LAL-B: basi molecolari e prospettive terapeutiche

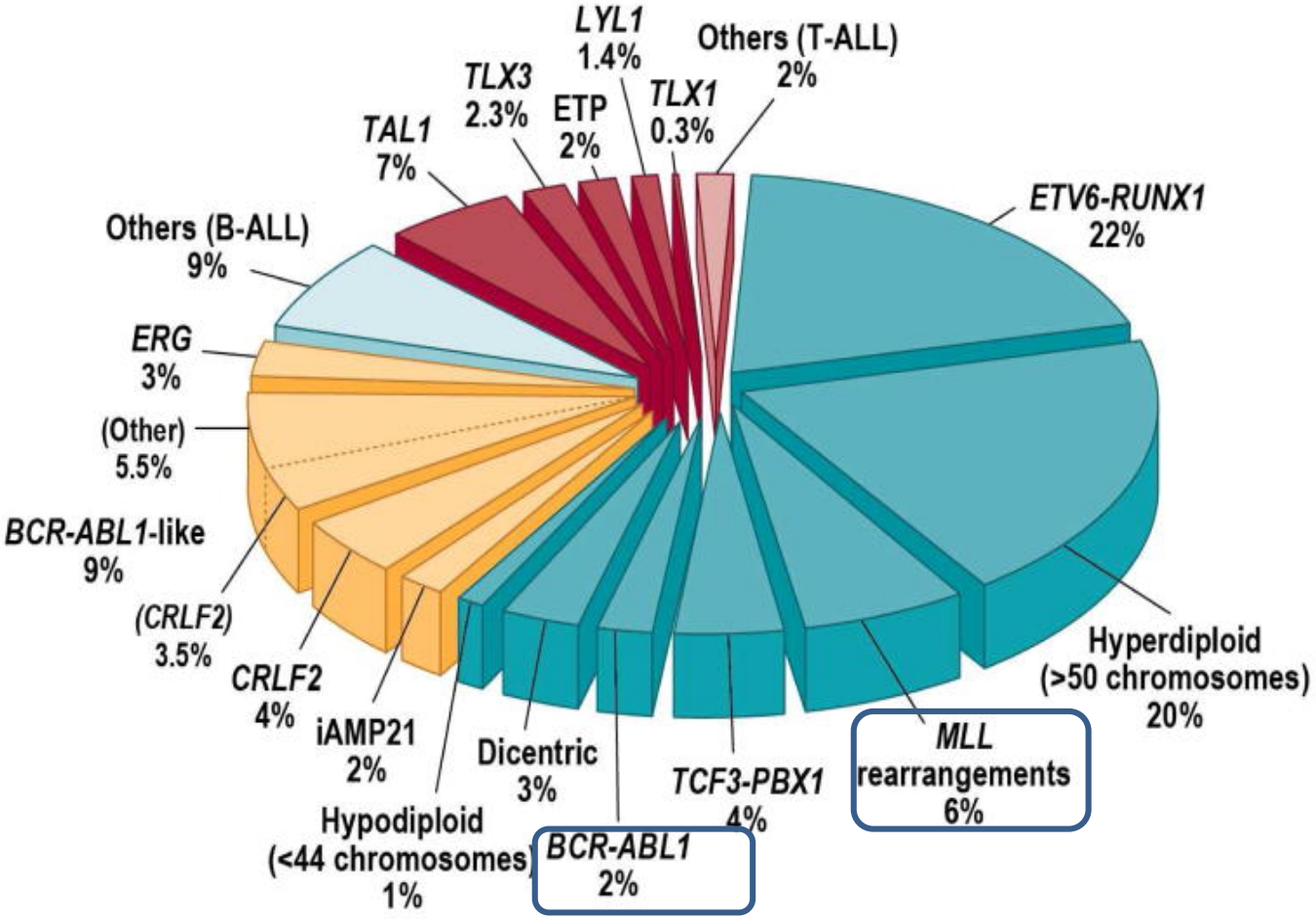
Sabina Chiaretti

SAPIENZA
UNIVERSITÀ DI ROMA

Topics

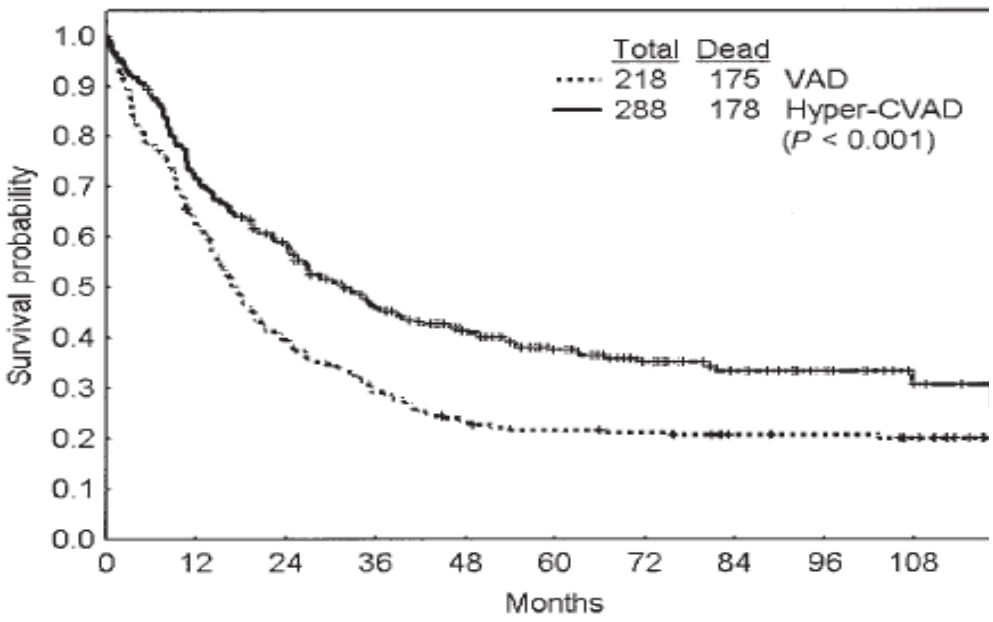
- BCR/ABL positive ALL
- BCR/ABL-like
- Novel subgroups

Cytogenetics/molecular biology

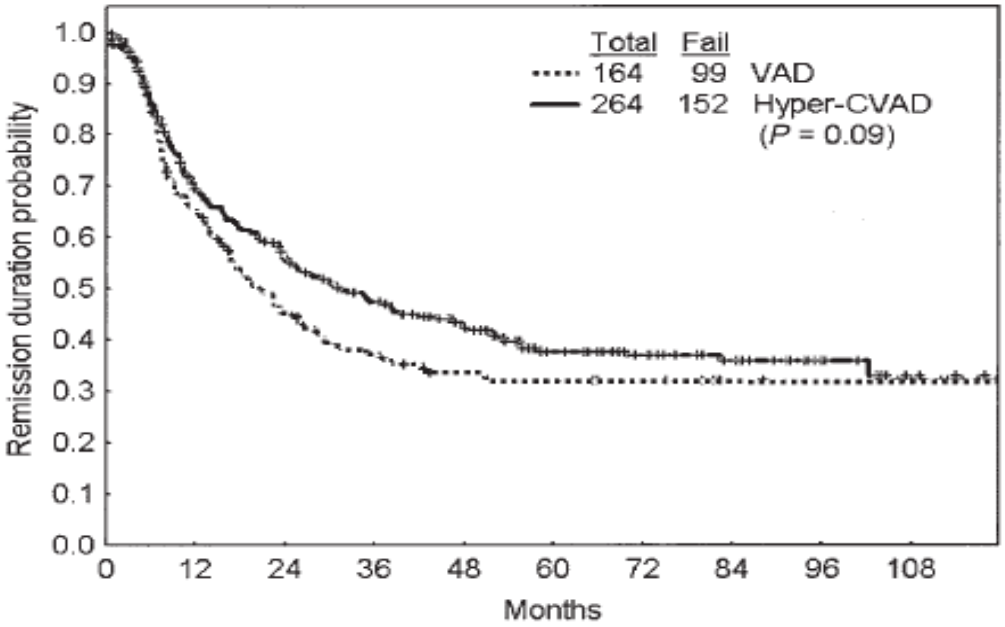


Ph+ ALL: historical outcome

Overall survival



Disease remission duration



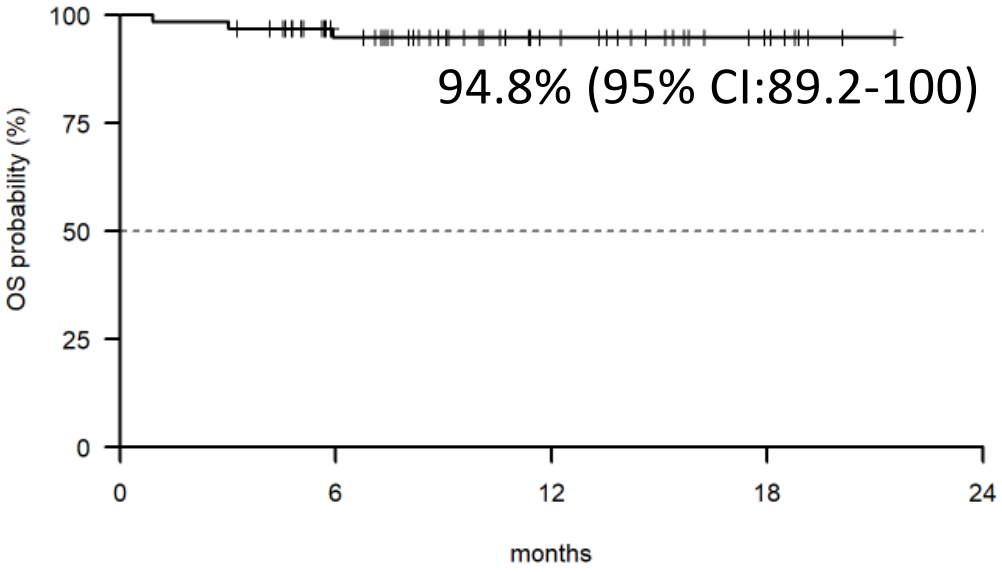
Kantarjian H et al. *Cancer* 2004

Only curative option: allo-SCT

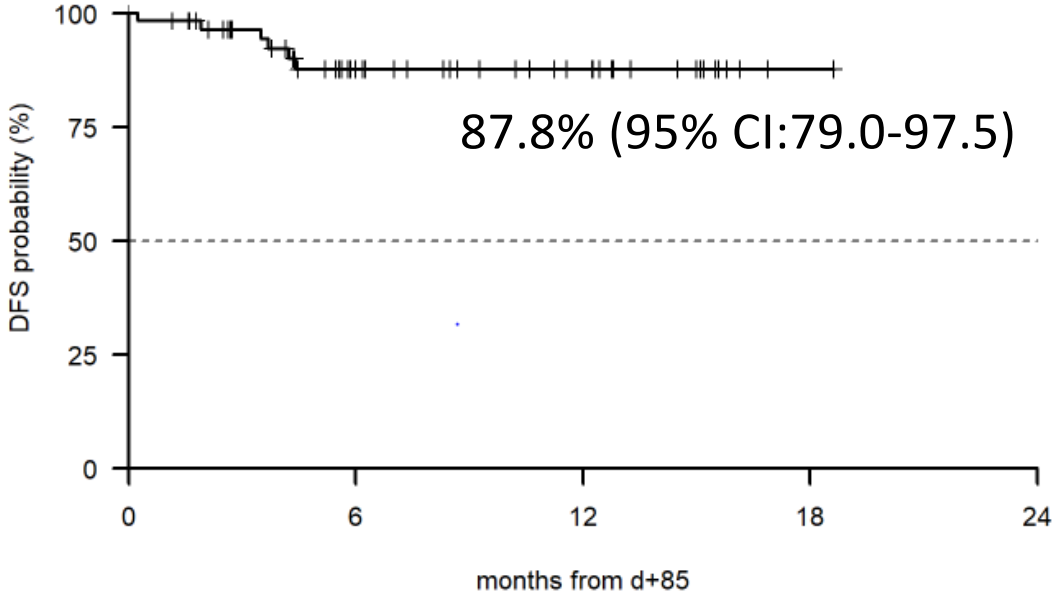
D-ALBA: OS and DFS

Chemo-free approach based on dasatinib followed by blinatumomab

OS

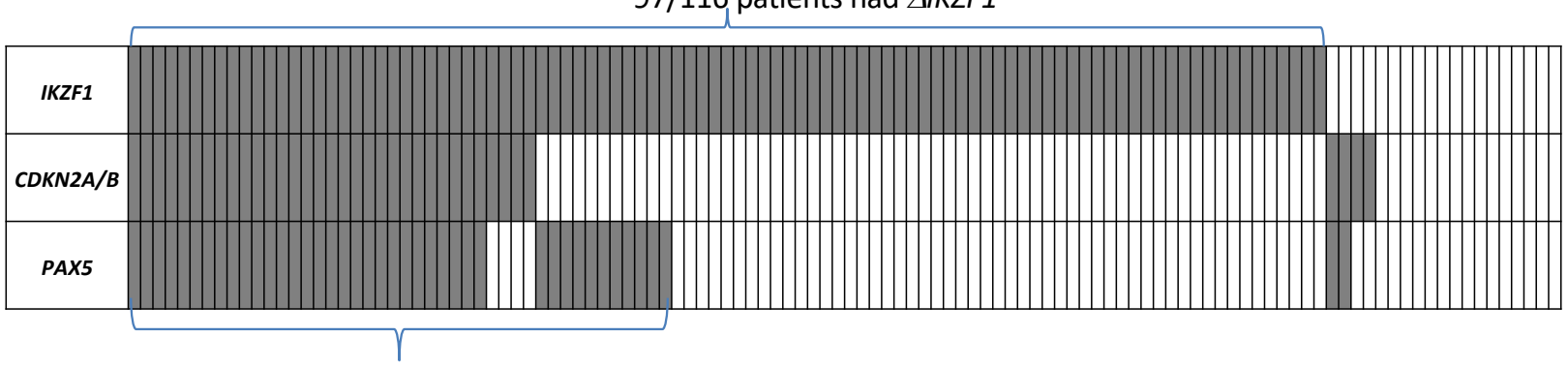


DFS



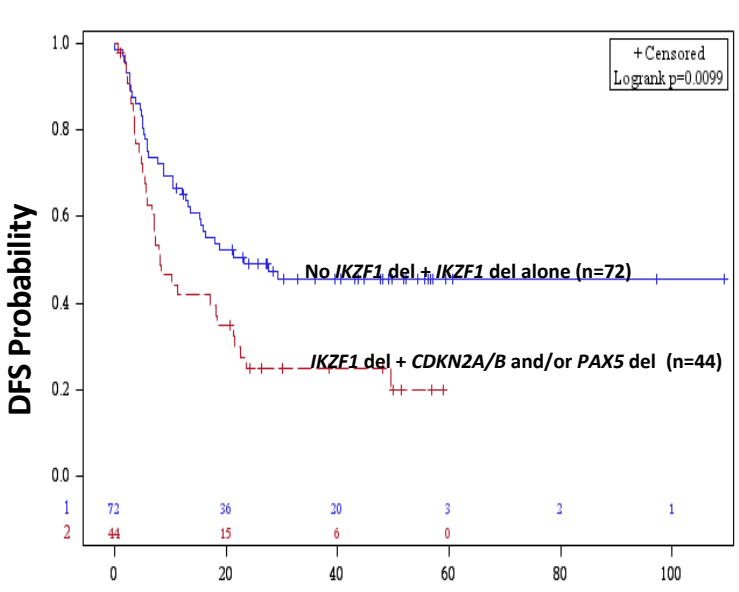
Median follow-up: 10.0 months (0.9-21.5)

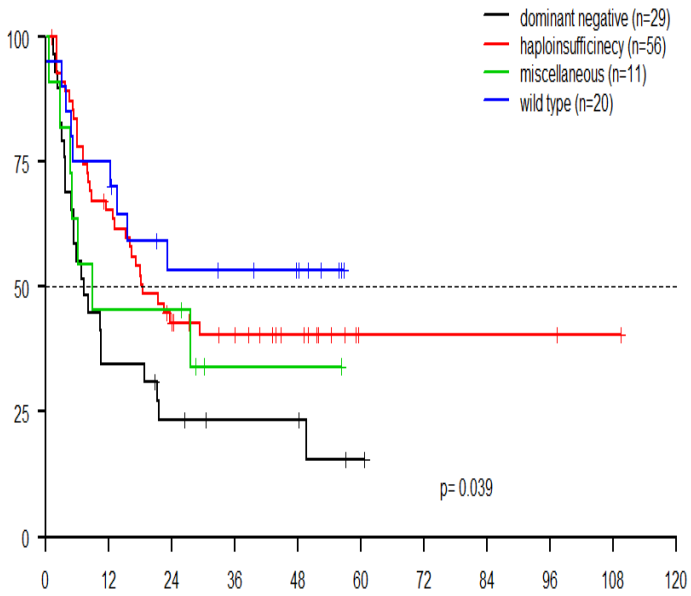
CNAs with negative prognostic impact (I)



✓ *IKZF1 plus* patients had worse DFS than *IKZF1 only* (24% *vs* 46% at 36 months). This finding retained statistical significance also on multivariate analysis.

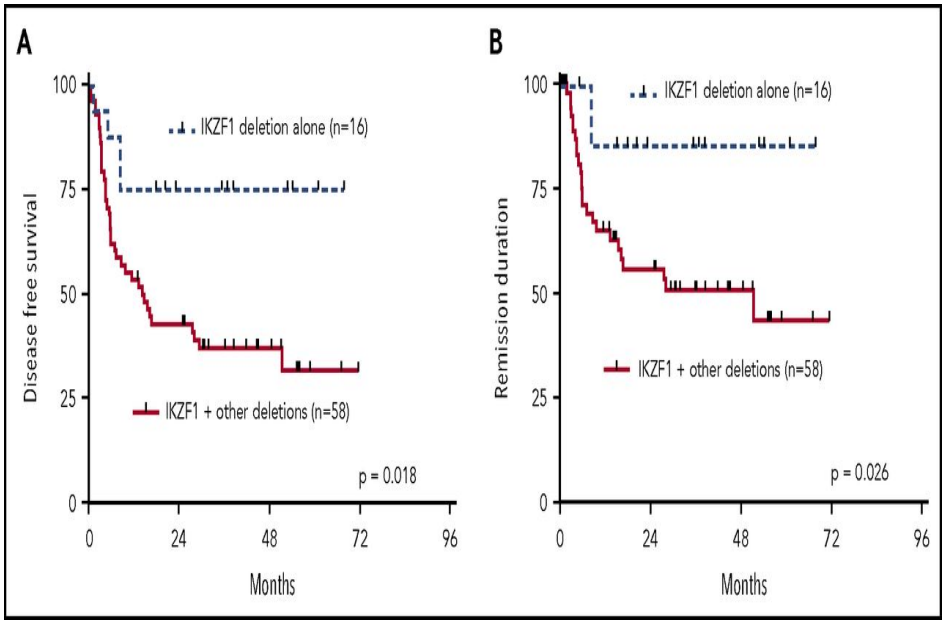
✓*IKZF1* dominant negative isofoms have in impact on DFS



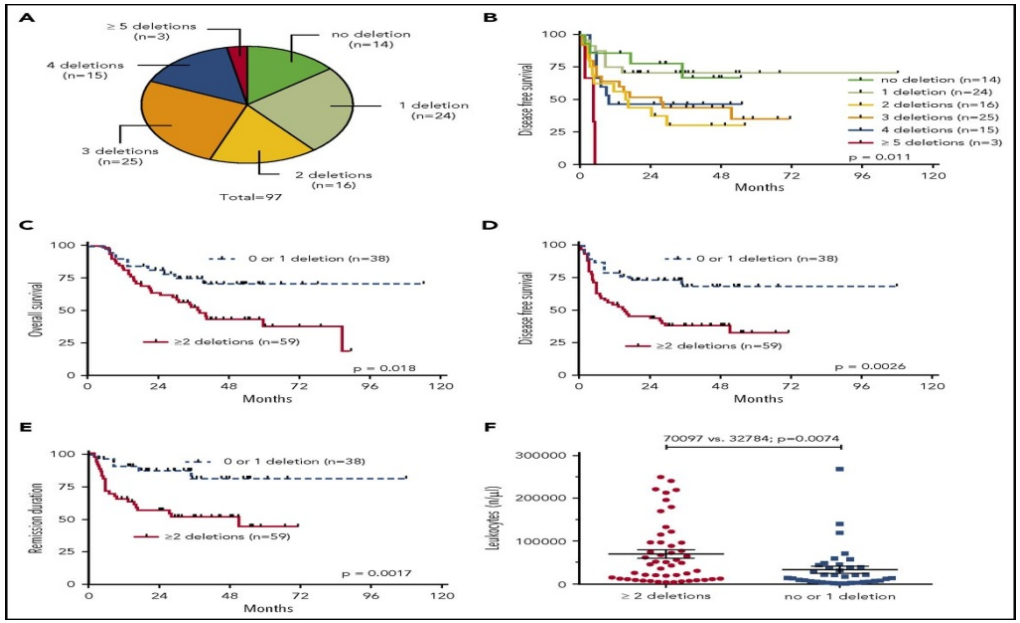


Fedullo AL et al; Haematologica 2019

CNAs with negative prognostic impact (II)



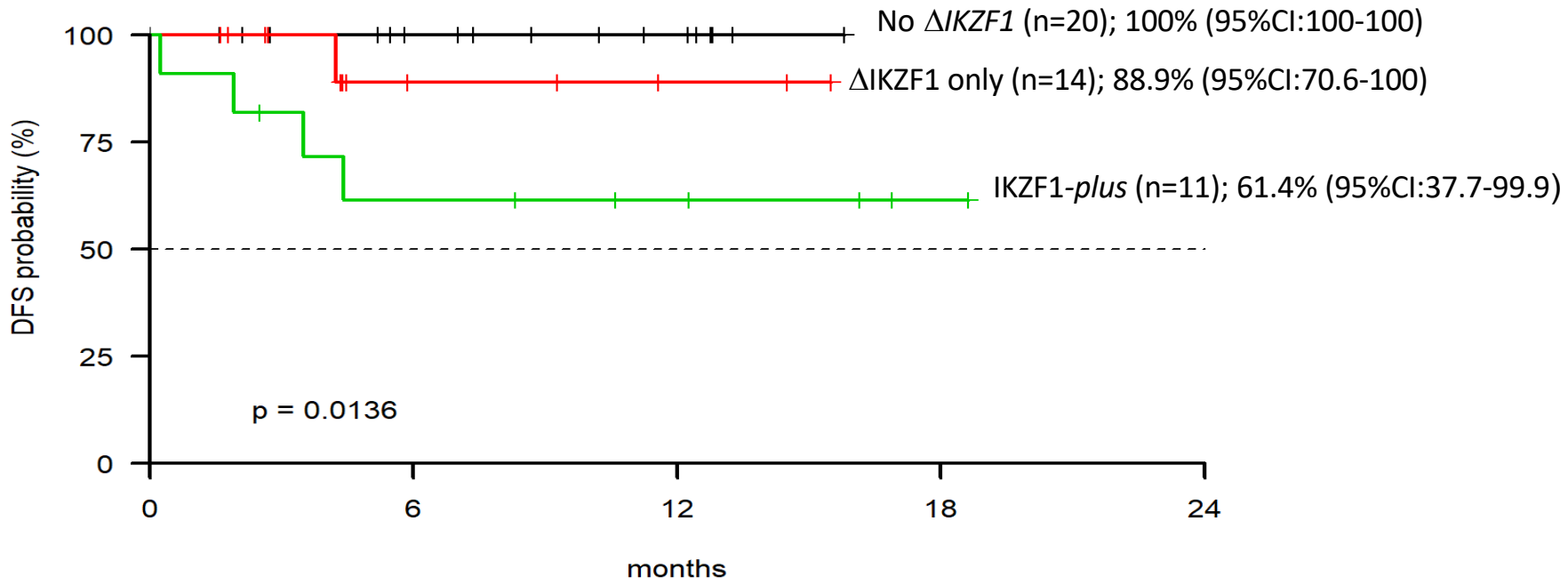
IKZF1 + other: *IKZF1, PAX5*, ***CDKN2A/2B***, *BTG1, EBF1, ETV6,* and *RB1*



Pfeifer H, et al Blood 2018 131:1464-1475

The presence of additional deletions, particularly those involving *CDKN2A/B*, and the number od additonal deltions have a significant impact on all outcome analyses. Retains staistical significance on multivariate analysis

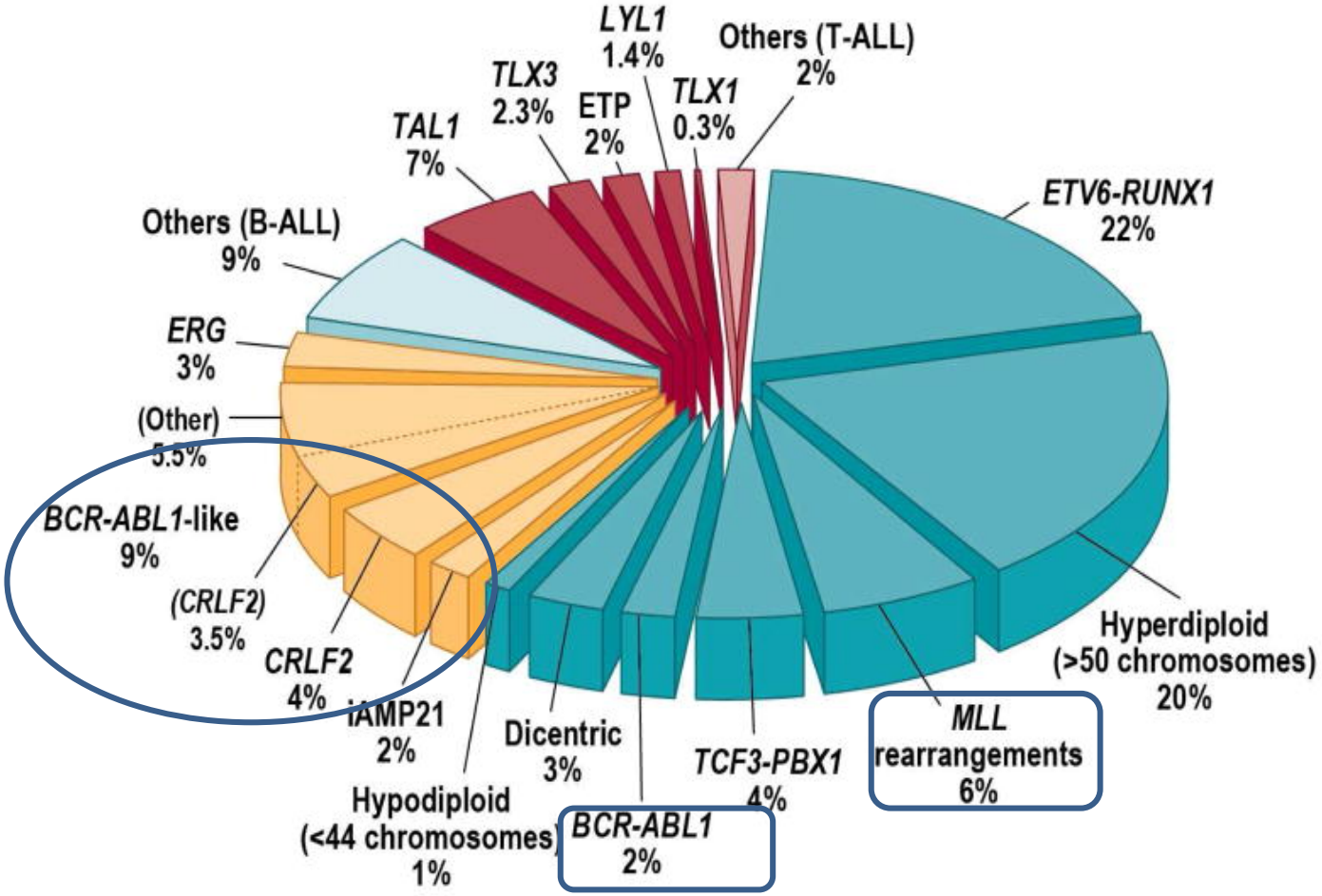
D-ALBA: impact of additional genomic lesions on DFS



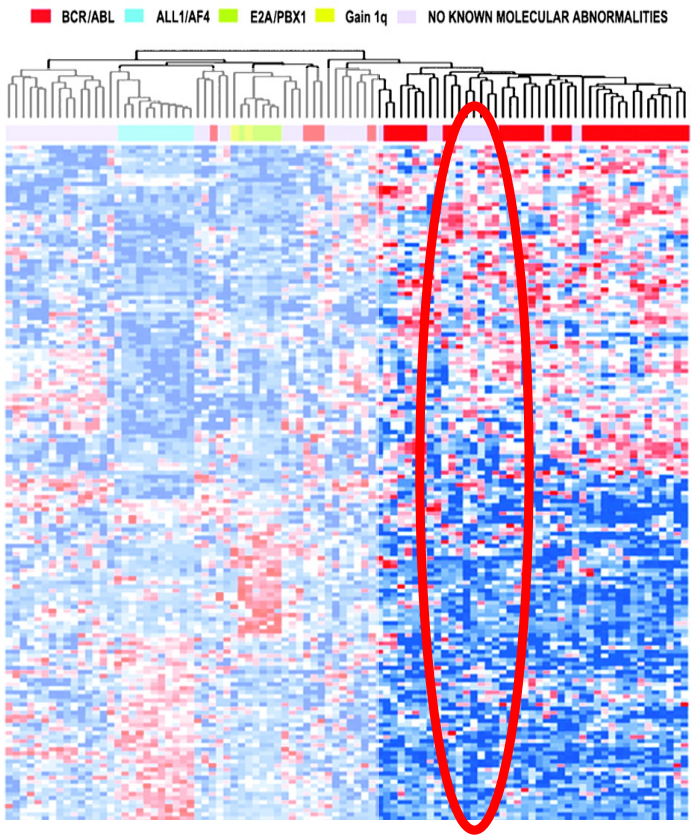
Among IKZF1-*plus* cases, 4 acquired *ABL1* mutation

Chiaretti et al, EHA 2019

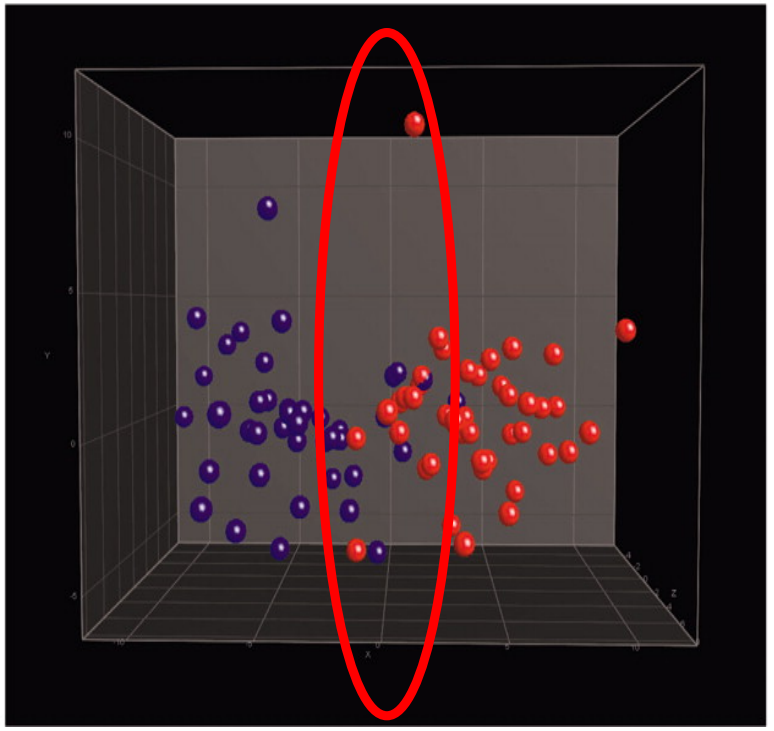
Cytogenetics/molecular biology. Changes over the years



First report in adult ALLs



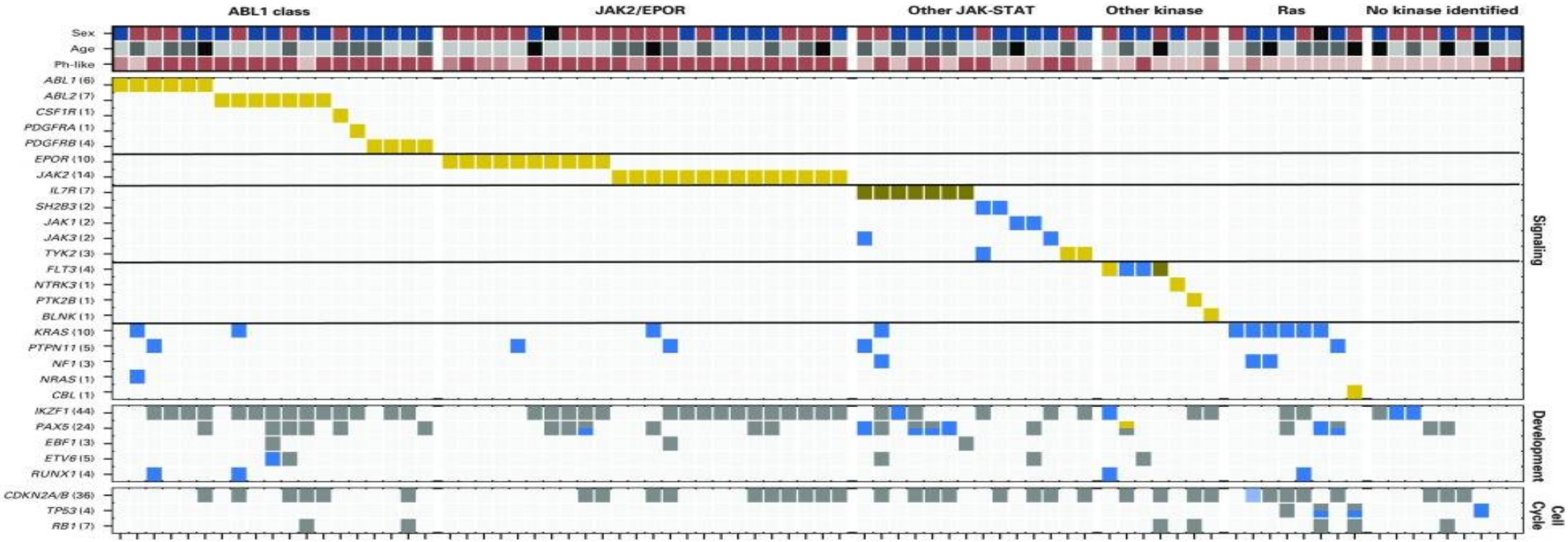
Chiaretti et al, CCR 2005



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

BCR/ABL1-like ALL in adults. Genetics



Higher frequency of other kinase involvement.
Some cases do no have any lesions.

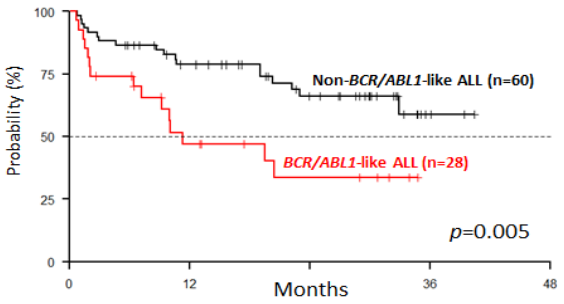
Roberts KG et al, JCO 2016

GIMEMA LAL1913. Outcome and BCR/ABL1-like status

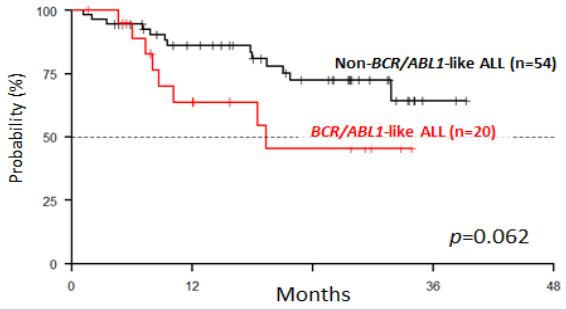
28/88 (31.8%) *BCR/ABL1*-like cases

		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

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

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

Chiarettti et al, under resubmission

Treating the target

Kinase	Tyrosine Kinase Inhibitor	Number of Gene Partners	Fusion Partner Genes
ABL1	Dasatinib	12	*CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1*
ABL2	Dasatinib	3	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Dasatinib	3	*SSBP2, MEF2D, TBL1XR1*
PDGFRB	Dasatinib	7	*ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8*
PDGFRA	Dasatinib	1	*FIP1L1*
CRLF2	JAK2 inhibitor	2	*IGH, P2RY8*
JAK2	JAK2 inhibitor	19	*ATF7IP, BCR, EBF1, ETV6, PAX5, PCM1, PPFIBP1, RFX3, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, GOLGA5, SMU1, HMBOX1, SNX29, ZNF340*
EPOR	JAK2 inhibitor	4	*IGH, IGK, LAIR1, THADA*
TSLP	JAK2 inhibitor	1	*IQGAP2*
DGKH	Unknown	1	*ZFAND3*
IL2RB	JAK1/JAK3 inhibitor	1	*MYH9*
NTRK3	TRK inhibitor	1	*ETV6*
PTK2B	FAK inhibitor	3	*KDM6A, STAG2, TMEM2*
TYK2	TYK2 inhibitor	3	*MYB, SMARCA4, ZNF340*
FLT3	FLT3 inhibitor	1	*ZMYM2*
FGFR1	Sorafenib/dasatinib	1	*BCR*
BLNK	?SYK/MEKi	1	*DNTT*

Pui CH et al, Clin Lymp Myel Leuk, 2017

Requires a deep knowledge of the genomic background of each case.
Time and cost consuming.
Feasible only in a few centers.

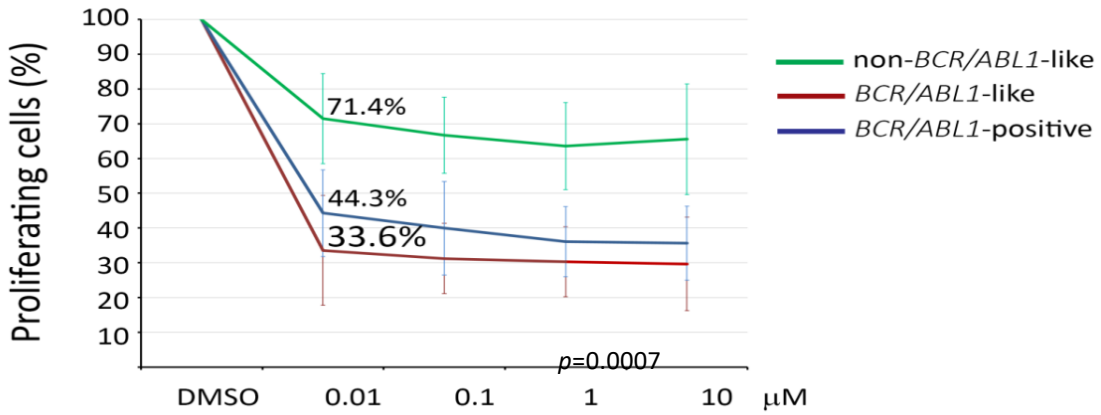
9 R/R pts have been treated.
Median age 24 yrs (range 18-62).
8 pts treated on the ruxolitinib arm (7 pts *CRLF2*-high, 1 with a *JAK2* fusion (*HMBOX1-JAK2*).
1 pt on the dasatinib arm (*NUP214/ABL1*).

No DLT, but no reponse on ruxo or dasa.

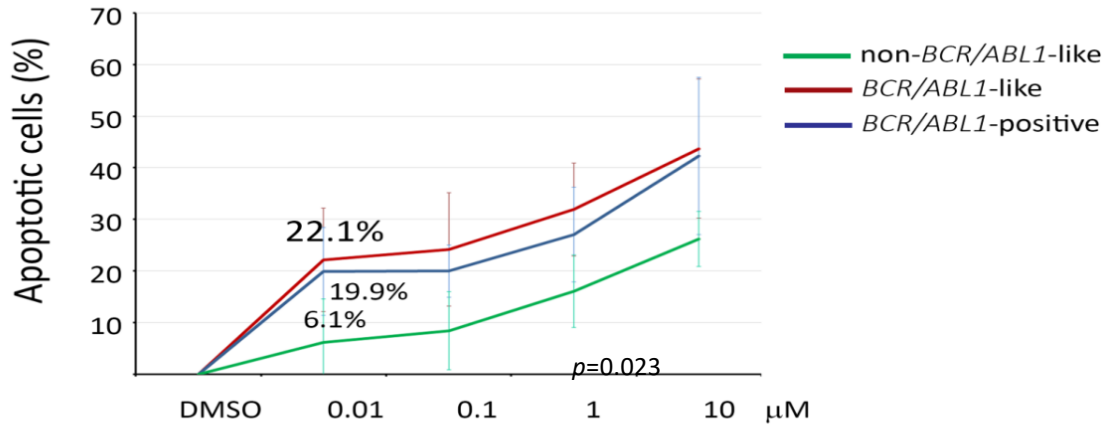
Jain N et al, ASH 2017

Wide-spectrum appraoch. Ponatinib

A



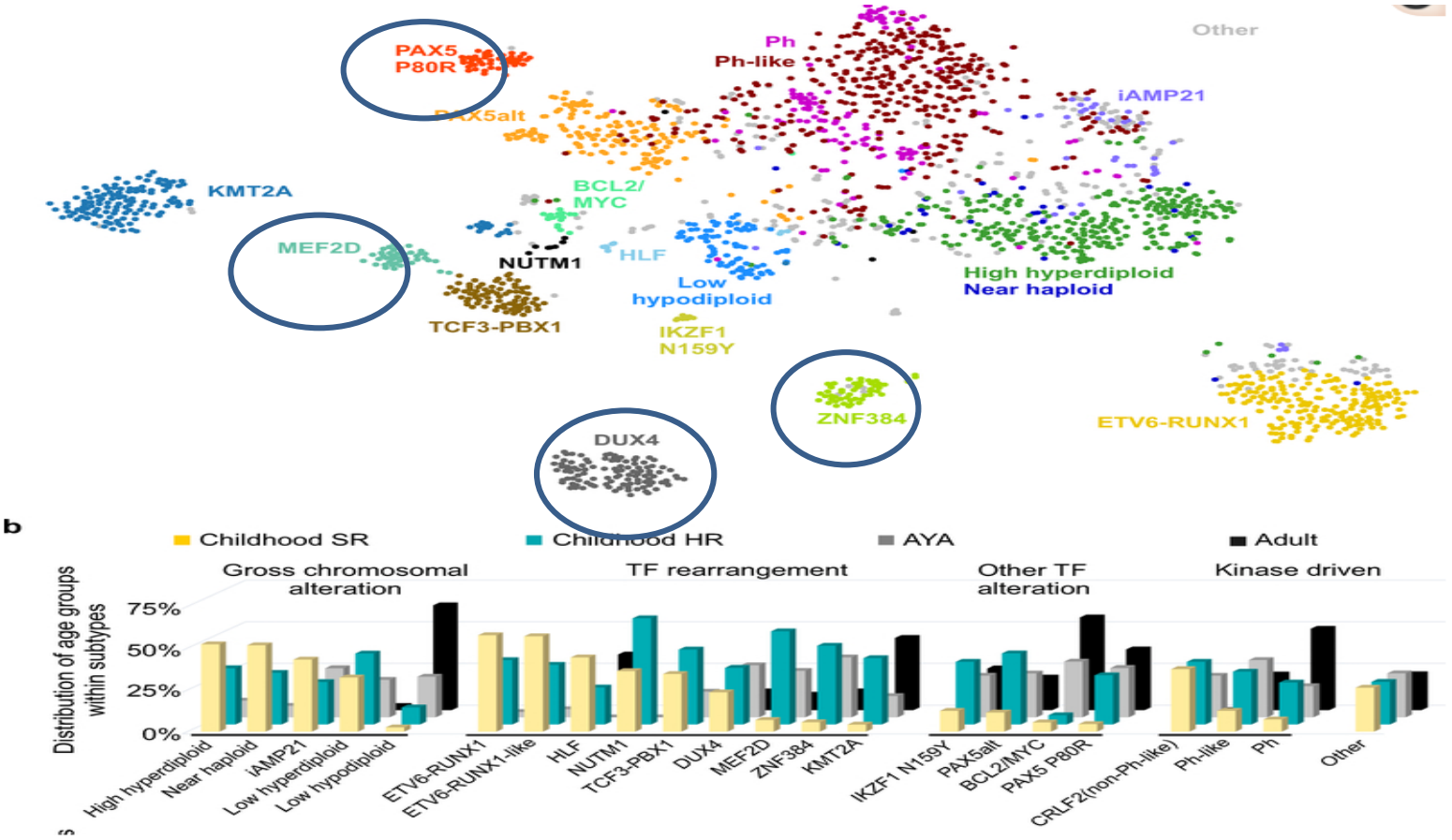
B



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*-positive, 1 *RCSD1/ABL1*, 3 WT for JAK/STAT and RAS mutations)**

Chiaretti S et al, BJH 2018

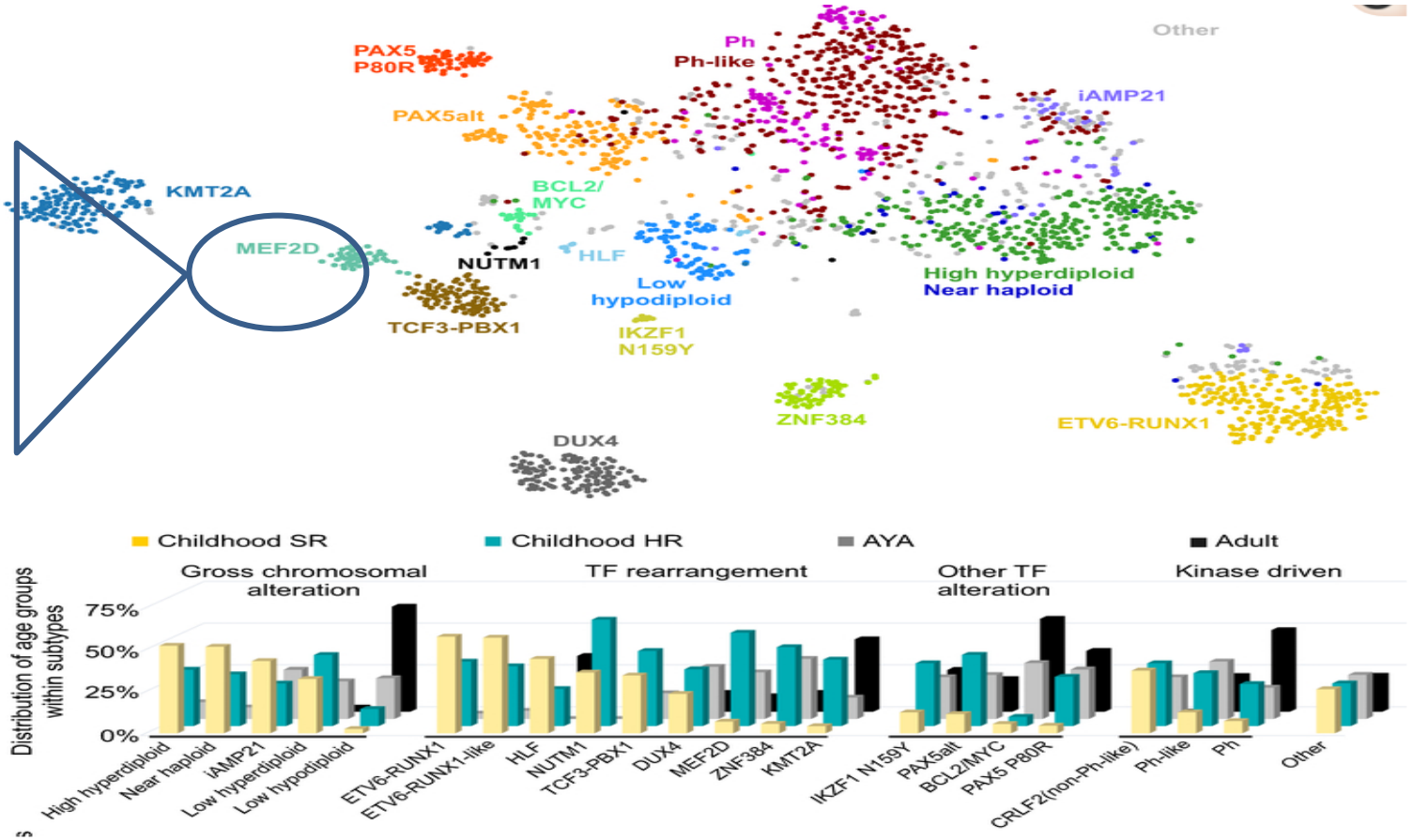
Molecular classification: the new



Gu et al, Nat comm 2019, 7:13331 Gu, et al, Nat Genet. 2019; 51: 296–307.

Molecular classification: the new

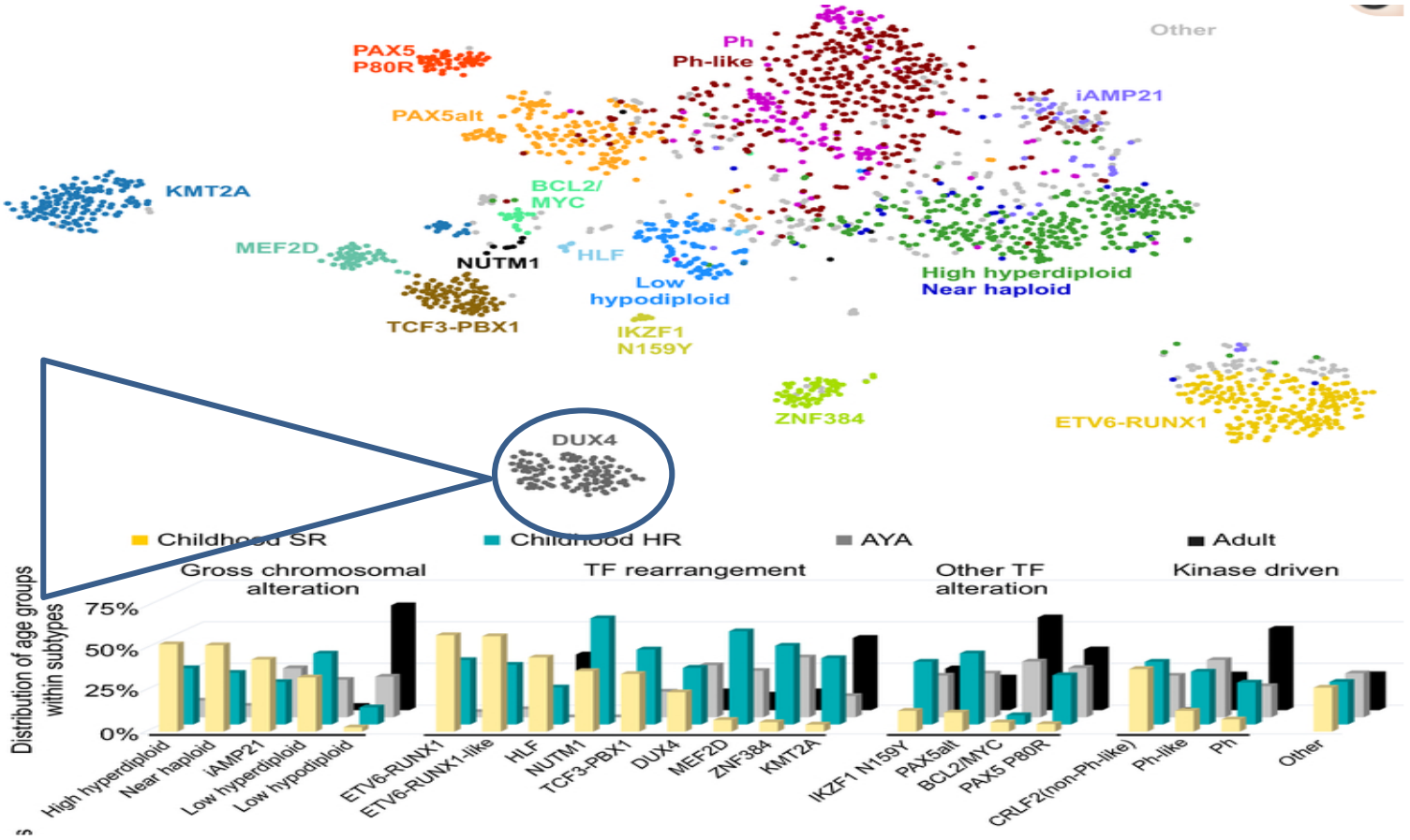
3.9% of childhood ALL
Peculiar IF (CD10- CD38 high)
Inferior outcome
In vitro response to HDAC



Gu et al, Nat comm 2016, 7:13331

Molecular classification: the new

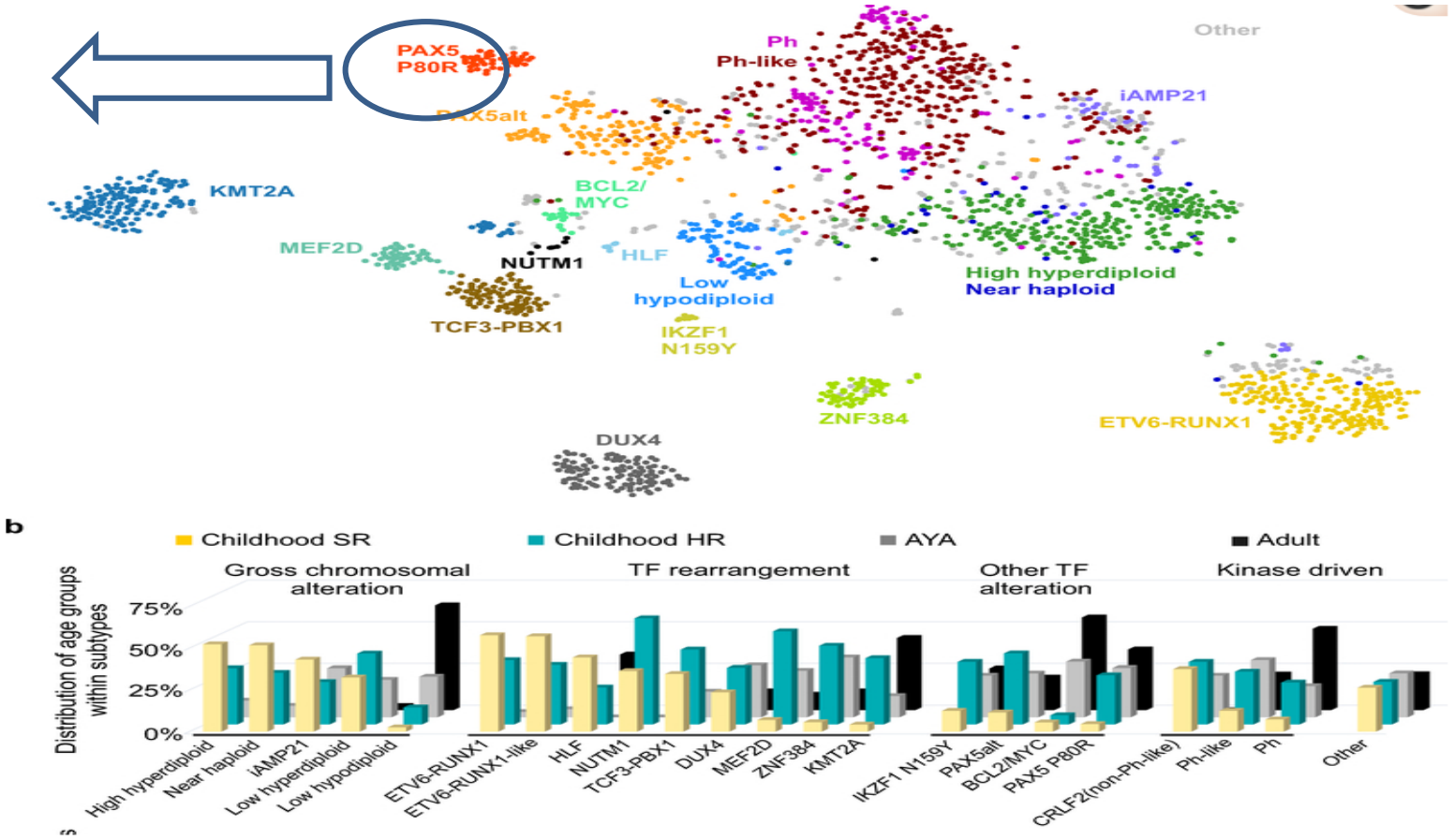
7.6% of childhood ALL
ERG deregulation
Excellent outcome



Zhang et al, Nat Gen 2016, 48: 481-1489.

Molecular classification: the new

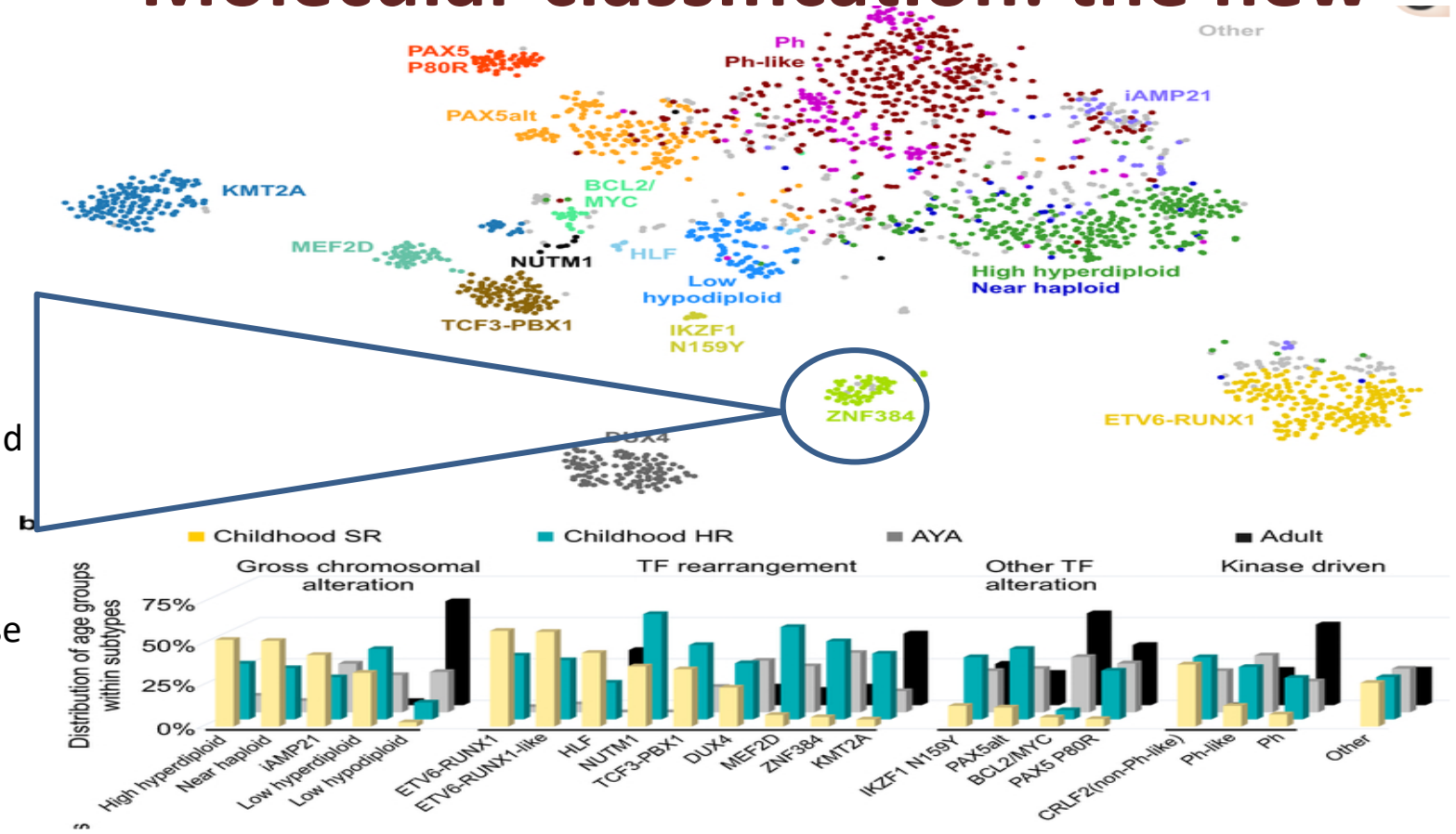
Primary leukemogenic event



Gu, et al, Nat Genet. 2019; 51: 296–307.

Molecular classification: the new

3% of cases
Typically detected in MPAL, T/myeloid and B/myeloid
High FLT3 expression
In vitro reposnse to TKIs



Gu et al, Nat comm 2019, 7:13331 Gu, et al, Nat Genet. 2019; 51: 296–307.

Conclusions

- The comprehension of the molecular bases of ALL has led to a dramatic improvement of the management of these patients:

  -BCR/ABL1+ ALL: identification of *ΔIKZF1*+→ poor prognosis with all approaches. Novel interventions required

  -BCR/ABL1-like ALL: design of *ad hoc* treatments, possibly upfront

- Genome-wide have led to the identification of 23 (26) subgroups whose prognostic significance is under investigation