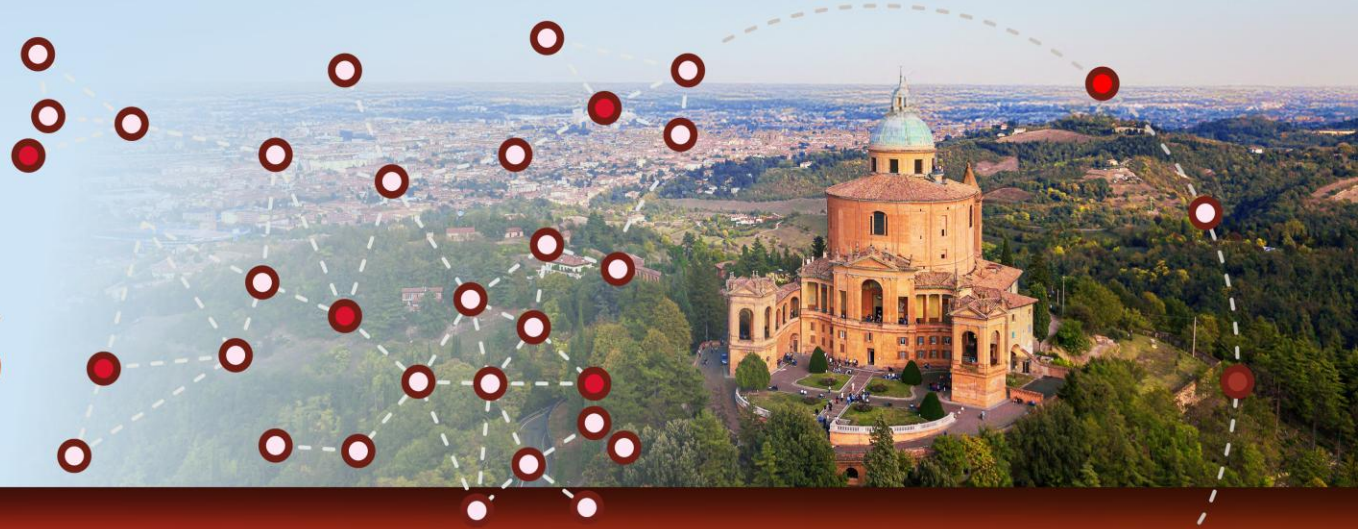
1ST INTERNATIONAL CONFERENCE ON

Ph+ Leukemias



Bologna, Royal Hotel Carlton **September 29-30, 2025**

Allo-SCT in Ph+ ALL: is it still necessary?

Alessandro Rambaldi

Department of Oncology-Hematology, University of Milan

And Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

Disclosure statement

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen			✔			✔	✔
Pfizer			✔				
Novartis			✔			✔	
Kite Gilead			✔			✔	✔
Jazz			✔			✔	✔
Omeros			✔			✔	✔
Incyte			✔				
Sanofi			✔				
Pierre Fabre			✔			✔	
Italfarmaco			✔			✔	✔

AlloHSCT for every possible Ph+ ALL in CR1?

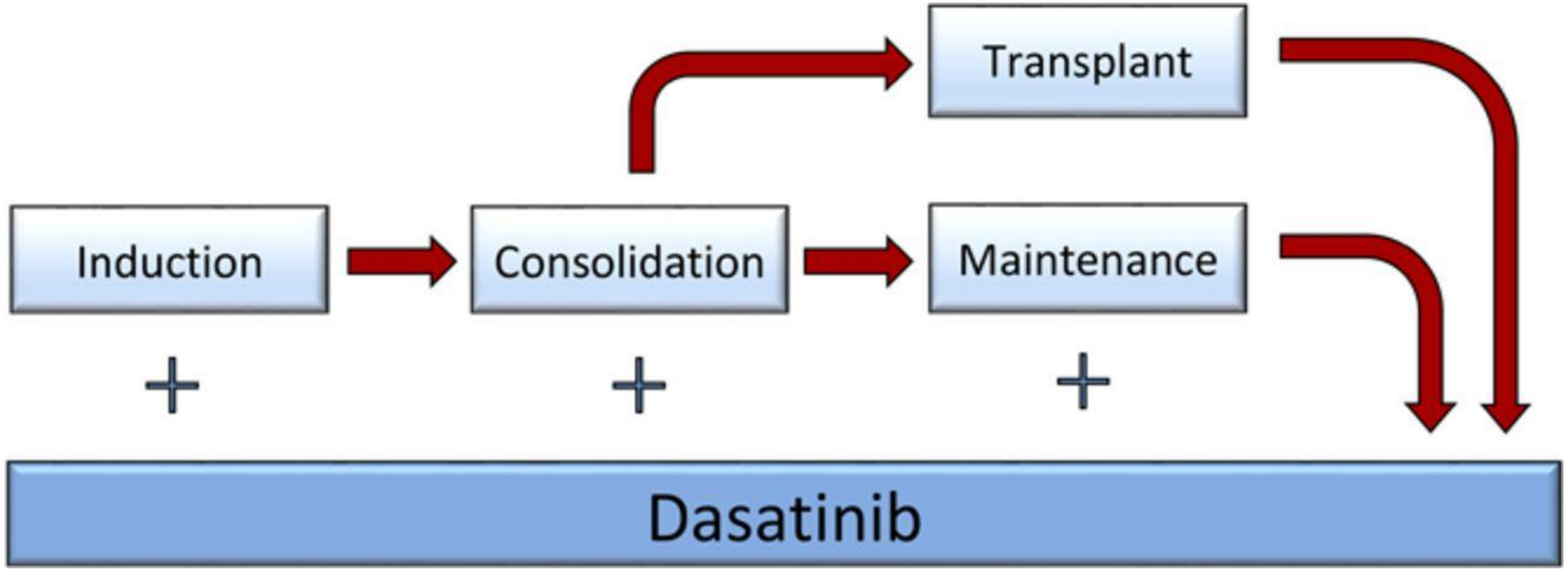
The answer would be, no thanks!

Allo-SCT in Ph+ ALL: is it still necessary?

The answer is yes, sometimes…

TKIs plus chemotherapy and alloHSCT remains the standard of care for many patients around the world

US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Ph+ ALL



Ravandi F. Blood Advance 2016;1 (3): 250-259

US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Ph+ positive ALL

Demographics	Median [range] or no(%)
Patients	94
Median age at diagnosis, y	44 [20-60]
Age >50 y	23 (24)
Sex: female	52 (55)
Laboratory	
WBC (× 10^9/L)	10 [1-410]
Marrow blast, %	83 [0-100]
CNS disease at diagnosis	
Absent	62 (66)
Not assessed	29 (31)
Present	3 (3)
Prior therapy before enrollment	
Untreated	60 (64)
Previously treated; achieved CR/CRi	16 (17)
Previously treated; remission status unknown	7 (7)
Previously treated; refractory	11 (12)
Previously treated; remission status unknown	7 (7)

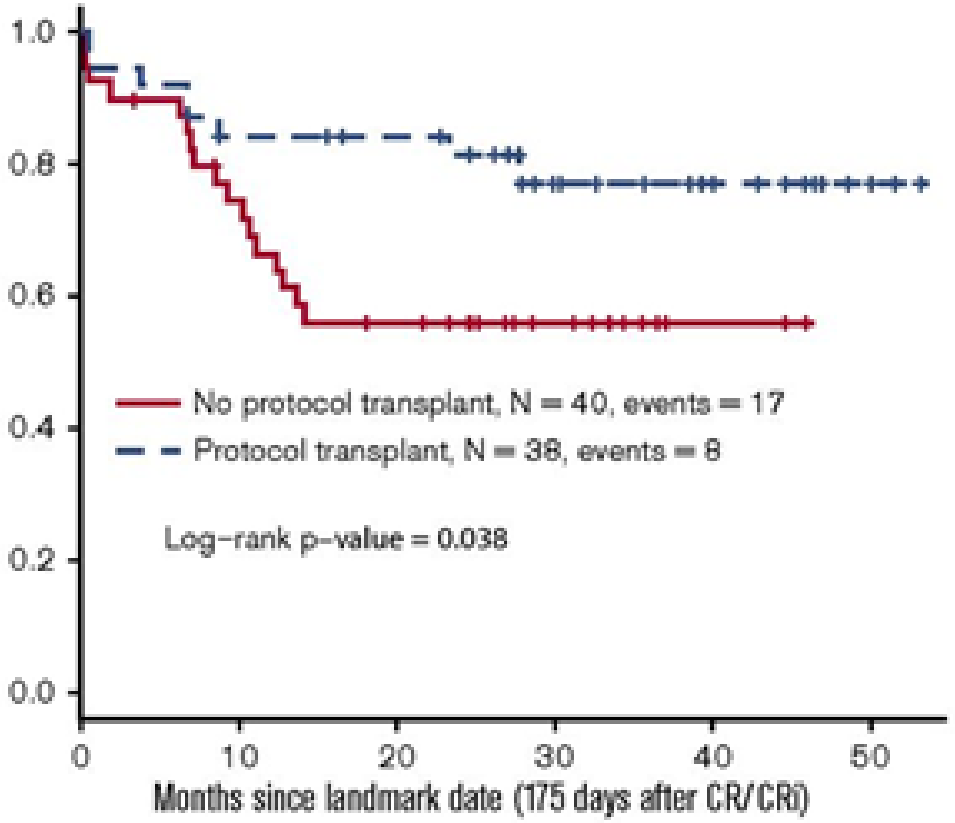
- All patients who achieved CR and had an available matched sibling or 10/10 unrelated donor would be encouraged to proceed to HCT (TBI 12 Gy in 6 fractions over 3 days and etoposide)
- All other patients remaining in CR would be enrolled in the maintenance portion of the study (continuous dasatinib 100 mg daily, monthly vincristine, and prednisone for 5 days per month, given for a total of 2 years

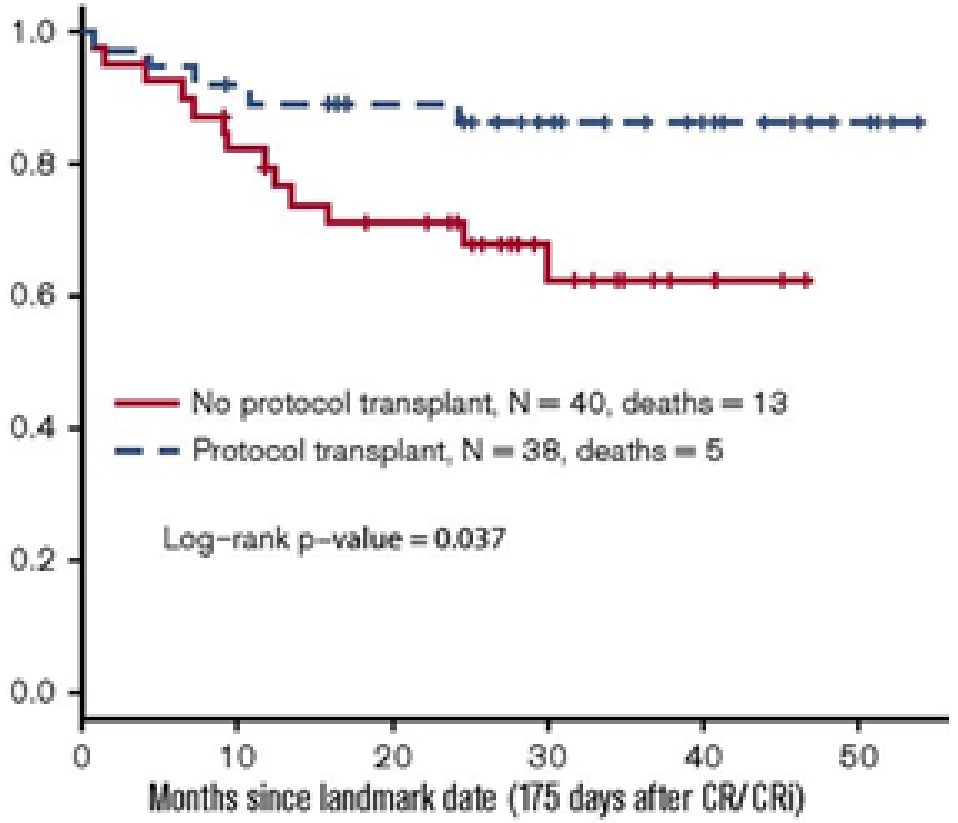
41 (49%)
alloHSCT in first CR

42 (52%)
no alloHSCT in first CR

Adapted from Ravandi F et al.: Blood Adv (2016) 1 (3): 250–259

Hyper-CVAD + dasatinib in Ph+ ALL
Landmark analysis No AlloHSCT vs AlloHSCT





Ravandi F. Blood Advance 2016;1 (3): 250-259

Nilotinib with or without cytarabine for Ph+ ALL

- In the randomized GRAAPH-2014 trial, authors used nilotinib and addressed the omission of cytarabine (Ara-C) in consolidation
- All patients were eligible for allogeneic stem cell transplant (SCT), whereas those in MMR could receive autologous SCT, followed by 2-year imatinib maintenance in both cases
- The primary objective was the major molecular response (MMR) rate measured by BCR::ABL1 quantification after cycle 4 (end of consolidation)

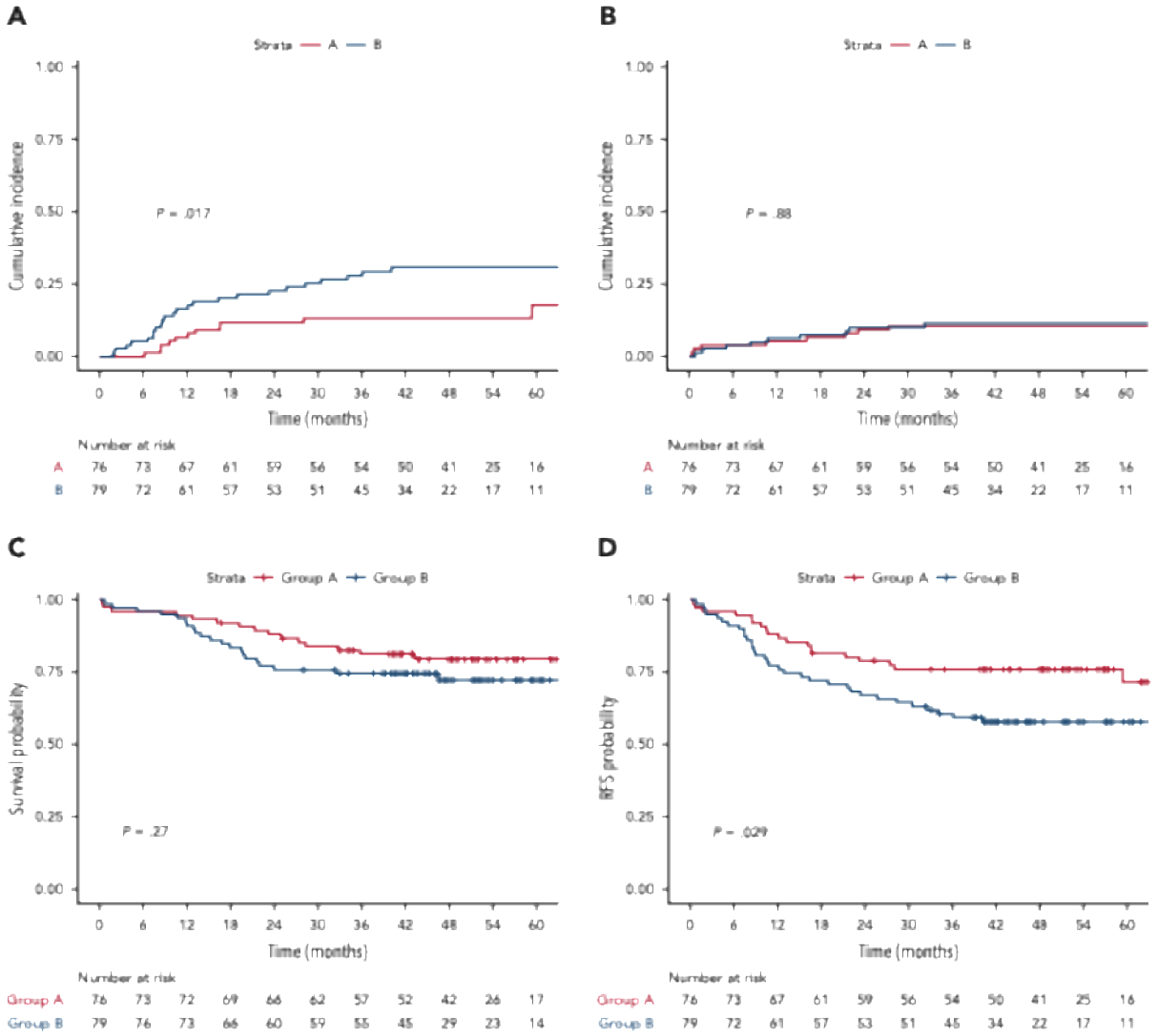
Characteristic	Randomized patients	Arm A	Arm B
Patients, N	155	76	79
Sex ratio, N (M/F)	80:75	38:38	42:37
Age, median (IQR), y	47.1 (38.8-53.8)	48.8 (38.8-54.0)	47.0 (39.1-53.5)
Aged ≥40 y, N (%)	113 (72.9)	55 (72.4)	58 (73.4)
BMI, median (IQR), kg/m^2	24.9 (22.1-28.4)	24.9 (22.0-29.1)	24.7 (22.5-22.8)
ECOG PS 0/1/2/3/unknown	53/73/24/2/3	22/39/11/2/2	31/34/13/0/1
CNS 3 disease, N (%)	12 (7.74)	6 (7.89)	6 (7.59)
WBC, median (IQR), 10^9/L	19.4 (6.4-65.2)	24.3 (7.2-109.0)	18.0 (6.2-49.0)
Karyotype*			
Failure, N (yes/no)	4/151	2/74	2/77
t(9;22), N (yes/no)	142/9	70/4	72/5
ACA, N (yes/no/unknown)	101/43/11	50/21/5	51/22/6
Monosomal karyotype, N (yes/no/unknown)	36/106/11	16/55/5	22/51/6
bcr subtype, m/M/variant	107/46/2	50/25/1	57/21/1

Chalandon I et al.: Blood 143, 23, 2363-2372, 2024

Nilotinib with or without cytarabine for Ph+ ALL

KEY POINTS

- **Alternating reduced-intensity and conventional chemotherapy with nilotinib followed by SCT resulted in 4-year OS of 79.4% in Ph$^+$ ALL.**
- **The omission of high-dose Ara-C during consolidation resulted in a significantly higher rate of relapses without affecting overall survival.**



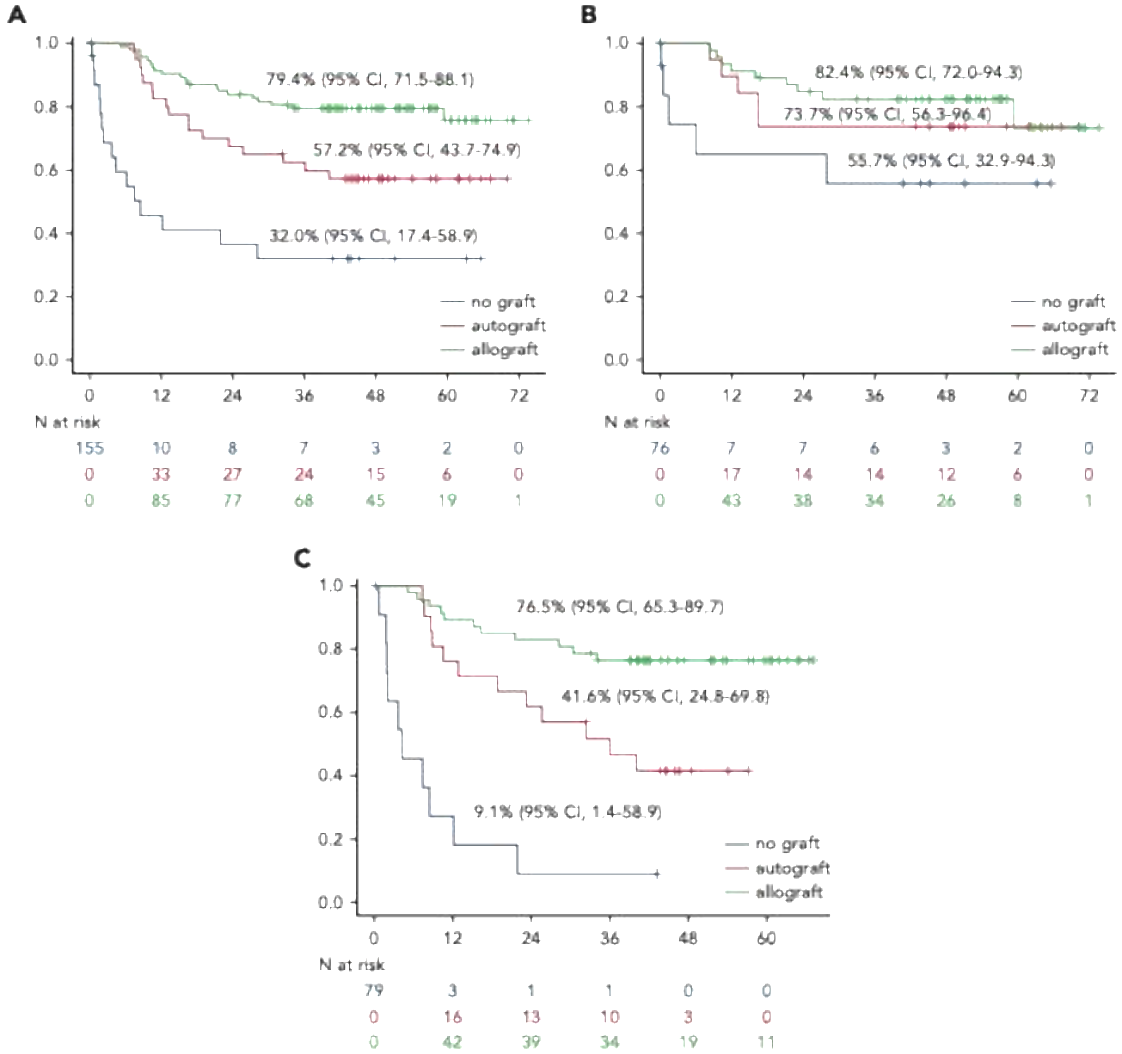
Chalandon I et al.: Blood 143, 23, 2363-2372, 2024

Relapse-free survival outcome by transplantation type and study arm

A. Simon-Makuch plots for evaluating the impact of allo-SCT and auto-SCT on RFS in the whole patient population. t0 was the time of hematologic CR achievement

B. Study Arm A

C. Study Arm B



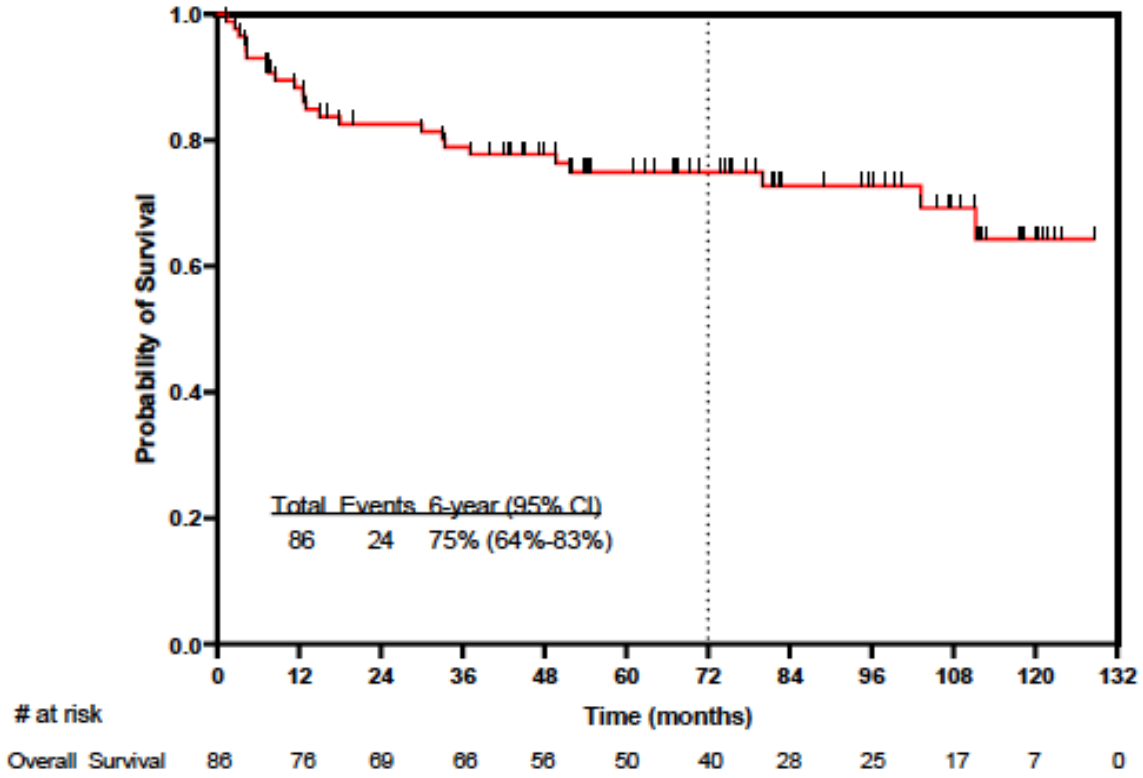
Chalandon I et al.: Blood 143, 23, 2363-2372, 2024

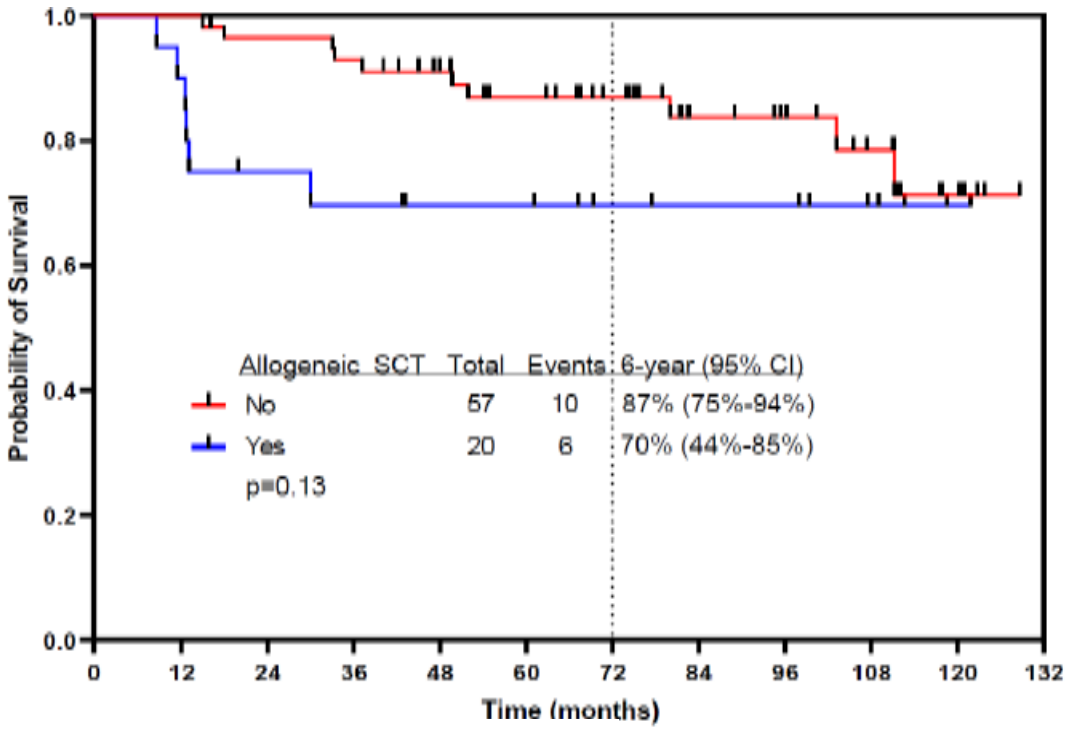
The GMALL Trial 08/2013 for Newly Diagnosed Adult Ph+ ALL with Imatinib, Dose-Reduced Induction Followed By Stem Cell Transplantation

- Between 09/2016 and 07/2022, 174 patients with a median age of 42 (18-55) years were recruited. Age-adapted TBI-based conditioning regimen was proposed in all patients (8 Gy TBI vs 12 Gy TBI).
- Hematologic CR rates after induction I, II and consolidation I were 85%, 96% and 95%. Early death and failure rates after consolidation 1 were 4% and 1% respectively.
- The MolCR rate increased from 9% after induction 1 to 24% after induction 2 and was 42% after consolidation.
- Overall survival (OS) at 3 years was 76%; remission duration at 3 years was 89% with a median follow up of 52 months. 3y-OS was 89%, 73% and 75% for patients aged 18-25, 26-45 and 46-55 years respectively (p >.05)
- The treatment-related mortality after 3 years was 16% (15% for pts <45yrs and 16% for ≥45 yrs).

Pfeifer H. et al .: ASH 2024 Abst 840, Blood Nov 2024

Perhaps not all TKIs are equal…
HyperCVAD+ Ponatinib: a landmark analysis





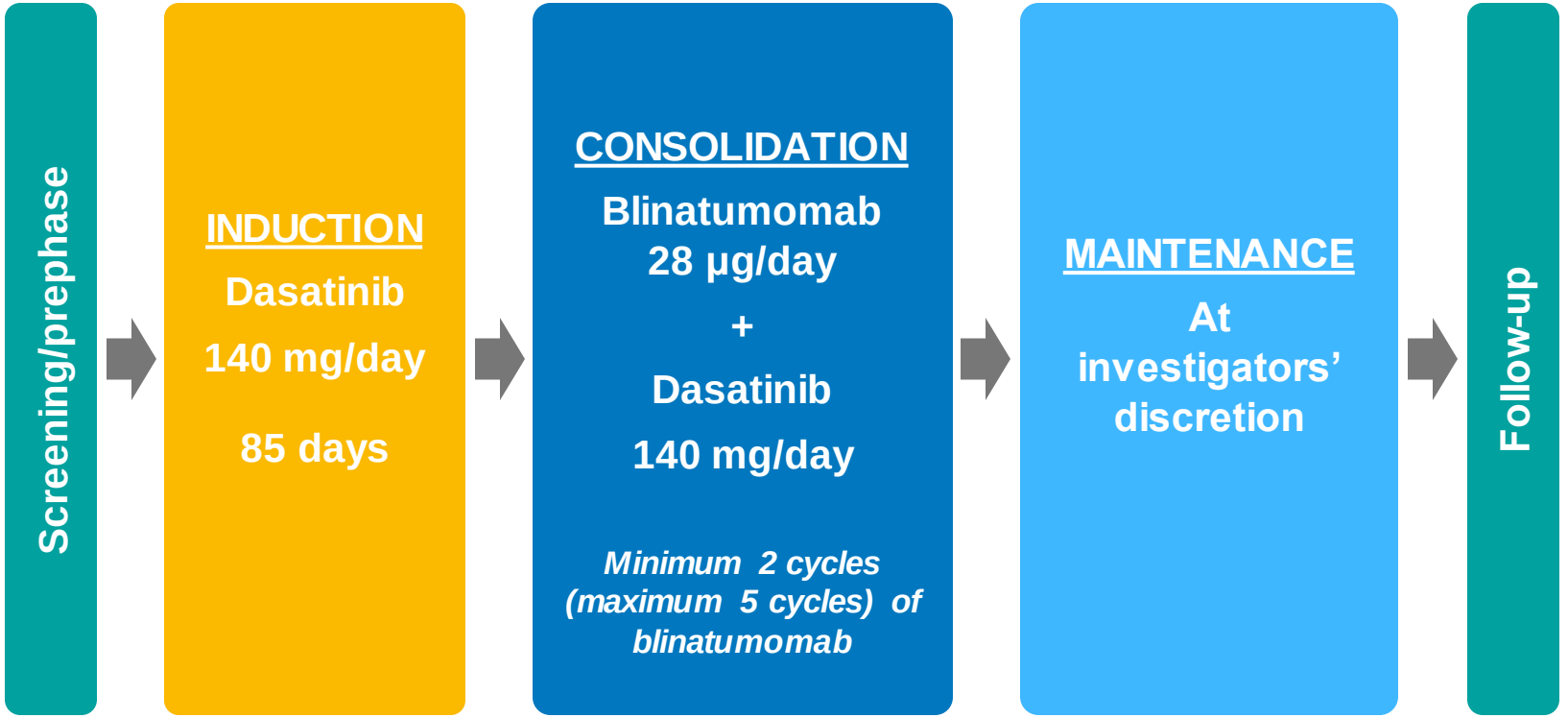
HSCT in CR1 in 20 pts (23%)

AlloHSCT according to physician/pts decision

Kantarjian H et al, Am J Hematol 2023

What about the lucky patients who may have access to a “chemo-free” option?

D-ALBA: baseline patient characteristics



Study endpoints

Primary

- Molecular response after 2 cycles of blinatumomab[e]

Key secondary

- Decreased level of MRD associated with blinatumomab
- DFS
- OS
- Cumulative incidence of relapse[f]
- Safety
- Molecular response, OS, and DFS rates according to molecular characteristics at baseline

Foà R, et al. N Engl J Med 2020;383:1613–23

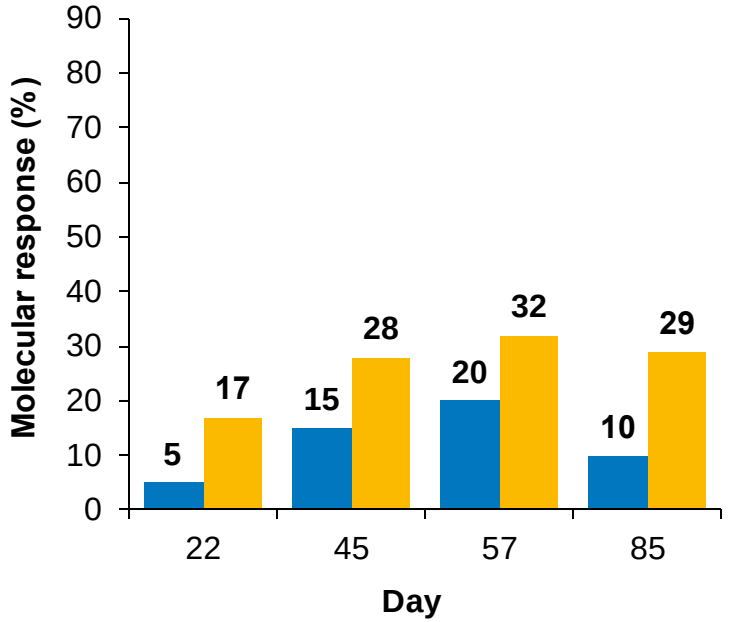
D-ALBA: open-label, single-arm, multicenter, Phase 2 study in first-line Ph+ B-ALL

Characteristic	Enrolled patients (N=63)
Age (years), median (range)[1,2]	54 (24–82)
Sex, n (%)	Male: 29 (46) Female: 34 (54)
WBC count (per mm^3), median (range)	13,000 (600–88,000)
Fusion protein, n (%)	p190: 41 (65) p210: 17 (27) p190 and p210: 5 (8)
***IKZF1* deletion, n/N, %**	25/46 (54)

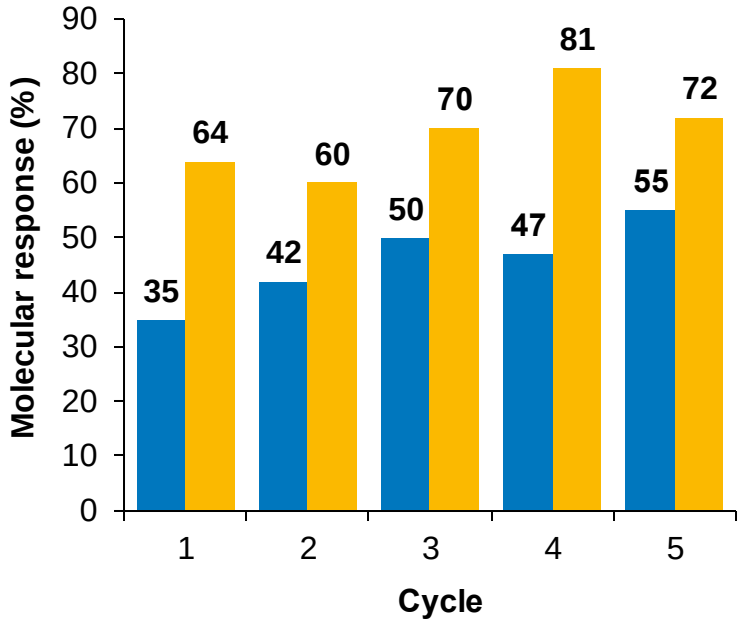
Foà R, et al. N Engl J Med 2020;383:1613–23

After 2 cycles of blinatumomab, 60% of patients had an overall molecular response

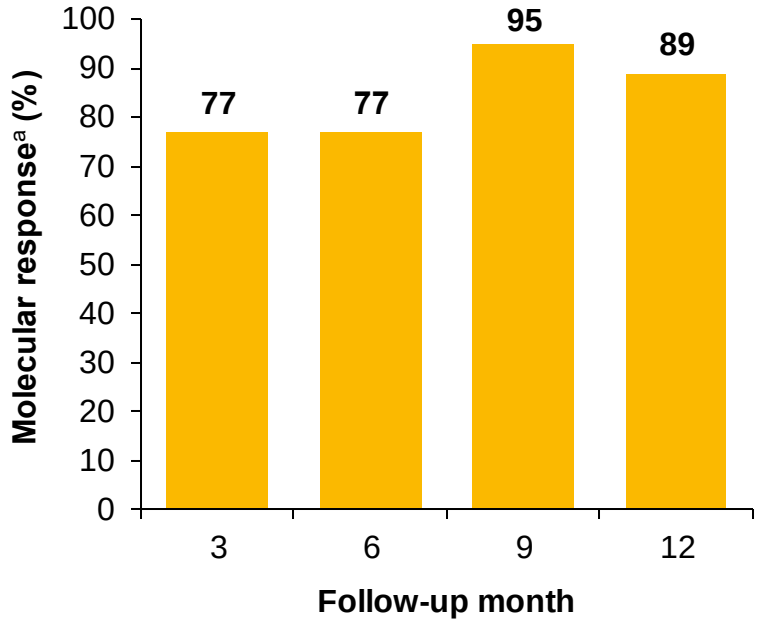
Induction period[1]



Consolidation period by blinatumomab cycle[1]



Follow-up period[2]



Complete molecular response[b] | Overall molecular response[c]

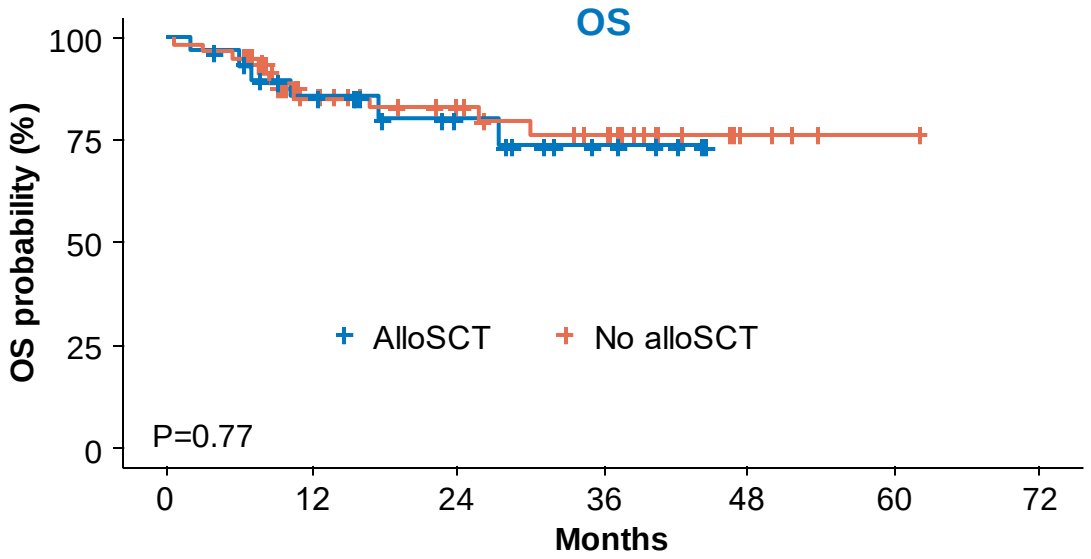
Overall molecular response was sustained throughout the follow-up period[1,2]

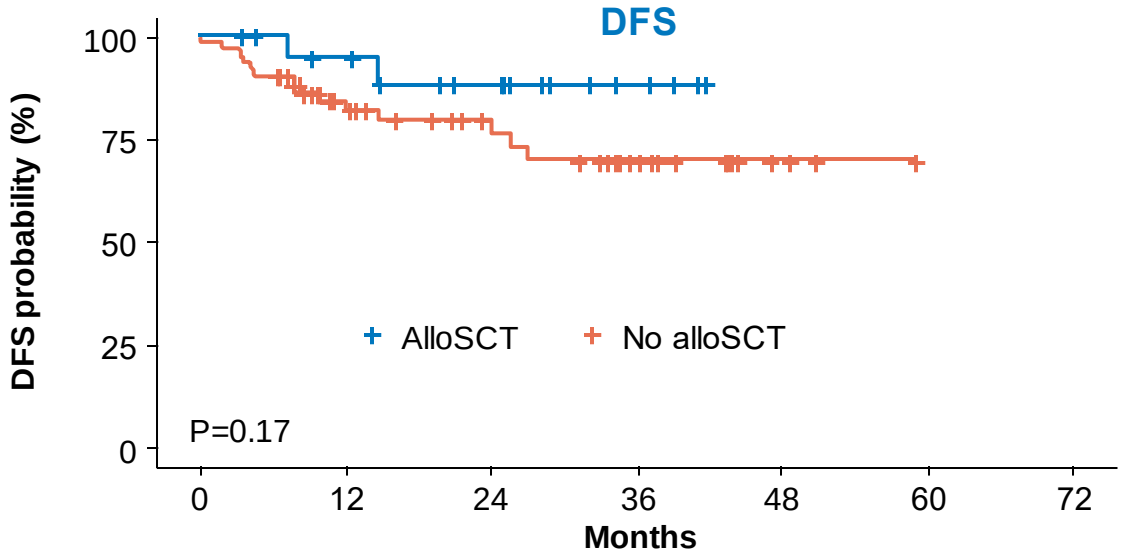
1. Foà R, et al. N Engl J Med 2020;383:1613–23; 2. Chiaretti S, et al. Slides presented at: European Hematology Association (EHA); June 9–17, 2021. Virtual.

[a]Conducted in a subset of the whole population;[2] [b]A complete molecular response was defined as a ratio of *BCR-ABL1* to *ABL1* of 0.1; [c]Overall molecular response was defined as a complete molecular response and a positive nonquantifiable response, ie, MRD+ samples outside the quantitative range.

OS and DFS of allografted and non-allografted patients

(median [range] follow-up: 40 [0.9–62.5] months)





- After blinatumomab treatment, 29 patients continued treatment with a TKI (72% with dasatinib)
- **46% of patients underwent alloSCT**; out of these, 6 were in second CHR

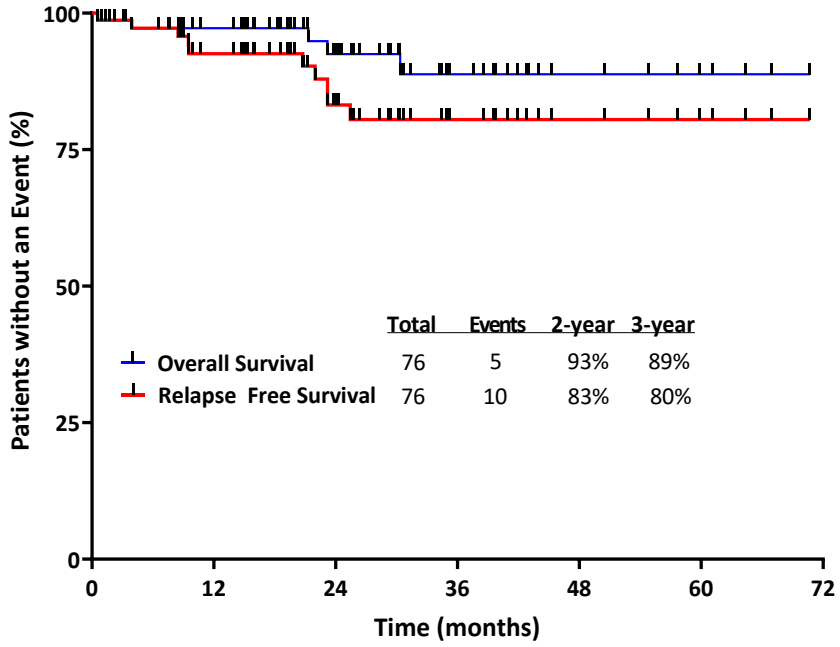
- Relapse was seen in 9 patients
  - 4 were hematologic relapses, 4 CNS, and 1 nodal relapse
  - Median time to relapse was 4.4 months (1.9–25.8)
- 6 deaths were reported in first CHR, of which 3 occurred after alloSCT

Foà R, et al. J Clin Oncol 2024;42:881–5; Chiaretti S, et al. Poster presented at: European Hematology Association (EHA); June 9–12, 2022; Vienna, Austria. Abstract P353.

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

- 76 pts with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs

Parameter	%
CR-CRi	98
% CMR	80
% NGS-MRD negative	99
% 3-yr OS	89



- Median F/U 24 months.
- 7 relapses (all p190): 5/7 high WBC , 4 CNS, 1 CRLF2+ (Ph-), 2 systemic
- 3-yr cumulative relapse 15%, 3-yr EFS 80%, OS 89%
- **Only 2 pts had SCT**(3%)

Kantarjian H et al, JCO 2024

Predictors of Poor Outcomes in Ph+ B-cell ALL

- MRD response

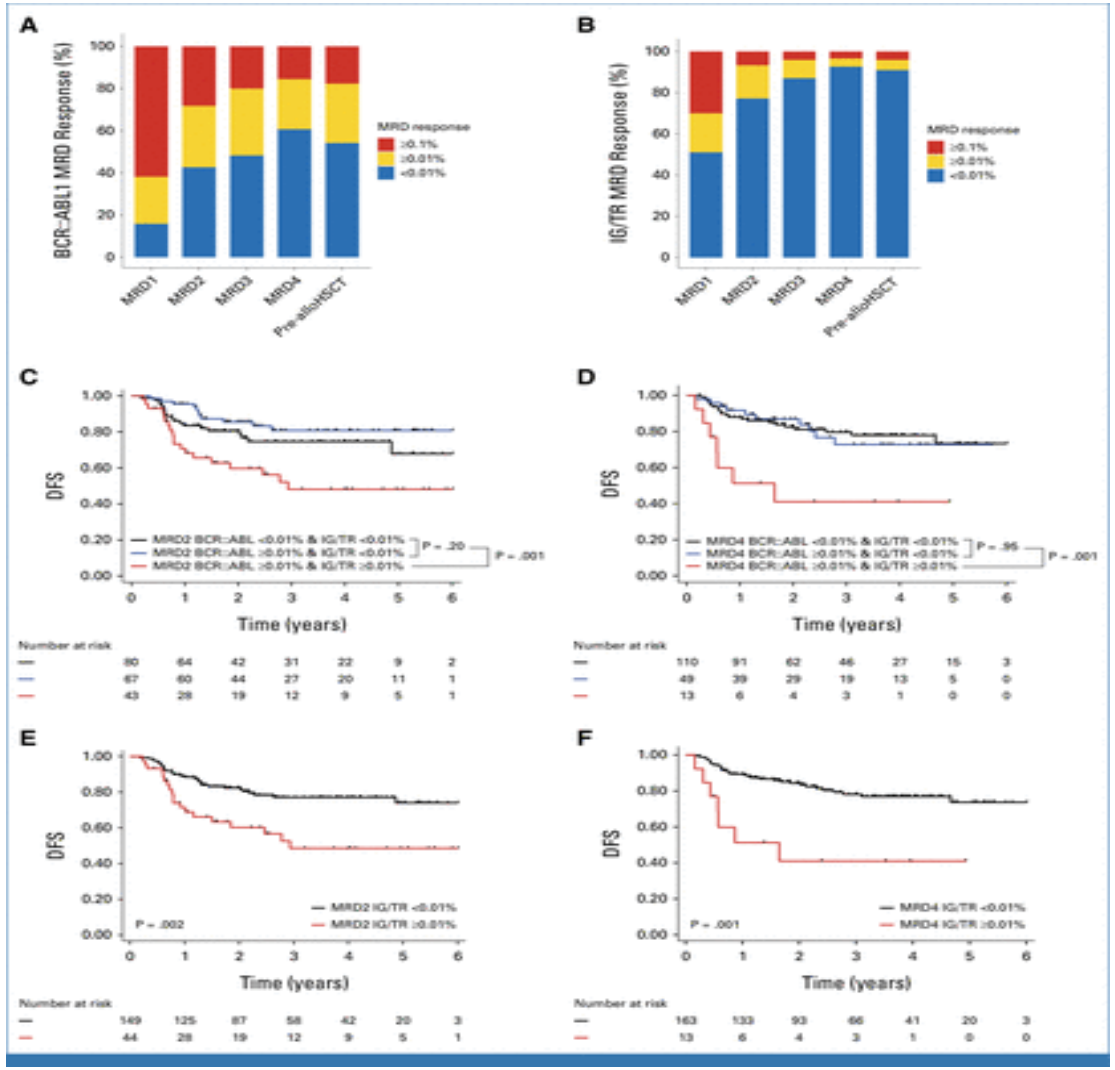
  the sooner and the deeper, (probably) the better

- Disease Biology

  WBC at diagnosis
  IKZF1^{del}, IKZF1^{plus}
  complex karyotypes, TP53 mutations,
  CRLF2 re-arrangement with BCR::ABL1 fusions

IG/TR but not BCR::ABL1 molecular response is associated with a better outcome

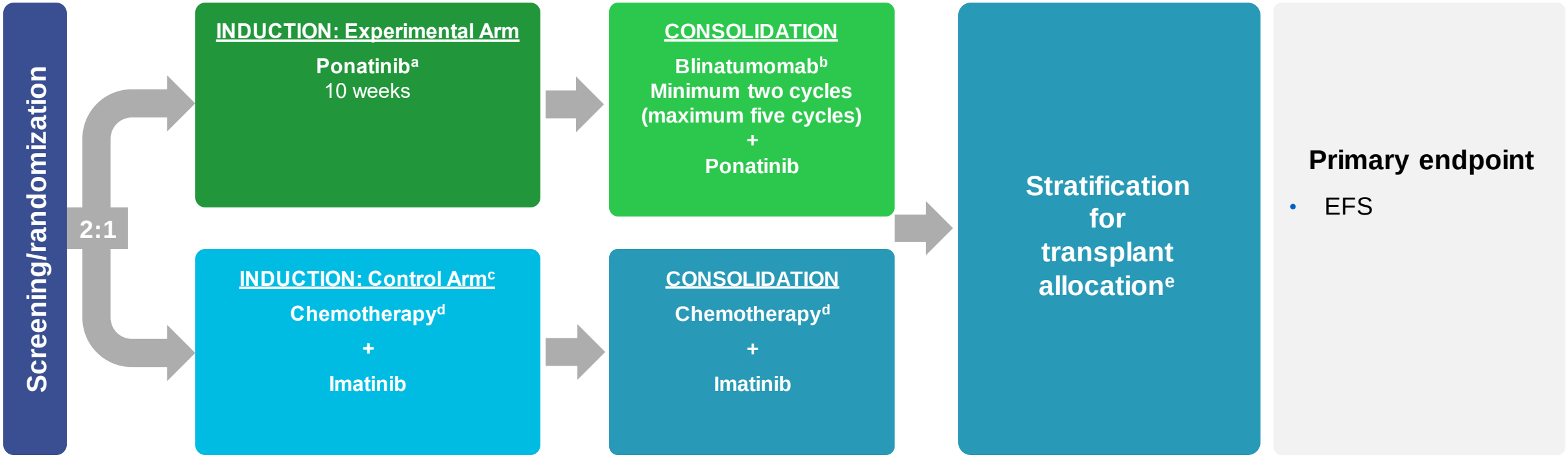
- The driver lesion *BCR::ABL1* is regarded as the gold-standard marker in Ph+ ALL, at least in adults and it is widely used for treatment adaptation, and achievement of major or complete molecular response as defined in CML.
- It has been used as the primary end point of clinical trials in Ph+ ALL.
- Multilineage involvement raises the possibility that *BCR::ABL1* MRD could be related to non-ALL cells. This has been indeed observed in pediatric Ph+ ALL harboring discrepancies between *BCR::ABL1* and *IG/TR* MRD results



Kim R et al.: JCO 2024 https://doi.org/10.1200/JCO.24.00108

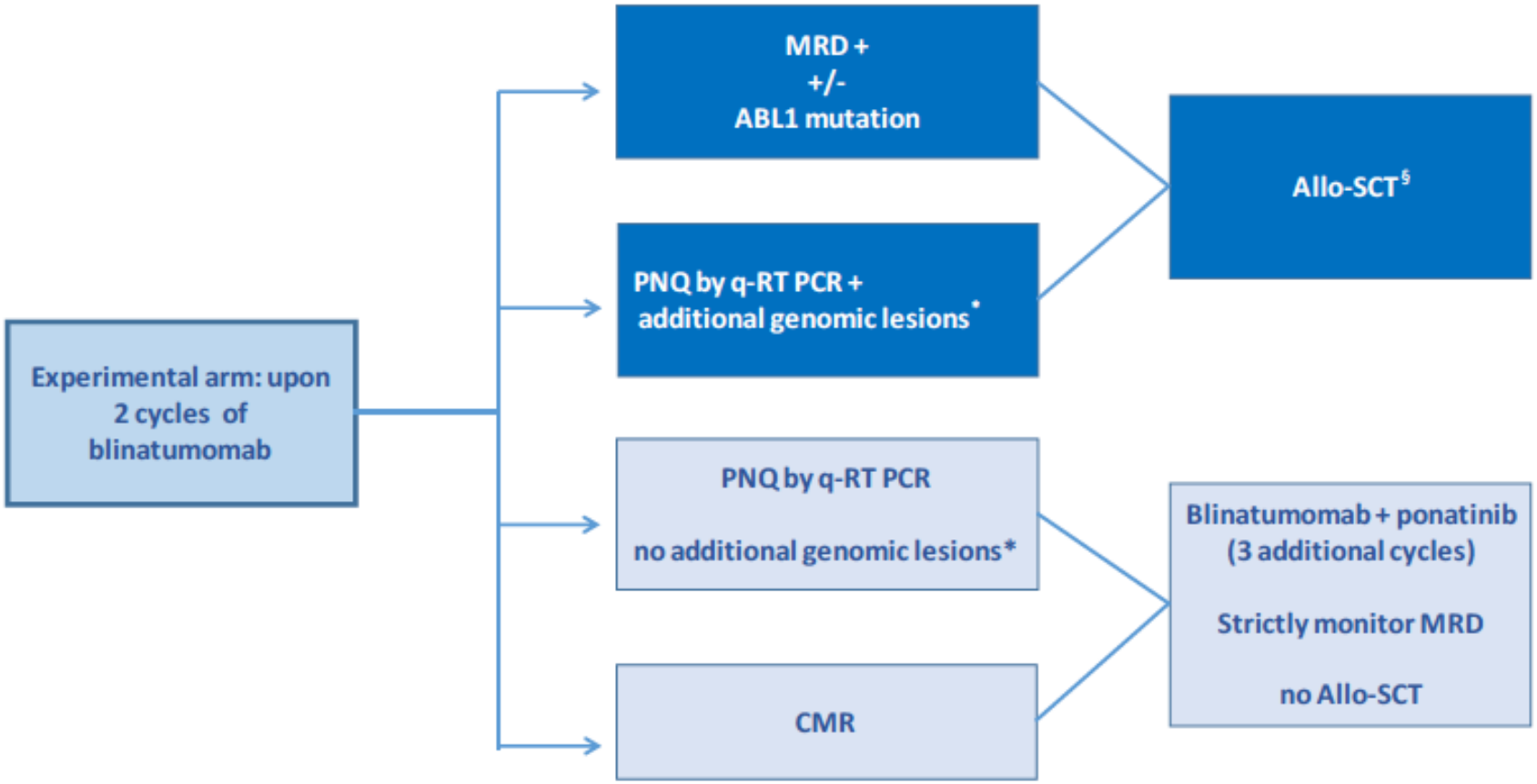
The role for alloHSCT in the consolidation of Ph+ ALL: ongoing clinical trials

The GIMEMA 2820 clinical trial



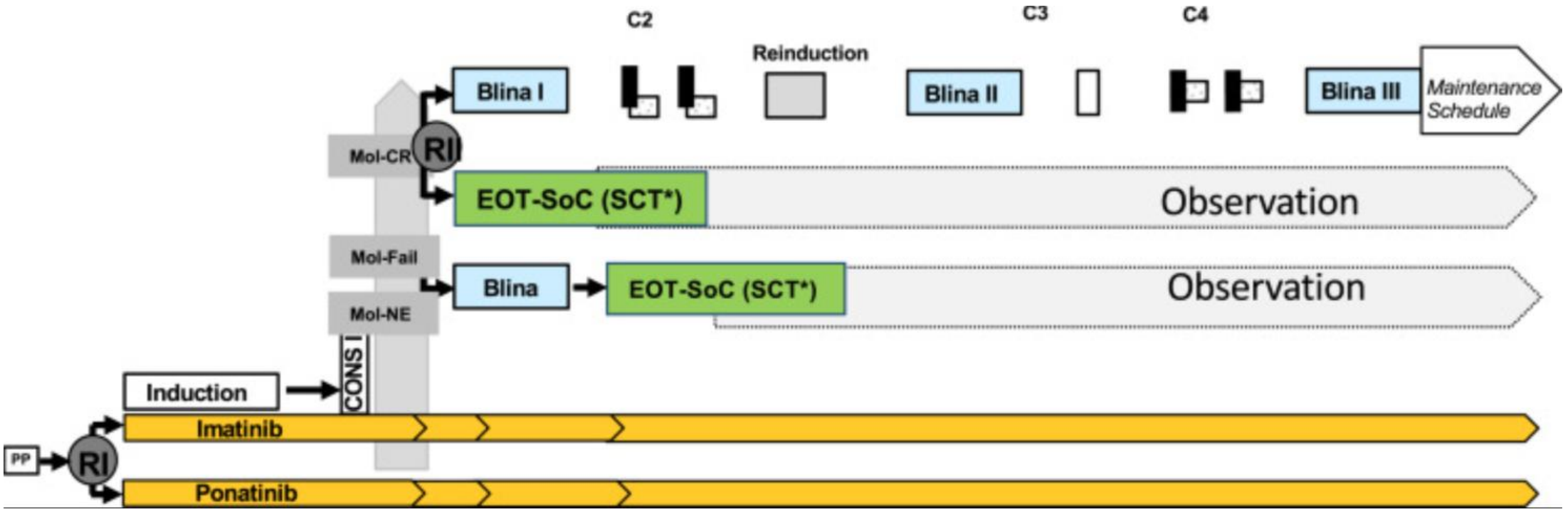
[a]Patients aged 18–65 will receive ponatinib at 45 mg/day for the first 22 days followed by dose reduction to 30 mg/day depending on morphologic and molecular responses; patients >65 years old will start ponatinib at 30 mg/day to avoid TEAEs. [b]Patients not achieving a CHR after 2 cycles of blinatumomab will go off-study. [c]Patients in the control arm who do not achieve a CHR and/or MRD negativity after the 6th consolidation cycle (week 20) and those who develop an *ABL1* mutation at any time during treatment will be switched to the experimental arm to receive blinatumomab. [d]Elderly patients (>65 years old) will receive mild, age-adjusted chemotherapy. [e]After 2 cycles of blinatumomab in the experimental arm and after consolidation in the control arm, patients aged 18–65 years will be stratified for transplant allocation.

The GIMEMA 2820 clinical trial



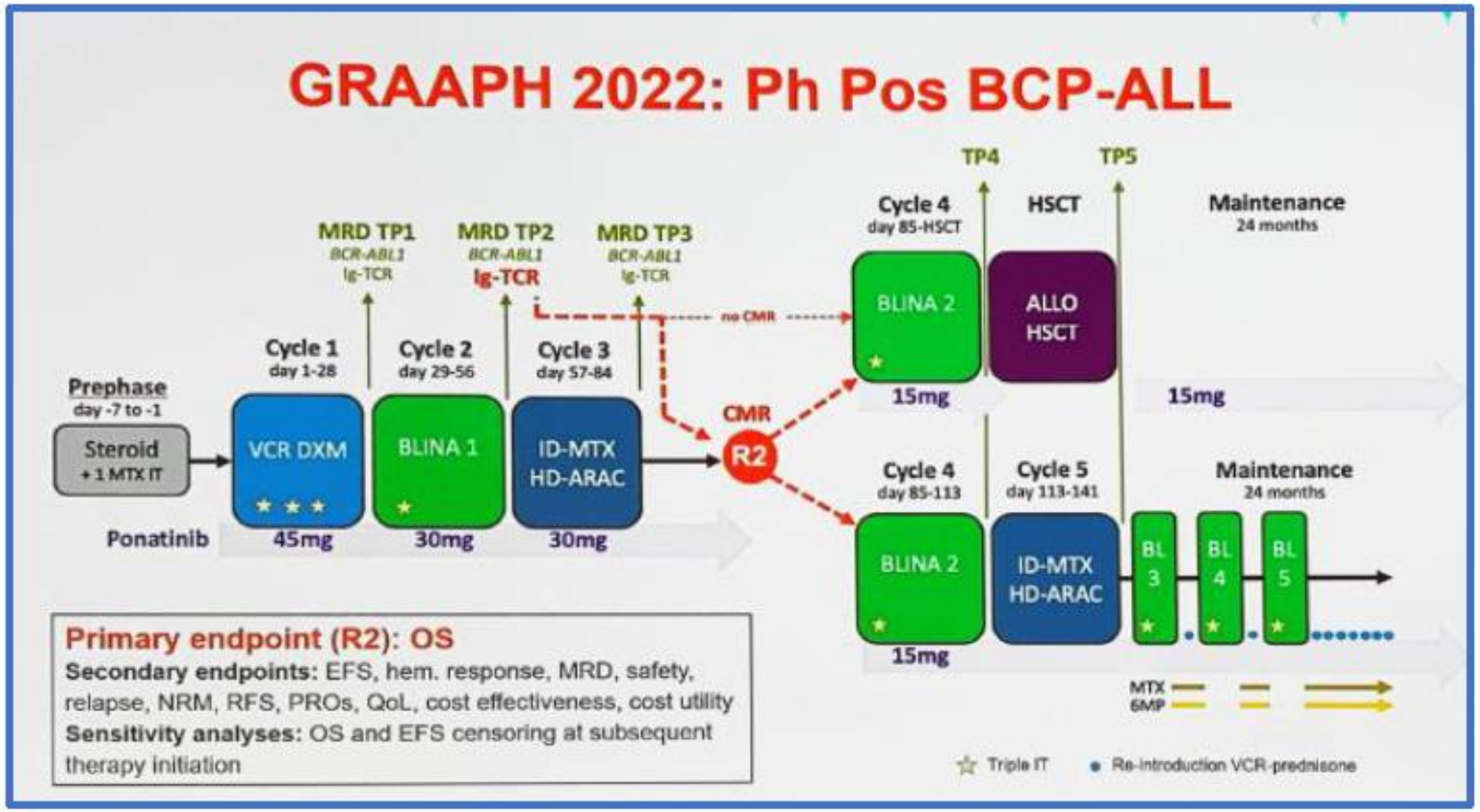
GIMEMA Gruppo Italiano Malattie EMatologiche dell'Adulto

The GMALL EVOLVE trial



Lang F et al, Oncol Res Treat 2024

The GRAAPH 2022 trial for Ph+ALL



Conclusions

- The ability of alloHSCT to cure patients with Ph+ ALL is well established, and remains a crucial tool in the therapeutic strategy

- The combination of immunotherapy and TKIs, may significantly reduce the need for alloHSCT

- In the coming years alloHSCT in CR1 is likely to be applied based on a risk-adapted approach
  - Patients achieving a CMR at three months appear to be the most suitable candidates for a transplant-free treatment

  - AlloHSCT in CR1 should be considered in younger and fit patients with a high leukemic burden at diagnosis, high-risk genetic features (e.g. complex karyotype, IKZF1+), or failing to achieve early molecular responses

- Frontline use of immunotherapy and ponatinib might limit salvage therapeutic options for the few patients who experience relapse