Disclosures

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

Aims of future trials in adult ALL

- **Reducing primary refractory disease and early relapse**

- **Improving the treatment of older patients (≥ 55)**

Aims of future trials in adult ALL

- **Reducing primary refractory disease and early relapse**

- Improving the treatment of older patients (≥ 55)

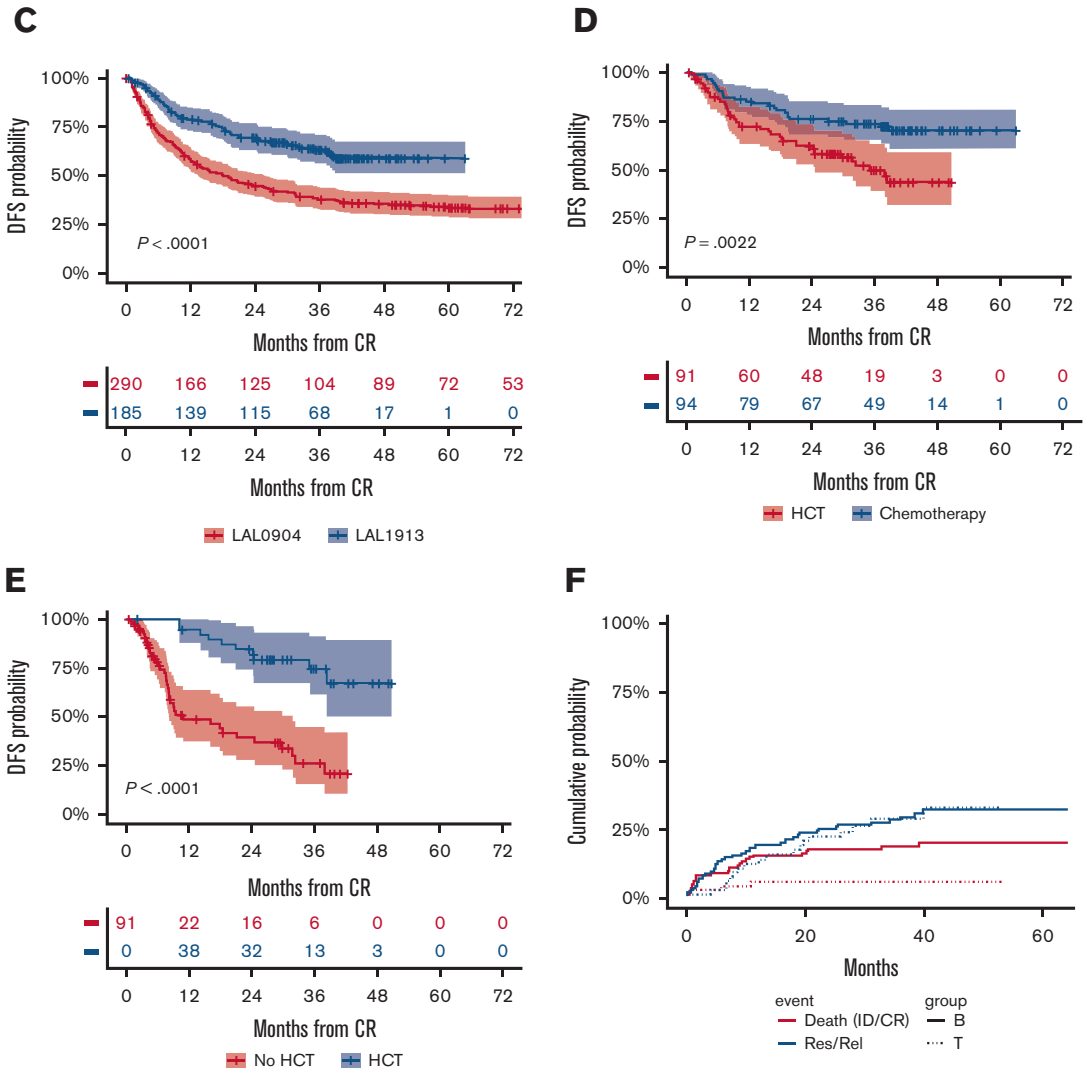
Pegaspargase-modified risk-oriented program for adult ALL: results of the GIMEMA LAL1913 trial: DFS

C) DFS, the primary study objective compared with prior GIMEMA study LAL 0904: median was not reached; 2-year rate, 70% (95% CI, 63-77) vs 45% (95% CI, 39-51); and 3-year rate, 63% (95% CI, 56-71) vs 38% (95% CI, 38-44), P < .0001

D) 3-year DFS per ITT risk-oriented therapy: chemotherapy, 74% (95% CI. 65-83), allogeneic HCT, 50% (95% CI, 39-63), P = .0022

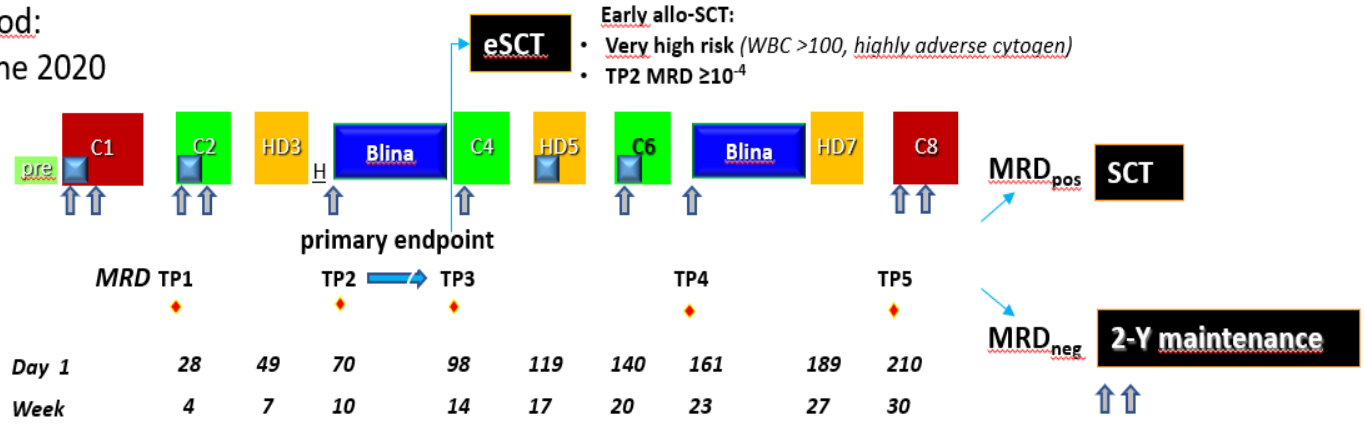
E) 3-year DFS in the ITT allogeneic HCT group per time-dependent HCT realization: HCT, 75% (95% CI, 55-89) vs no HCT, 26% (95% CI, 15-45), P < .0001

F) Cumulative incidence of TRM during induction (ID) and CR, and of resistance/relapse (Res/Rel) based on B- or T-ALL/LL diagnosis



GIMEMA LAL 2317: a phase II front-line trial evaluating sequential chemotherapy and blinatumomab for Adult Ph-negative, BP-ALL patients

Enrollment period:
August 2018-June 2020



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

Endpoints

Primary

- **MRD response after cycle 1 of blinatumomab (TP3)**

Key secondary

- CR
- DFS
- OS
- Safety

Eligibility

Key Inclusion criteria

- **Age 18-65 years**
- **A diagnosis of untreated Ph- B-ALL**
- ECOG PS ≤ 3

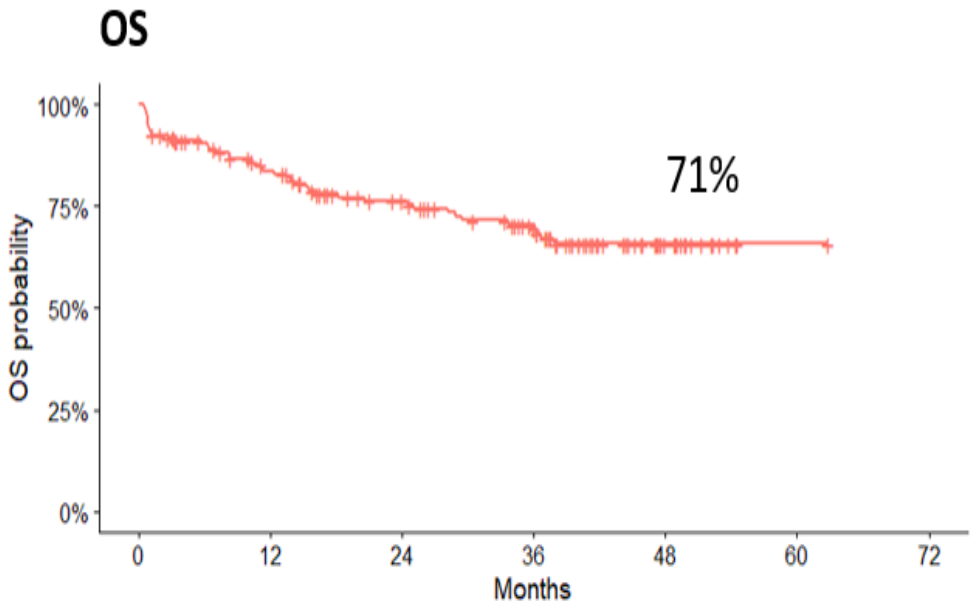
Key exclusion criteria

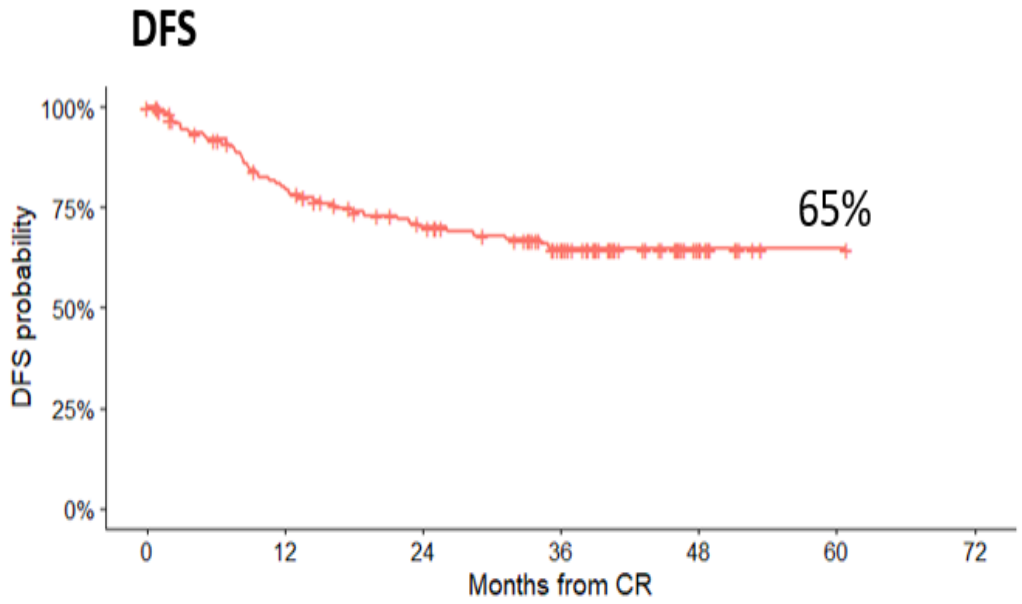
- Diagnosis of Burkitt's leukemia or lymphoma, Ph+ ALL-, T-ALL
- Down's syndrome
- Pre-existing, uncontrolled pathology
- Active CNS leukemia

DFS, Disease-free Survival; mFu, Median follow-up; MRD, minimal residual disease; OS, Overall Survival; TP3, time-point 3; y, yeras

Chiaretti S, et al. Oral and Poster Abstracts 826 (ASH) Meeting December 2023; San Diego, USA.

GIMEMA LAL 2317: a phase II front-line trial evaluating sequential chemotherapy and blinatumomab for Adult Ph-negative, BP-ALL patients



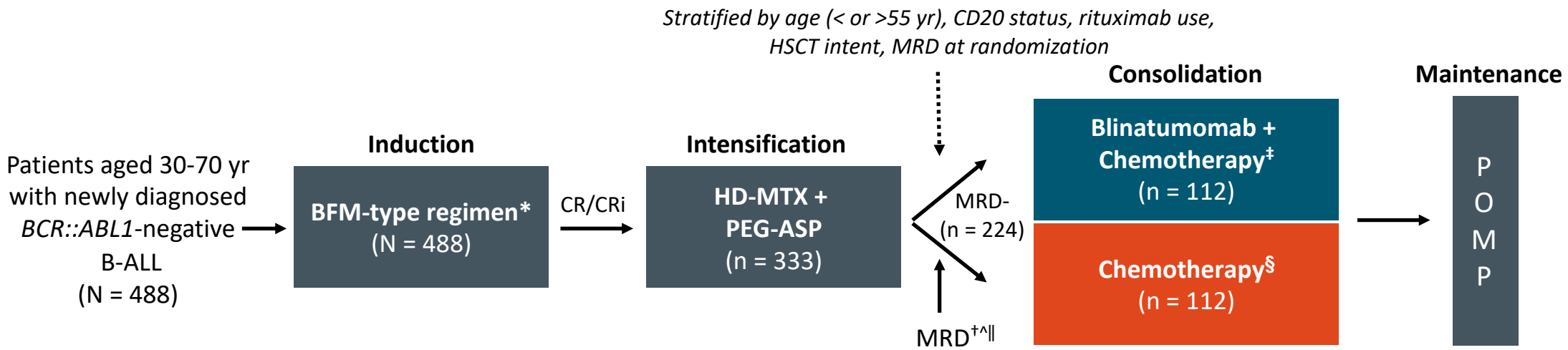


DFS, Disease-free Survival; mFu, Median follow-up; MRD, minimal residual disease; OS, Overall Survival; TP3, time-point 3; y, yeras

Chiaretti S, et al. Oral and Poster Abstracts 826 (ASH) Meeting December 2023; San Diego, USA.

Can we improve these results?

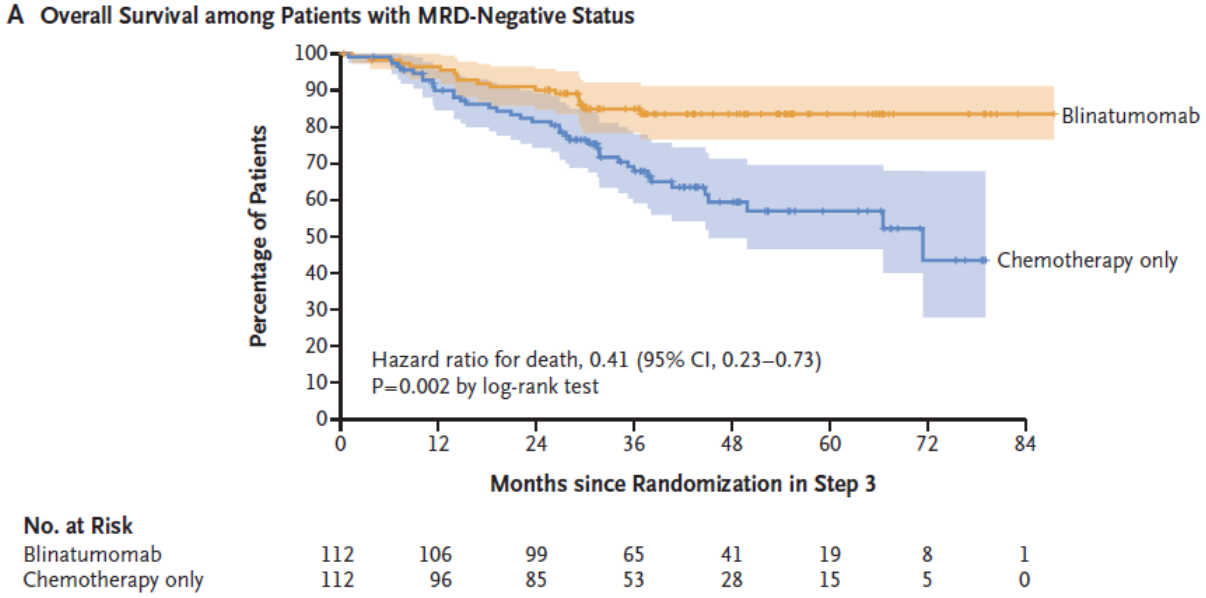
Chemotherapy Induction Followed by Blinatumomab Plus Chemotherapy or Chemotherapy Alone in Adults With Newly Diagnosed Ph– B-ALL: ECOG-ACRIN E1910 Study

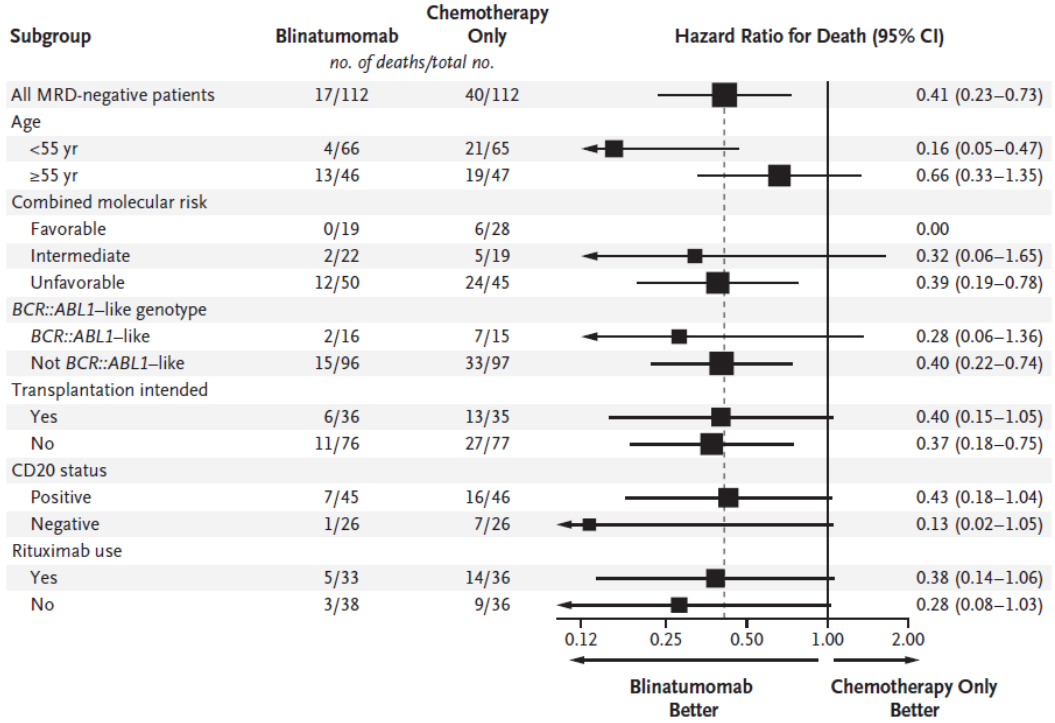


- **Primary endpoint:** OS in MRD^{neg} patients
- **Key secondary endpoints:** MRD status, RFS

- Mark R. Litzow et al.: N Engl J Med 2024;391:320-33

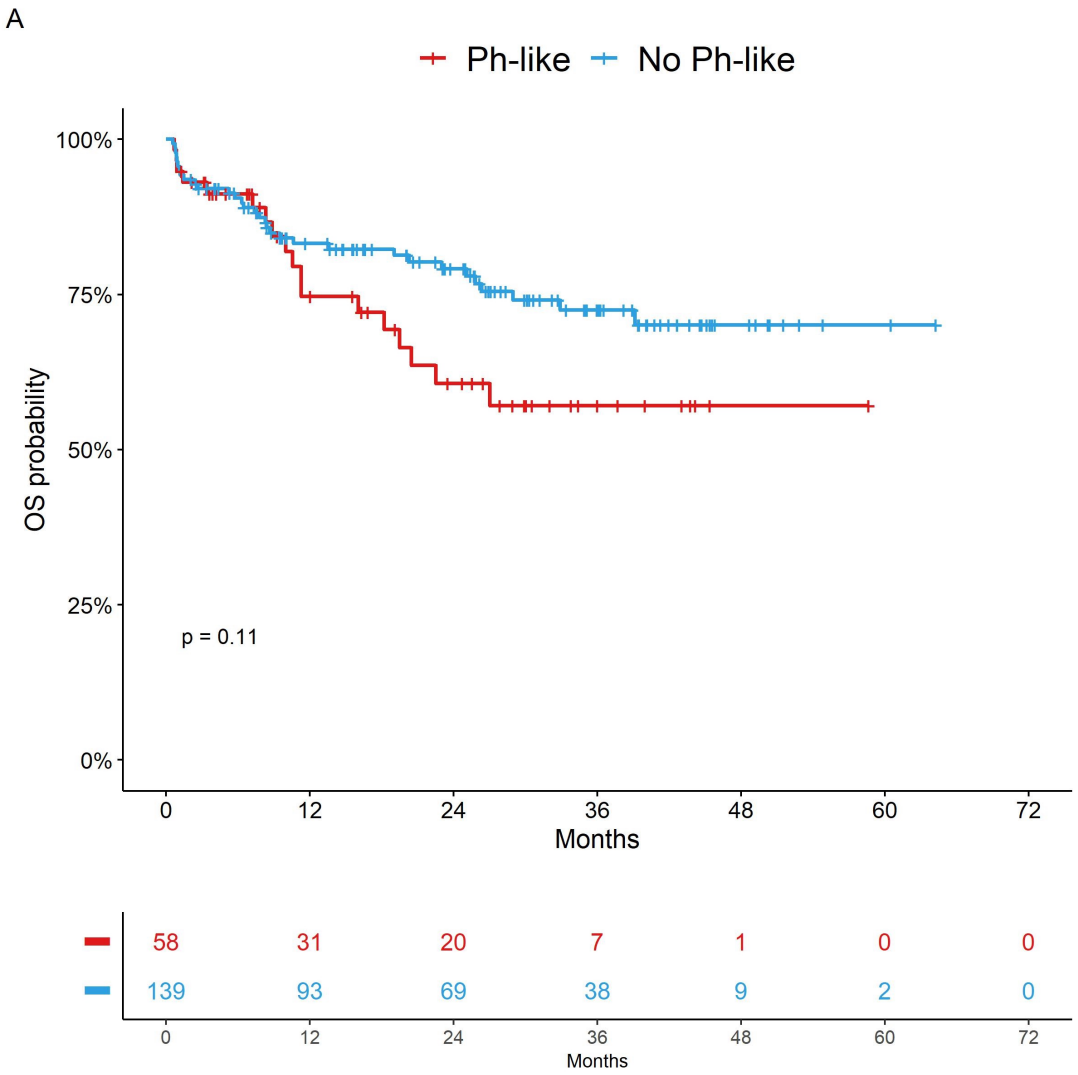
Blinatumomab for MRD-Negative Adult ALL Patients with Newly Diagnosed Ph– B-ALL: The ECOG-ACRIN E1910 Study

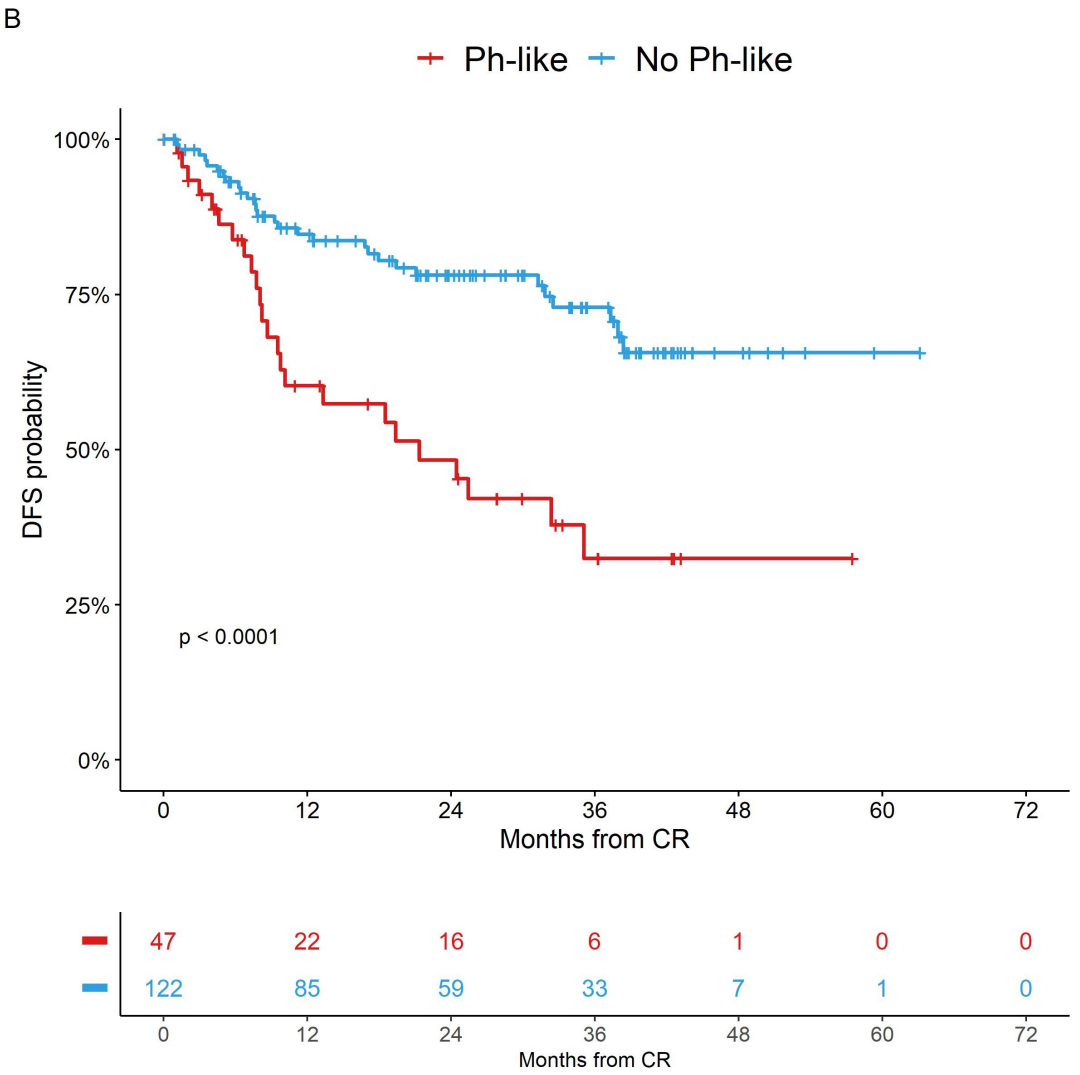




Mark R. Litzow et al.: N Engl J Med 2024;391:320-33

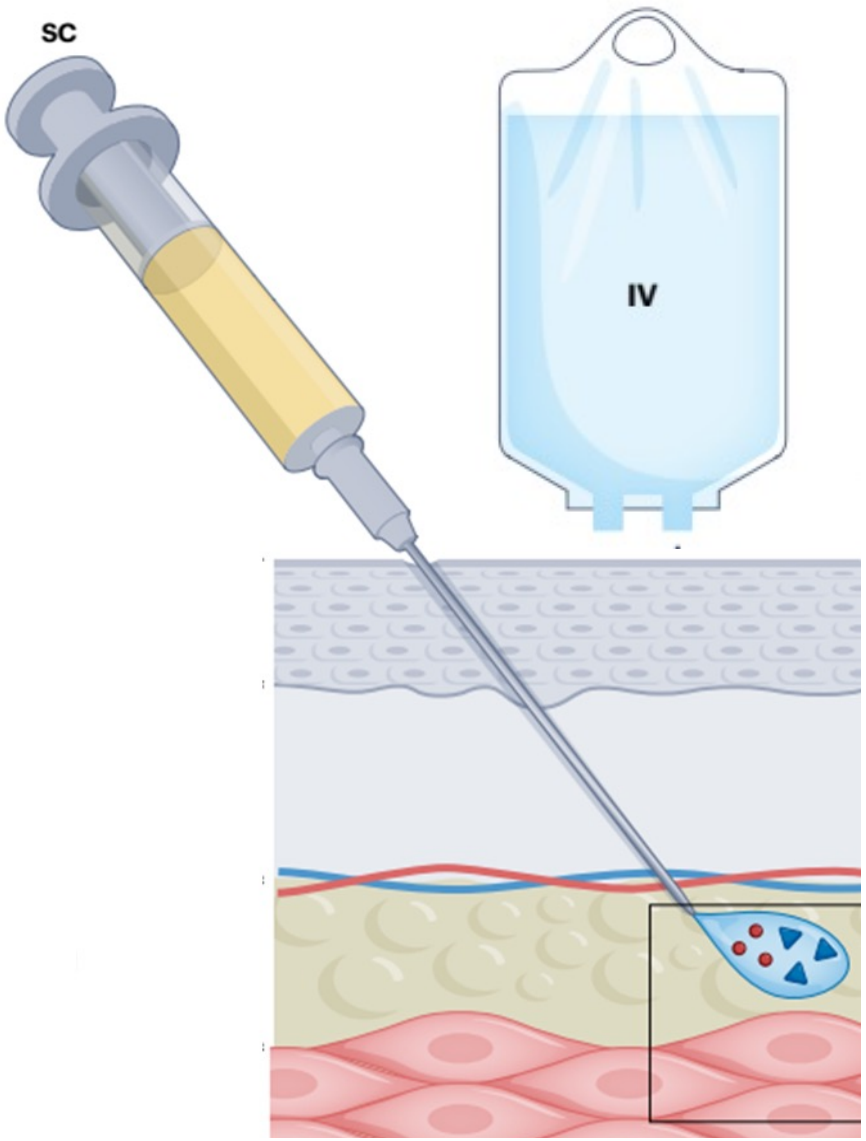
Overall and disease-free survival by Ph-like status





What about the Next Future?

Subcutaneous (SC) Administration of Blinatumomab



Blinatumomab as a continuous IV infusion is a standard treatment regimen utilized in patients with R/R B-ALL

SC delivery of blinatumomab was developed to evaluate higher doses with an aim to further improve efficacy and simplify administration to enhance convenience for patients

- **Can simplify administration, improve convenience, reduce treatment burden, and decrease cost for patients**
- **Eliminate the need for a central line or continuous venous access and an infusion device (pump)**
- **Abrogate the risk of device-related complications such as overdose caused by incorrect pump settings and dose interruptions from intravenous line occlusion**
- **Deliver the target dose earlier (cycle 1, day 1) and over all a higher dose of blinatumomab to patients**
- **Improve overall health health-related quality of life of the patients**

Martinez Sanchez, P et al. Presented at: 64th Annual Meeting of the American Society of Hematology: December 10-13, 2022; New Orleans, LA. Poster 2727. B-ALL, B-cell precursor acute lymphoblastic leukemia; BiTE, bispecific T-cell engager; CD, cluster of differentiation; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; SC, subcutaneous.1. Jabbour E, et al. Am J Hematol. 2024;99:586–595

Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia (ID: NCT04521231)

Multicenter, single-arm, open-label, phase 1b, dose-escalation, and dose-expansion study (ClinicalTrials.gov ID: NCT04521231)

Key Eligibility Criteria

- Age ≥ 18 years
- Diagnosis of B-ALL
- Relapsed/refractory disease, including
  - Refractory to primary induction therapy or at least one salvage therapy
  - Untreated first or greater relapse or refractory relapse
  - Relapse after allogeneic hematopoietic stem cell transplant
- ECOG PS score ≤ 2
- ≥ 5% blasts in the bone marrow
- Ph+ B-ALL intolerant or refractory to prior tyrosine kinase inhibitors
- Prior CD19-directed therapy (eg, blinatumomab or CAR T-cell therapy) received more than 4 weeks before enrollment was allowed

Dose-Escalation Phase

- **Primary Endpoints:** Safety and tolerability

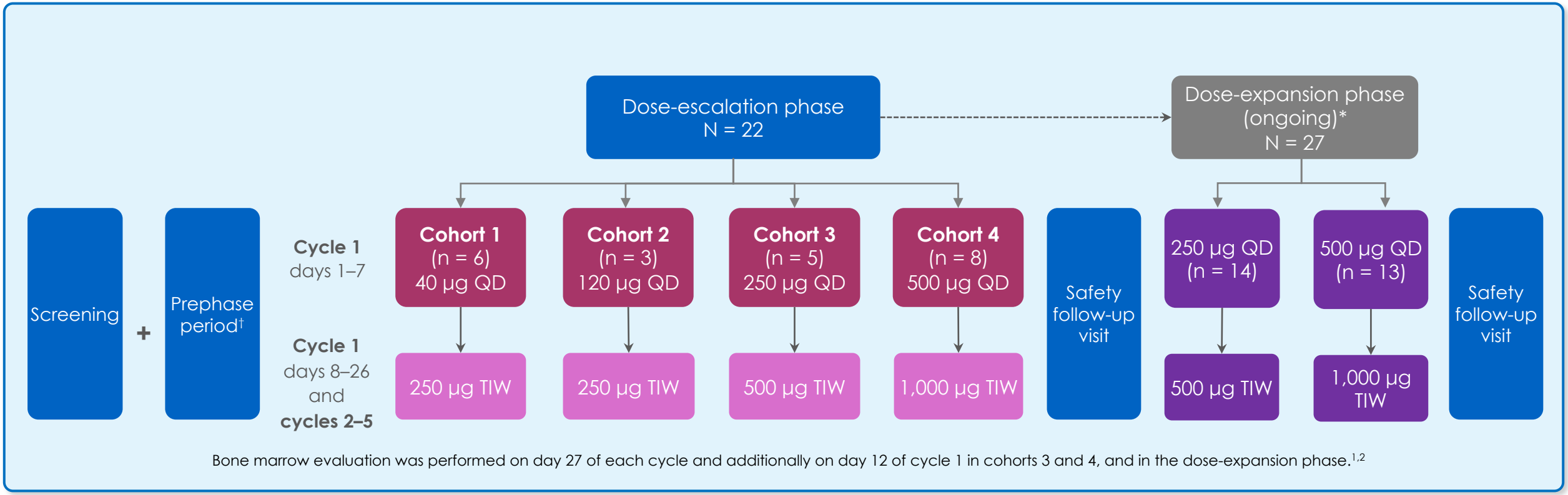
Dose-Expansion Phase

- **Primary Endpoints:** CR/CRh within two cycles

*The complete list of eligibility criteria can be found at https://clinicaltrials.gov/ct2/show/NCT04521231. Accessed February 25, 2024.
B-ALL, B-cell precursor acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, pharmacodynamics; Ph+, Philadelphia chromosome positive; PK, pharmacokinetics.
1. Martínez-Sánchez P, et al. Poster presented at: 64th ASH Meeting; December 10-13, 2022; New Orleans, LA. 2. Jabbour E, et al. *Am J Hematol*. 2024;99:586–595.

Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia (ID: NCT04521231)

Study Design



Bone marrow evaluation was performed on day 27 of each cycle and additionally on day 12 of cycle 1 in cohorts 3 and 4, and in the dose-expansion phase.[1,2]

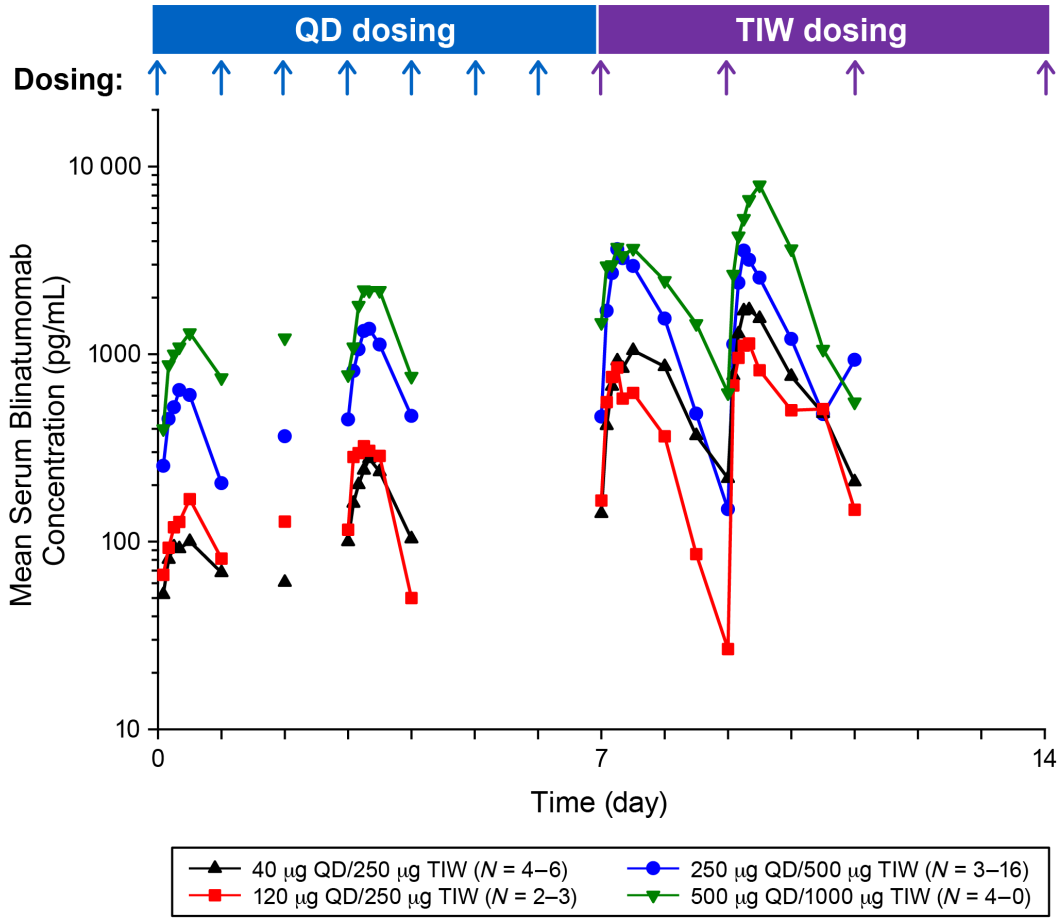
*Patients in the dose-expansion phase were enrolled between October 24, 2022, and July 31, 2023. The data cutoff date was September 15, 2023.[2] †In order to reduce tumor burden and the incidence of tumor lysis syndrome, low dose chemotherapy and/or dexamethasone was recommended prior to the start of SC blinatumomab in cycle 1. The recommended doses and schedule were as follows: dexamethasone IV or orally 10 mg/m^2/day divided every 8 hours to a maximum of 24 mg/day for up to 4 days and/or cyclophosphamide IV 200–300 mg/m^2/dose daily for up to 4 days, with a total maximum dose of 1,200 mg/m^2 and/or vincristine 1–2 mg IV given as a single dose.[1]

B-ALL, B-cell precursor acute lymphoblastic leukemia; IV, intravenously; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TIW, three times weekly.

1. Jabbour E, et al. *Am J Hematol*. 2024;99:586–595. (supplemental material). 2. Jabbour E, et al. *Am J Hematol*. 2024;99:586–595.

Pharmacokinetics of blinatumomab following subcutaneous administration

- Median time to maximum concentration ranged from approximately 6–12h.
- Dose-related increase in exposure was observed over the dose range.
- Mean apparent elimination half-life was approximately 8–12 h after repeat dosing.
- An apparent increase in half-life for SC blinatumomab (8–12 h vs. 2 h for cIV) allowing for convenient three times in a week TIW dosing after the first 7 days

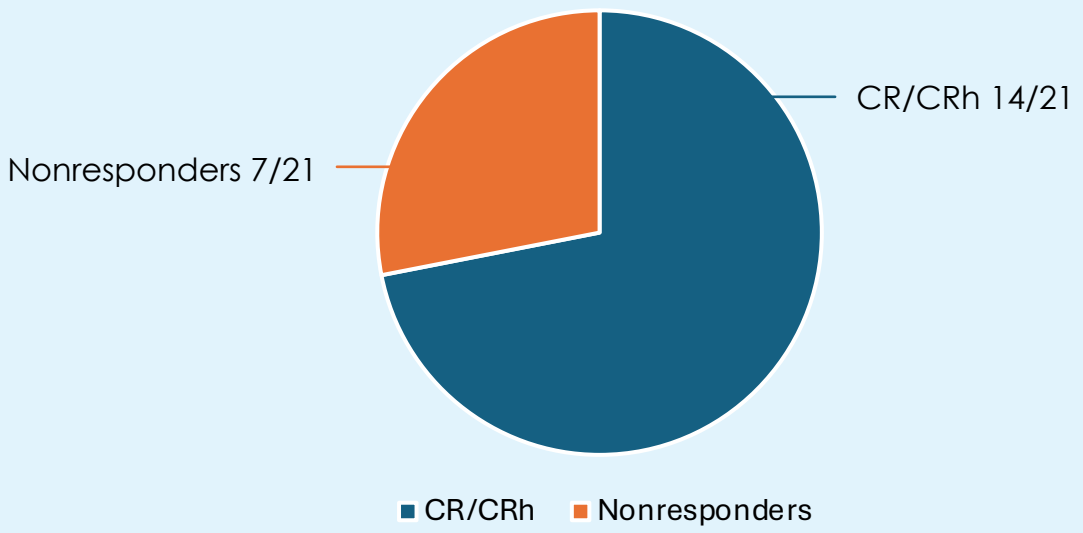


Jabbour E et al.: Am J Hematol. 2024

Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia (ID: NCT04521231)

Dose-Escalation Phase: Efficacy

Response Rates With SC Blinatumomab



- Response evaluation was available for only 21* of 22 patients.
- Fourteen of 21 (66.7%) evaluable patients achieved CR/CRh within one cycle of SC blinatumomab:
  - Cohort 1: 3 of 6 (50%) patients
  - Cohort 2: 2 of 3 (66.7%) patients
  - Cohort 3: 4 of 5 (80%) patients
  - Cohort 4: 5 of 7 (71.4%) patients
    - Two patients who did not respond were underexposed to SC blinatumomab based on the serum levels of blinatumomab.
- Thirteen of 14 patients with CR/CRh were MRD-negative after cycle 1 of SC blinatumomab:
  - Eight of 14 patients underwent bone marrow evaluation at day 12, of whom 100% were MRD-negative on day 12.

*Response evaluation was not done for one patient either at day 12 or at day 27 since he developed bleeding complications unrelated to SC blinatumomab and was taken off treatment Additionally, bone marrow evaluation was not done as the patient was too sick.

CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; MRD, measurable residual disease; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous.

Martínez-Sánchez P, et al. Poster presented at: 64th ASH Meeting; December 10-13, 2022; New Orleans, LA.

Single Agent Subcutaneous Blinatumomab for Advanced Acute Lymphoblastic Leukemia (ID: NCT04521231)

Dose-Expansion Phase: Efficacy

Best hematologic response within two cycles after treatment initiation

Characteristics, n (%)	250 µg/ 500 µg dose (N = 14)	500 µg/ 1,000 µg dose (N = 13)
CR	10 (71.4)	12 (92.3)
CRh	2 (14.3)	0
CR/CRh	12 (85.7)	12 (92.3)
MRD-negative in patients with CR/CRh‡	9 (75)	12 (100)
Not evaluated	2 (14.3)	1 (7.7)

- All patients with BM assessment at day 12 and day 27 (n = 18 and n = 24, respectively) of cycle 1 had blast-free BM (< 5%).
- Nine of 27 patients (33.3%) with MRD-negative CR/CRh received alloHSCT.
- One patient developed CD19-negative relapse.

MRD negativity in patients with central RQ-PCR and clonoSEQ® assessments

n/N	250 µg/ 500 µg dose (N = 14)	500 µg/ 1000 µg dose (N = 13)
MRD negativity (< 10^{-5}) by central MRD RQ-PCR assessment	6/7	5/6
MRD negativity (< 10^{-6}) by central clonoSEQ assessment	4/5	5/5

*The data cutoff date was September 15, 2023. †CR was defined as ≤5 % bone marrow blasts and no evidence of disease, and it was further characterized according to the extent of recovery of peripheral blood counts as follows: CR (platelet count > 100,000/µL and absolute neutrophil count > 1,000/µL) and CRh (platelet count of > 50,000/µL and absolute neutrophil count of > 500/µL). ‡MRD was reported based on a minimum sensitivity of $<10^{-4}$.

alloHSCT, allogeneic hematopoietic stem cell transplantation; BM, bone marrow; CD19, cluster of differentiation 19; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; MRD, measurable residual disease; PD, pharmacodynamics; PK, pharmacokinetics; RQ-PCR, real-time quantitative polymerase chain reaction.

Jabbour E, et al. *Am J Hematol*. 2024;99:586–595.

SC Blinatumomab for the treatment of relapsed refractory ALL: Bergamo experience

Demographics

Patients' characteristics

Characteristics	Cohort 250-500 (n=4)	Cohort 500-1000 (n=7)
Age, median (range)	65,5 (29-69)	59 (27-70)
Gender		
F	1 (25%)	3 (43%)
M	3 (75%)	4 (57%)
Diagnosis		
ALL B Ph-	1 (25%)	4 (57%)
ALL B Ph-like	1 (25%)	0
ALL B Ph+	2 (50%)	3 (43%)
Status at enrollment		
1st relapse/refractoriness	2 (50%)	5 (72%)
≥2nd relapse	2 (50%)	2 (28%)

Previous therapies

Previous therapies	Cohort 250-500 (n=4)	Cohort 500-1000 (n=7)
N previous therapies		
1	0	3 (43%)
2	1 (25%)	0
3	1 (25%)	2 (28%)
4	1 (25%)	1 (14%)
5	1 (25%)	1 (14%)
Previous blina IV		
No	1 (25%)	5 (72%)
Yes	3 (75%)	2 (28%)
Previous inotuzumab		
No	1 (25%)	4 (57%)
Yes	3 (75%)	3 (43%)
Previous HSCT		
No	4 (100%)	3 (43%)
Yes	0	4 (57%)

Biological features: karyotype and CD19 expression at relapse

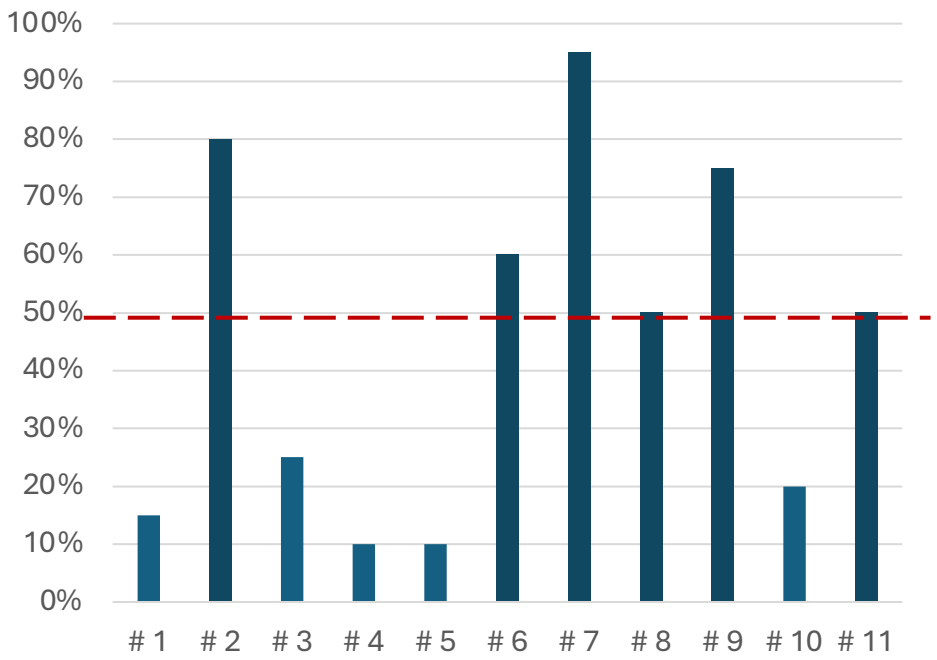
Patient	Cytogenetics at onset	Cytogenetics at enrollment		Cytogenetics	CD 19
1	46, XX	Not done	**Relapse** after SC Blinatumomab	Not done	**NEGATIVE**
2	**Hypodiploid karyotype**	Not done	**Relapse** after SC Blinatumomab	Not done	**NEGATIVE**
3	46, XY	46, XY			
4	46, XY	Not done	**Relapse** after SC Blinatumomab	Not done	**NEGATIVE**
5	46, XX t(9;22)	Not done			
6	**46, XX add(6), del(11)**	**As onset with additional anomalies**			
7	**46, XY, der(3), del(3), i(18)**	Not evaluable			
8	46, XY t(9;22)	Not done			
9	46, XY t(9;22)	Not done			
10	**Complex karyotype***	Not done			
11	**46, XX t(9;22), der(3)t(1;3)[9]**	Not done			

*46, XY t(9;22) [12], 47, XY, del(5), der (9), der(12)t(9;12), der(22)t(9;22)x2[2]

All relapses (3/11) after SC Blinatumomab were characterized by **CD19 loss**

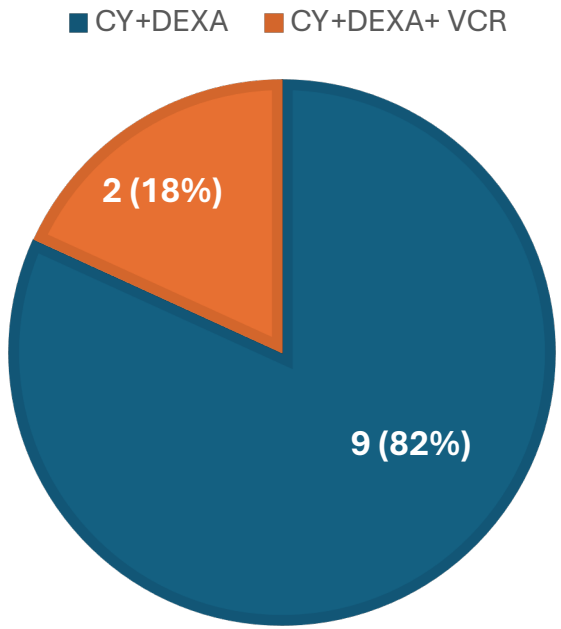
Disease Burden

Percentages of BM blasts at enrollment



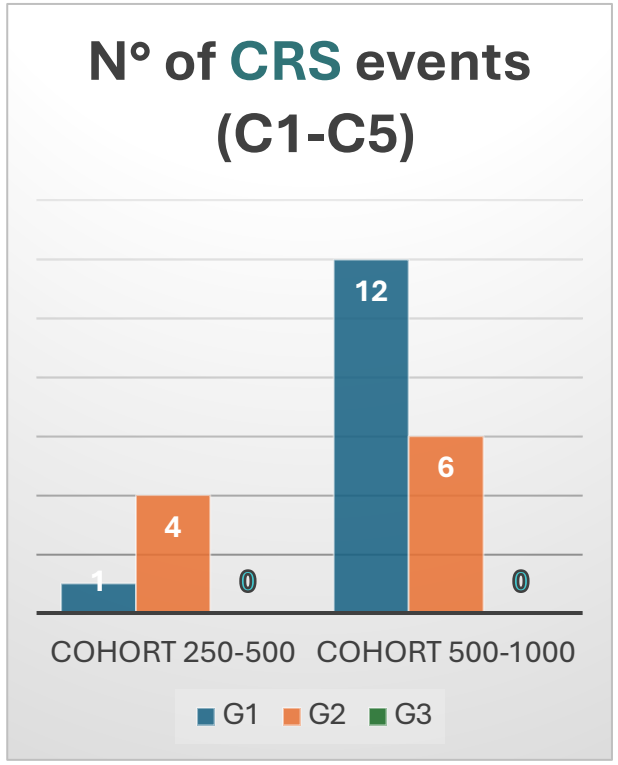
- **6/**11 (55%) had **≥ 50%** of blasts at enrollment

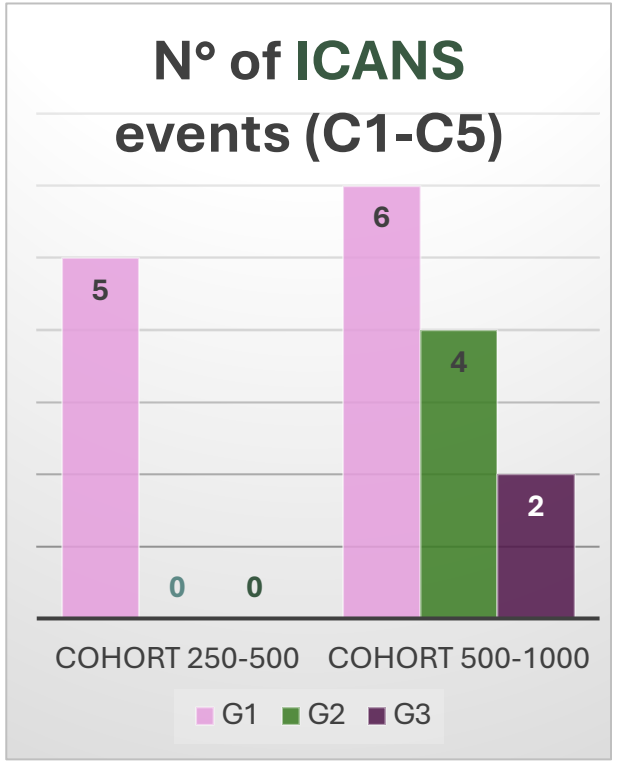
Pre-phase before SC Blinatumomab



- **2/**11 Cyclophosphamide, steroid and vincristine
- **9/**11 Cyclophosphamide and steroid

CRS and ICANS



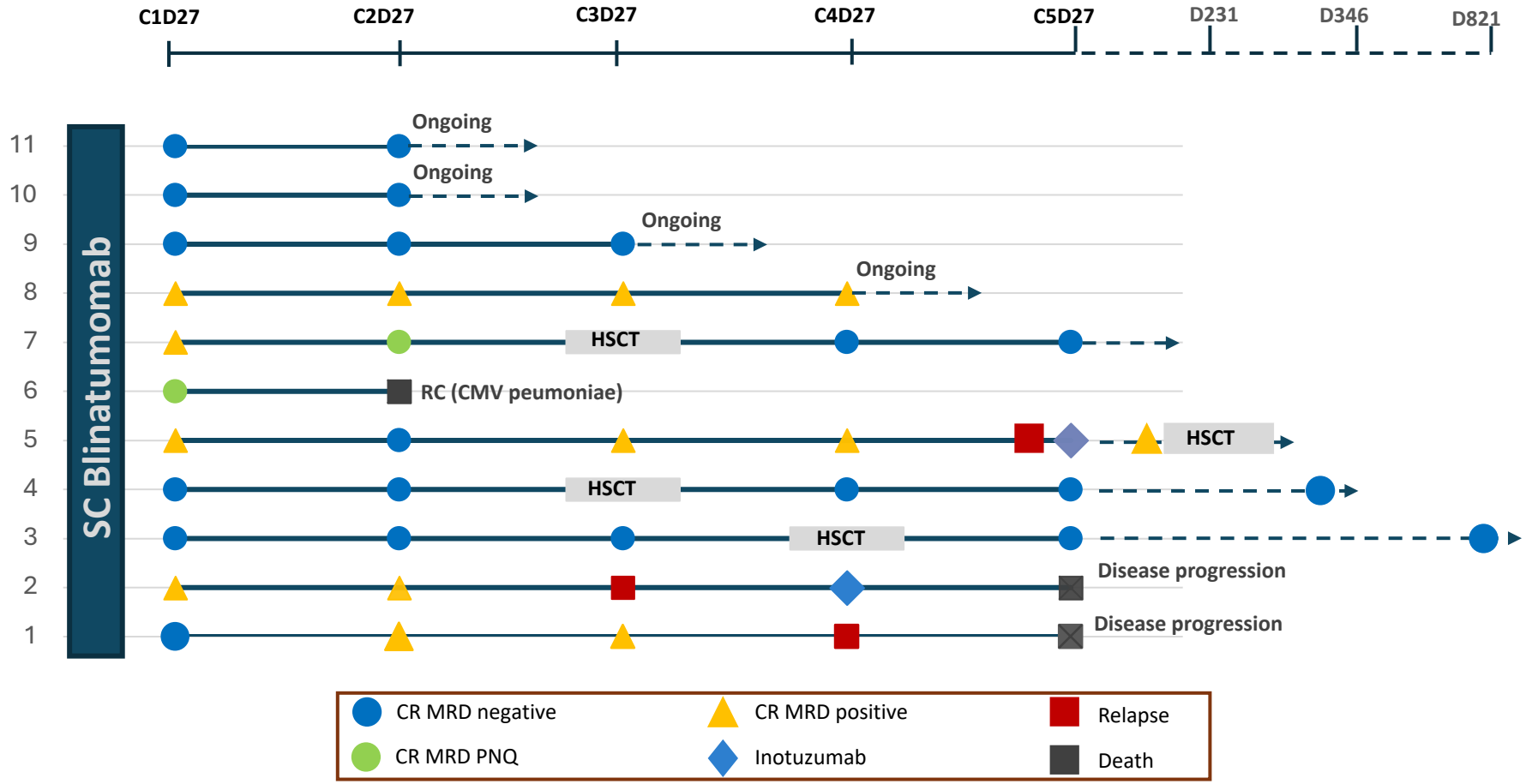


- **All** patients (11) experienced CRS and/or ICANS during **the first 72 h** after **C1D1**
- **5/**11 patients experienced CRS/ICANS **at Cycle 2**
  - 1 cohort 250-500 (ICANS G1)
  - 4 cohort 500-1000 (2 ICANS G2; 1 ICANS G1; 1 CRS G1; 1 CRS G2)
- **All events** completely **resolved within 72 h except for**
  - Patient #6 (cohort 500-1000 µg) that experienced **ICANS G1 evolved in ICANS G2** during cycle 1

1 month to resolve

Response

#	Dosage (µg)	Response C1D12
1	250-500	**CR** MRD-
2	500-1000	**CR** PNQ
3	500-1000	**CR** MRD-
4	500-1000	**CR** MRD-
5	500-1000	**CR** MRD-
6	500-1000	**CR** PNQ
7	250-500	**CR** MRD+
8	250-500	**CR** MRD+
9	500-1000	**CR** MRD+
10	250-500	**CR** MRD-
11	500-1000	**CR** MRD NV



Strategies to minimize severe CRS and ICANS

WHAT to do to **prevent severe CRS/ICANS?** *(Bergamo experience)*

- Prophylaxis of ICANS/Neurotoxicities with **Levetiracetam (1000mg/die) before starting** and **up to the end** of therapy with SC Blinatumomab
- Use of **steroid,** as per protocol recommendations (particularly in case of persistent or unresponsive G1 CRS or G1 ICANS). In these latter cases, **quick tapering** upon response
- In case of persistent ≥ Grade2 CRS or ICANS, **interruption** of SC Blinatumomab until **≤ Grade1**
- In case of previous toxicities, we consider **steroid premedication** (DEXA 4 mg/8mg) at D1 of SC Blinatumomab during following cycles as allowed by study protocol

Single Agent Subcutaneous Blinatumomab for Advanced ALL (ID: NCT04521231)

Conclusions

Treatment with SC blinatumomab as monotherapy in patients with R/R B-ALL resulted in higher CR and MRD response rates than in those reported with cIV blinatumomab, with comparable toxicity.

- ***CR/CRh rates after two cycles of SC blinatumomab:***
- ***85.7% with a 75% MRD response rate at the 250 µg/500 µg dose***
- ***92.3% with a 100% MRD response rate at the 500 µg/1000 µg dose***
- ***All patients received the efficacious dose from day 1 with no lower initial dose required as with cIV formulation, and all 18 patients assessed on day 12 achieved CR/CRh.***

These data validate the continued investigation of SC blinatumomab as an option for patients with R/R B-ALL and warrant the initiation of randomized controlled trials.

- B-ALL, B-cell precursor acute lymphoblastic leukemia; cIV, continuous intravenous; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; MRD, measurable residual disease; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; SC, subcutaneous.
- Jabbour E, et al. *Am J Hematol*. 2024;99:586–595.

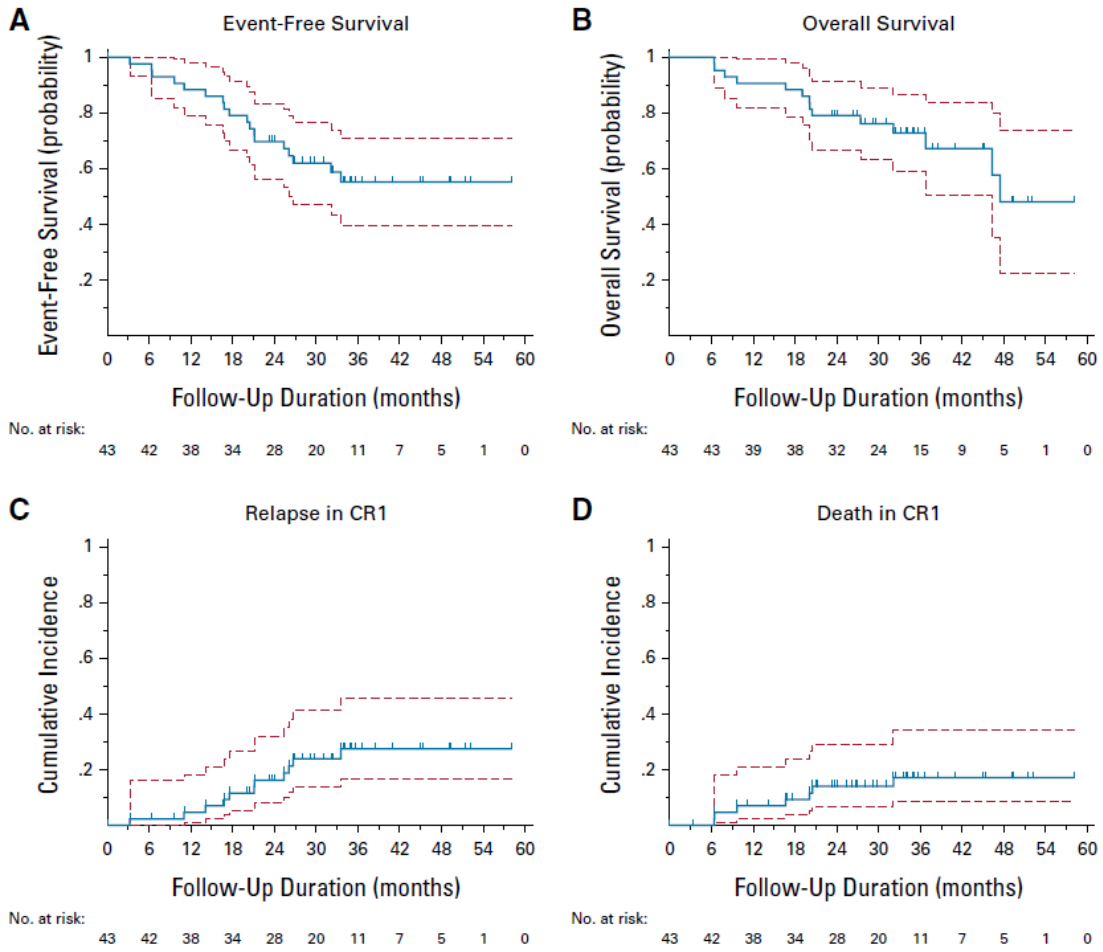
Aims of future trials in adult ALL

- Reducing primary refractory disease and early relapse

- **Improving the treatment of older patients**

First-Line Inotuzumab Ozogamicin in Older Patients With BP-ALL

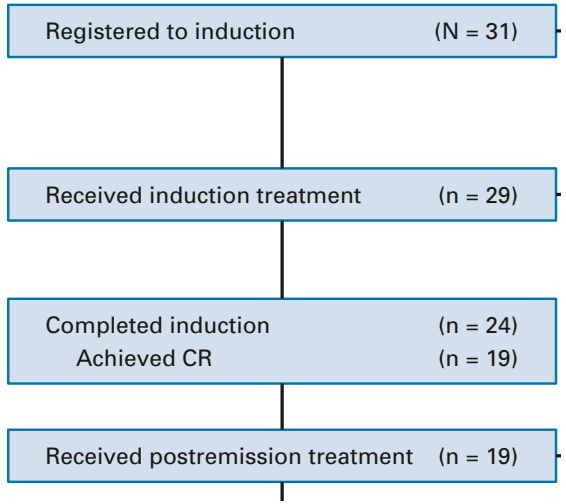
- 43 BP-ALL with a median age of 64 years (range, 56-80), two cycles of inotuzumab ozogamicin induction therapy.
- All patients achieved complete remission (CR/CR with incomplete hematologic recovery).
- (53%) and (71%) patients had no evidence of molecularly assessed MRD (minimum 10^{-4} threshold) after 2nd and 3rd inductions, respectively.
- After a median follow-up of 2.7 years, EFS at one (primary endpoint) and 3 years was 88% and 55% while overall survival (OS) was 91% and 73%, respectively.



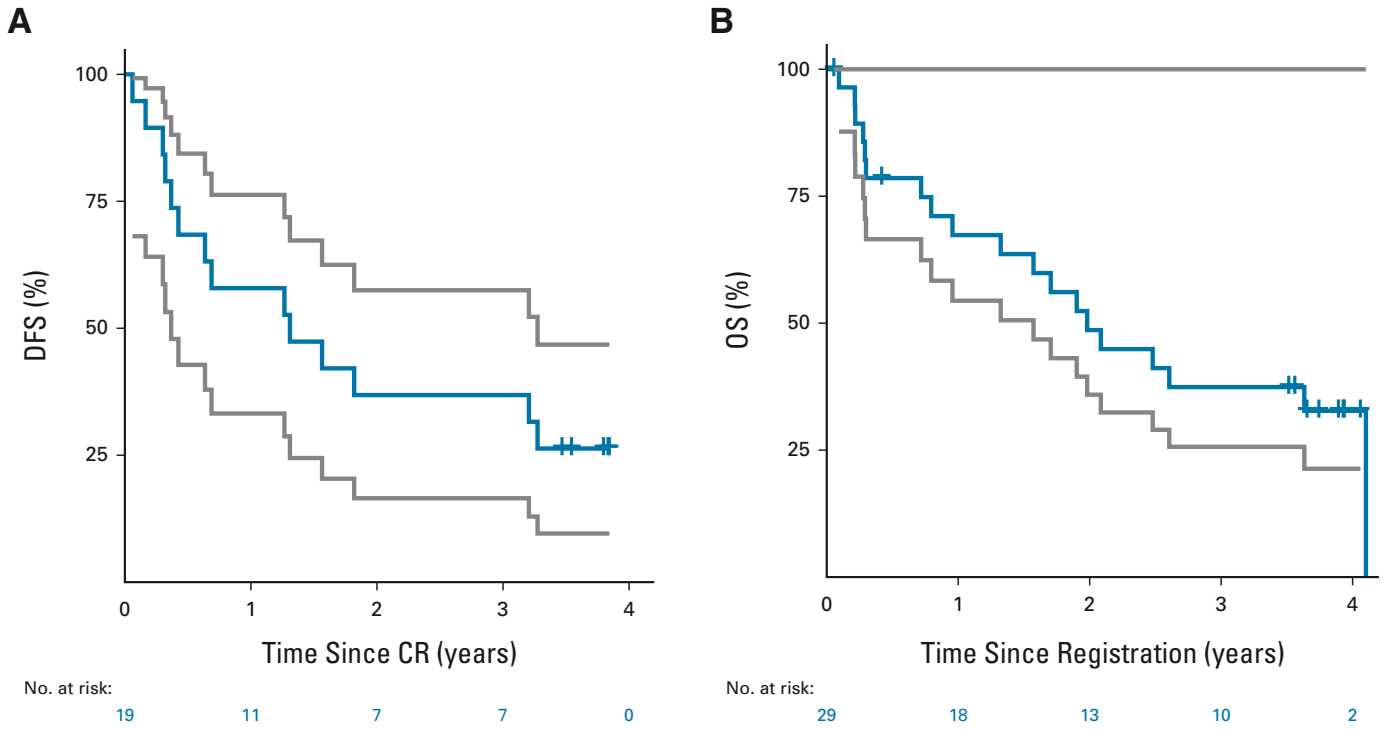
Stelljes M et al.: J Clin Oncol. 2024 Jan 20;42(3):273-282

SWOG 1318: A Phase II Trial of Blinatumomab Followed by POMP Maintenance in Older Patients With Newly Diagnosed Philadelphia Chromosome–Negative BP-ALL

Characteristic	No. (% or range)
Median age, years	75 (66-84)
Sex (male), No. (%)	22 (76)
Baseline WBC, median (range)	3.0 × 10^3/μL (0.3-520.8)
Bone marrow blast %, median (range)	87 (30-100)
NCCN cytogenetic risk, No. (%)	
Poor	10 (34)
Standard	16 (55)
Good	1 (3)
Unknown	2 (7)
Ph-like ALL (14 patients tested), No. (%)	5 (36)
CD19 expression %, median (range)	99 (19-99)

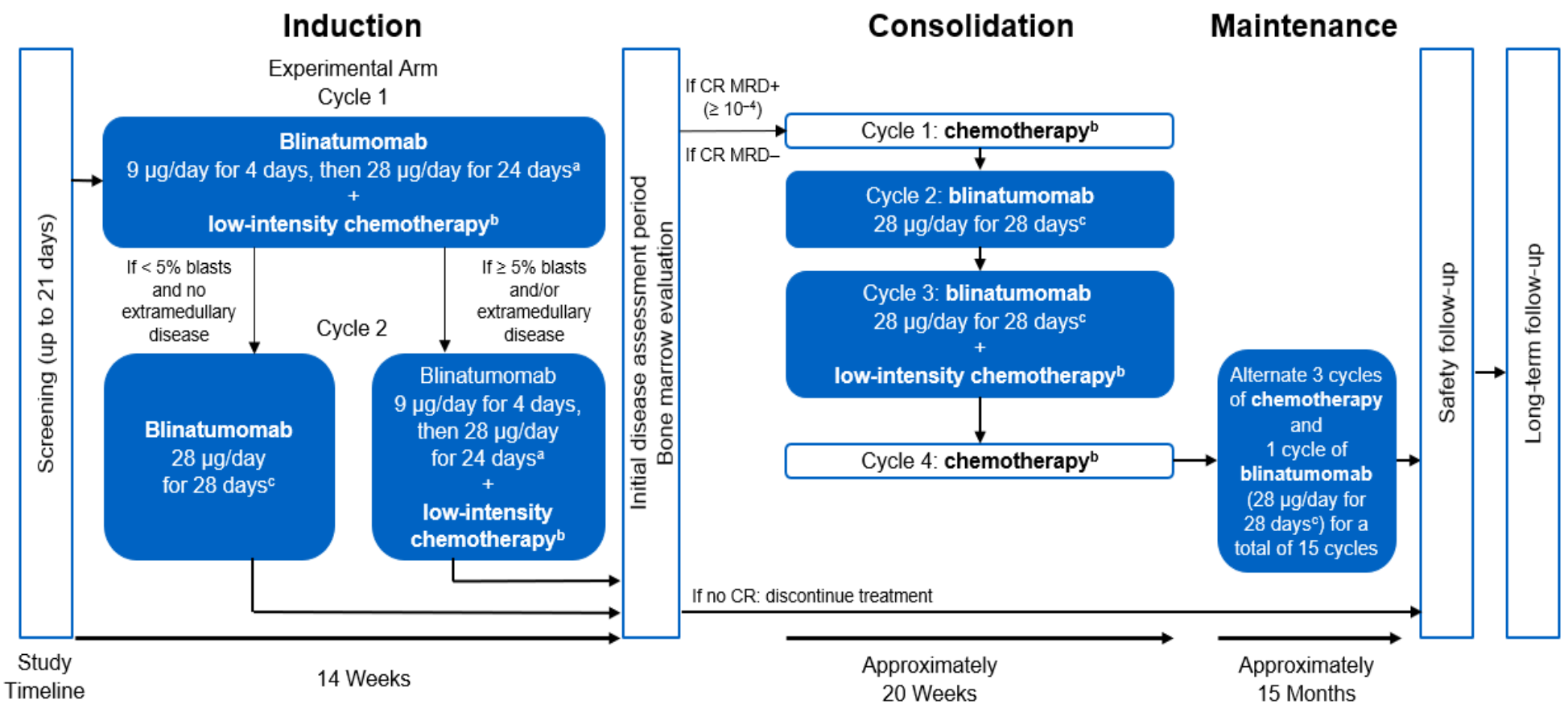


CR= 61%



Advani AS et al.: Journal of Clinical Oncology 40:1574-1582, 2022

Blinatumomab Alternating With Low-Intensity Chemotherapy (CT) Treatment for Older Adults With Newly Diagnosed Philadelphia (Ph)-Negative BCP-ALL: the Phase 3 Randomized Controlled Golden Gate Study



Endpoints

Primary

- **Safety run-in: safety and tolerability**
- **Phase 3: EFS, OS**

Key secondary

- Safety run-in: CR, MRD, RFS
- Phase 3: CR, MRD, RFS, safety, global health status

Population

- **Adults ≥55 years and 40 to <55 years with at least 1 of comorbidities***
- **Newly diagnosed Ph– B-ALL**
- Simple size: **284 pts**

- *Jabbour, e et al.: Blood (2022) 140 (Supplement 1): 6134–6136.*

Conclusions

- In Ph negative adult ALL, immunotherapy has improved the clinical outcome of front-line treatment of adult ALL
- This improvement has been gained (for the first time) not by increasing the chemotherapy dose intensity
- Immunotherapy is changing the therapeutic landscape of older ALL patients
- In the relapsed/refractory setting, SC blinatumomab has shown a remarkably better PK profile and a much higher rate of MRD-CR.
- More is coming soon with SC Blinatumomab in the front-line setting for bot young and older ALL.