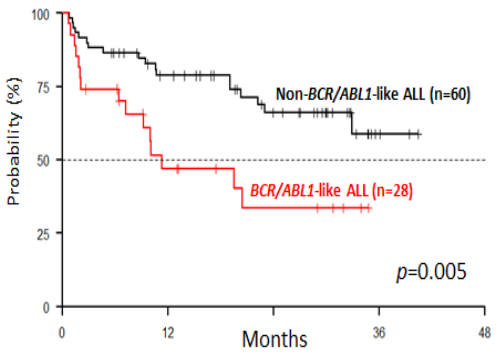
Outline del protocollo per le LAL Ph-like

Outcome of GIMEMA LAL1913 according to BCR/ABL1-like status

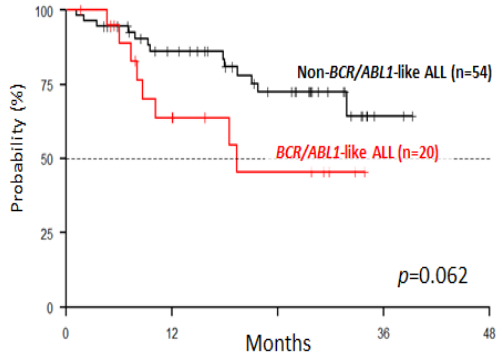
28/88 (31.8%) *BCR/ABL1*-like cases

		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

***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.**

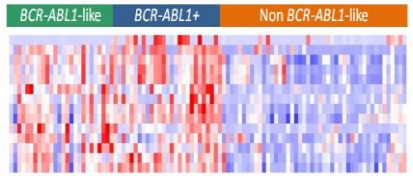
The prognostic role of the *BCR/ABL1*-like status is independent from the other clinico-biological and genetic features

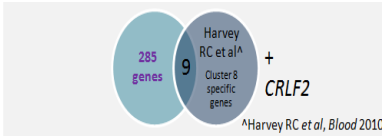
Chiarettti et al, in resubmission

Development of the *BCR/ABL1*-like predictor & screening

Selection of *BCR/ABL1*-like specific genes and validation by Q-PCR → **Development of *BCR/ABL1*-like predictor*** → **Screening**

1. Selection of 10 predictive genes





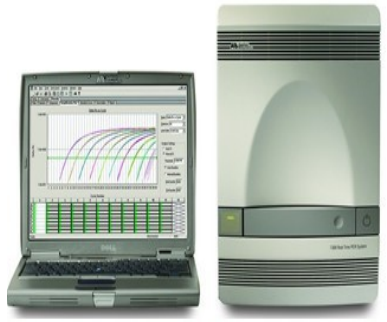
2. Validation by Q-PCR in 52 B-NEG ALL

1. Identification of principal components (PCs)

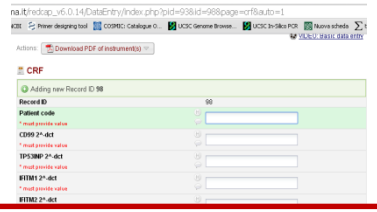
		Factor loadings		
		PC1	PC2	PC3
Gene1 ΔCt)	2^(-	0.87921	-0.08451	0.19315
Gene2 ΔCt)	2^(-	0.87162	0.41262	0.05974
Gene3 ΔCt)	2^(-	0.80540	0.30143	0.22085
Gene4 ΔCt)	2^(-	0.66775	0.40903	0.41369
Gene5 ΔCt)	2^(-	0.57903	0.48726	0.48781
Gene6 ΔCt)	2^(-	0.17357	0.90884	0.08792
Gene7	2^(-	0.61788	0.68881	0.14372

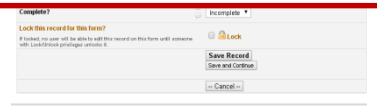
2. Definition of a score

1. Q-PCR of predictor genes in 129 B-NEG ALL



2. *BCR/ABL1*-like predictor



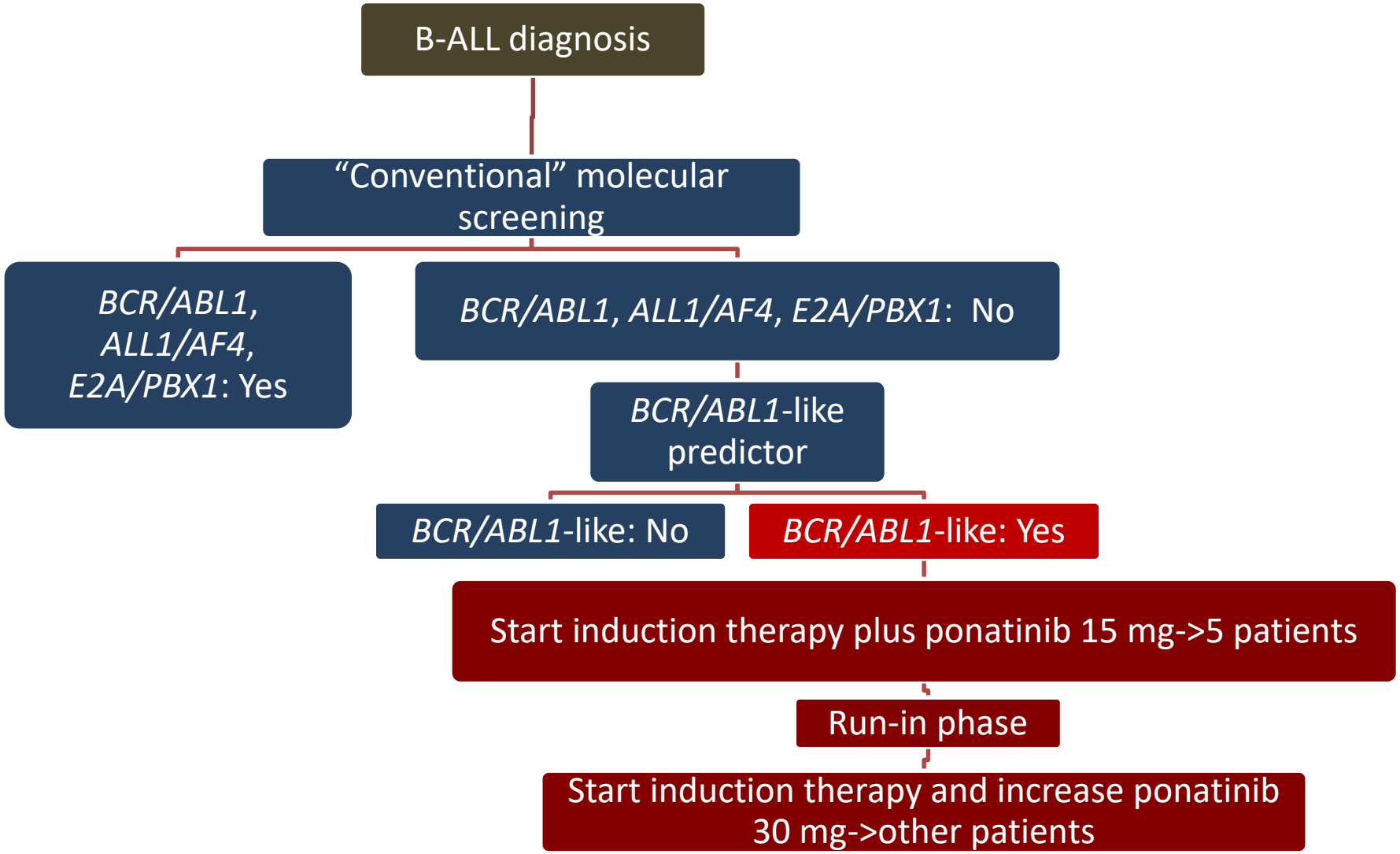


54/194 newly identified *BCR/ABL1*-like patients (28%): 9.5% children, 29% AYA, 30% adults

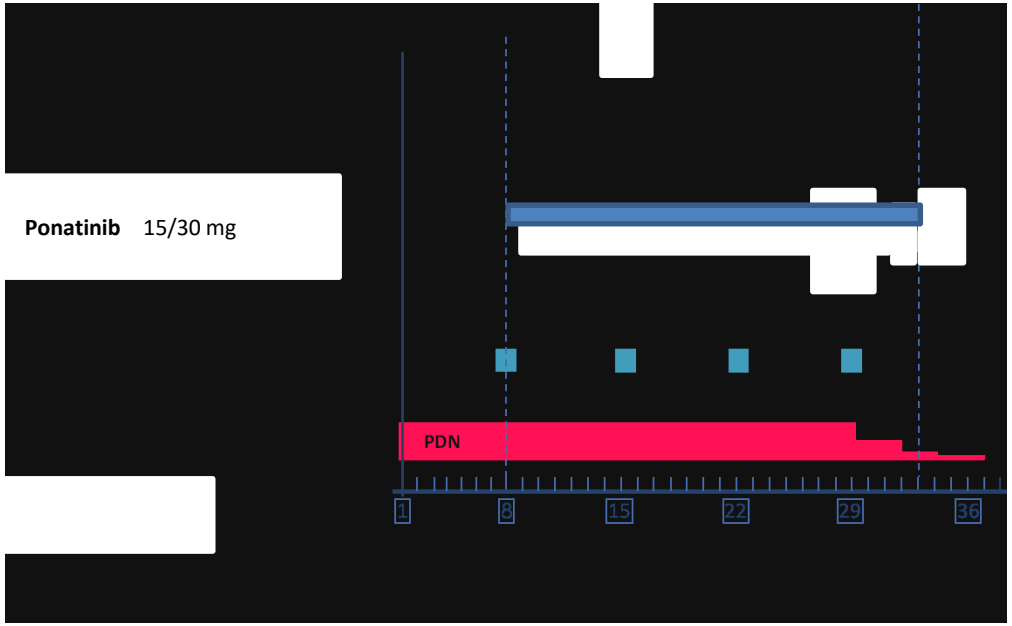
*https://redcap.gimema.it/redcap

Chiaretti S et al, BJH 2018

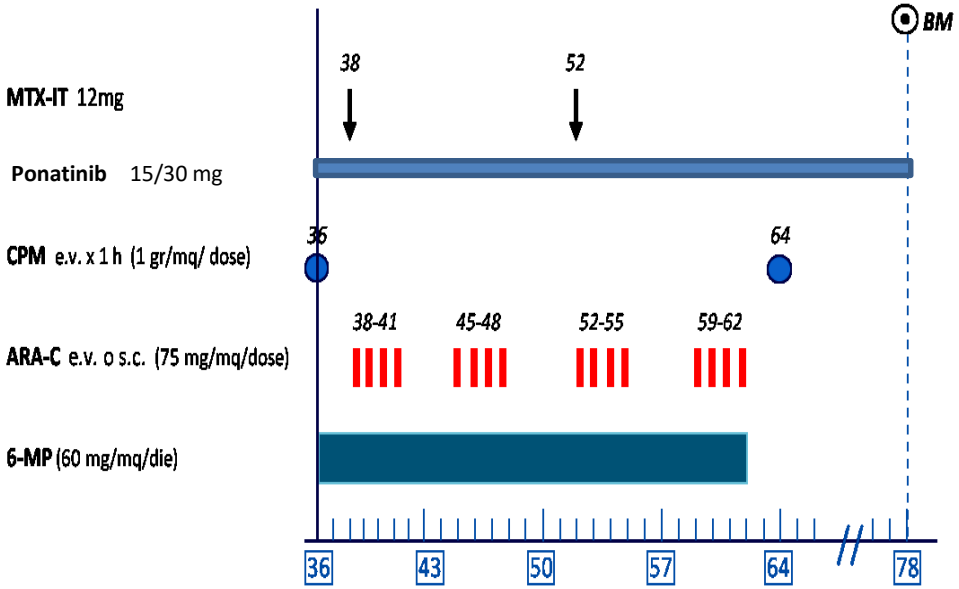
Outline of new protocol for *BCR/ABL1*-like ALL cases



Phase Ia induction



Phase Ib induction



Objectives of the study

Primary

To evaluate the clinical response - in terms of complete hematologic remission (CHR) and MRD negativity - in **32** patients with a BCR/ABL1-like profile.

Secondary

To evaluate the EFS and OS of patients treated with ponatinib and chemotherapy.
To evaluate the feasibility of a combination approach with ponatinib and chemotherapy, in terms of side effects, adverse events and serious adverse events, both hematologic and non-hematologic.

Exploratory

To investigate the underlying molecular lesion in each BCR/ABL1-like case by performing RNA-sequencing and targeted mutational screening.
To evaluate, on the basis of the underlying molecular lesion, the efficacy of ponatinib.