LEUKEMIA2022
Rome, Hotel NH Collection - Vittorio Veneto
May 5-6, 2022
AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

New treatment strategies for Ph-like ALL (and Ph+ ALL)

Sabina Chiaretti

May 6th, 2022

SAPIENZA
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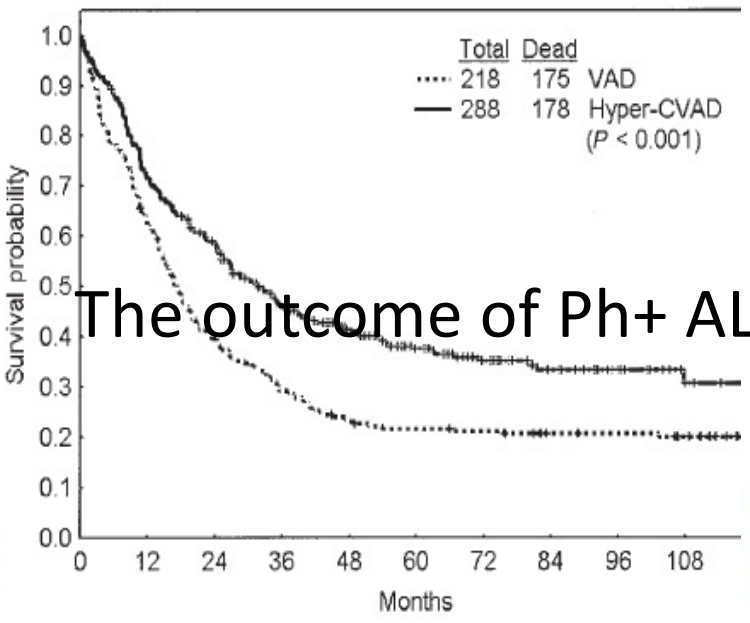
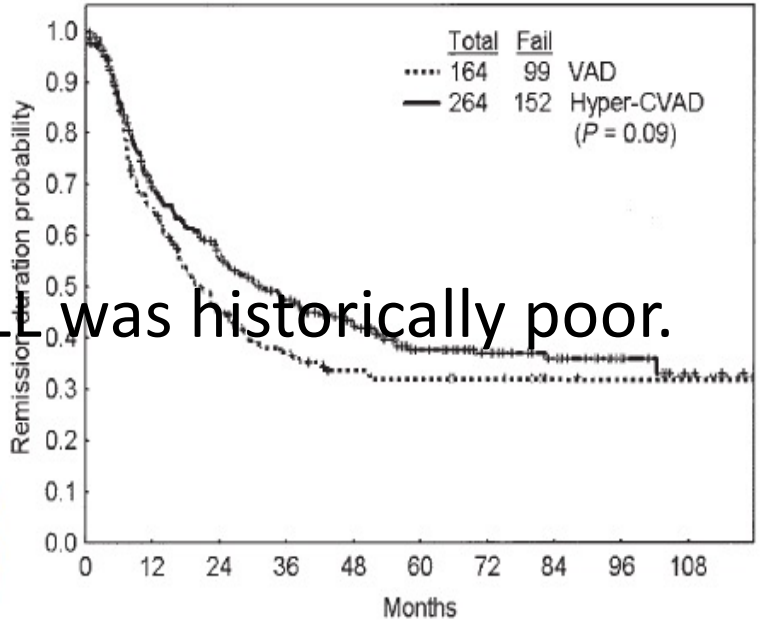
Dipartimento di
Medicina Traslazionale e di Precisione

Background on Ph+ ALL

Kantarjian H et al. *Cancer* 2004

Overall survival



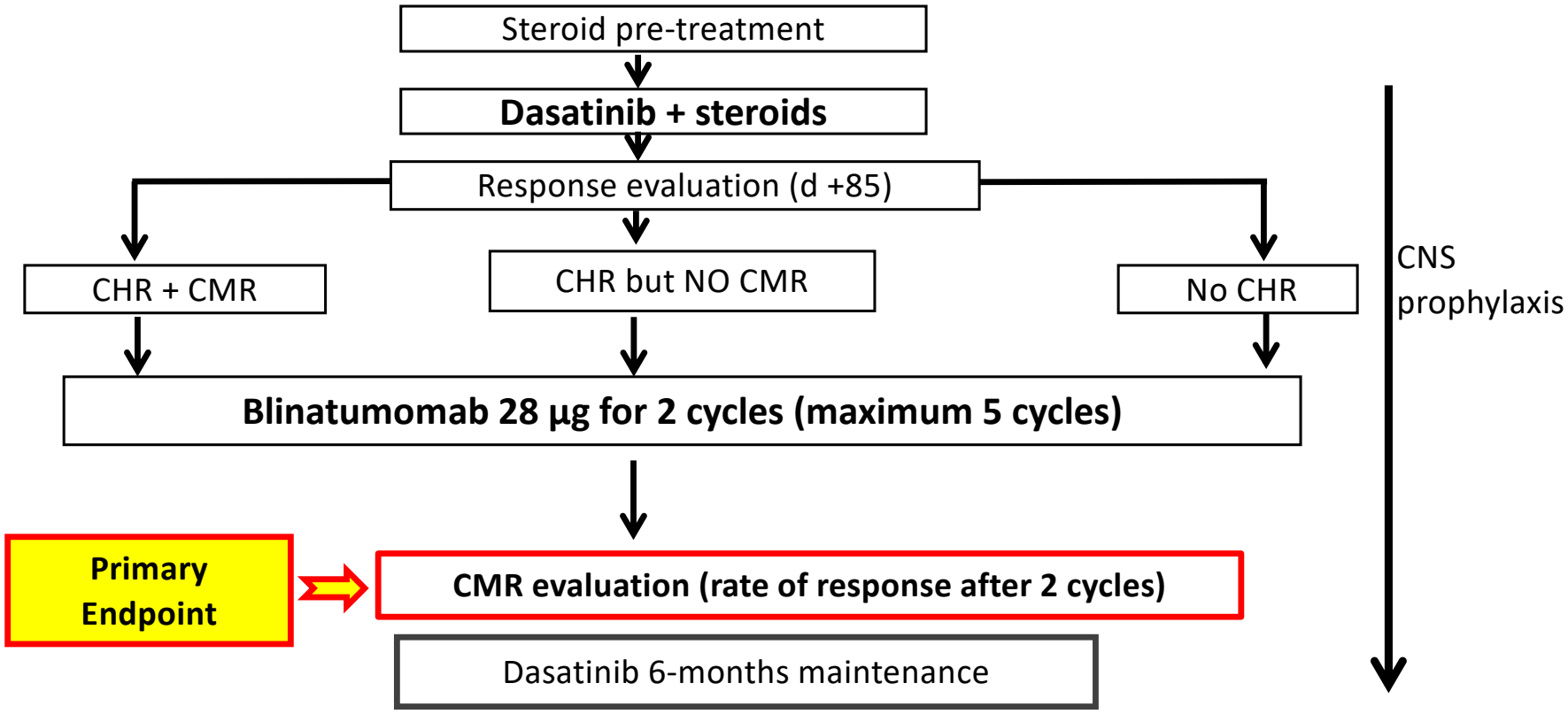


Disease remission duration

The outcome of Ph+ ALL was historically poor.

The introduction of TKIs, with or without chemotherapy, has led to overall survival (OS) rates approaching 50%.

D-ALBA: treatment scheme



Foà R et al, NEJM 2020;383:1613-1623

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

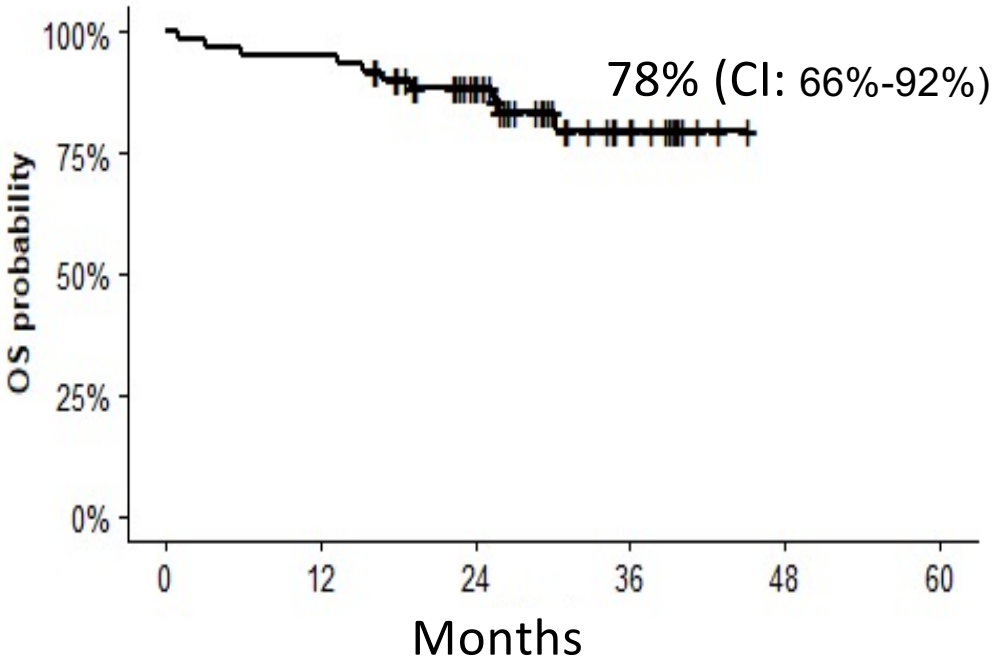
Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, 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

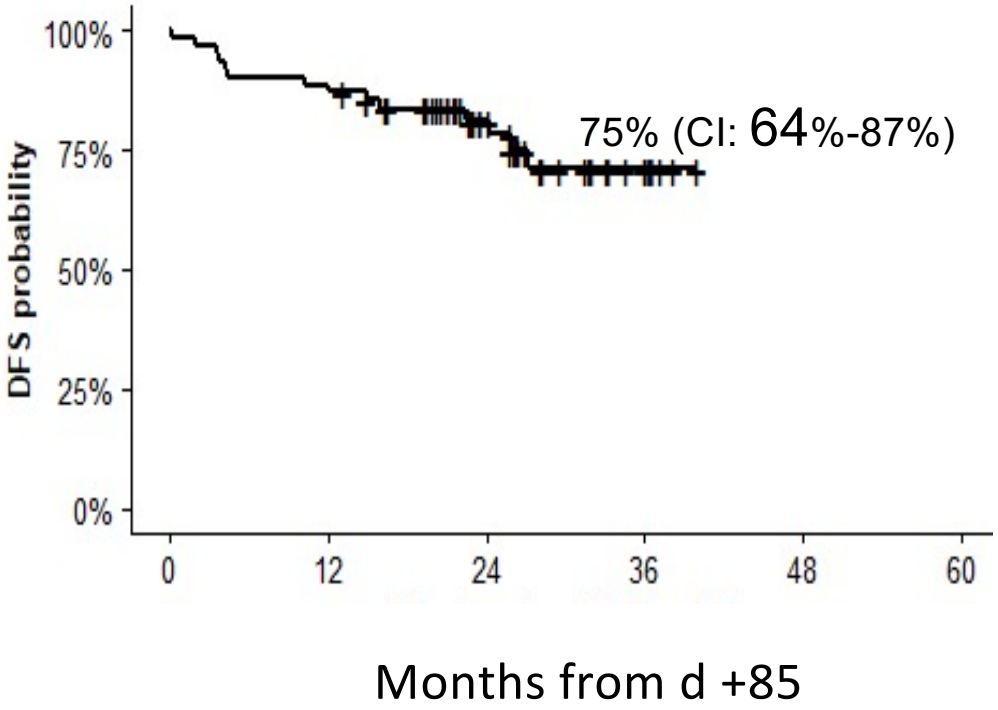
Foà et al, NEJM 2020; 383(17):1613-1623

Updated D-ALBA: estimated 48 ms OS and DFS

OS

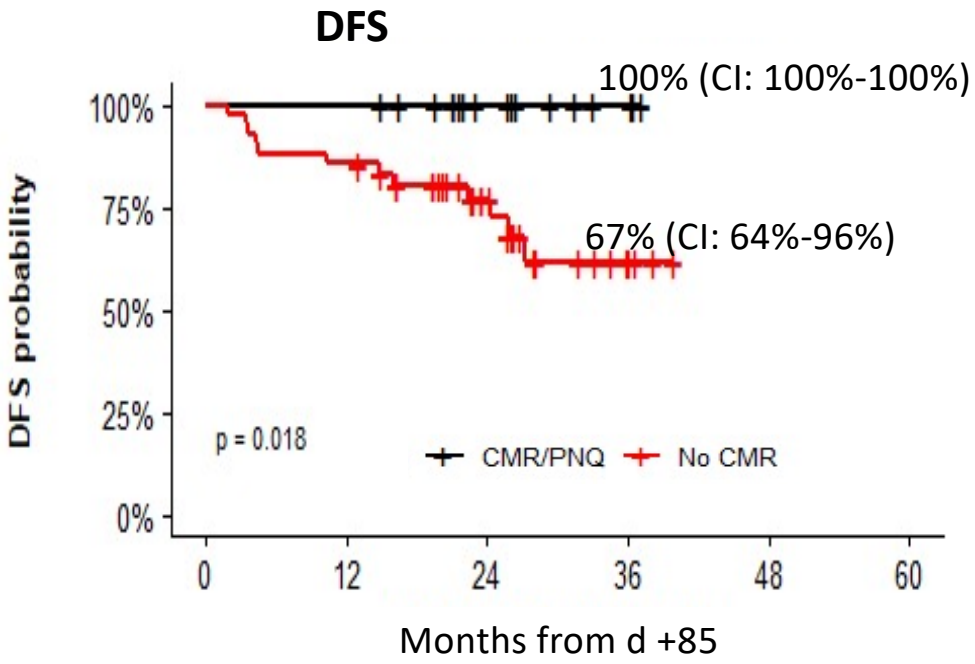


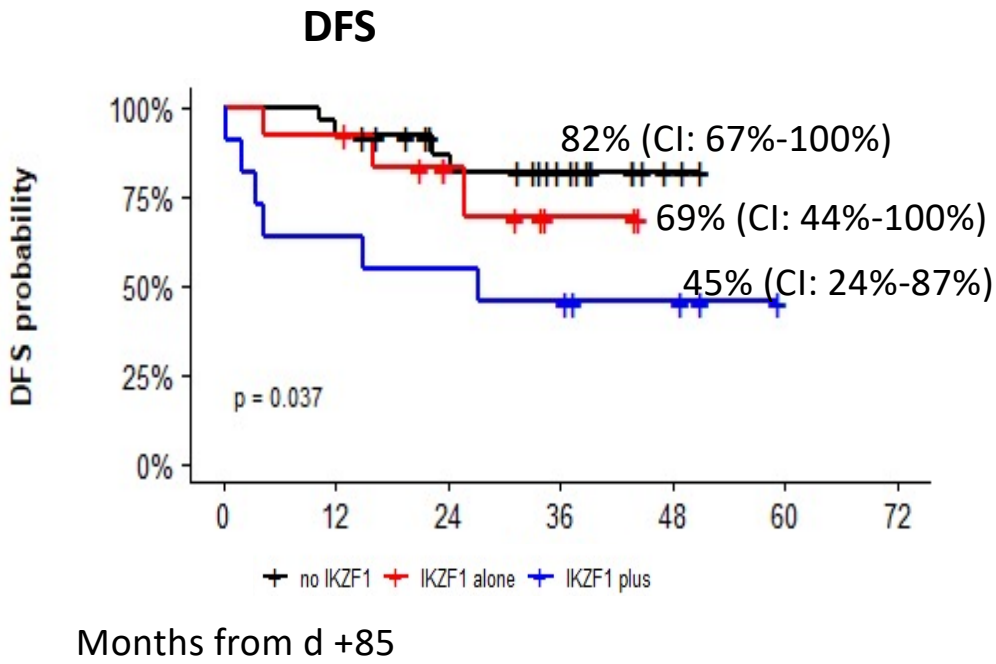
DFS



Median follow-up: 40ms (0.9-62.5)

Updated D-ALBA: estimated 48 ms DFS according to molecular responses and CNAs

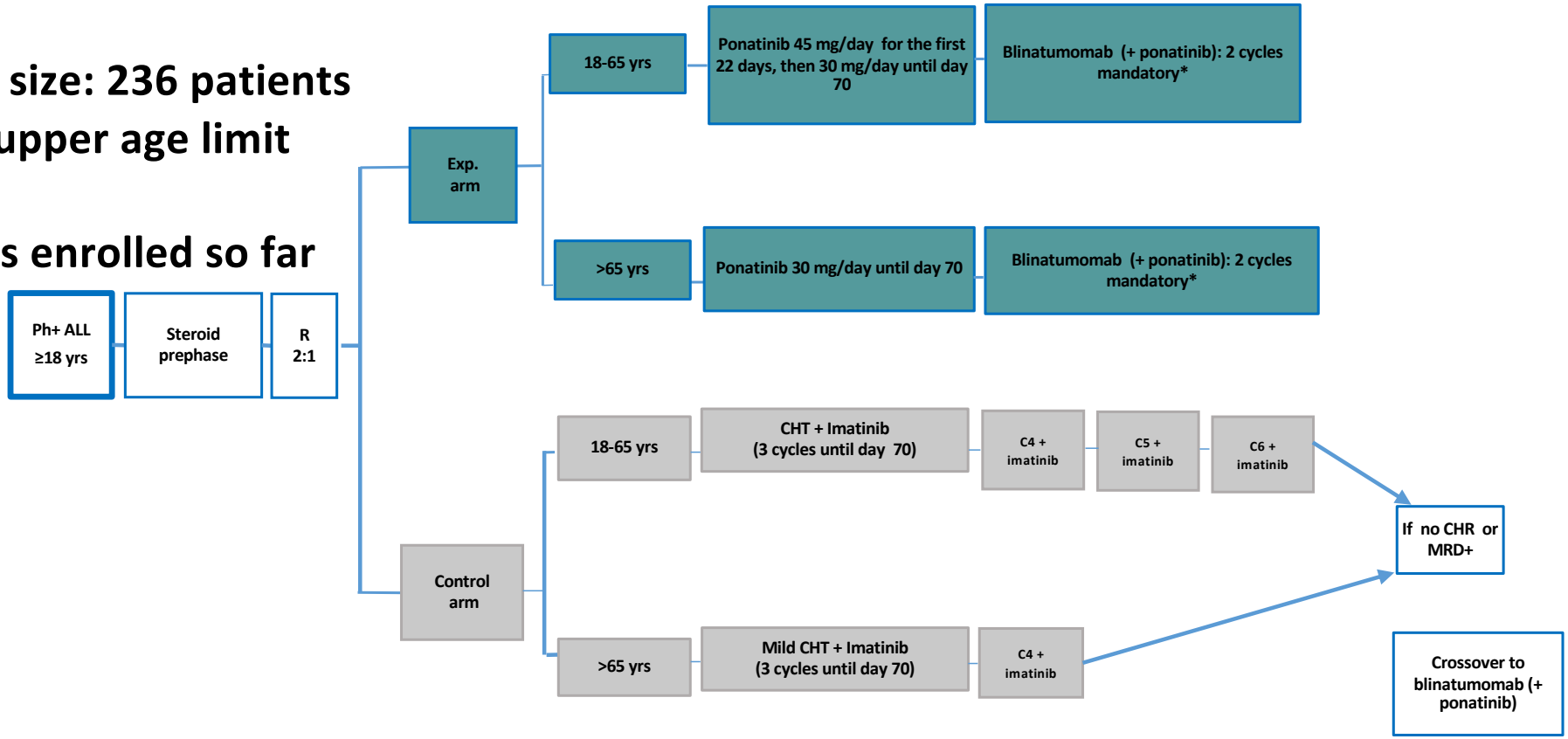




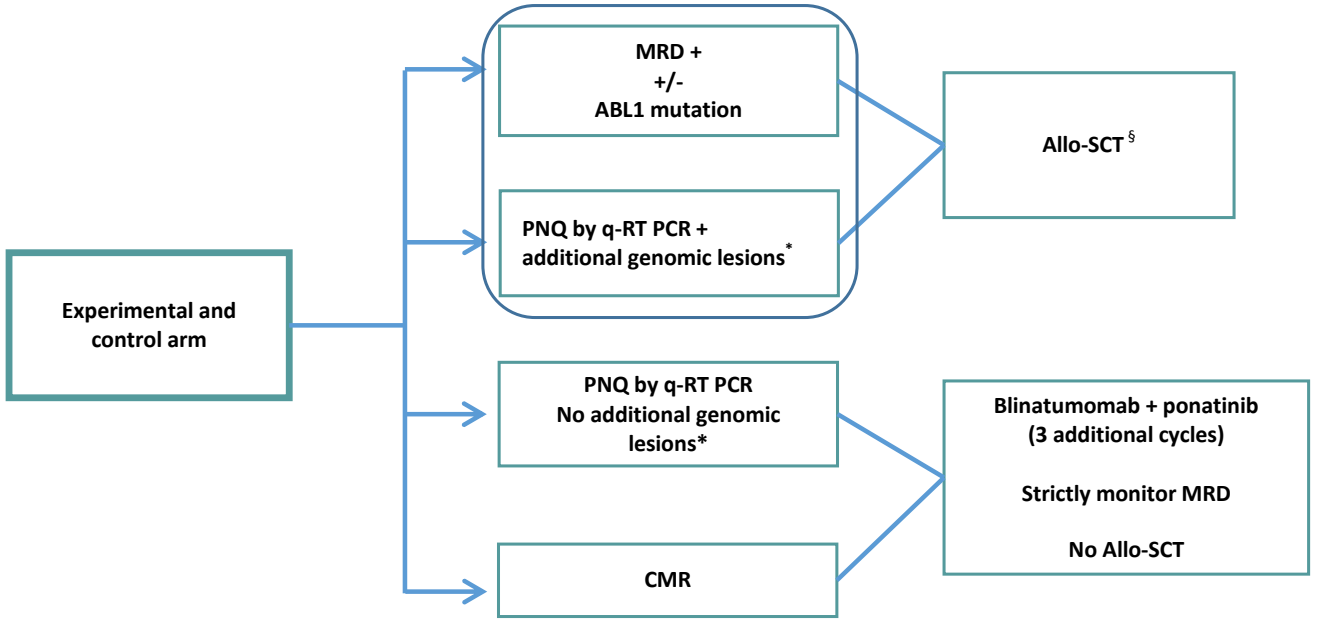
Ongoing present : GIMEMA ALL2820 (I)

Sample size: 236 patients
No upper age limit

28 pts enrolled so far

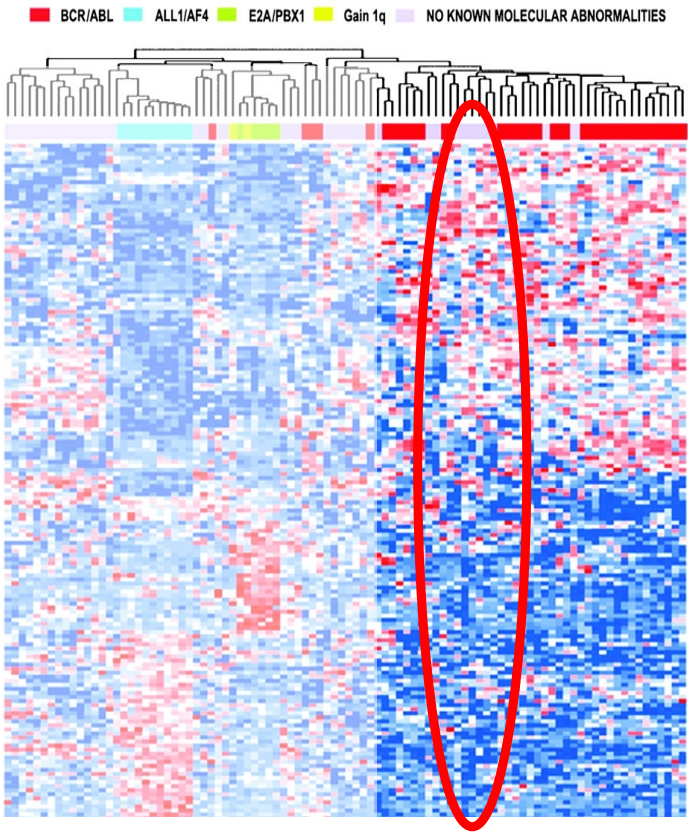


Ongoing present: GIMEMA ALL2820 (II)

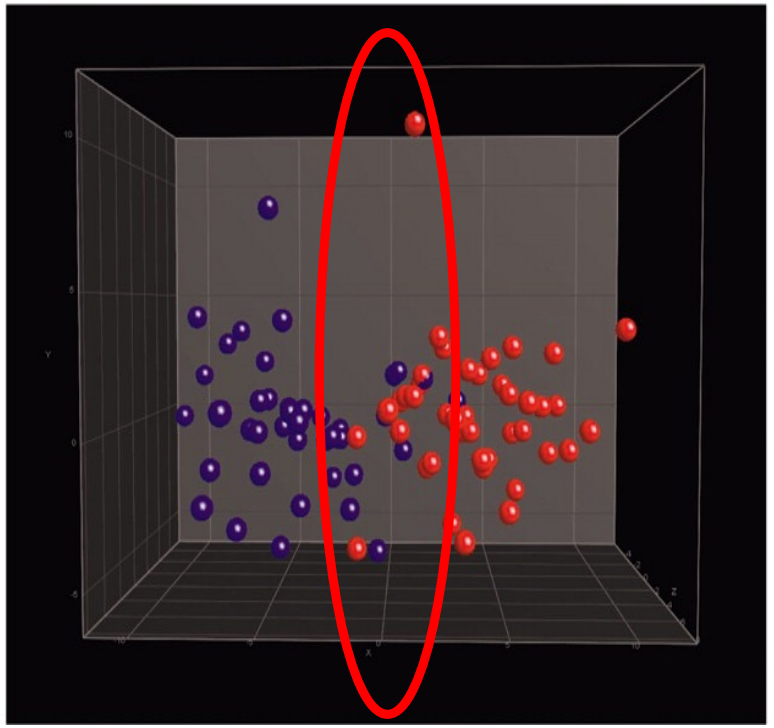


*_IKZF1_-plus _CDKN2A/B_ and/or _PAX5_ deletions; §Additional blinatumomab cycles are allowed before allo-SCT at medical discretion

Background on Ph-like ALL



Chiaretti et al, CCR 2005



Haferlach et al, Blood 2005

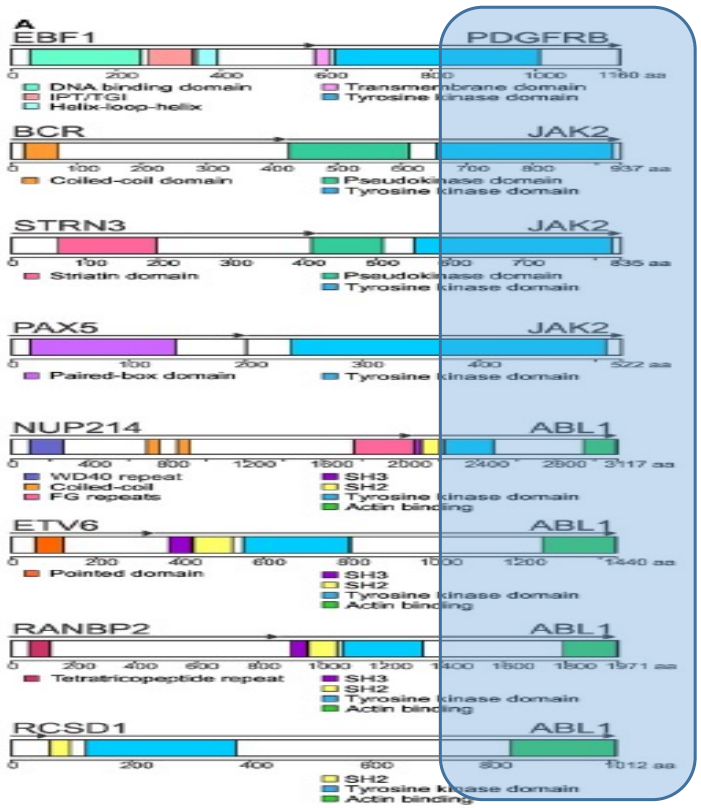
2005: first identification, by GEP, of a subset of adult B-lineage ALL clustering together with *BCR/ABL1*+ ALL cases

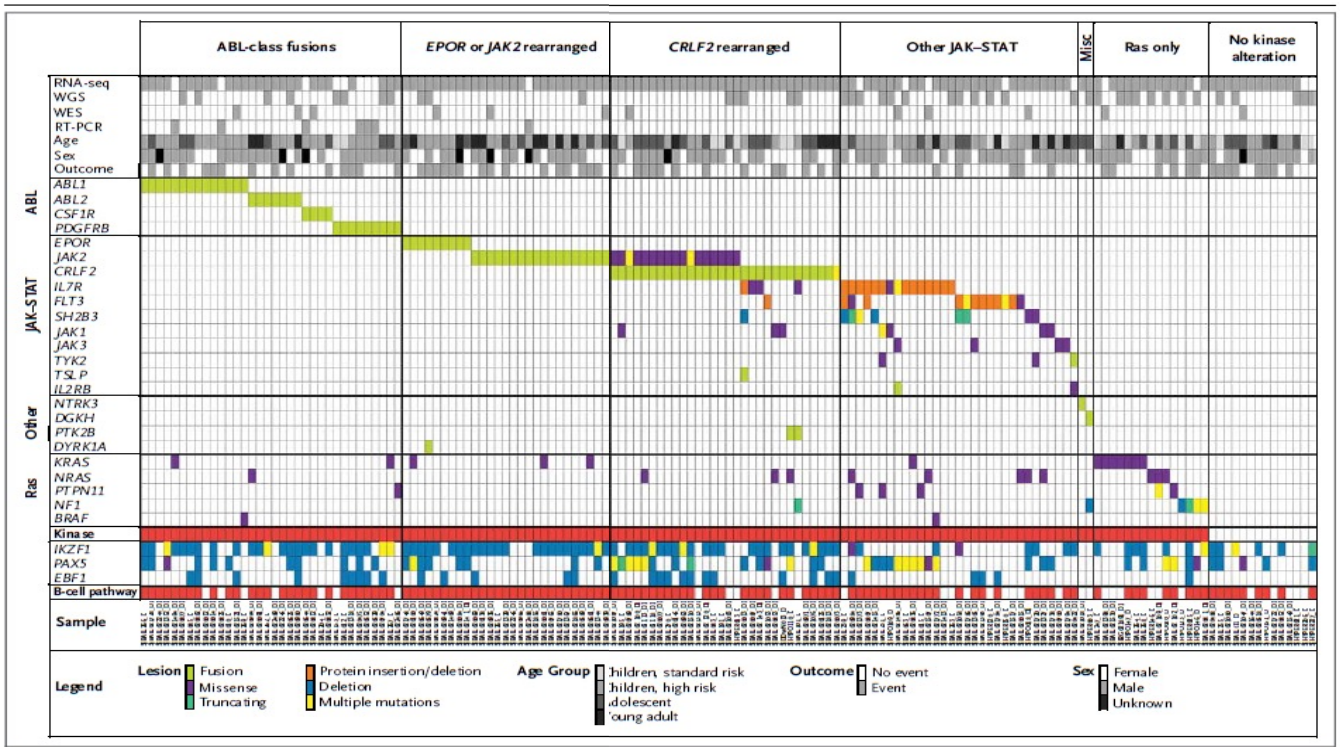
Cancer Cell
Article

Genetic Alterations Activating Kinase and Cytokine Receptor Signaling in High-Risk Acute Lymphoblastic Leukemia

Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia

K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.-L. Yang, D. Pei, K. McCastlain, L. Ding, C. Lu, G. Song, J. Ma, J. Becksfort, M. Rusch, S.-C. Chen, J. Easton, J. Cheng, K. Boggs, N. Santiago-Morales, I. Iacobucci, R.S. Fulton, I. Wen, M. Valentine, C. Cheng

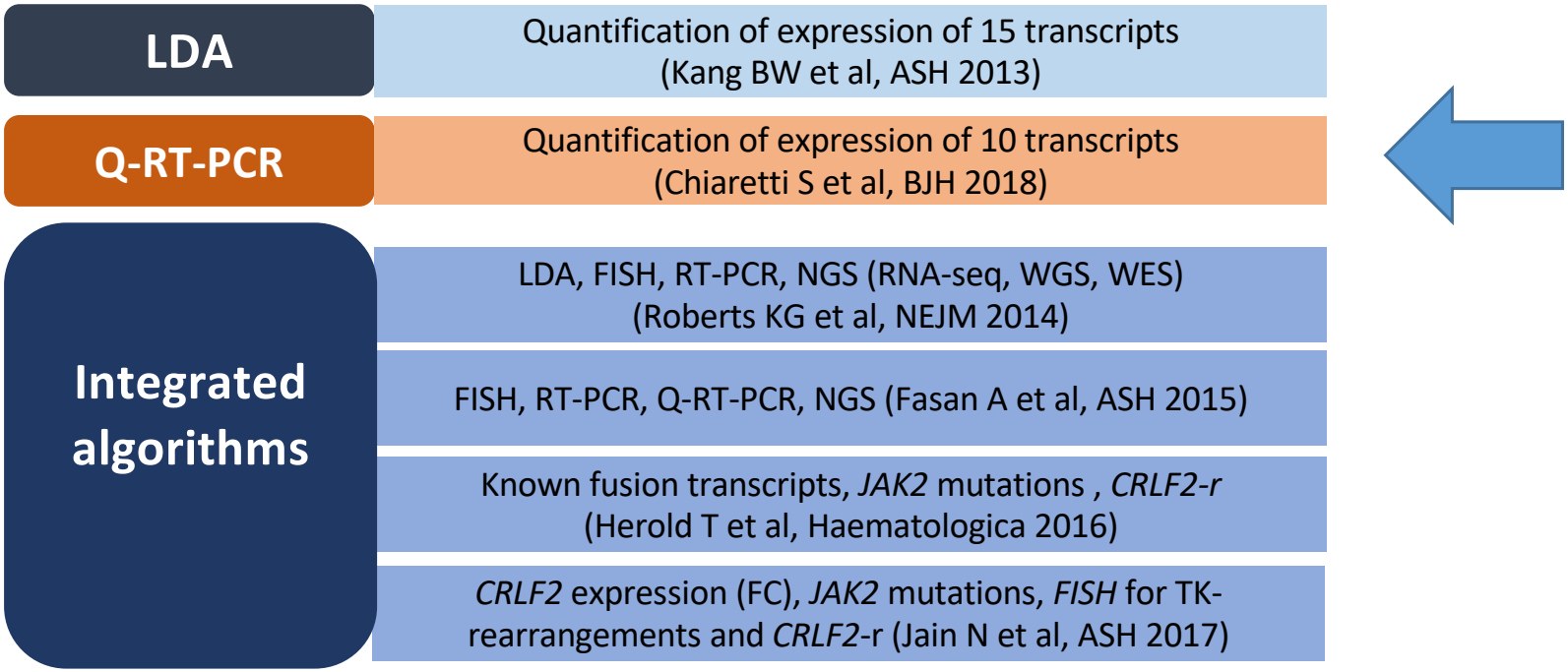




In high risk ALL, RNA-seq has identified novel mutations that involve TKs in the majority of cases. They appear to have transforming capability and to respond to TKIs.

Roberts KG. *Cancer Cell* 2012; 22:153-66 Roberts KG, *et al. N Engl J Med* 2014;371:1005–10

Main problem with Ph-like ALL cases



As far as possible, diagnostic assays should be available in most centers (or in centralized laboratories)

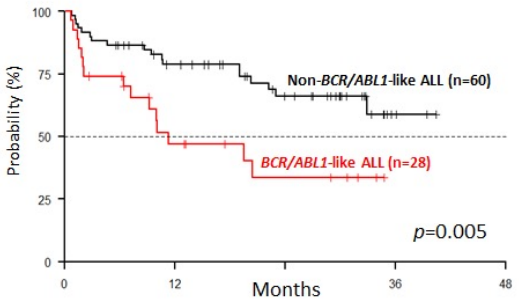
Outcome of GIMEMA LAL1913 according to Ph-like status

28/88 (31.8%) *BCR/ABL1*-like cases

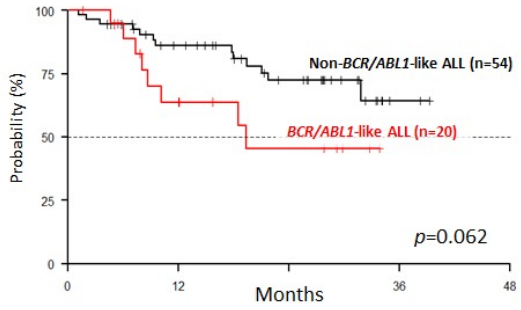
		BCR/ABL1-like	Non-*BCR/ABL1*-like	*p*-value
No		28	60	
CR (%)	No CR	**7 (25.9)**	**5 (8.5)**	0.044
	CR	20 (74.1)	54 (91.5)	
TP1_MRD (%)	TP1 MRD positive	**14 (77.8)**	**19 (41.3)**	0.012
TP2_MRD (%)	TP2 MRD positive	**9 (52.9)**	**9 (20.5)**	0.029
TP3_MRD (%)	TP3 MRD positive	**5 (41.7)**	**5 (13.5)**	0.05

	OR (95%CI)	*p*-value
BCR/ABL1-like vs non-*BCR/ABL1*-like	4.5 (1.373-15.508)	0.014

Event-free survival at 24 months



Disease-free survival at 24 months



	HR (95%CI)	*p*-value
BCR/ABL1-like *vs* non-*BCR/ABL1*-like	2.3 (1.124-4.92)	0.023

***BCR/ABL1*-like status is ALL is characterized by a lower CR rate, MRD persistence and shorter survival also in a pediatric-oriented and MRD-driven clinical trial.**

The prognostic role of the *BCR/ABL1*-like status is independent from the other clinico-biological and genetic features

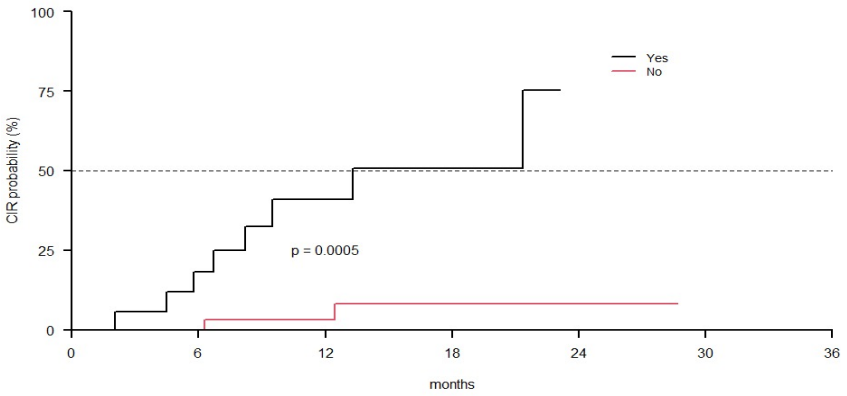
Chiaretti et al, Haematologica 2020

Outcome of GIMEMA LAL2317 according to Ph-like status

32 Ph-like cases identified, median follow-up 13 months (0.5-31)

		Post-blinatumomab 1 MRD (w14)		
Characteristic	**Overall (N)**	**MRD_{neg}**	**MRD_{pos}**	**p-value**
Post-chemo #3 MRD (w10), n (%)	94	89	5	0.001
MRD_{neg}	68	68 (100%)	0 (0%)	
MRD_{pos}	26	21 (81%)	5 (19%)	

95% MRD_{neg} after chemo #3 and blin 1
81% MRD_{pos} became MRD_{neg} after blin 1
– incl. 10/10 (100%) Ph-like ALL

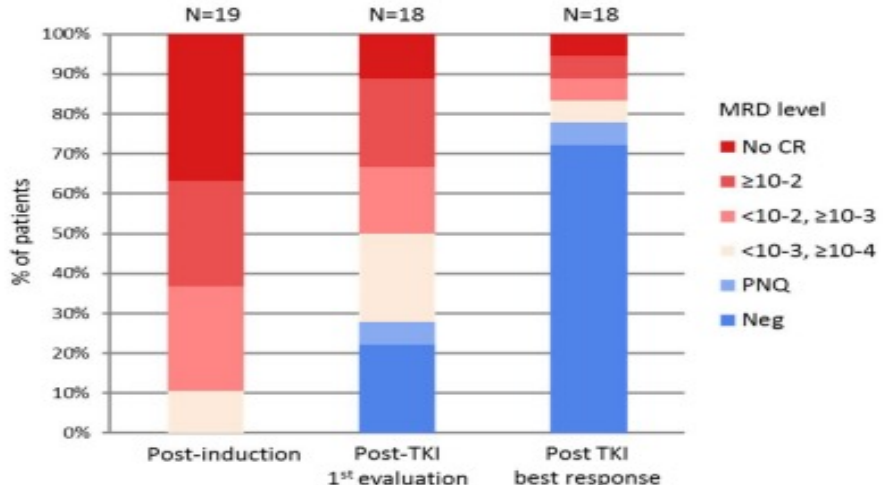


1-year relapse rate

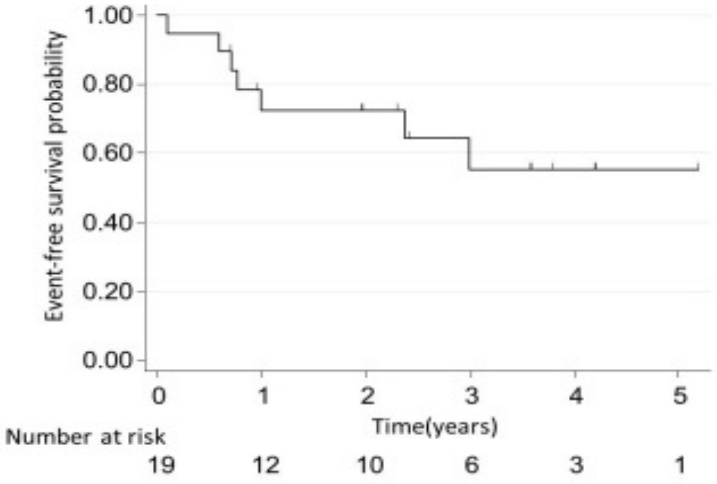
Ph-like 40.1 %
No Ph-like 3.2 %
P=0.0005

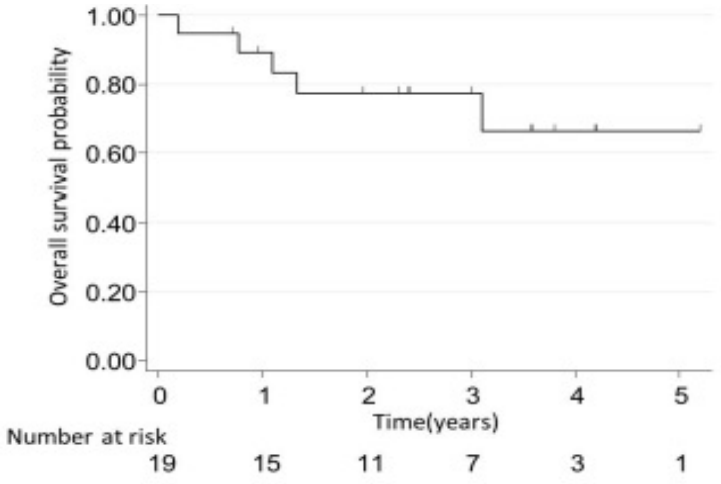
Bassan et al, EHA 2021

Use of TKIs



Use of TKIS induces hematologic and molecular remission

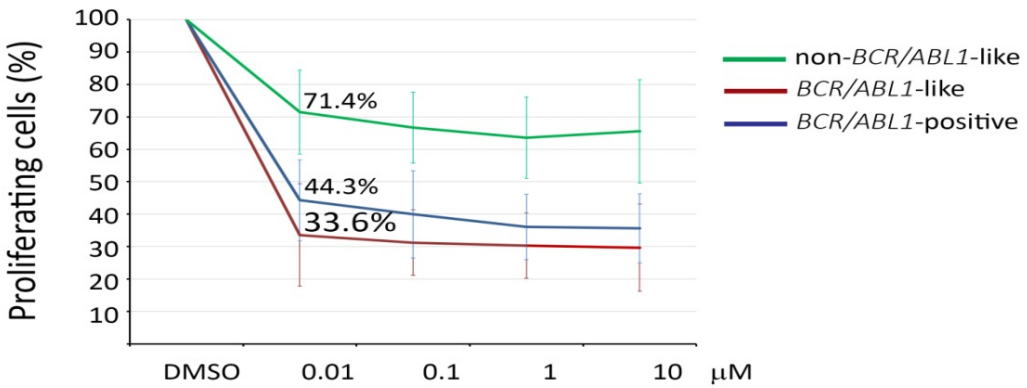




Tanasi et al, Blood 2019

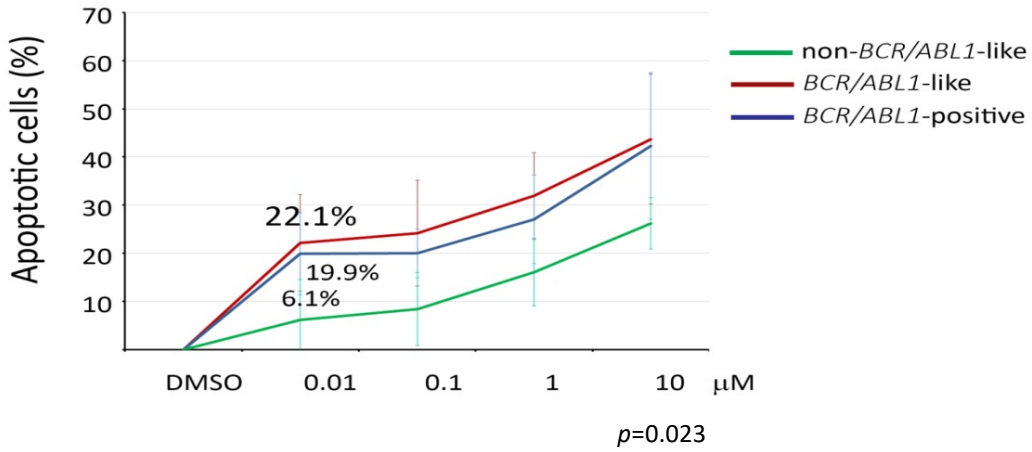
Wide-spectrum appraoch. Ponatinib

A



p=0.0007

B



p=0.023

In vitro use of ponatinib on primary cells: effect on proliferation and apoptotic response similar in _BCR/ABL1_+ and _BCR/ABL1_-like cases (2 _EBF1/PDGFRB_-positive, 1 _JAK2_-mutated and _P2RY8/CRLF2_-r, 1 _RCSD1/ABL1_, 3 WT for JAK/STAT and RAS mutations)

Chiaretti S et al, BJH 2018

Blood Cancer Journal

Blood Cancer J. 2015 Mar; 5(3): e292.
Published online 2015 Mar 13. doi: 10.1038/bcj.2015.13
PMCID: PMC4382656
PMID: 25768406

Drug response profiling can predict response to ponatinib in a patient with t(1;9)(q24;q34)-associated B-cell acute lymphoblastic leukemia

Y Collette,[1,3,*] T Prébet,[1,2,3] A Goubard,[1] J Adélaïde,[1] R Castellano,[1] N Carbuccia,[1] S Garnier,[1] A Guille,[1] C Arnoulet,[1,2] A Charbonier,[1,2] M J Mozziconacci,[1,2] D Birnbaum,[1] M Chaffanet,[1,3] and N Vey[1,2]

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2021, VOL. 62, NO. 3, 755–757
https://doi.org/10.1080/10428194.2020.1842401
Taylor & Francis
Taylor & Francis Group
Check for updates

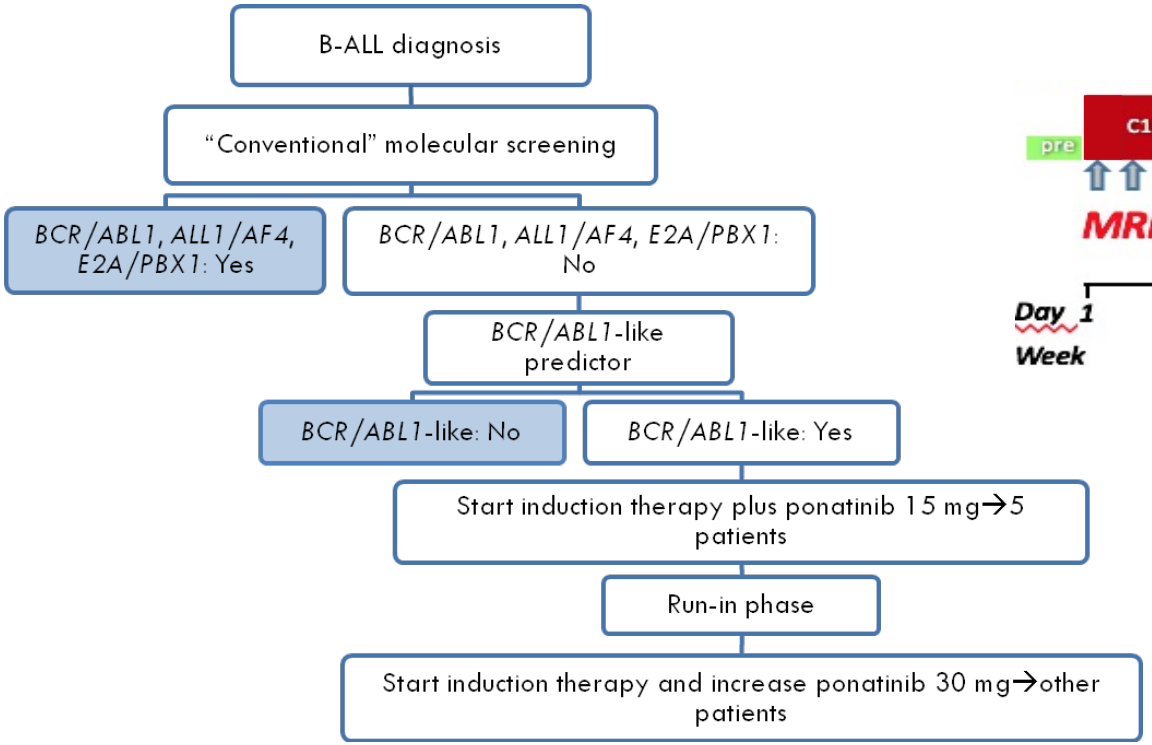
LETTER TO THE EDITOR

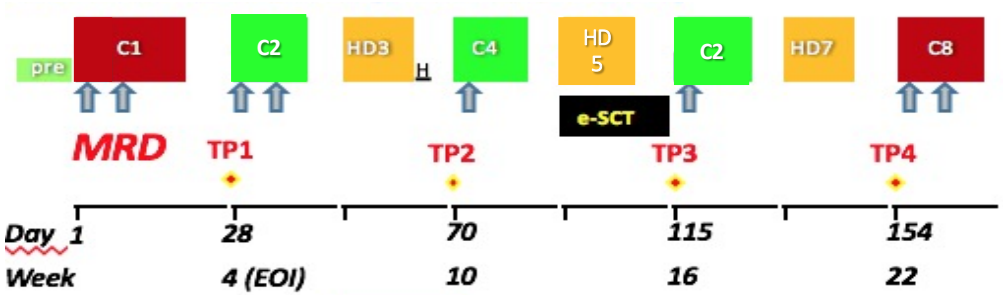
Ponatinib for the treatment of Ph-like acute lymphoblastic leukemia

Monia Lunghi[a], Andrea Patriarca[a], Mariangela Greco[a], Akram Taherinasab[b], Irene Della Starza[b], Marzia Cavalli[b], Gianluca Gaidano[a], Robin Foà[b] and Sabina Chiaretti[b]; on behalf of the Campus ALL

Combination of Ponatinib Plus Chemotherapy As Frontline Treatment For Patients With BCR/ABL1-Like Acute Lymphoblastic Leukemia (BCR/ABL1-Like ALL) - BALLik

GIMEMA ALL2922





- Same backbone of GIMEMA LAL1913
- Sample size: 32 patients
- Removal of ASP
- Introduction of ponatinib
- Age adjusted treatment

Ongoing studies for Ph-like ALL

Dasatinib	Newly diagnosed Ph+ ALL or Ph-like ALL (with ABL-class rearr) in elderly	NCI	Phase 2	Cohort II: dasatinib plus steroids in induction followed by blinatumomab	Recruiting	NCT02143414
	R/R Ph-like ALL in children (>10 years old), adults and older adults	MDACC	Phase 1/2	Dasatinib or ruxolitinib (depending on the lesion) with chemotherapy	Completed	NCT02420717
	Newly diagnosed Ph-like ALL in pediatric patients with ABL-class rearr	SJCRH	Phase 2/ 3	Total therapy strategy including dasatinib in induction in case of ABL-class rearrangements	Recruiting	NCT03117751
	Newly diagnosed Ph-like ALL in pediatric patients and young adults with ABL-class rear	NCI	Phase 3	Subarm with dasatinib plus chemotherapy	Active, not recruiting	NCT02883049
Ponatinib	R/R or T315I+ Ph+ ALL and R/R Ph-like ALL in pediatric patients	Takeda	Phase 1/2	Ponatinib plus chemotherapy	Recruiting	NCT04501614
Ruxolitinib plus dasatinib	Newly diagnosed and R/R Ph+ ALL or R/R Ph-like ALL in adults and older adults	MSKCC	Phase 1	Adding ruxolitinib to combination of dasatinib plus dexamethasone	Active, not recruiting	NCT02494882
Ruxolitinib	Newly diagnosed Ph-like ALL in pediatric patients with JAK/STAT mutations	SJCRH	Phase 2/3	Total therapy strategy including ruxolitinib in induction in case of JAK/STAT mutations	Recruiting	NCT03117751
	Newly diagnosed Ph-like ALL in pediatric patients with JAK/STAT mutations	COG	Phase 2	Ruxolitinib in combination with chemotherapy	Recruiting	NCT02723994
Ruxolitinib plus dasatinib	Newly diagnosed and R/R Ph+ ALL or R/R Ph-like ALL in adults and older adults	MSKCC	Phase 1	Adding ruxolitinib to combination of dasatinib plus dexamethasone	Active, not recruiting	NCT02494882

Other biology based targets for Ph-like ALL (experimental)

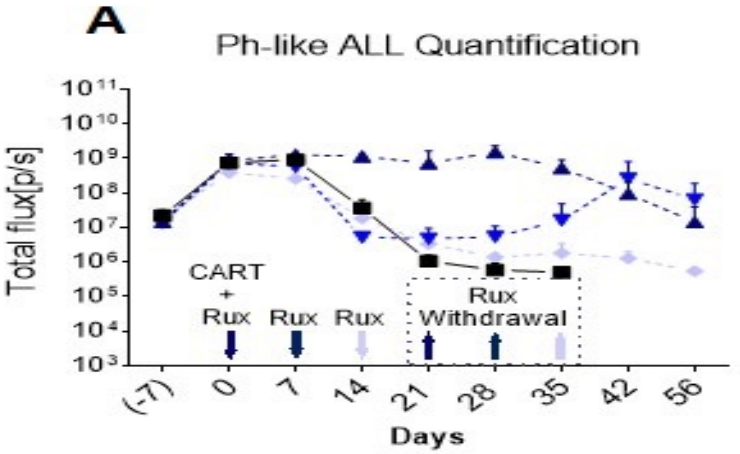
PLENARY PAPER | DECEMBER 9, 2021

Degradation of Janus kinases in *CRLF2*-rearranged acute lymphoblastic leukemia

Yunchao Chang, Jaeki Min, Jamie A. Jarusiewicz, Marisa Actis, Shanshan Yu-Chen Bradford, Anand Mayasundari, Lei Yang, Divyabharathi Chepyala, Lisa J. Alcock, Kathryn G. Roberts, Stanley Nithianantham, Dylan Maxwell, Lauren Rowland, Randolph Larsen, Aman Seth, Hiroaki Goto, Toshihiko Imamura, Koshi Akahane, Baranda S. Hansen, Shondra M. Pruett-Miller, Elisabeth M. Paietta, Mark R. Litzow, Chunxu Qu, Jun J. Yang, Marcus Fischer, Zoran Rankovic, Charles G. Mullighan

Key Points

- PROTAC design based on crystal structures of JAK2 kinase domain in complex with ruxolitinib and baricitinib.
- PROTACs targeting JAKs are efficacious in vivo in *CRLF2*r ALL; the most effective degrade multiple targets, including IKZF1, and GSPT1.



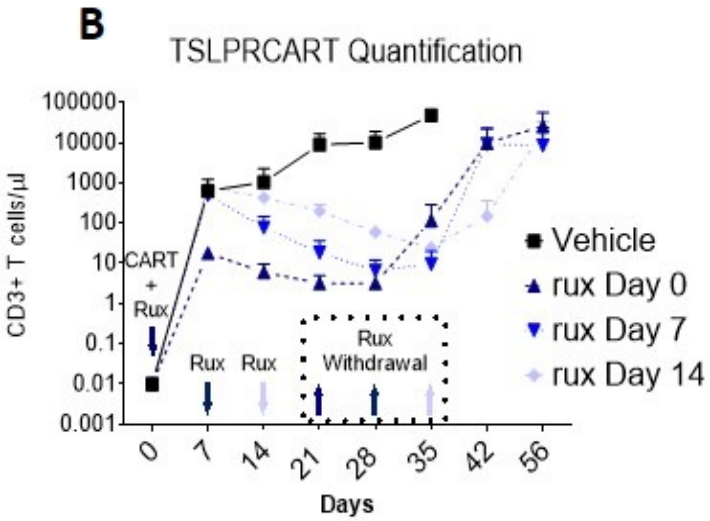
LYMPHOID NEOPLASIA | FEBRUARY 3, 2022

Genome-wide CRISPR-Cas9 screen identifies rationally designed combination therapies for *CRLF2*-rearranged Ph-like ALL

Kensuke Sasaki, Takuji Yamauchi, Yuichiro Semba, Jumpei Nogami, Hiroshi Imanaga, Tatsuya Terasaki, Fumihiko Nakao, Koshi Akahane, Takeshi Inukai, Els Verhoeven, Koichi Akashi, Takahiro Maeda

Key Points

- STAT signaling is dispensable for survival of *IgH-CRLF2*-r Ph-like ALL cells.
- A precision medicine approach based on mutational status, namely of *RAS*, is key for treatment of *IgH-CRLF2*-r Ph-like ALL.



Bagashev A, et al, abstract 1705

Take home messages

Ph+ ALL: almost a success story…

Open issues: 1) how to improve *IKZF1*^{plus} ;2) transplant

Ph-like ALL: Long way to go

Open issues: 1) identification; 2) Therapeutic strategies

TKIs incorporation in the front-line settings will hopefully improve the outcome of these patients

Experimental models are paving the way for alternative strategies in case of treatment failure

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