I trattamenti “chemotherapy-free”: a che punto siamo nella LAL ?

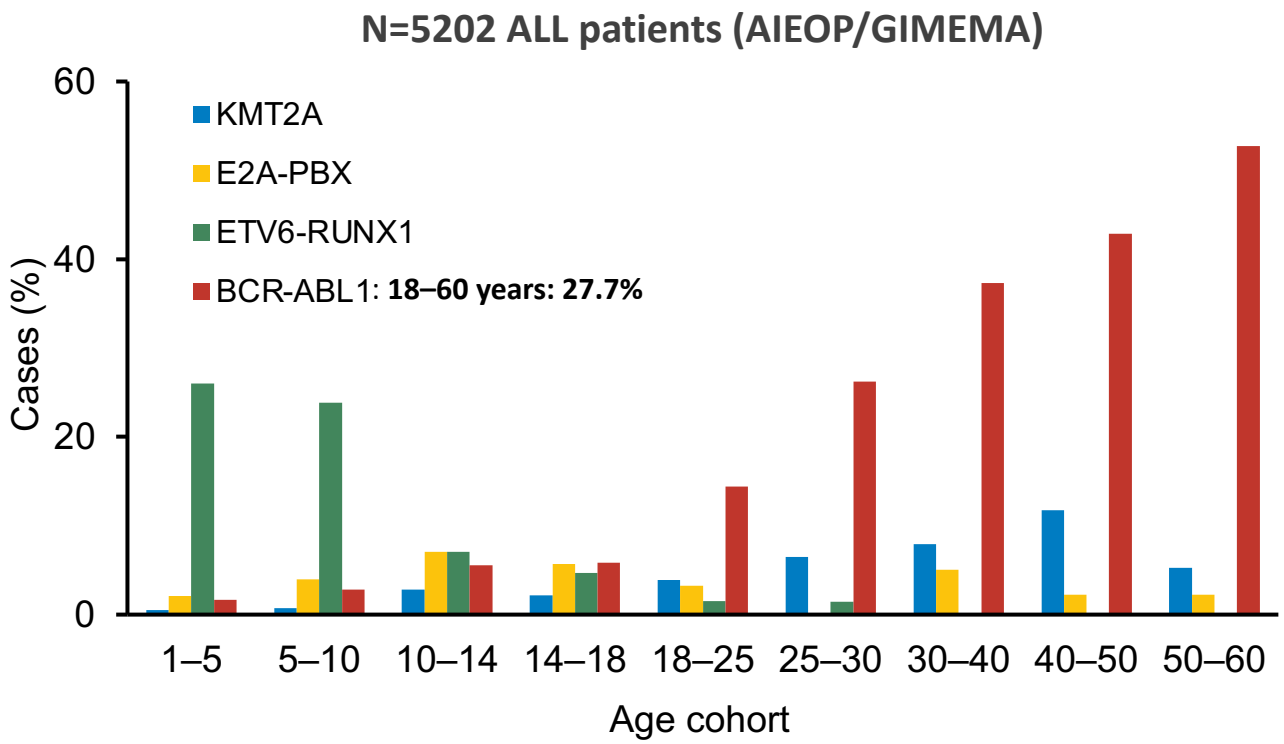
Renato Bassan

Disclosures of Renato Bassan

- Advisory boards: Novartis, Kite Pharma/Gilead
- Travel grants/honoraria: Amgen, Incyte, Servier, Jazz Pharmaceuticals, Pfizer

The records of Ph+ ALL

- Highest incidence in adults
- First recognised recurrent chromosomal abnormality: **t(9;22)**
  - Pathogenetic ***BCR-ABL1***$_{p190/210}$ fusion gene in 22q- chromosome, with abnormal **tyrosine kinase** expression
- Actionable pathogenetic mechanism (**TKIs**), **immunotherapy** effective
  - *No longer very high-risk*
  - ***'Curable' without chemo/SCT?***

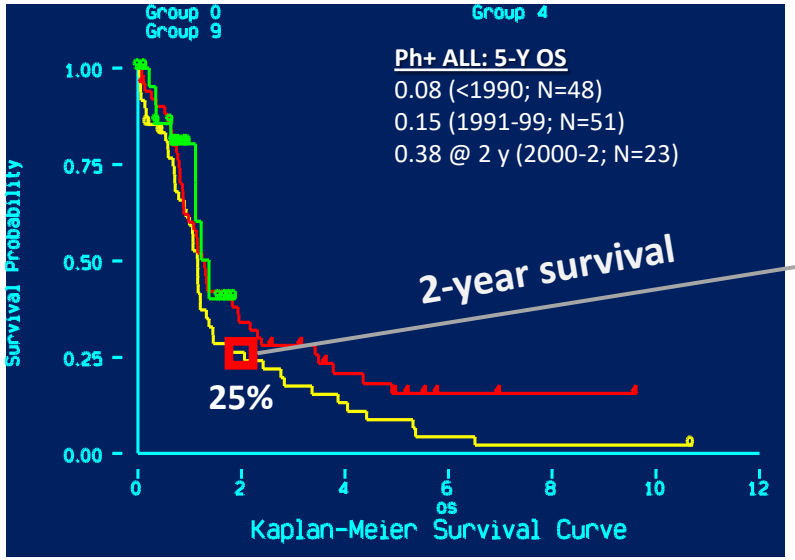


Chiaretti S, et al. Haematologica 2013;98:1702–10.

Evolution

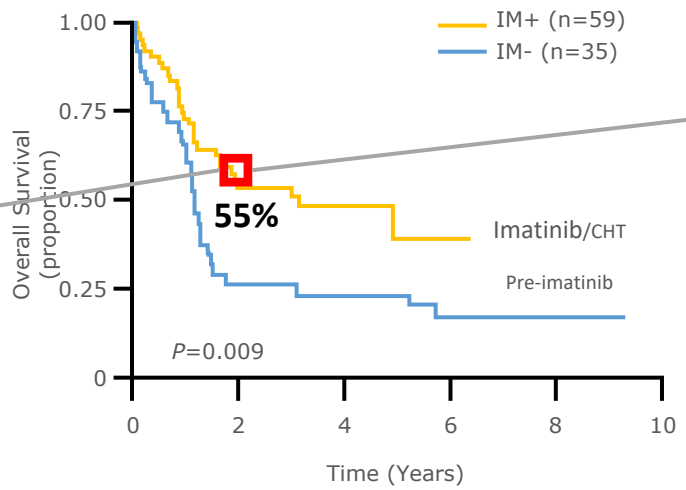
No targeted therapy[1]

*Chemo/**FEW** transplants*



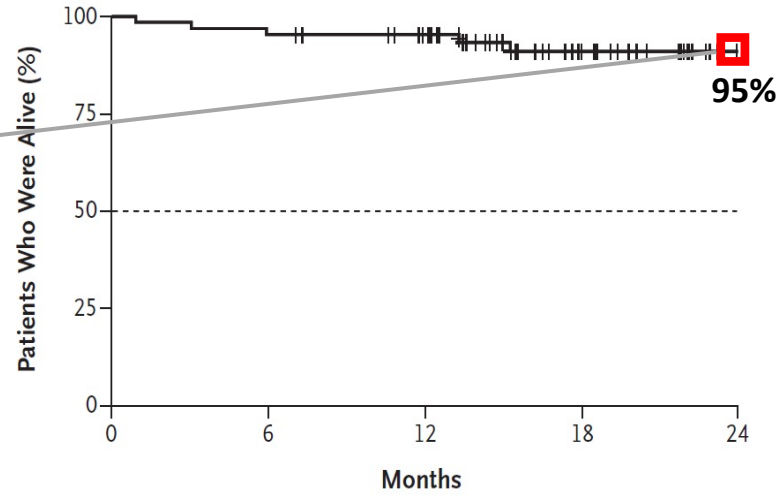
Targeted therapy[2] (1G TKI)

Chemo/transplants



Dual targeted therapy[3] (2G TKI/blinatumomab)*

***NO** chemo[#]/**FEWER** transplants*



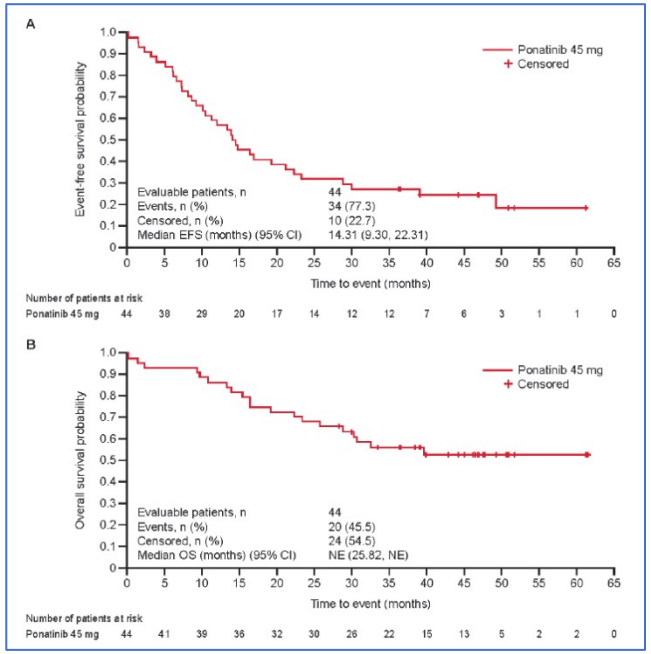
[#]except IT CNS prophylaxis

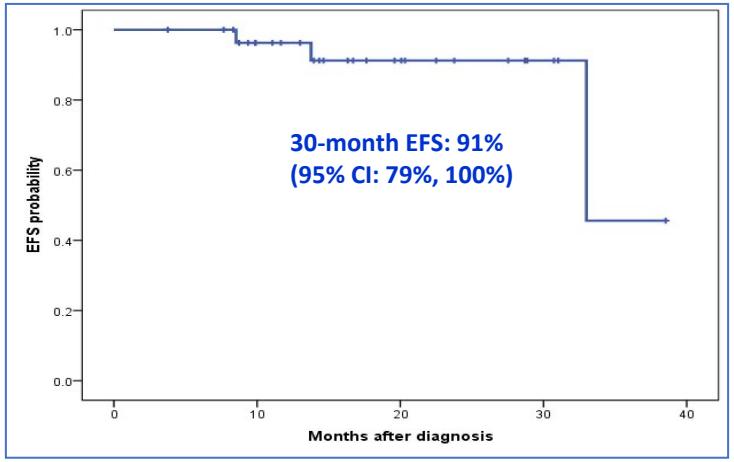
1. Bassan R, et al. Hematology J 2000;1:226–34 (plus data on file: NILG database);
2. Bassan R, et al. J Clin Oncol 2010;28:3644–52;
3. Foà R, et al. N Engl J Med 2020;383:1613–23.

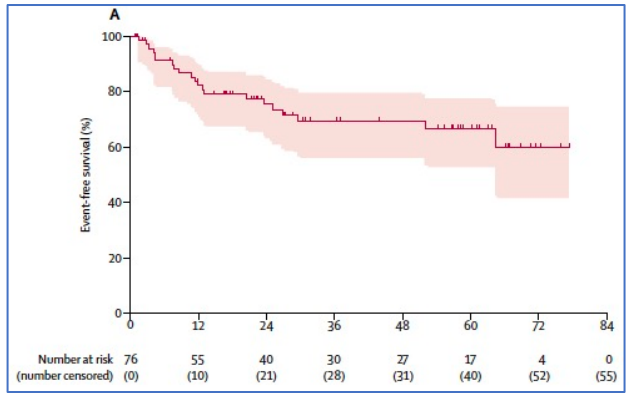
*Blinatumomab and current 2G TKI are not not licensed for first-line use, nor in combination.

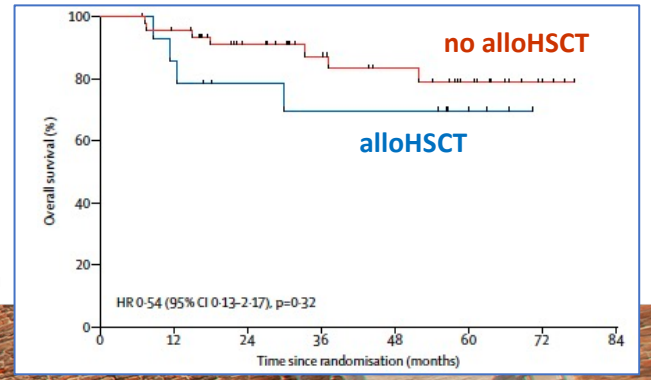
Ponatinib strikes out

INCB84344-201[1]	PETHEMA[2]	MDACC[3]
• **30 elderly/unfit adult patients** (median age 66; range 26–85) • **No chemotherapy / No allogeneic HSCT** • **Ponatinib 45/30 mg/day**	• 30 adult patients (median age 50; range 20–59) • Moderate-intensity chemotherapy • Allogeneic HSCT (n=28/30) • **Ponatinib 30 mg/day**	• 76 adult patients (median age 47; range 39–61) • Intensive chemotherapy • Allogeneic HSCT optional (n=15) • **Ponatinib 45/30/15 mg/day**
CR 95% **CMR** 82%	**CR** 100% **CMR** 68%	**CR** 100% **CMR** 83%







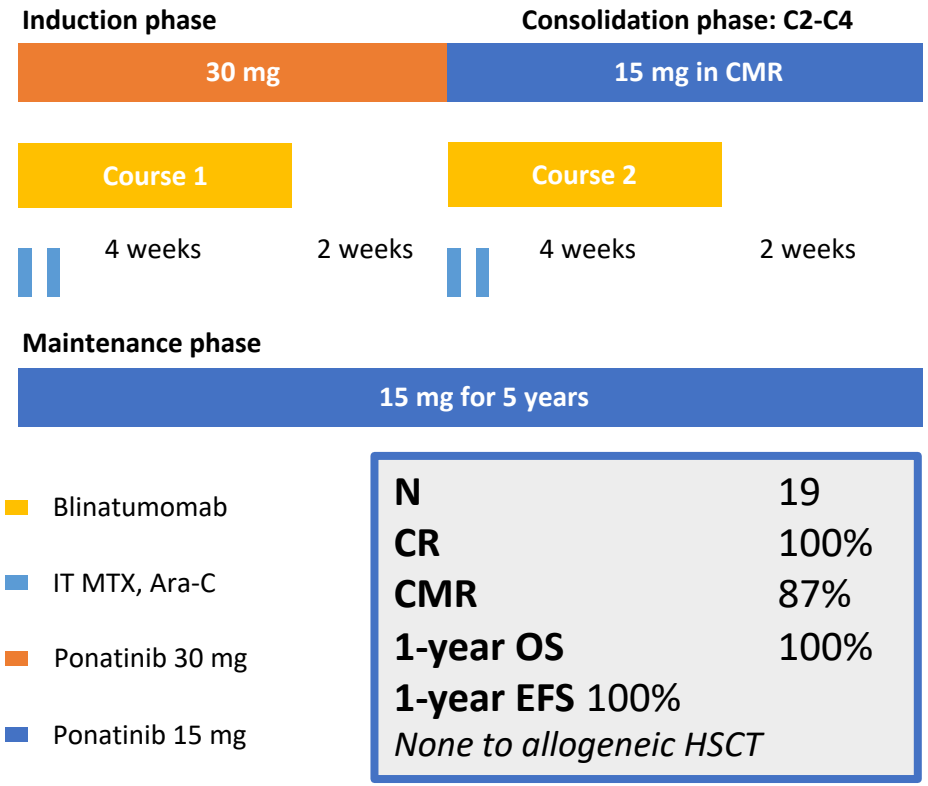


1. Martinelli G, et al. Blood Adv 2021 (in press); 2. Ribera JM, et al. ASH 2020; Abstract 984; 3. Jabbour E, et al. Lancet Haematol 2018;5:e618–27.

CR, complete remission; CMR, complete molecular remission

«Chemo-free» dual targeted therapy

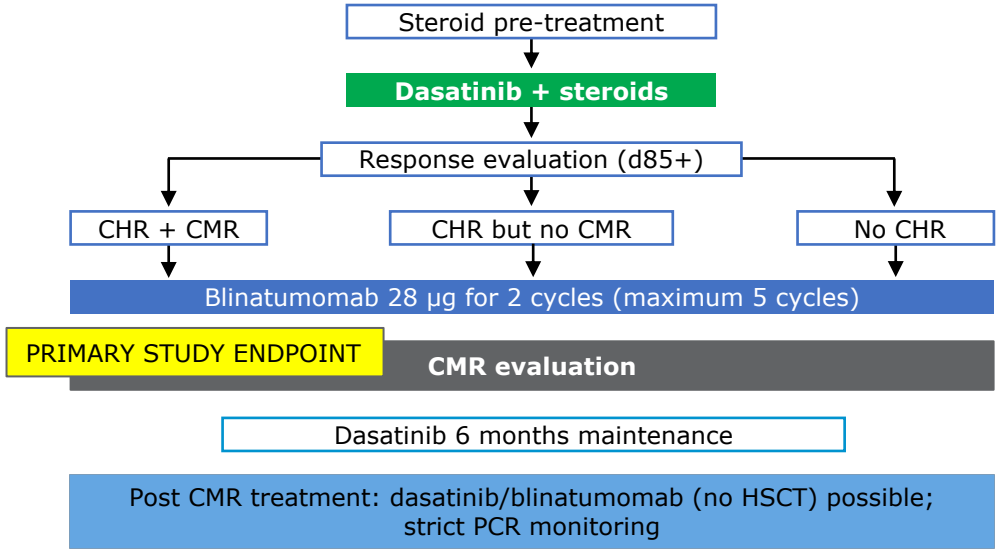
MDACC: ponatinib/blinatumomab[1,2]



N	19
CR	100%
CMR	87%
1-year OS	100%
1-year EFS	100%

None to allogeneic HSCT

GIMEMA 2116: dasatinib/blinatumomab[3,4]

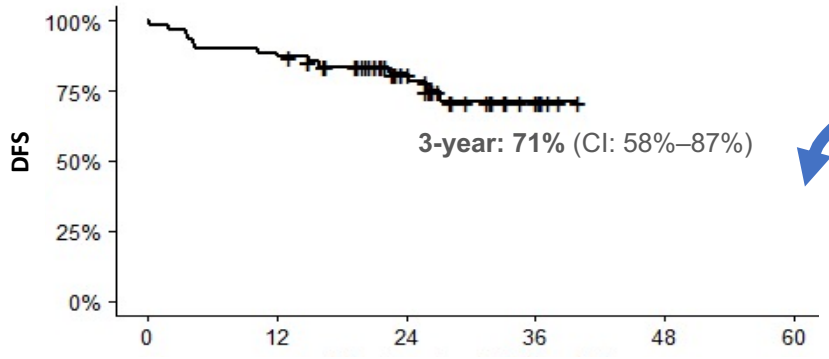


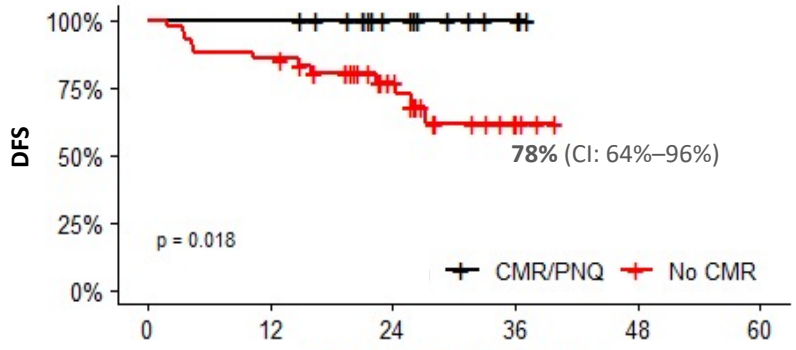
N	63
CR	98%
CMR	73–89%
2-year OS	88%
2-year DFS	80%

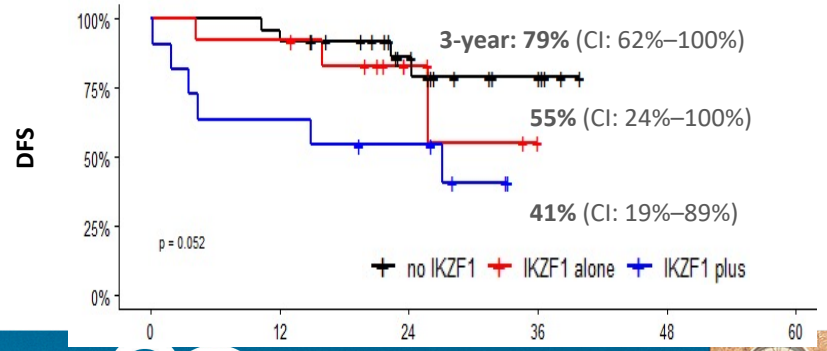
29 to allogeneic HSCT (46%)

1. E Jabbour, personal communication (courtesy of P. Rousselot); 2. Short N, et al. EHA 2021; Abstract S114;
3. Foà R, et al. N Engl J Med 2020;1613–23; 4. Chiaretti S, et al. EHA 2021; Abstract S112;

GIMEMA trials update







from

2116 **dasatinib/blinatumomab*** (Phase 2)[1]

to

2820 **ponatinib/blinatumomab*** (Phase 3)[2]

vs chemo/imatinib[2]

Age ≥18 years
(ponatinib 30 and
de-intensified chemo >65 years)

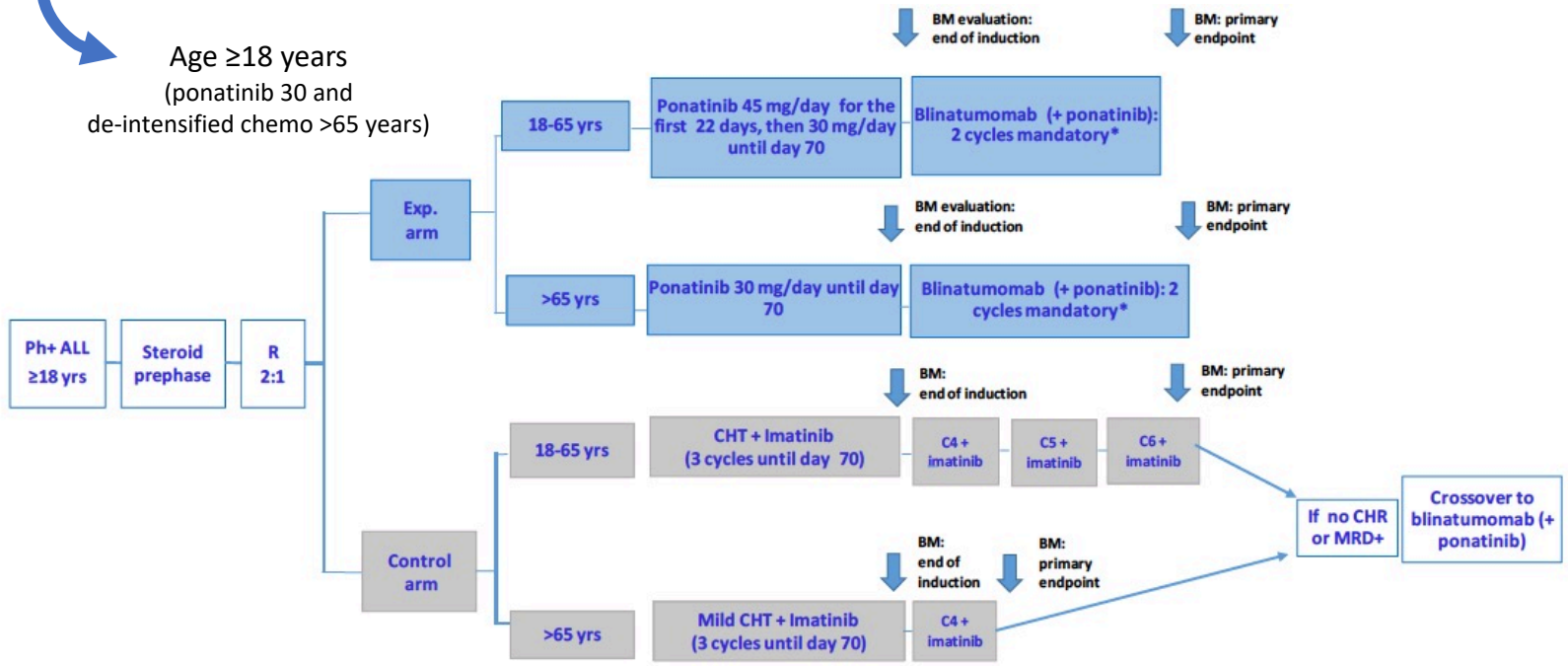


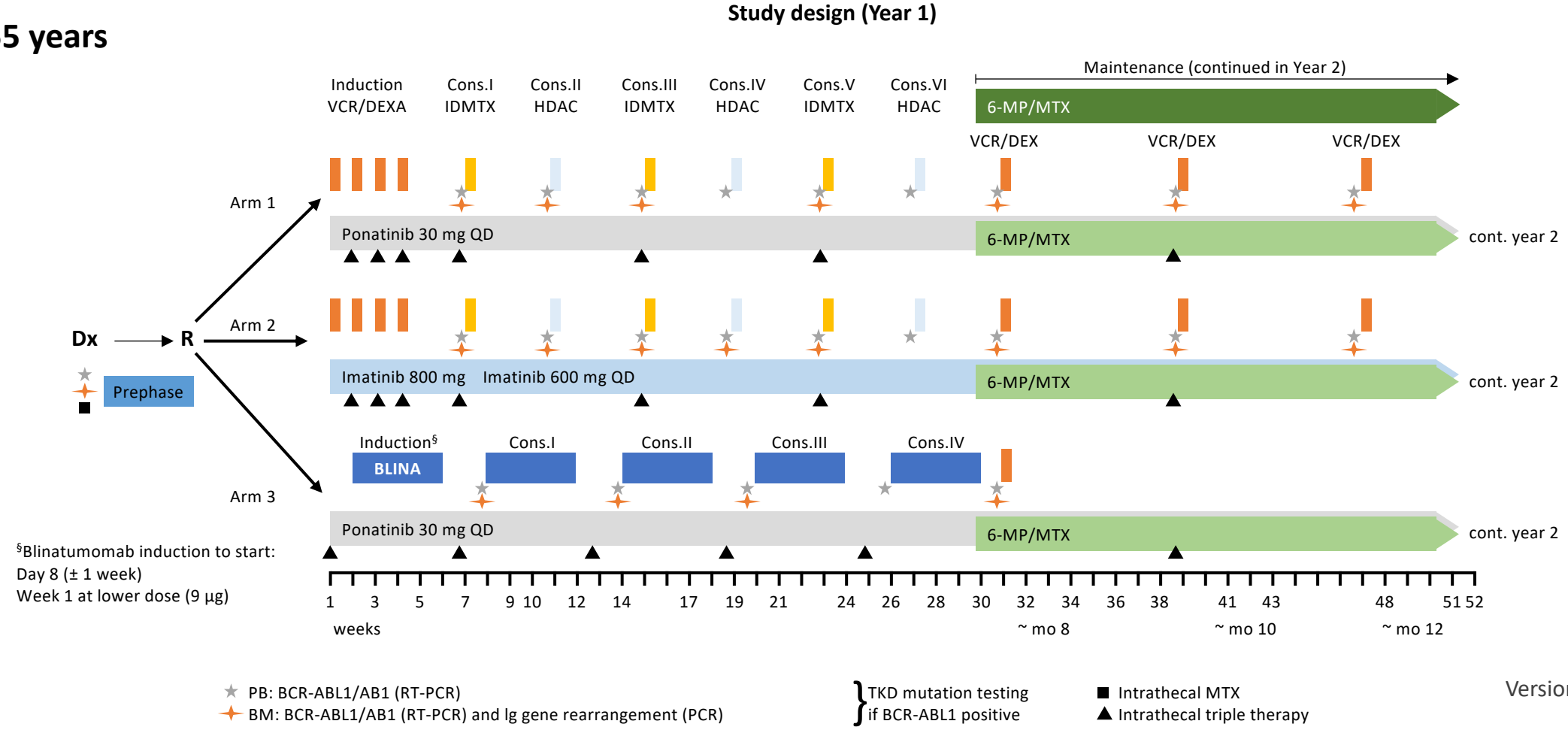
Figure 1. Overall scheme of the trial. Sample size: 236.

*Blinatumomab is not licensed for first-line use, nor in combination with TKIs.

1. Chiaretti S, et al. EHA 2021; Abstract S112; 2. Courtesy of S. Chiaretti, https://clinicaltrials.gov/ct2/show/NCT04722848.

EWALL 3-arm trial

Age ≥55 years



Version 5,25.06.2017

Blinatumomab is not licensed for first-line use, nor in combination with TKIs.
Courtesy of O. Ottmann (EudraCT ref: 2018-003350-25).

BLINA, blinatumomab;
EWALL, European Working Group on Adult ALL (ELN WP 6).

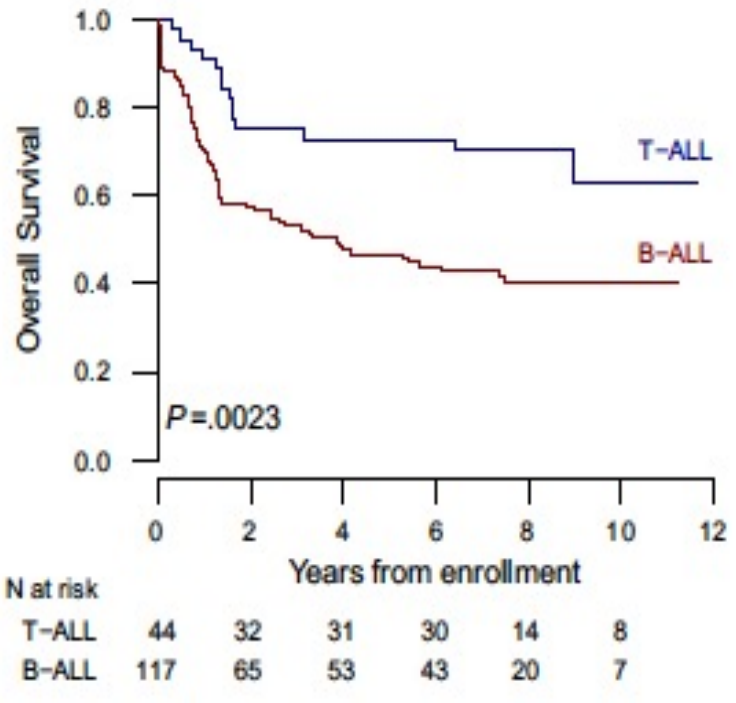
What about Ph- B-ALL ?

Ph– B-ALL, *age 18-65 Y*

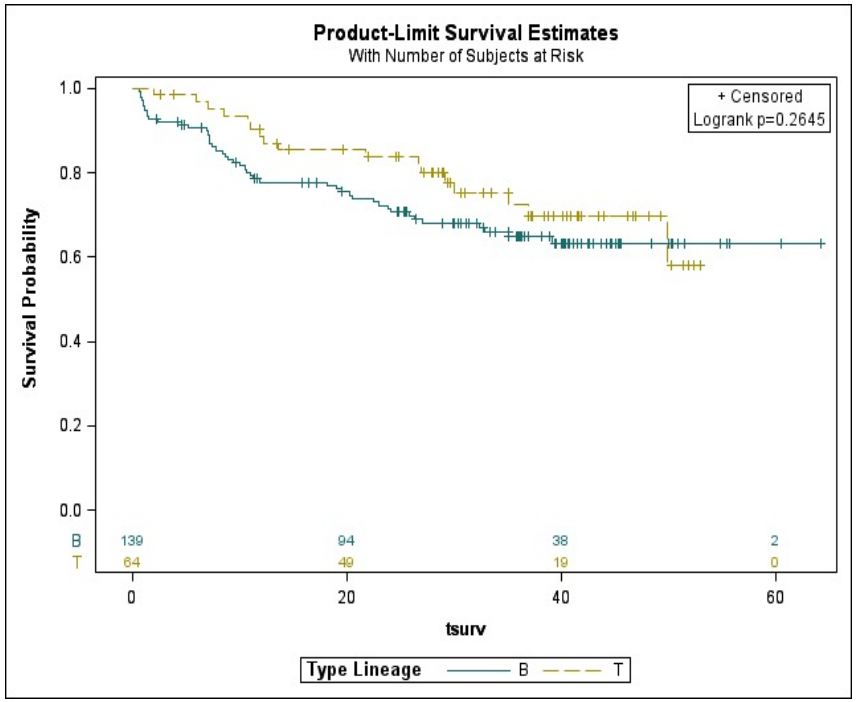
OS:
median 3.8 y (47% @ 5-y)[1]
median N/R (64.9% @ 3-y)[2]

- **Risk of failure:** 35-50%
- **Higher risk:** > 55 years, MRD_{pos}[1-3], Ph-like[4]

NILG 10/07[1]



GIMEMA LAL 1913[2]



Same as N10/07 but:

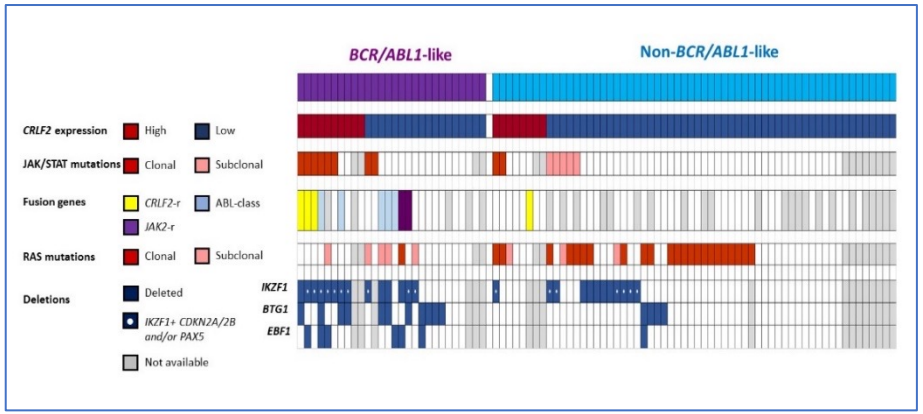
- less intensive chemo >55 Y
- Peg-ASP introduced

[1]Bassan R et al, Blood Cancer J 2020; [2]Bassan R et al, HemaSphere (EHA abstr # 919) 2018; [3]Goekbuget N et al, Hematology 2019; [4]Chiaretti S et al, Haematologica 2020

The new public enemy no. 1

Ph-like or *BCR/ABL1*-like

molecular diagnostic algorithm

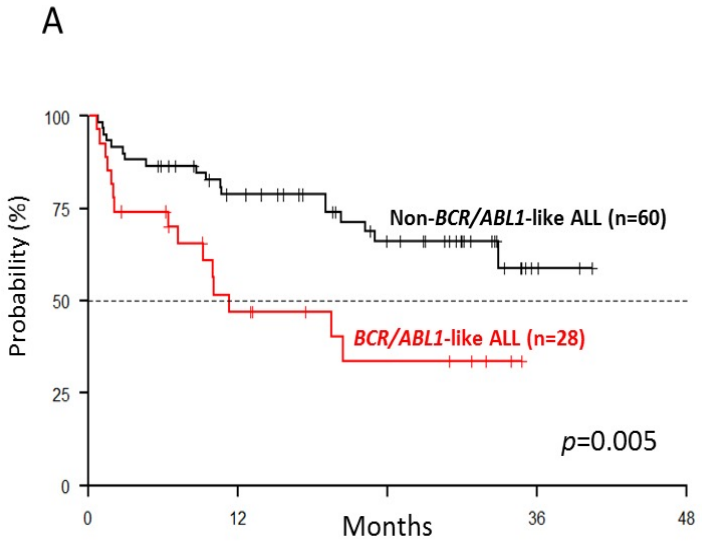


96 'B-other' ALL evaluable

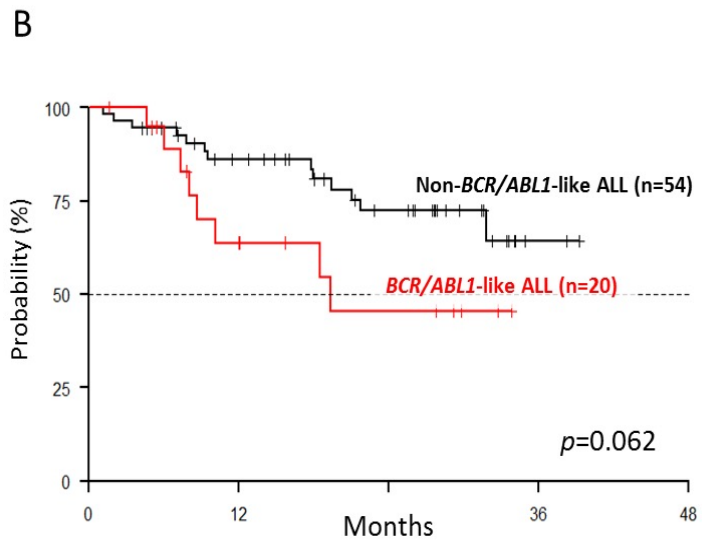
28 Ph-like (29.1%)

Chiaretti S et al, *Br J Haematol* 2018;
Chiaretti S et al, *Haematologica* 2021

Event-free survival

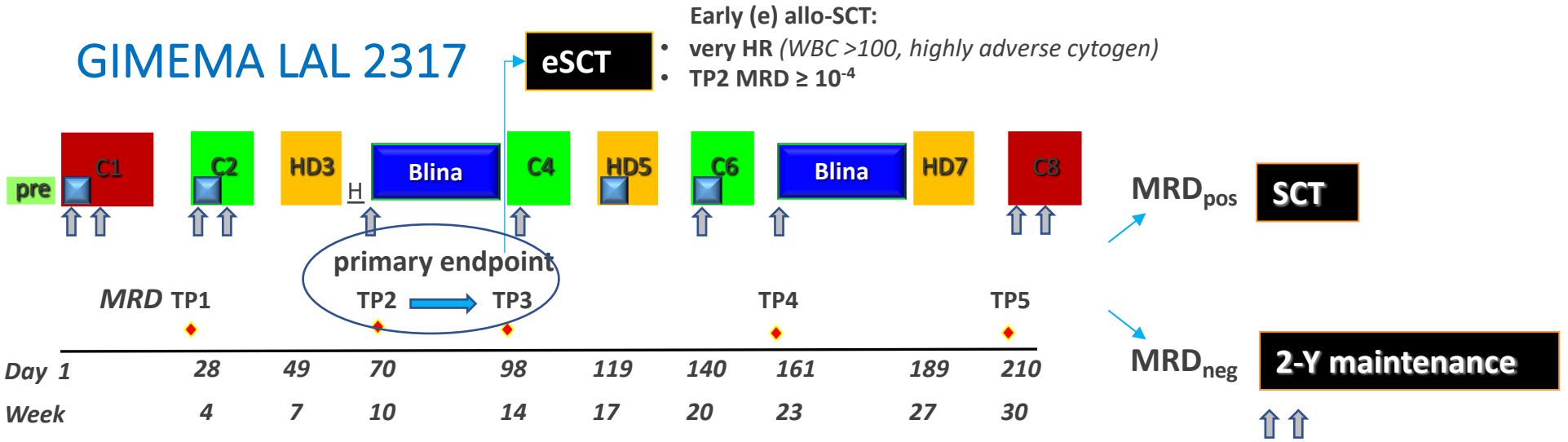


Disease-free survival



	Non Ph-like	Ph-like
Complete remission (%)	91	75 (P .07)
MRD <10^{-4} @ w10 (%)	81.6	47.1 (P .009)

Blinatumomab again in Ph- ALL



Treatment elements/strategy

Induction/reinduction (**pre**: CY/PDN; **Ind:** VCR/Dex/IDR/Peg-ASP [C1])

SD consolidation (IDR/CY/DXM/6MP/Ara-C/Peg-ASP [C2,5])

HD consolidation (MTX 2.5 g/m^2 and Ara-C [HD3,7] or Peg-ASP/6MP [HD5]; MTX 1.5 g/m^2 >55 y)

CNS prophylaxis (TIT)

H Stem cell harvest

Blinatumomab 28 mcg/d CIV dd 1-28

Risk/MRD-specific therapy

ClinicalTrials.gov ID NCT03367299

First results

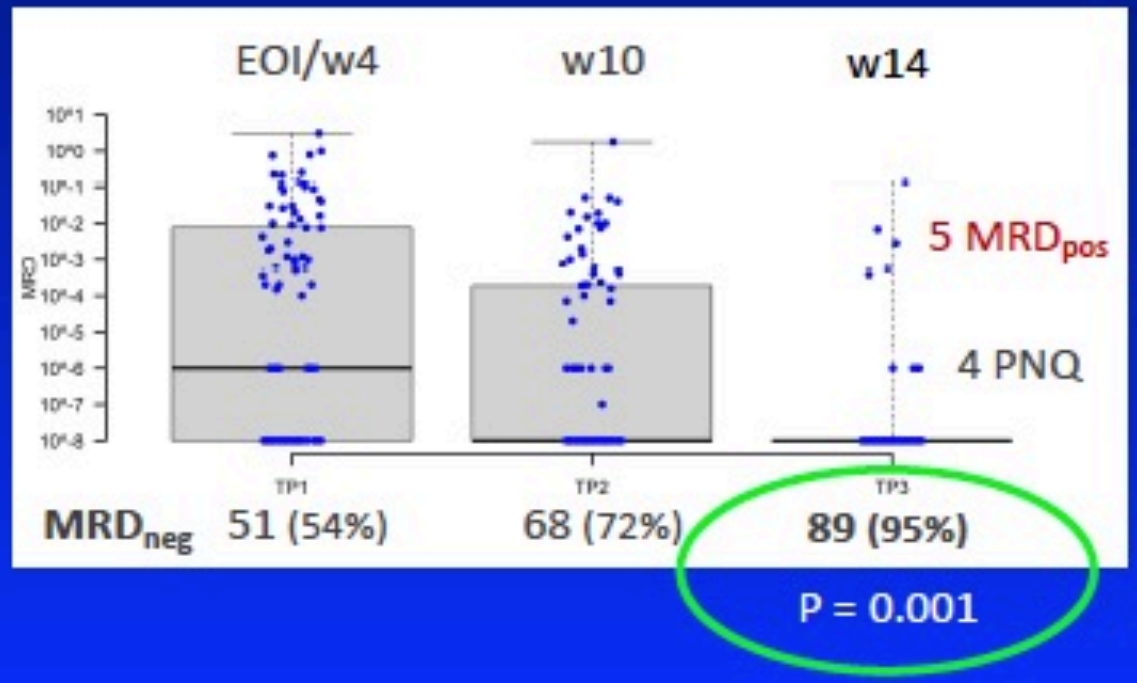
Presented EHA, 2021

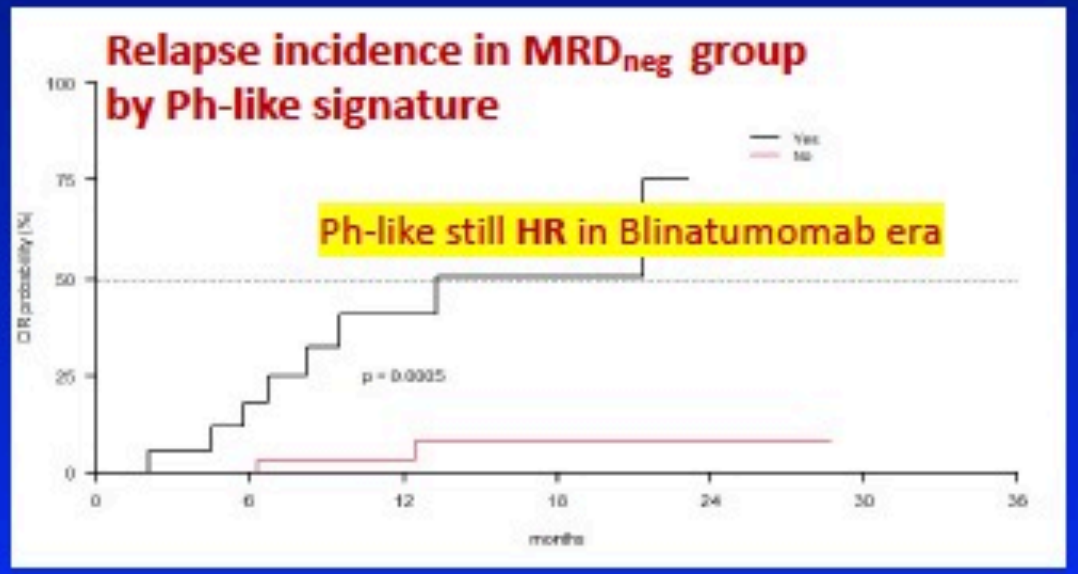
- *Study closed Aug 2020*
- ***94 MRD-evaluable CR patients with paired MRD samples w10 – w14***

1-year relapse rate

Ph-like 40.1 %

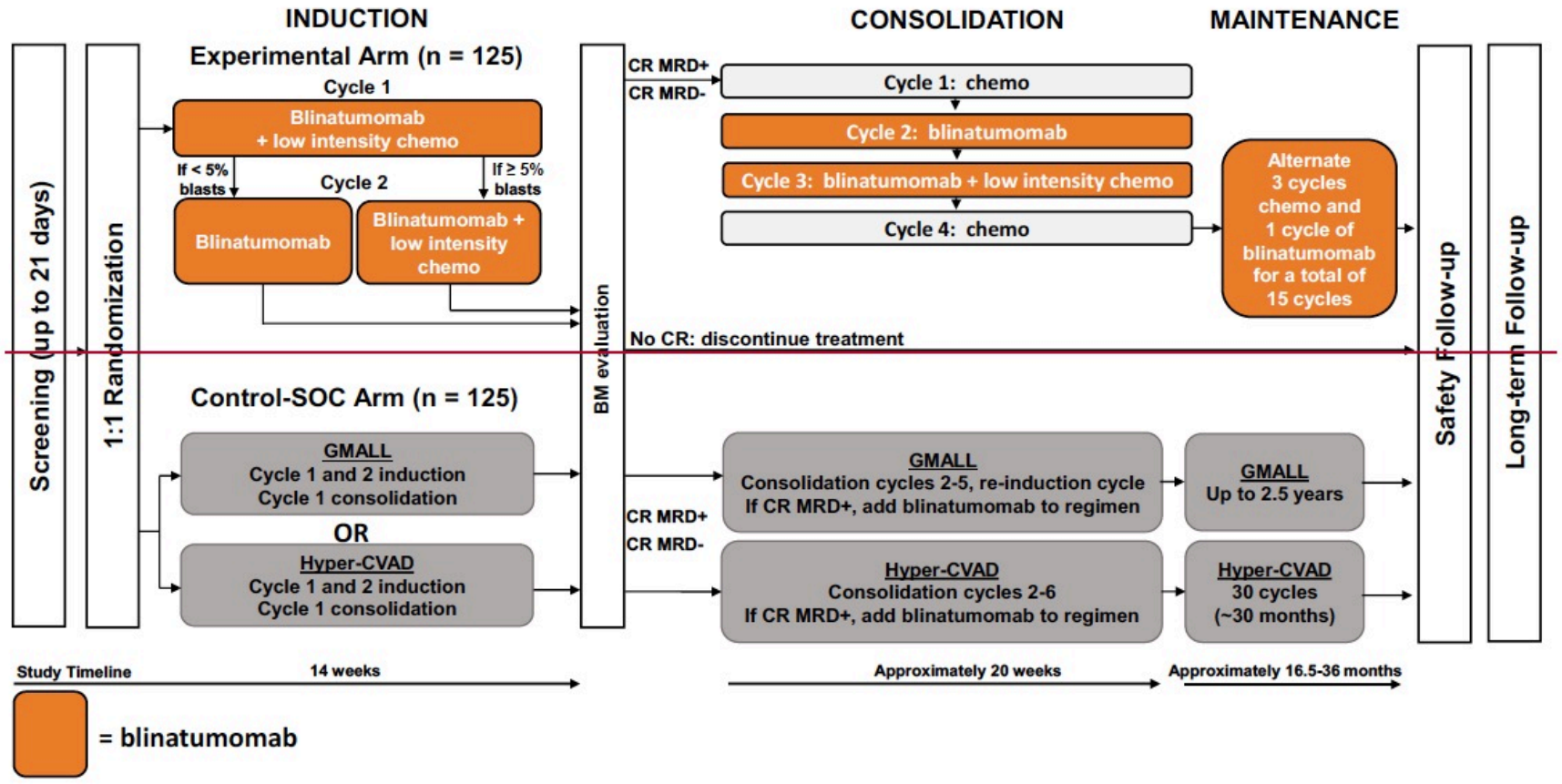
No Ph-like 3.2 % P=0.0005



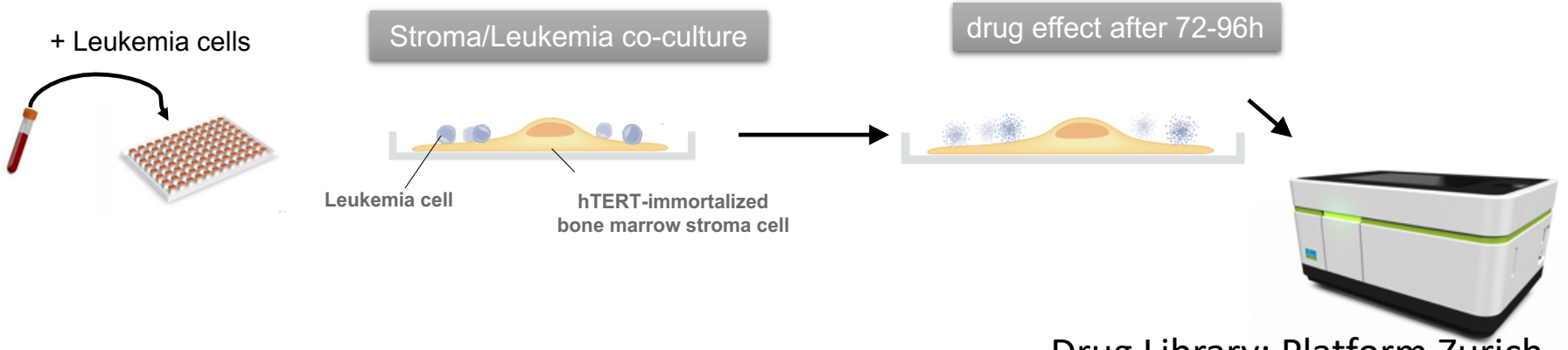


International study 360 in elderly ALL

Age 55+



Drug response profiling (DRP) for «hard» ALL subsets

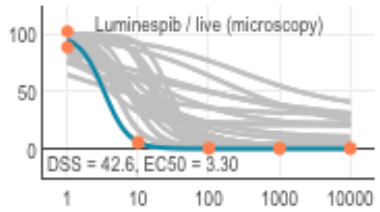


Drug Library: Platform Zurich
Up to130 drugs

collaboration with P. Horvath* (ETH, SCT Sezged) and Imre Västrik* (FIMM)

Healthcare Cloud

Database integration



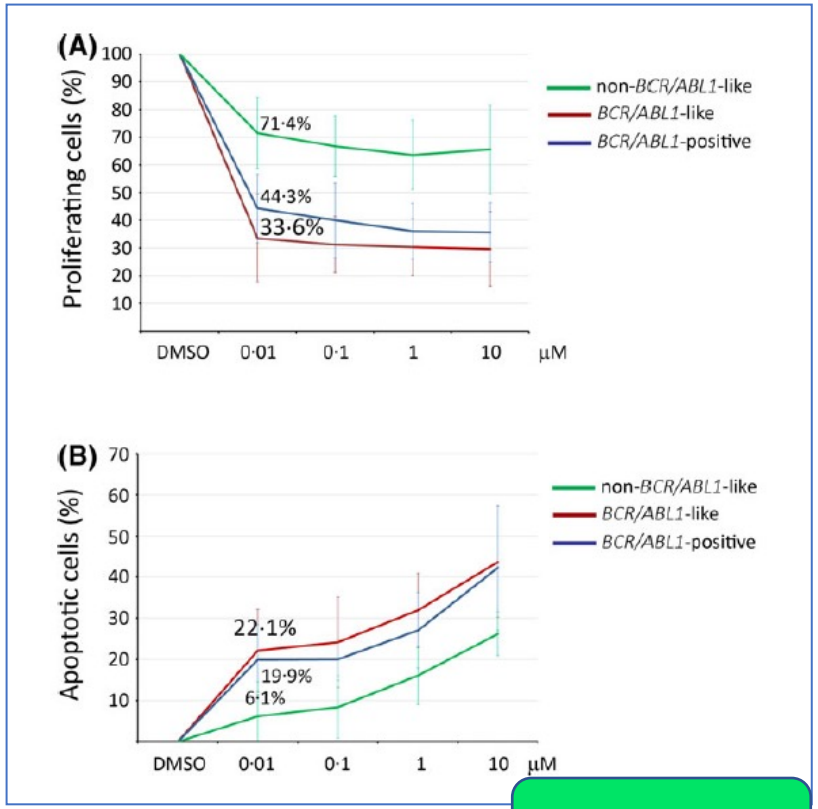
Analytical pipeline

Automated Image Analysis

J-P Bourquin (Zurigo, CH)

DRP: back to Ph-like ALL

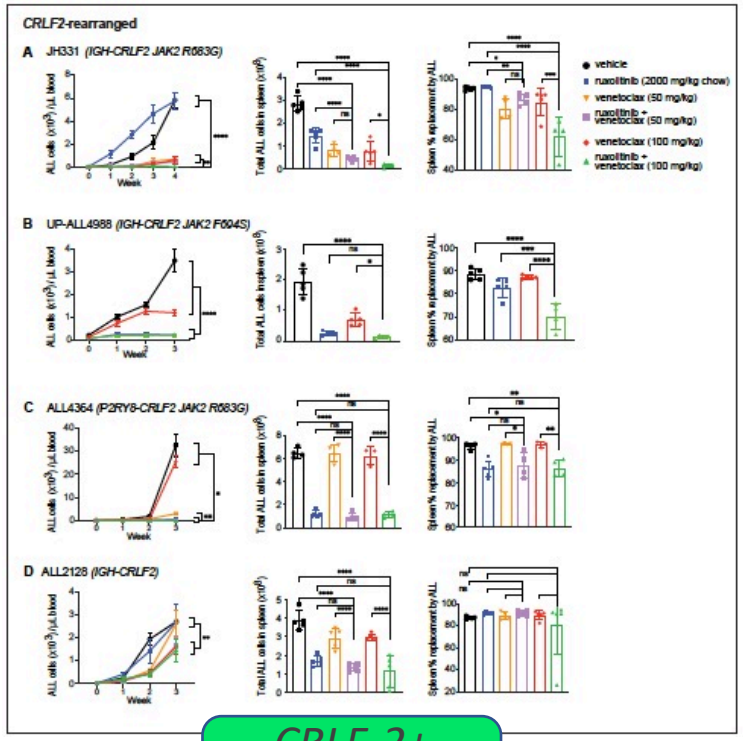
Ponatinib efficient killing of Ph-like ALL *(supporting <u>new</u> GIMEMA clinical trial)*



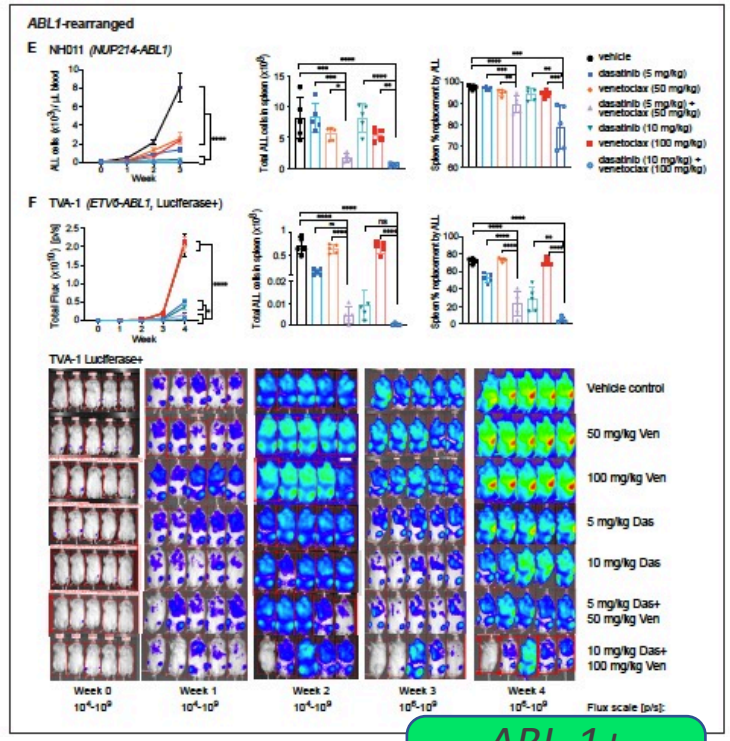
Chiaretti S et al, *Br J Haematol* 2018

PONATINIB

Combinatorial drug discovery (venetoclax with dasatinib *or* ruxolitinib) based on systematic interrogation of synergistic vulnerability pathways with pharmacologic inhibitor validation in preclinical human leukemia models



CRLF-2+
VEN-RUX

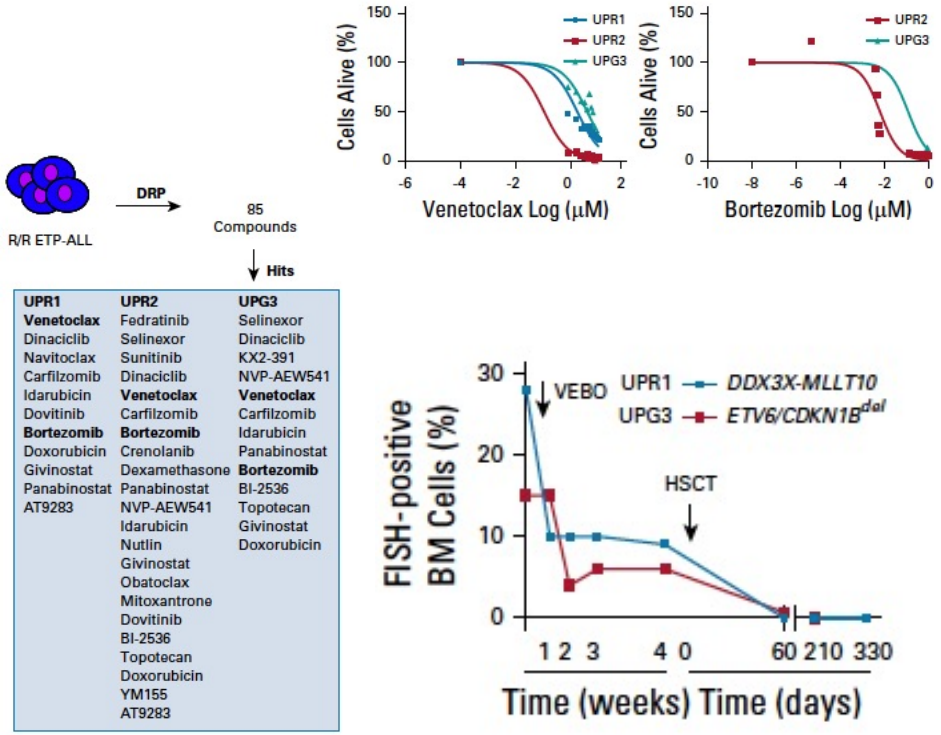


Ding Y-Y et al. *Clin Cancer Res* 2021

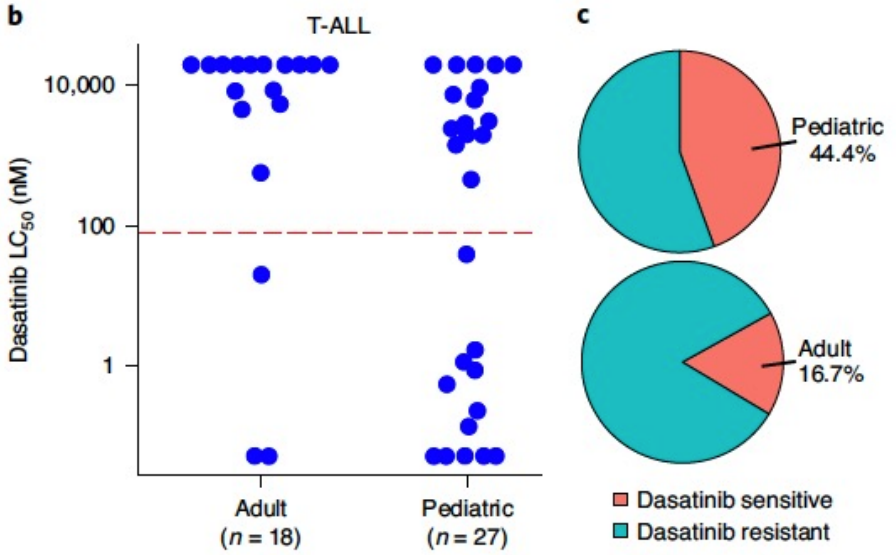
ABL-1+
VEN-DAS

What about T-ALL ?

- Highly refractory ETP-ALL sensitive to **bortezomib-venetoclax**



- T-ALL subset sensitive to **dasatinib**



- LCK tyrosine kinase
- High BCL-XL
- Low BCL2
- Venetoclax resistance

La Starza R et al, *Cancer Discov* 2019

Gocho Y et al, *Nat Cancer* 2021

Concluding remarks on «chemo-free» strategies in adult ALL

- **It's happening, and it's already upfront**:
  - Expanding/highly promising in Ph+ ALL
  - More experimental in Ph- B-ALL, aiming to lower the chemo burden – differences expected among disease subsets
  - Even more experimental in T-ALL, so far only at resistance/relapse

- **It's supported by:**
  - Molecular ALL characterization, MRD study, DRP studies

THANK YOU: S Chiaretti, R Foà, A Rambaldi, G Roti, J-P Bourquin, O Ottmann, C Mecucci and GIMEMA