9° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Bologna, Aula "G. Prodi", 19-20 maggio 2025

Chemo-free approaches in Philadelphia positive acute lymphoblastic leukemia: what challenges are left?

Sabina Chiaretti

SAPIENZA
UNIVERSITÀ DI ROMA

Disclosures di Sabina Chiaretti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AMGEN					X	X	
INCYTE					X	X	
GILEAD					X	X	
PFIZER					x		

Topics

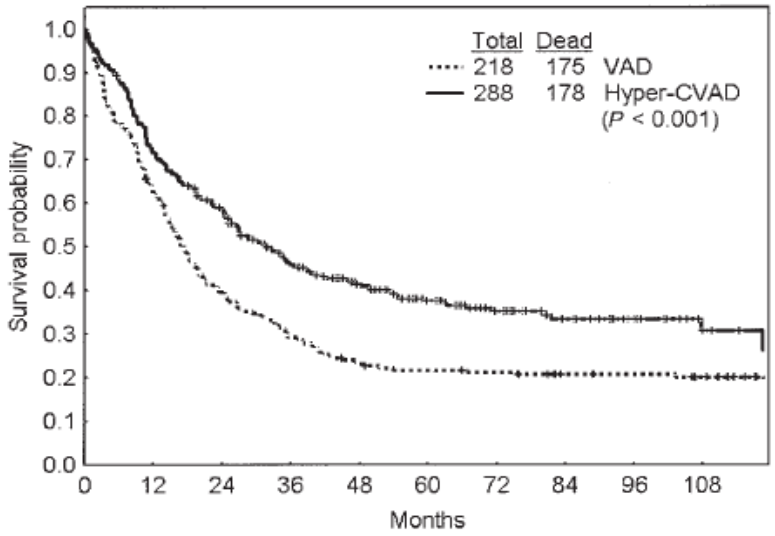
The past

The current ideal management of Ph+ALL

MRD monitoring: how?

Can we predict relapse?

Where did we start from?



Study protocol	Age (yrs)	Induction therapy	CHR rate	OS rate
LAL 0201-B[1]	60–89	IMA + PDN	100%	48 (1 y)
LAL 1205[2]	18–84	DAS + PDN	100%	51 (20 ms)
LAL 0904 3rd amendment[3]	16–60	IMA + HAM (± transplant)	96%	49 (5 yrs)
LAL 1408[4]	>60	NIL + IMA + PDN*	94%	-
LAL 1509[5]	18–60	Total therapy strategy (DAS)	97%	56 (5 yrs)
LAL 1811[6]	>60	PON + PDN	95%	Median, nr

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. Haematologica 2021;6. Martinelli G. et al ASH 2017

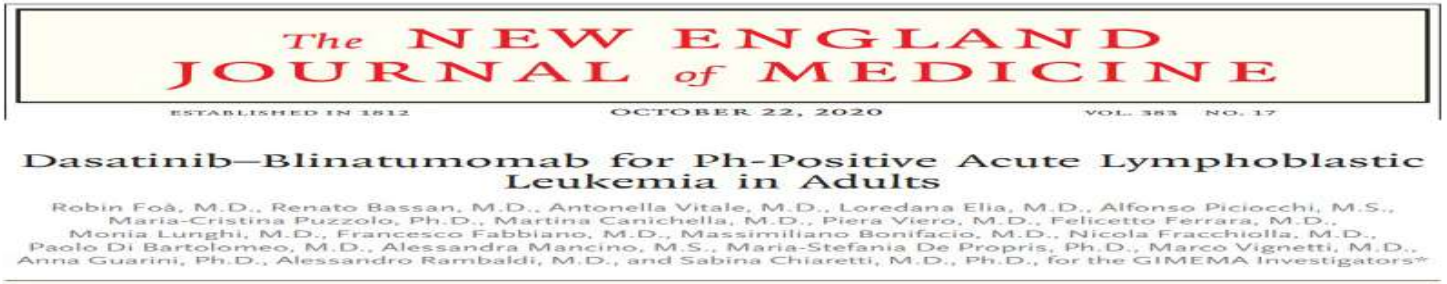
Kantarjian H et al. *Cancer* 2004

Topics

The current ideal management of Ph+ALL

MRD monitoring: how?

Can we predict relapse?


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

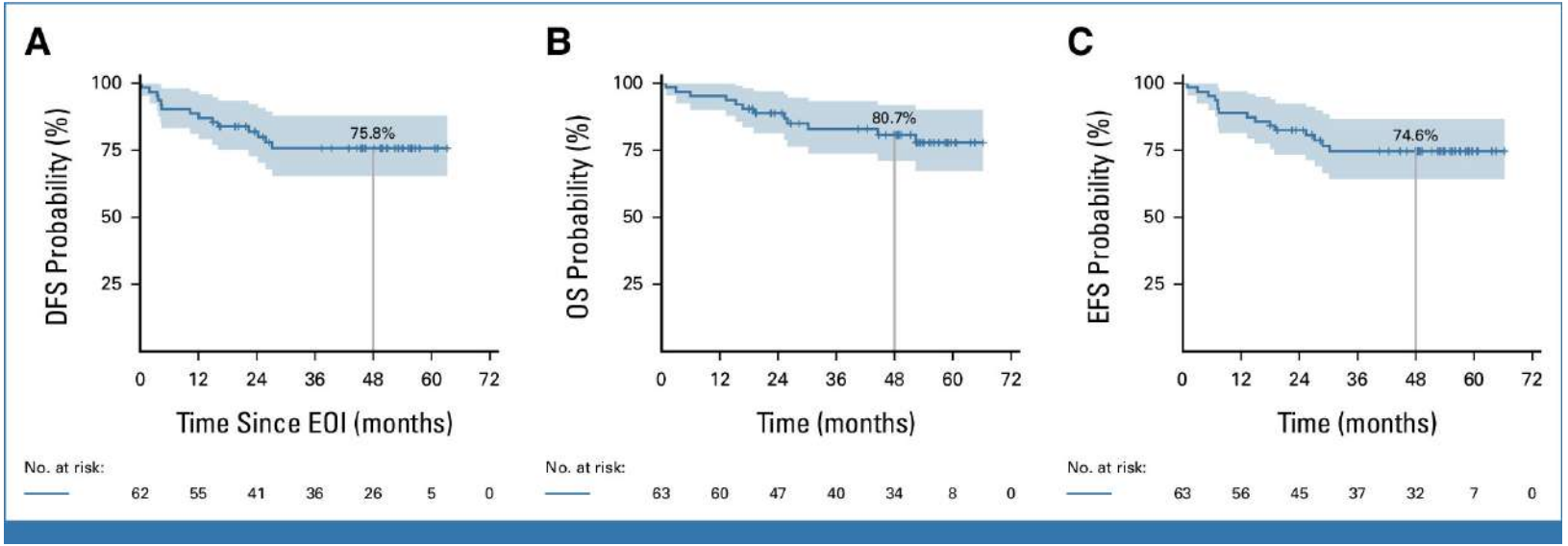
Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*

- At the primary endpoint (after 2 cycles of Blinatumomab), molecular responses were recorded in 60% of cases
- OS was 95%
- DFS was 88%
- *IKZF1*^{plus} cases emerged as the subset with the poorest DFS

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

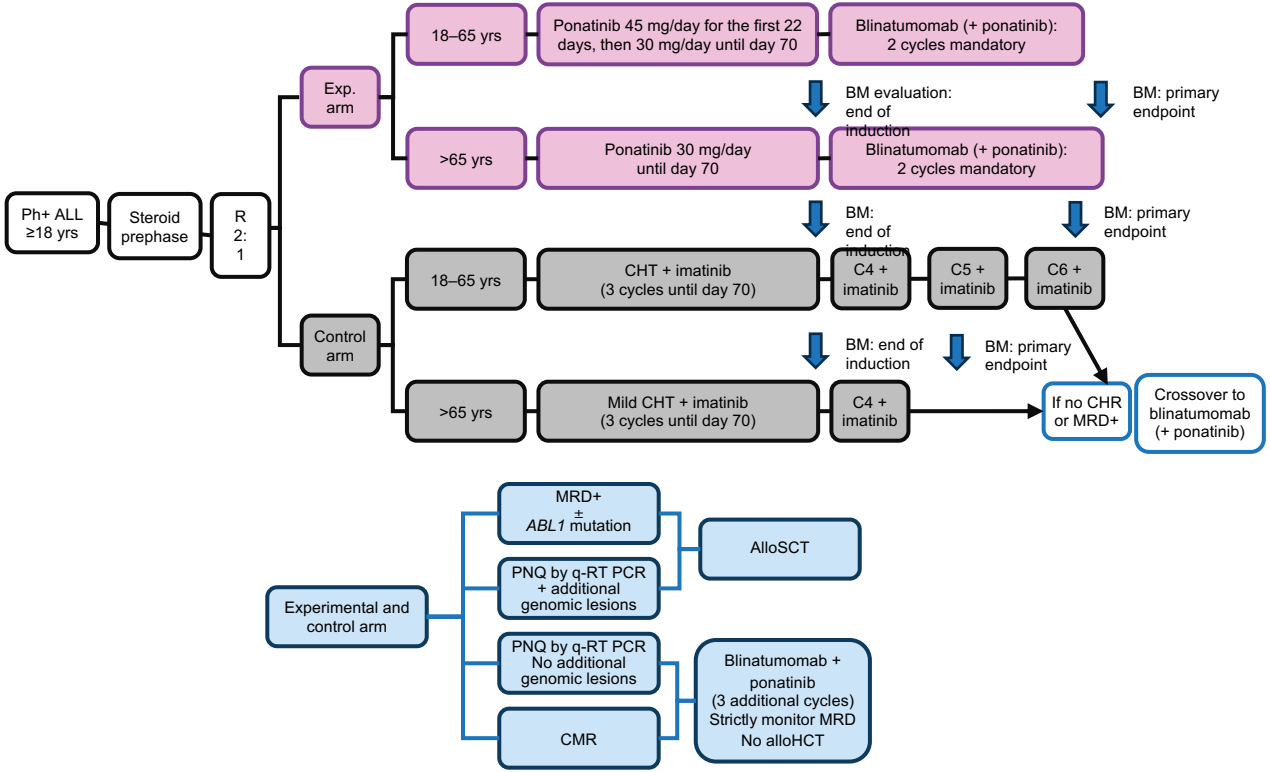
Long-term results of D-ALBA



At a median follow-up of 53 months, DFS, OS and EFS are **75.8%** , **80.7%** and **74.6%** respectively.

Foà R, et al. *JCO* 2024

Ph+ ALL. GIMEMA ALL2820: Ponatinib-blinatumomab frontline

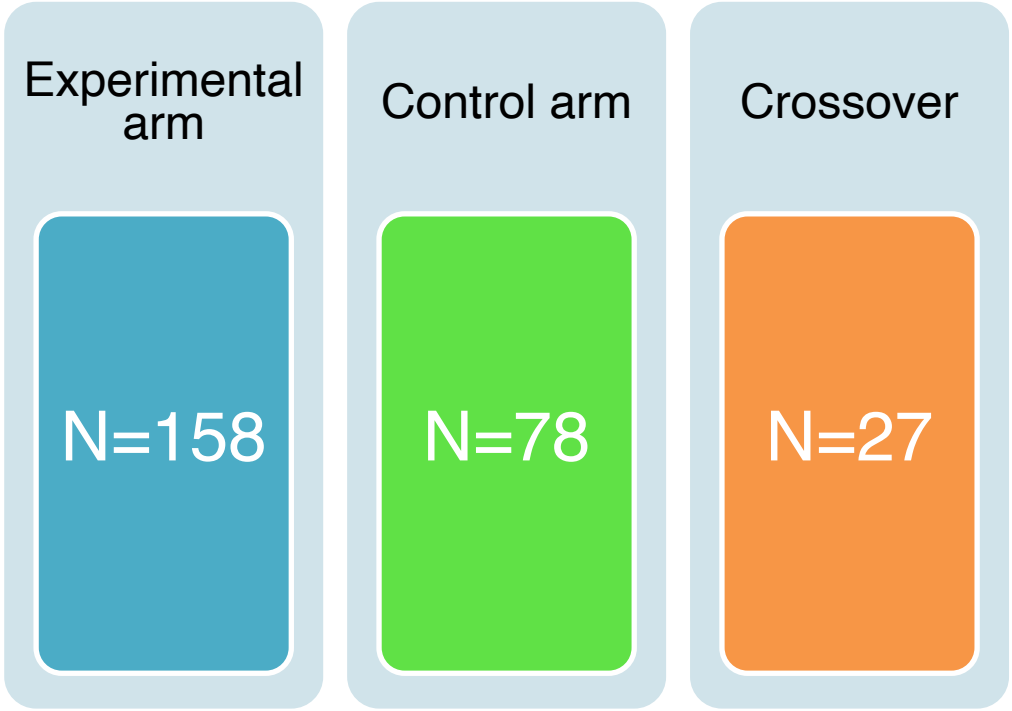


-Protocol closed to enrolment in January 2025.

- Last patient predicted to reach primary endpoint in June.

Chiaretti et al, abs 835, ASH 2024

GIMEMA ALL2820. Patients' disposition and features



	Experimental arm N=158	Control arm N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	47 (30)	21 (26.6)
Gender: M/F (%)	79/79 (50/50)	48/31(61/39)
WBC x10^9/l, median (range)	14 (0.3-356)	13.4 (0.7-250)
≥30 (%)	49 (31)	24 (30)
≥70 (%)	23 (15)	10 (12.7)
p190(%)	110 (69)	50 (63)
p210, p190/210 (%)	40 (25), 8 (4)	25 (31.7)
IKZF1^{plus} (%)	45 (32)	18 (25)

GIMEMA ALL2820. Experimental arm: hematologic and molecular responses

End of induction (d +70)	Experimental arm (N=158)
CHR	151 **(95.6%)**
Deaths	4 **(2.5%)***
Refractory	-
Off treatment	3 **(1.9%)**

*Median age: 67 yrs

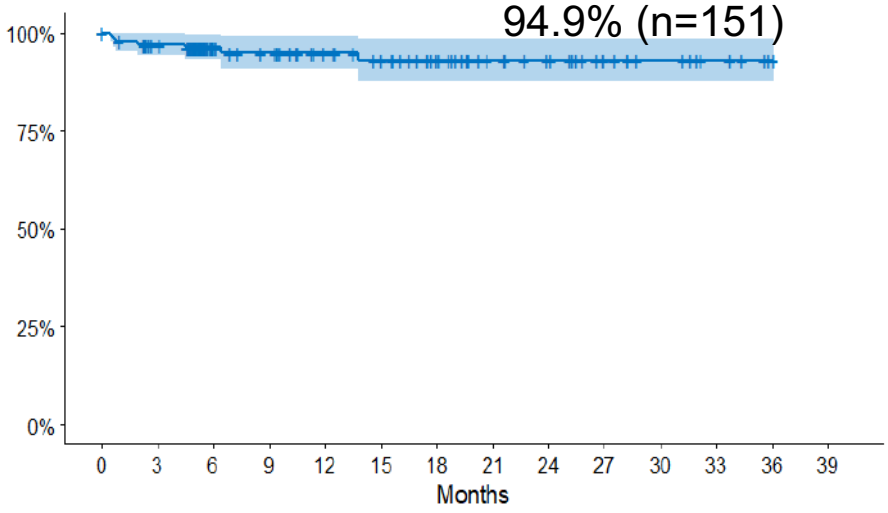
Relapses	Experimental arm (N=151)
Overall	7 (4.6%)
In trial*	4 (2.6%)
Off-treatment	2 (1.3%)

*1 relapse was due to a Ph- clone

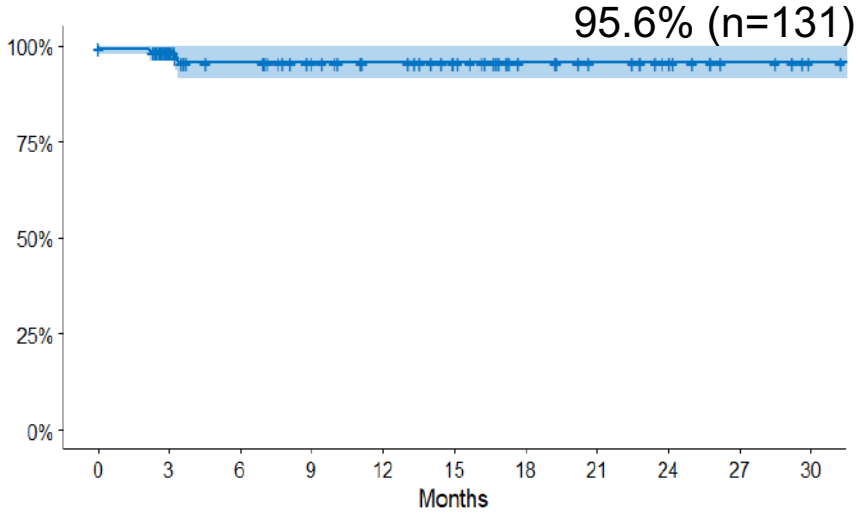
Experimental arm N=159	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)
End induction (d +70)	76/148 (51)	46/148	26/148	72/148 **(49)**
After 2 blina cycles	32/134 (24)	71/134	31/134	102/134 **(76)**

GIMEMA ALL2820. Experimental arm: estimated 12-ms OS & DFS

OS



DFS

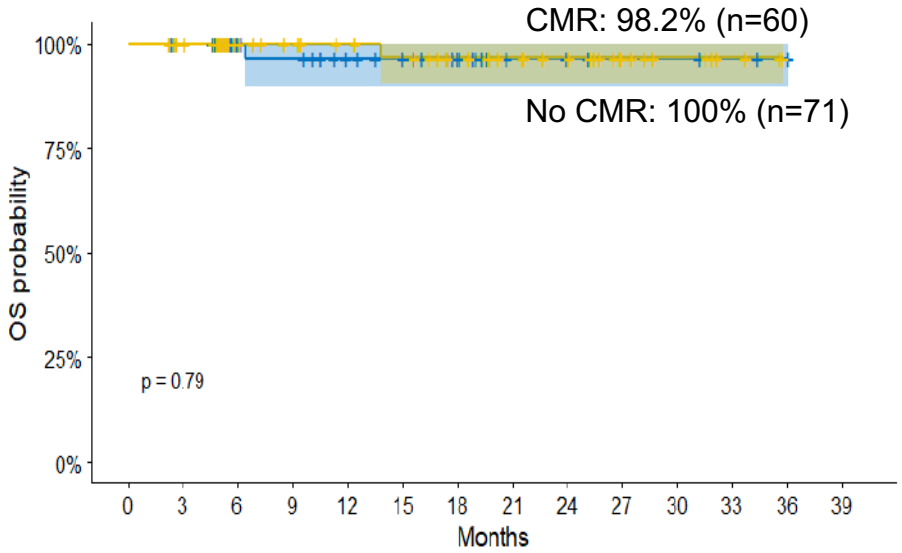


Median follow-up: 8.5 months (0.1 - 36.1)

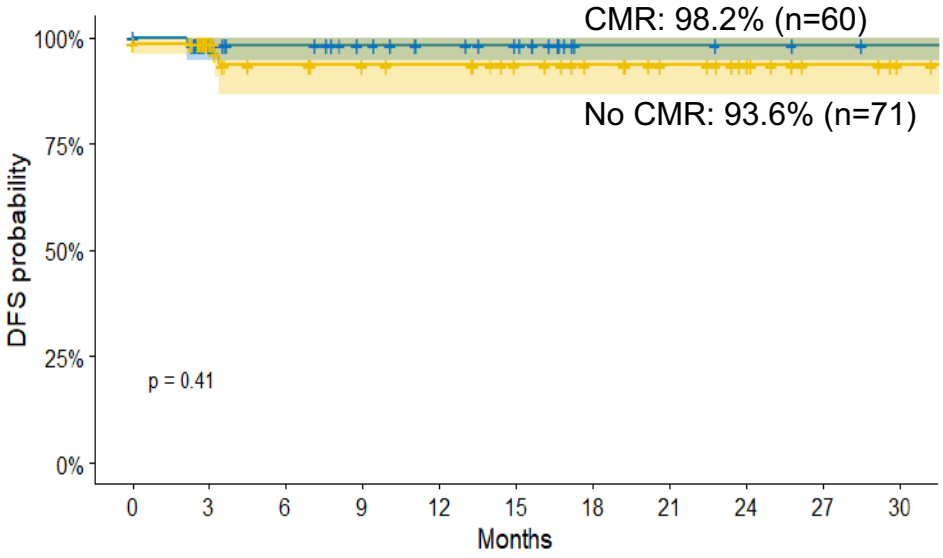
Chiaretti et al, abs 835, ASH 2024

GIMEMA ALL2820. Experimental arm: estimated 12-ms OS & DFS by molecular response at EOI

OS



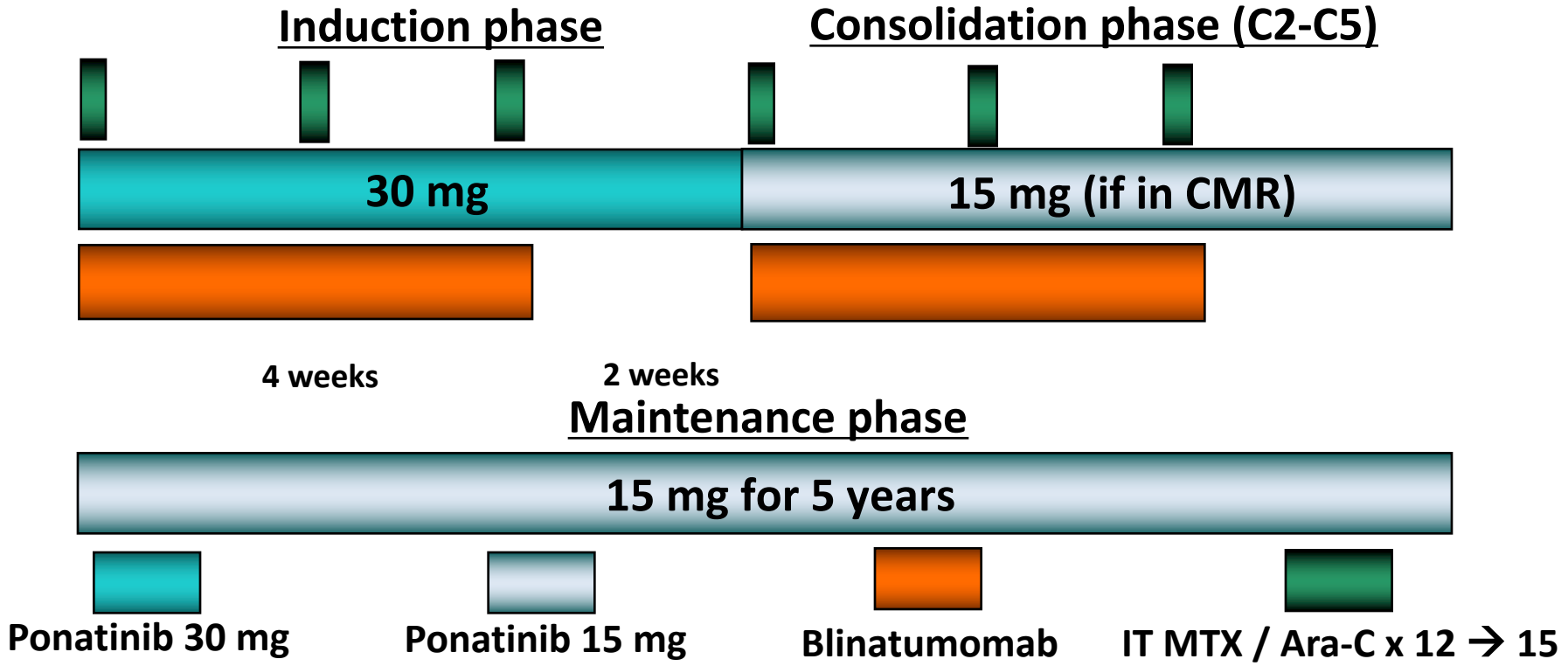
DFS



MRD not necessary anymore with powerful compounds?

Chiaretti et al, abs 835, ASH 2024

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Short et al, abs 837, ASH 2024

Ponatinib + Blinatumomab in Ph+ ALL: responses

Response, n/N (%)	N = 76
CR/CRi*	52/53 (98)
CR	51/53 (96)
CRi	1/53 (2)
Early death	1/53 (2)
MMR**	64/66 (97)
CMR**	57/69 (83)
After 1 cycle	41/69 (59)
NGS MRD negative	55/57 (96)
After 1 cycle	17/36 (47)

* 23 pts in CR at start

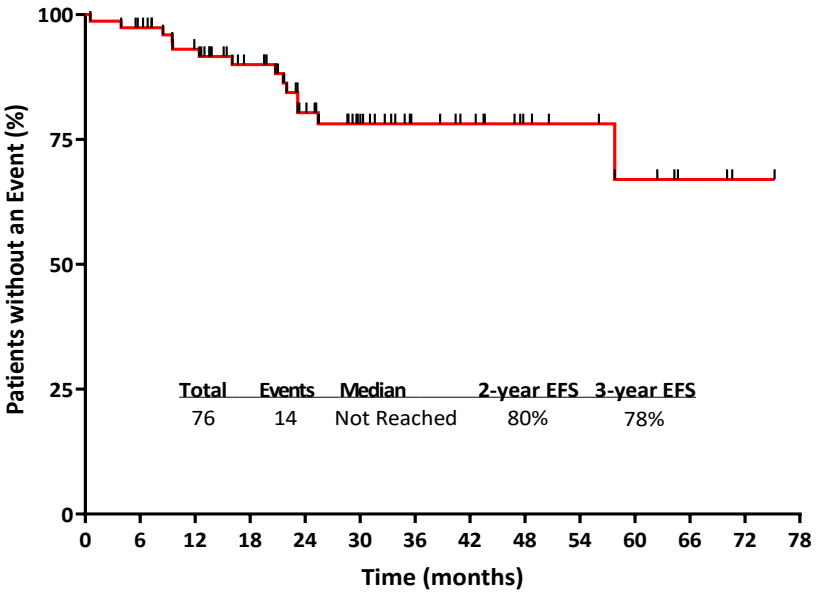
** 10 pts were in MMR, 7 were in CMR, and 2 were NGS MRD negative at start

8/8 of tested pts not achieving CMR were NGS MRD negative

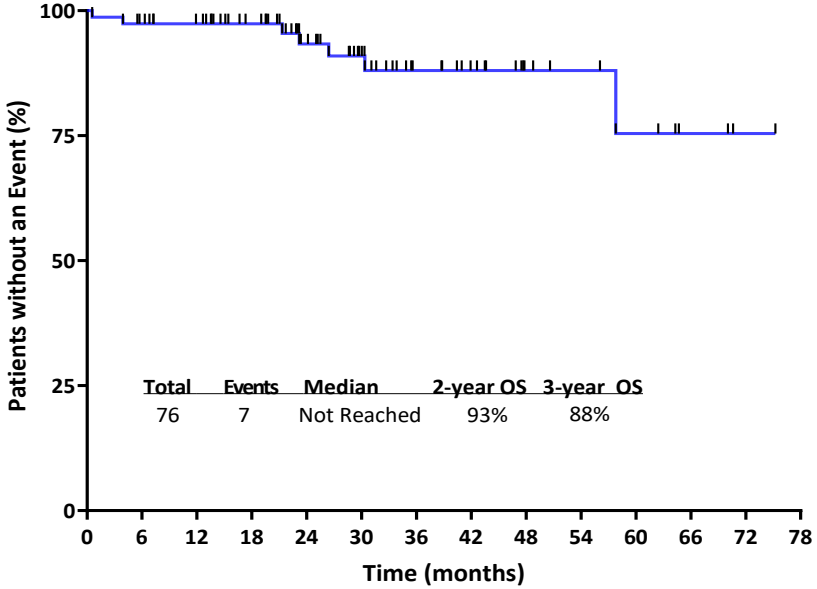
Short et al, abs 837, ASH 2024

Ponatinib + Blinatumomab in Ph+ ALL: survival

Event-Free Survival



Overall Survival



Median follow-up: 29 months (range: 5-75 months)
1 relapse due a Ph- clone

Short et al, abs 837, ASH 2024

Topics

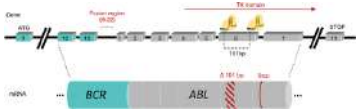
MRD monitoring: how?

Can we predict relapse?

BCR::ABL1 or IG/TR?

<u>*BCR::ABL1* fusion gene transcript</u>

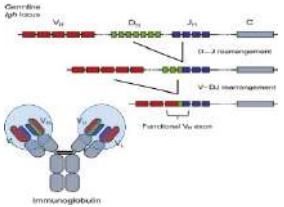
- **Leukemia-specific** biomarker
- Leukemia **driver-lesion**



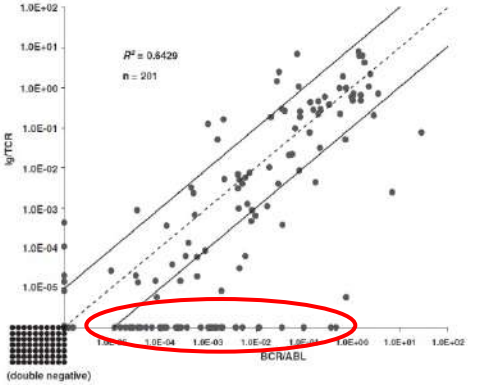
❖ **Gold standard biomarker in adult Ph+ ALL**

<u>Immunoglobulin/T-cell receptor (IG/TR) clonal gene rearrangements</u>

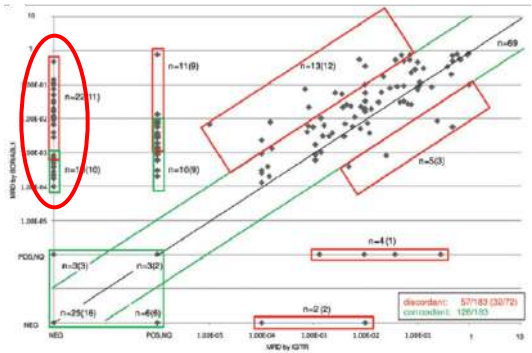
- **Patient-specific** biomarker
- **Not directly linked** to the **pathogenesis** of the leukemia



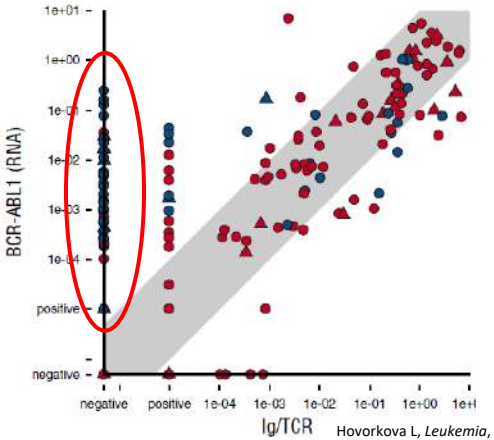
❖ **Gold standard biomarker in Ph- pediatric and adult ALL, scarcely explored in adult Ph+ ALL**



Zaliova M et al, *Leukemia*, **2009**



Cazzaniga G et al, *Hematologica*, **2018**

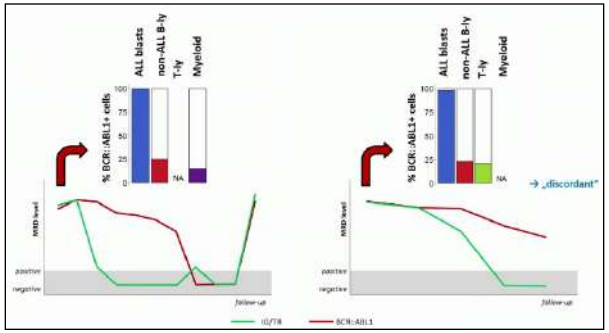


Hovorkova L, *Leukemia*, **2017**

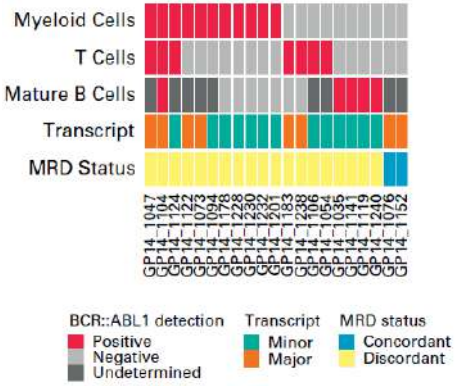
- Most data come from studies conducted on **pediatric setting, few data in the adult patients**
- **Poor overall MRD concordance rate** between *BCR::ABL1* and IG/TR: ~ 60%
- The majority of discordant cases are persistently ***BCR:: ABL1* positive and IG/TR negative**

BCR::ABL1 or IG/TR: biological meaning?

- Flow-cell sorting on samples derived from the discordant cases reveals ***BCR::ABL1*** **expression in non leukemic cell lineages** (non-ALL B-cells, T-cells, myeloid cells)



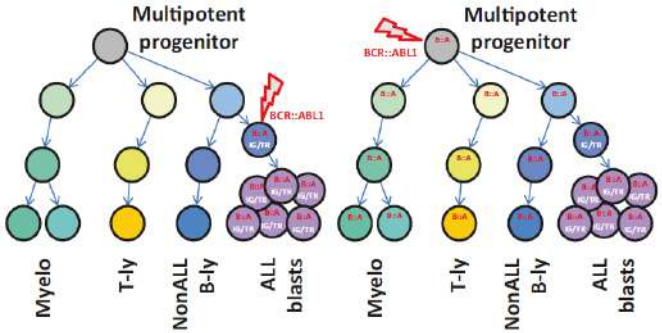
Zuna J et al, *EHA*, 2022



Kim R et al, *JCO*, 2024

Lymphoid/typical Ph+ ALL

Multilineage/CML-like Ph+ ALL



Zuna J et al, *Leukemia*, 2022

- Based on these observations, the Ph+ ALL was divided into two subgroups: **Ph+ ALL lymphoid only (or typical)** and **Ph+ ALL multilineage (or CML-like)**

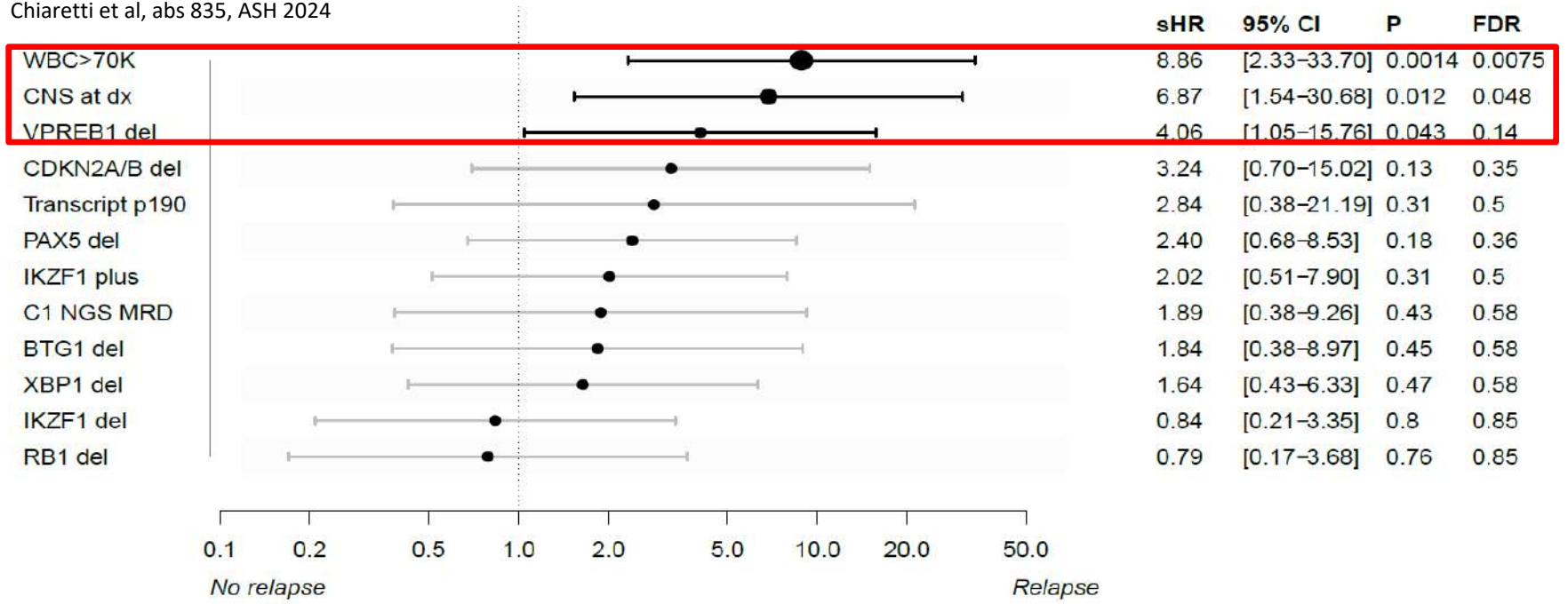
Topics

Can we predict relapse?

Predictors of inferior response in ponatinib + Blinatumomab

Correlation between molecular response and protein fusion type (p190 *vs* p210) at the end of induction (p=0.02), and WBC after 2 cycles of blinatumomab (>30x10^9/l and >75x10^9/l, p=0.047 and 0.016, respectively)

Chiaretti et al, abs 835, ASH 2024



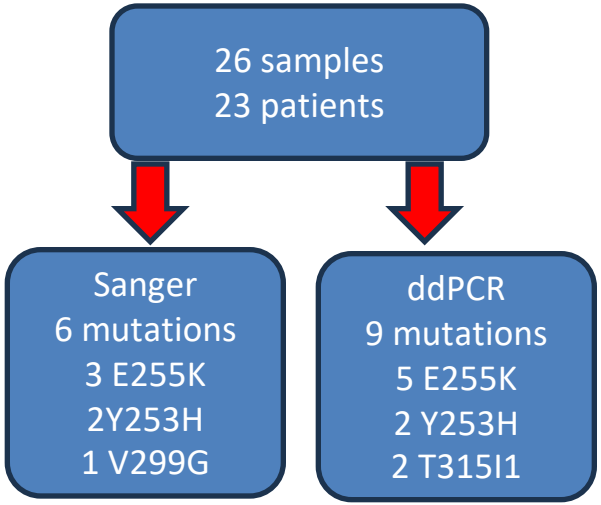
Short et al, abs 837, ASH 2024

What else?

Dual ABL1 mutational screening in MRD increase patients

	Arm	TKI	*BCR::ABL1* isoform	MRD value at previous time point by qRT-PCR	MRD value by qRT-PCR	*ABL1* mutations by ddPCR	*ABL1* mutations by SS	*IKZF1* plus signature
102820051-3	control/crossover	Imatinib	p190	0	0.11	wt	wt	*IKZF1* loss
102820163-5	control/crossover	Imatinib	p190	0	0.05	wt	wt	*IKZF1* loss
102820163-5	control/crossover	Ponatinib	p190	0.01	0,07	wt	wt	*IKZF1* loss
102820163-5	control/crossover	Ponatinib	p190	0.07	2.5	wt	wt	*IKZF1* loss
102820086-6	control	Imatinib	p210	0	0.29	wt	wt	*IKZF1* loss
102820005-6	control/crossover	Imatinib	p210	32.21	16.96	wt	wt	*IKZF1* loss
102820085-2	control	Imatinib	p210	PNQ	0.17	wt	wt	*IKZF1* plus
102820005-7	control/crossover	Imatinib	p190	onset	29.71	wt	V299G	wt
102820096-3	control/crossover	Imatinib	p190	0.1	1.84	Y253H	Y253H	*IKZF1* plus
102820008-1	control/crossover	Imatinib	p210	0	0.01	wt	wt	*IKZF1* loss
102820027-4	**control/crossover**	**Imatinib**	**p190**	**0**	**0.32**	**T315I**	**wt**	**wt**
102820027-4	**control/crossover**	**Imatinib**	**p190**	**0.32**	**33.05**	**T315I, E255K**	**E255K**	**wt**
102820017-2	control	Imatinib	p190	7.12	153.4	E255K	E255K	*IKZF1* plus
102820101-1	control	Imatinib	p210	0,03	322.5	E255K	E255K	wt
102820095-1	experimental	Ponatinib	p210	PNQ	0,09	T315I	wt	*IKZF1* plus
102820099-3	experimental	Ponatinib	p210	7.58	10,04	wt	wt	NA
102820045-4	**experimental**	**Ponatinib**	**p210**	**0.08**	**0.16**	**E255K**	**wt**	***IKZF1* loss**
102820163-1	experimental	Ponatinib	p190	0,008	0.03	wt	wt	*IKZF1* loss
102820101-2	experimental	Ponatinib	p190	0	1.76	wt	wt	*IKZF1* plus
102820010-4	**experimental**	**Ponatinib**	**p210**	**0.03**	**0.1**	**E255K**	**wt**	**wt**
102820027-6	experimental	Ponatinib	p190	0.05	111	Y253H	Y253H	*IKZF1* loss
102820115-1	experimental	Ponatinib	p190	0.06	1.8	wt	wt	*IKZF1* loss
102820027-5	experimental	Ponatinib	p190	0.02	0.18	wt	wt	wt
102820037-3	experimental	Ponatinib	p190	PNQ	2.57	wt	wt	wt
102820017-1	experimental	Ponatinib	p210	0	0.02	wt	wt	wt
102820043-2	experimental	Ponatinib	p210	0	0.85	wt	wt	*IKZF1* plus

Abbreviations: TKI, tyrosine kinase inhibitor; PNQ, positive-not-quantifiable; NA, not available; wt, wild-type. *IKZF1* plus: *IKZF1*, *CDKN2A-B* and/or *PAX5* deletion.
*expressed as (*BCR::ABL1*/*ABL1*) × 100/µL;



DdPCR detected all the mutations identified by Sanger

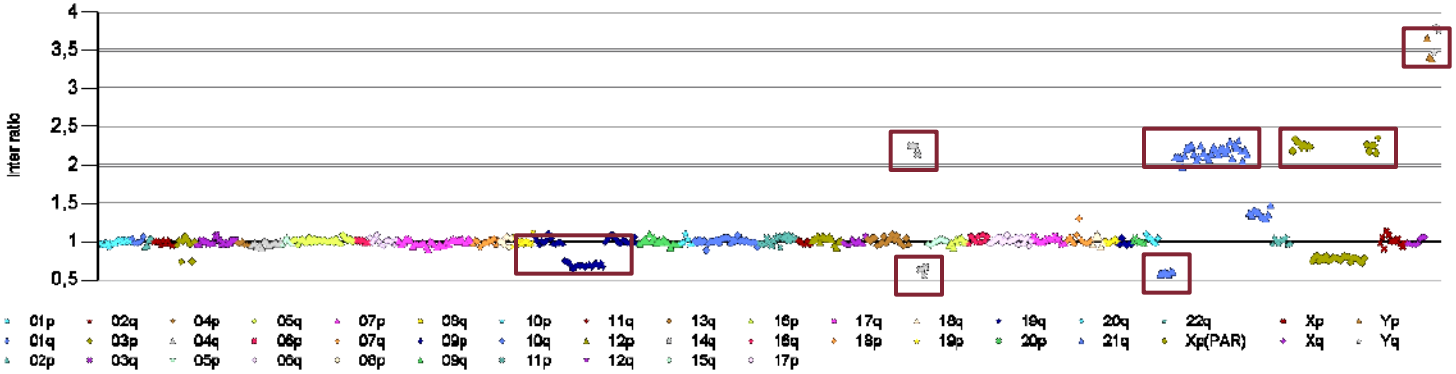
Apparently more sensitive also at low levels

Cardinali D et al. Leuk Lymphoma 2023

What else?

DMLPA for refined detection of CNV

Ph+ ALL, FISH t(9;22): Negative → Further relapse of Ph-Neg clone.



9p del, 14q del and gain, 21q del and gain XPAR region

F. Kaiser, work in progress

Conclusions

In the front-line setting, a chemo-free based on targeted and immunotherapy has proven feasible and effective at all ages: inferior death rates, higher remission rates, excellent survival, possibly less need of transplant

MRD: not relevant anymore, depending on treatment?? IG/TR??? Possibly, indicative of a different biology

Relapse: WBC, *IKZF1*^{plus}, but also anticipation of intervention in case of *ABL1* mutations, complex kariotype and immune compartment

Acknowledgments

Loredana Elia
Irene della Starza
Vittorio Bellomarino
Marco Beldinanzi
Deborah Cardinali
Michela Ansuinelli
Francesca Kaiser
Maria Stefania De Propris
Antonella Vitale
Marco Cerrano
Mariangela Di Trani
Maurizio Martelli
Anna Guarini
Alessandro Rambaldi
Renato Bassan
Robin Foà

Alfonso Piciocchi
Monica Messina
Valentina Arena
Stefano Soddu
Paola Fazi
Marco Vignetti

GIMEMA Centers

5x1000
AIRC RICERCA