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Strategie chemo-free della leucemia linfoblastica Ph positiva

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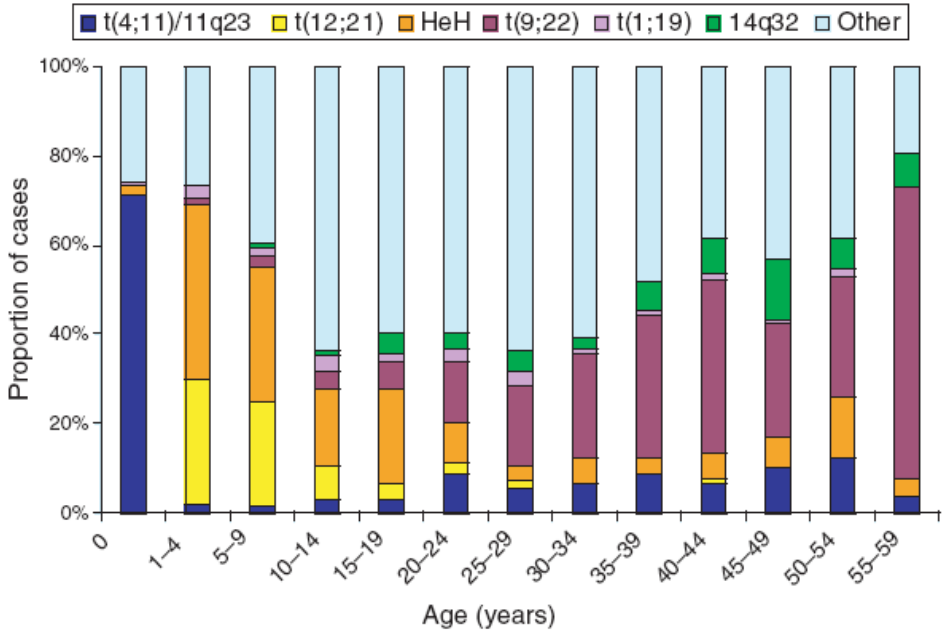
Disclosures of Federico Lussana

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer					X	X	
Abbvie					X	X	
Amgen					X		
Incyte					X		
Clinigen					X		
Bristol Myers Squibb					X	X	

Cytogenetics is a function of age

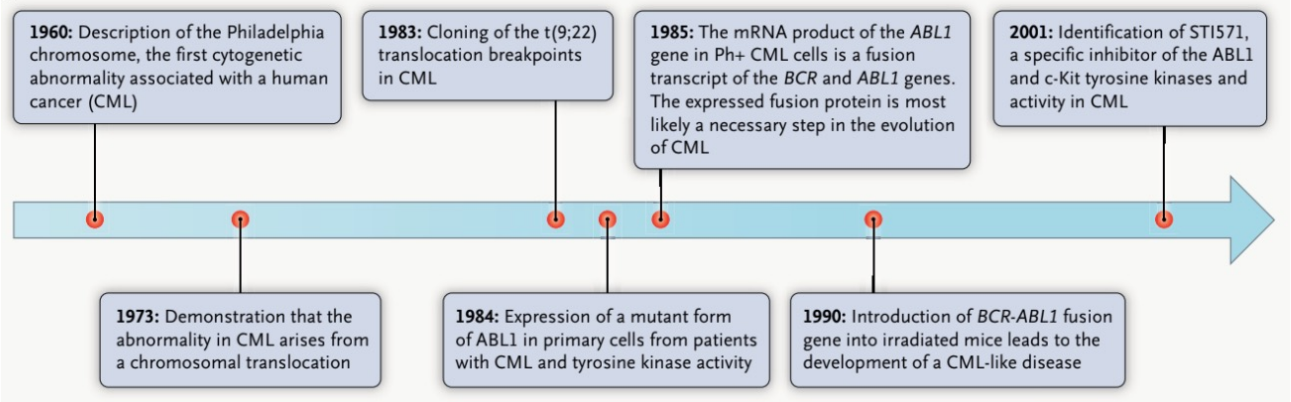
- The frequency of patients with BCR–ABL positive acute lymphoblastic leukaemia increases with age: 2–5% in childhood, 6% in AYAs, and **more than 50% in adults >55 years**

- Most frequent subset in adult /elderly ALL→ unfit for intensive chemotherapy



Moorman A et al. Brit J Haemat 2008; Chiaretti S. et al. Haematologica 2013, Foà R, Chiaretti S. NEJM 2022

Ph+ leukemia: the history



Foà R, Chiaretti S. NEJM 2022;386(25):2399-2411

CLINICAL OUTCOME OF Ph+ ALL PATIENTS TREATED IN A PRE-IMATINIB ERA (1990 - 2000)

N	80
CR	63/80 (79%)
Allo TRX	**16 (20%)**

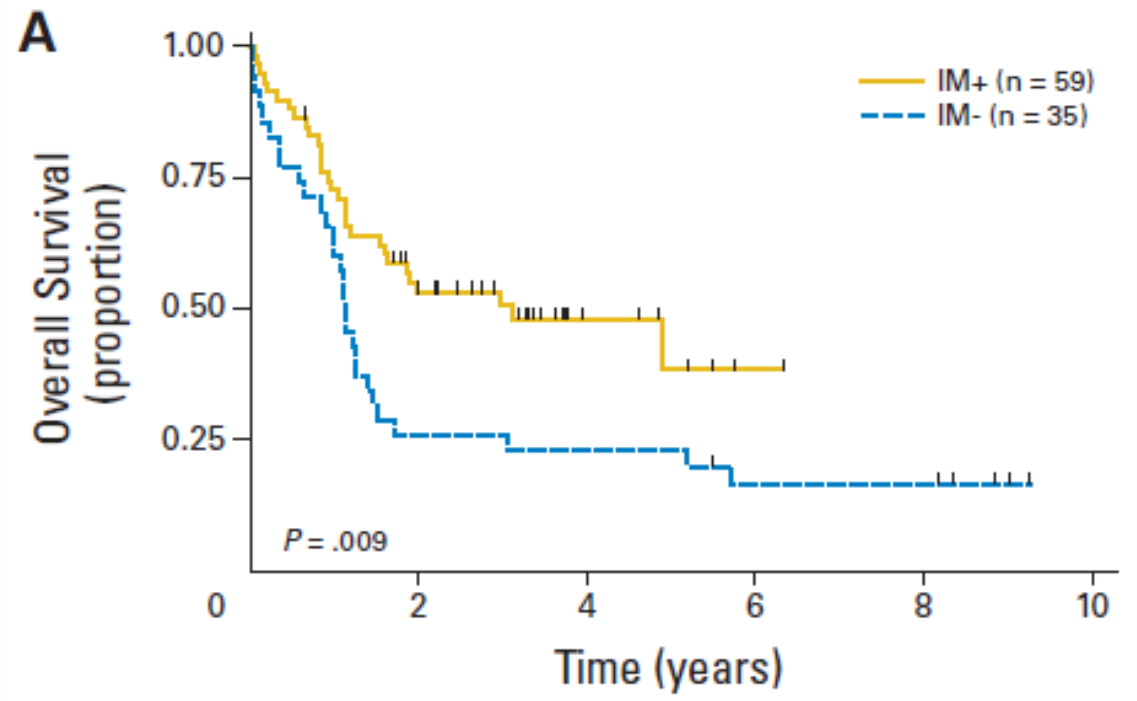
Disease Free Survival (n=63)

Overall Survival (n=80)

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

nilg northern italy leukemia group

Chemotherapy-Phased Imatinib Pulses for Adult Patients with Ph+ ALL
Northern Italy Leukemia Group Protocol 09/00



Bassan R et al.: J Clin Oncol 28:3644-3652. 2010

Targeted ABL kinase inhibitors have been game changers!

The GIMEMA Strategy: a TKI without systemic chemotherapy during Induction

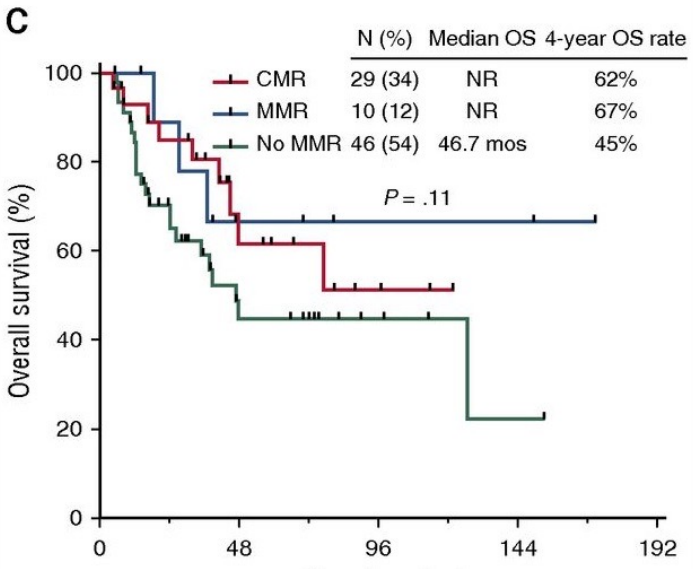
Study protocol	Age (years)	Induction therapy	CHR rate
LAL 0201-B[1]	60–89	IMA + PDN	100%
LAL 1205[2]	18–84	DAS + PDN	100%
LAL 0904 3rd amendment[3]	16–60	IMA + HAM (± transplant)	96%
LAL 1408[4]	>60	NIL + IMA + PDN*	94%
LAL 1509[5]	18–60	Total therapy strategy (DAS)	97%
LAL 1811[6]	>60	PON + PDN	95%

High CR rates (94-100%)

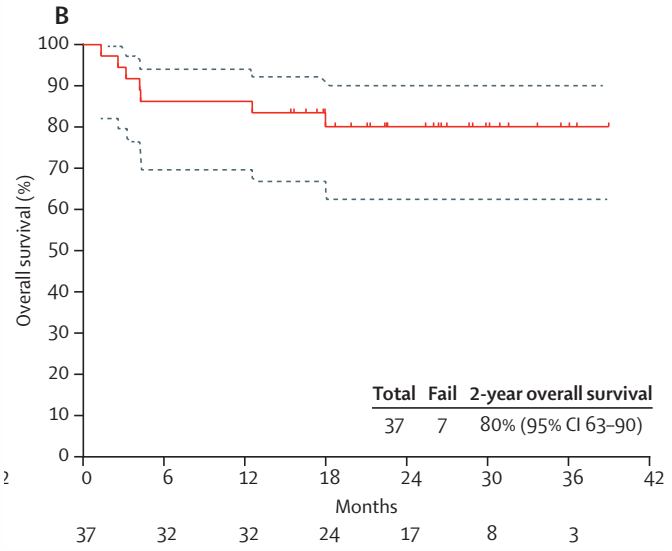
* Alternating 6 week schedules of nilotinib/imatinib
CHR, complete hematologic remission; DAS, dasatinib; HAM, high-dose cytarabine and mitoxantrone; IMA, imatinib; NIL, nilotinib; PDN, prednisone; PON, ponatinib

1. Vignetti M, et al. Blood 2007;109:3676–8; 2. Foà R, et al. Blood 2011;6521–8
3. Chiaretti S, et al. Haematologica 2016, 101:1544-1552
4. Martinelli G, et al. AACR 2014, Abstract 5552 and poster presentation
5. Chiaretti S, et al. haematological 2021
6. Martinelli G. et al ASH 2017

Importance of achieving a molecular remission



Short NJ et al. Blood, 2016



Jabbour, E et al. Lancet Oncol 2015

Recent excellent outcome results in Ph+ ALL patients without AlloHSCT

Chemo-free therapy for Ph+ ALL: TKI in combination with tumor specific BITE antigen targets

Blinatumomab

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

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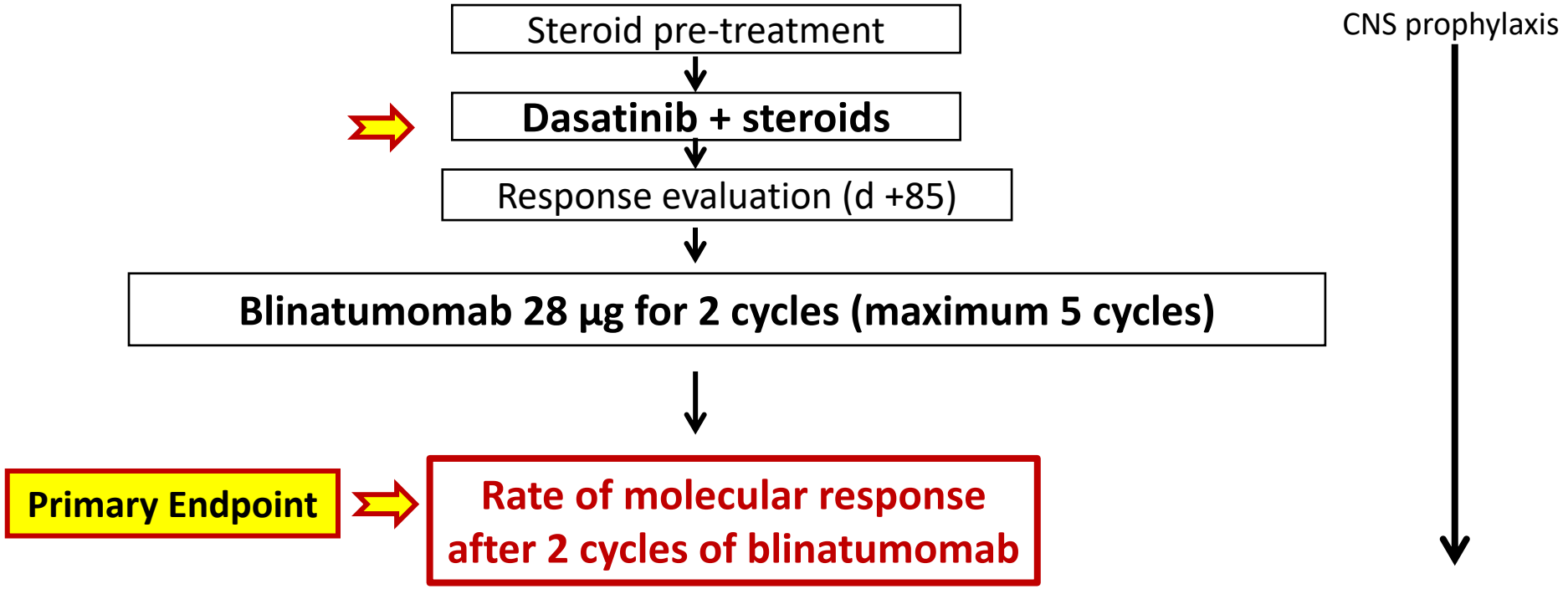
Ph+ ALL D-ALBA (GIMEMA LAL 2116) frontline protocol (>18 yrs)



Post consolidation treatment left at the investigator choice

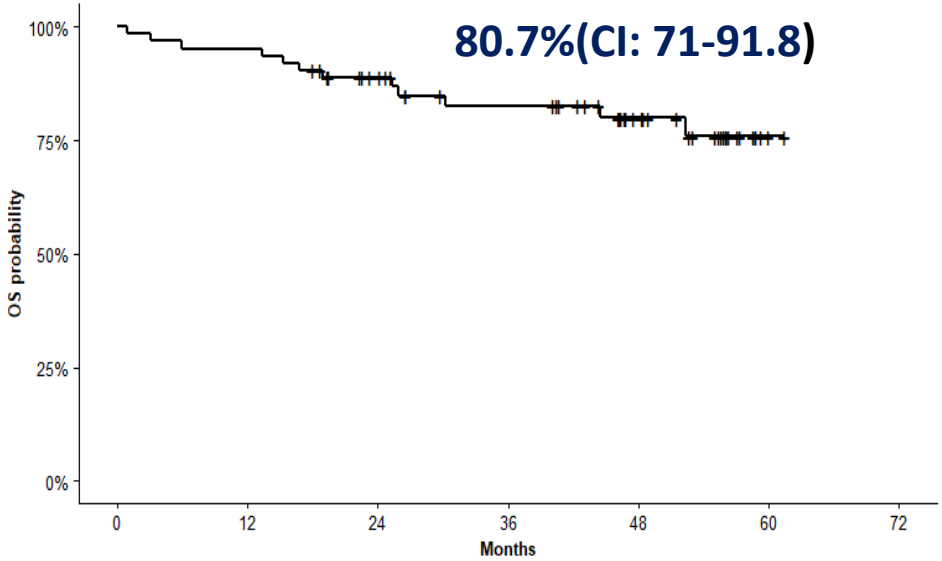
Foà et al, NEJM 2020;383:1613-1623

Ancillary Observational Study of Post-Frontline Sequential Treatment of Adult Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Patients with Dasatinib and the Bispecific Monoclonal Antibody Blinatumomab

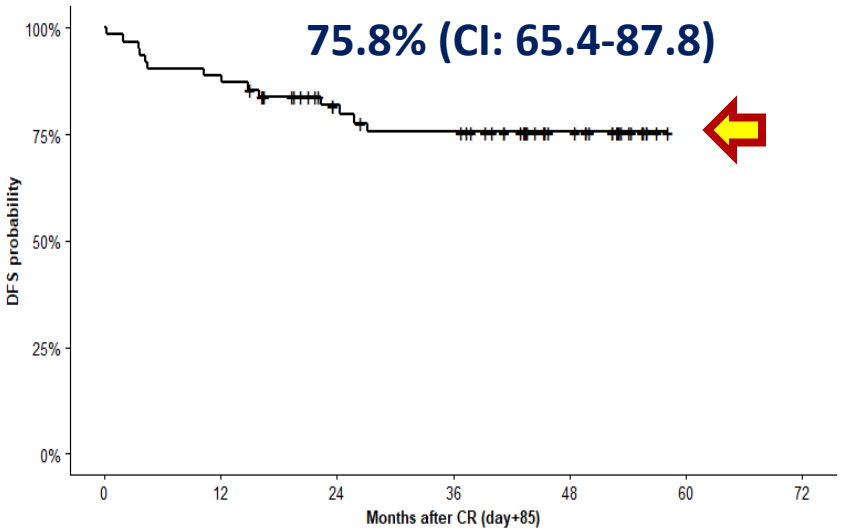
GIMEMA LAL2217

D-ALBA protocol. Updated 4-year OS and DFS*

OS



DFS

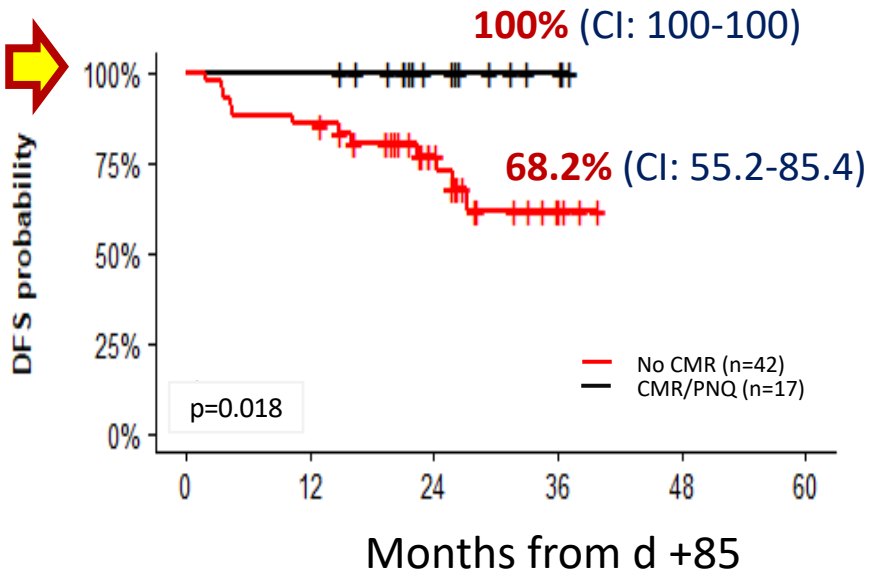


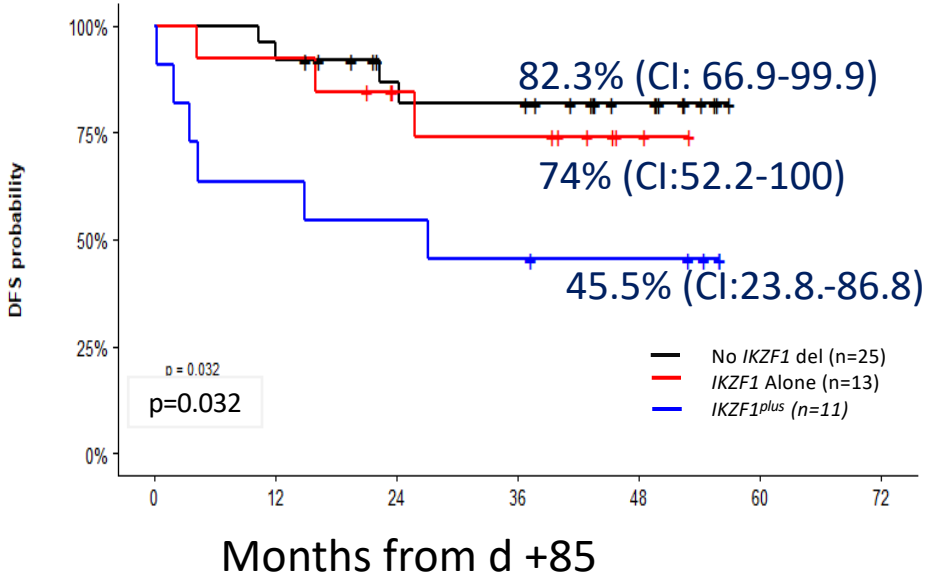
Median follow-up: 53 months (range: 0.9-66.2)

9 relapses occurred - 4 hematologic, 4 involving the CNS and 1 nodal - at a median of 4.4 months (1.9-25.8)

Slide courtesy of S Chiaretti; Foà et al, JCO in press

Updated D-ALBA. Estimated 4-years DFS according to molecular responses and CNAs

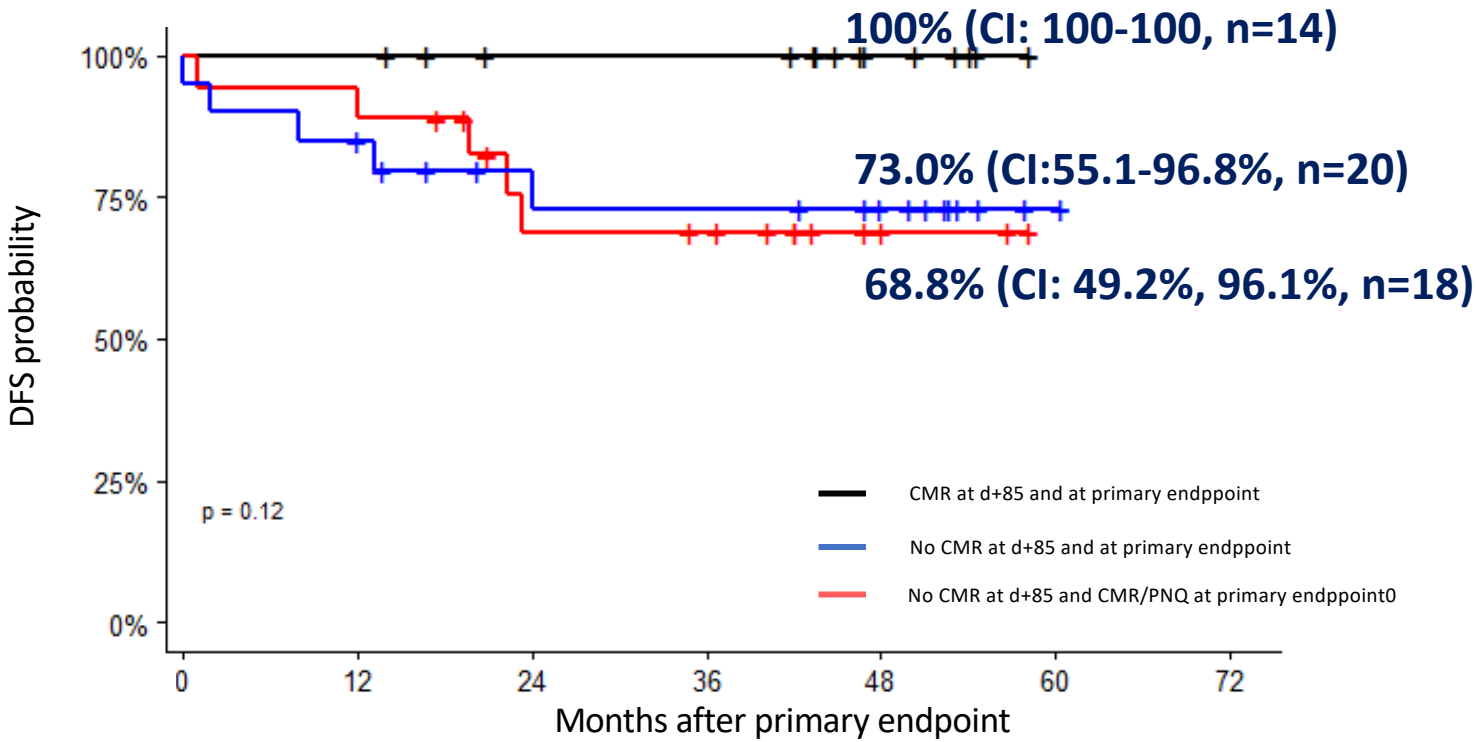




IKZF1^{plus} cases emerged as the subset with the poorest DFS

Slide courtesy of S Chiaretti; Foà et al, JCO in press

DFS according to molecular response



Slide courtesy of S Chiaretti; Foà et al, JCO in press

Post-D-ALBA treatment

29 continued TKIs

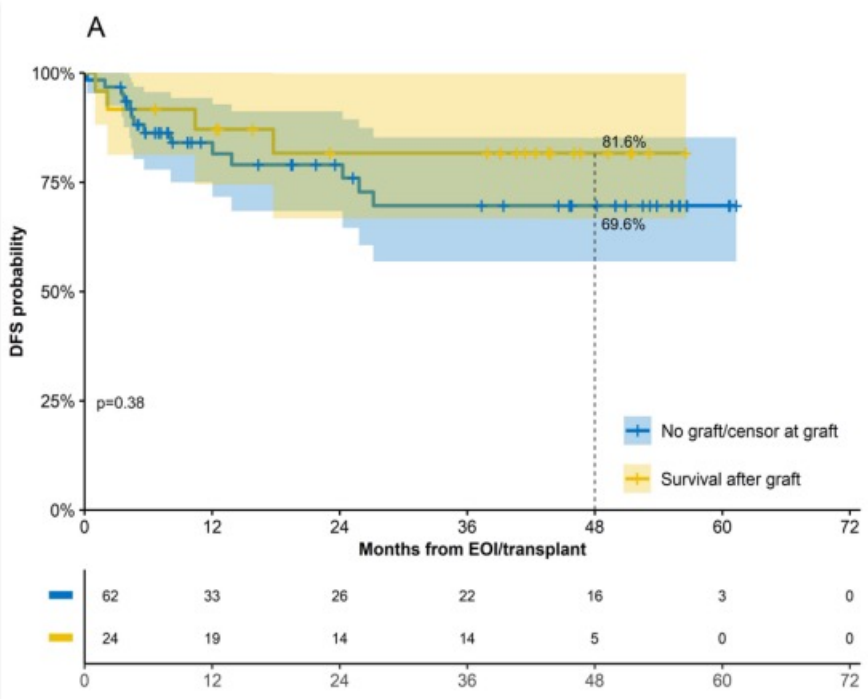
- 21 continued dasatinib
- 5 shifted to imatinib
- 5 pts to ponatinib (1 performed double shift)

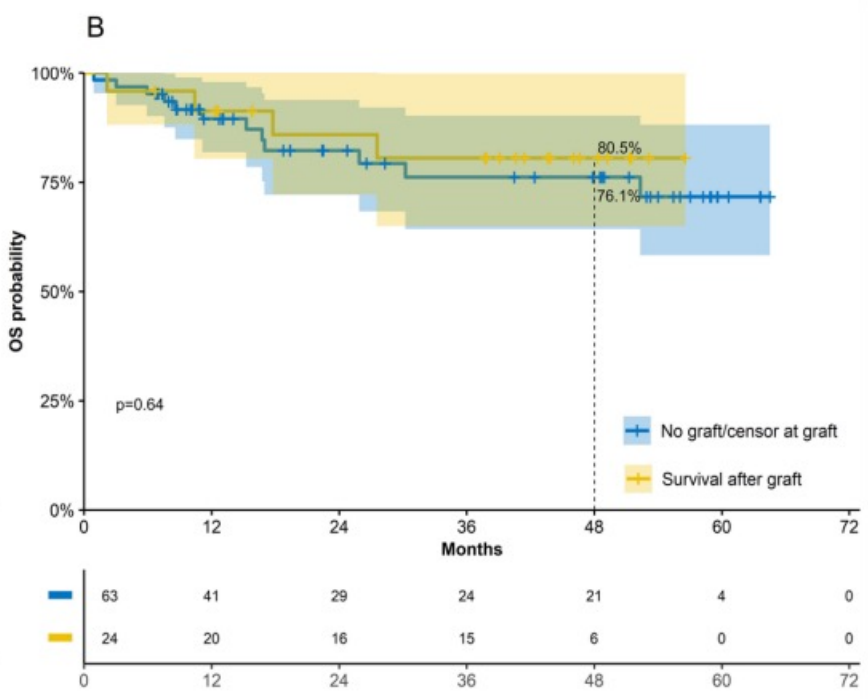
29 allografted (6 in 2nd CHR)

- 9 sibling
- 13 MUD
- 6 haploidentical donor
- 1 cord blood

Slide courtesy of S Chiaretti

Updated D-ALBA. Role of transplant

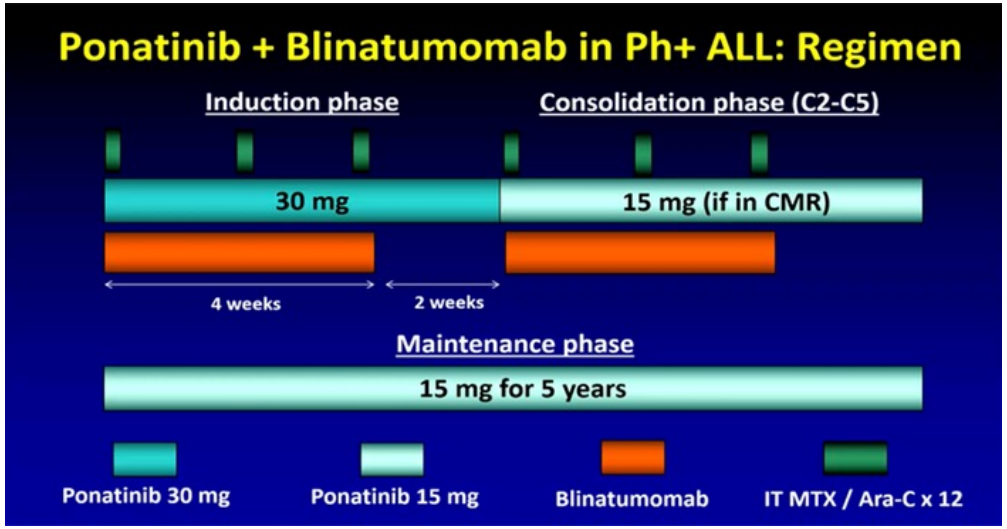


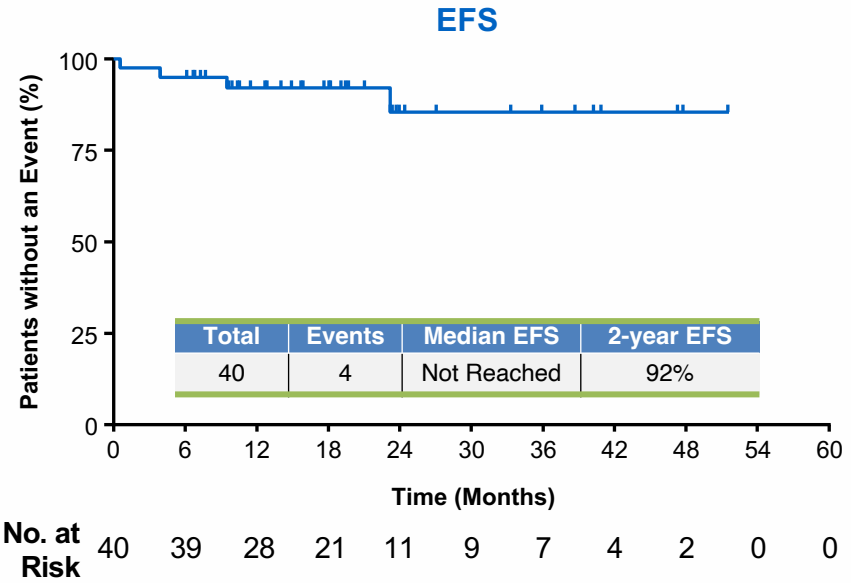


- Enrichment in MRD+ cases in allo-SCT cohort
- **Very low** non-relapse mortality : 10%

Slide courtesy of S Chiaretti; Foà et al, JCO in press

Ponatinib and Blinatumomab for patients with newly diagnosed Ph+ ALL: a phase II study





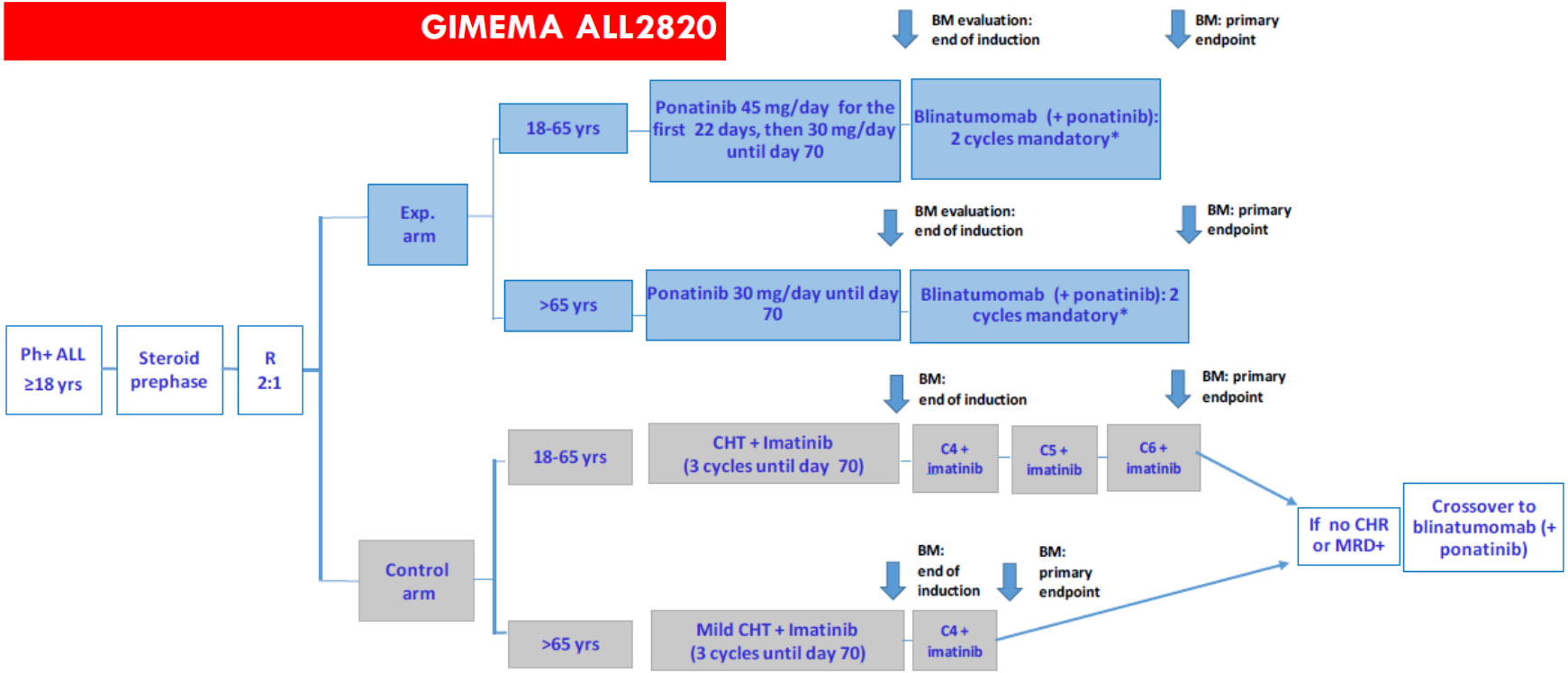
- The CR/CR with incomplete count recovery rate was 96%
- The rates of CMR was 87%
- With a median follow-up of 18 months, the estimated 2-year OS and EFS rates were 95% and 92%, respectively
- Notably, only 1 (3%) patient underwent alloHSCT in CR1 owing to persistently detectable BCR:ABL1

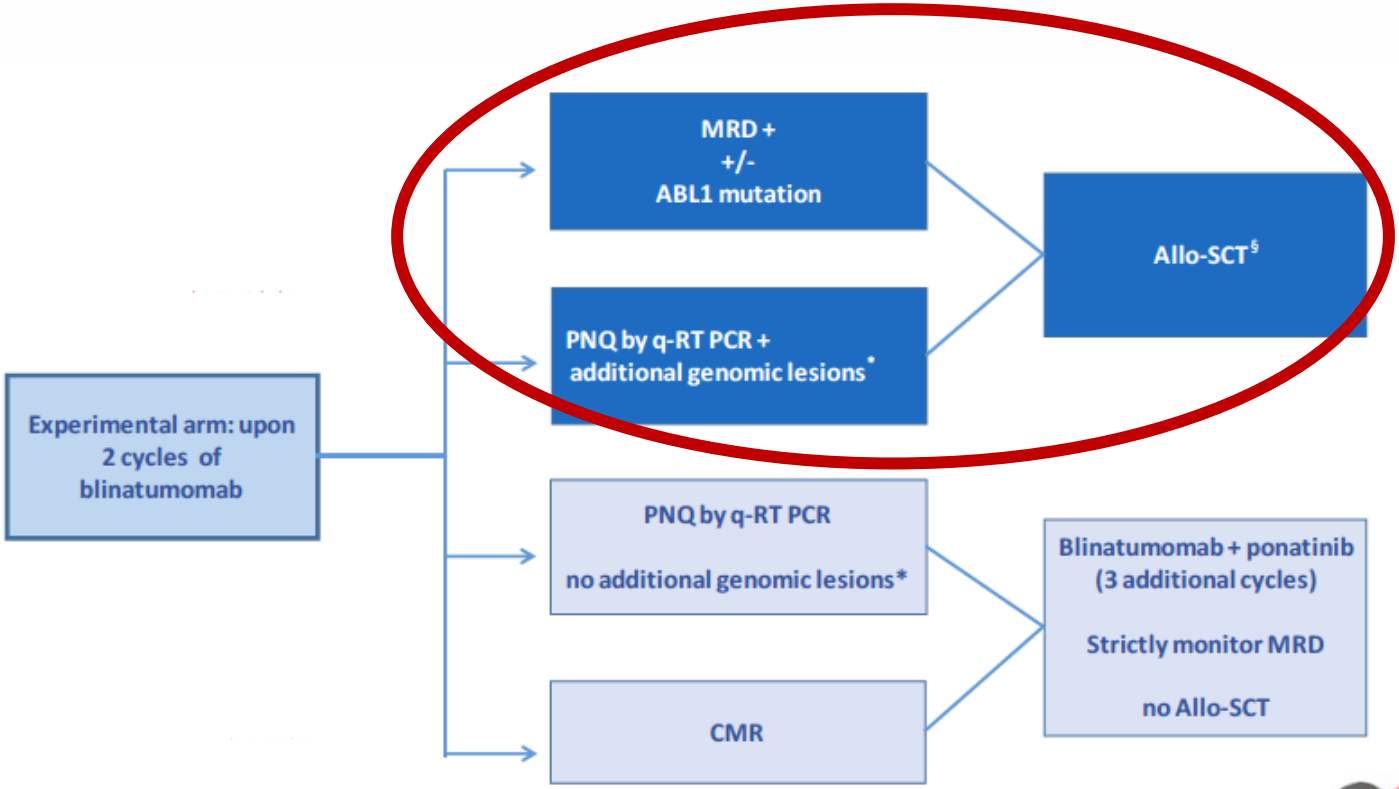
Short NJ, et al. Slides presented at: American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA. 2. *Jabbour E et al. Lancet Haematol 2023*

IS THERE A BEST STRATEGY?

- Opening new questions:
  - Head-to-head comparison of these new treatment approaches (e.g. dasatinib/ponatinib + blinatumomab) against the TKI plus attenuated chemotherapy approach to confirm superiority are needed
  - Allo SCT in young/fit patients: is it still mandatory CR1?
    - Maybe only for MRD+ patients and patients with additional genomic lesions?
  - Novel combination that could possibly overcome poor risk biology, such as the IKZF1plus aberration (e.g. ponatinib + blinatumomab?)
  - Best positioning of blinatumomab in future upfront therapeutic regimens

Newly Diagnosed Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL). Sequential Treatment with Ponatinib and the Bispecific Monoclonal Antibody Blinatumomab vs Chemotherapy and Imatinib





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Gruppo Italiano Malattie EMatologiche dell'Adulto

Chemo-free strategies and fitness

Table 2. Pragmatic clinical recommendations for tailored cardiovascular monitoring of patients with CML receiving BCR-ABL TKIs.

Assessment	Imatinib	Bosutinib	Dasatinib	Ponatinib	Nilotinib
	More favorable CV profile	More favorable CV profile	Pulmonary HTN, effusions	HTN, vascular events[a]	Hyperglycemia, vascular events[a], and QT prolongation
Baseline					
Clinical cardiovascular assessment	GCP	Recommend	Recommend	Recommend	Recommend
Blood pressure check	GCP	As needed	As needed	Recommend	Recommend
Fasting glucose	GCP	As needed	As needed	Recommend	Recommend
Fasting lipid panel	GCP	As needed	As needed	Recommend	Recommend
Echocardiogram	GCP	As needed	If CP sx	As needed	As needed
ECG	GCP	As needed	Recommend	As needed	Baseline, after 7 days, and after each dose change
ABI	GCP	As needed	As needed	Recommend	Recommend
1-month follow-up					
Clinical cardiovascular assessment	GCP	Recommend	Recommend	Recommend	Recommend
Blood pressure check	GCP	As needed	As needed	Recommend	Recommend
3- to 6-month follow-up					
Clinical cardiovascular assessment	GCP	Recommend	Recommend	Recommend	Recommend
Blood pressure check	GCP	As needed	As needed	As needed	Recommend
Fasting glucose	GCP	As needed	As needed	Recommend	Recommend
Fasting lipid panel	GCP	As needed	As needed	Recommend	Recommend
Echocardiogram	GCP	As needed	If CP sx	As needed	As needed
ECG	GCP	As needed	As needed	As needed	If dose changes
ABI	GCP	As needed	As needed	Recommend	Recommend

[a]Vascular events include coronary, cerebral, and peripheral vascular events.
ABI, ankle–brachial index; CML, chronic myeloid leukemia; CP sx, cardiopulmonary symptoms; CV, cardiovascular; ECG, electrocardiogram; GCP, good clinical practice; HTN, hypertension; TKIs, tyrosine kinase inhibitors.

Ponatinib associated with serious arterial thrombotic events, hepatotoxicity, and pancreatitis

Kondapalli L et al, Vascular Medicine 2020

CONCLUSIONS

- Ph+ ALL is now a relatively favorable prognosis ALL subtype
- TKIs have dramatically changed remission rates, survival
- MRD negativity must be considered the treatment goal for any treatment strategy in Ph+ ALL
- Low intensity treatments with minimal or NO traditional chemotherapy may become a new standard of care
  - The D-ALBA 4-year results show that a chemo-free induction/consolidation approach is feasible and translates into very good results (and low TRM)
- *IKZF1*^{plus} remains an unmet need → novel strategies required

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