University of Modena and Reggio Emilia
Department of Medical and Surgical Sciences

"Therapeutic approaches to relapsed Philadelphia-positive ALL"

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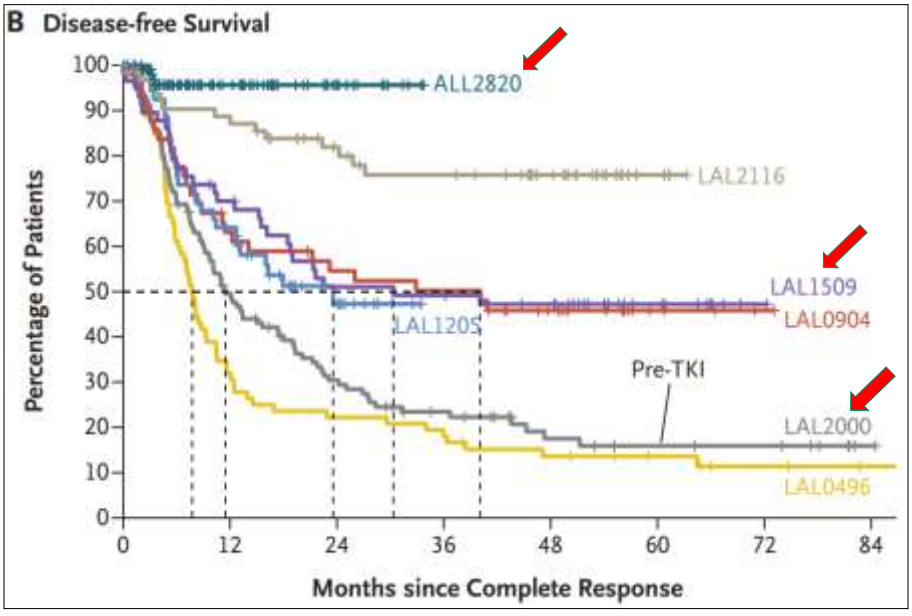
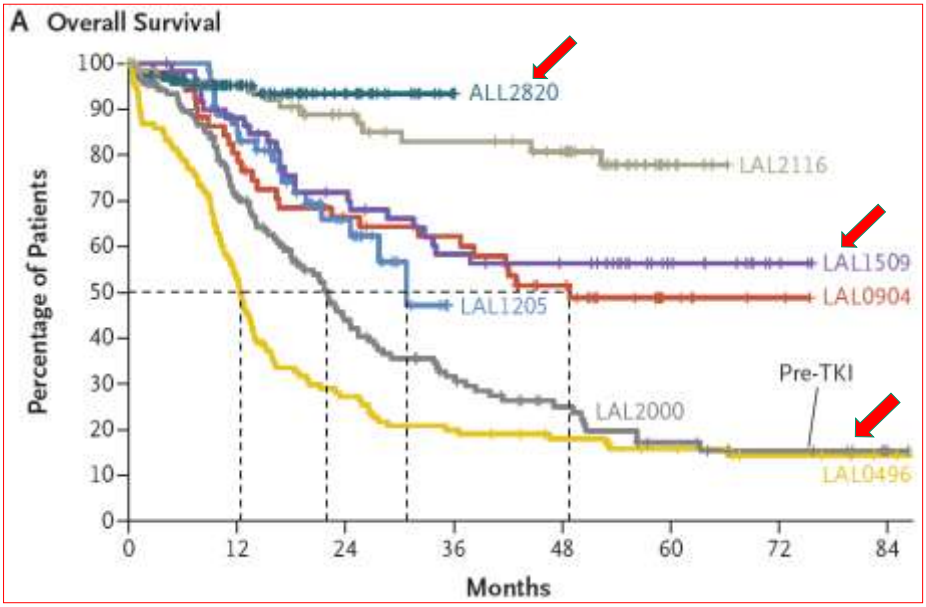


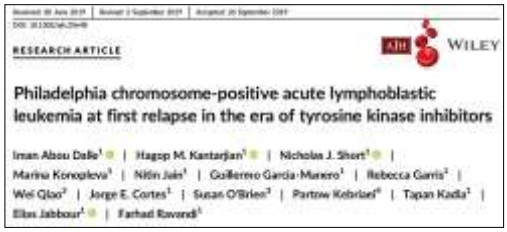
R/R Ph+ ALL: the magnitude of this issue accross different treatment eras
Foà R. N Engl J Med 2025



R/R Ph+ ALL: the magnitude of this issue accross different treatment eras

Foà R. N Engl J Med 2025

Total N = 57 patients	At first relapse, N (%) - Median [Range]
CNS Involvement	22 (39)
Isolated CNS relapse	14 (25)
MRD recurrence/persistence before overt relapse	24 (42%)
Time from MRD recurrence to overt relapse (months)	3.9 [0.5-26]
Phase of treatment	
Consolidation phase	1 (2)
Maintenance phase	42 (73)
After allogeneic stem cell transplantation	5 (9)
Completed therapy	5 (9)
None - Noncompliance	3 (5)
Blinatumomab	1 (2)
TKI received at the time of relapse	
Imatinib	16 (28)
Dasatinib	30 (53)
Nilotinib	2 (4)
Ponatinib	3 (5)
None	6 (10)


RESEARCH ARTICLE

WILEY

Philadelphia chromosome-positive acute lymphoblastic leukemia at first relapse in the era of tyrosine kinase inhibitors

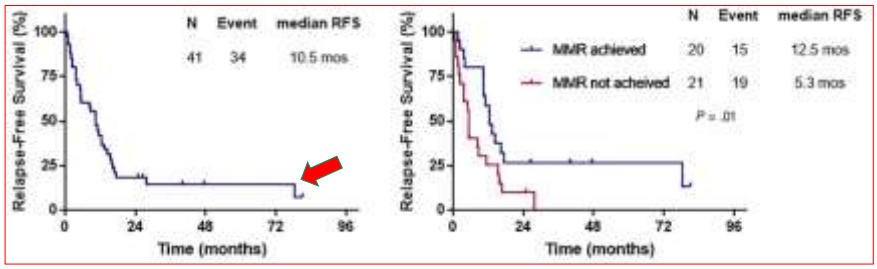
Overall, **20-30%** of patients receiving **Hyper-CVAD combined with TKI experienced relapse**

Patients who received **MRD-directed treatments** had a longer time to overt relapse (5.3 vs 2.4 months, p=0.002)

In 53% of the examined cases, **ABL1 kinase domain mutations** were detected, mainly T315I

75% patients received TKI in combination with other salvage treatments, with **CR2 rates** with incorporation of TKI ranging from **80% to 100%.** Of note, only 56% of patients changed to a different TKI

Abou Dalle et al, Am J Hematol 2019



Survival outcomes

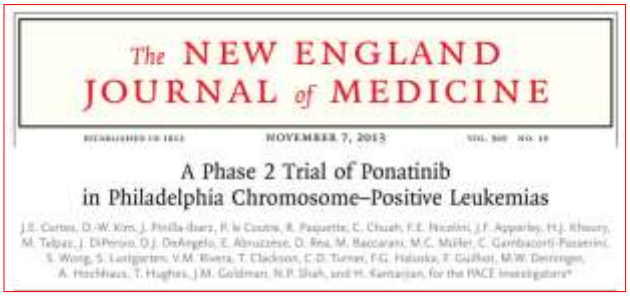
MMR was achieved in 66% of patients after a median of 1.8 months from start of salvage treatment.

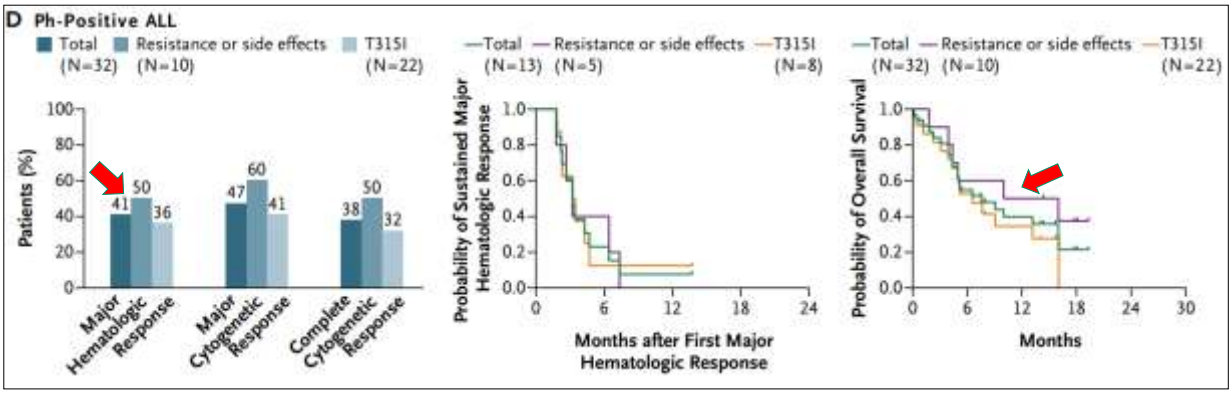
41% of patients received allo-HSCT in CR2

Abou Dalle et al, Am J Hematol 2019

	Multivariate Model for OS		Multivariate Model for RFS	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Duration of CR1 ≥ 12 months	1.28 (0.56,2.89)	.56	-	-
LDH ≥ 1200 IU at relapse	2.82 (1.11,7.16)	.029	-	-
ECOG status at relapse (≥2 vs <2)	1.98 (0.88,4.47)	.097	-	-
MMR achieved at CR2	0.39 (0.16,0.94)	.035	0.48 (0.23,0.98)	.04
Imatinib or No TKI vs others	2.39 (1.07,5.39)	.034	1.53 (0.64,3.66)	.33

"Ponatinib–based approaches in R/R Ph-positive ALL"





Single-agent ponatinib in R/R Ph+ ALL: results from the PACE trial

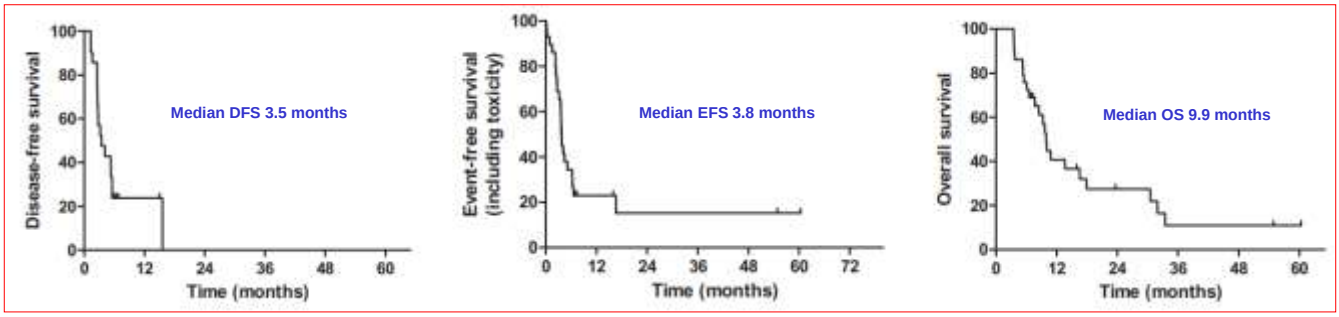
Cortes et al, N Engl J Med 2013

Major hematologic response in 41% of patients
1-year OS 40%, 1-year PFS 7%

Ponatinib alone or combined with mild chemotherapy: results from the OPAL retrospective analysis

Tavitian et al, Leuk Lymphoma 2020

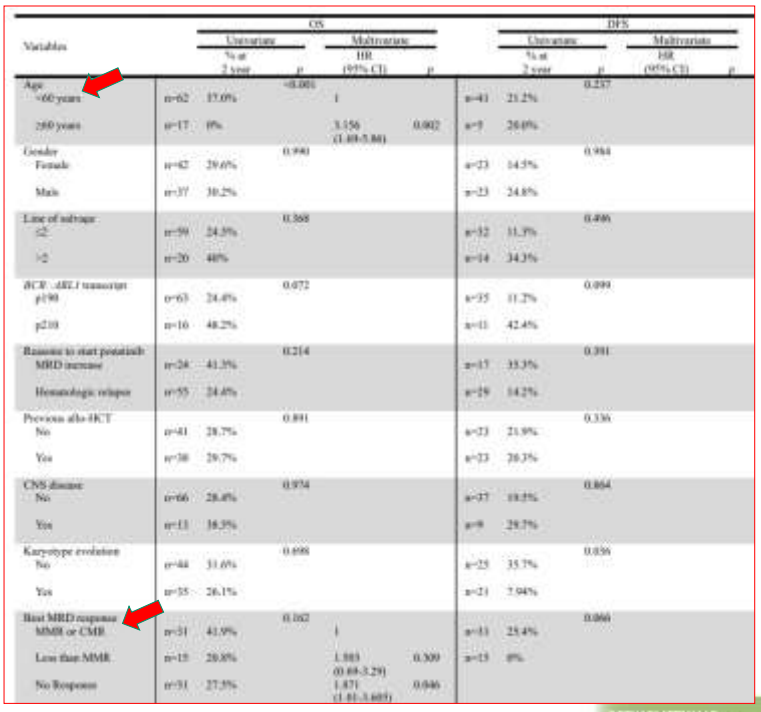
- 93% of the 29 patients had previously received **at least one 2G-TKI**
- BCR::ABL1 kinase domain mutations in 57% of evaluable cases
- **91%** of patients achieved **morphologic CR**



Ponatinib monotherapy for hematologic (55 cases) or MRD (24 patients) relapse: a real-world retrospective analysis

Min et al, Acta Haematol 2025

- **CR** obtained in **60.7%** of patients
  - **CMR** in **47.8%** of cases
  - Poor 2-year **OS 29.5%**
  - **Allo-HSCT** performed in 38 patients, with 2-year OS 29.1%
- In MVA **age under 60 years and MRD response** better than MMR were linked to **improved OS**

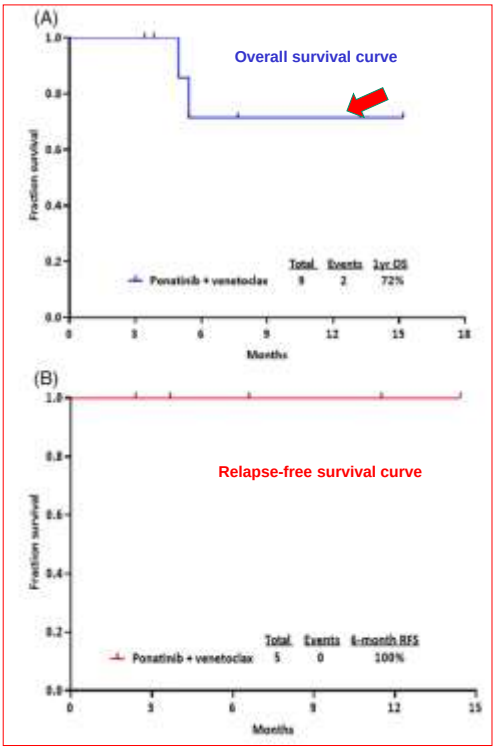


Variables		OS				DFS			
		Univariate		Multivariate		Univariate		Multivariate	
		% at 2 year	p	HR (95% CI)	p	% at 2 year	p	HR (95% CI)	p
Age			<0.001				0.237		
<60 years	n=62	37.0%		1		n=41	21.2%		
≥60 years	n=17	0%		3.156 (1.69-5.86)	0.002	n=9	28.6%		
Gender			0.941				0.984		
Female	n=42	29.6%				n=23	14.5%		
Male	n=37	30.2%				n=23	24.8%		
Line of salvage			0.368				0.406		
≤2	n=59	24.5%				n=32	11.3%		
>2	n=20	48%				n=14	34.3%		
BCR -ABL1 transcript			0.072				0.099		
p190	n=63	24.4%				n=35	11.2%		
p210	n=16	48.2%				n=11	42.4%		
Reasons to start ponatinib			0.214				0.391		
MRD increase	n=24	41.3%				n=17	33.3%		
Hematologic relapse	n=55	24.4%				n=29	14.2%		
Previous allo-HCT			0.891				0.336		
No	n=41	28.7%				n=23	21.9%		
Yes	n=38	29.7%				n=23	20.3%		
CNS disease			0.974				0.864		
No	n=66	28.4%				n=37	18.5%		
Yes	n=13	38.5%				n=9	28.7%		
Karyotype evolution			0.698				0.036		
No	n=44	31.6%				n=25	35.7%		
Yes	n=35	26.1%				n=21	7.94%		
Best MRD response			0.002				0.066		
MMR or CMR	n=31	41.9%		1		n=11	25.4%		
Less than MMR	n=15	20.8%		1.503 (0.69-3.29)	0.309	n=13	8%		
No Response	n=31	27.5%		1.871 (1.01-3.465)	0.046				

An effective chemotherapy-free regimen of ponatinib plus venetoclax for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia

Short et al, Am J Hematol 2021

- **9 heavily pretreated patients** (with a median of 3 prior regimens, including 78% having received ponatinib)
  - **CR/CRi in 56%** of cases
- **1-year OS 72%,** a result comparing favorably with the PACE trial



	Newly diagnosed Ph-positive acute lymphoblastic leukaemia cohort (n=40)	Relapsed or refractory Ph-positive acute lymphoblastic leukaemia cohort (n=14)
Haematological responses*		
Overall response	27/28 (96%)	12/13 (92%)
Complete response	26/28 (93%)	11/13 (85%)
Complete response with incomplete hematologic recovery	1/28 (4%)	1/13 (8%)
Partial response	0	0
No response	0	1/13 (8%)
Early death	1/40 (3%)	0
Molecular responses†		
Complete molecular response		
Overall	33/38 (87%)	11/14 (79%)
After cycle one	26/38 (68%)	10/14 (71%)
After cycle two	31/38 (82%)	11/14 (79%)
After cycle five and maintenance	33/38 (87%)	..
Major molecular response or better	36/37 (97%)	12/14 (86%)
No major molecular response or complete molecular response	1/38 (3%)	2/14 (14%)
Survival analysis		
1-year event-free survival	95 (80–99)	57 (28–78)
Number of events	2 (5%)	7 (50%)
1-year overall survival	95 (80–99)	79 (47–93)
Number of events	2 (5%)	5 (36%)

Efficacy of a chemo-free approach based on ponatinib and blinatumomab also in R/R Ph+ ALL: the MDACC experience

Jabbour et al, Lancet Haematol 2023

85% of patients obtained CR, after one treatment cycle

CMR in 79% of cases

46% of responders (6 cases) proceeded to **allo-HSCT**

Encouraging **survival outcomes**

LEUKEMIA & LYMPHOMA
2021, VOL. 62, NO. 3, 635–639
Taylor & Francis

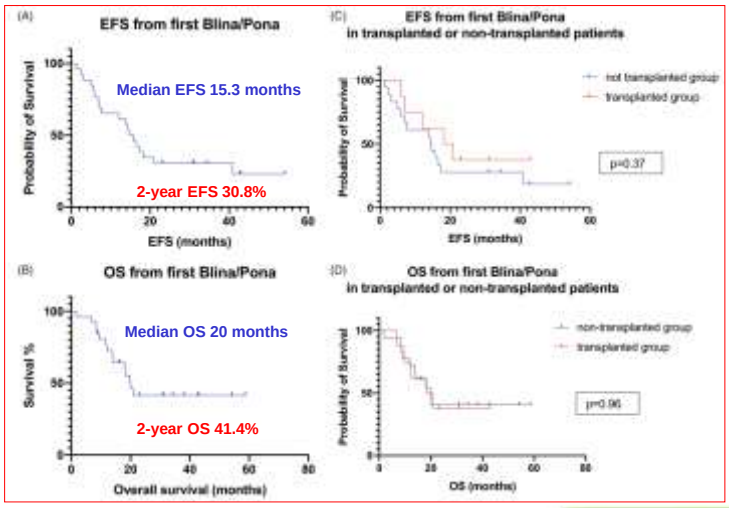
ORIGINAL ARTICLE

Blinatumomab + ponatinib for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia in adults

Marie-Anne Couturier[a], Xavier Thomas[b], Emmanuel Raffoux[c], Françoise Huguet[d], Céline Berthon[e], Célestine Simand[f], Maria-Pilar Gallego-Hernanz[g], Yosr Hicheri[h], Mathilde Hunault Berger[i], Colombe Saillard[j], Thibaut Leguay[k], Clémence Loiseau[l], Marie-Christine Béné[m,n] and Patrice Chevallier[o]

- Morphologic **CR 96.2%**
- **CMR** rate **88.5%**
- 8 (32%) patients underwent **allo-HSCT**

N = 26 Ph + ALL	
Median age: years (range)	58 (18–81)
Gender	
Male/female	14/12
Status at diagnosis	
De novo Ph + ALL/Blast crisis of CML	22/4
Central nervous system disease	1
Extramedullary disease	2
p190 protein/p210 protein/unknown	16/9/1
Status at the time of blina/pona	
First relapse	12
Second relapse or more	13
Primary refractory	1
Previous allograft (sibling/MUD)	9 (4/5)
Previous autograft	5
Molecular status	
No mutation	14
p.T315I mutation	8
p.T315I + p.E255K	1
p.Y253H mutation	1
p.E255K mutation	1
p.F371L + Y253H mutations	1
Previous TKI	
1	8
2	14
3	4



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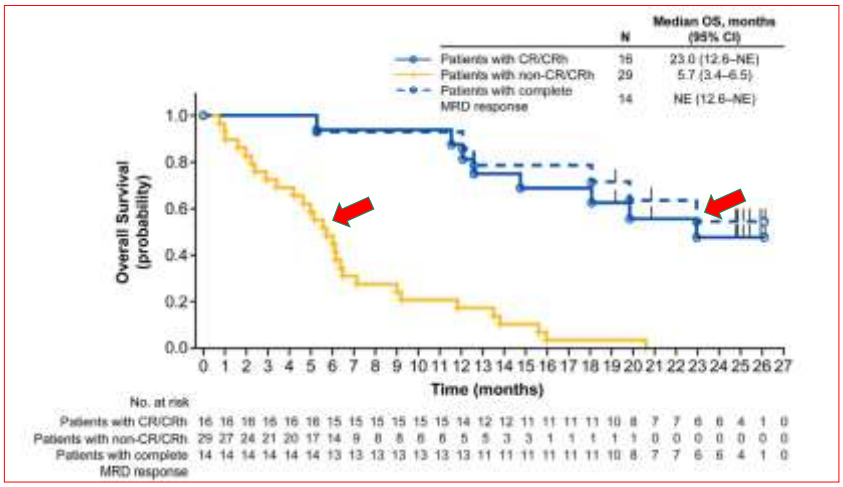
More on immunotherapeutic strategies: the ALCANTARA study

Martinelli et al, J Clin Oncol 2017; Martinelli et al, Eur J Cancer 2021

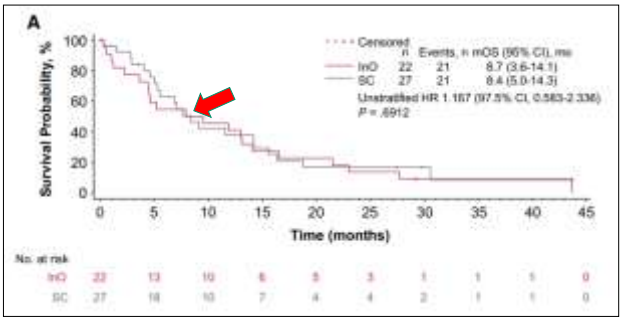
- 16 of 45 (**35.6%**) patients obtained **CR/CRh** within the first two **Blinatumomab** cycles
- Median **RFS 6.8 months**
- Median **OS 9.0 months** for the whole cohort
- **MRD response** observed in 14 (87.5%) CR/CRh responders
- 9 patients (20%) received allogeneic **HSCT**



More on immunotherapeutic strategies: the 1010 and INOVATE trials

Kantarjian et al, N Engl J Med 2016; Stock et al, Cancer 2021

Efficacy Endpoints	Study 1022 InO (n = 22)	Study 1022 SC (n = 27)	Study 1022 P	Study 1010 InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])
OS				
Median, mo (95% CI)	8.7 (3.6-14.1)	8.4 (5.0-14.3)		7.4 (4.3-11.3)
HR (95% CI)	1.17 (0.64-2.14)		.6912	—
PFS				
Median, mo (95% CI)	3.9 (2.1-9.2)	3.1 (1.1-6.2)		4.4 (1.8-5.9)
HR (95% CI)	0.65 (0.34-1.25)		.0963	—

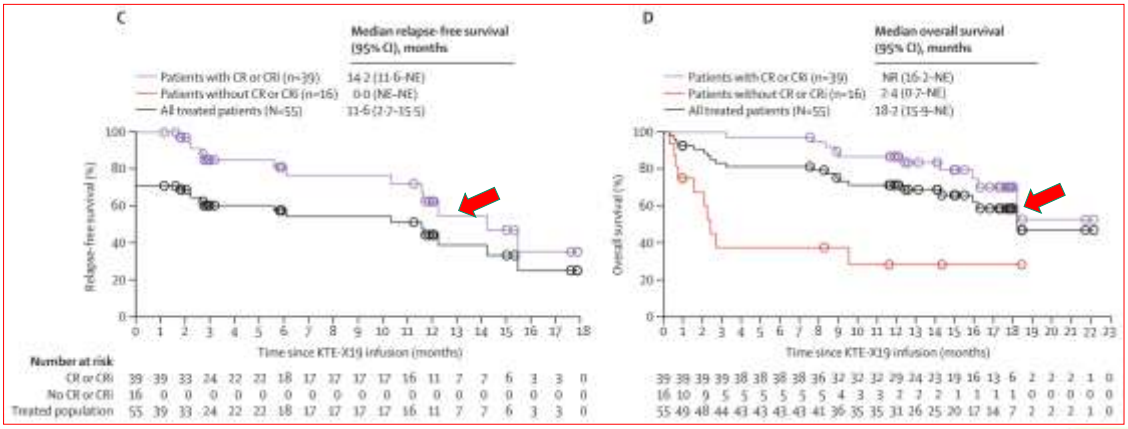


- **Higher CR/CRi** and MRD-negativity rates with **Inotuzumab-Ozogamicin**
- **HSCT rate** in study 1022 was 41% versus 19% for InO versus SC.
- However, there was **no benefit in survival outcomes** (median OS: 8.7 vs 8.4 months)

More on immunotherapeutic strategies: anti-CD19 CAR-T cells

Shah et al, Lancet 2021

- 15 of the 55 **(27%) patients** who received **Brexu-cel** infusion in ZUMA-3 trial were Ph+.
- **CHR** achieved on **71%** of patients, and *BCR::ABL1* positivity had no impact on response, RFS and OS

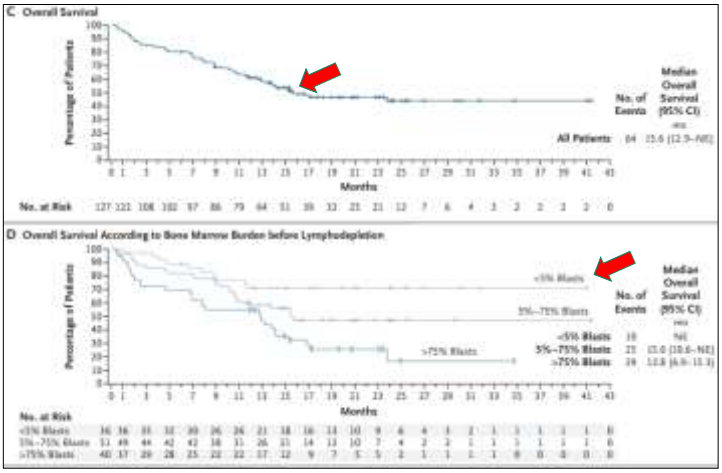


More on immunotherapeutic strategies: anti-CD19 CAR-T cells

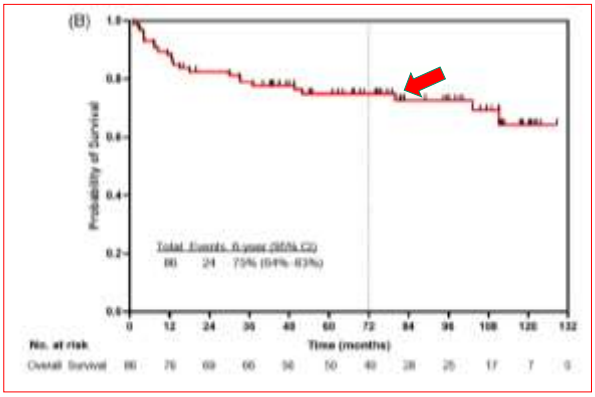
Roddie et al, N Engl J Med 2024

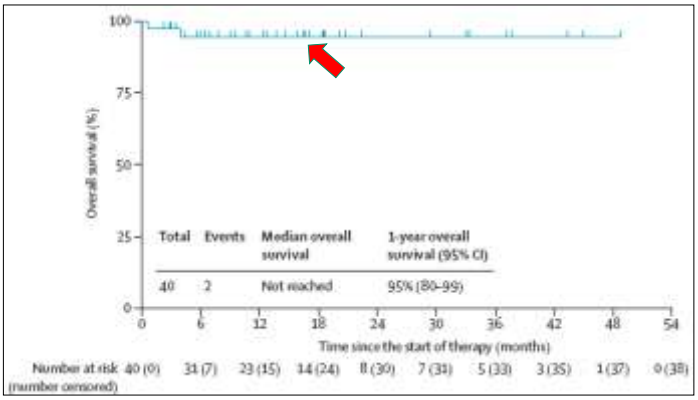
- 36 of the 127 **(28%) patients** who received **Obe-cel** infusion in FELIX trial were Ph+.

- **Median EFS 11.9 months**, with estimated 12-month EFS 49.5%.
- **Median OS 15.6 months**, with estimated 12-month OS 61.1%
- **BM burden** before lymphodepletion correlated with survival outcomes



What about Ph+ ALL relapsing after frontline ponatinib containing treatments?





Frontline combination of ponatinib and Hyper-CVAD: 80-months follow-up results of MDACC phase 2 study

Kantarjian et al, Am J Hematol 2023

Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial

Jabbour et al, Lancet Haematol 2023

First results of the Phase III GIMEMA ALL2820 trial comparing ponatinib plus blinatumomab to imatinib and chemotherapy for newly diagnosed adult Ph+ acute lymphoblastic leukemia patients

S. Chiaretti, M. Di Trani, C. Skert, L. Elia, G. Almici, I. Della Starza, D. Cardinali, V. Bellomarino, S. Soddu, M. Messina, M.R. Marino, M.S. De Propris, E. Borlenghi, F. Di Raimondo, M. Ansuinelli, C. Alati, D.G. Mattei, V. Mancini, P. Chiusolo, B. Scappini, M.P. Martelli, P. Salutari, M. Cerrano, B. Serio, A. Cucca, M. Luppi, D. Vallisa, C. Pasciolla, C. Romani, M. Chiarucci, F. Mosna, M. Bonifacio, N.S. Fracchiolla, M. Bocchia, S. Imbergamo, C. Califano, G.R. Nunziata, M. Annunziata, A. Mulé, P. Zappasodi, F. Giglio, D. Pietrasanta, M. Della Porta, M. Musso, M. Lunghi, F. Zaja, E. Todisco, C.M. Basilico, A. Piciocchi, P. Fazi, A. Rambaldi, R. Foà

SAPIENZA UNIVERSITÀ DI ROMA

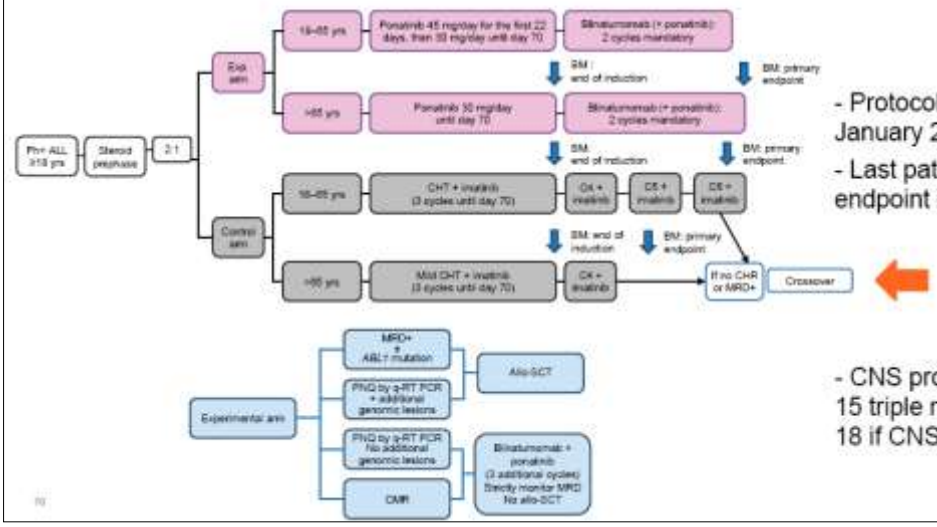
fondazione GIMEMA onlus

Oral communication, ASH Congress 2025

SCENARI ATTUALI E PROSPETTIVE FUTURE NEL TRATTAMENTO DELLE LAL PH+

GIMEMA ALL2820 Phase III Trial

Frontline treatment of adult Ph+ ALL (≥18 years, no upper age limit) with ponatinib plus steroids followed by blinatumomab compared to chemotherapy with imatinib



- Protocol closed to enrolment in January 2025.
- Last patient reached primary endpoint in June 2025.

- CNS prophylaxis strengthened: 15 triple medicated lumbar punctures 18 if CNS+ at diagnosis.

GIMEMA ALL2820. Hematologic responses

End of induction (d +70)	Experimental arm (n=158)	Control arm (n=78)	p
CHR	149 **(94.3%)**	62 **(79.4%)**	**0.004**
Deaths	4 **(2.5%)**	8 **(10.2%)**	
Refractory	-	1 **(1.3%)**	
Off-treatment	5 **(2.8%)**	7 **(8.9%)**	

GIMEMA ALL2820. Molecular responses by ITT

Experimenal arm (n=158)	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)
End of induction	84 (53.2)	48 (30.4)	26 (16.5)	**74 (46.8)**
After 2 blina cycles	46 (29.1)	82 (51.9)	30 (19)	**112 (70.9)**
Control arm (n=78)				
End of induction	44 (56.4)	28 (35.9)	6 (7.7)	**34 (43.6)**
After 4/6 CHT cycles*	40 (51.3)	29 (37.2)	9 (11.5)	**38 (48.7)**

*Depending on age

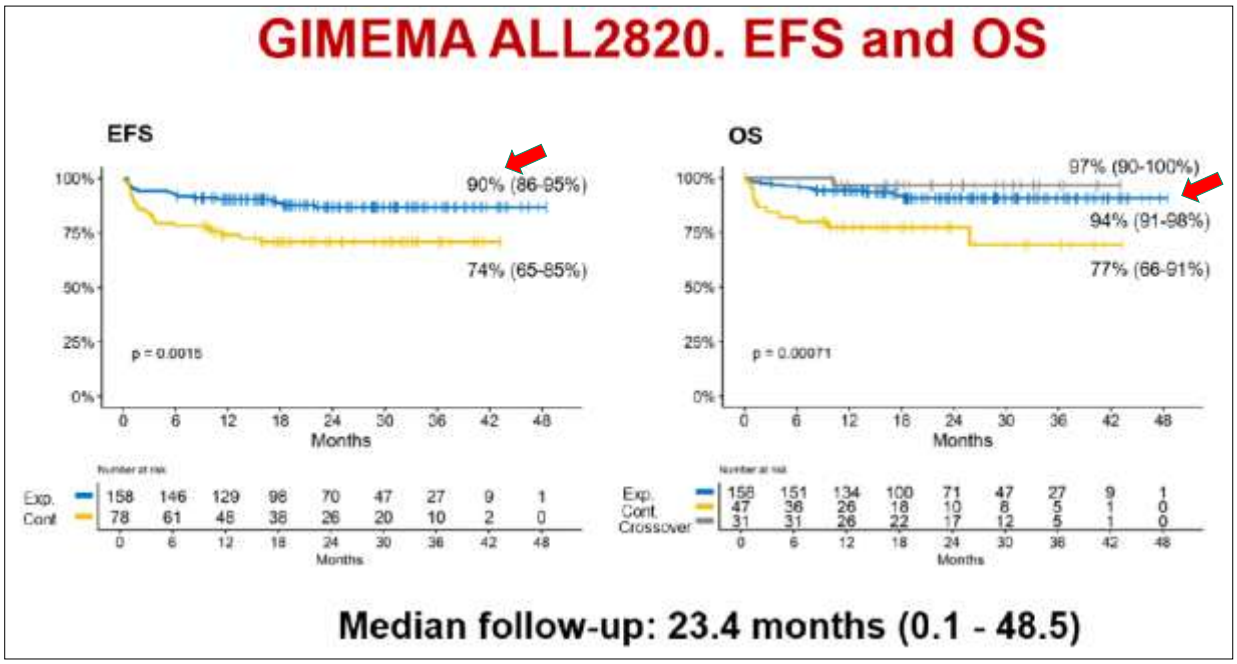
D-ALBA (n=63):	Overall molecular responses (%)
End of induction	**17 (26.9)**
After 2 blina cycles	**33 (52.4)**

p= <0.001

GIMEMA ALL2820. Relapses and deaths in CHR

Relapses	Experimental arm (n=149)	Control arm (n=62)
Overall	9 (6%)	5 (8%)
On trial	6	5
Off treatment	3	-
Median time to relapse	5.6 (2.6- 21.9)	11.3 (3.5-15.8)
BM/CNS/other	6/1/2	5/0/0
Age	53	57
WBC x10^9/l (median, range)	36 (2-207)	12 (10-27)
p190/p210	8/1	3/2
IKZF1^{del}	4	2
Mutations	3 (2 T315I, 1 E255K + Y253H)	3 (2 E255K, H295P)
Ph- relapse	1	1

Deaths	Experimental arm (n=149)	Control arm (n=62)
Overall	7 (4.7%)	5 (8%)
Age	61 (40.8-83.8)	72 (60.6-74)
Causes of death:		
Pneumonia	2 (1 viral, 1 bacterial)	-
Cardiac arrest	1	
Septic shock		3
Post-AlloSCT	4	-
Pulmonary hemorragy	-	3
MOF	-	1



Chiaretti et al, ASH Congress 2025

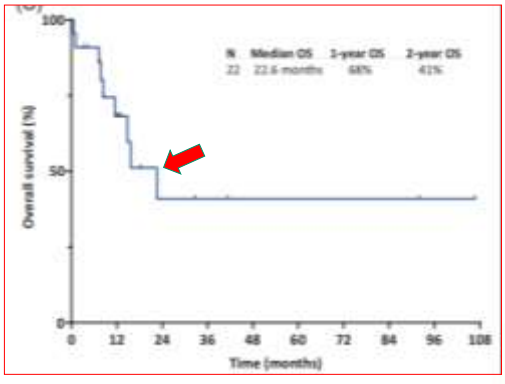
CORRESPONDENCE

WILEY

Characteristics and outcomes of patients with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia after failure of a frontline ponatinib-containing therapy

Short et al, Am J Hematol 2024

- **22 out of 201 (10.9%)** patients experienced treatment failure following ponatinib-containing regimens (16 in combination with chemotherapy and 6 chemo-free regimens). No patients had prior allo-HSCT.
- 7 cases (32%) **extramedullary relapse** (mainly CNS)
- **T315I** in 31% of analyzed samples
- All patients received **TKI-based salvage therapy**, ponatinib in 40% of cases, but not TKI monotherapy
- **80%** of cases received blinatumomab, InO or CAR-T
- Second remission in 90% of cases
- Five patients (**28%**) proceeded to **HSCT in CR2**



Journal of Hematology & Oncology

RESEARCH Open Access

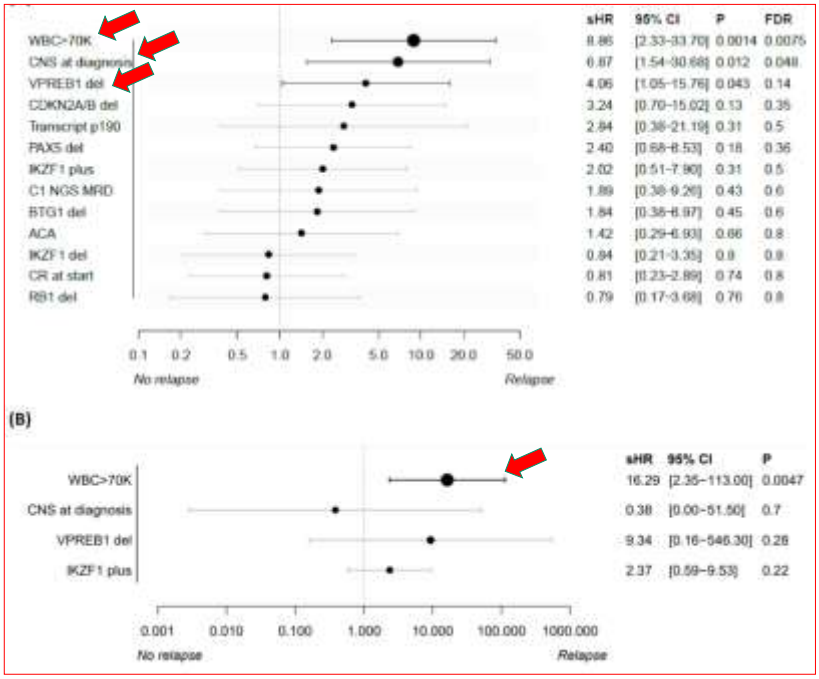
Molecular characterization and predictors of relapse in patients with Ph + ALL after frontline ponatinib and blinatumomab

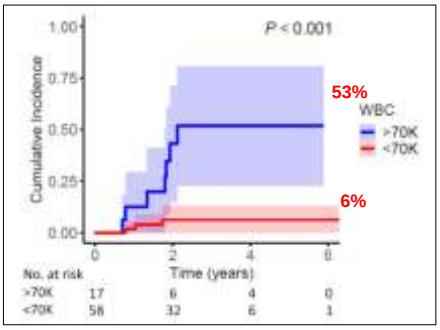
Nicholas J. Short[1†], Hagop Kantarjian[1], Ran Furudate[1†], Nitin Jain[1], Farhad Ravandi[1], Omer Kantar[1], Sanam Loghavi[2], Lewis Nasr[1], Fadi G. Haddad[3], Jayastu Senapati[3], Rebecca Garris[1], Koichi Takahashi[1†] and Elias Jabbour[1*†]

- Among the 76 treated patients, **13% experienced relapse**
- Median **time to relapse** 18 months
- **Isolated CNS relapse** in 5 cases
- **CD19 expression** remained high at relapse in all patients

Table 2 – Clinical and molecular characteristics of relapsed patients

Patient	Age	WBC at diagnosis (x 10^9/L)	Transcript type	Mutations (targeted sequencing)	Gene deletions (SNP array)	NGS MRD response after C1	PCR MRD response after C1	Duration of CR1 (months)	Type of relapse
#1	57	2.0	p190	*IKZF1*	*CDKN2A/B, PAX5, VPREB1, BTG1, RB1, XBP1*	Negative	CMR	8.6	Peritoneum and lymph nodes (Ph-negative)
#2	60	322.1	p190	*IKZF1*	*CDKN2A/B, PAX5*	Not done	CMR	24.5	Bone marrow
#3	44	152.6	p190	None	*CDKN2A/B*	Positive (1/million)	CMR	7.6	Bone marrow
#4	18	4.5	p190	None	Not done	Positive (below LOD)	CMR	11.3	Bone marrow
#5	48	95.5	p190	None	*IKZF1, CDKN2A/B, PAX5, BTG1*	Not done	Not done	17.0	Bone marrow + vitreous fluid
#6	28	270.5	p190	Not done	*IKZF1, CDKN2A/B, PAX5, VPREB1*	Not done	CMR	22.0	CNS
#7	43	12.9	p190	*BCORL1*	*IKZF1, VPREB1*	Negative	CMR	19.8	CNS
#8	49	84.9	p190	None	*IKZF1, CDKN2A/B, RB1, XBP1*	Not done	CMR	23.2	CNS
#9	44	236.7	p190	None	*IKZF1, CDKN2A/B, XBP1*	Positive (57/million)	CMR	8.5	CNS
#10	70	181.2	p210	*DNMT3A, SF3B1, TET2*	*IKZF1*	Positive (below LOD)	CMR	20.7	CNS





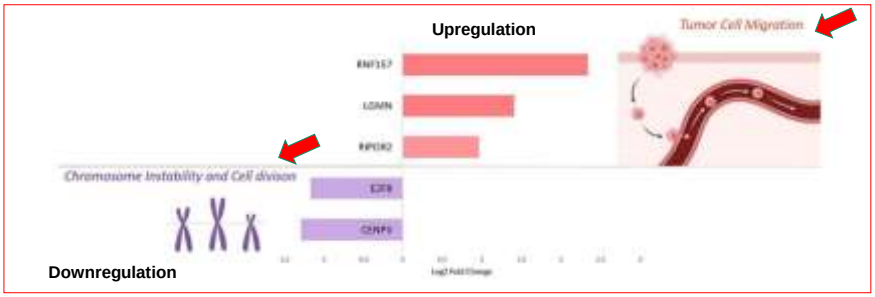
WBC count ≥70 x 10^9/L was independently associated with an **increased risk of relapse**, superseding the prognostic value of early MRD clearance and baseline genomic alterations such as *IKZF1*^{plus} genotype

Short et al, J Hematol Oncol 2025

A focus on CNS relapse

Chiaretti and Foà. Blood 2025; Foà et al, N Engl J Med 2020; Jabbour et al, Lancet Haematol 2023

- While overall improving survival, **chemo-free regimens**, which **omit systemic HD-MTX and Ara-C**, could predispose to a **higher relative risk of CNS relapses (nearly half of relapse cases)**
- **CNS penetration** with targeted compounds is less effective
- Number of lumbar punctures with **prophylactic TIT increased to 15** in recent clinical trials
- Suggestion to administer **2 cycles of HD chemotherapy** to patients with **WBC count ≥70 x 10^9/L**
- **Molecular profiling** to identify patients at higher risk of CNS dissemination (Sapienza et al, Hematol Oncol 2023)



Further strategies for R/R Ph-positive ALL:

allosteric BCR::ABL1 inhibitor or **newer 3G-TKI** as monotherapy or in combinational approaches

Kondo. Br J Haematol 2024

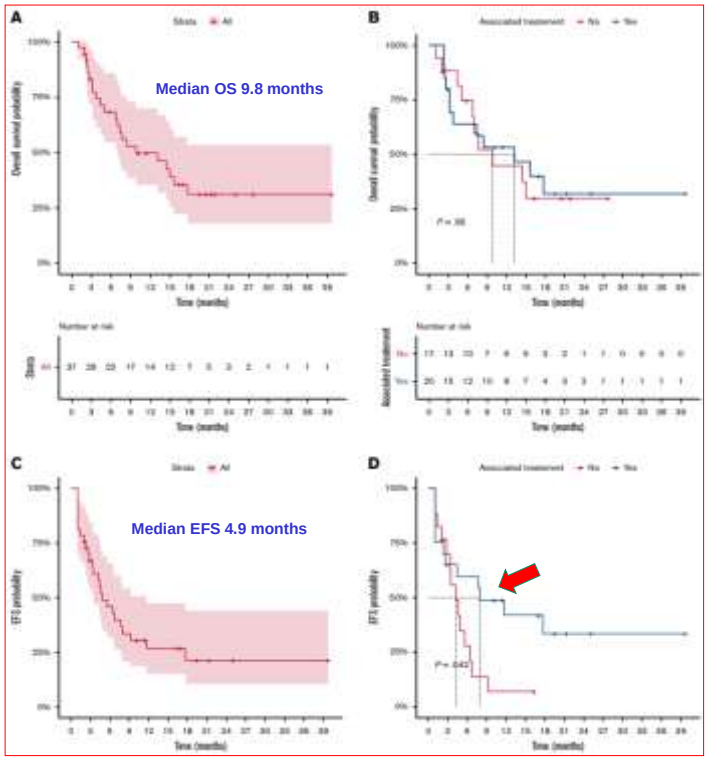
1G-TKI	Imatinib 2001 FDA 2001 EMA					
2G-TKI		Dasatinib 2006 FDA 2006 EMA	Nilotinib 2007 FDA 2007 EMA	Bosutinib 2012 FDA 2013 EMA	Radotinib 2012 Korea	Flumatinib 2019 China
	Neither nilotinib nor bosutinib is approved for Ph-positive ALL.					
3G-TKI					Ponatinib 2012 FDA 2013 EMA	Olverembatinib 2021 China
STAMP-I **(Specifically Targeting the ABL Myristoyl Pocket – inhibitor)**						Asciminib 2021 FDA 2021 EMA

Asciminib: the EWALL-OBS22 retrospective observational study

Chanut et al, Blood Adv 2025

Disease type, n (%)	
R/R Ph+ BCP-ALL	33 (80.5)
LBC-CML	8 (19.5)
No. of previous TKIs, median (min-max)	3 (2-5)
Previous use of ponatinib, n (%)	38 (92.7)
Prior CAR T-cell therapy, n (%)	2 (4.8)
Prior allo-HSCT, n (%)	18 (43.9)
Previous line of therapy, n (%)	41
First line (LBC-CML)	2 (4.9)
Second line of treatment	7 (17.1)
Third line of treatment or more	32 (78)
Disease status, n (%)	
Hematological relapse	24 (58.5)
Refractory	5 (12.2)
CNS-only relapse	1 (2.4)
Molecular relapse	7 (17.1)
Complete remission (intolerance)	4 (9.8)
CNS involvement at time of ASC initiation, n (%)	8 (19)

ABL mutations analyzed before ASC treatment, n (%)	35 (85.4)
Absence of mutations, n (%)	8 (22.9)
Presence of mutations, n (%)	27 (77.1)
T315I	14 (51.9)
E255V/K	2 (7.4)
T315I + E255V	3 (11.1)
T315I + E255K + M244T	1 (3.7)
T315I + V299L	1 (3.7)
E255K + G250E + Y253H	1 (3.7)
F311L	1 (3.7)
F317L	1 (3.7)
Y253H	1 (3.7)
E255K + E255V	1 (3.7)
T315A + V299L	1 (3.7)
ASC dose, n (%)	
High dose (200 mg twice daily)	34 (82.9)
Low dose (40 mg twice daily)	7 (17.1)
Associated treatment, n (%)	41
ASC monotherapy, including 2 patients with ITT, n (%)	20 (48.8)
ASC in combination, n (%)	21 (51.2)
High dose chemotherapy	2 (4.9)
Low dose chemotherapy	8 (19.5)
Immunotherapy (blinatumomab or InO)	6 (14.6)
Other TKI	3 (7.3)
DLI	1 (2.4)
CAR T cell	1 (2.4)



Parameters	Value (%) or range (min, max)
Hematological response rate (efficacy population), n (%)	36
CR	28 (77.8)
CRi	2 (5.6)
Failure	6 (16.7)
MRD response in CR + CRi patients with evaluable bone marrow samples, n (%)	23
No CMR	10 (43.5)
CMR (BCR ABL <0.01% in bone marrow)	13 (56.5)
Post ASC treatment, n (%)	37
No HSCT or CAR T cells	27 (73)
Allo-HSCT	3 (8)
CAR T cell	5 (13.5)
Allo-HSCT + CAR T cell	2 (5.4)

High response rates with asciminib-based regimens in a real-life cohort of R/R Ph+ ALL

29% of patients bridged to a **cellular therapy**

Higher EFS when asciminib was used **in combination**, compared with monotherapy

Chanut et al, Blood Adv 2025

ELSEVIER

Blood 146 (2025) 1572–1573

The 67th ASH Annual Meeting Abstracts

POSTER

613. ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES EXCLUDING ALLOGENEIC TRANSPLANTATION

Asciminib for relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) and lymphoid blast crisis of chronic myeloid leukemia (LBC-CML) in Italy: A Campus ALL real life study

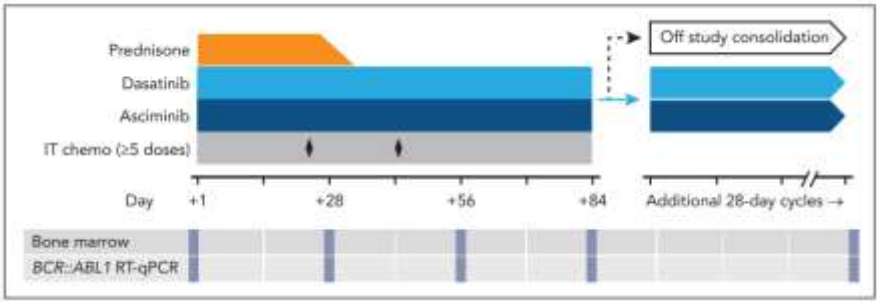
Matteo Dragani[1], Patrizia Chiusolo[2], Giulia Rivoli[1], Marco Cerrano[3], Lara Aprile[4], Erika Borlenghi[5], Benedetta Cambò[6], Eleonora De Bellis[7], Marzia Defina[8], Ludovica Fucci[9], Rachele Giubbolini[10], Carmela Gurnari[11], Cristina Papayannidis[12], Elisa Roncoroni[13], Marina Aurora Urbano[14], Robin Foà[9], Sabina Chiaretti[9]

- **19 patients** (11 hematologic relapse, 7 MRD persistence/recurrence, 1 MRD-negative)
- A median of **2 TKI** (range 1-3) prior to asciminib and **immunotherapy** in most cases
- **Mutation of ABL1 TK domain** in 66.6% of cases

- **Asciminib monotherapy** in 63% of cases, in **combination** in 37% of patients
- **CR achieved in 68.4%** of patients (MMR in 7 of 13 cases, 53.8%)
- Estimated **1-year OS 62.9%** in heavily pretreated patients, with **survival benefit** with administration of **asciminib in combination**. Allo-HSCT consolidation in 4 cases.

Asciminib-based upfront therapy in Ph+ ALL: encouraging activity in a phase 1 study

Luskin et al, Blood 2025



	No. of patients with response/total evaluable patients (%)		
	Day 28	Day 56	Day 84
Hematologic CR	19/20 (95)	18/18 (100)	18/18 (100)
Cytogenetic CR	14/17 (82)	16/17 (94)	16/16 (100)
Flow-negative MRD ($<10^{-4}$)	12/20 (60)	15/18 (83)	16/18 (89)
***BCR::ABL1* RT-qPCR**			
Molecular response 1	18/20 (90)	16/17 (94)	19/19 (100)
Molecular response 2	10/20 (50)	14/17 (82)	18/19 (95)
Molecular response 3	5/20 (25)	8/17 (47)	14/19 (74)
Molecular response 4	3/20 (15)	3/17 (18)	5/19 (26)

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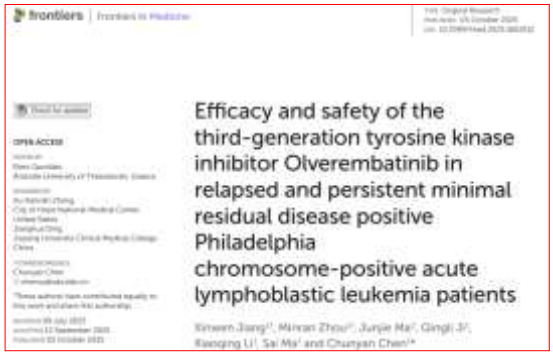

frontiers | Frontiers in Medicine

OPEN ACCESS

Efficacy and safety of the third-generation tyrosine kinase inhibitor Olverembatinib in relapsed and persistent minimal residual disease positive Philadelphia chromosome-positive acute lymphoblastic leukemia patients

Xinwen Jiang[†], Minran Zhou[†], Junjie Ma[†], Qingli Ji[†], Xiaoqing Li[†], Sai Ma[†] and Chunyan Chen[†]*

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BJHaem

SHORT REPORT

Haematological Malignancy – Clinical

Efficacy and safety of olverembatinib in adult BCR::ABL1-positive ALL with T315I mutation or relapsed/refractory disease

Weiyang Liu[1] | Cheng Wang[1] | Wanyan Ouyang[1] | Jie Hao[2] | Jiayi Ren[1] | Lijun Peng[1] | Sijie Tang[1] | Yuanfang Liu[1] | Yongmei Zhu[1] | Xiangqin Weng[1] | Duohui Jing[1] | Saijuan Chen[1] | Jin Wang[1] | Jian-Qing Mi[1]

American Journal of Hematology

WILEY

CORRESPONDENCE

Efficacy and Safety of the Third-Generation Tyrosine Kinase Inhibitor Olverembatinib in Combination With Inotuzumab Ozogamicin for the Treatment of Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Patients With Refractory/Relapsed Disease or Persistent Minimal Residual Disease Bridging to Hematopoietic Stem Cell Transplantation

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Blood 142 (2023) 1798–1800

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

632 CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Update of Olverembatinib (HQP1351) Overcoming Ponatinib and/or Asciminib Resistance in Patients (Pts) with Heavily Pretreated/Refractory Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph + ALL)

Elias Jabbour, MD[1], Hagop M. Kantarjian, MD[2], Paul B. Koller, MD[3], Omer Jamy, MD[1], Vivian G. Oehler[4], Elza Lomaia[5], Anthony M. Hunter, MD[1], Olga Ugarenkova[6], Svetlana Samarina[7], Sudipto Mukherjee, MDPHDMPH[8], Maria R. Baer, MD[9], Vera Zherebtsova[10], Vasily Shuvaev[11], Anna Turkina, MD[12], Igor Deydkin[13], Jorge Cortes, MD[14], Huanshan Guo[15], Zi Chen[15], Lei Fu[15], Hongbiang Wang[15], Lixin Jiang[15], Conlin Wang[15], Dajun Yang[15,16], Yifan Zhai[15,16]

Cytogenetic and molecular responses to olverembatinib monotherapy in advanced Ph+ leukemias: a TKI option beyond ponatinib

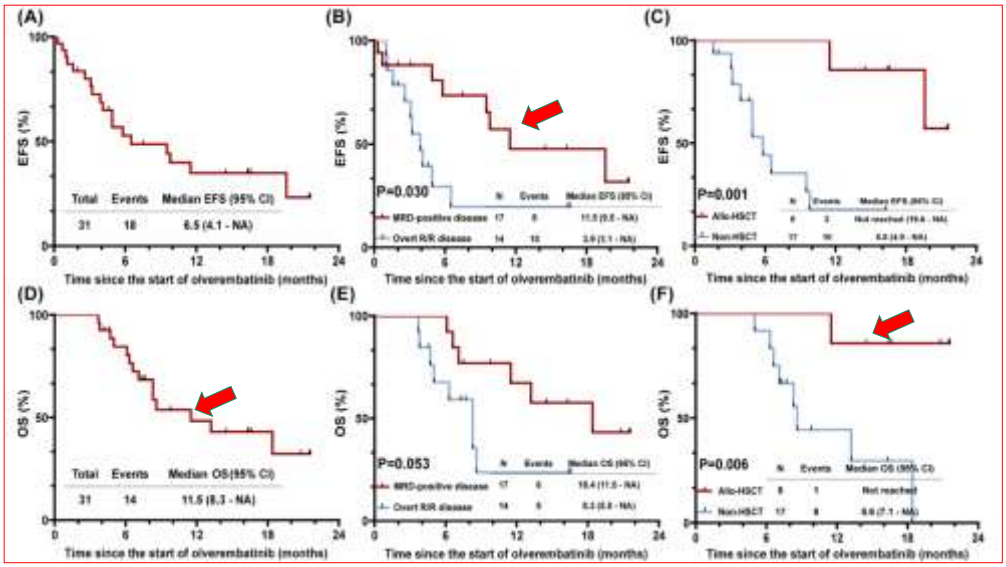
Jabbour et al, ASH 2023

CML-CP	Total	*T315I* mutation		Ponatinib pretreated		Asciminib pretreated	
		Positive	Negative	Resistant	Intolerant	Resistant	Intolerant
Efficacy population	50	16	34	16	6	8	2
Cytogenetic response							
No. of evaluable subjects-n	44	15	29	15	4	7	0
CCyR, n (%)	25 (56.8)	9 (60.0)	16 (55.2)	8 (53.3)	3 (75.0)	3 (42.9)	0
Molecular response							
No. of evaluable subjects-n	49	16	33	16	6	8	2
MMR, n (%)	21 (42.9)	7 (43.8)	14 (42.4)	6 (37.5)	1 (16.7)	3 (37.5)	0
Advanced Ph+ leukemia	Total	*T315I* mutation		Ponatinib pretreated		Asciminib pretreated	
		Positive	Negative	Resistant	Intolerant	Resistant	Intolerant
Efficacy population	13	5	8	9	2	6	0
Cytogenetic response							
No. of evaluable subjects-n	11	5	6	7	2	5	-
MCyR, n (%)	4 (36.4)	1 (20.0)	3 (50.0)	3 (42.9)	0	1 (20.0)	-
CCyR, n (%)	3 (27.3)	1 (20.0)	2 (33.3)	2 (28.6)	0	0	-
Molecular response							
No. of evaluable subjects-n	13	5	8	9	2	6	-
MMR, n (%)	3 (23.1)	1 (20.0)	2 (25.0)	2 (22.2)	0	0	-

SCENARI ATTUALI E PROSPETTIVE FUTURE NEL TRATTAMENTO DELLE LAL PH+

Promising clinical outcomes with olverembatinib in patients who experienced treatment failure with 2G-TKI, particularly those with MRD-positive disease and a single T315I mutation.

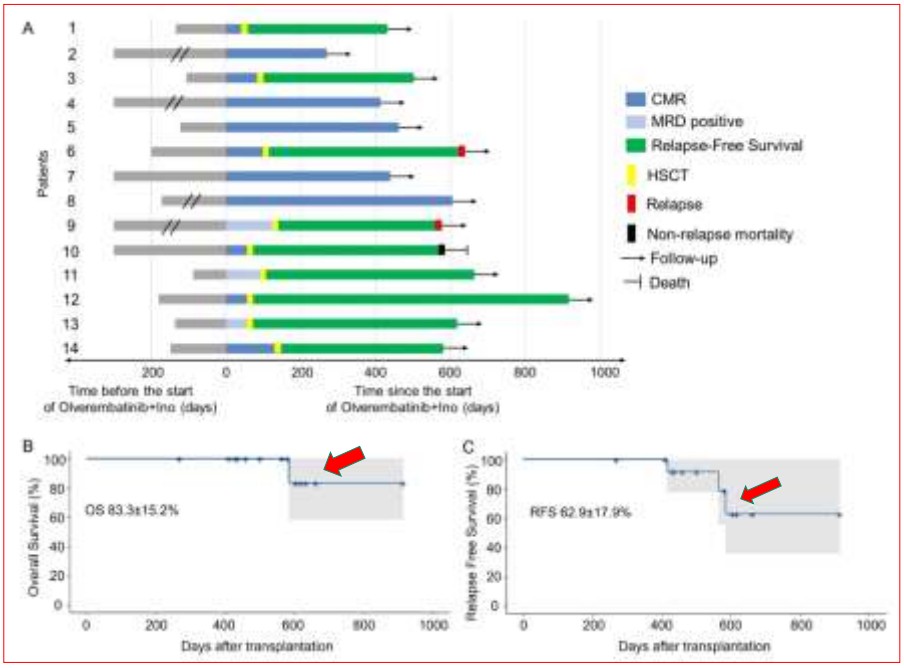
Liu et al, Br J Haematol 2024



- **Morphologic CR** rate **71.4%** in 14 patients with **overt R/R disease**
- **CMR** achieved in **47%** of 17 **MRD-positive cases**
- Overall, 24 patients (**77.4%**) harboured *BCR::ABL1* **T315I mutation**
- **Allo-HSCT** (8 cases) may further improve survival outcomes

Possible combination strategies: olverembatinib and InO bridge to HSCT

Zhang et al, Am J Hematol 2025



5 patients treated for **hematologic relapse**, while 9 cases had **MRD** persistent positive/relapse

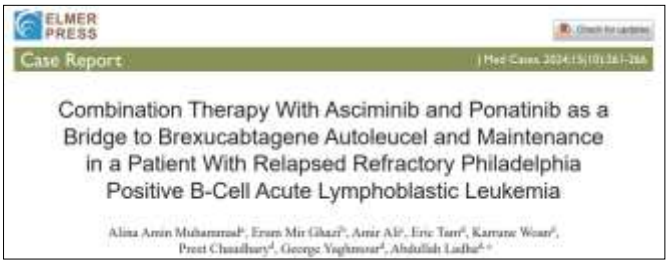
Overall **CMR rate 76.4%**

9 patients (64.3%) were successfully **bridged to allo-HSCT**

2-year OS 83.3%
2-year RFS 62.9%

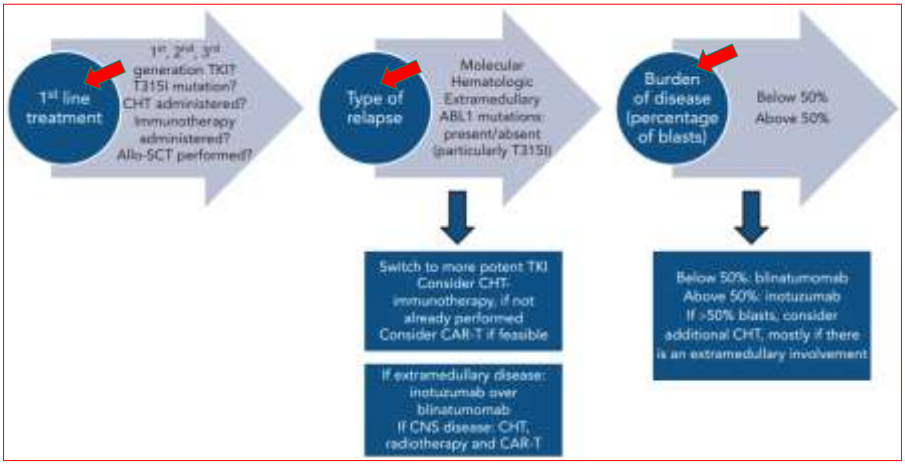
Case reports exploring further potentially effective combinational approaches

Chiaretti and Foà. Blood 2025; Abou Dalle et al, Leukemia 2025



Algorithm of treatment decision for Ph+ ALL at relapse

Chiaretti and Foà. Blood 2025



- **Management** of relapse in the **era of modern targeted therapy is challenging**
- **CNS relapse** is becoming an emerging issue
- **Allo-HSCT** resulted in lower DFS and OS in patients **beyond CR1**
- The availability of **multiple newer generation TKIs** in addition to immunotherapic approaches led to a **global improvement** in survival outcomes, though **still unsatisfactory**

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