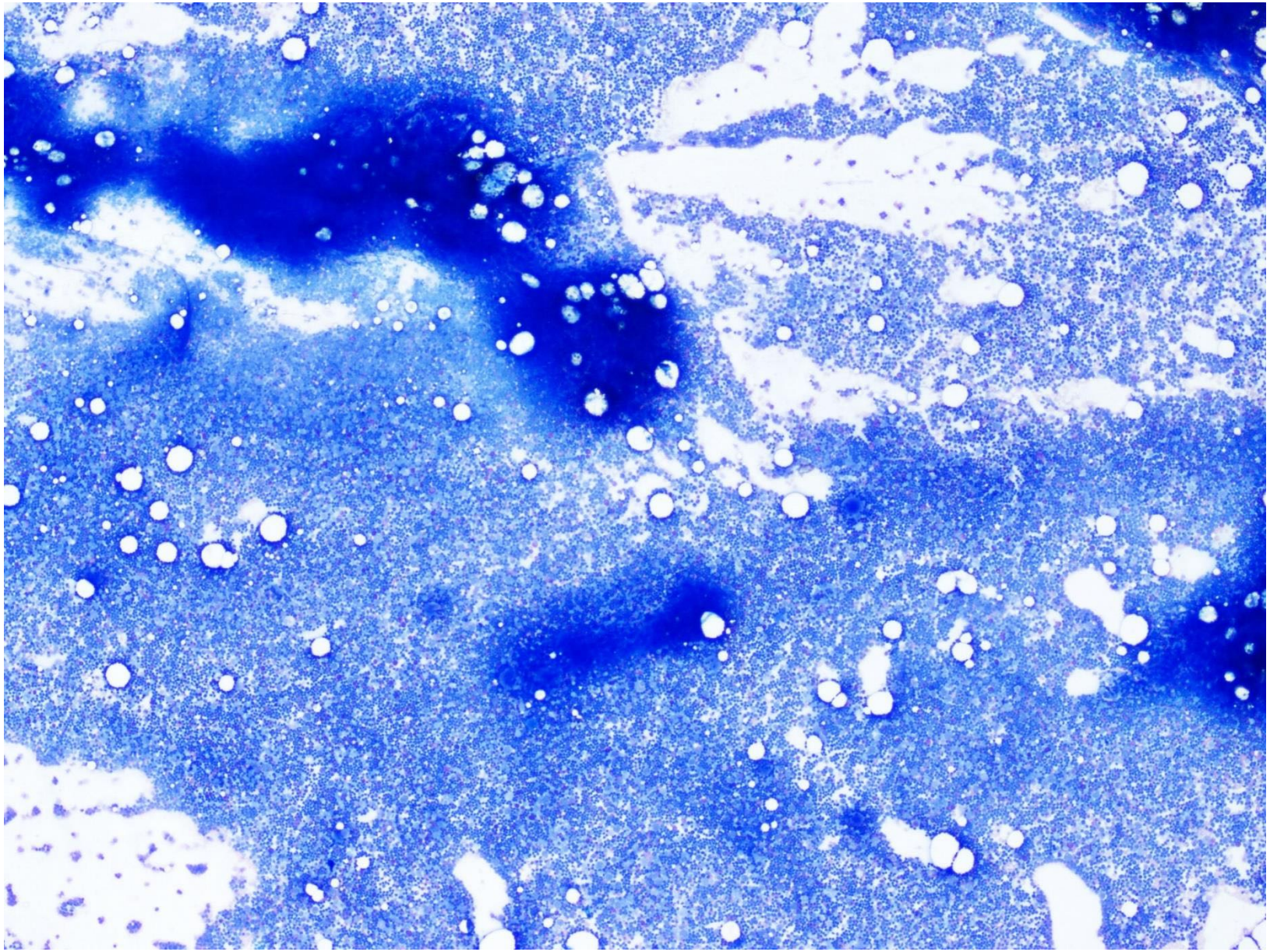
Présentation biologique

- Hémogramme : leucopénie ou franche leucocytose constituée de lymphoblastes, neutropénie fréquente, parfois hyperéosinophilie. Anémie arégénérative. Thrombopénie.
- Crase : CIVD/fibrinolyse possibles si hyperleucocytose
- LDH augmentés +/- syndrome de lyse tumorale

Cytologie sang



Cytologie moelle



Features of Ph+ ALL

- Restricted to B-precursor ALL (pre-B, c-ALL)
- Frequent co-expression of myeloid antigens
- Propensity for CNS involvement during ttt
- Higher median age
- Over 50% for age > 50 years

ALL

	Children	Adults
Peak incidence	**4 years**	**50 years**
%Leukemia	**80-85%**	**15%**
Chromosomes		
Ph+	**3%**	**25-30%**
MLL	**1-2%**	**7%**
TEL/AML1	**20%**	**2%**
T-cell	**10-15%**	**20-25%**
Mature B	**1-2%**	**3-5%**

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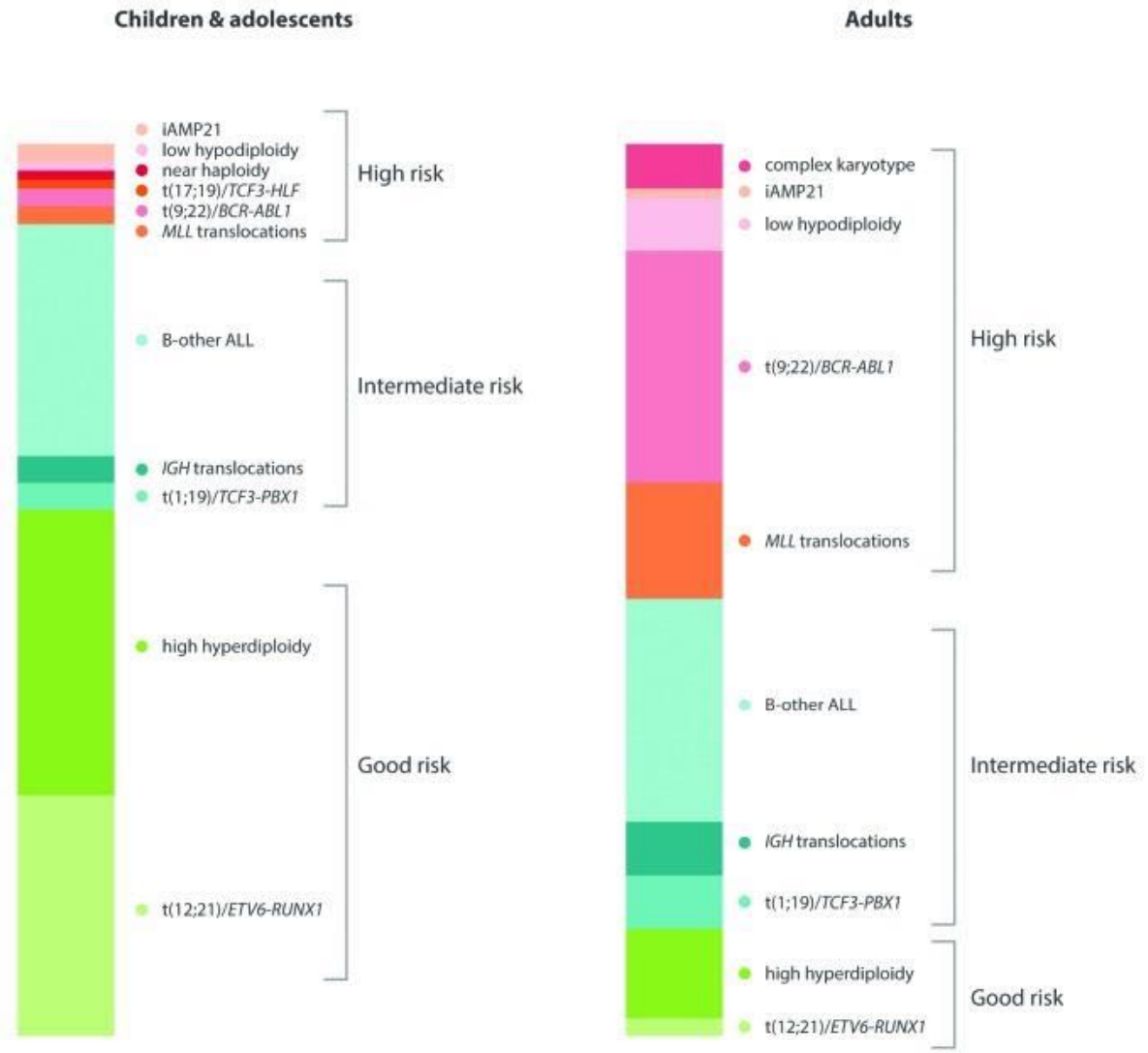
Background

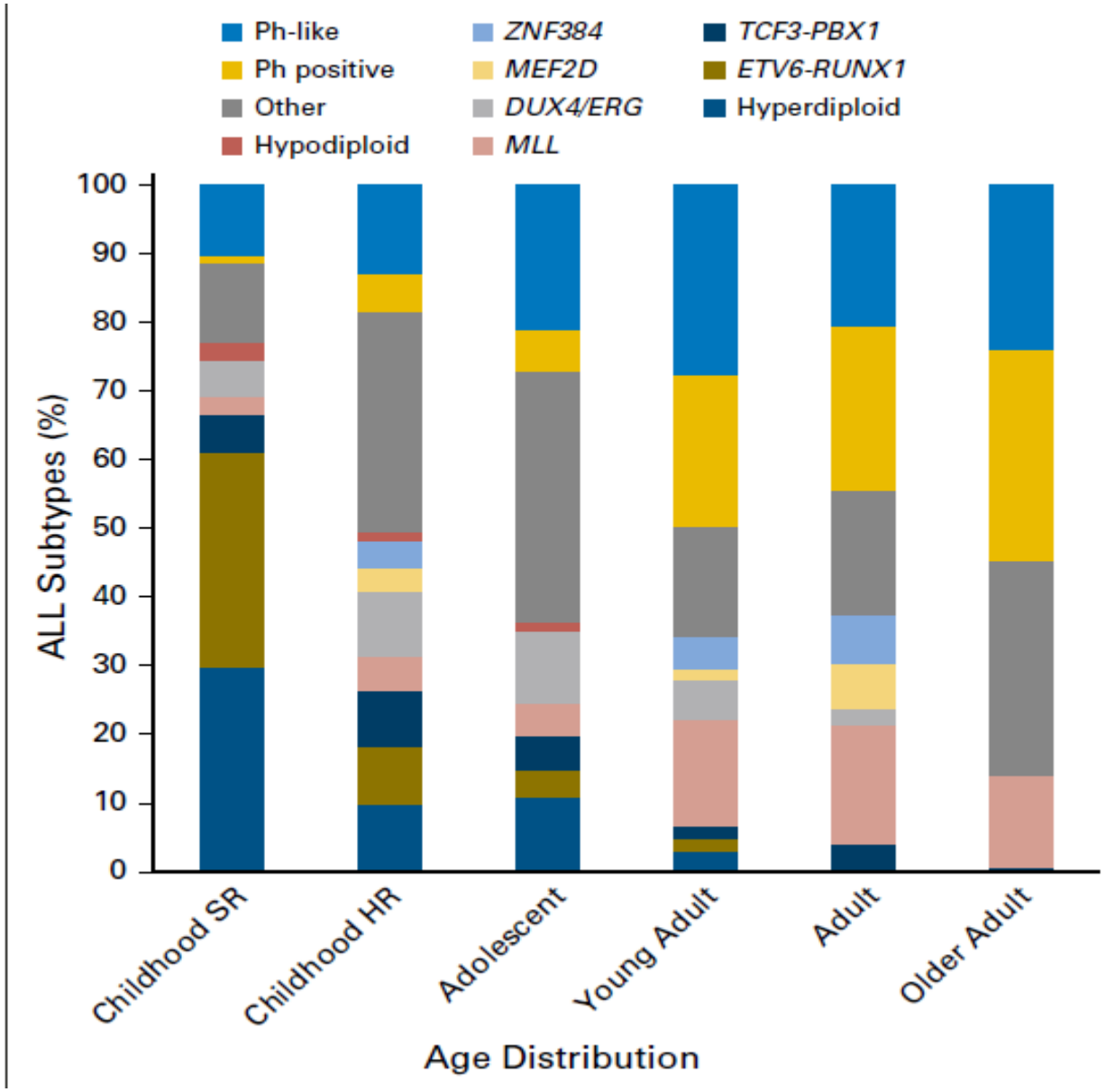
- ✓ **Ph+ confers a bad prognosis to ALL**
- ✓ **Long-term OS with chemotherapy <20% in the “pre-imatinib era”**
- ✓ **Advent of the targeted therapy imatinib, specific BCR-ABL inhibitor → major changes in Ph+ ALL outcome**

Frequency of the cytogenetic abnormalities in children and adults with BCP-ALL



A.V. Moorman Haematologica 2016;101:407

BCP-ALL heterogeneity



I Iacobucci and CG Mullighan JCO 2017;35:975

Genomic alterations in Ph+ ALL

Alteration	Function	Incidence	Prognosis
IKZF1	Normal lymphoid development	60%-80% (deletions) 10%-15% (mutations)	↓ Survival in most studies (especially with other alterations, ie, "*IKZF1* plus")
CDKN2A/B	Cell cycle regulation	Approximately 40%	↓ Survival
PAX5	Normal lymphoid development	Approximately 40%	Conflicting data
BTG1	Regulator of apoptosis	10%-20%	↓ Survival
EBF1	Normal lymphoid development	<15%	Unknown (↓ survival in Ph^- ALL)
RB1	Cell cycle regulation	<15%	Unknown (↓ survival in Ph^- ALL)
TP53	Cell cycle regulation	<5%	Unknown (conflicting data in Ph^- ALL)

Abbreviations: ALL = acute lymphoblastic leukemia; Ph = Philadelphia chromosome.

NJ Short et al. Clinical Lymphoma Myeloma & Leukemia 2018;18:439

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Outcomes of patients with newly diagnosed Ph+ ALL treated with chemotherapy only

Clinical Trial (year)	N	Median Age, [range]	Chemotherapy	CR, %	SCT in CR1, %	OS, %
Gotz (1992)[53]	25	44 [21-74]	BFM	76	8	6 at 40 mo
Larson (1995)[54]	30	32 [16-80]	CALGB	70	NA	16 at 36 mo
Thomas (2001)[6]	51	35 [14-89][a]	LALA	NA	16	10 at 60 mo
Gleissner (2002)[55]	175	45 [15-65]	GMALL	68	NA	15 at 36 mo
Takeuchi (2002)[3]	51	31 [15-59][a]	JALSG	51	NA	5 at 72 mo
Kantarjian (2004)[4]	48	40 [15-92][a]	HyperCVAD	92	23	12 at 60 mo
Pullarkat (2008)[5]	36	47 [17-64]	SWOG	67	NA	8 at 60 mo

ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munich protocol; CALGB, Cancer and Leukemia Group B; CR, complete remission; GMALL, German Multicenter Study Group for Adult ALL; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate; JALSG, Japan Adult Leukemia Study Group; LALA, Leucémie Aiguë Lymphoblastic chez l'Adulte; mo, months; N, number of patients; NA, not available; OS, overall survival; Ph+, Philadelphia chromosome–positive; SCT in CR1, stem cell transplant in first CR; SWOG, Southwest Oncology Group

[a] Age for the whole study cohort, including patients with Ph-negative ALL.

M Yilmaz et al. Clinical Advances in Hematology & Oncology 2018;12:216

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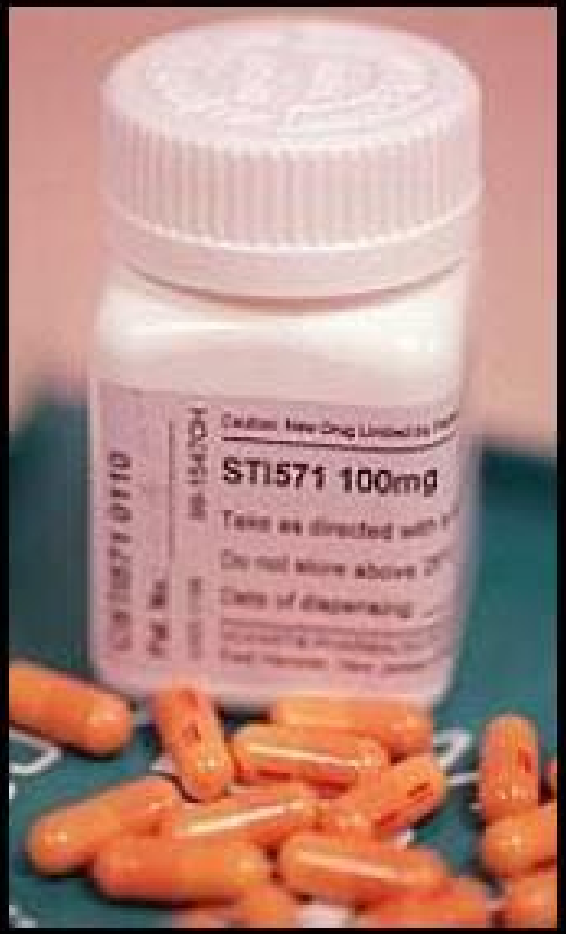
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

28 mai 2001

Imatinib mesylate (STI571 - Glivec)

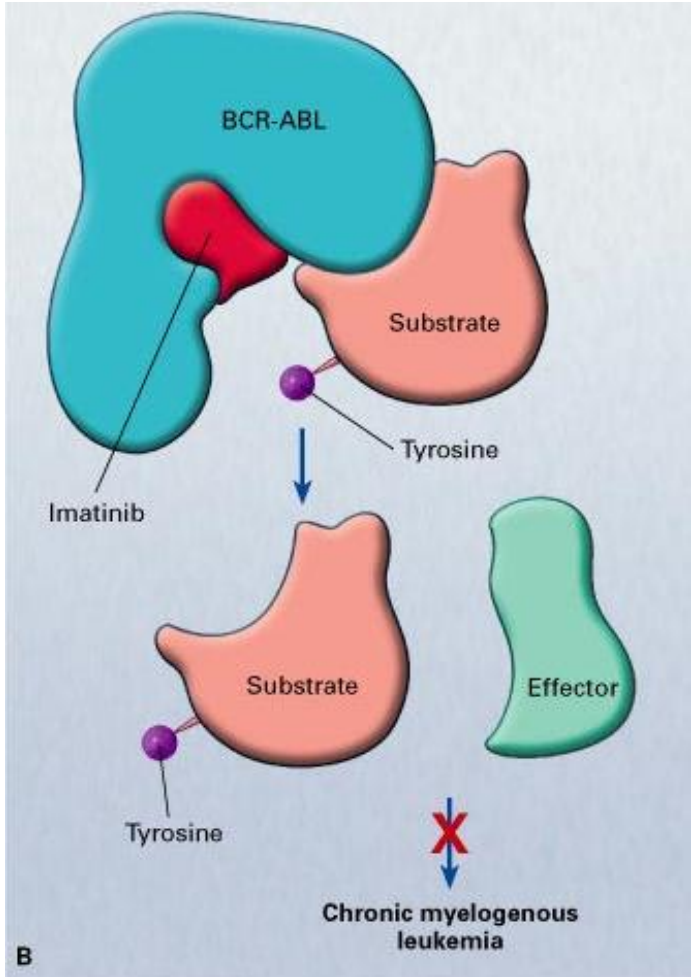
$(C_{30}H_{35}N_7SO_4)$

1998



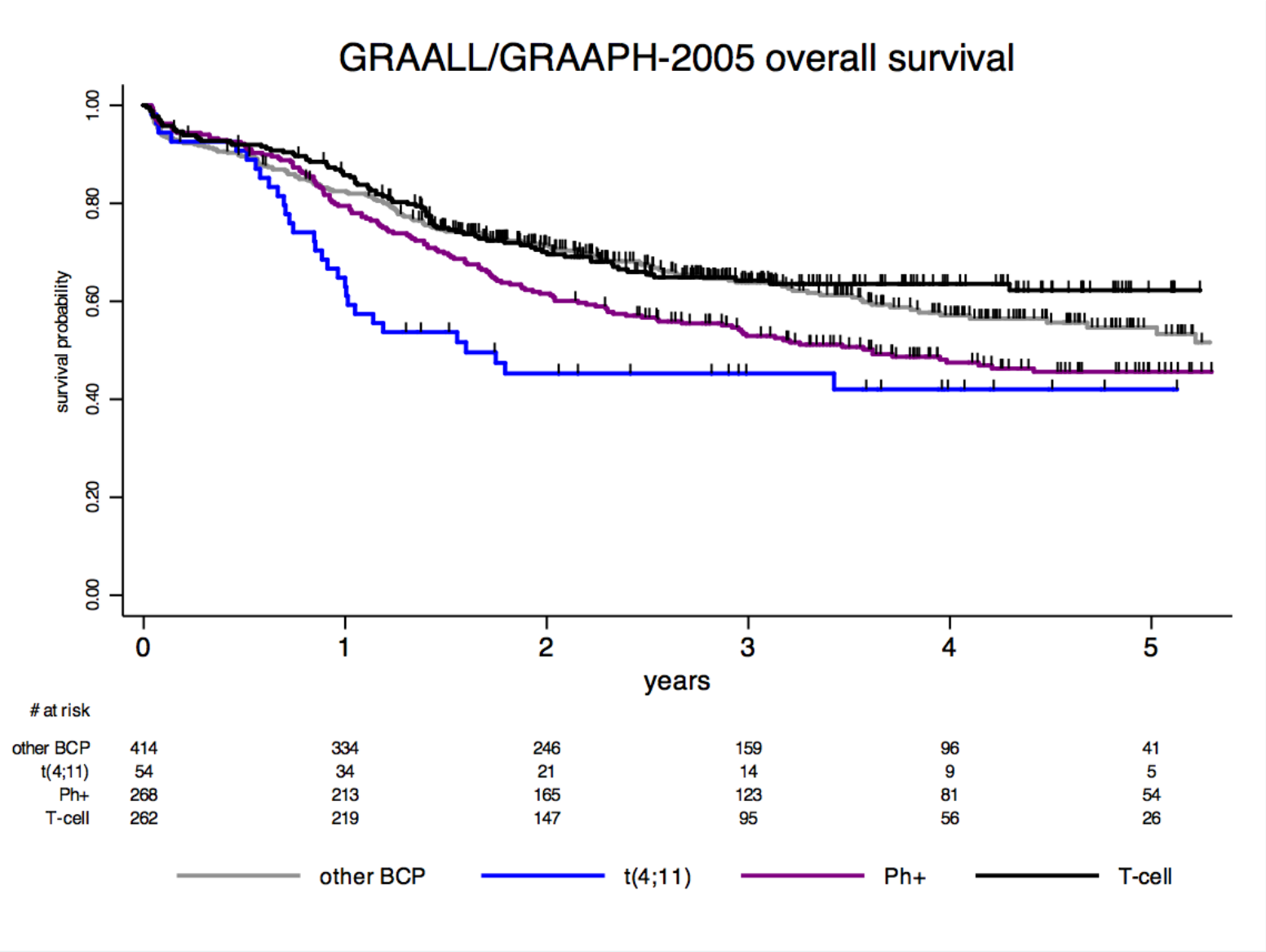
Advent of targeted molecular therapy of CML

Specific ttt by inhibition of TK ABL: imatinib



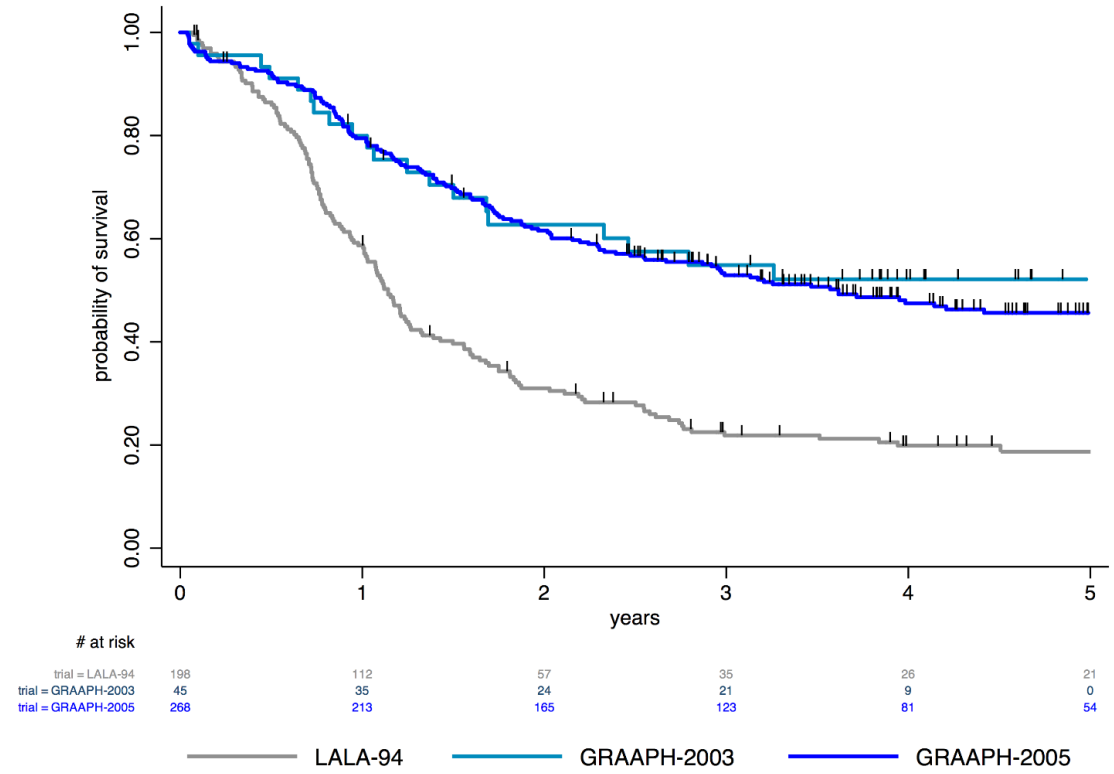
Savage & Antman
NEJM 2002;346:683-93

Advances made with imatinib



Overall survival of Ph+ ALL

Three consecutive GRAALL/LALA trials



H. Dombret et al. Blood 2002 A. de Labarthe et al. Blood 2007; A. Tanguy-Schmidt et al. BBMT 2013; Y. Chalandon et al. Blood 2015

Initial therapy for Ph+ALL : Similar high CR rates in combination with chemotherapy or no and deeper molecular response with 2nd and 3rd gen TKI

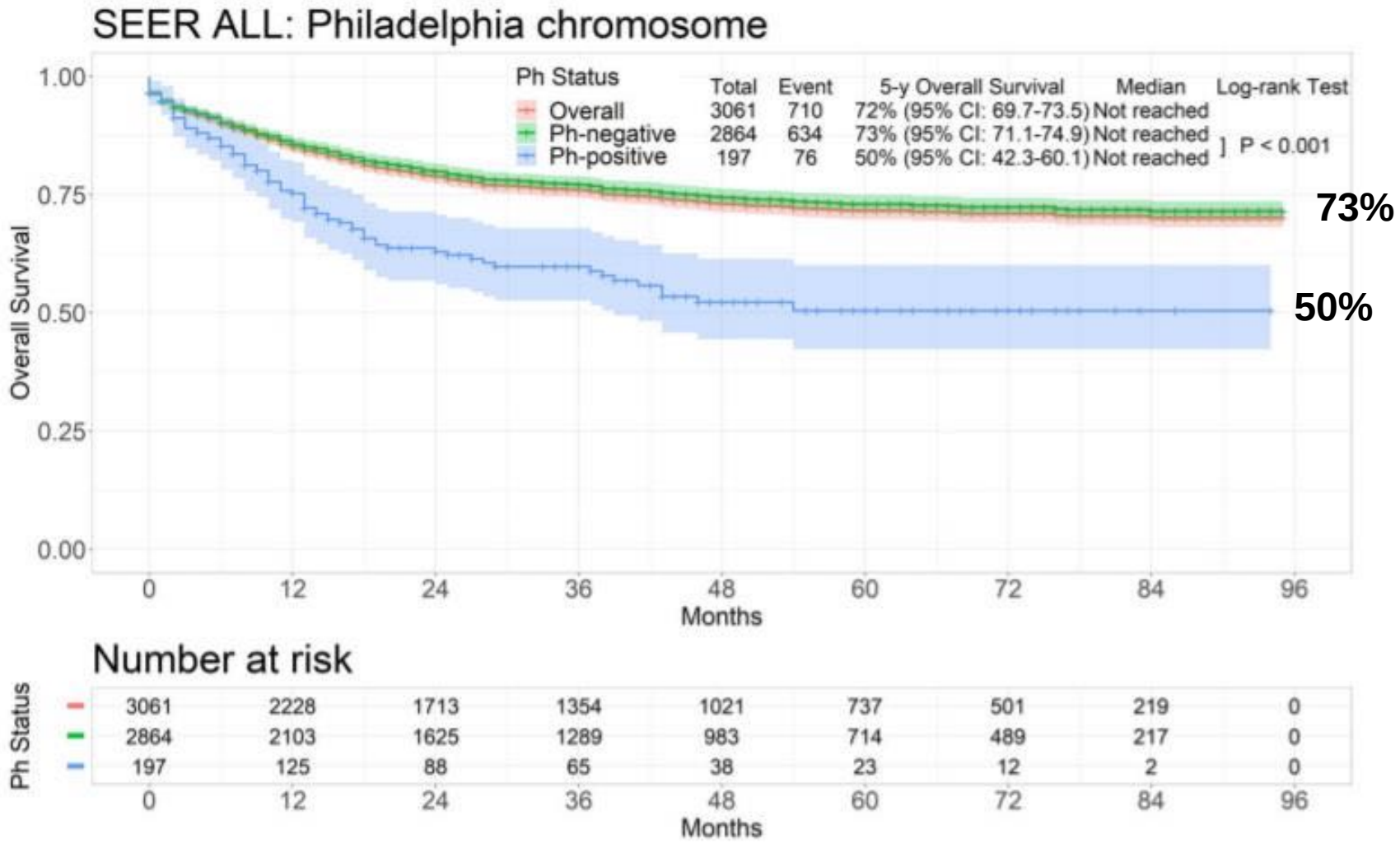
TKI	N	Median age, y (range)	Overall CMR rate, %	HSCT rate, %	RFS rate, %	OS rate, %	Reference
Intensive Chemotherapy + TKI							
Imatinib	54	51 (17-84)	45	30	43 (5-y)	43 (5-y)	15
Imatinib	169	42 (16-64)	NR	72	50 (4-y)	38 (4-y)	23
Dasatinib	97	44 (20-60)	NR	42	62 (3-y)	69 (3-y)	27
Dasatinib	72	55 (21-80)	60	17	44 (5-y)	46 (5-y)	16
Nilotinib	90	47 (17-71)	86	70	72 (2-y)	72 (2-y)	28
Ponatinib	86	46 (21-80)	86	22	68 (5-y)	74 (5-y)	17,18
Low-Intensity Chemotherapy + TKI							
Imatinib	135	49 (18-59)	28	62	37 (5-y)	46 (5-y)	26
Dasatinib	71	69 (59-83)	24	10	28 (5-y)	36 (5-y)	13
Dasatinib	60	42 (19-60)	19	42	49 (3-y)	58 (3-y)	37
Nilotinib	79	65 (55-85)	58	16	42 (4-y)	47 (4-y)	29
Nilotinib	60	47 (18-59)	NR; MMR 80	52	85 (1-y)	96 (1-y)	38
Corticosteroids + TKI							
Imatinib	30	69 (61-83)	4	NR	48 (1-y)	74 (1-y)	30
Dasatinib	53	54 (24-77)	15	34	51 (2-y)	69 (2-y)	31
Ponatinib	42	69 (27-85)	46	NR	NR	62 (2-y)	32
Blinatumomab + TKI							
Dasatinib	63	55 (24-82)	81	19	71 (36-month)	80 (36-month)	35
Ponatinib	20	62 (34-83)	85	0	93 (2-y)	93 (2-y)	36

TKI = tyrosine kinase inhibitor; CMR = complete molecular response; NR = not reported; MMR = major molecular response; HSCT = allogeneic stem cell transplant; RFS = relapse-free survival; OS = overall survival

NJ Short et al. Clin Lymph Myel Leuk in press

Outcome of ALL patients in US by Ph status

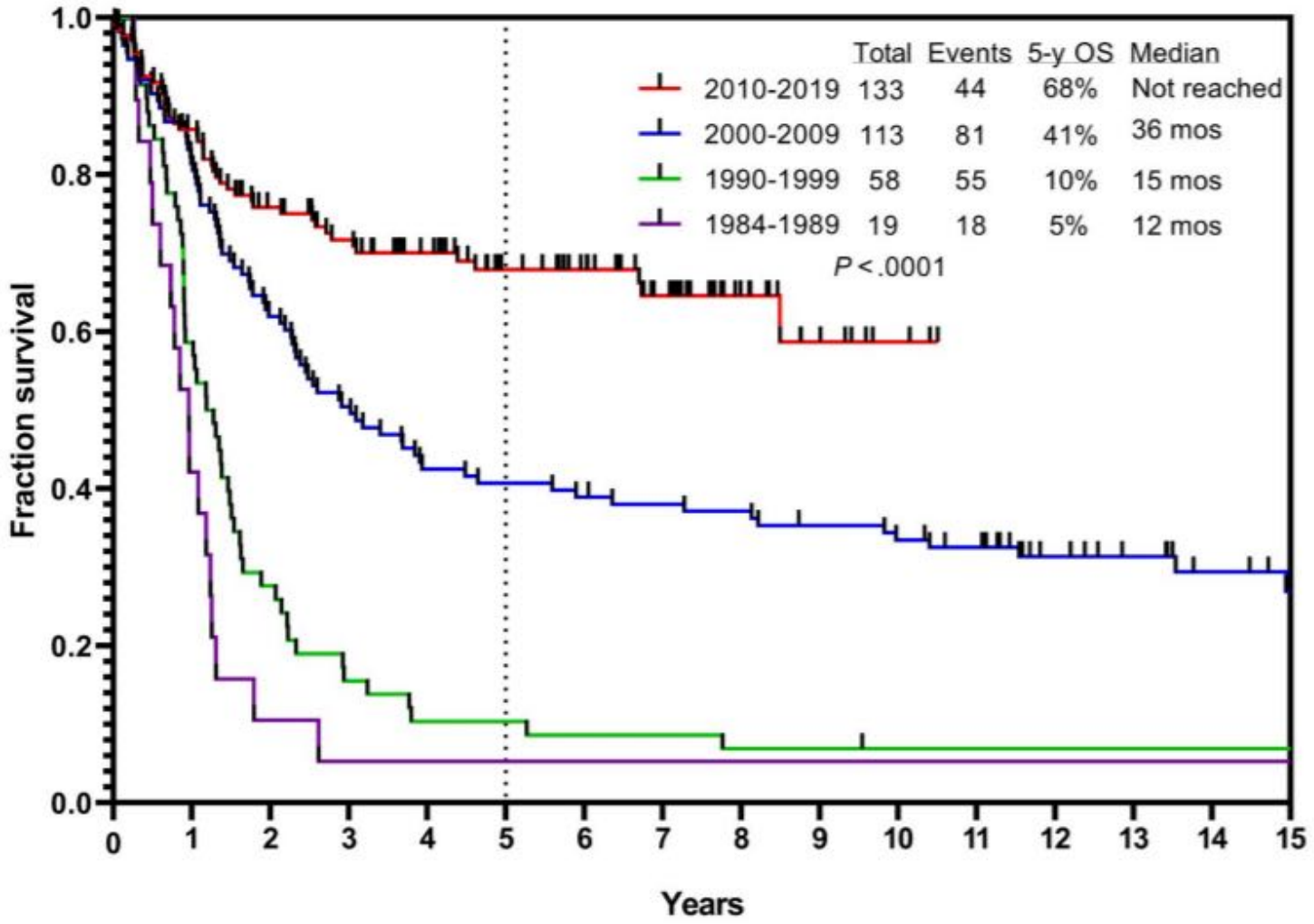
SEER 1980-2017



K Sasaki et al. , Am.J.Hematol. 2021;96:650

OS of Ph+ ALL in MD Anderson over 5 decades

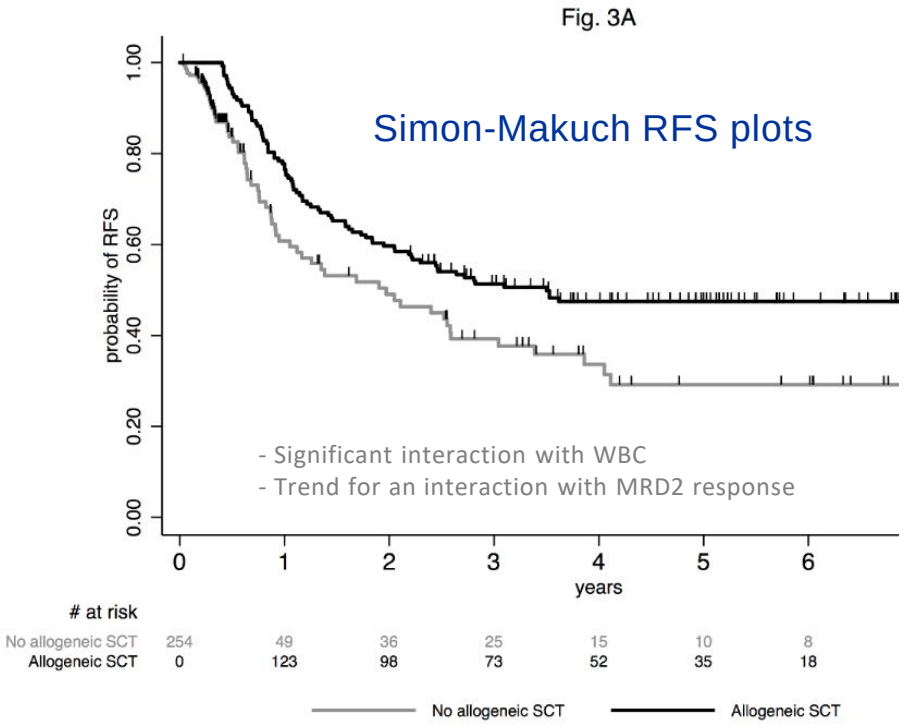
1984-2019

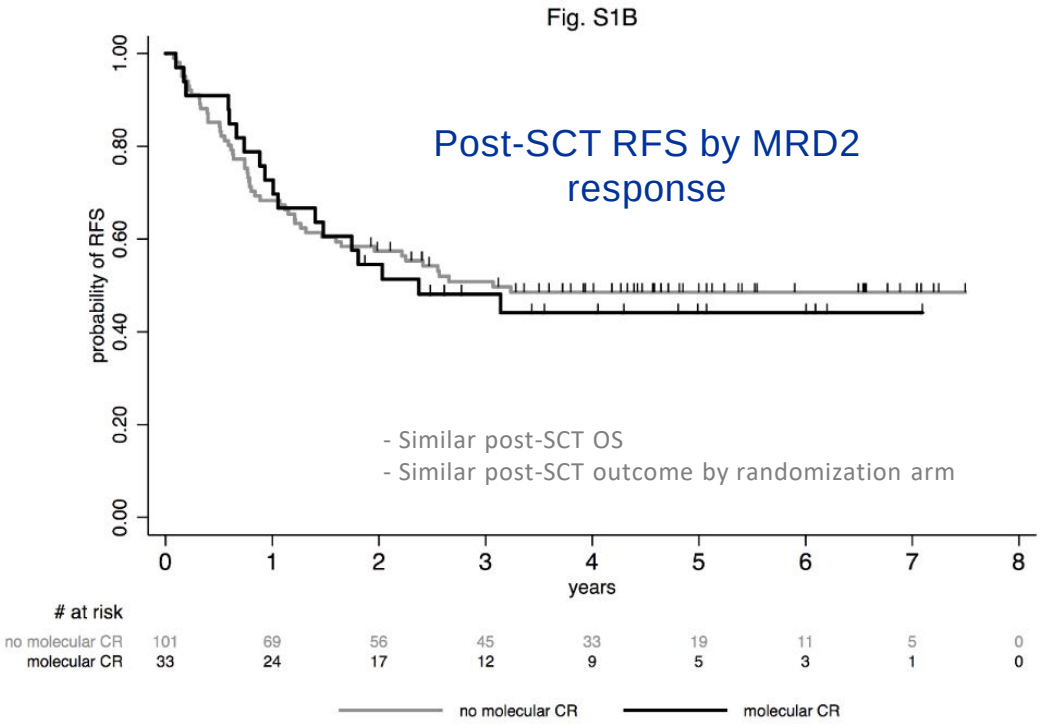


H Kantarjian et al. , Cancer 2022;128::240

Allogeneic SCT in CR1

GRAAPH-2005 results





Hazard ratio, 0.69 [95% CI, 0.49 to 0.98]; p=0.038

Hazard ratio, 1.27 [95% CI, 0.93 to 1.72]; p=0.13

Y. Chalandon et al. , Blood 2015

GRAAPH 2005:Post-alloHSCT outcome by conditioning regimen

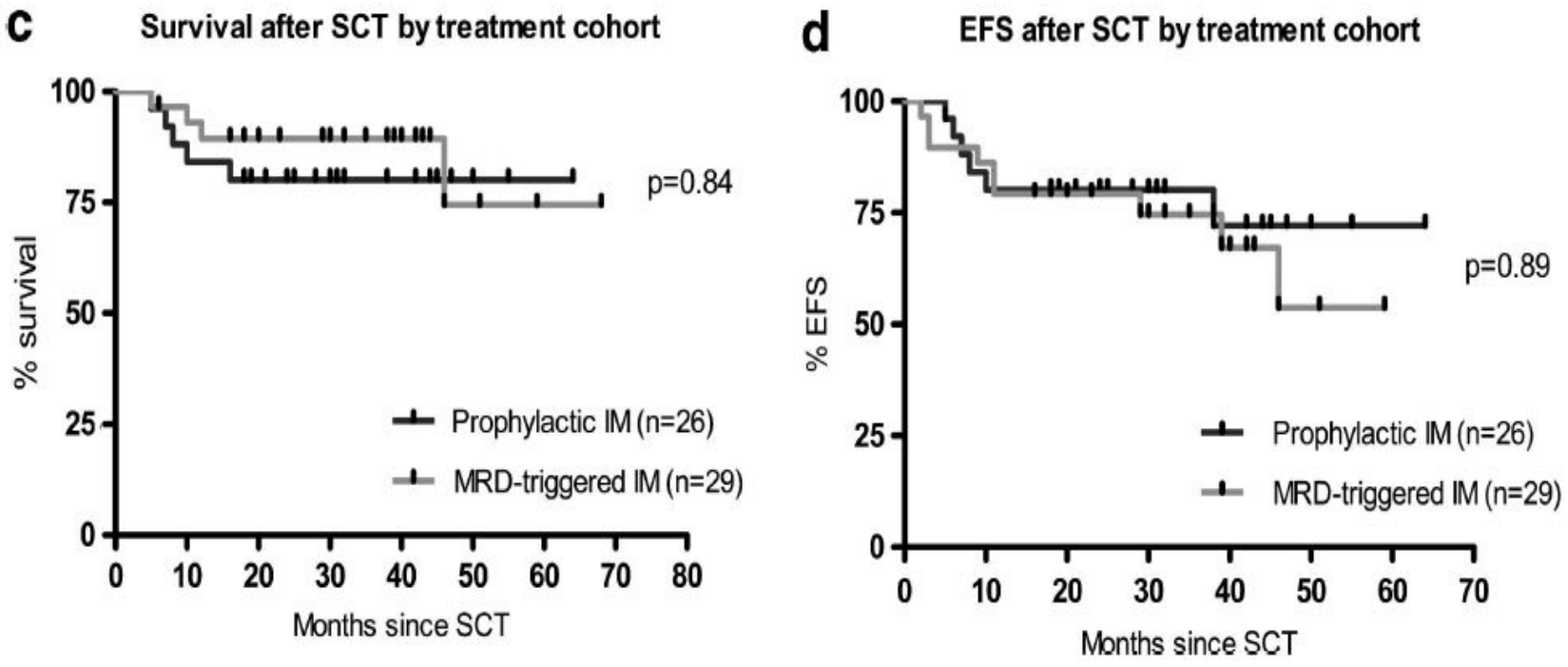
	All patients n= 161	MAC n= 124	RIC n= 37
Allogeneic SCT cohort 5-year estimates (95% CI)			
CIR	25.4% (19.3-33.0)	21.5% (15.2-30.0)	38.1% (24.6-55.7)
CI of NRM	25.8% (19.7-33.4)	24.6% (17.9-33.3)	29.9% (17.8-47.5)
RFS	48.3% (40.2-56.0)	53.5% (44.1-62.0)	31.7% (17.5-46.9)
OS	56.7% (48.4-64.2)	58.9% (49.3-67.3)	50.1% (32.8-65.1)

MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; CIR: cumulative incidence of relapse; NRM: non-relapse mortality; RFS: relapse-free survival; OS: overall survival; all outcome data were calculated from the SCT date.

Y. Chalandon et al. Blood 2015;125:3711

Post-SCT maintenance with TKI

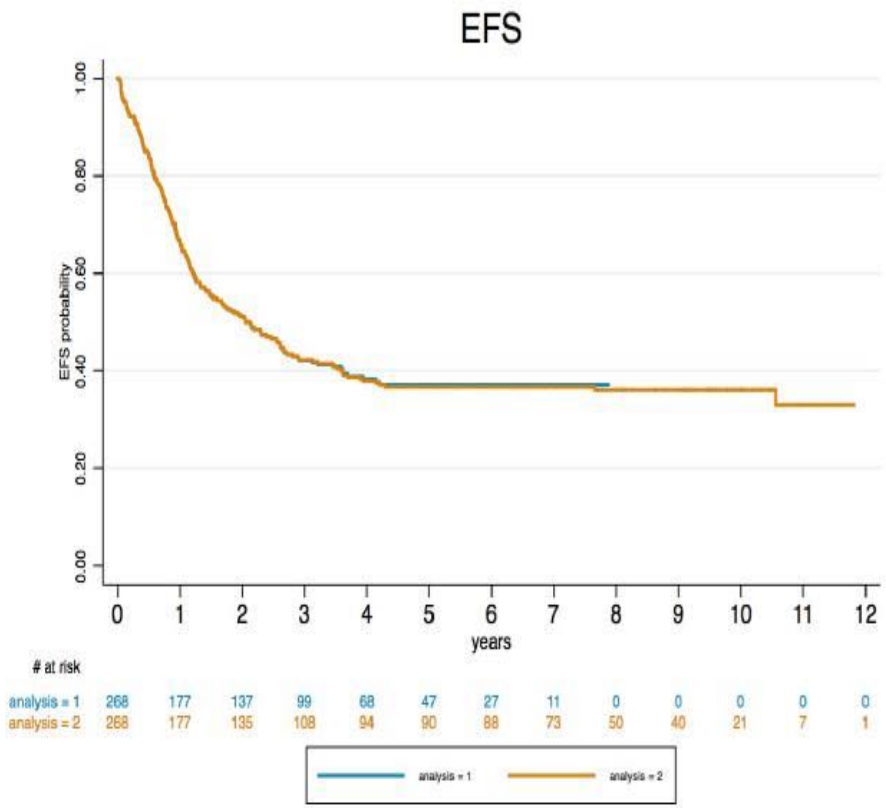
- Prophylactic *versus* MRD-driven imatinib

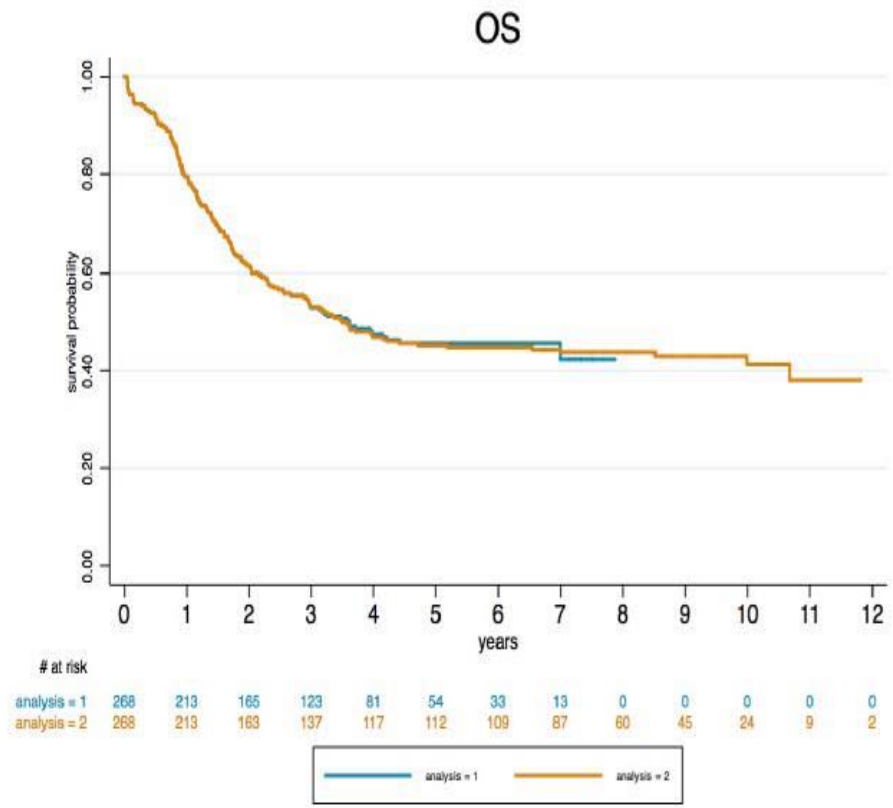


H. Pfeifer et al. Leukemia 2013;27:1254

GRAAPH-2005
2018 update with a longer follow-up

Final analysis	Long FU analysis
Median FU, 4.8y	Median FU, 7.8y
92 relapses	98 relapses
140 deaths	151 deaths





Lessons from GRAAPH 2005

- ↓ intensity of chemotherapy possible with TKI without ↑ risk of relapse
- ↓ chemotherapy intensity associated with ↓ early death→ higher CR rate. However no impact on the transplantation rate
- For patients in MMolR → similar results auto vs alloHSCT→ importance of MRD for stratification of therapy
- MAC better than RIC for alloHSCT (but few patients with RIC)

Front-line TKI in Ph+ ALL

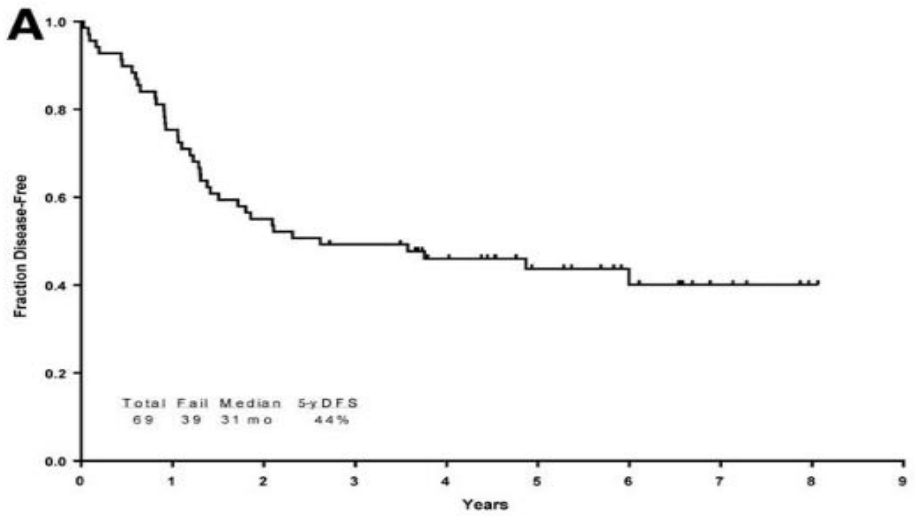
- Dasatinib front-line
  - GIMEMA
  - MDACC
  - EWALL (older patients)
- Nilotinib front-line
  - EWALL (older patients)
  - Korean group
- Ponatinib front-line
  - MDACC

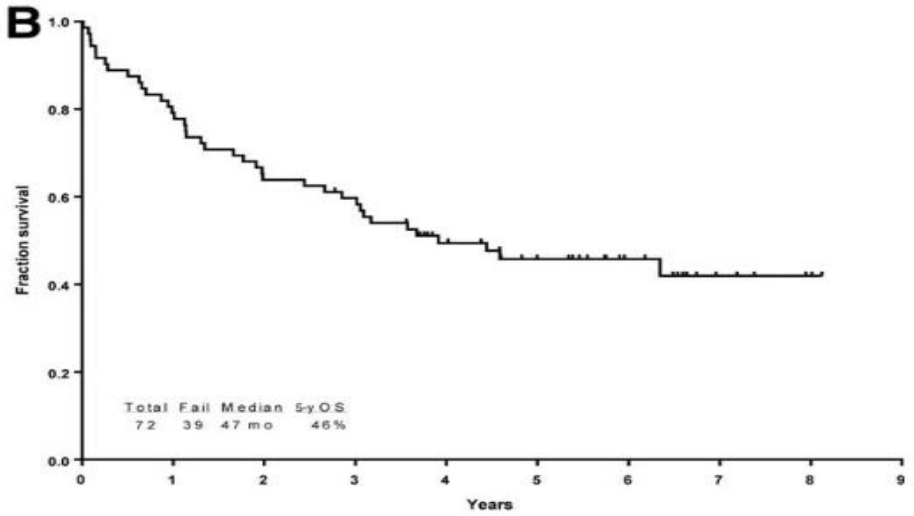
No randomized comparative study

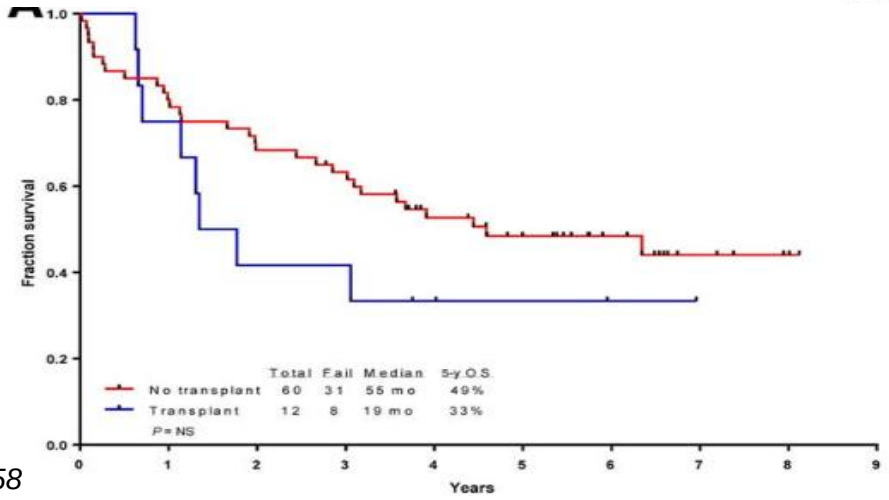
Dasatinib front-line

MDACC study (>18y)

N= 72 patients (median age, 55y); CR rate, 96%, fup: 67 mths





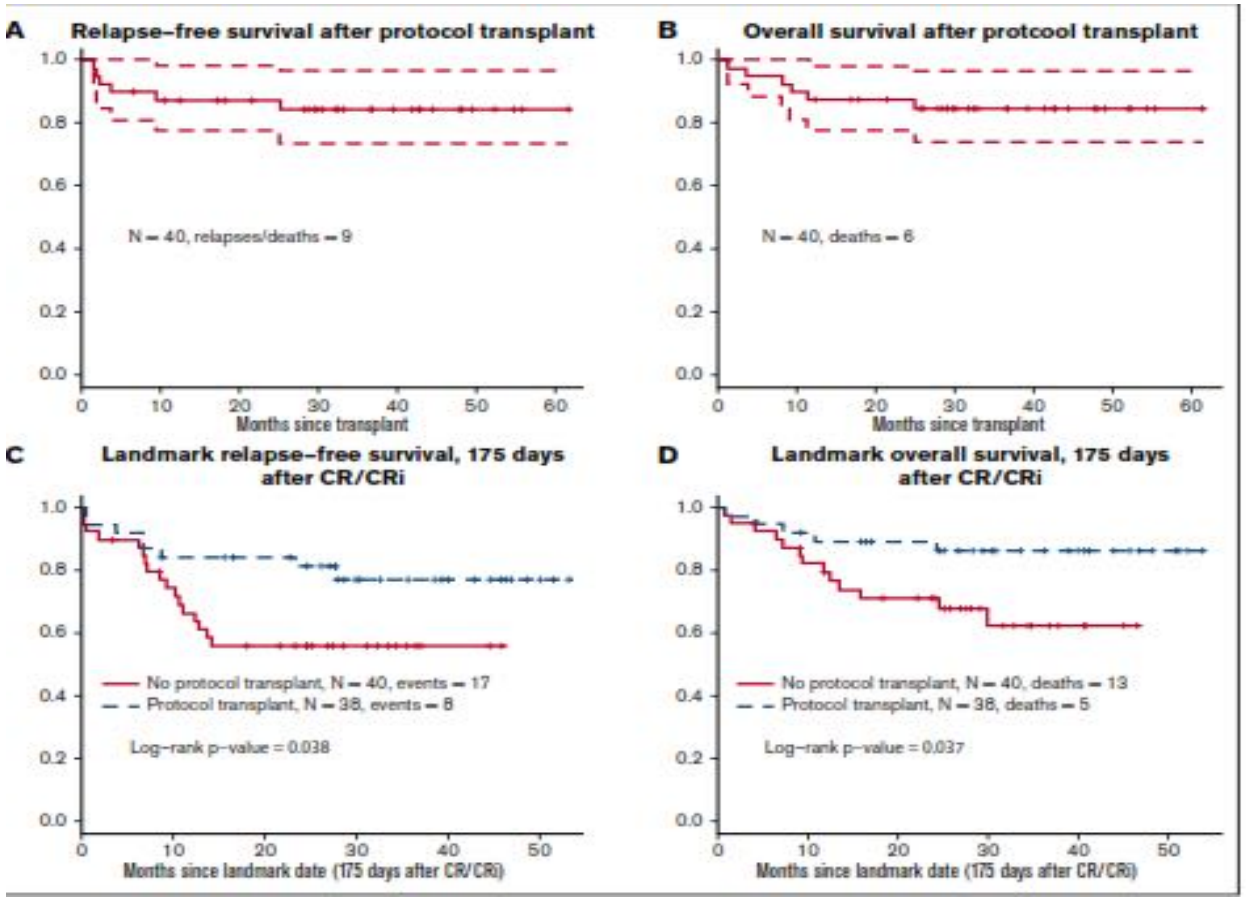


F. Ravandi et al.Cancer 2015;121:4158

US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL

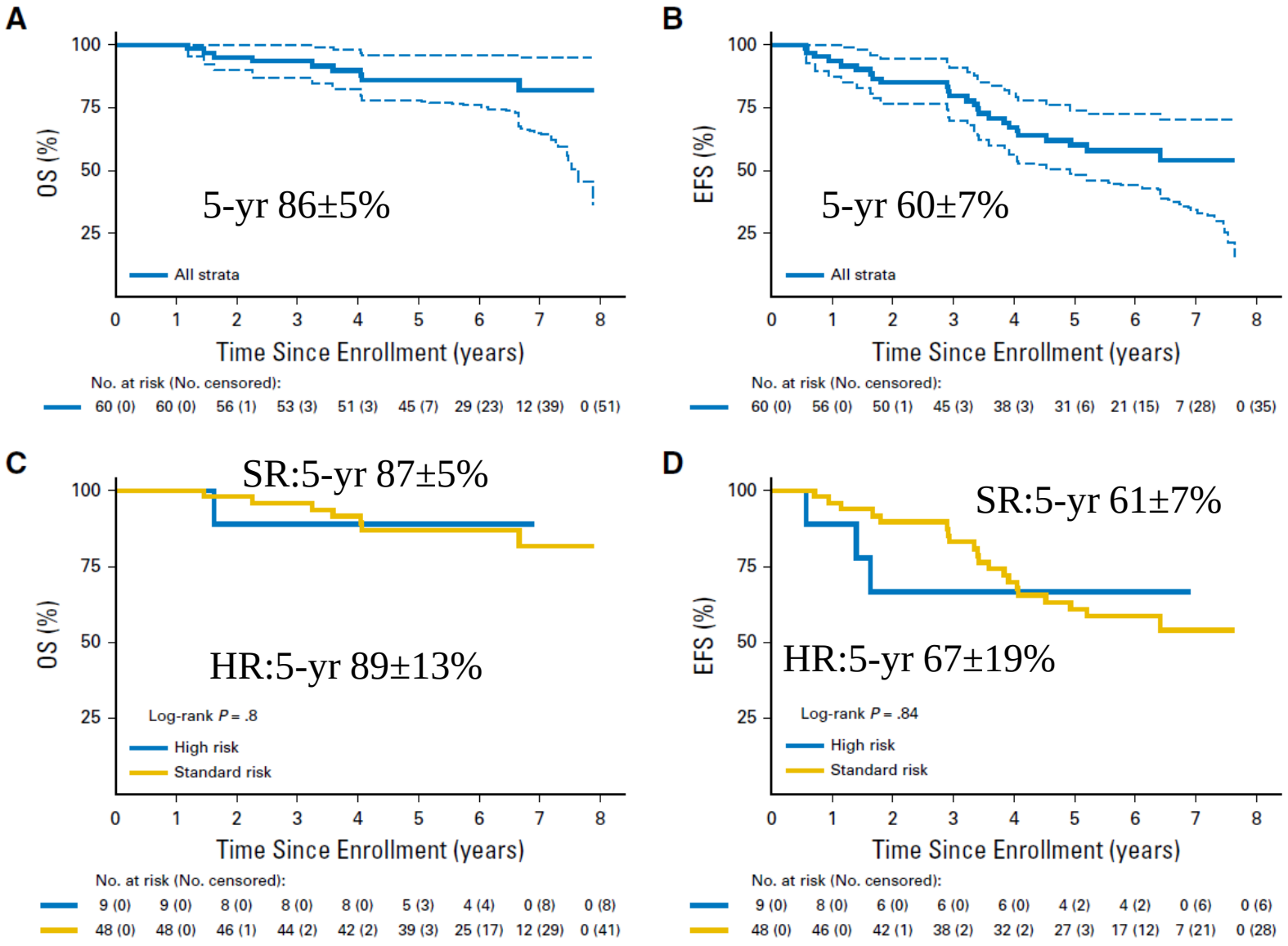
N= 94 patients (median age, 44y); CR rate, 88%, fup: 36 mths

3 yrs OS 69%, EFS 55%, RFS 62%



F. Ravandi et al.Blood Adv 2016;1:250

Dasatinib combined with chemotherapy in children



WB. Slayton et al.JCO 2018;36:2306

Dasatinib combined with chemotherapy children and young adults no difference if alloHSCT or not

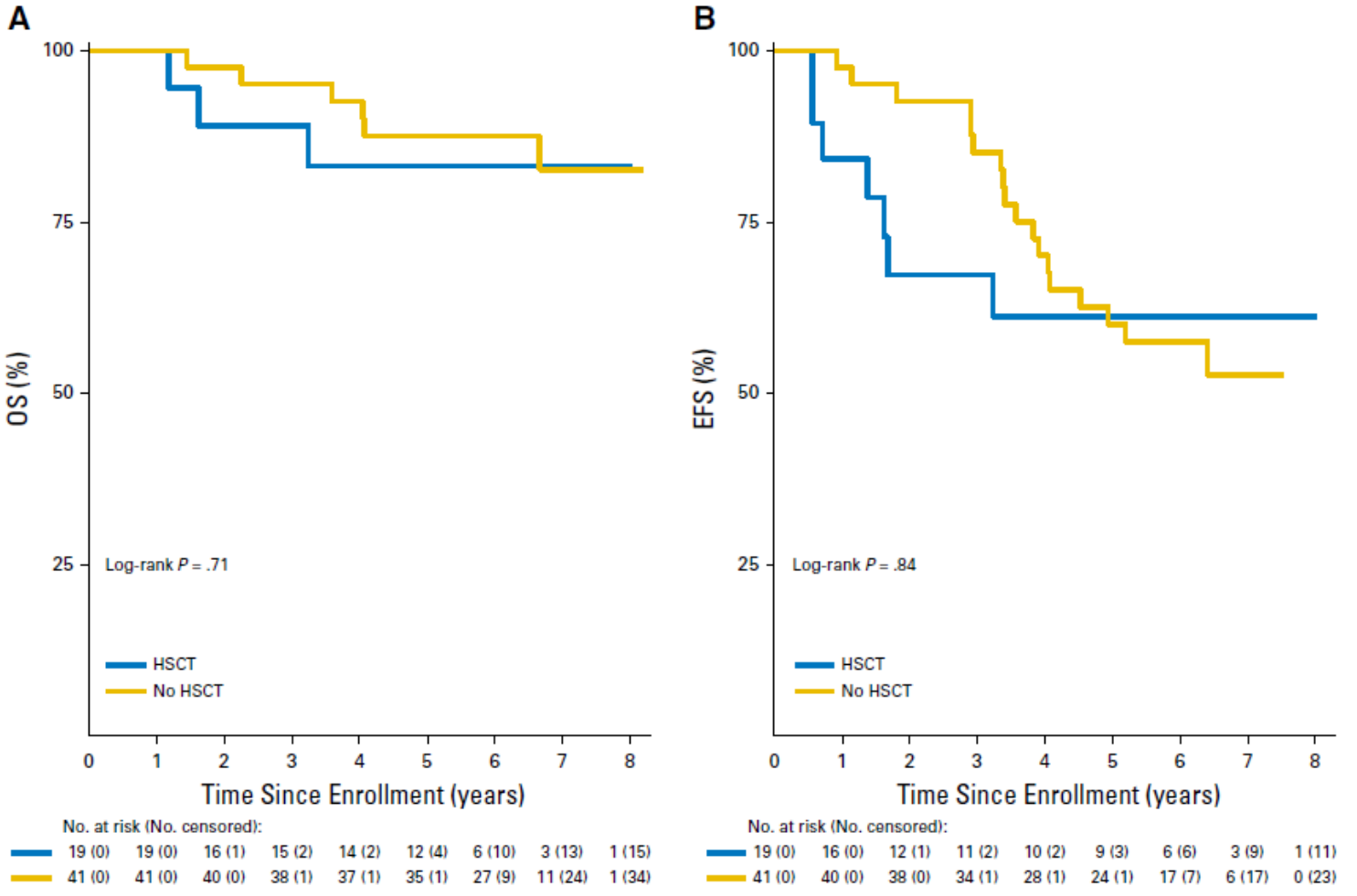
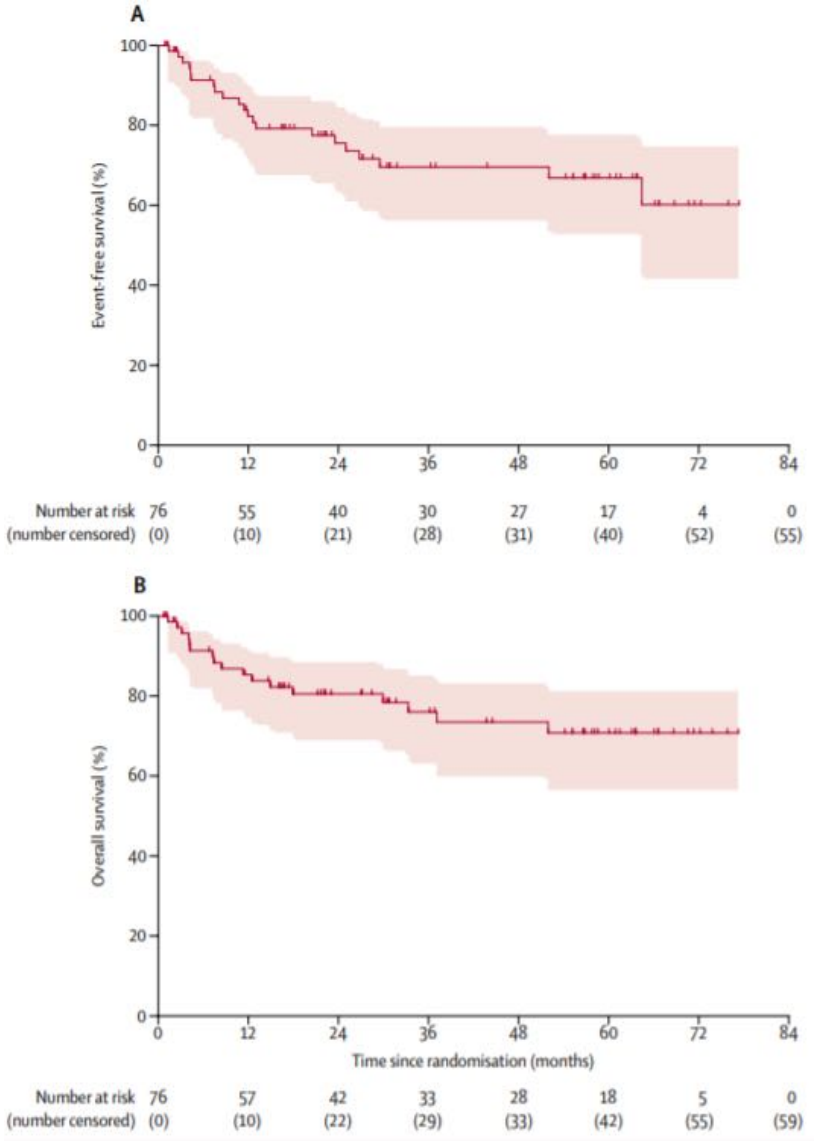
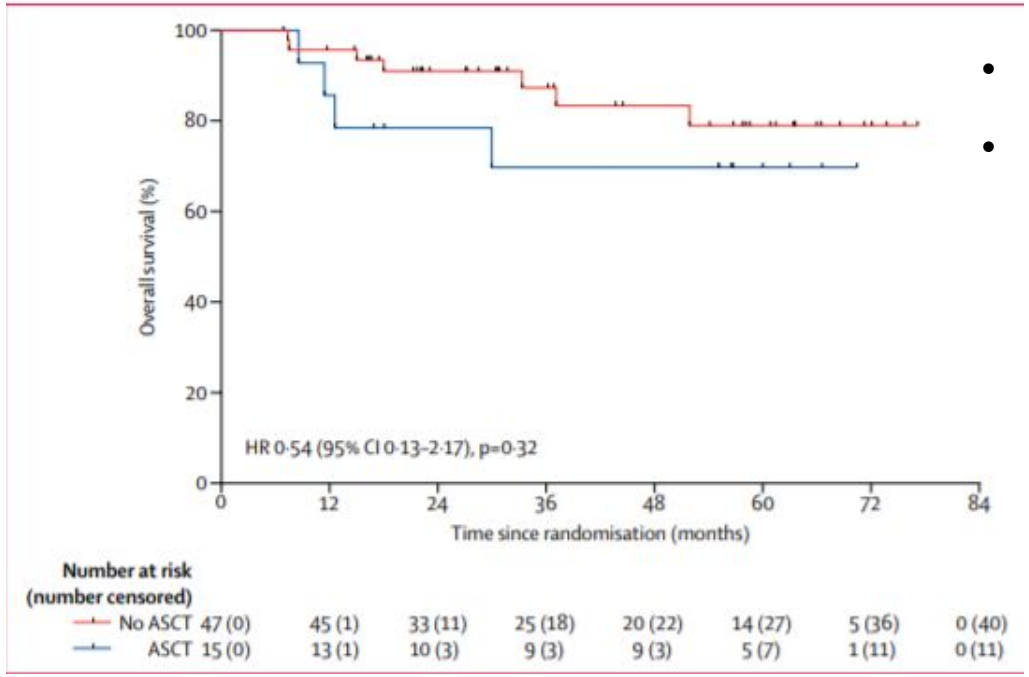


Fig 2. Outcomes comparing patients who underwent and did not undergo bone marrow transplantation: (A) Overall survival (OS) and (B) event-free survival (EFS).

WB. Slayton et al.JCO 2018;36:2306

Ponatinib front-line combined with hyperCVAD

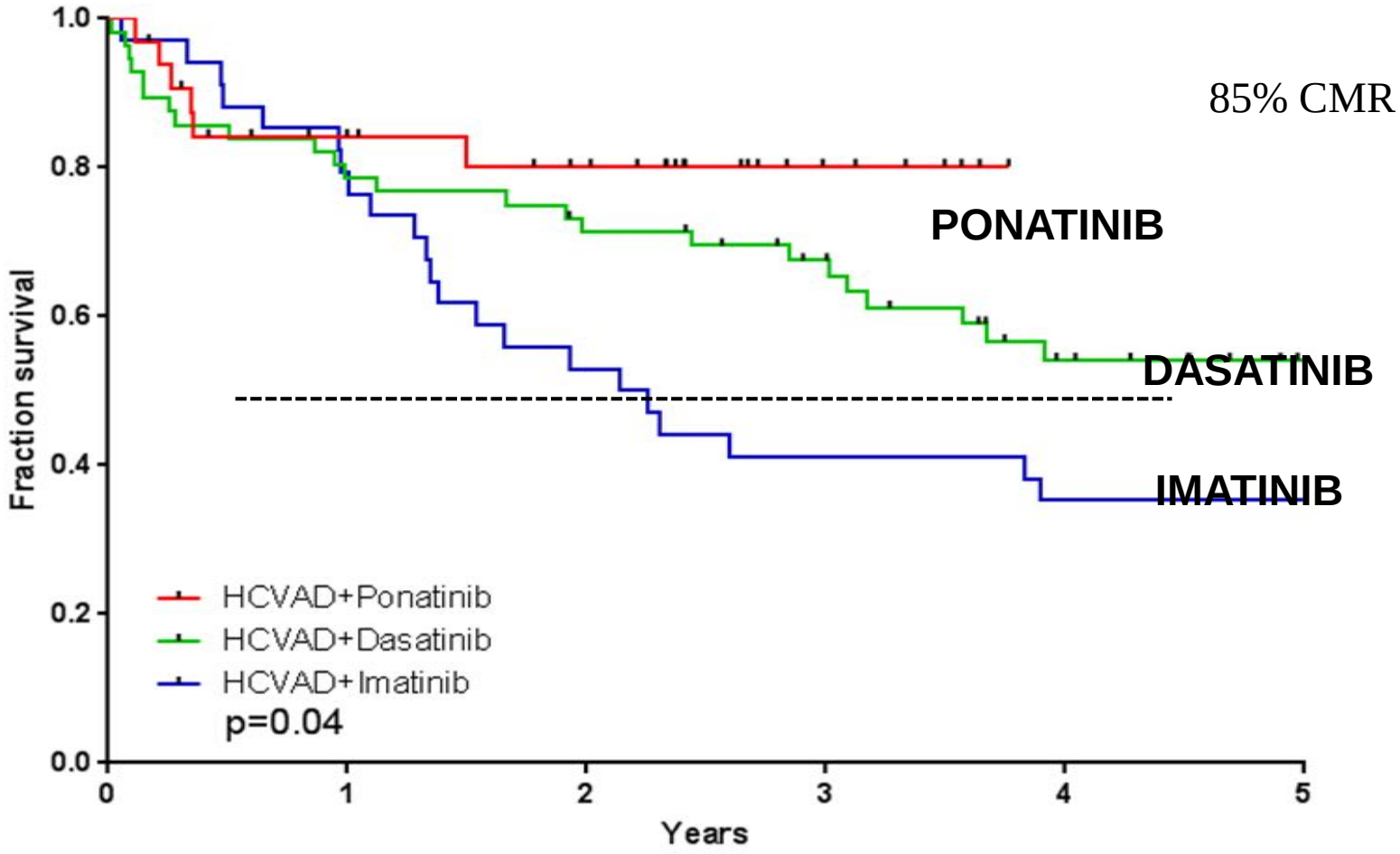




- **MDACC study with ponatinib**
  N= 76 patients (median age, 47y)
  CR rate, 100%, fup 36 mths, CMR 83%.
- 3 yrs EFS 70% and OS 76%
- 15 alloHSCT vs 47 non HSCT no diff of OS when censored at transplant

E. Jabbour et al. Lancet Hemato 2018;5:e618

Summary from the MDACC : HCVAD + ….



85% CMR with ponatinib

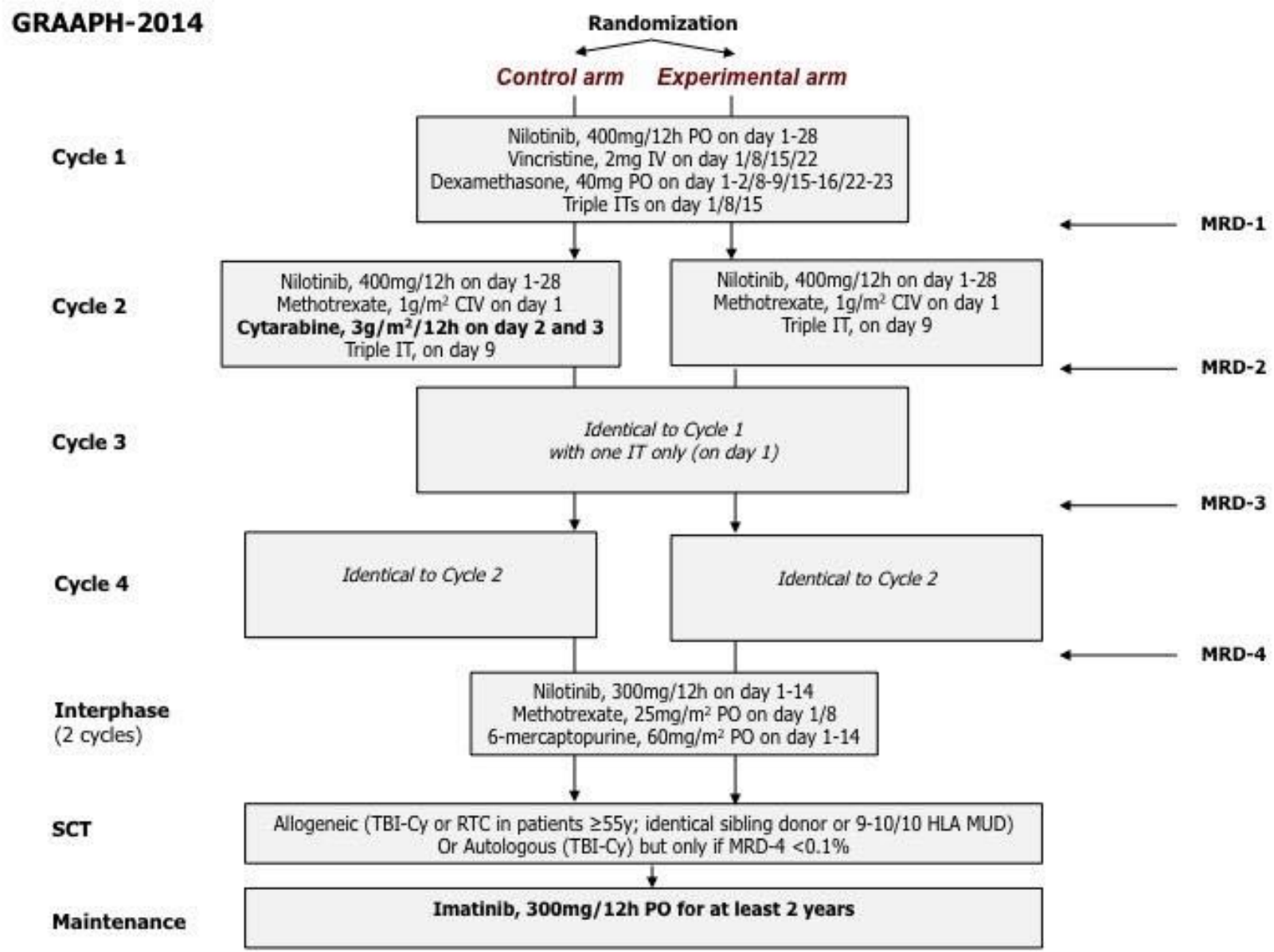
Courtesy from E Jabbour

Attempt to decrease the intensity of chemotherapy in combination with TKI

- Can we decrease chemotherapy intensity in patients aged <60y with Ph+ ALL ?
- GRAAPH 2005 :
  - To compare two different treatment strategies in younger patients (18-60y) with *de novo* Ph+ ALL
  - A less-CTx IM-based treatment arm to the more intensive IM-HyperCVAD standard arm
  - Induction : randomization Imatinib + VCR, DEX versus Imatinib + HyperCVAD
  - Consolidation idem
  - Intensification idem

GRAAPH-2014

Ph+ ALL front-line 18 – 60y



Interim analysis
Aim
80%: BCR-ABL1 < 0.1%

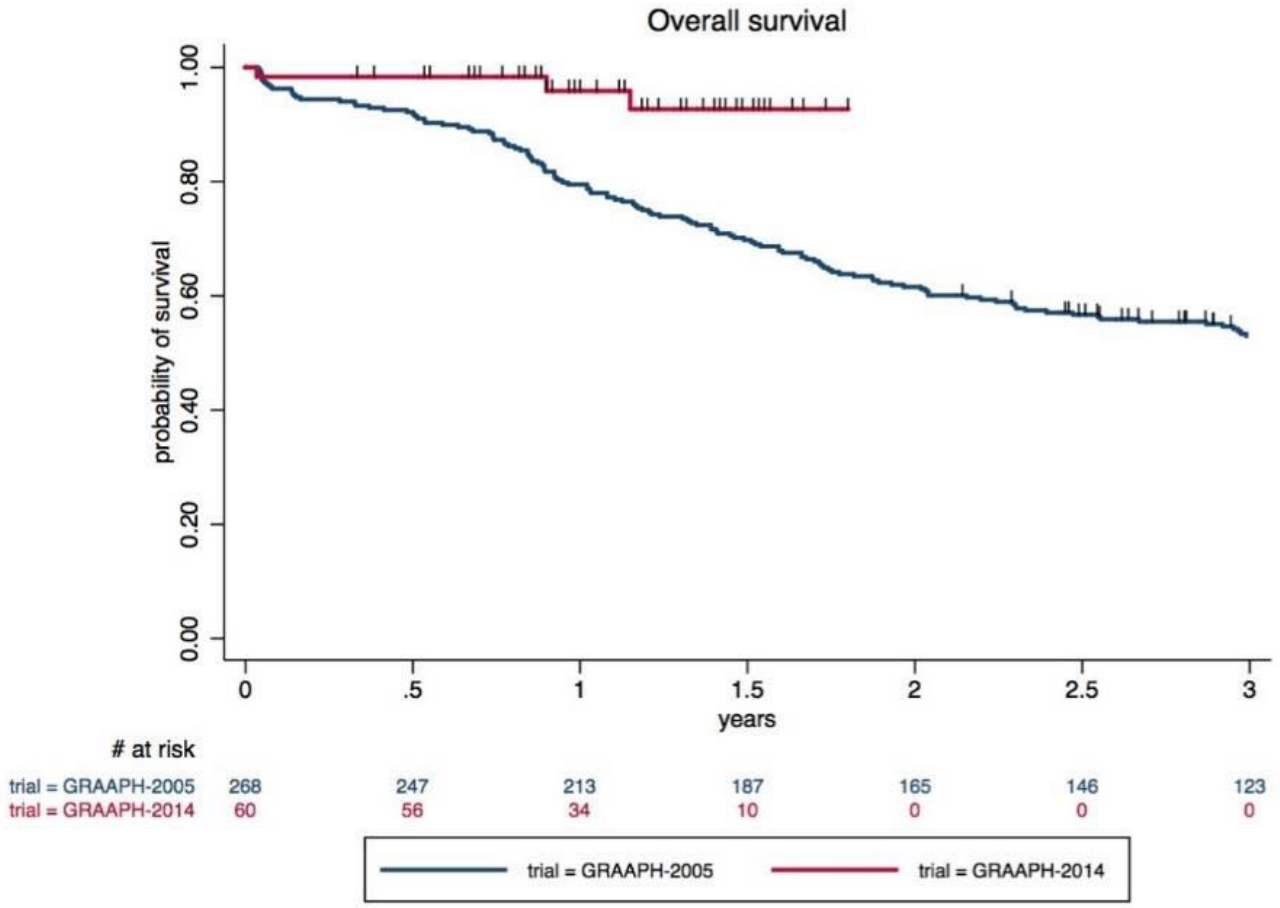
Final analysis
BCR-ABL1 < 0.1%
Equivalent

GRAALL

Y. Chalandon et al. EHA 2018 poster

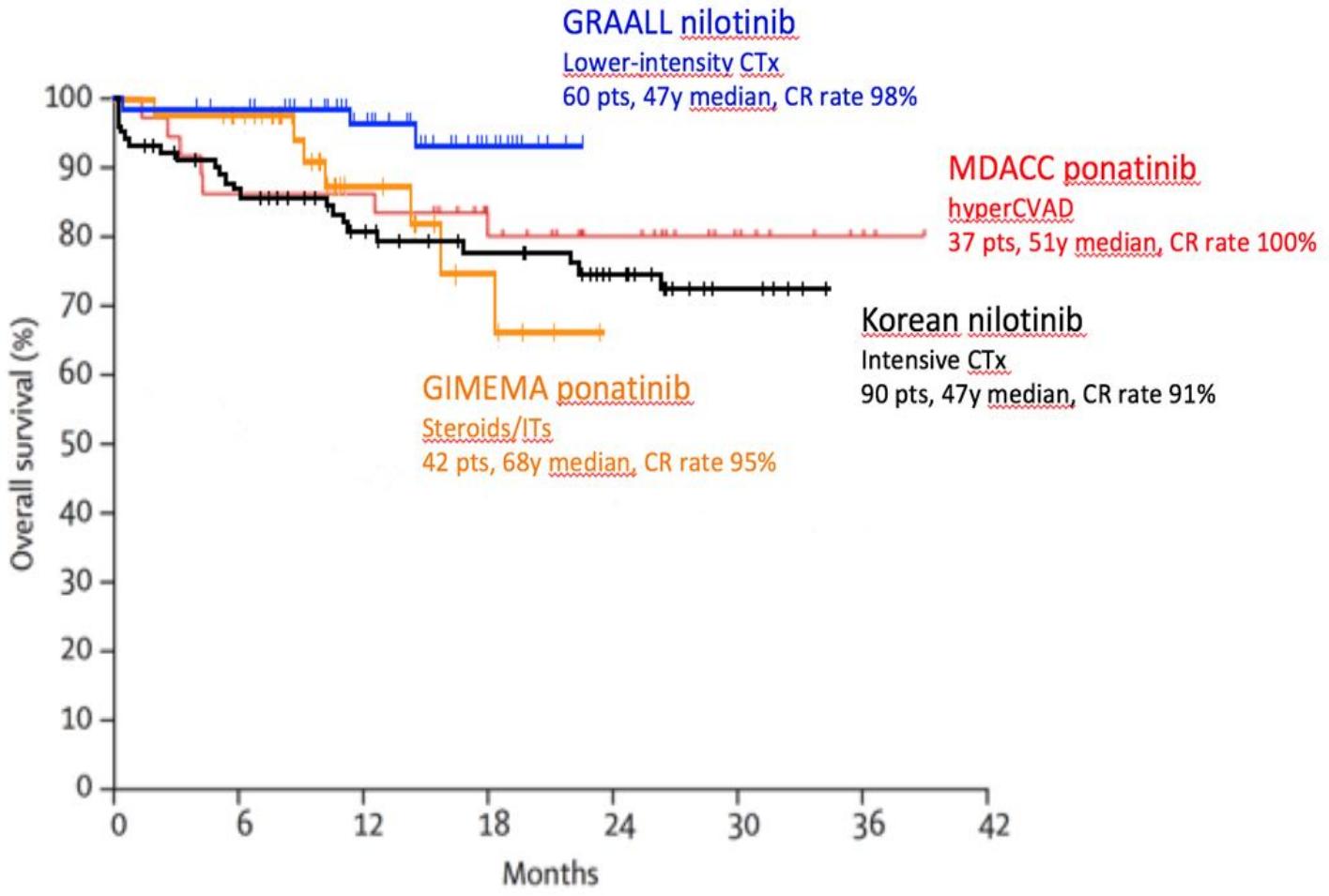
GRAAPH-2014 interim analysis (60 patients)

- Four switches (3 dasatinib, 1 imatinib)
- Transplants, 31 allogeneic and 13 autologous HSCT
- MMolR 80% (BCR-ABL<0.1%)
- Seven relapses
  1-year PFS, 84.5%
- Three deaths
  1-year OS, 96%



Y. Chalandon et al. EHA 2018 poster

Ph+ ALL studies with nilotinib / ponatinib



DY. Kim et al. Blood 2015
E. Jabbour et al. Lancet Oncol 2015
G. Martinelli et al. ASH 2017
Y. Chalandon et al. EHA 2018

Ponatinib vs earlier TKI with chemo front-line Ph+ ALL : a meta-analysis

Efficacy of Ponatinib Versus Earlier Generation Tyrosine Kinase Inhibitors for Front-line Treatment of Newly Diagnosed Philadelphia-positive Acute Lymphoblastic Leukemia

Elias Jabbour,[1] Maral DerSarkissian,[2] Mei Sheng Duh,[2] Nora McCormick,[2] Wendy Y. Cheng,[2] Lisa J. McGarry,[3] Ariadne Souroutzidis,[2] Hui Huang,[3] Susan O'Brien,[4] Farhad Ravandi,[1] Hagop M. Kantarjian[1]

Clinical Lymphoma, Myeloma & Leukemia, Vol. 18, No. 4, 257-65

Ponatinib vs earlier TKI with chemo front-line Ph+ ALL : a meta-analysis

Table 2 Meta-analysis Results

Outcomes	All (n = 26 Studies)	Ponatinib (n = 1 Study)	First- and Second-Generation TKIs (n = 25 Studies)
Response			
CMR	34 (26-43)	79 (66-89)[a]	32 (25-40)
Survival			
2-y OS	59 (53-65)	83 (70-92)[a]	58 (53-63)
3-y OS	52 (43-60)	79 (66-89)[a]	50 (42-58)

Data presented as % (95% confidence interval).
Abbreviations: CMR = complete molecular response; OS = overall survival; TKI = tyrosine kinase inhibitor.
[a]For subgroups with only 1 observation, 95% CIs were calculated assuming a binomial distribution.

Table 3 Meta-Regression Results

Meta-Regression Results	OR	95% CI	*P* Value
CMR (n = 25 arms)			
Ponatinib versus first- and second-generation TKIs	6.09	1.16-31.90	.034
Median age	1.02	0.98-1.06	.356
Proportion of male patients	0.99	0.93-1.05	.720
2-y OS (n = 27 arms)			
Ponatinib versus first- and second-generation TKIs	3.70	0.93-14.73	.062
Median age	0.98	0.95-1.01	.167
Proportion of male patients	0.99	0.95-1.04	.637
3-y OS (n = 19 arms)			
Ponatinib versus first- and second-generation TKIs	4.49	1.00-20.13	.050
Median age	0.97	0.92-1.01	.144
Proportion of male patients	0.99	0.94-1.05	.712

Abbreviations: CI = confidence interval; CMR = complete molecular response; OS = overall

The GIMEMA Strategy: A TKI without systemic chemotherapy during Induction

Study protocol	Age (years)	Induction therapy	CHR rate
LAL 0201-B[1]	60–89	IMA + PDN	100%
LAL 1205[2]	18–84	DAS + PDN	100%
LAL 0904 3rd amendment[3]	16–60	IMA + HAM (± transplant)	96%
LAL 1408[4]	>60	NIL + IMA + PDN*	94%
LAL 1509[5]	18–60	Total therapy strategy (DAS)	97%
LAL 1811[6]	>60	PON + PDN	95%

High CR rates (94-100%)

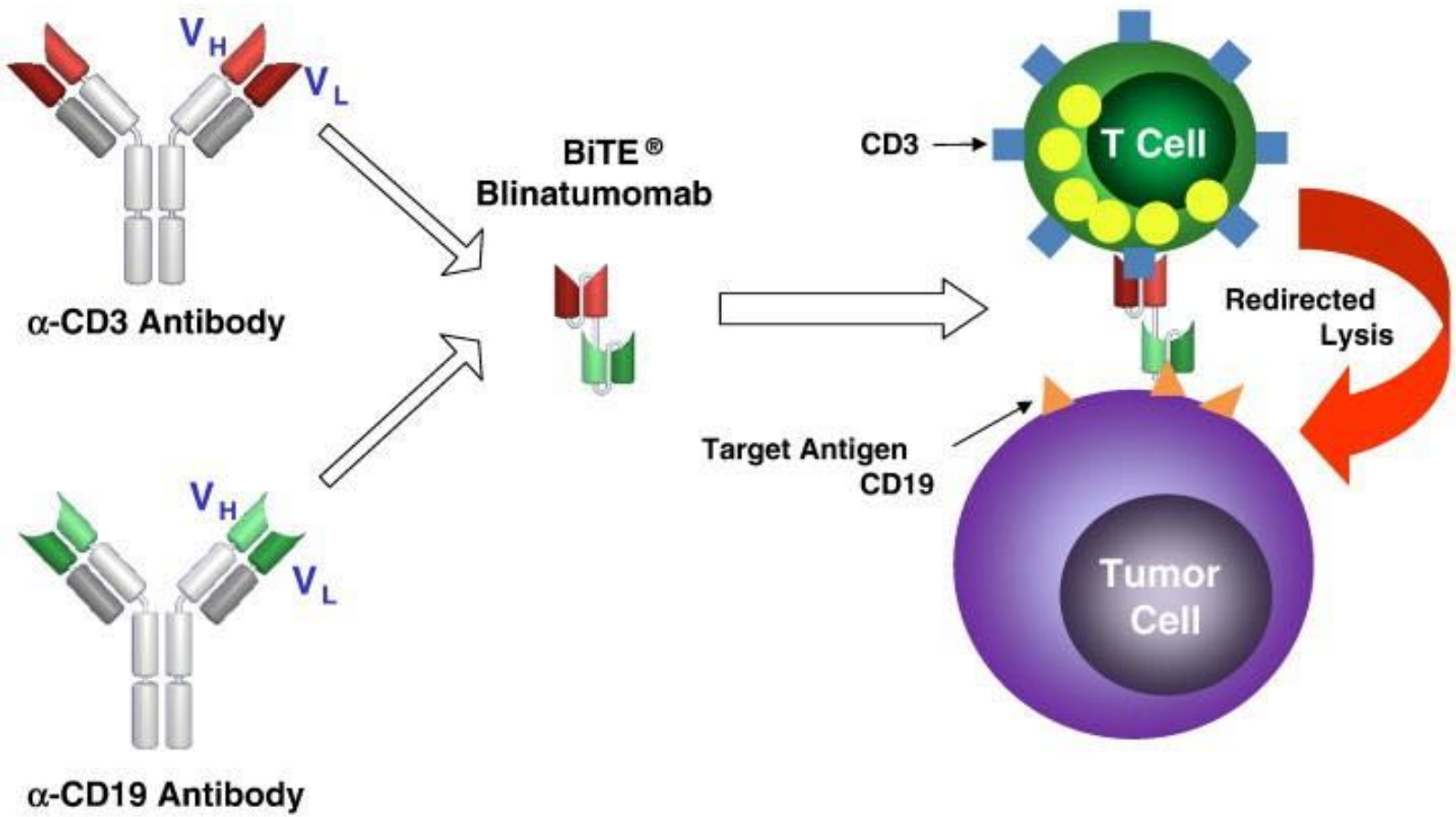
* Alternating 6 week schedules of nilotinib/imatinib

CHR, complete hematologic remission; DAS, dasatinib; HAM, high-dose cytarabine and mitoxantrone; IMA, imatinib; NIL, nilotinib; PDN, prednisone; PON, ponatinib

1. Vignetti M, et al. Blood 2007;109:3676–8; 2. Foà R, et al. Blood 2011;6521–8
3. Chiaretti S, et al. Haematologica 2016, 101:1544-1552
4. Martinelli G, et al. AACR 2014, Abstract 5552 and poster presentation
5. Chiaretti S, et al. ASH 2014, Abstract 797; ASH 2015 Absract 81;
6. Martinelli G. et al ASH 2017

S. Chiaretti et al. EHA 2019

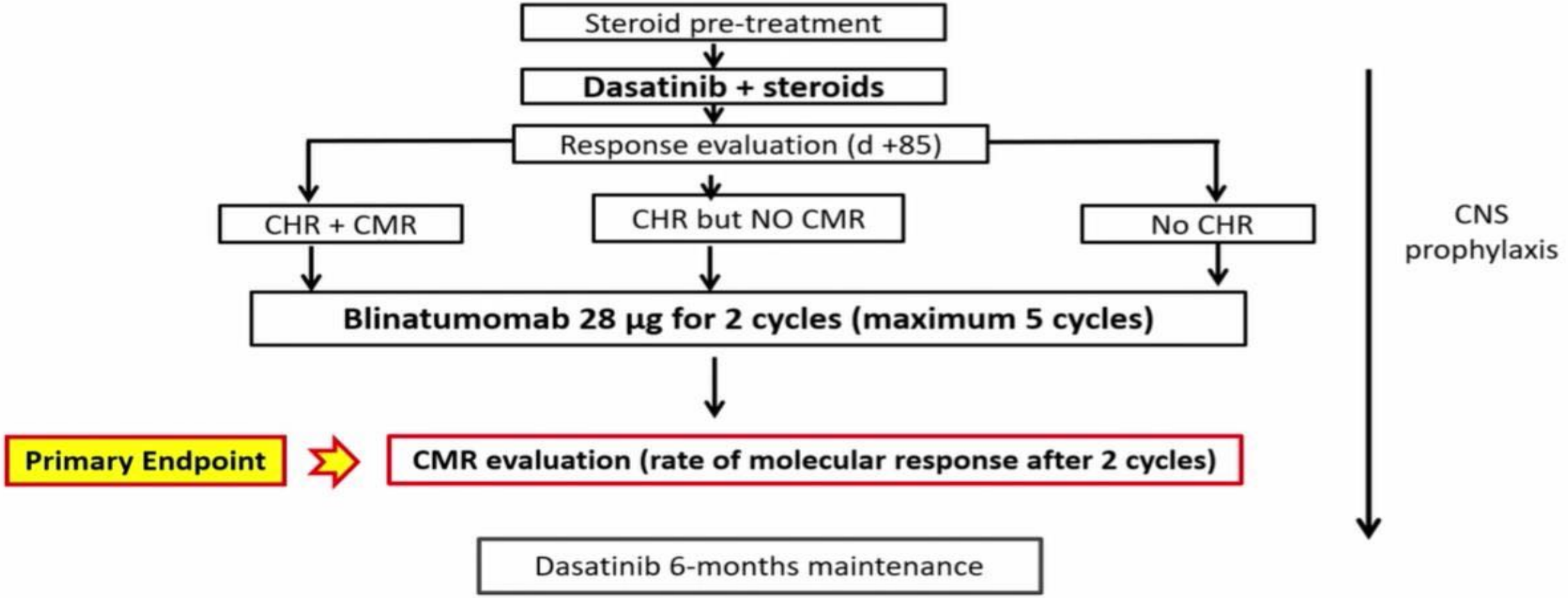
Blinatumomab (antiCD19/CD3)



Dasatinib + Blinatumomab for 1st -line treatment of Ph+ ALL: The GIMEMA LAL2116 D-ALBA trial

D-ALBA: treatment scheme

Designed for newly diagnosed Ph+ ALL, no upper age limit; sample size: 63

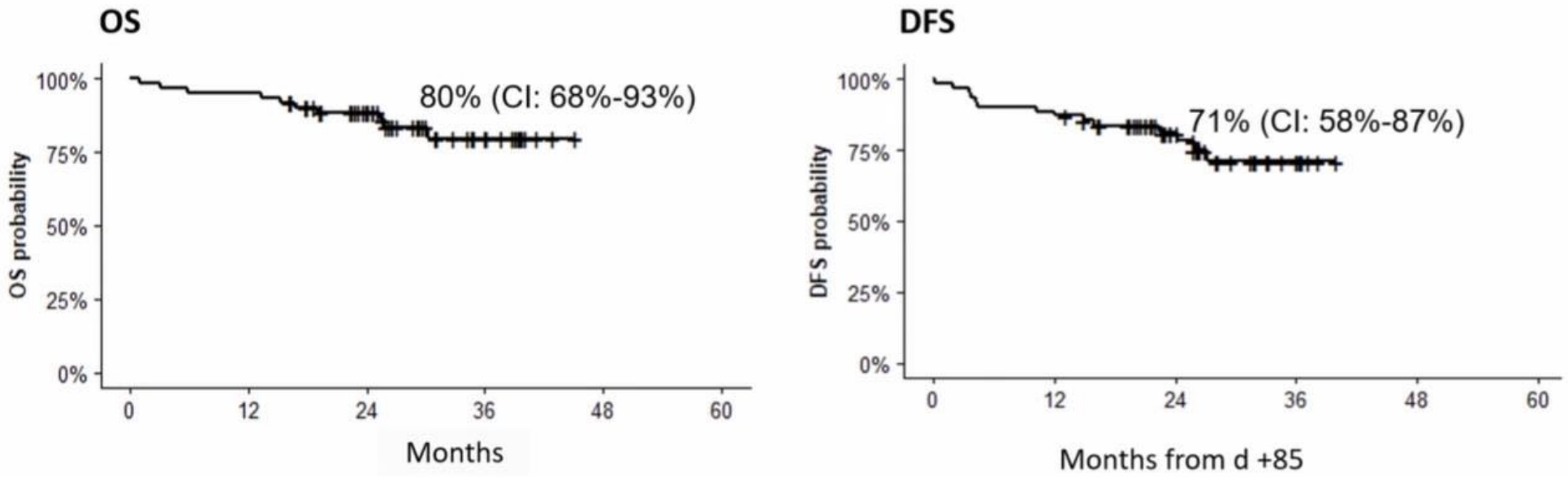


Foà et al, NEJM 2020; 383(17):1613-1623

TKI-Blinatumomab

The GIMEMA approach: D-ALBA update results at 3 years

Updated D-ALBA: estimated 36 ms OS and DFS



Median follow-up: 28.81 ms (0.9-45.16)

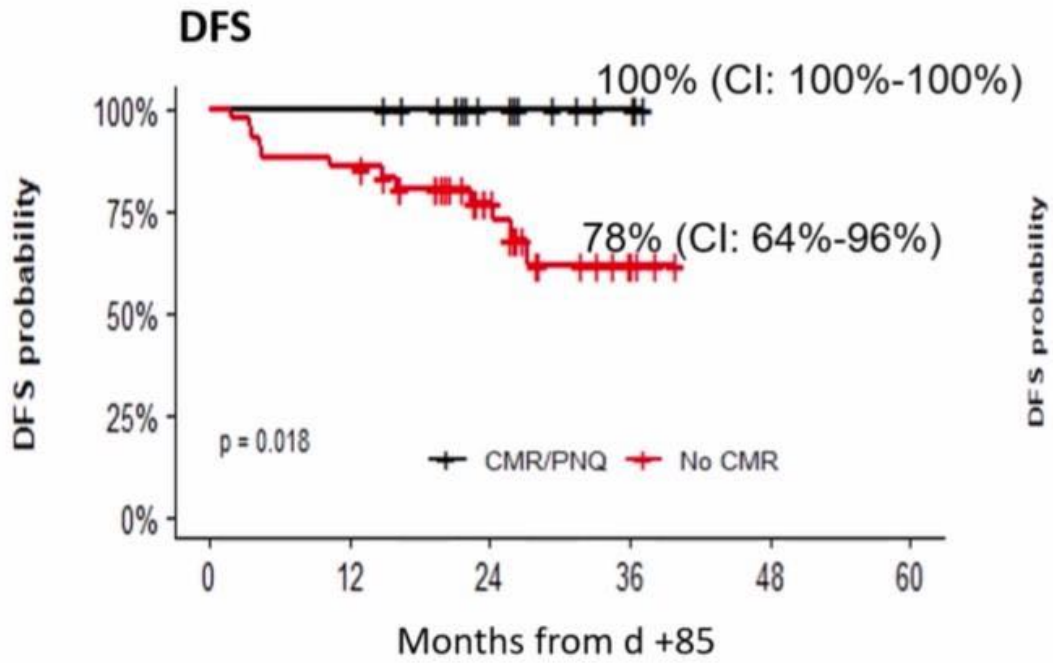
S Chiaretti et al. EHA 2021

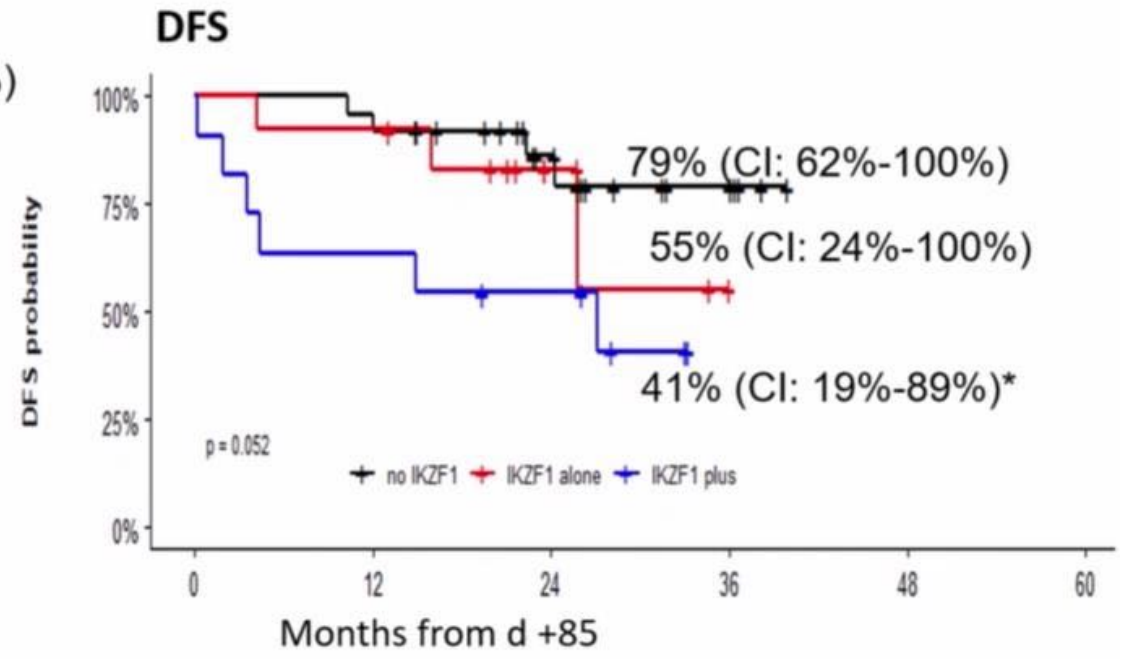
- 29 patients: alloSCT. NRM 14%, no difference between allo and non alloSCT but allo had more MRD+
- Caveat: increased rate of CNS relapse

TKI-Blinatumomab

The GIMEMA approach: D-ALBA impact of Mol response on DFS

Updated D-ALBA: estimated 36 ms DFS according to molecular responses and CNAs



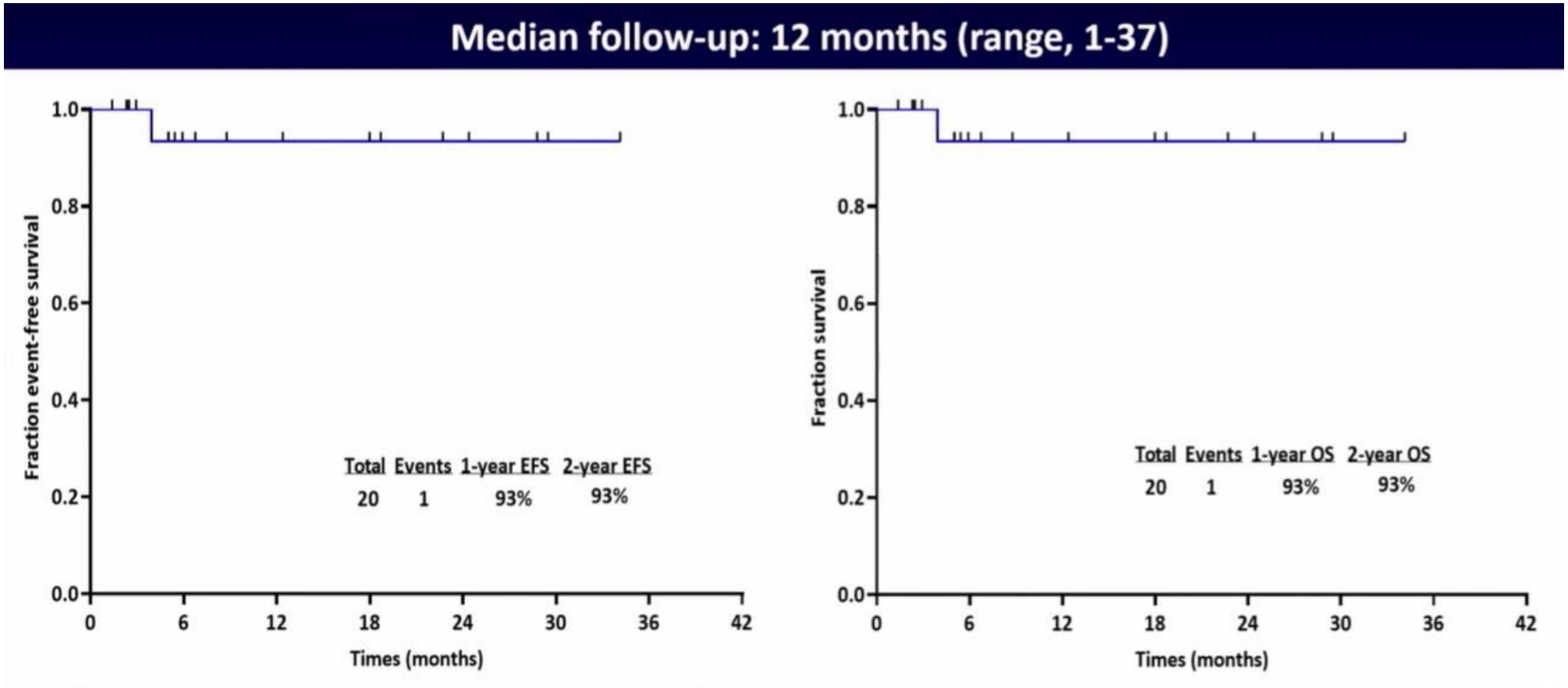


*30 months

S Chiaretti et al. EHA 2021

Blinatumomab + Ponatinib

MD Anderson phase II interim analysis N=20 patients

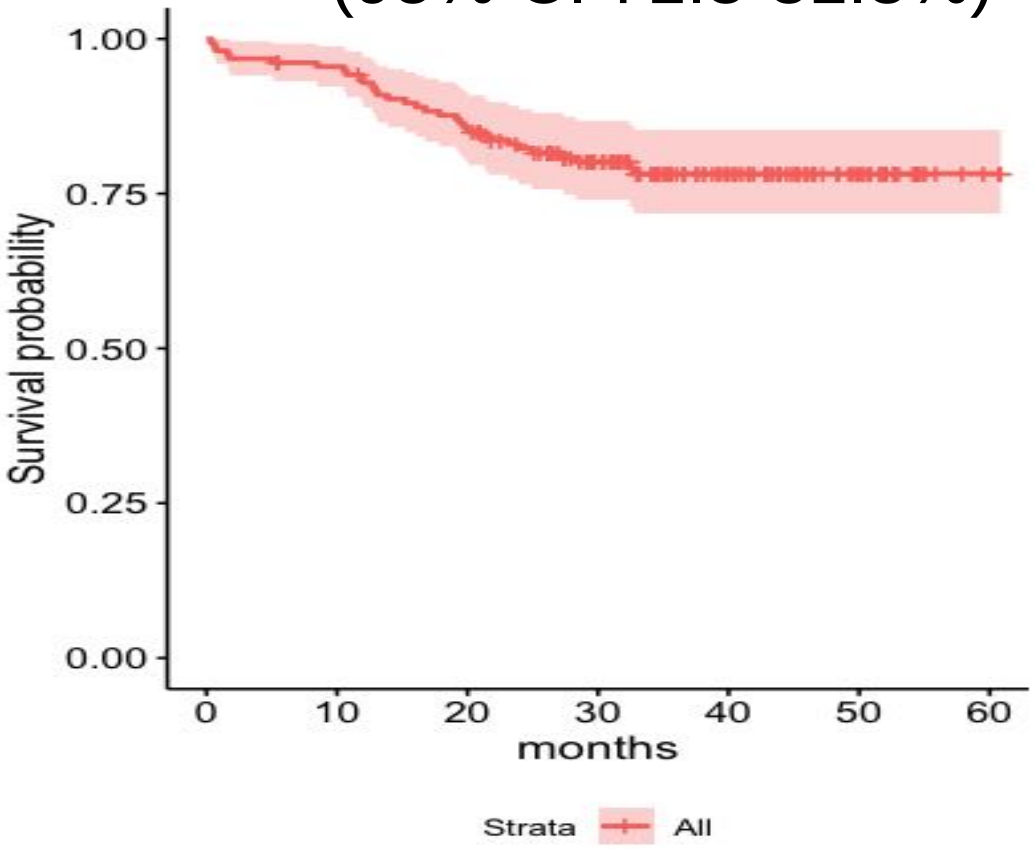


- Primary endpoint: CMR:85%
- CR: 100%
- 1 death, 19 without alloHSCT, median CR duration 6 months (range 1-33 months)

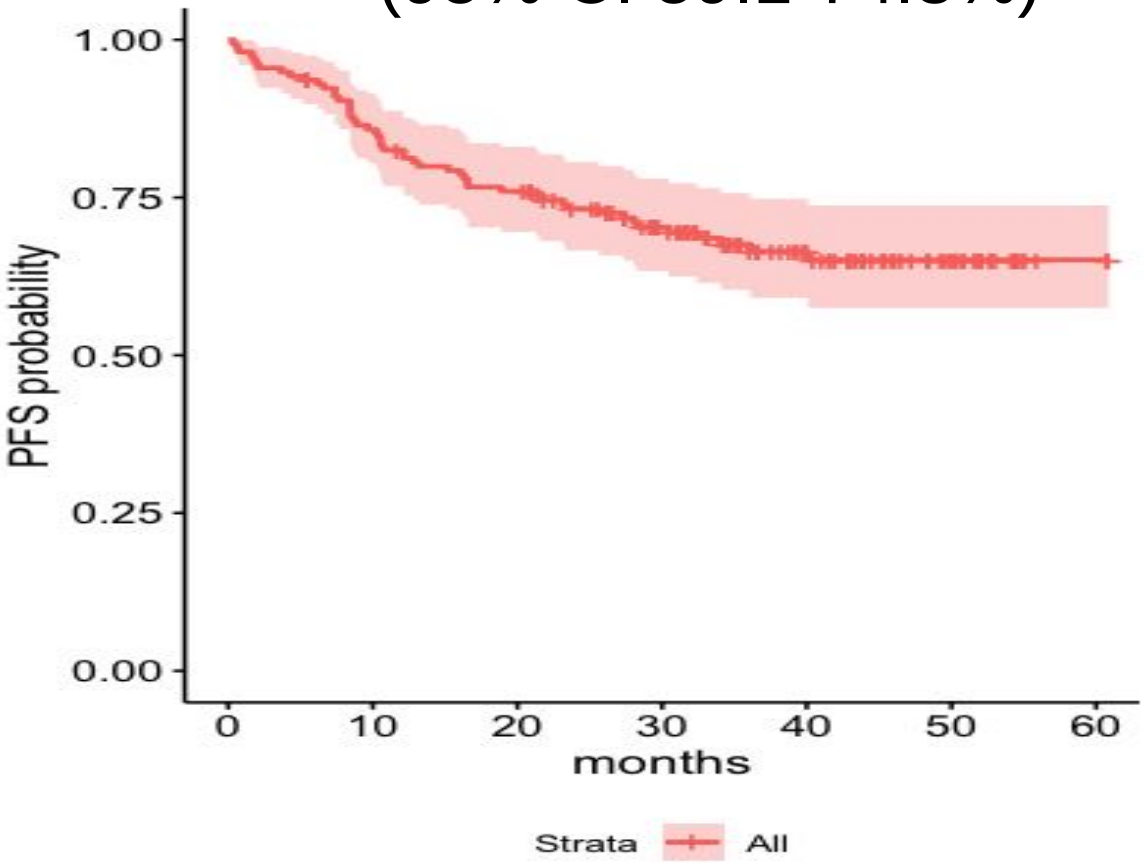
NJ. Short et al. EHA 2021

GRAAPH 2014:
Overall survival and relapse-free survival

3-yr OS= **78.2%**
(95% CI 71.8-81.3%)



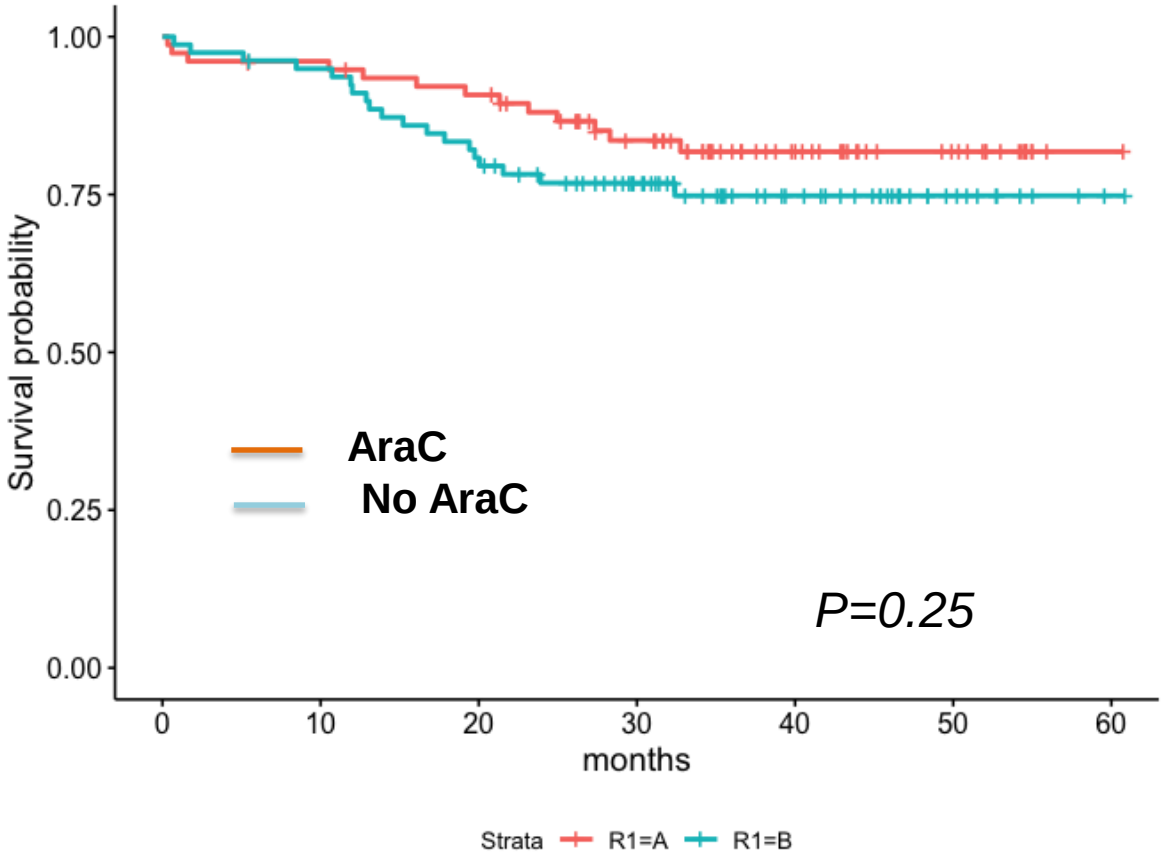
3-yr RFS= **66.5%**
(95% CI 59.1-74.8%)



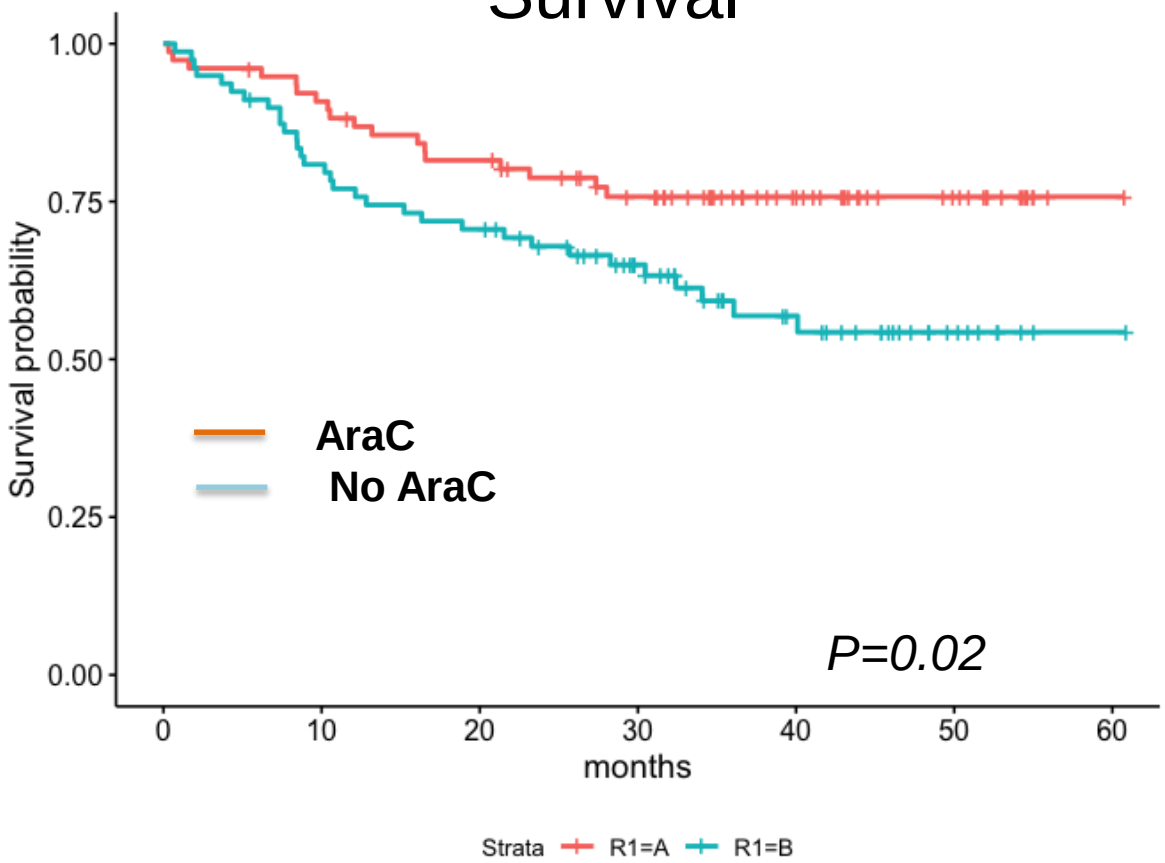
Ph. Rousselot et al. ASH 2021

GRAAPH 2014: OS and RFS by arm

Overall Survival

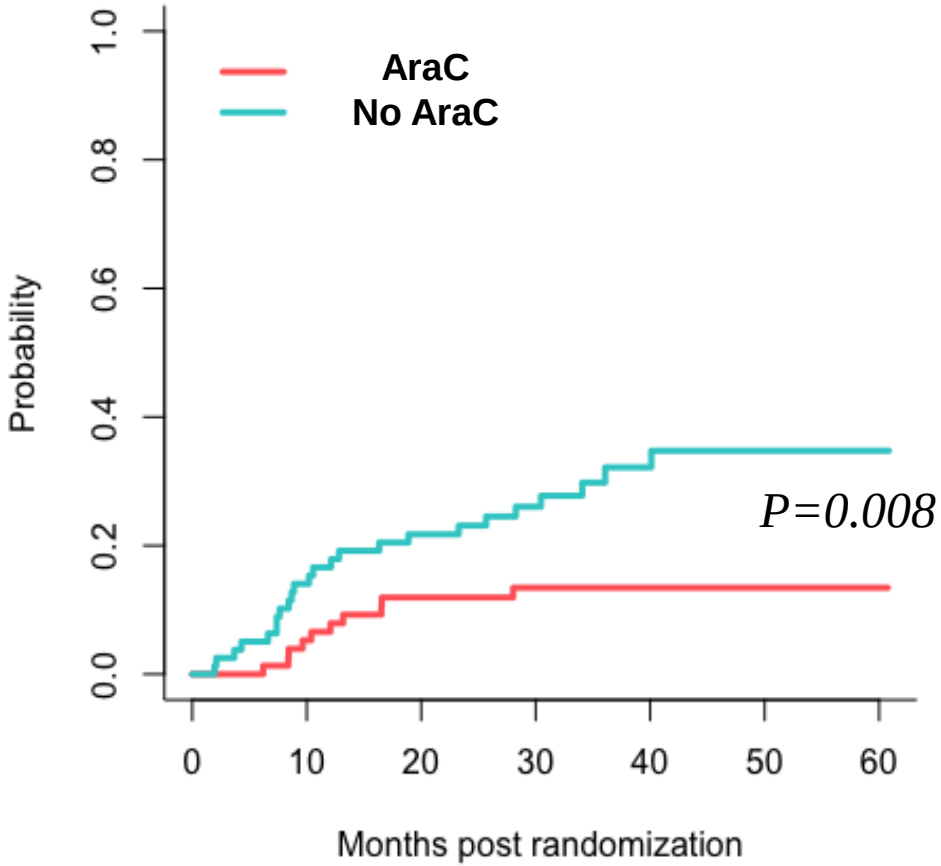


Relapse Free Survival



Ph. Rousselot et al. ASH 2021

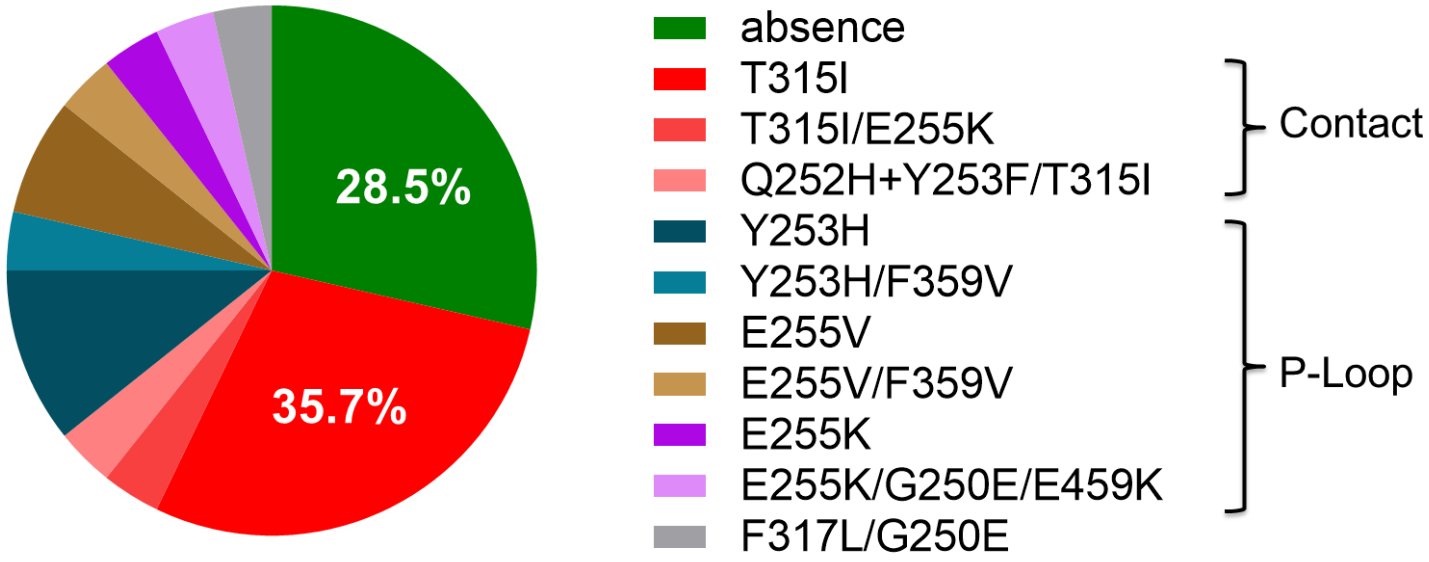
GRAAPH 2014:
Cumulative Incidence of Relapses and Mutations



20/28 evaluable pts (NGS) with ABL1 TKD mutations (71.4%)

Median time to relapse shorter for patients with mutations

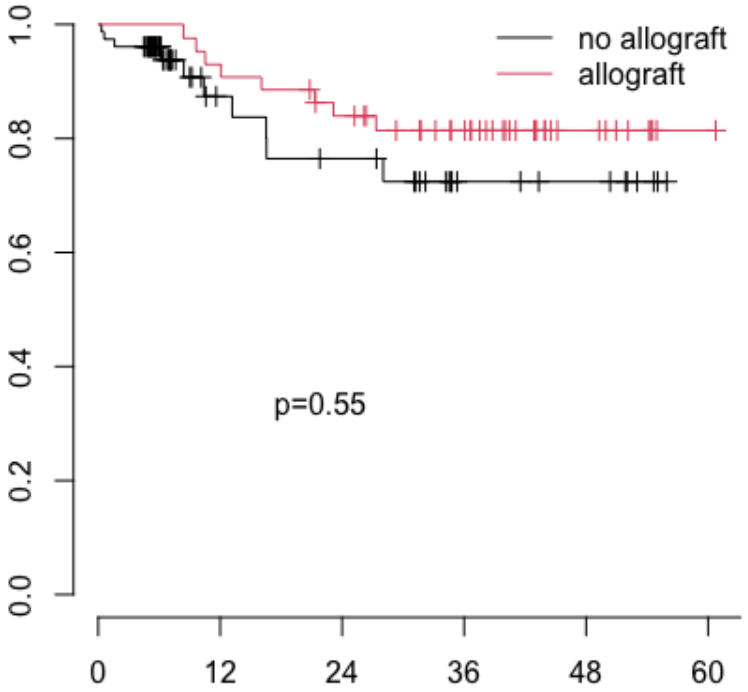
8.6 versus 23.7 months



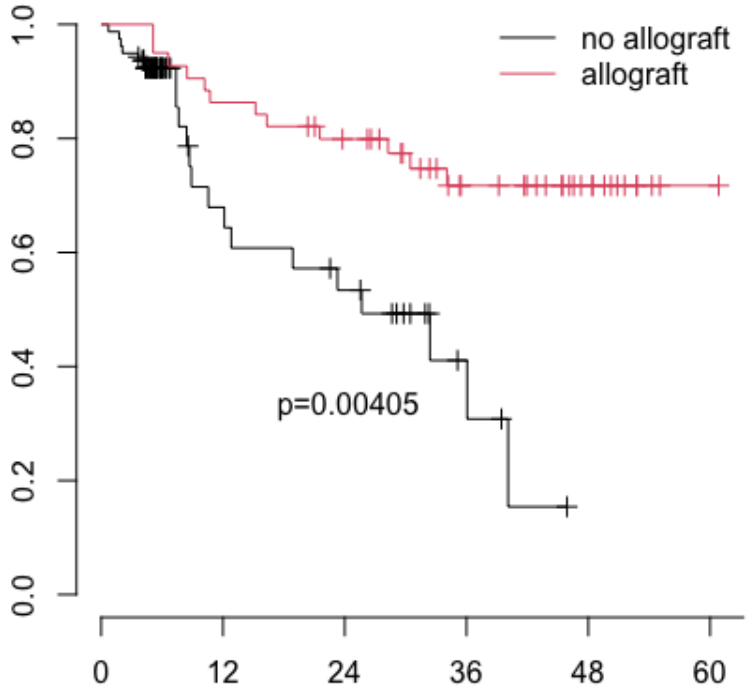
Ph. Rousselot et al. ASH 2021

Survival according to allograft
(Simon and Makuch plots)

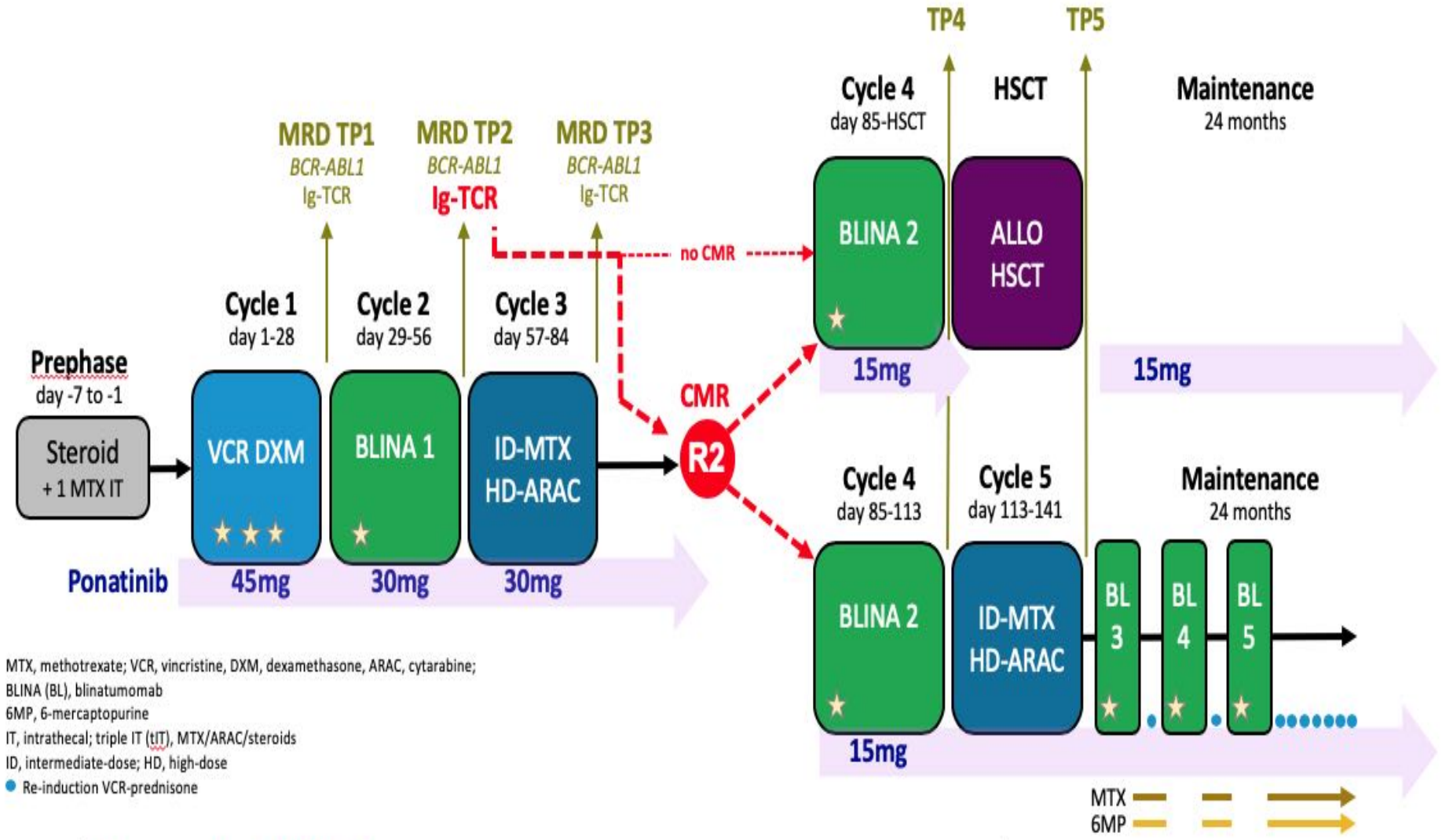
AraC arm



No AraC arm



GRAALL 2022: Ph pos BCP-ALL



MTX, methotrexate; VCR, vincristine, DXM, dexamethasone, ARAC, cytarabine;
BLINA (BL), blinatumomab
6MP, 6-mercaptopurine
IT, intrathecal; triple IT (tIT), MTX/ARAC/steroids
ID, intermediate-dose; HD, high-dose
● Re-induction VCR-prednisone

Primary endpoint (R2): OS

Secondary endpoints: EFS, hem. response, MRD, safety, relapse, NRM, RFS, PROs, QoL, cost effectiveness, cost utility
Sensitivity analyses: OS and EFS censoring at subsequent therapy initiation

☆ Triple IT

LAL Ph+ plan

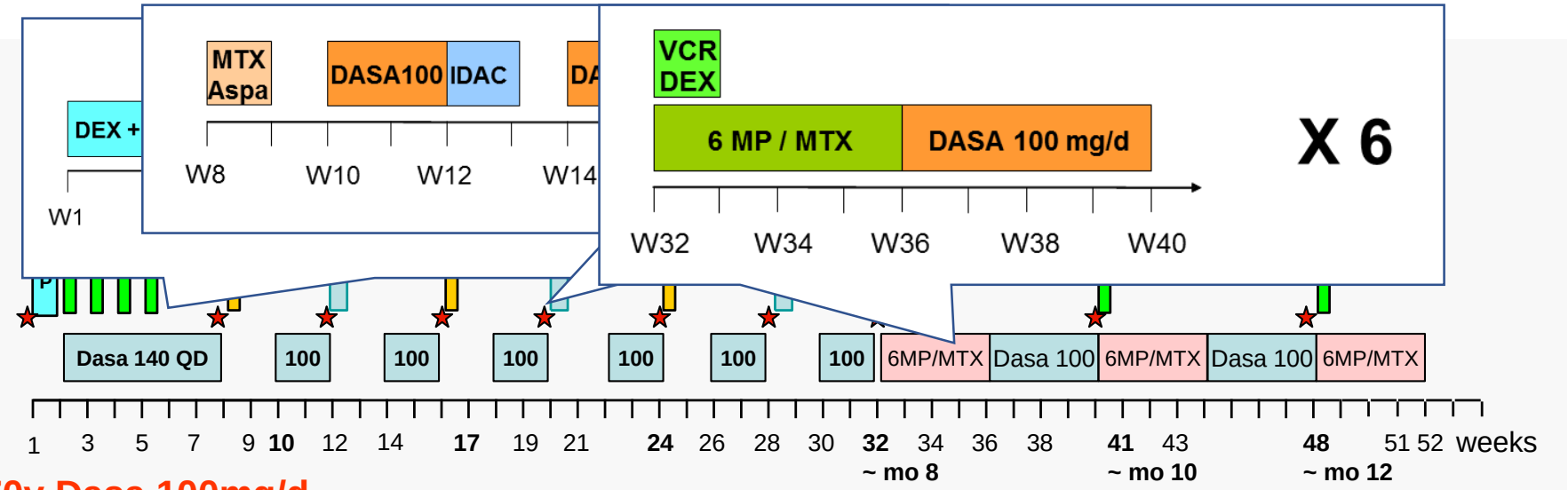
- Epidémiologie et facteurs prédisposant aux LAL/LAL Ph+
- Présentation clinique
- Diagnostic
- Facteurs pronostics
- Devenir avant l'ère des inhibiteurs de tyrosine kinase
- **Stratégies thérapeutiques de 1ère ligne:** - jeune adulte
  - adulte âgé
- Prise en charge de la rechute
- Impact de la MRD

Dasatinib (Sprycel®) and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia positive ALL aged 55 and over: long term results of the EWALL-PH-01study.

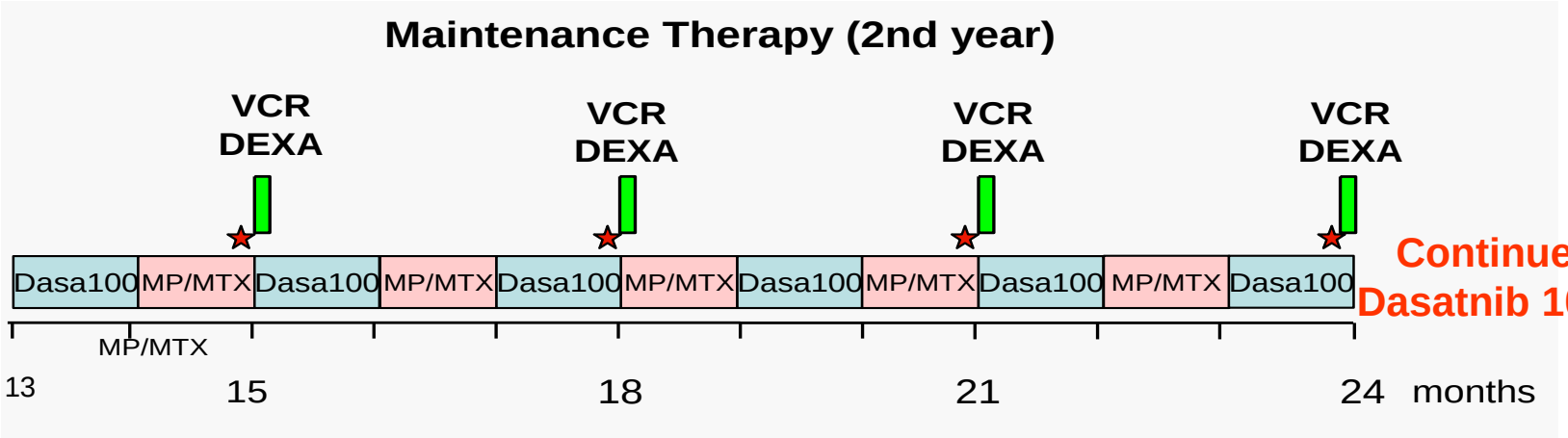
Ph Rousselot
Université de Versailles Saint-Quentin-en-Yvelines
Hôpital André Mignot, Hôpitaux de Versailles, France

On behalf of the EWALL group

Treatment schedule



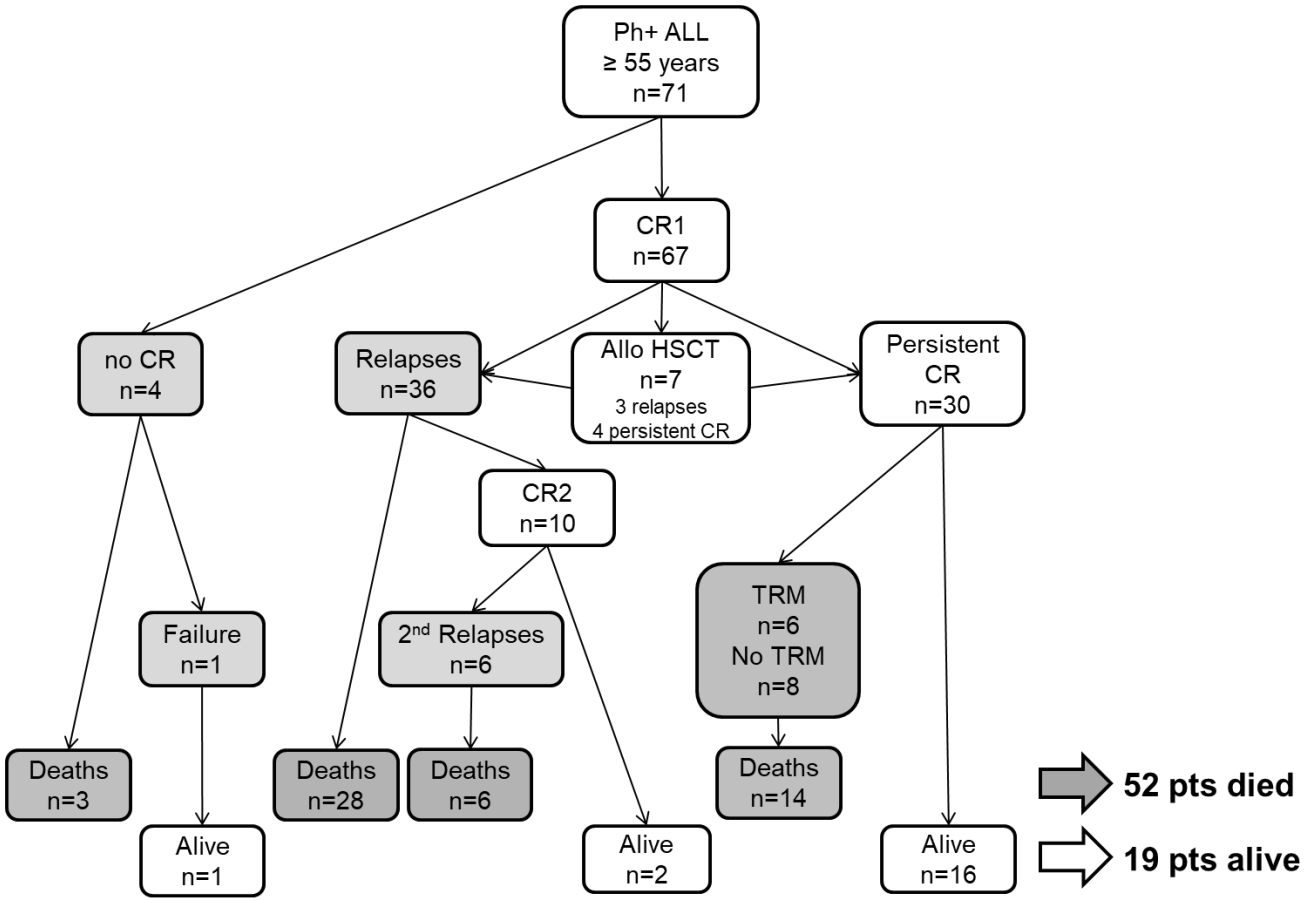
> 70y Dasa 100mg/d and Dex 20mg



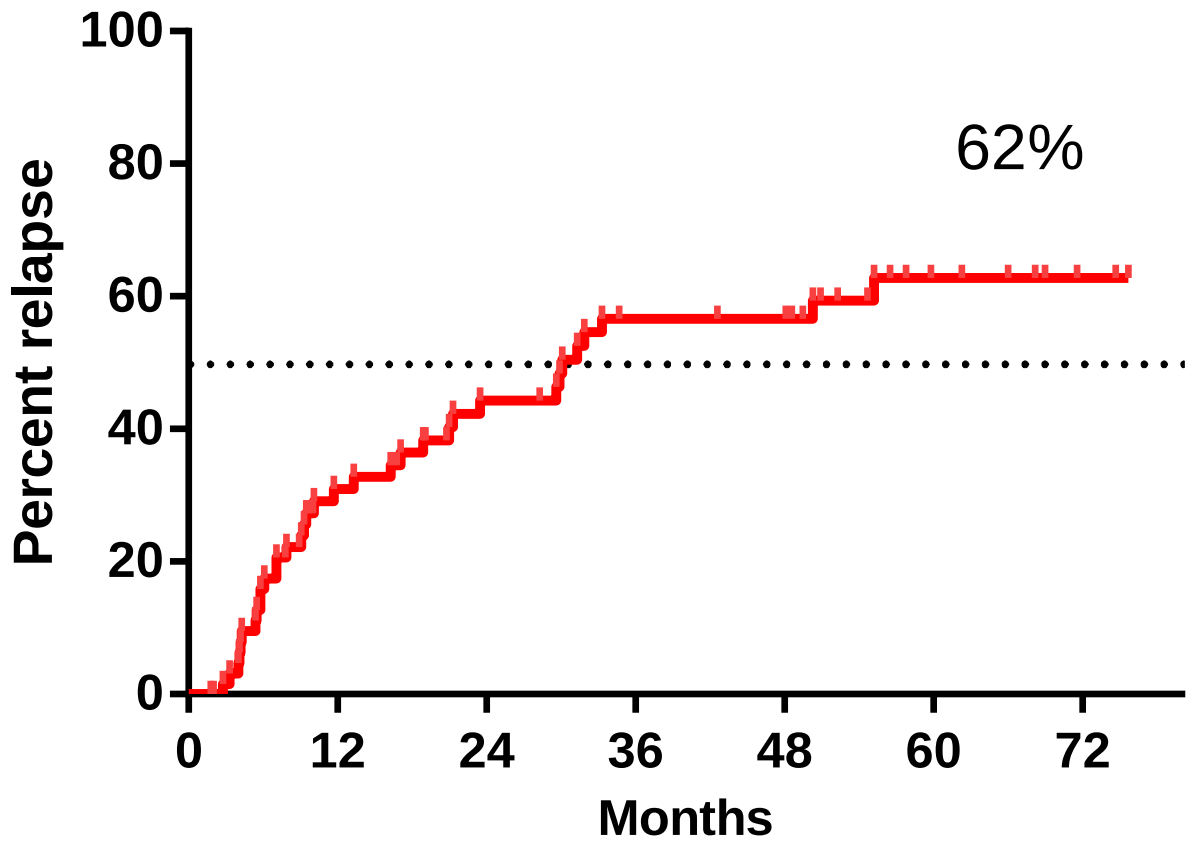
Continue with Dasatnib 100mg/d

Consort diagram

- CR rate (ITT analysis) : 94%
  - 67 out of 71 patients (3 deaths, 1 patient primary resistant)

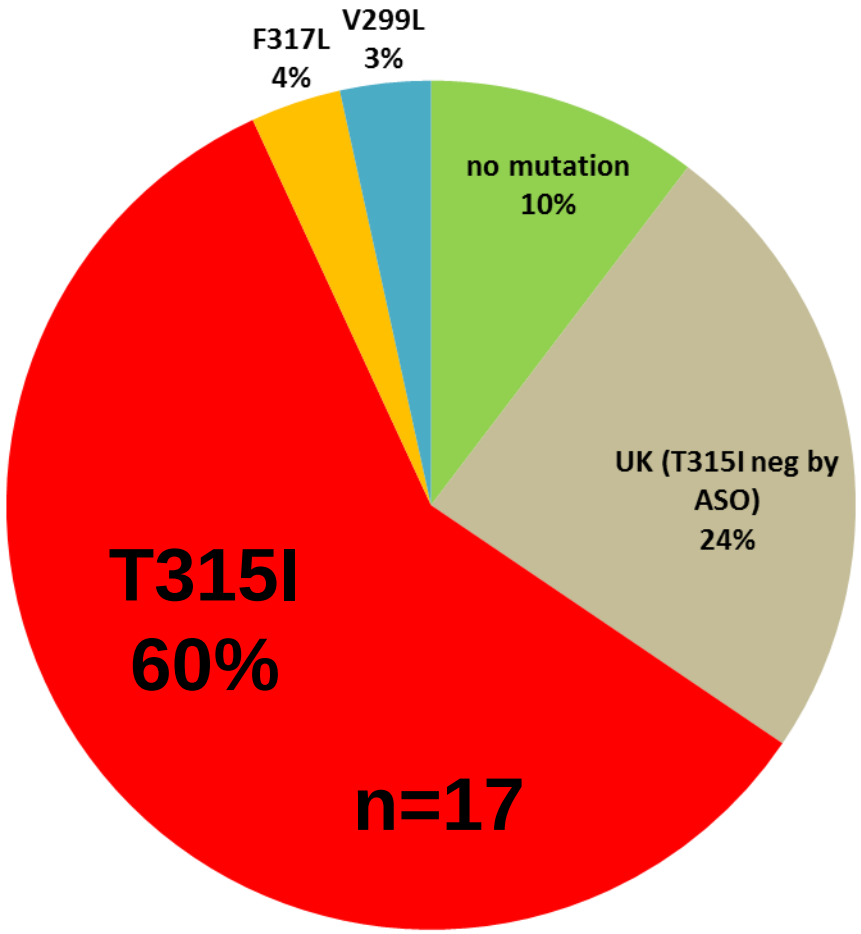


Cumulative incidence of relapse



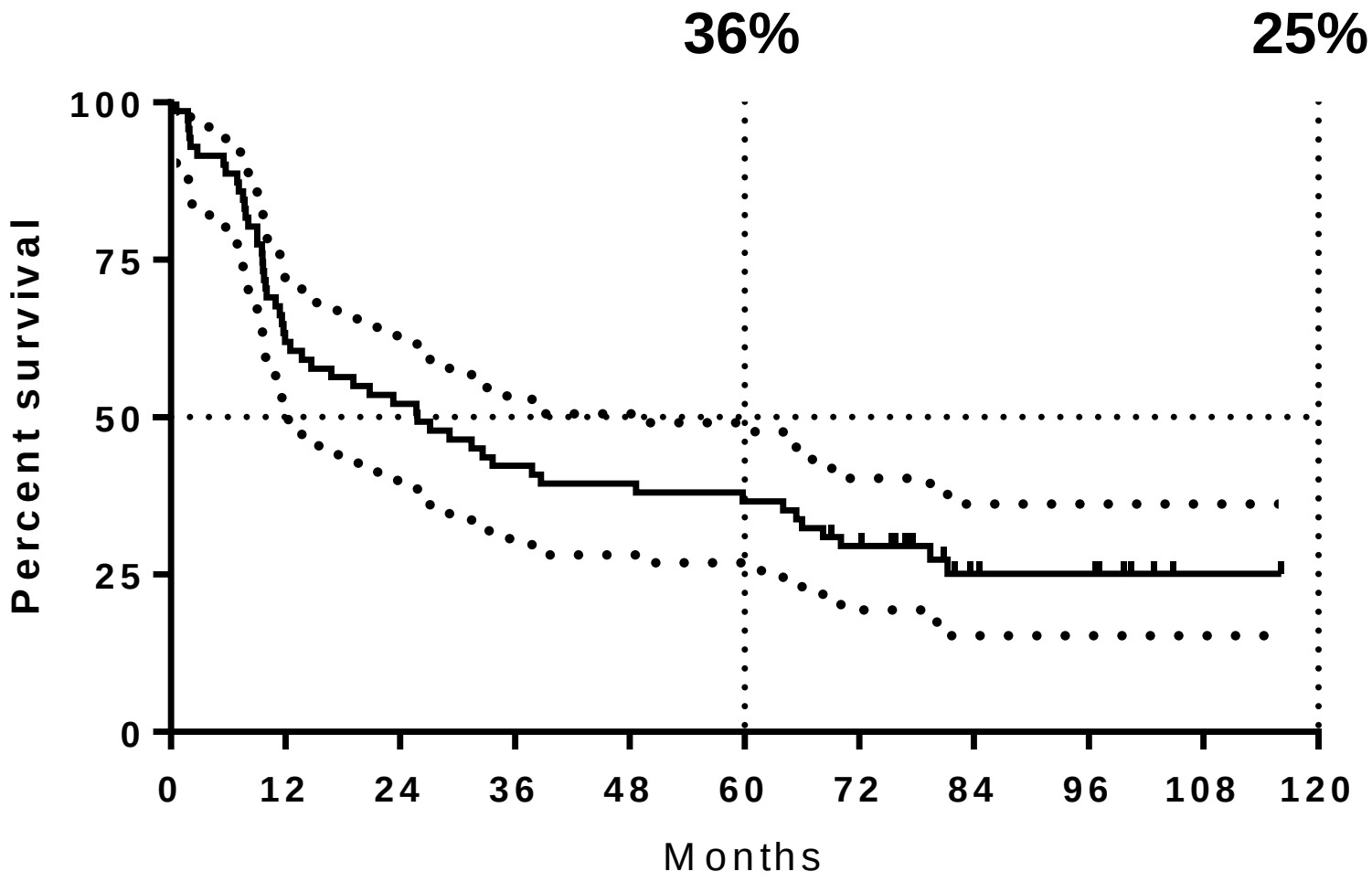
Relapses

Time to relapse : **median 18.9 months** (range 1.8 – 75.7)



Overall survival

Follow-up : 10y



Four out of 19 long term survivors were allografted

Nilotinib (Tasigna®) and Low Intensity Chemotherapy for First-Line Treatment of Elderly Patients with *BCR-ABL1-* Positive Acute Lymphoblastic Leukemia: Final Results of a Prospective Multicenter Trial (EWALL-PH02)

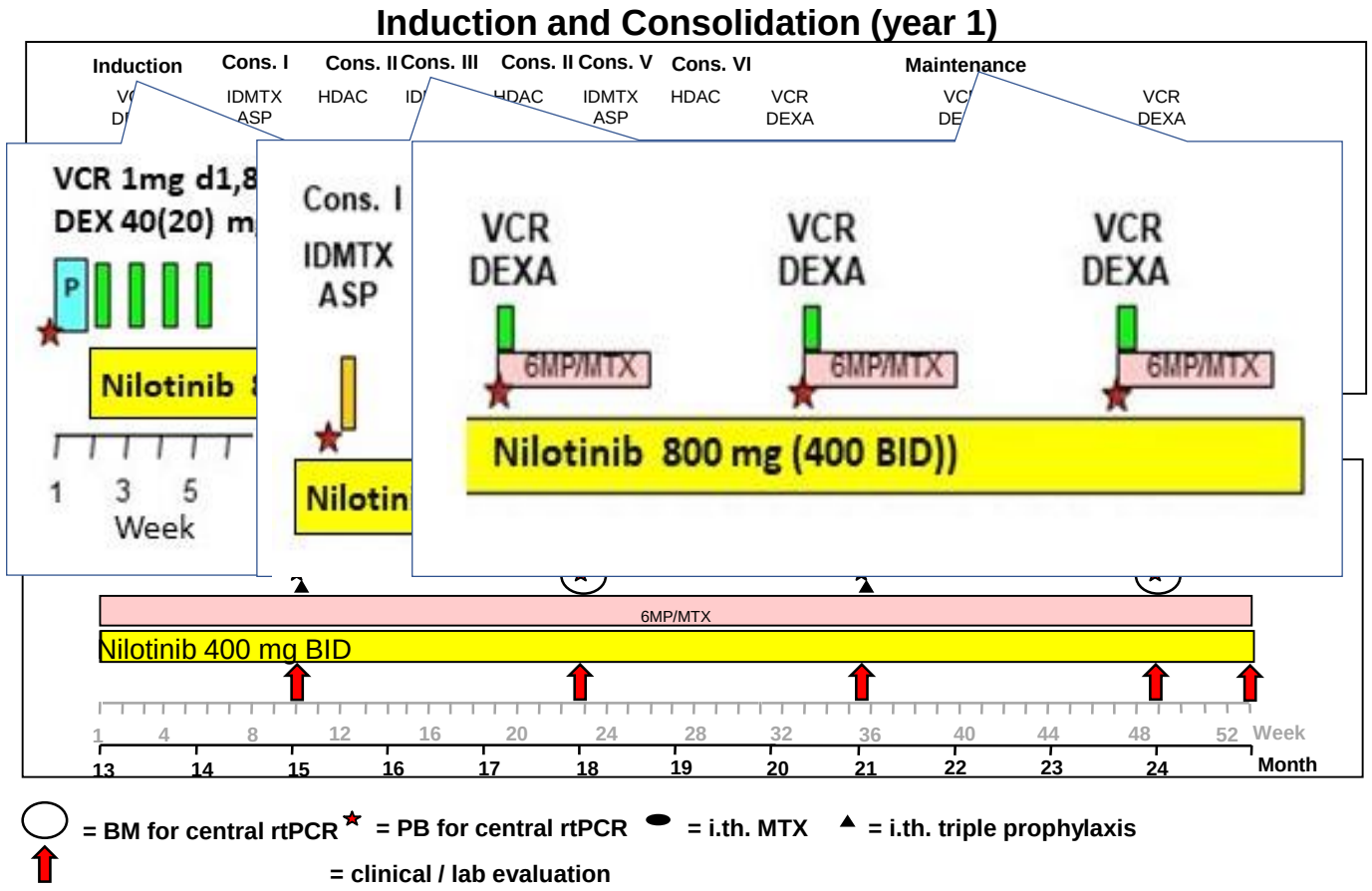
60th ASH Annual Meeting
San Diego; Dec 1, 2018

Oliver Ottmann

Department of Haematology

Cardiff University /
University Hospital of Wales

Study Schema: EWALL PH02



Efficacy (n=72)

Complete remission

68 (94.4%)

(ITT analysis)

Median time to CR [range]

41 d [31-73]

Refractory

1 (1.4%)

Induction death (<60 d)

1 (1.4%)

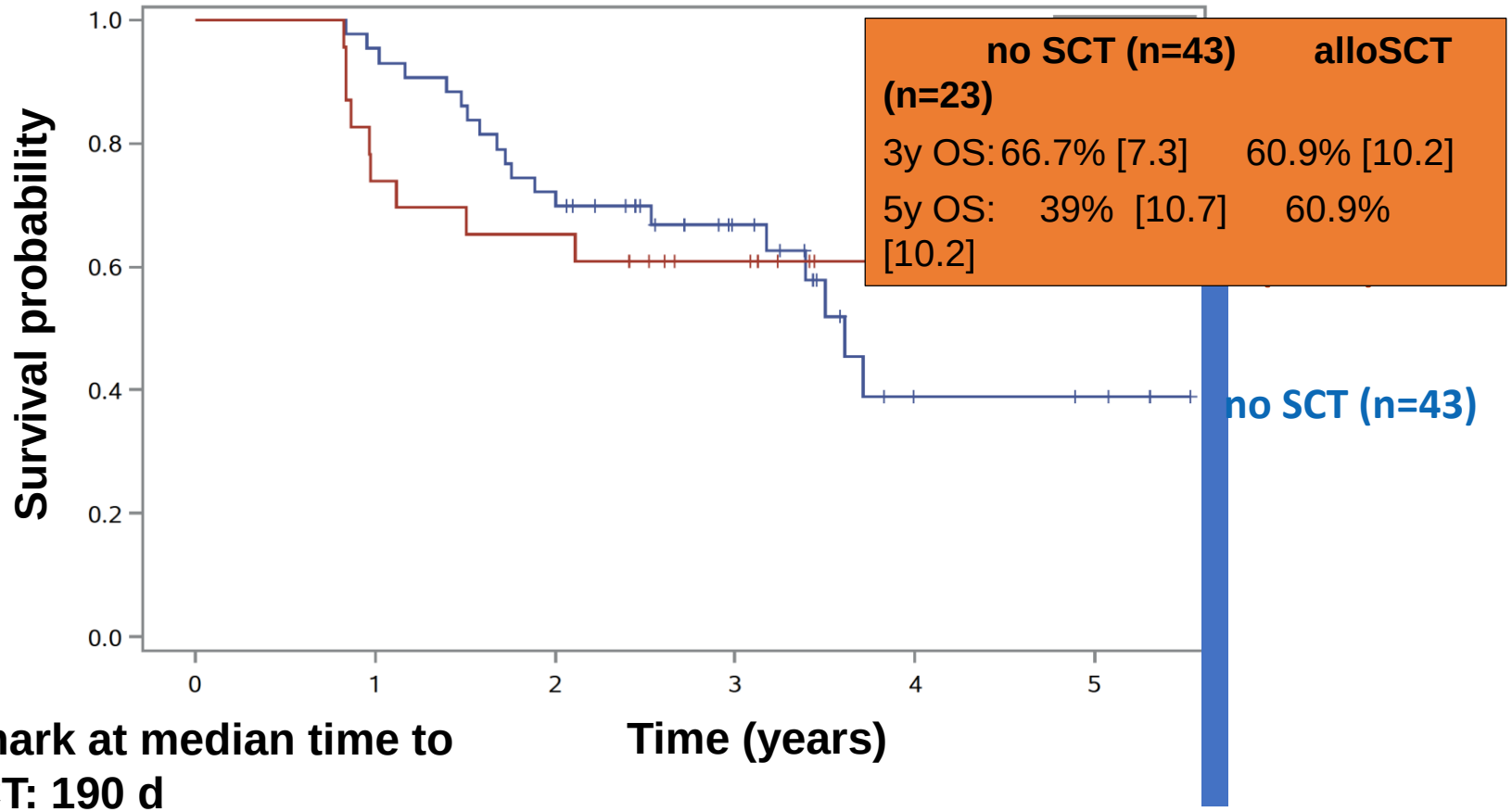
Early discontinuation)

2 (2.8%)

(tox. pre response assessment)

Survival in Patients undergoing alloSCT vs. no SCT

Landmark analysis



Landmark at median time to alloSCT: 190 d

- Non-transplanted pts: all alive in CR at landmark
- alloSCT pts.: all included; OS from start of induction

Outcomes of older patients with newly diagnosed Ph+ ALL

Clinical Trial (year)	N	Age, median [Range]	Chemotherapy	TKI, mg/d	CR, %	SCT in CR1, %	OS, %
Ottmann (2007)[15]	28	66 [54-79]	GMALL	IM 400	96	0	42 at 24 mo
Vignetti (2007)[14]	30	69 [61-83]	Prednisone	IM 800	100	0	50 at 24 mo
Delannoy (2006)[60]	29	66 [58-78]	GRALL-AFR09	IM 600	72	0	66 at 12 mo
Rousselot (2016)[32]	71	69 [59-83]	EWALL-Ph-01	DAS 100-140	96	10	36 at 60 mo
Ottmann (2014)[24]	47	65 [55-85]	EWALL-Ph-02	NIL 800	87	20	67 at 24 mo

ALL, acute lymphoblastic leukemia; CR, complete remission; d, day; DAS, dasatinib; EWALL, European Working Group on Adult ALL; GMALL, German Multicenter Study Group for Adult ALL; GRALL, Group for Research on Adult ALL; IM, imatinib; mo, months; NIL, nilotinib; OS, overall survival; Ph+, Philadelphia chromosome–positive; SCT in CR1, stem cell transplant in first CR; TKI, tyrosine kinase inhibitor.

M Yilmaz et al. Clinical Advances in Hematology & Oncology 2018;12:216

LAL Ph+ plan

- Epidémiologie et facteurs prédisposant aux LAL/LAL Ph+
- Présentation clinique
- Diagnostic
- Facteurs pronostics
- Devenir avant l'ère des inhibiteurs de tyrosine kinase
- Stratégies thérapeutiques de 1ère ligne: - jeune adulte
  - adulte âgé
- **Prise en charge de la rechute**
- Impact de la MRD

Treatment options for relapse Ph pos ALL

- Change TKI
  - Ponatinib
- Monoclonal antibodies
  - Inotuzumab
  - Blinatumumab
- Combinations

ELN Wokpackage 6 (ALL)
Mannheim, February 11, 2019

Outcome of patients with Ph+ ALL in first molecular vs. overt relapse included in the trial ALL PH08 from the PETHEMA Group

JM Ribera

ICO-Hospital Germans Trias i Pujol

Josep Carreras Research Institute

Universitat Autònoma de Barcelona

PETHEMA Group

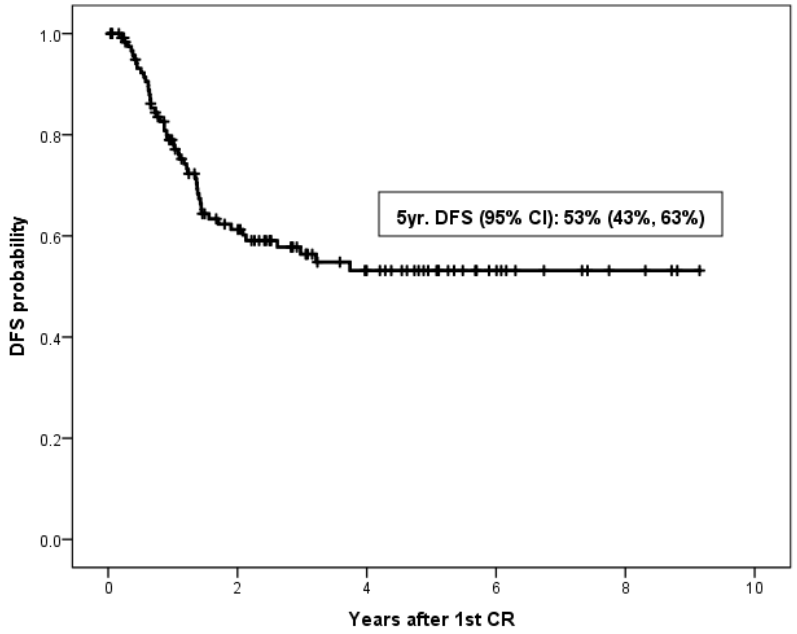
Badalona, Spain

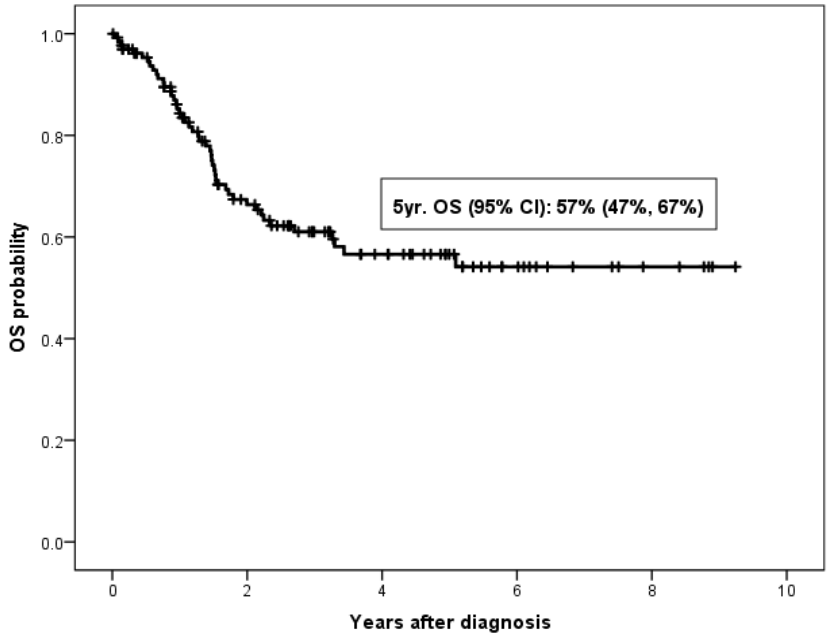
Treatment of relapse

	Molecular relapse (n=11)	Overt relapse (n=17)
Type of treatment	Increase imatinib dose (n=2) Change to dasatinib (n=9)†	TKI+ Intensive chemotherapy (n=11),†,‡ Intensive chemotherapy without TKI (n=2) Change TKI without salvage chemotherapy (n=2) § No treatment (n=2)
Morphologic CR	-	12/16 (75%)¶
Molecular CR	8/10 (80%)ʅ	9/10
Second HSCT in CR2	0	7
Relapse	3/8	9/12
DFS (median, 95%CI), months	16.9 (NE)	6.3 (2.1-10.4)
Death	5/11	12/17
OS (median, 95% CI), months	28.7 (NE)	11.5 (8.5-14.5)

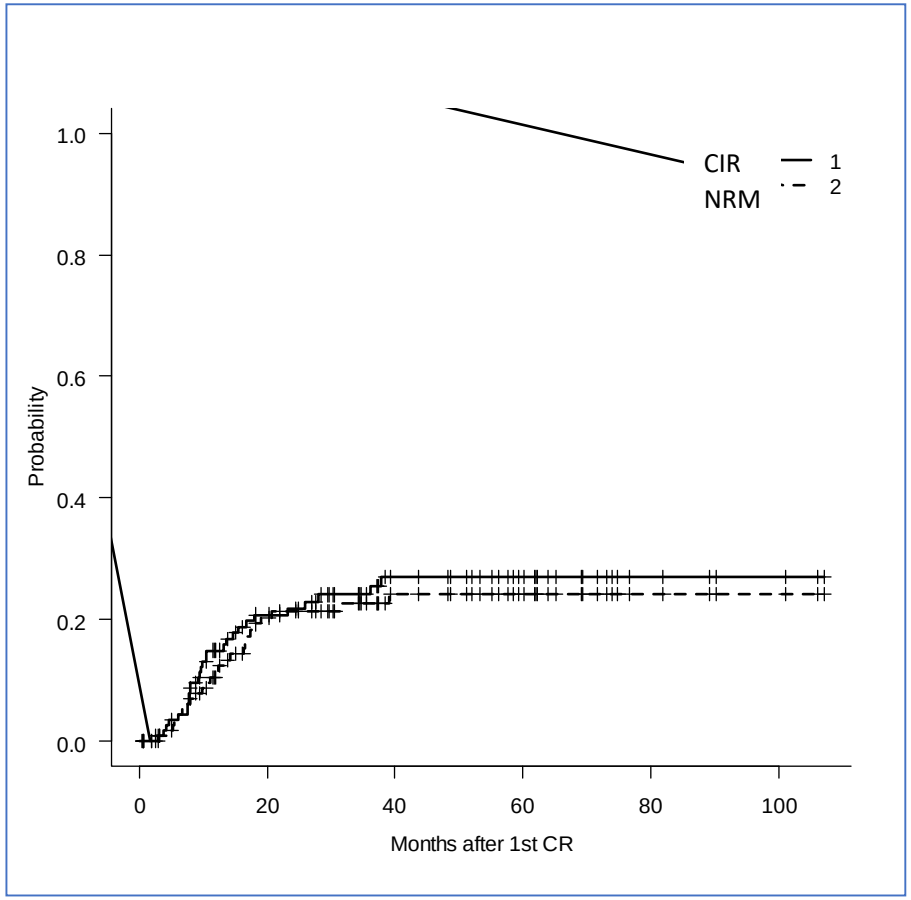
†One patient from each group received DLI concomitant with rescue therapy; ‡Increase imatinib dose (n=1), dasatinib (n=5), nilotinib (n=1), ponatinib (n=4); §Nilotinib (n=1), dasatinib (n=1); ¶One patient under treatment and 2 patients died during rescue therapy; ʅOne patient not evaluated.

Disease-free survival and overall survival



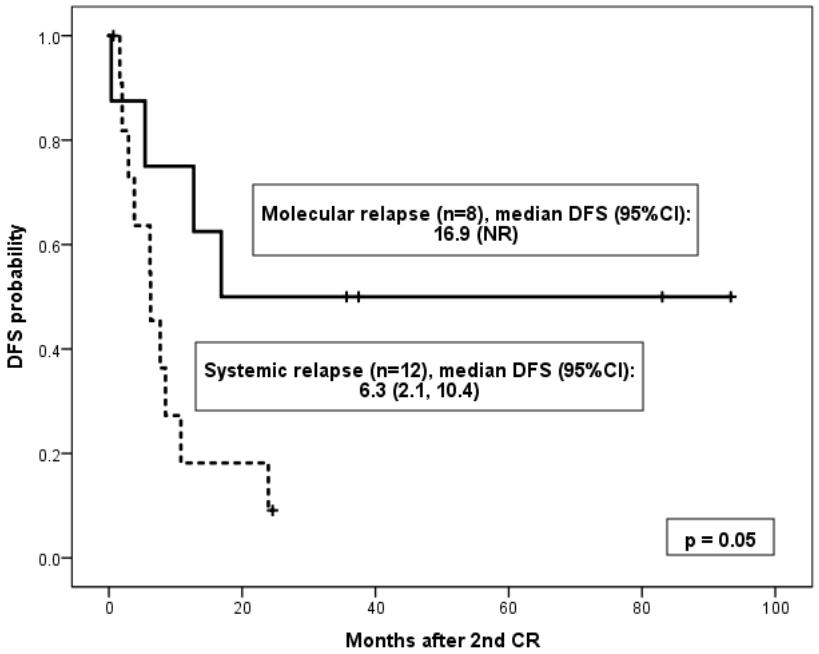


Reasons of failure

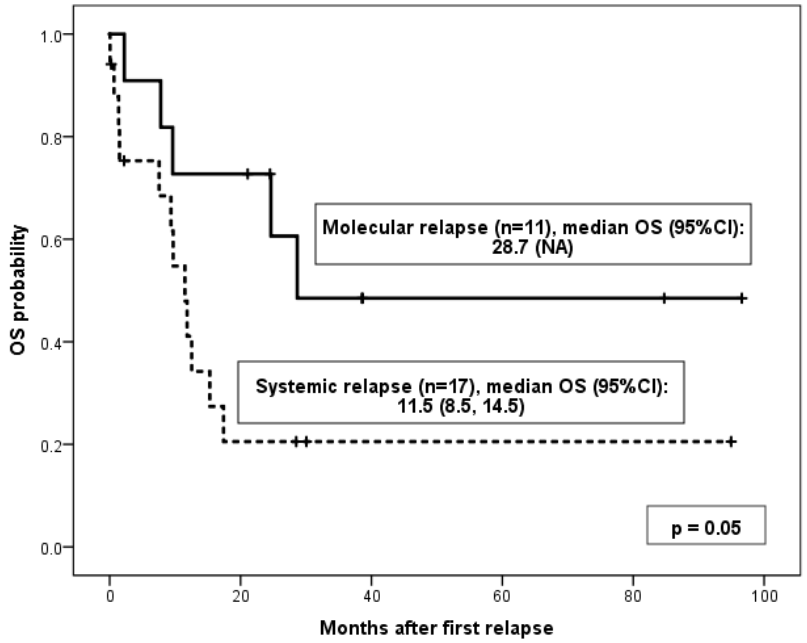


Disease-free survival and overall survival according to the type of relapse

DFS



OS

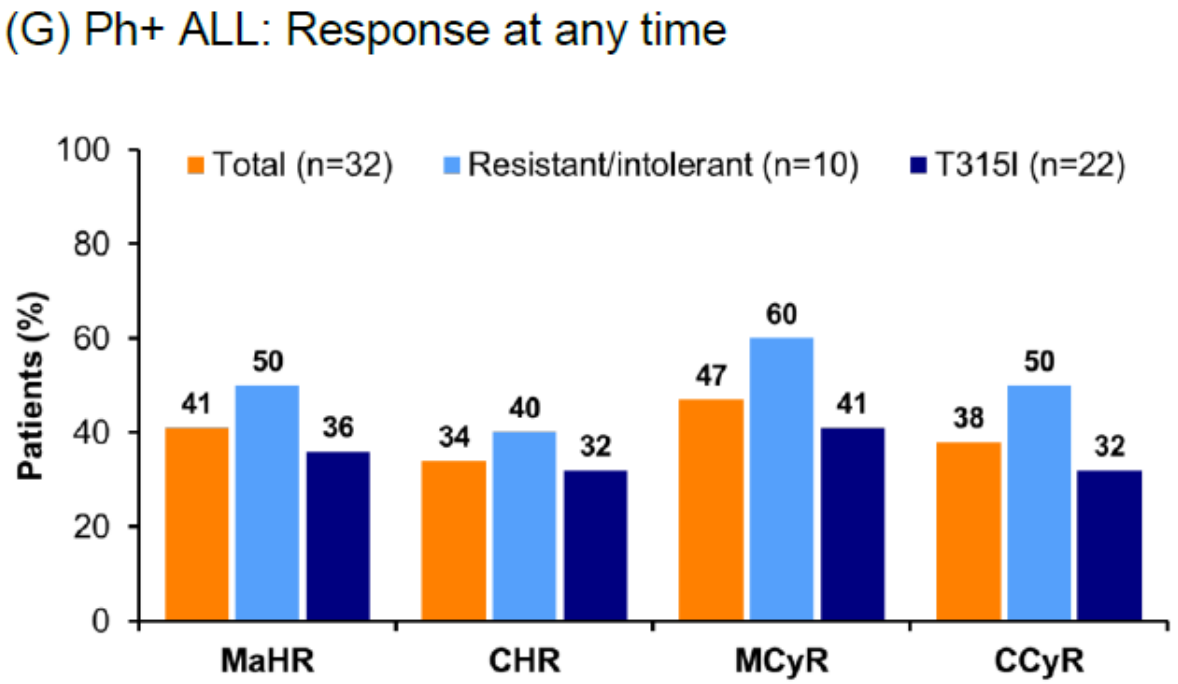


Conclusions

- CIR of 27% in young and older patients with Ph+ ALL treated with imatinib and standard chemotherapy followed by alloHSCT when possible.
- Most of the relapses occurred after HSCT and were molecularly detected in 40% of the patients.
- Therapeutic approach different in patients with molecular and overt relapses,
  - Increased dose of TKI or change of the TKI in molecular relapse
  - Chemotherapy plus changed TKI followed by a second HSCT when possible in systemic relapse.
- Despite this more intensive approach, the outcome was poorer in patients with overt relapse.

Change TKI : Ponatinib

- PACE study (Ph+ ALL) : PONATINIB post TKIs

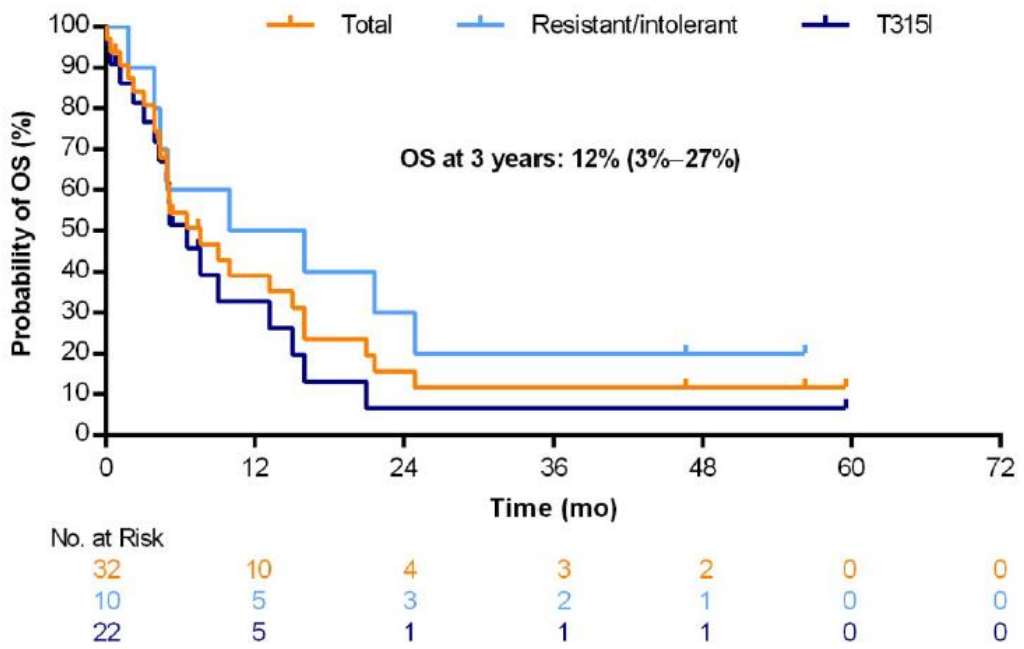


Cortes JE, et al. Blood. 2018 Mar 22.
[Epub ahead of print]

OS with ponatinib (Relapse Ph+ ALL)

- OS at 3 years in Ph+ ALL: 12% (median 8 months)

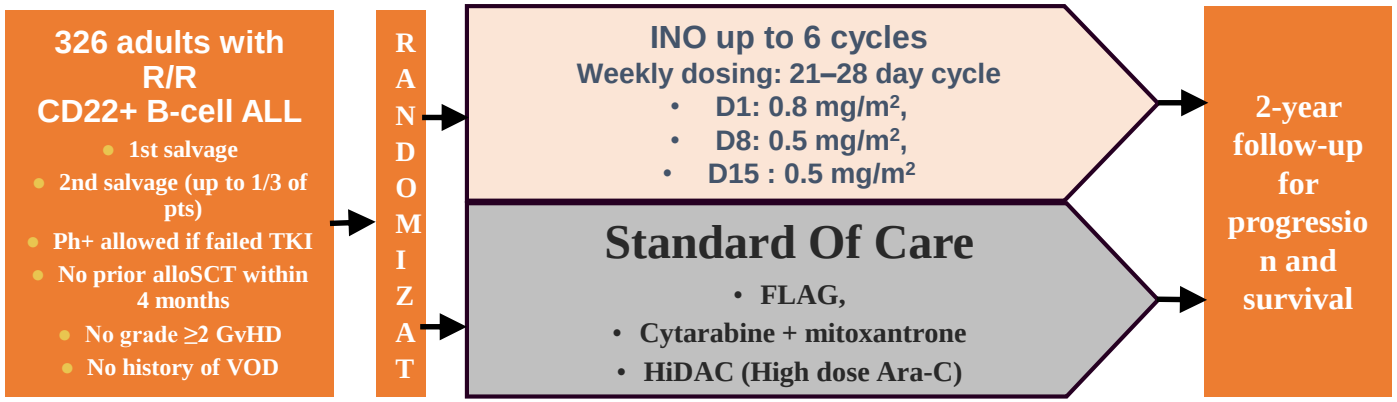
(I) Ph+ ALL: Overall survival



Cortes JE, et al. Blood. 2018 Mar 22. [Epub ahead of print]

Inotuzumab Ozogamycin in relapsed Ph+ ALL

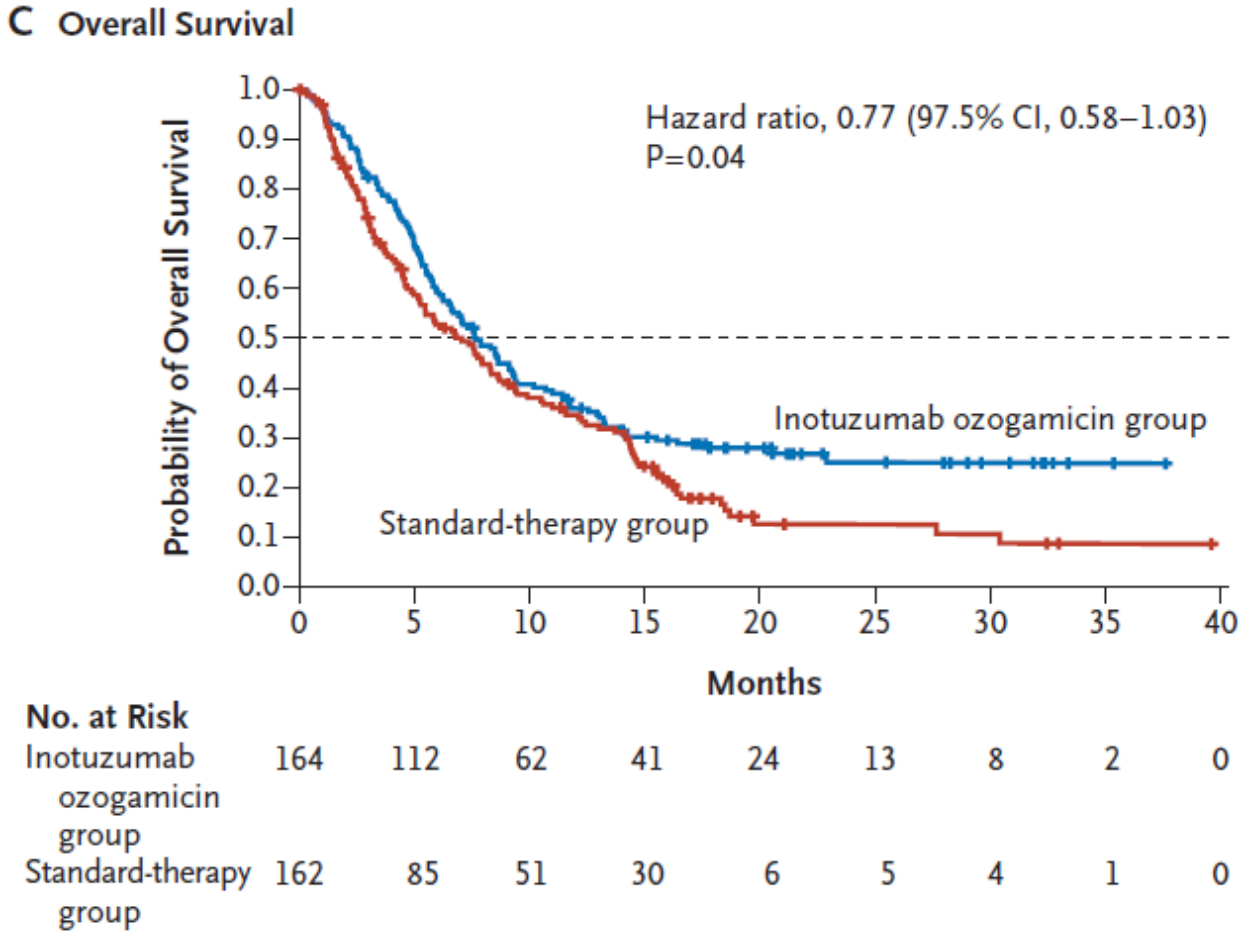
- INO – VATE study



- **INO reduced to 1.5 mg/m2/cycle once the patient achieved CR/CRi**
- **Primary endpoint: CR (CR + CRi)**

Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53

INO-VATE : overall survival



2 years OS

INO : 23% (95CI 16-30)

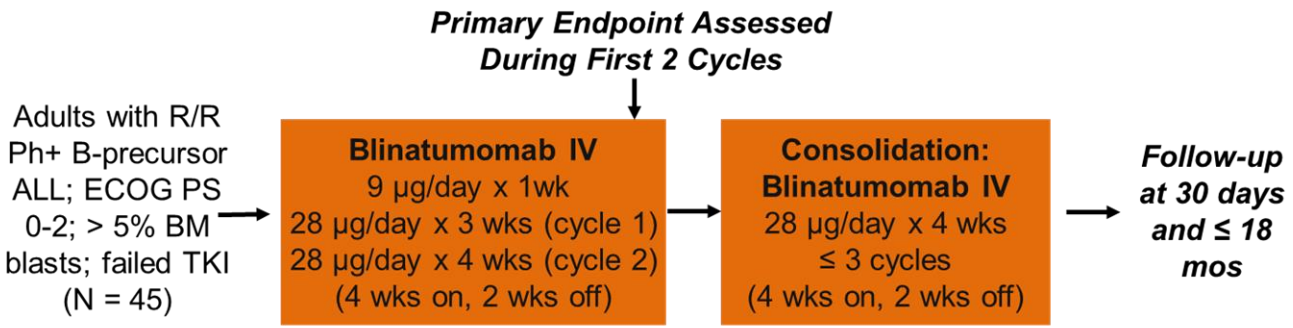
SOC : 10% (95% CI 5-16**)**

Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53

Blinatumomab in relapsed Ph+ ALL

ALCANTARA: Blinatumomab Shows Activity in R/R Ph+ B-Precursor ALL

Phase II single arm study



Primary endpoint: CR/CRh during first 2 cycles

Secondary endpoints: best CR, MRD, RFS, OS, allogeneic HSCT rate, and safety

Martinelli G, et al. Blood. 2015;126(23):679; published ahead of print December 4, 2015.

ALCANTARA: results

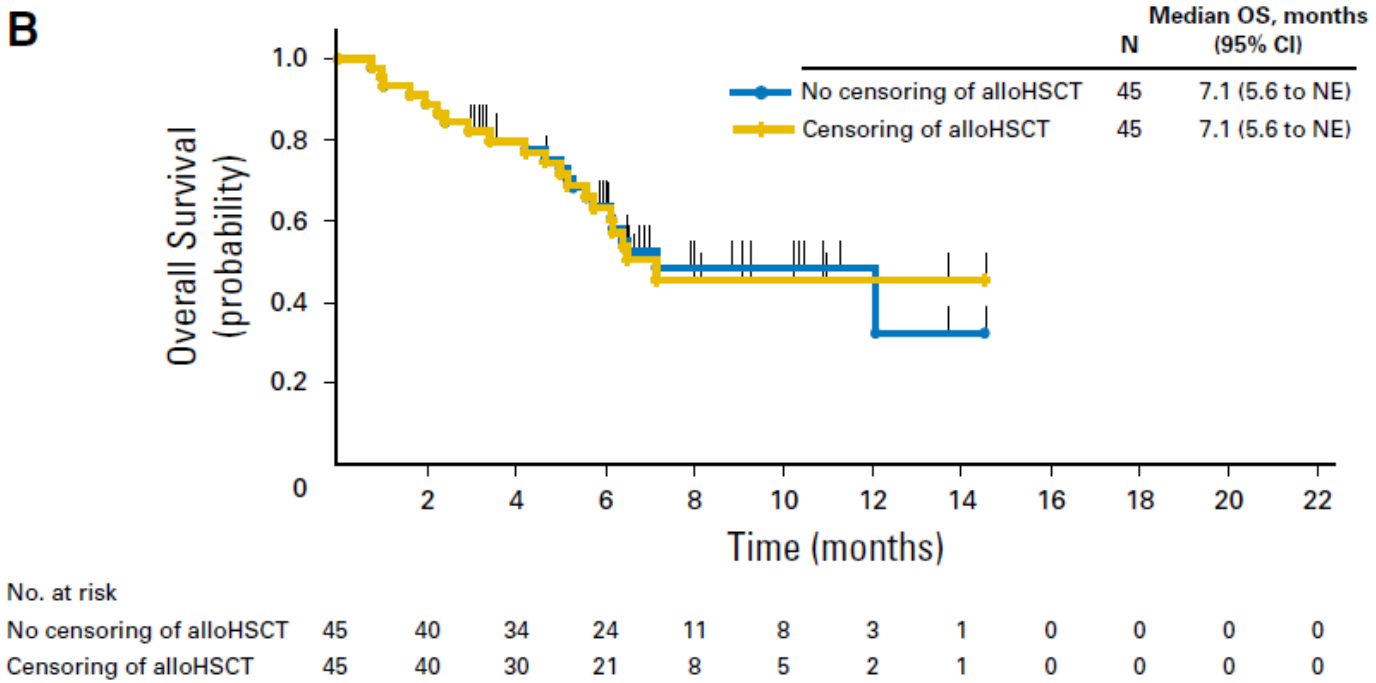
- **Median RFS: 6.7 mos (95% CI: 4.4-NE)**
- **Median OS: 7.1 mos (95% CI: 5.6-NE)**

Parameter	Response, %
Primary endpoint	
CR/CRh (first 2 cycles)	36
▪T315I mutation	40
▪≥ 2 prior 2+ gen TKI	41
▪Prior ponatinib treatment	35
Secondary endpoints	
Best response (first 2 cycles)	
▪CR	31
▪CRh	4
▪CRi (not including CRh)	4
Complete MRD response*	88
▪MRD response in pts with ABL-kinase mutations	100
Proceeded to allogeneic HSCT	25

*Includes all 4 CR/CRh T315I pts.

Martinelli G, et al. *Blood*. 2015;126(23):679; published ahead of print December 4, 2015.
Martinelli G, et al. J Clin Oncol. 2017; 35:1795-1802.

ALCANTARA : overall survival



Martinelli G, et al. J Clin Oncol. 2017; 35:1795-1802.

Blinatumomab and TKIs in relapsed Ph+ ALL

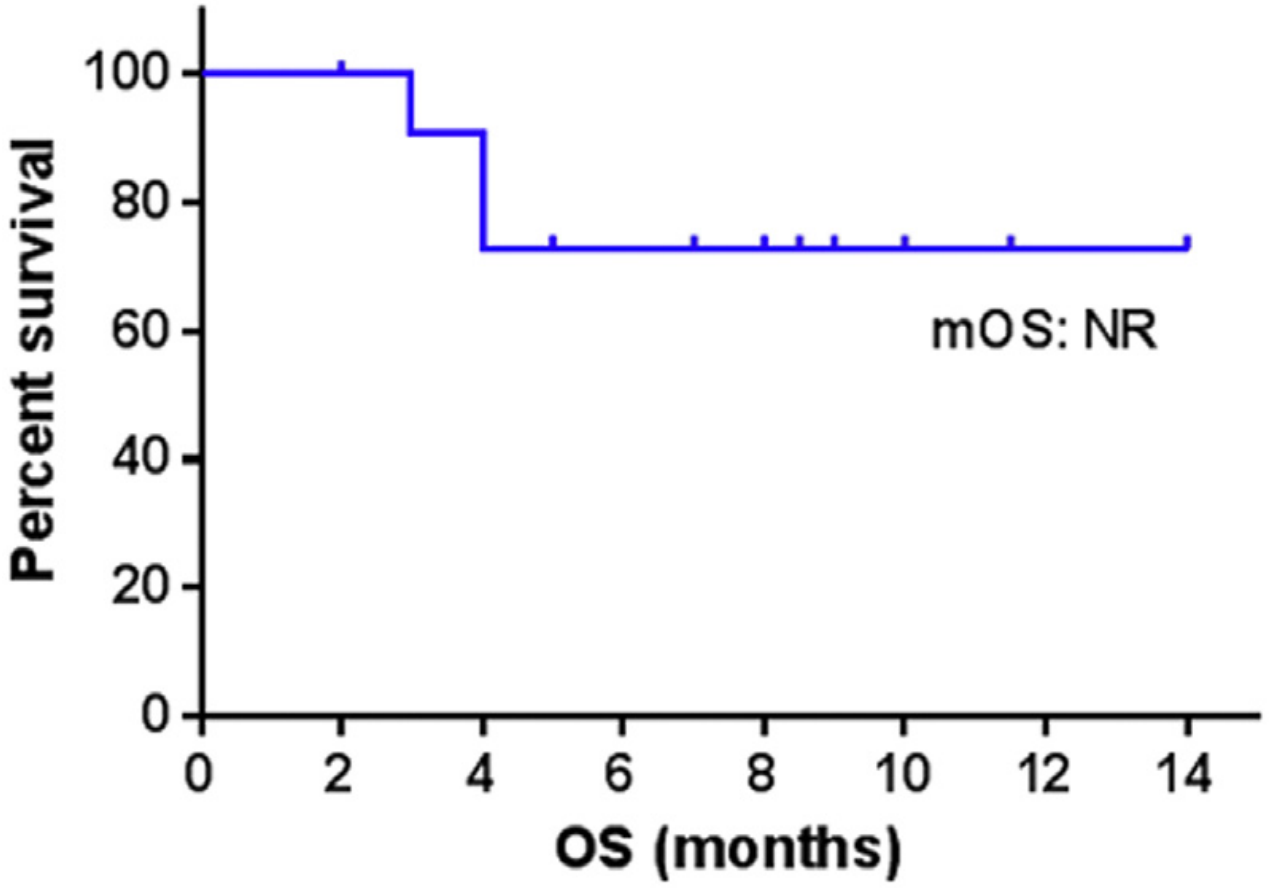
Table 1 Baseline Characteristics and Summary of Outcomes and Toxicities of Patients Treated With Blinatumomab and Tyrosine Kinase Inhibitor

Patient No.	Age, y	Disease	No. Prior Chemo	No. Prior TKI	TKD, m	Type of Relapse	CNS Disease	TKI	No. Cycles	Response	TTR, d	Allo-SCT	DOR, mo	Status	OS, mo	Toxicities
1	48	Ph+ ALL	2	4	V299L	Overt	No	Bosutinib	2	CR, CCyR, CMR	30	No	6	Alive	7	None
2	70	Ph+ ALL	1	1	Neg	MRD+ (FC/Mol)	No	Ponatinib	3	CR, CMR	35	No	9	Alive	10	CRS (G2), tremor (G1)
3	46	Ph+ ALL	2	2	E255K	Overt	No	Dasatinib	1	PR	—	No	—	Dead	4	CRS (G2), pneumonia (G5)
4	32	Ph+ ALL	1	1	T315I	Overt	No	Ponatinib	2	CR, CCyR, CMR	36	Yes	13	Alive	14	Headaches
5	72	Ph+ ALL	3	3	Neg	Overt	Yes	Ponatinib	1	NR	—	No	—	Dead	3	Status epilepticus (G3), pneumonia (G5)
6	50	Ph+ ALL	1	1	ND	MRD+ (FC)	Yes	Ponatinib	2	CR, CCyR, CMR	35	Yes	10	Alive	11.5	Sublinical seizures (G3), speech and memory problems (G3)
7	47	Ph+ ALL	3	2	T315I	Overt	No	Ponatinib	1	NR	—	No	—	Dead	4	Blurred vision (G1)
8	70	Ph+ ALL	1	2	ND	MRD+ (FC/Mol)	No	Ponatinib	1	CR, CMR	65	No	3	Alive	5	AMS (G1), somnolence (G1), cognitive impairment (G1)
9	69	CML-LBC	2	2	Neg	MRD+ (MoL)	No	Ponatinib	1	CR, CMR	30	No	8	Alive	9	None
10	61	CML-LBC	2	2	Neg	MRD+ (FC/Mol)	No	Ponatinib	2	CR, CCyR, CMR	30	Yes	7	Alive	8.5	Short-term memory loss (G1)
11	77	CML-LBC	1	3	Neg	Overt	Yes	Dasatinib	2	CR, CCyR, CMR	56	No	6	Alive	8	Confusion (G1)
12	77	Ph+ ALL	1	1	Neg	MRD+ (FC/Mol)	No	Dasatinib	2	CR, CMR	35	No	1	Alive	2	None

Abbreviations: allo-SCT = allogeneic stem cell transplantation; AMS = altered mental status; CCyR = complete cytogenetic remission; Chemo = chemotherapy regimen; CMR = complete molecular remission; CNS = central nervous system; CR = complete remission; CRS = cytokine release syndrome; DOR = duration of remission; FC = flow cytometry; G = grade; Mol = molecular for BCR-ABL; MRD+ = positive minimal residual disease; ND = not done; OS = overall survival; PR = partial response; TKD(m) = tyrosine kinase domain mutation; TKI = tyrosine kinase inhibitor; TTR = time to response.

Assi R et al. Clinical Lymphoma, Myeloma & Leukemia 2017;12:897-901.

Blinatumomab + TKIs : Overall survival



Assi R et al. Clinical Lymphoma, Myeloma & Leukemia 2017;12:897-901.

LAL Ph+ plan

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- Facteurs pronostics
- Devenir avant l'ère des inhibiteurs de tyrosine kinase
- Stratégies thérapeutiques de 1ère ligne: - jeune adulte
  - adulte âgé
- Prise en charge de la rechute
- **Impact de la MRD**

Impact of MRD after TKI in Ph+ ALL

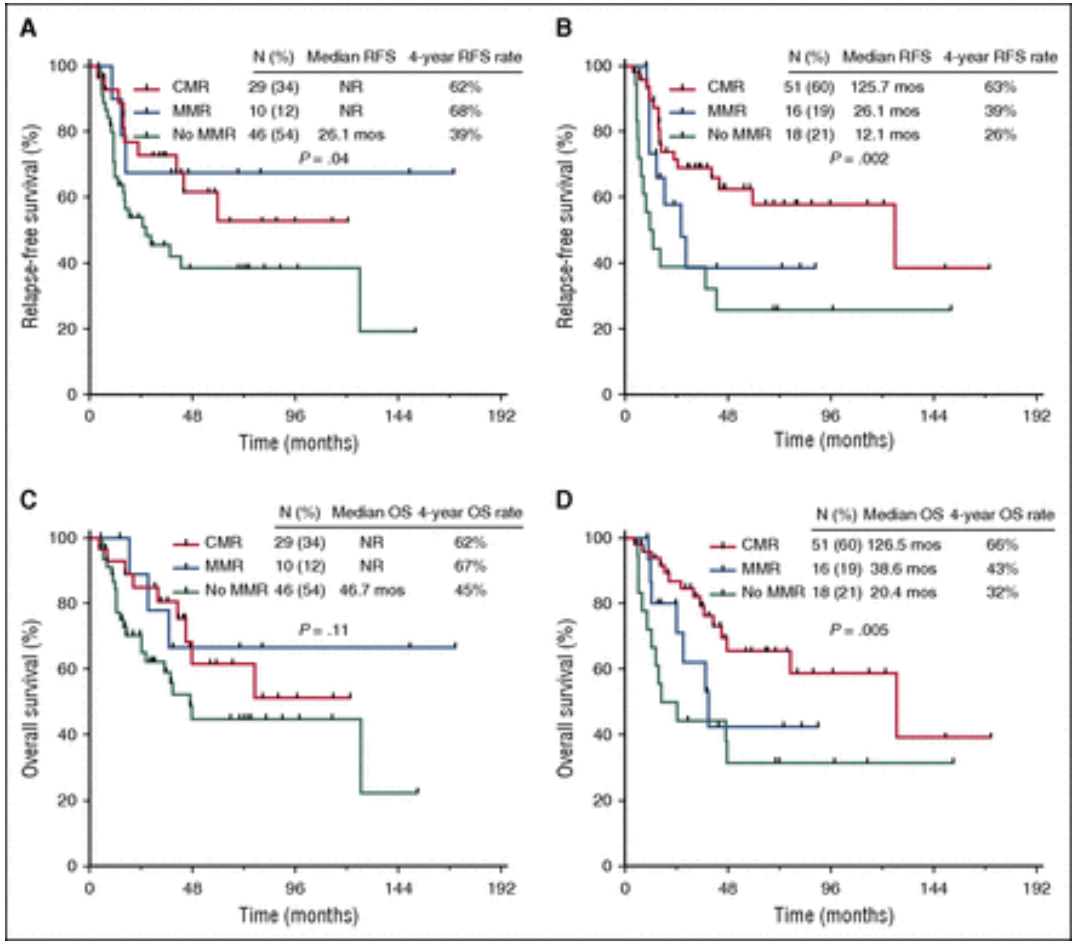
2001-2015 MD Anderson 202 ALL Ph+
HyperCVAD + TKI
(27% Ima, 46% Dasa, 27% Pona)

96% CR 196 pts
122 MRD at CR and at 3 mths
- 37 alloSCT
= 85pts included

CMR < 0,01%
MMolR < 0,1% or 3 log reduction of p190

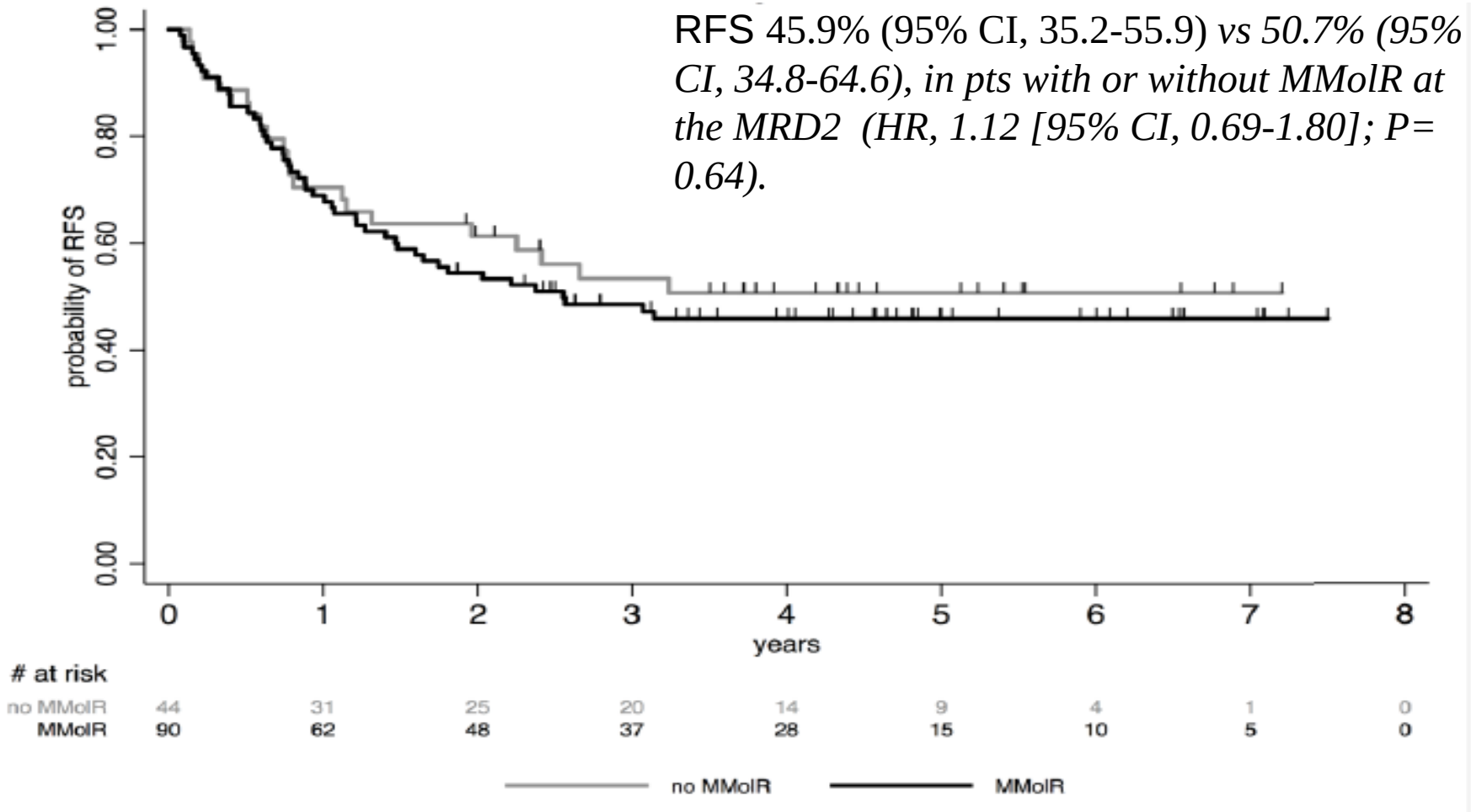
Multivariée
ACA HR 0,42 for RFS only
CMR 3 mo HR 0,41 for RFS and OS

MRD at CR MRD at 3 mths



NJ Short et al. Blood 2016;128:504

Impact of MRD2 level on alloHSCT outcome at 5 yrs: MMolR



RFS 45.9% (95% CI, 35.2-55.9) *vs 50.7% (95% CI, 34.8-64.6), in pts with or without MMolR at the MRD2 (HR, 1.12 [95% CI, 0.69-1.80]; P= 0.64).*

- **Similar results were observed for RFS in Mol CR and in OS**
- **No impact on post-allograft DFS and OS when MRD2 level was tested as a continuous log covariate**

Y. Chalandon et al. Blood 2015;125:3711

Imatinib post allogeneic HSCT

TABLE 1. Prospective Studies of the Use of TKIs After Allogeneic Hematopoietic Stem Cell Transplantation

Study	Type of TKI	Strategy	No.[a]	Median Treatment Duration, mo	Treatment Stop Due to Adverse Events	Relapse Rate	LFS	OS
Single-arm								
Wassmann 2005[17]	Imatinib	Preemptive	27 (including 2 autoHSCTs)	Not reported	Not reported	55% (8 mo)	Not reported	Not reported
Carpenter 2007[18]	Imatinib	Prophylactic	22 (ALL + CML)	11 (ALL)	9% (ALL + CML)	13% (ALL)	Not reported	80% (1.3 y, ALL)
Ribera 2010[10]	Imatinib	Prophylactic	13 (including 4 autoHSCTs)	9	20%	33%	Not reported	Not reported
Chen 2012[19]	Imatinib	Prophylactic	62	3	16%	10% (5 y)	82% (5 y)	87% (5 y)
Shimoni 2015[21]	Nilotinib	Prophylactic	16 (ALL + CML)	6 (ALL + CML)	37.5% (ALL + CML)	Not reported	Not reported	Not reported
Randomized								
Pfeifer 2013[20]	Imatinib	Prophylactic	26	7	67%[b]	8% (30 mo)	69% (5 y, all patients)	77% (5 y, all patients)
		Preemptive	29	4	71%[b]	17% (32 mo)		

Abbreviations: ALL, acute lymphoblastic leukemia; autoHSCT, autologous hematopoietic stem cell transplantation; CML, chronic myeloid leukemia; LFS, leukemia-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor.

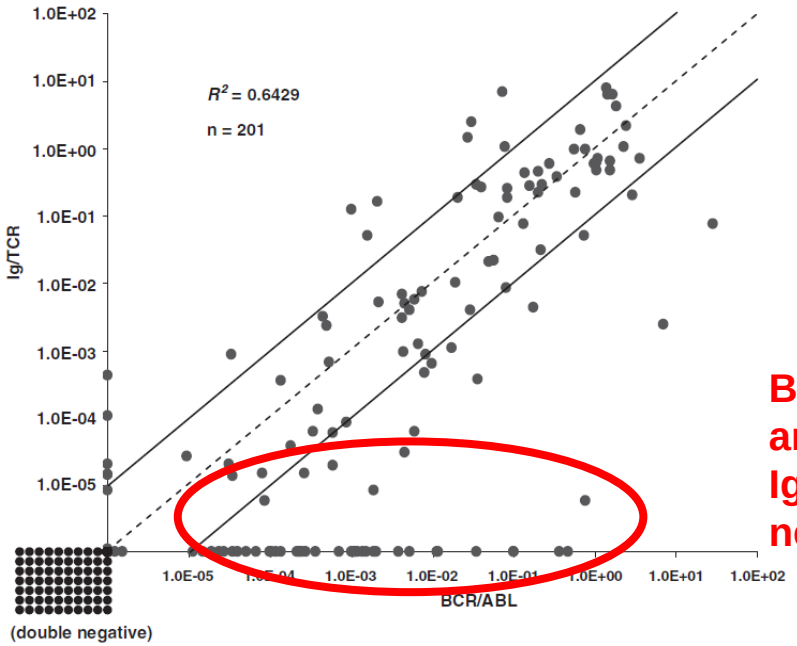
[a] For single-arm studies, only patients effectively treated with TKIs were considered.

[b] Treatment discontinuation for any reason.

Geibel S et al. Cancer 2016;122:2941-51

Comparison of BCR-ABL1 and Ig/TCR MRD in children Ph+ ALL

E.Clappier et al.
EHA 2018 Oral S1568



BCR-ABL positive and Ig/TCR low or negative

-> Lower sensitivity level for detection of Ig/TCR vs BCR-ABL1 ?

Zaliova, Leukemia 2009

-> Persistence of BCR-ABL1-positive, non lymphoblast cells?

23rd Congress of the European Hematology Association
Stockholm, June 17th 2018

Persistent BCR-ABL1 clonal hematopoiesis after blast clearance identifies a CML-like subgroup of Ph+ ALL: interim results from the GRAAPH-2014 trial

Emmanuelle Clappier

on behalf of the Group for Research in Adult Acute Lymphoblastic Leukemia (GRAALL)

Saint-Louis Hospital and Research Institute

Paris, France

GRAALL
LALA GOELAMS SAKK

Blinatumomab In MRD+ BCP-ALL The BLAST trial

- Phase II
- MRD-positive BCP-ALL
- Blina 15 mg/m²/day 4w on, 2w off
- 1 + 3 cycles
- Primary enpoint : MRD negativity rate
  - **Overall : 80%**
- **5 patients with Ph+ ALL**
  - **3 out 5 in MRD neg**

Gökbuget et al. Blood. 2018;131(14):1522-1531

Conclusions 1

- There has been major changes with the treatment combining new generations TKIs with chemo or with blinatumomab
- TKI plus CTx or plus steroid only→high CR rate with deeper MolR with 2nd and 3nd generation TKI→ may ↑ duration of CR
- BUT follow up too short and only non randomized studies with too few patients to draw any conclusion regarding possible cure

Conclusions

- There is a caveat when reducing too much the intensity of chemotherapy in consolidation cycles when combining it with 2nd generation TKI as it leads to decreased DFS and also with selection pressure on T315I mutation with Rel
- Chemo-free therapy combining 2nd or possibly better, 3rd generation TKI + blinatumomab seems promising with high rate of MolR, high OS and DFS but the follow up is also still short as well as the lack of randomized studies to be able to draw firm conclusion on long term effects and possible cure. Concerns with CNS relapse→ may need nevertheless some chemo (MTX, ARA-C, it).
- Probably there is a proportion of patients, mainly the one being in complete MolR, who may be cured with the chemo-free regimen

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