MRD-driven strategy in Ph-like ALL: does it work?

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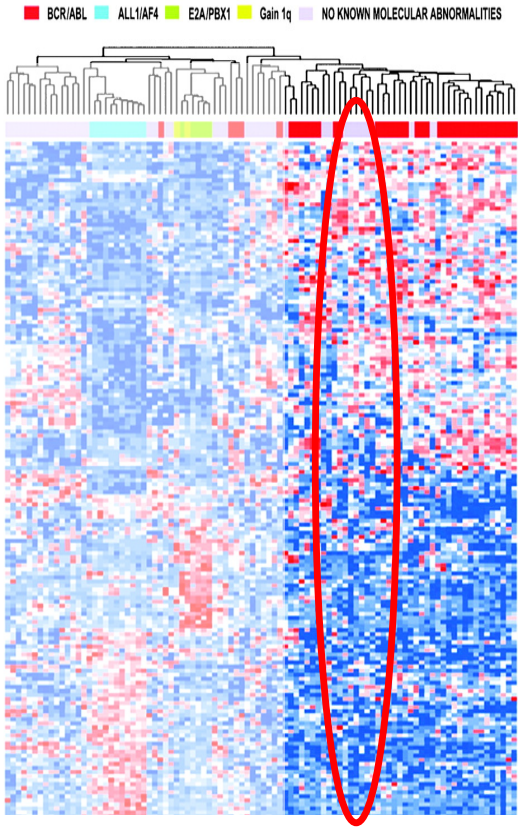
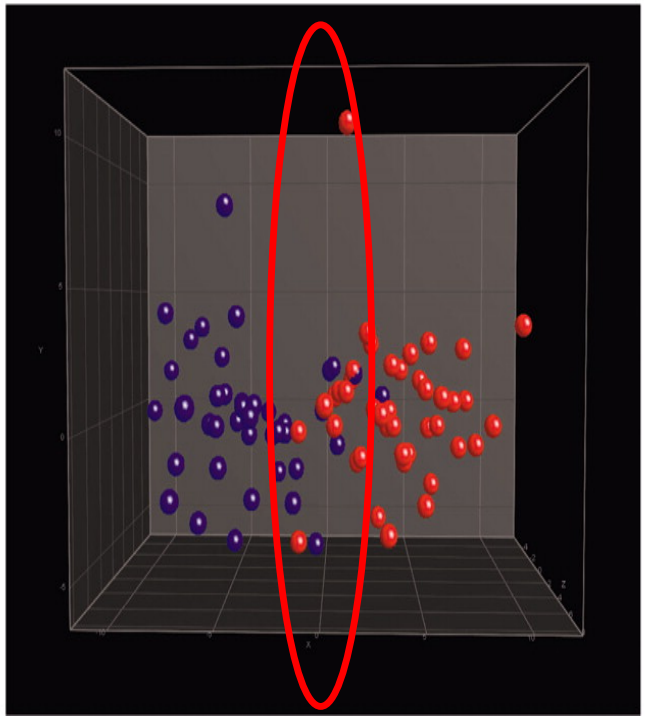
Ph-like ALL: first report in adults

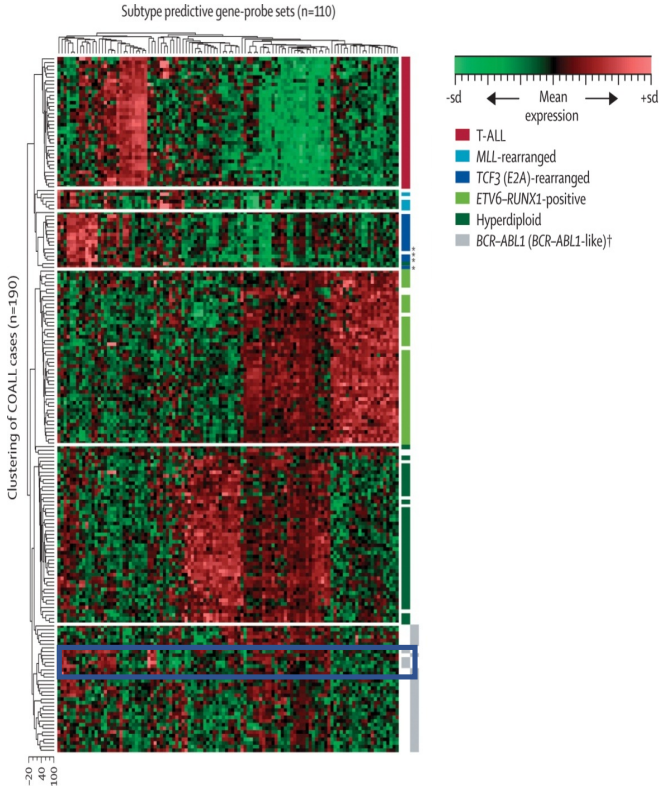


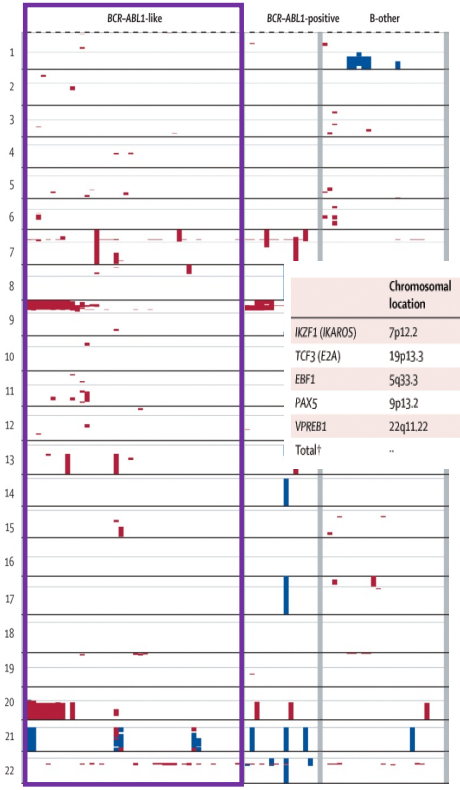
Chiaretti et al, CCR 2005



Haferlach et al, Blood 2005

Ph-like ALL: genetic characterization





Deletions are visualised in red, whereas amplifications are shown in blue.

	Chromosomal location	BCR-ABL1-like (n=44)	BCR-ABL1-positive (n=15)	B-other (n=25)*
IKZF1 (IKAROS)	7p12.2	17 (39%)	11 (73%)	4 (16%)
TCF3 (E2A)	19p13.3	3 (7%)	0	0
EBF1	5q33.3	6 (14%)	0	0
PAX5	9p13.2	16 (36%)	6 (40%)	3 (12%)
VPREB1	22q11.22	15 (34%)	6 (40%)	6 (24%)
Total†	..	36 (82%)	12 (80%)	9 (36%)

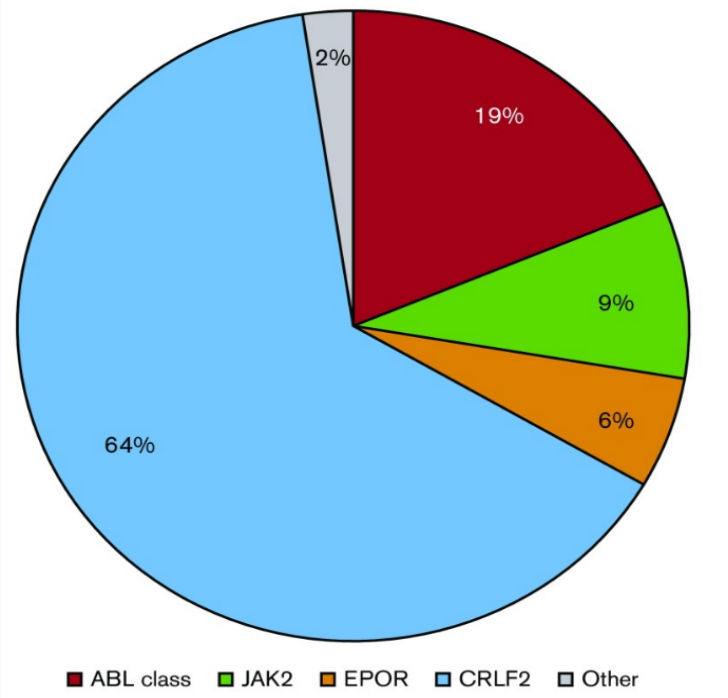
Den Boer et al, Lancet 2009;
Mullighan et al, NEJM 2009

GEP: Identification, within children (n=297), of a subset with a transcriptional profile resembling that of *BCR/ABL1*+ cases (≈15-20%)

Clinical features: Hyperleukocytosis, poor response to VCR, ASP and DNM, poor prognosis (reduced DFS at 5 years and increased resistance to induction)

Array-CGH: *IKZF1*, *PAX5*, *TCF3* and *VPREB1* deletions, *CRLF2* deregulation

Ph-like ALL: genetic characterization



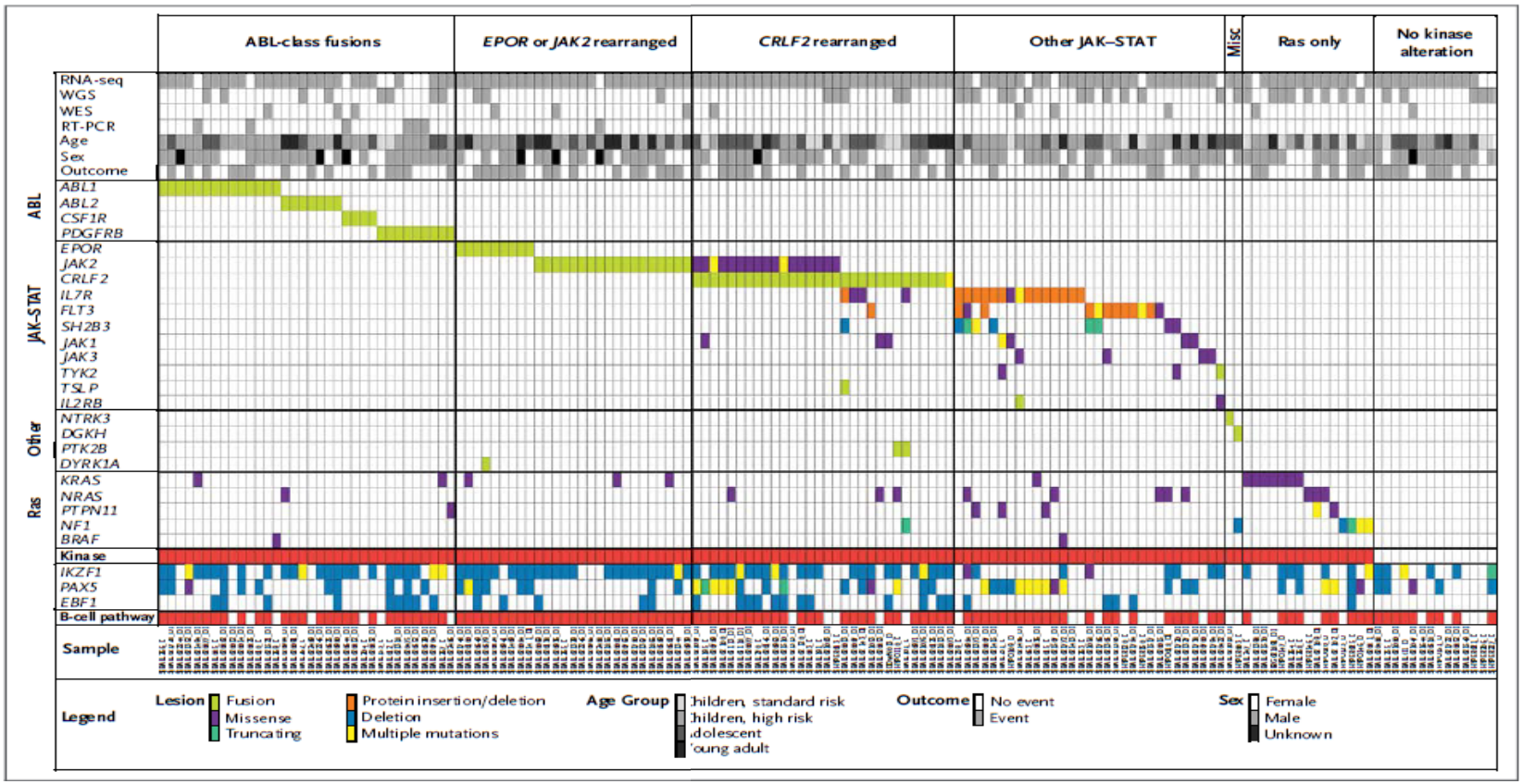
Harvey RC and Tasian SK. *Blood Adv*, 2020

Kinase gene	Fusion partners, n	Patients, n	5' genes
ABL1	6	14	ETV6, NUP214, RCSD1, RANBP2, SNX2, ZMIZ1
ABL2	3	7	PAG1,* RCSD1,* ZC3HAV1*
CSF1R	1	4	SSBP2*
PDGFRB	4	11	EBF1, SSBP2,* TNIP1,* ZEB2*
CRLF2	2	30	IGH, P2RY8
JAK2	10	19	ATF7IP,* BCR, EBF1,* ETV6, PAX5, PPFIBP1,* SSBP2, STRN3, TERF2,* TPR*
EPOR	2	9	IGH, IGK*
DGKH	1	1	ZFAND3*
IL2RB	1	1	MYH9*
NTRK3	1	1	ETV6†
PTK2B	2	1	KDM6A,* STAG2*
TSLP	1	1	IQGAP2*
TYK2	1	1	MYB*

Roberts KG, *et al. N Engl J Med* 2014;371:1005–1015

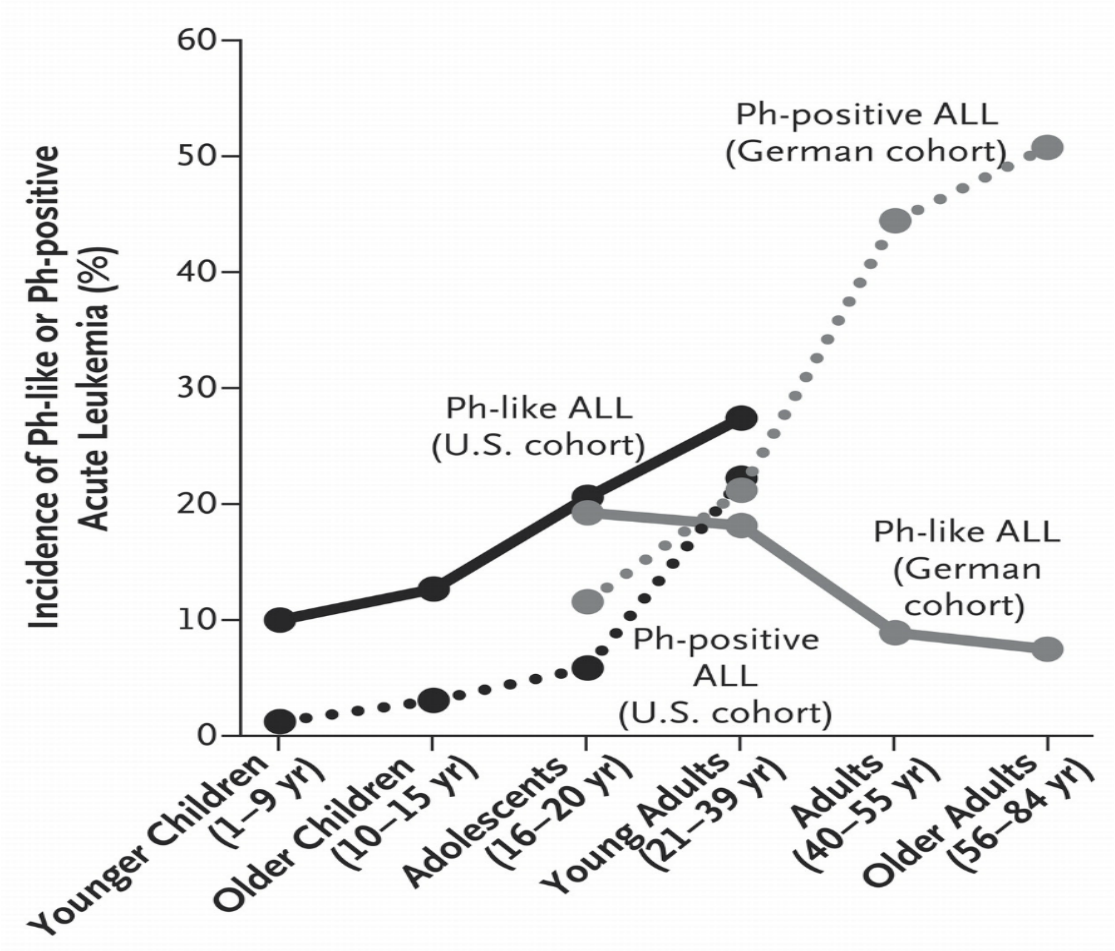
Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia

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, J. Wen, M. Valentine, C. Cheng



Roberts KG. *Cancer Cell* 2012; 22:153-66 Roberts KG, *et al. N Engl J Med* 2014;371:1005–1015

BCR-ABL1-like. Incidence



Incidence is higher in AYA (10% in children; 27% in AYA). NEVER detected in cases positive for known fusion transcripts (*BCR/ABL1*, *KMT2A*-r, *TCF3/PBX1*)

However:

- It highly depends on the denominator (all B-lineage ALL or B-neg ALL) and

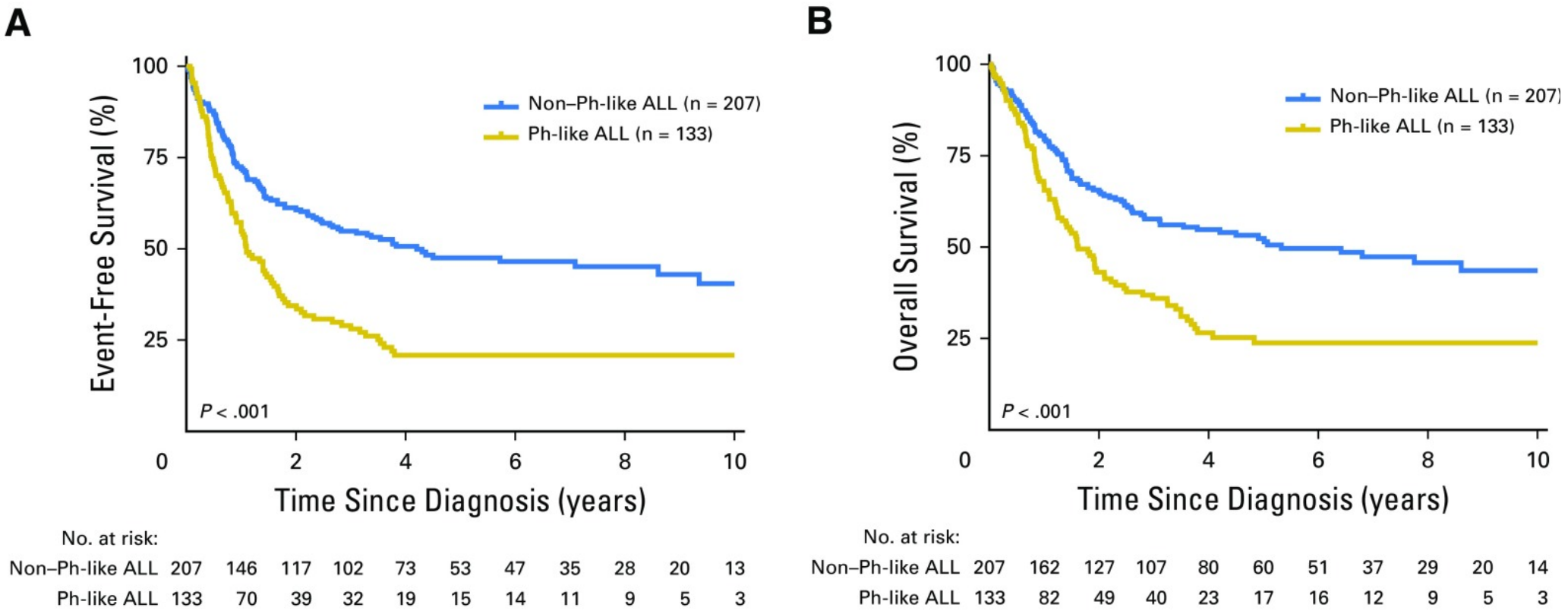
- on the assay used for *BCR/ABL1*-like identification

- More adult cases are being evaluated → incidence in adults is almost equal to AYA ≥ 25%

Roberts KG, NEJM 2014 371:1005-15; Heroldt T, NEJM 2014 371:2235; Chiaretti S et al, in press

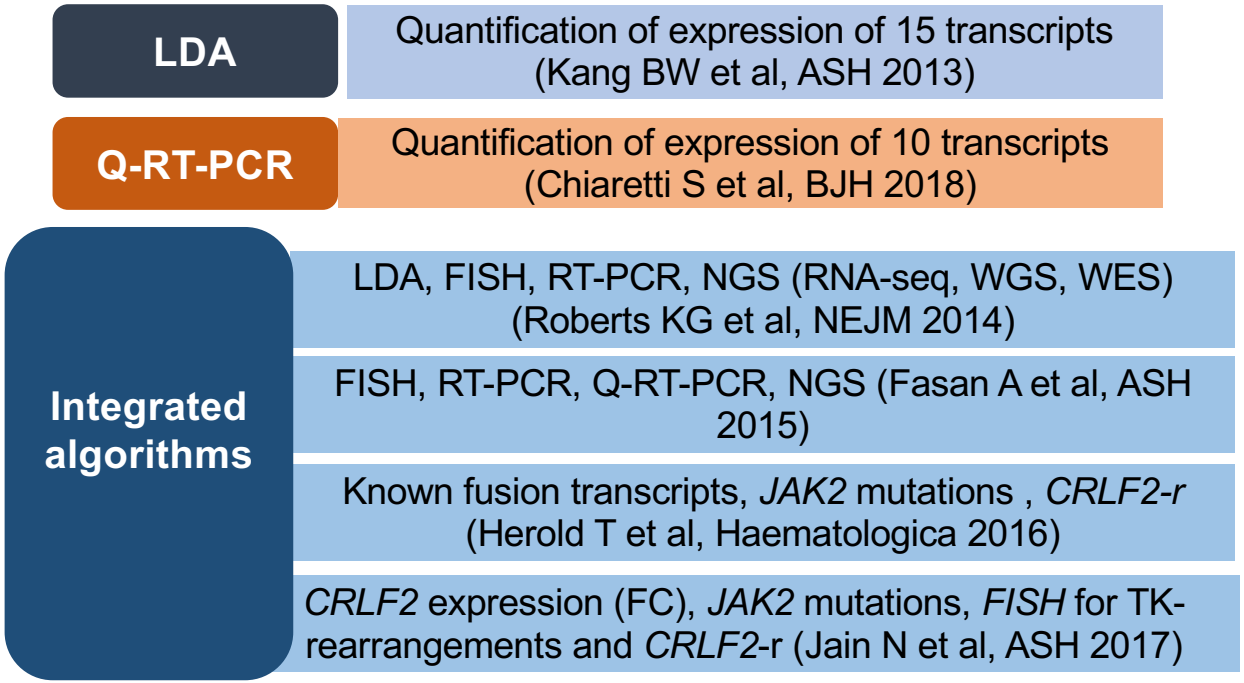
Survival in adults

- **Significantly inferior survival (EFS, DFS, OS) in all reported studies**



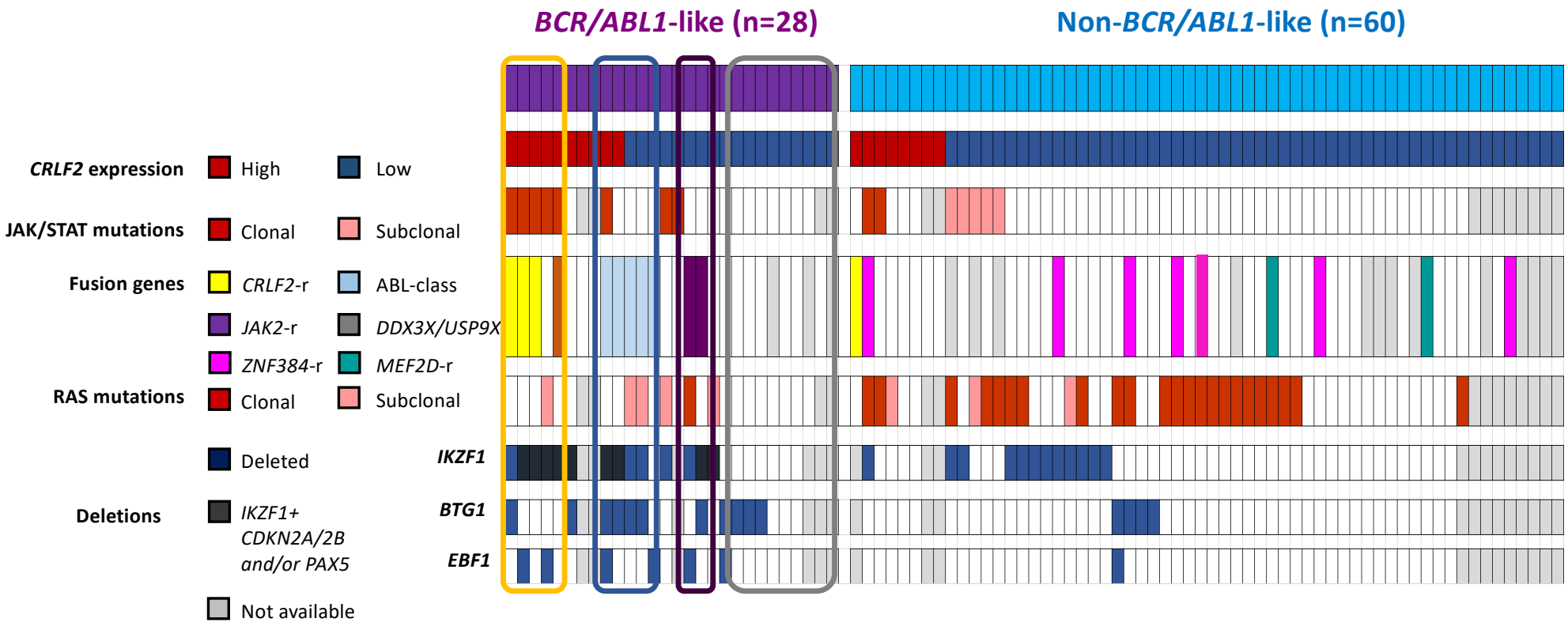
Roberts KG et al, JCO 2016

Ph-like ALL: diagnosis



Not yet available a gold standard

Biological features of GIMEMA LAL1913 patients according to the *BCR/ABL1*-like status



BCR/ABL1-like associated lesions identified in 69.6%

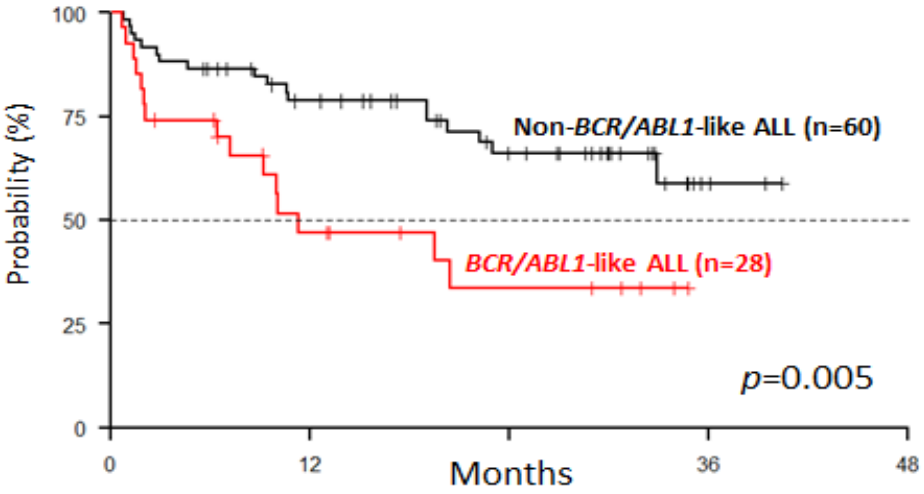
CRLF2 deregulation

ABL-class genes + other TKs

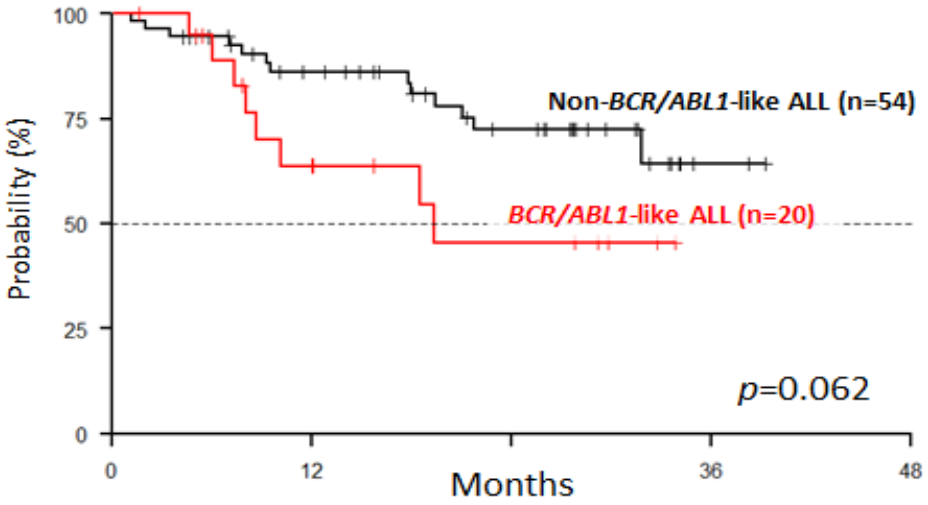
No fusions

Ph-like ALL in GIMEMA LAL1913: outcome

EFS at 24 months



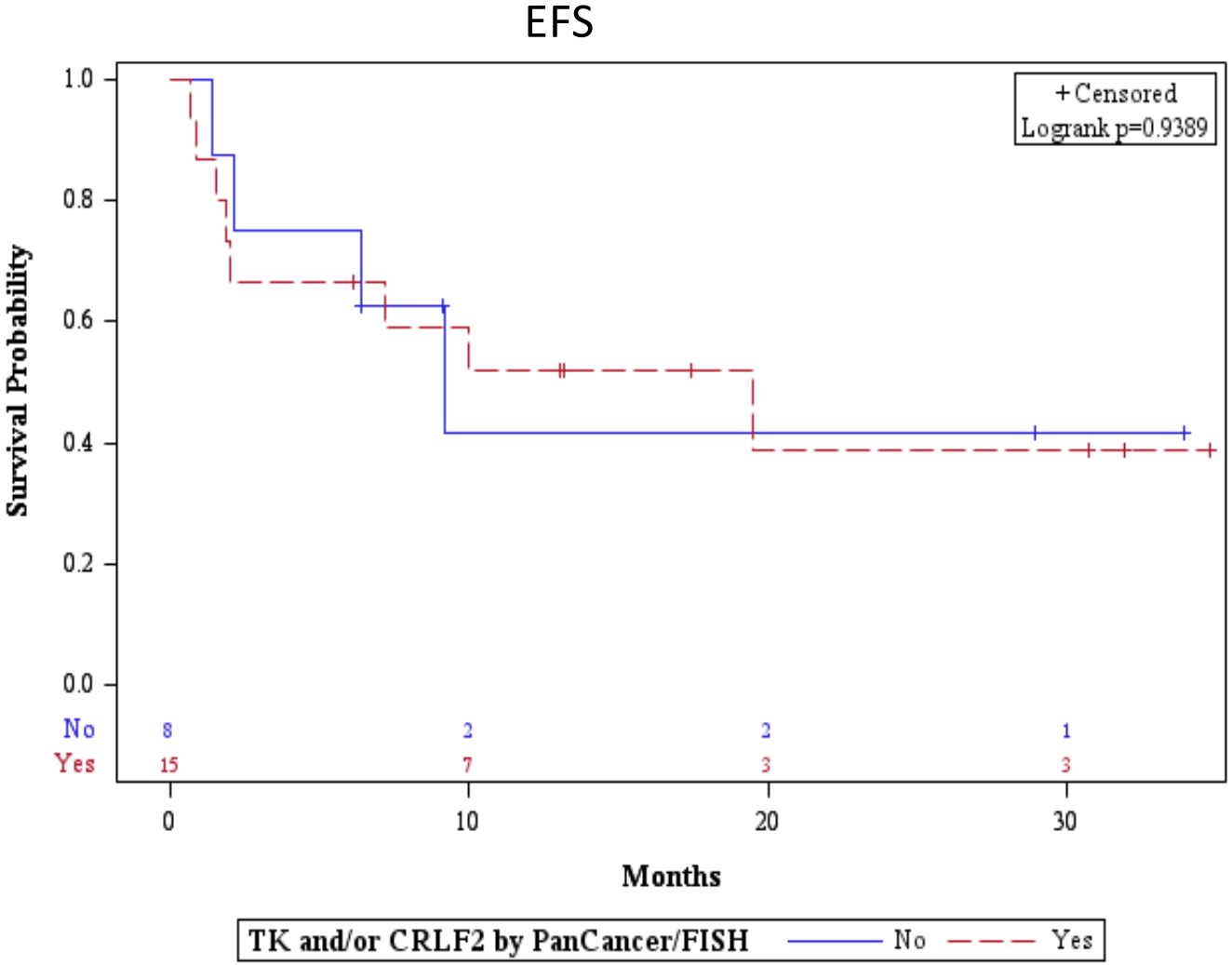
DFS at 24 months



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

Chiaretti S, *et al. Haematologica* 2020; ePub ahead of print.

Clinical outcome of GIMEMA LAL1913 patients according to the presence/absence of well-defined molecular lesions in BCR/ABL1-like cases (I)



All cases with ABL-class lesions experienced an event within 10 months from diagnosis

Ph-like ALL in GIMEMA LAL1913 : MRD

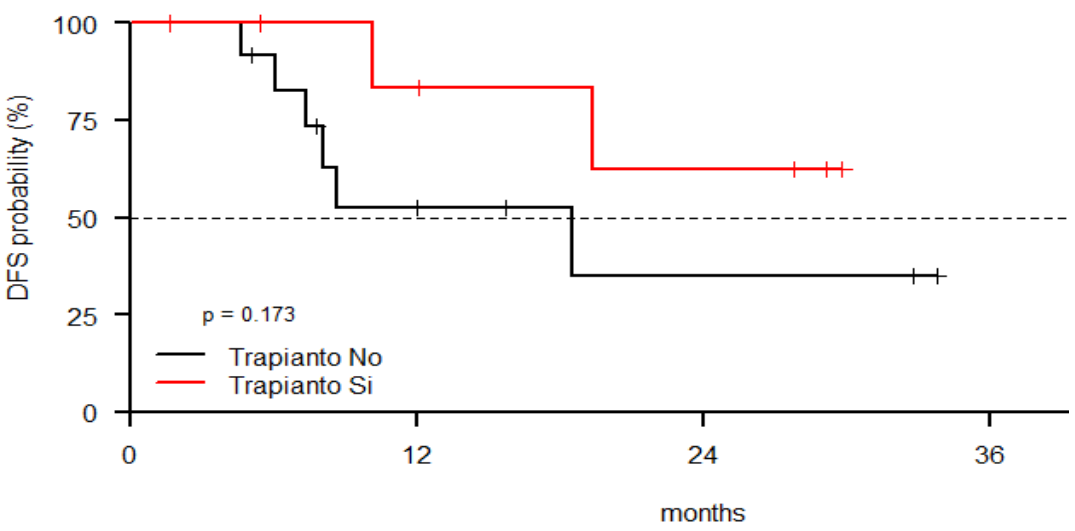
28/88 (31.8%) *BCR/ABL1*-like cases		*BCR/ABL1*-like	Non-*BCR/ABL1*-like	p-value
N		28	59	
CR (%)	No CR	7 (25.9)	5 (8.5)	0.044
	CR	20 (74.1)	54 (91.5)	
TP1_MRD (%)	TP1 MRD positive	14 (77.8)	19 (41.3)	0.012
TP2_MRD (%)	TP2 MRD positive	9 (52.9)	9 (20.0)	0.029
TP3_MRD (%)	TP3 MRD positive	5 (41.7)	5 (13.5)	0.05

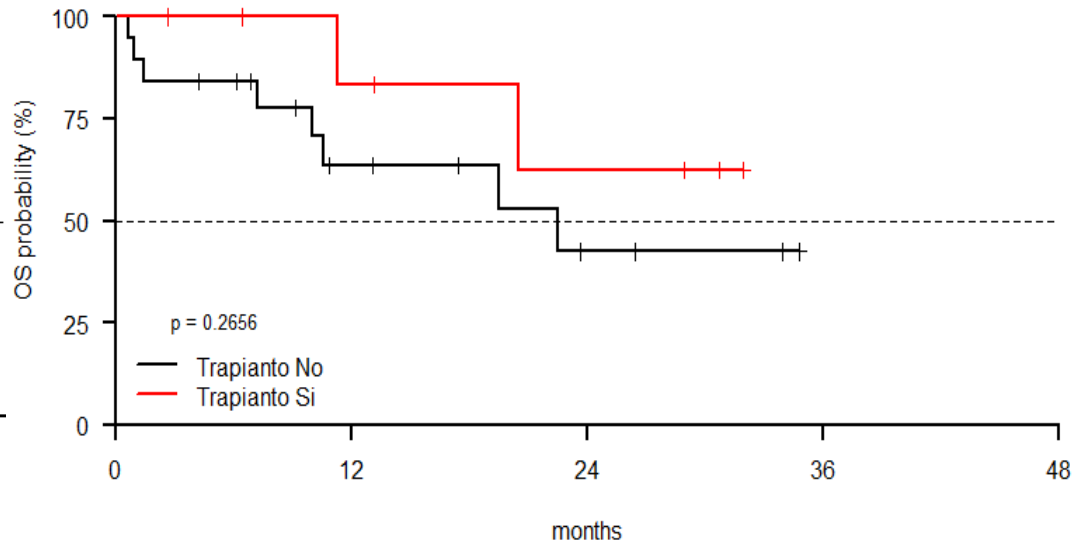
A *BCR/ABL1*-like status is characterized by a lower CR rate, MRD persistence and shorter survival also in a pediatric-oriented and MRD-driven clinical trial.
The prognostic role of the
BCR/ABL1-like status is independent from the other clinico-biologic and genetic features.

Chiaretti S, *et al. Haematologica* 2020; ePub ahead of print.

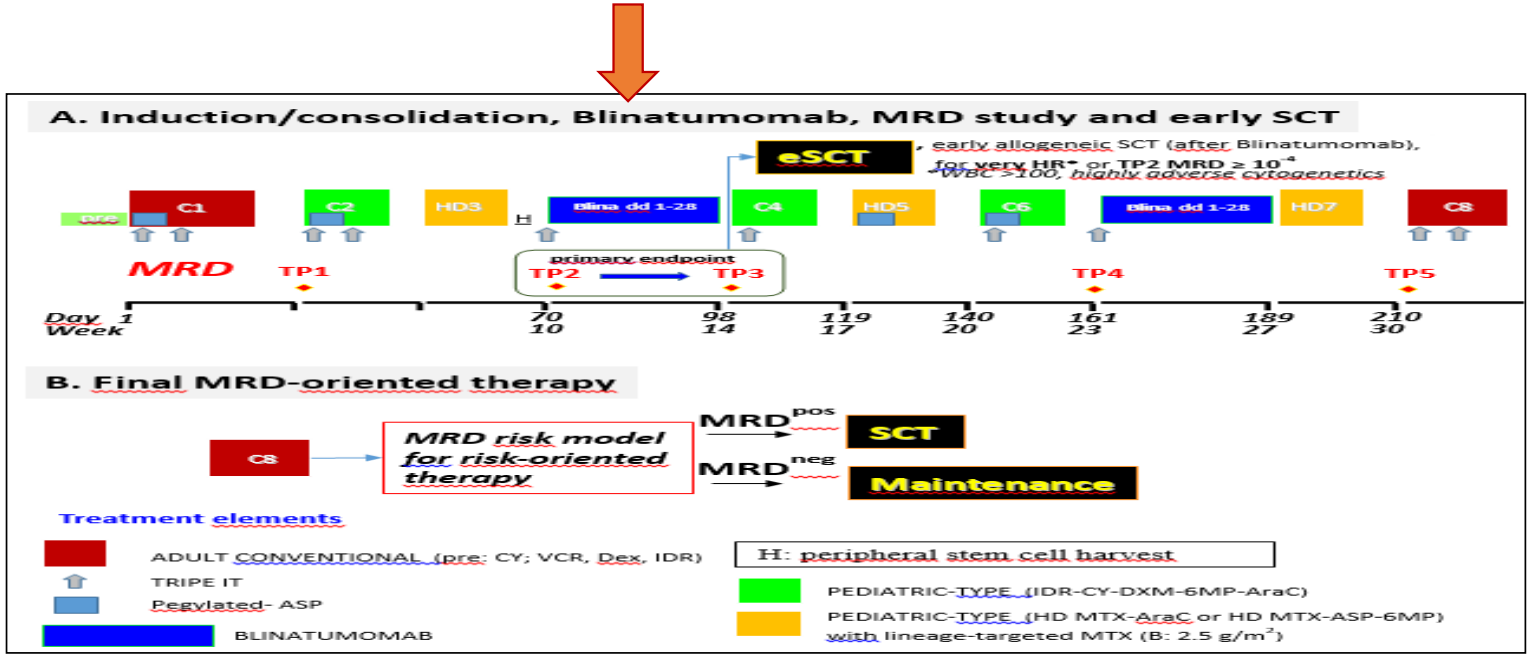
Role of transplant within GIMEMA 1913 in BCR/ABL1-like patients

	Transplant	No transplant	p
BCR/ABL1-like	9	11	0.003
Non BCR/ABL1-like	6	48	





Ph-like ALL, MRD and monoclonal antibodies



Blinatumomab effective in eradicating MRD: 10/25 patients MRD-positive after early consolidation and all became MRD-negative (Bassan et al, EHA 2021)

Inotuzumab reported to be effective in these patients

Conclusions

-Early recognition should be always carried out (possibly, at diagnosis)

- MRD often positive; no enrichment among various subgroups
- Allo-SCT should be carried out
- TKIs might/should be incorporated, at least, in MRD+ positive patients

Acknowledgments

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