Immunoterapia e HSCT: un'evoluzioone continua nel trattamento della Leucemia Acuta Linfoblastica (dell'adulto) con Blinatumomab

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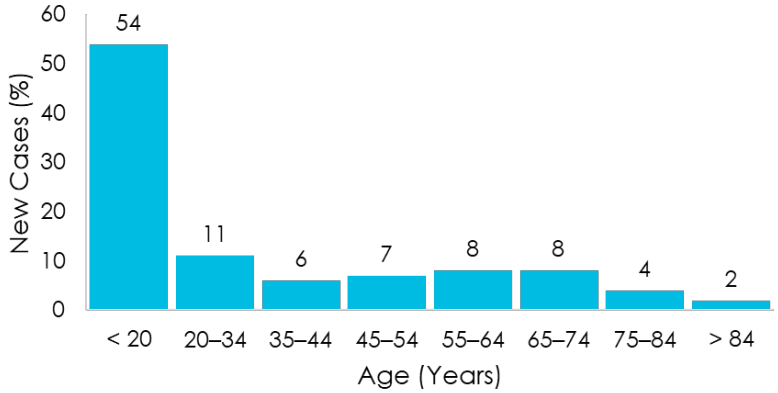
Disclosure statement

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

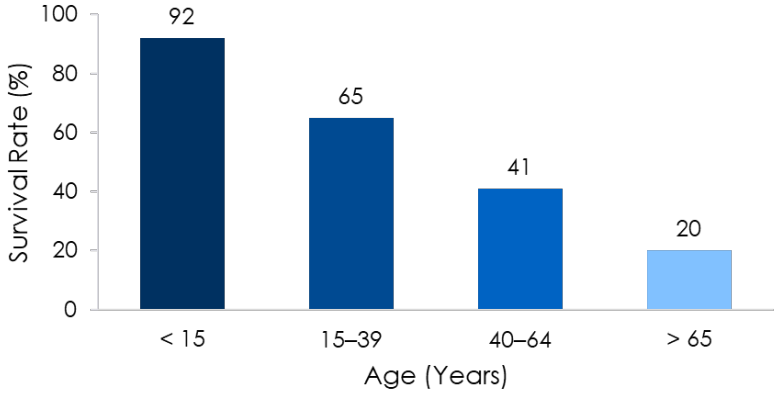
ALL Is a Rare but Often Fatal Disease That May Occur at Any Age[1]

In 2022, about 6,660 new cases of ALL and 1,560 deaths due to ALL in the US[1]

New Cases of ALL by Age Group[1]



5-Year Survival Rates by Age Group[2]

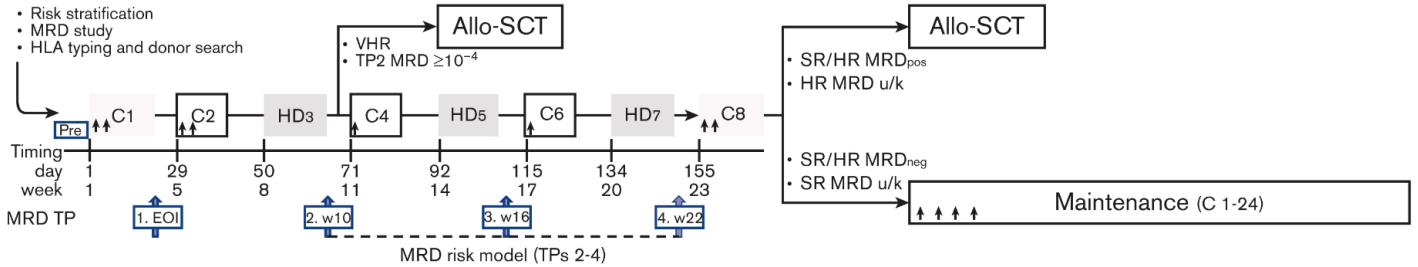


Adult patients generally have poorer survival rate outcomes compared with children, especially as they age[2]

ALL, acute lymphoblastic leukemia; US, United States.

1. National Cancer Institute. Cancer Stat Facts: Leukemia – ALL. https://seer.cancer.gov/statfacts/html/alyl.html. Accessed September 7, 2022. 2. National Cancer Institute. Cancer Statistics Explorer Network: ALL. https://seer.cancer.gov/statistics-network/explorer. Accessed September 7, 2022.

GIMEMA LAL1913: the first Italian prospective phase II study evaluating an intensive chemotherapy backbone and MRD risk-oriented model in untreated ALL adult patients



Treatment phase	Drugs	Dosing and administration	Days
Prephase	Prednisone Cyclophosphamide	20 mg/m² PO q12h 300 (200 if age >55) mg/m² IV over 30'	−5 to −1 −3 to −1
Course 1	Idarubicin Vincristine Dexamethasone Pegaspargase IT prophylaxis(†)	12 (9 if age >55) mg/m² IV over 30' 1.4 mg/m² (max. 2 mg) IV push 5 mg/m² IV over 5' q12h 2000 (1000 if age >55) IU/m² IV over 120'	1,2 1,8,15,22 1-5, 15-19 10 1,15
Courses 2,4,6	Vincristine Idarubicin Cyclophosphamide Dexamethasone Cytarabine Pegaspargase 6-mercaptopurine IT prophylaxis (†)	1.4 mg/m² (max. 2 mg) IV push 12 (9 if age >55) mg/m² IV over 30' 1000 mg/m² IV over 60' 5 mg/m² PO q12h 75 mg/m² SC 2000 (1000 if age >55) IU/m² IV over 120' 60 mg/m² PO q12h	1,8 (no course 2) 1 1 1-5 2-5 8 (no course 4) 1-10 1(and 15, course 2)
HD courses 3,7	Methotrexate Cytarabine	2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24h; FAR 2000 mg/m² IV q12h	1 3,4

† Methotrexate 12.5 mg, Cytarabine 50 mg, Dexamethasone 4 mg (or Methylprednisolone 40 mg)

Treatment phase	Drugs	Dosing and administration	Days
HD course 5	Methotrexate Pegaspargase 6-mercaptopurine	2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24 h; FAR 2000 (1000 if age >55) IU/m² IV over 120' 25 mg/m² PO	1 3 8-18
Course 8	Vincristine Idarubicin Dexamethasone Cyclophosphamide Prednisone IT prophylaxis (†)	1.4 mg/m² (max. 2 mg) IV push 10 (7.5 if age >55) mg/m² IV over 30' 5 mg/m² PO q12h 300 (200 if age >55) mg/m² IV over 30' 20 mg/m² PO q12h	1,8 1,8 1-5 1-3 8-12 1,15
Maintenance courses 1,3,5,7,9,11	Cyclophosphamide 6-mercaptopurine Methotrexate IT prophylaxis (†)	100 mg/m² PO 75 mg/m² PO 15 mg/m² PO/IM	1-4 8-28 8,15,22 1 (courses 3,5)
courses 2,4,6,8,10,12	Vincristine Prednisone 6-mercaptopurine Methotrexate IT prophylaxis (†)	1 mg/m² (max. 2 mg) IV push 20 mg/m² PO q12h 75 mg/m² PO 15 mg/m² PO/IM	1 1-5 8-28 8,15,22 1 (courses 2,4)
courses 13-24	6-mercaptopurine Methotrexate	75 mg/m² PO 15 mg/m² PO/IM	8-28 1,8,15,22

Bassan R et al.: Blood Advances 22 AUGUST 2023 VOLUME 7, NUMBER 16, 4448-4461

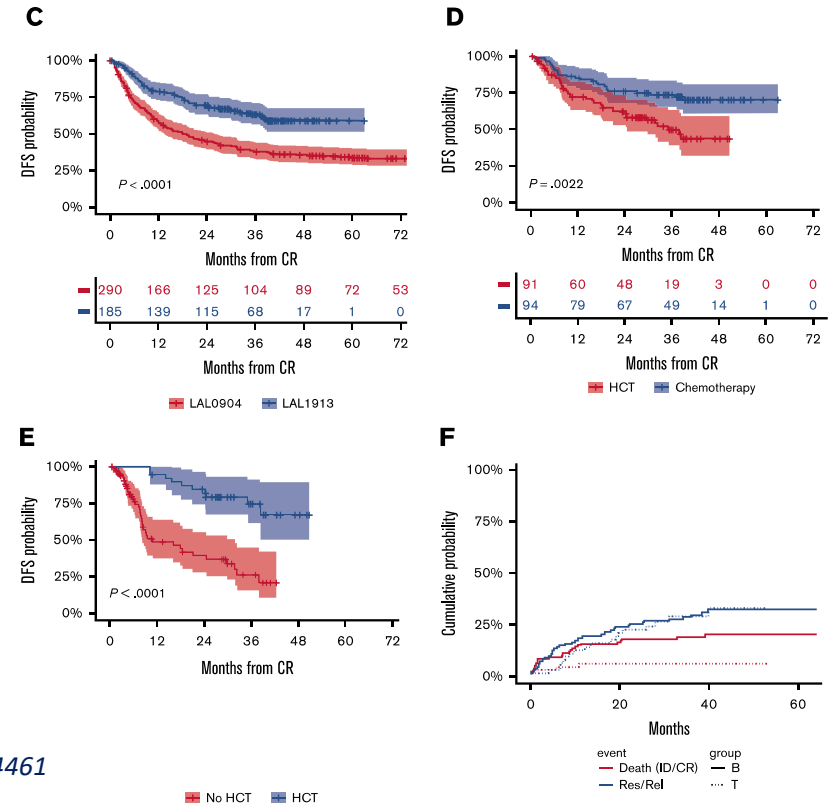
Pegaspargase-modified risk-oriented program for adult ALL: results of the GIMEMA LAL1913 trial: DFS

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



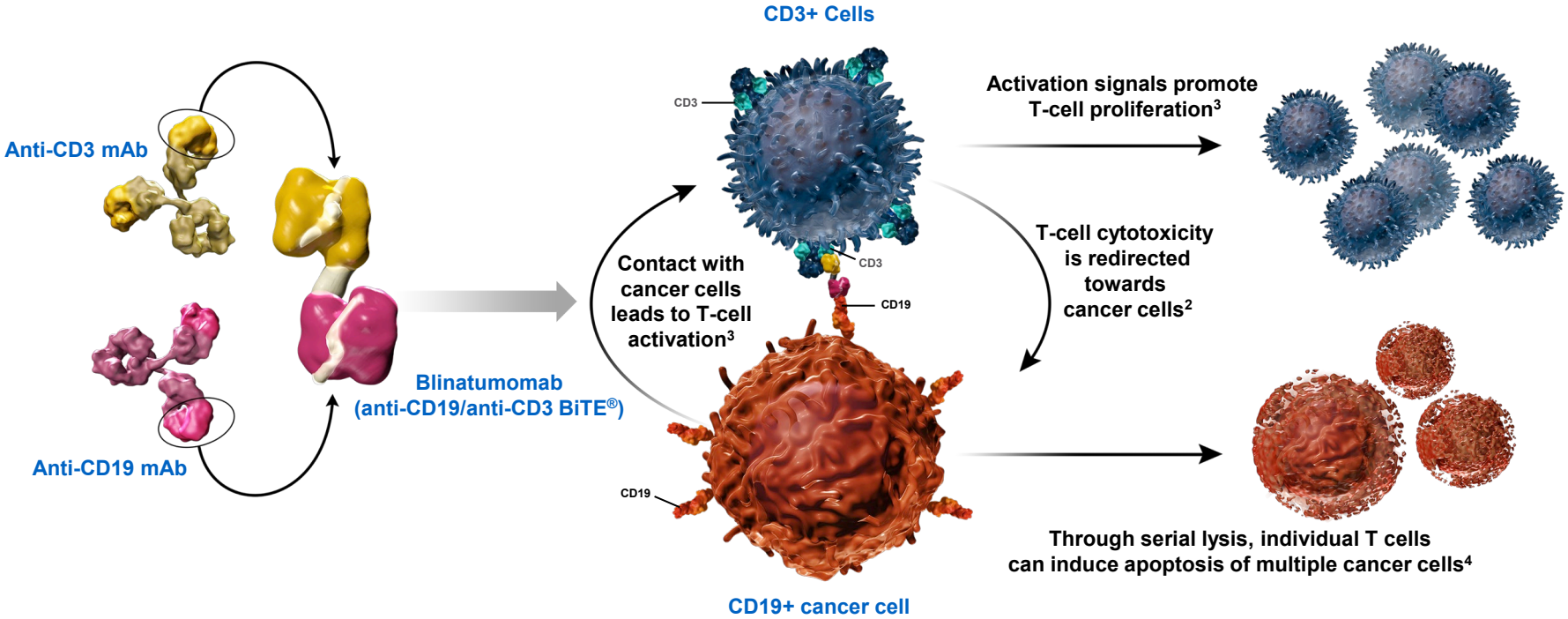
Bassan R et al.: Blood Advances 22 AUGUST 2023 VOLUME 7, NUMBER 16, 4448-4461

Efficacy outcomes support the use of protocol GIMEMA LAL1913 in Italian clinical practice for treatment of adult patients with Ph- B-ALL

Bassan R et al.: Blood Advances 22 AUGUST 2023 VOLUME 7, NUMBER 16, 4448-4461

How to improve the outcome of both MRD+ and MRD- BP-ALL patients?

Blinatumomab MoA Summary: A BiTE® Molecule Designed to Bridge T Cells to CD19-Expressing Cancer Cells, Inducing Apoptotic Cell Death[1]



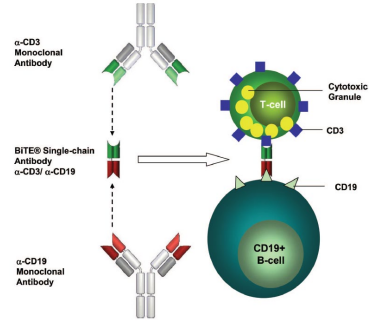
BiTE®, Bispecific T Cell Engager; CD, cluster of differentiation; mAb, monoclonal antibody; MoA, mechanism of action.

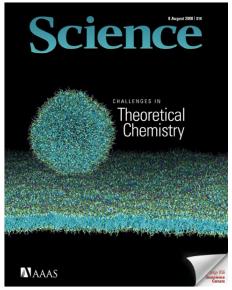
1. Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944. 2. Bargou R, et al. *Science.* 2008;321:974-977.
3. Klinger M, et al. *Blood.* 2012;119:6226-6233. 4. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

Int. J. Cancer: **115,** 98–104 (2005)

Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct

Patrick Hoffmann[1], Robert Hofmeister[1], Klaus Brischwein[1], Christian Brandl[1], Sandrine Crommer[1], Ralf Bargou[2], Christian Itin[1], Nadja Prang[1] and Patrick A. Baeuerle[1]*
[1]*Micromet AG, Munich, Germany*
[2]*Robert-Rössle-Clinic, University Medical Center Charité, Humboldt University of Berlin, and Helios Kliniken, Berlin, Germany*

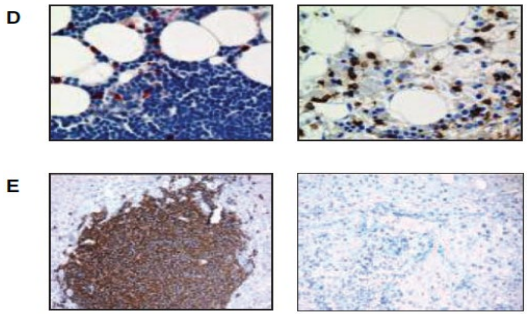




Tumor Regression in Cancer Patients by Very Low Doses of a T Cell–Engaging Antibody

Ralf Bargou,[1,2]* Eugen Leo,[3]*† Gerhard Zugmaier,[3] Matthias Klinger,[3] Mariele Goebeler,[1,2] Stefan Knop,[2] Richard Noppeney,[4] Andreas Viardot,[5] Georg Hess,[6] Martin Schuler,[7] Hermann Einsele,[2] Christian Brandl,[3] Andreas Wolf,[3] Petra Kirchinger,[3] Petra Klappers,[3] Margit Schmidt,[3] Gert Riethmüller,[8] Carsten Reinhardt,[3] Patrick A. Baeuerle,[3]‡ Peter Kufer[3]

15 AUGUST 2008 VOL 321 SCIENCE



Leukemia & Lymphoma, June 2009; 50(6): 886–891

informa healthcare

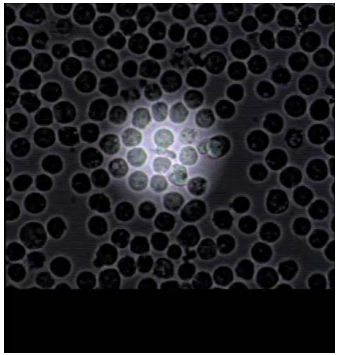
REVIEW

Immunotherapy of lymphoma and leukemia with T-cell engaging BiTE antibody blinatumomab

DIRK NAGORSEN[1], RALF BARGOU[2], DOMINIK RÜTTINGER[1], PETER KUFER[1], PATRICK A. BAEUERLE[1], & GERHARD ZUGMAIER[1]

[1]*Micromet AG, Staffelseestr. 2, 81477 Munich Germany and* [2]*Department of Hematology and Oncology and Phase I Unit of the Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Klinikstraße 6-8, 97070 Würzburg, Germany*

(Received 20 January 2009; revised 25 March 2009; accepted 1 April 2009)



T cell

NALM-6 B-precursor leukaemia cell

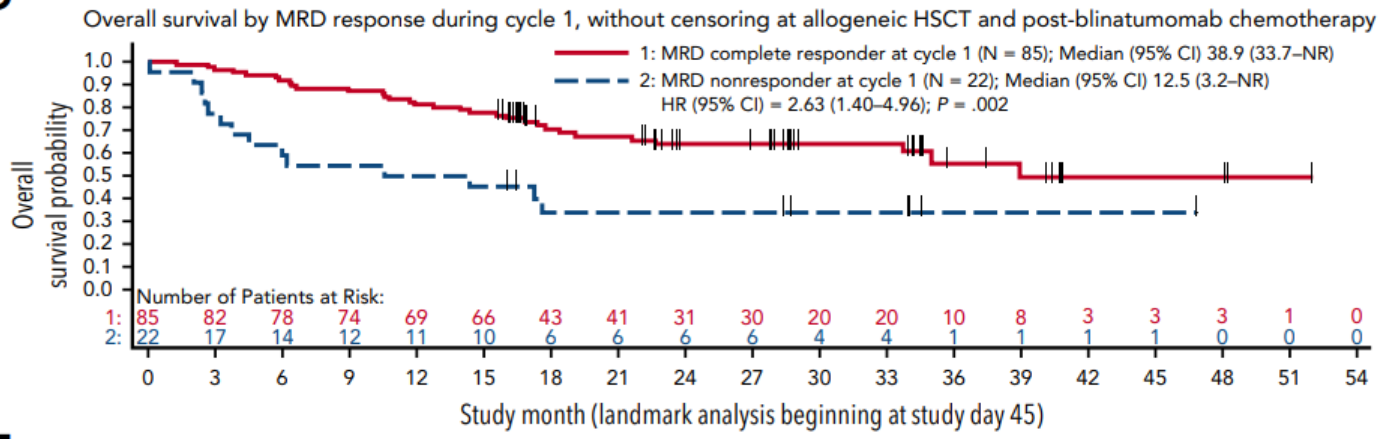
Targeted apoptotic leukaemia cells

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

KEY POINTS

- **Among adults with MRD-positive ALL in hematologic remission after chemotherapy, 78% achieved a complete MRD response with blinatumomab.**
- **Complete MRD response after blinatumomab treatment in this population was associated with significantly improved OS.**

D



Gokbuget N et al.: Blood. 2018;131(14):1522-1531

Front-line treatment of adult BP-ALL

The power of blinatumomab-containing, pediatric-inspired programs for both MRD- and MRD+ adult ALL

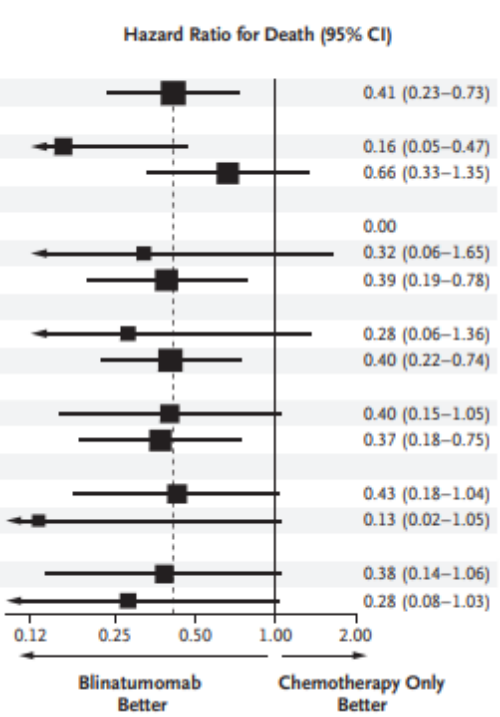
ECOG-ACRIN E1910: A Global, Randomized, Controlled, Phase 3 Trial of Blinatumomab Alternating With Chemotherapy vs Chemotherapy Alone in Frontline Consolidation in Adult Patients With Ph– B-ALL

ECOG-ACRIN E1910 phase 3 Trial:
OS in MRD-negative patients

Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults: the E1910 randomized phase 3 trial

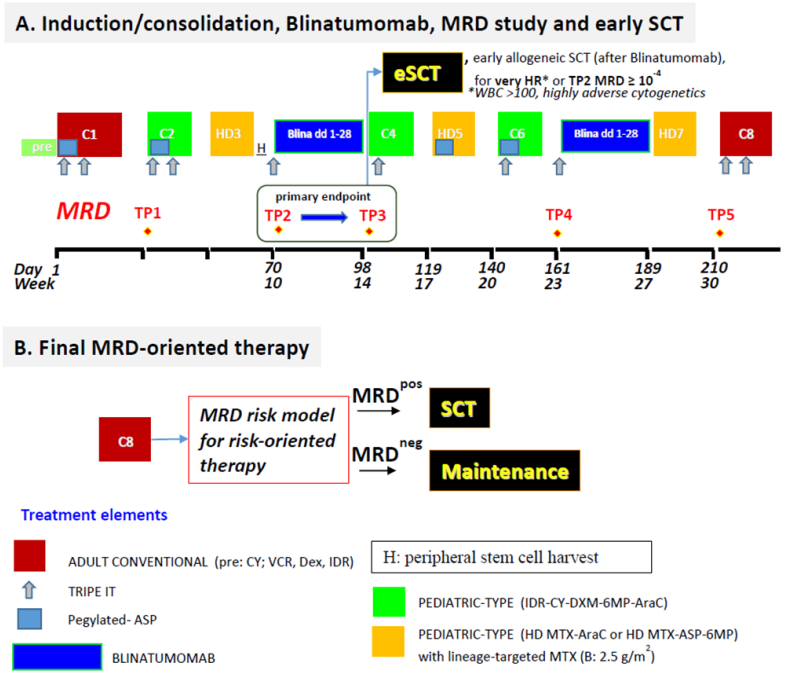
B Subgroup Analysis

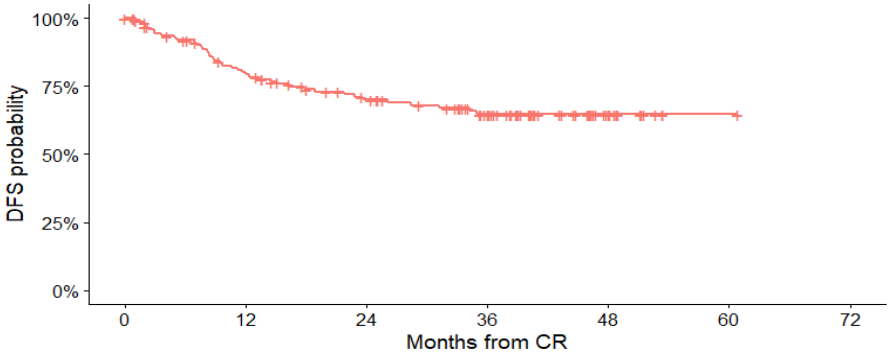
Subgroup	Blinatumomab (no. of deaths/total no.)	Chemotherapy Only (no. of deaths/total no.)	Hazard Ratio for Death (95% CI)
All MRD-negative patients	17/112	40/112	0.41 (0.23–0.73)
Age			
<55 yr	4/66	21/65	0.16 (0.05–0.47)
≥55 yr	13/46	19/47	0.66 (0.33–1.35)
Combined molecular risk			
Favorable	0/19	6/28	0.00
Intermediate	2/22	5/19	0.32 (0.06–1.65)
Unfavorable	12/50	24/45	0.39 (0.19–0.78)
BCR::ABL1–like genotype			
BCR::ABL1–like	2/16	7/15	0.28 (0.06–1.36)
Not *BCR::ABL1*–like	15/96	33/97	0.40 (0.22–0.74)
Transplantation intended			
Yes	6/36	13/35	0.40 (0.15–1.05)
No	11/76	27/77	0.37 (0.18–0.75)
CD20 status			
Positive	7/45	16/46	0.43 (0.18–1.04)
Negative	1/26	7/26	0.13 (0.02–1.05)
Rituximab use			
Yes	5/33	14/36	0.38 (0.14–1.06)
No	3/38	9/36	0.28 (0.08–1.03)

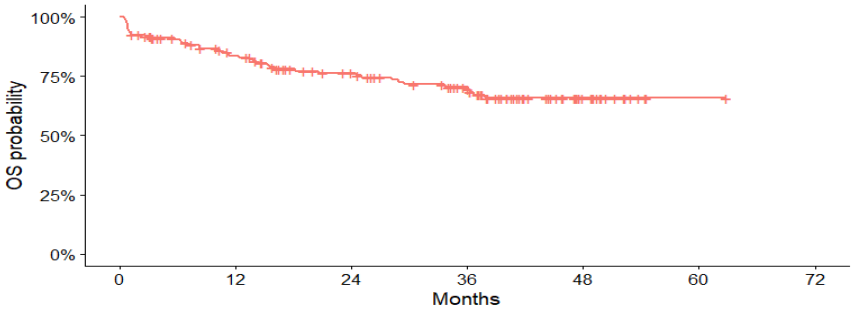


Litzow MR et al.: N Engl J Med 2024;391:320-33. DOI: 10.1056/NEJMoa2312948

Upfront Blinatumomab Improves MRD Clearance and Outcome in Adult Ph- B-lineage ALL. The GIMEMA LAL2317 Phase 2 Study



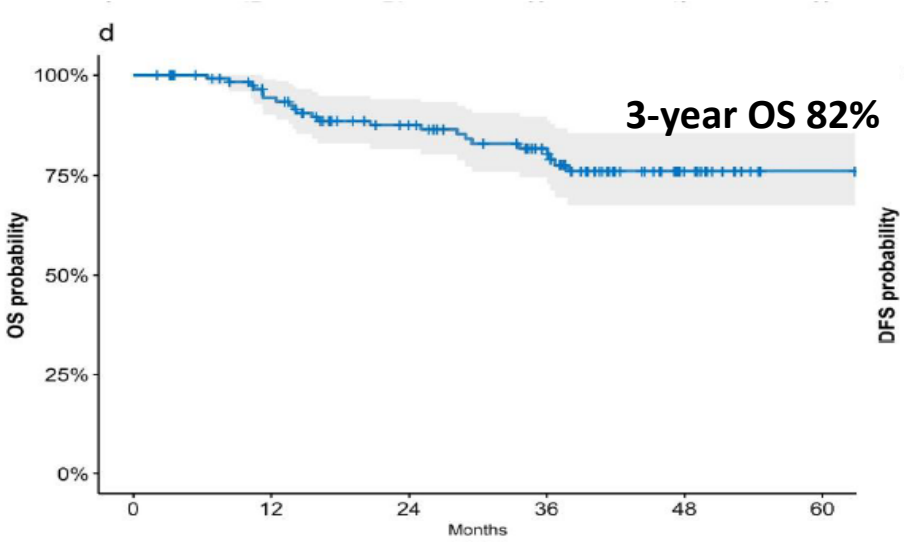


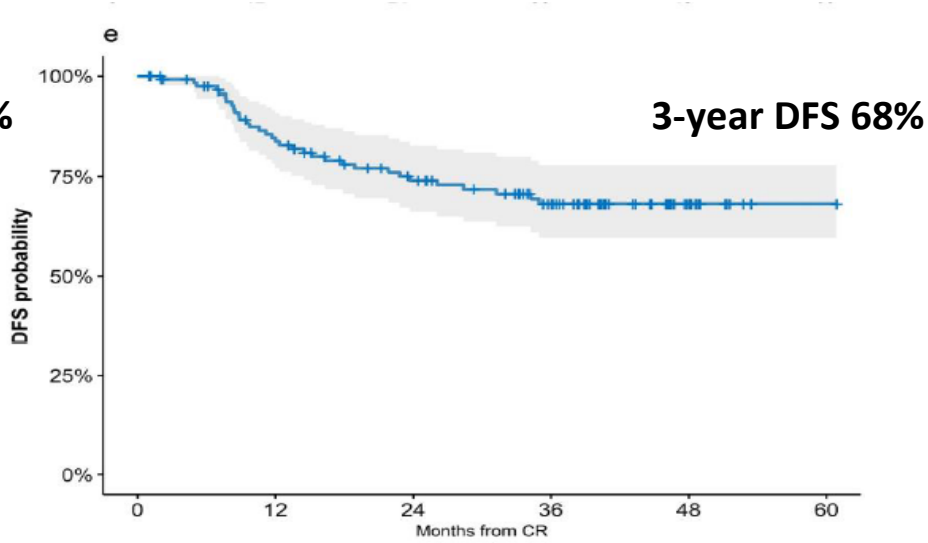


Bassan R. et al, Blood (2025) in press

Clinically meaningful benefit in patients who received at least one cycle of blinatumomab during the early treatment phase

Median follow-up: 38.1 months





Bassan R. et al, Blood (2025) in press

The role of AlloHSCT in the Blina era

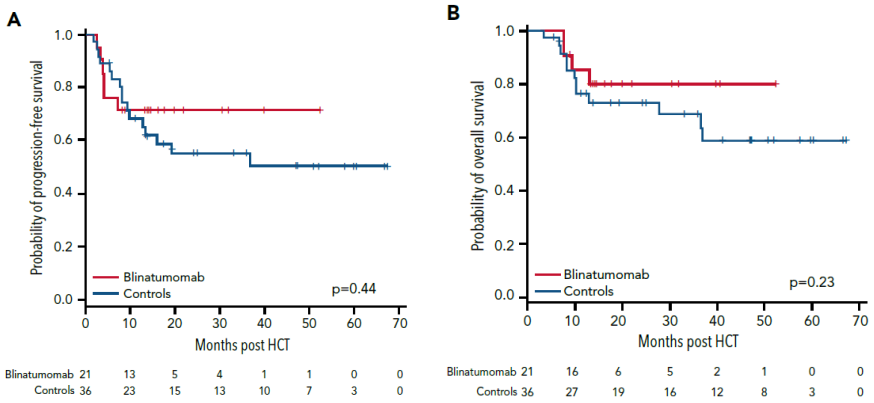
Indications for alloHSCT in young adults with Ph-negative AL

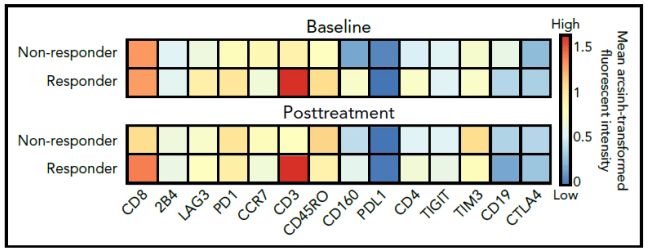
OS and RFS Among MRD- Patients Who Underwent AlloHCT

Time-dependent analysis confirmed the therapeutic advantage of allo-HSCT

Bassan R. et al, Blood (2025) in press

Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage ALL





MAIN RESULTS

- 12/ 23 pts (57%) completed all 4 cycles (17 pts were alive at the end of the study; 6 pts relapsed)
- With a median follow up of 14 3 months, the 1year OS, PFS, and non relapse mortality rates were 85%, 71% and 0%. CIR,29%
- The cumulative incidence of acute GVHD grades 2 to 4 and 3 to 4 were 33% and 5%, respectively; 2 cases of mild (10%) and 1 case of moderate (5%) chronic GVHD were noted
- In a matched analysis with a contemporary cohort of 57 patients, no significant difference between groups regarding blinatumomab's efficacy
- Responders had greater numbers of CD3, CD4, CD160 T cells compared with non responders. In addition, responders had higher levels of CD8 T cells after therapy
- Blinatumomab is safe and feasible for use in B-ALL after allogeneic HCT
- The composition of a patient's T-cell subsets at the time of treatment is indicative of whether they will respond to blinatumomab

ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; HCT, hematopoietic stem cell transplantation; HR, high-risk; PFS, progression free survival; OS, overall survival; NRM, non relapse mortality

Gaballa M, et al. Blood 2022 Mar 24;139(12):1908-1919 .

The role of alloHSCT in the D-ALBA trial

GIMEMA ALL 2820 trial

GIMEMA ALL 2820 trial: *the biologically-driven allo-SCT allocation reduced the rate of transplant*

	N=16
Age, median (range)	49 (27-67)
>65 years	1 (27)
Gender: M/F (%)	13/3 (50/50)
WBC, median (range)	23 (2-207)
p190	10
p210, p190/210	5, 1
IKZF1^{plus}	9

Reasons for transplant

- MRD persistence (n=7)
- *IKZF1*^{plus} (n=9)
- Both (n=5)

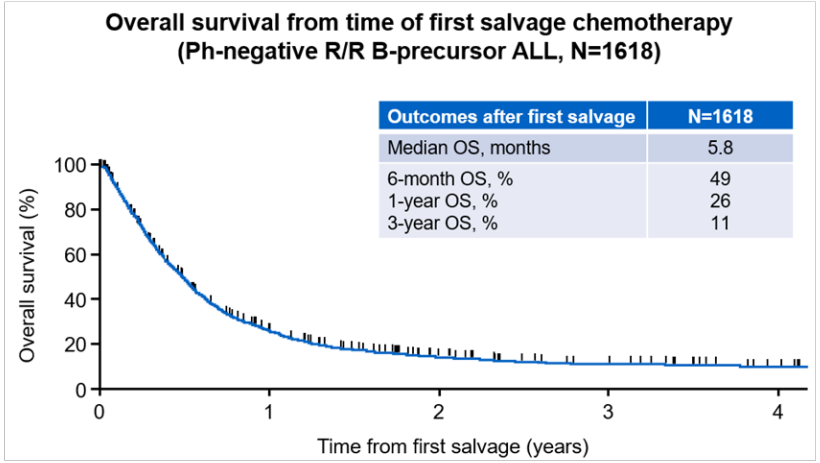
So far, no relapses nor transplant-related deaths

By Courtesy of Prof S. Chiaretti

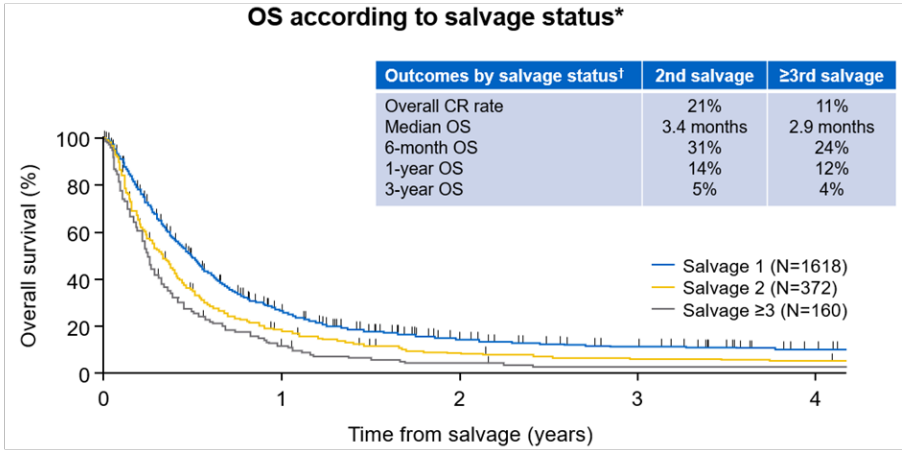
Blinatumomab for Relapse/Refractory ALL

Management of relapsed/refractory ALL before Immunotherapy

Salvage therapy of R/R ALL is associated with very poor outcomes



Only ~1 in 5 patients achieve CR following second or greater salvage therapy



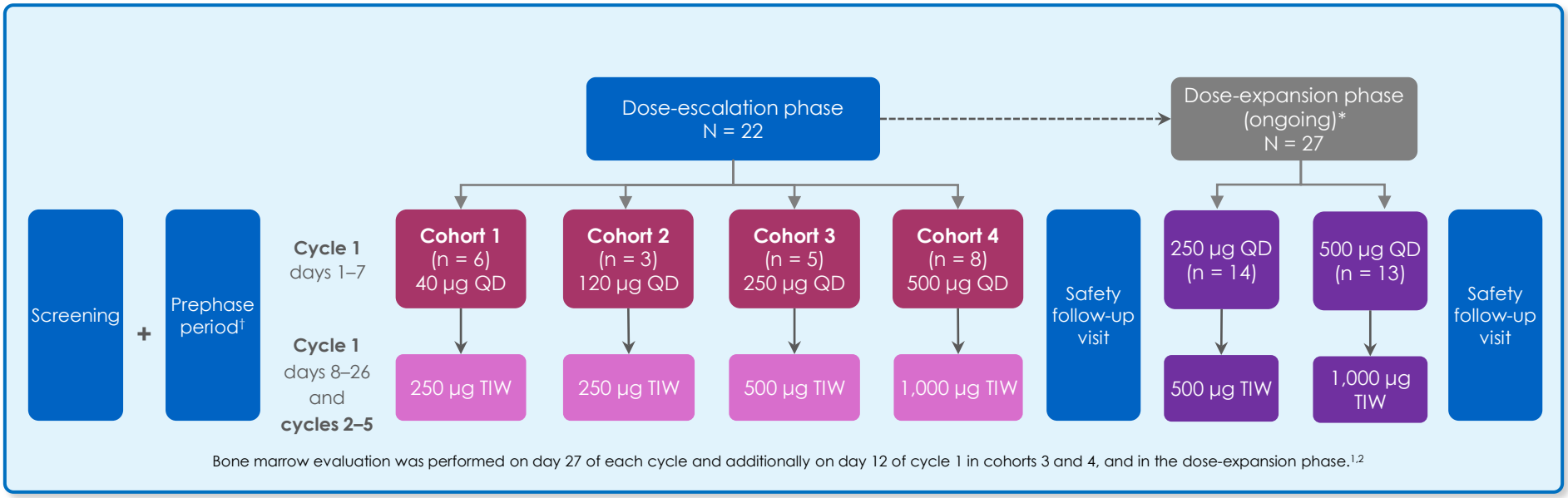
Adapted from Gökbuget N, et al. *Haematologica* 2016;101:1524–33.

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Kantarjian H et al.: N Engl J Med 2017;376:836-47. DOI: 10.1056/NEJMoa1609783

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

Study Design



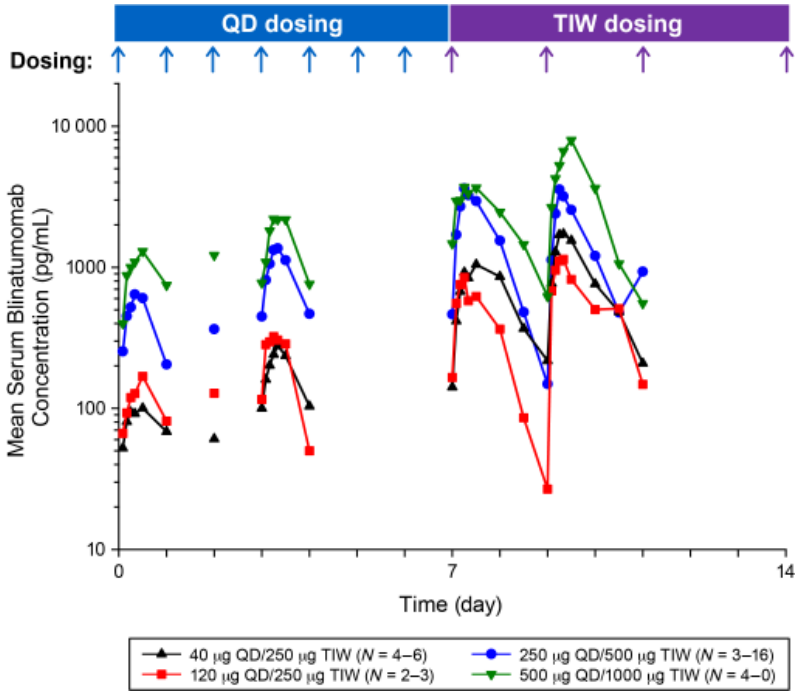
*Patients in the dose-expansion phase were enrolled between October 24, 2022, and July 31, 2023. The data cutoff date was September 15, 2023.[2] †In order to reduce tumor burden and the incidence of tumor lysis syndrome, low dose chemotherapy and/or dexamethasone was recommended prior to the start of 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

Best hematologic response within two cycles after treatment initiation

Response category	250 µg/500 µg dose ($N = 14$)	500 µg/1000 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 (75.0)	12 (100.0)
Not evaluated	2 (14.3)	1 (7.7)

Jabbour E et al.: Am J Hematol. 2024

Demographics

Patients' characteristics

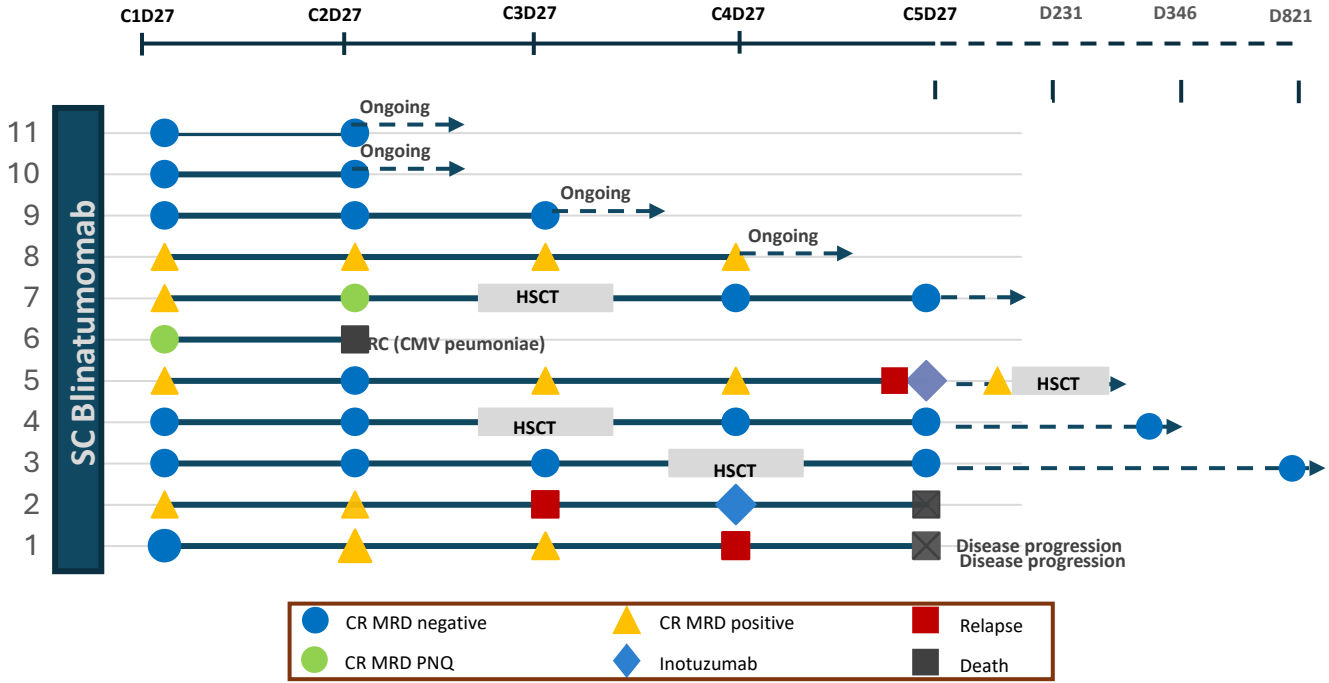
Characteristics	Cohort 250-500 (n=4)	Cohort 500-1000 (n=7)
Age, median (range)	65,5 (29-69)	59 (27-70)
Gender		
F	1 (25%)	3 (43%)
M	3 (75%)	4 (57%)
Diagnosis		
ALL B Ph-	1 (25%)	4 (57%)
ALL B Ph-like	1 (25%)	0
ALL B Ph+	2 (50%)	3 (43%)
Status at enrollment		
1st relapse/refractoriness	2 (50%)	5 (72%)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

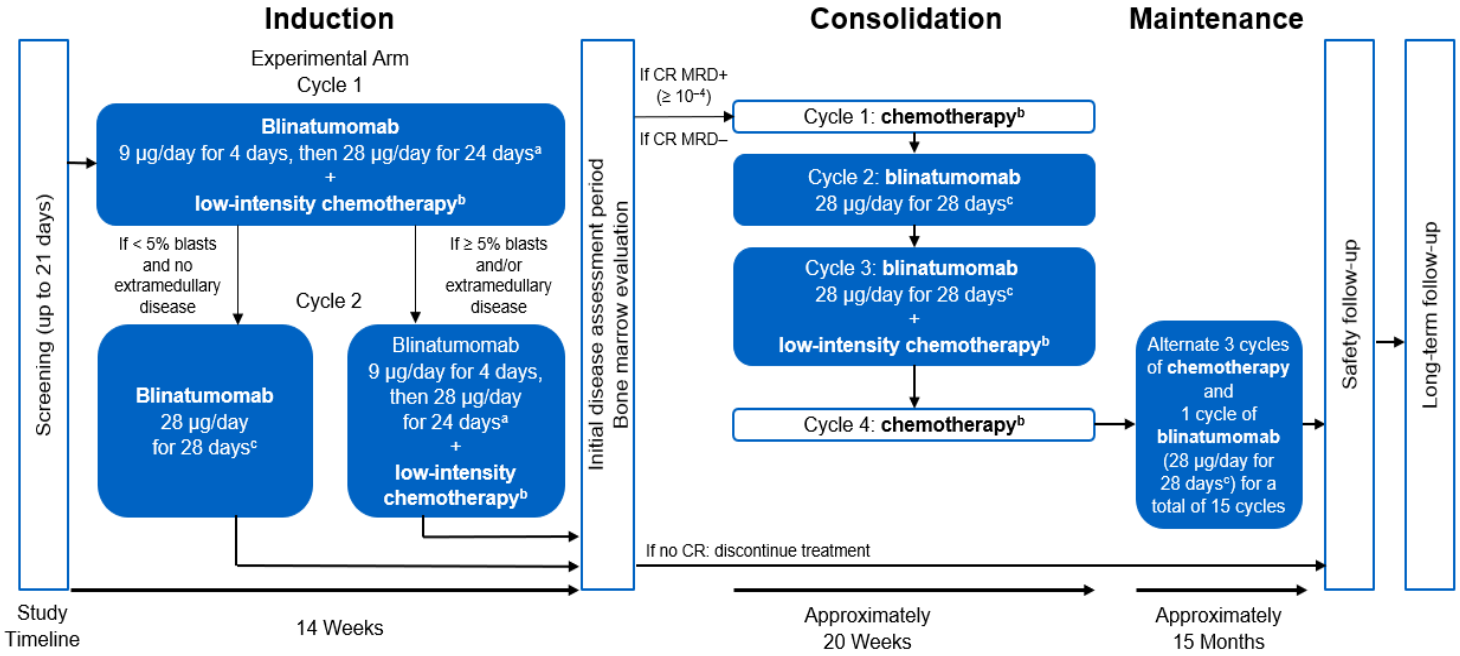
Response

#	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



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

The GOLDEN GATE study: a phase III multicenter, randomized, controlled trial with blinatumomab alternating with low-intensity chemo in older patients with ND Ph- B-ALL



Endpoints

Primary

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

Key secondary

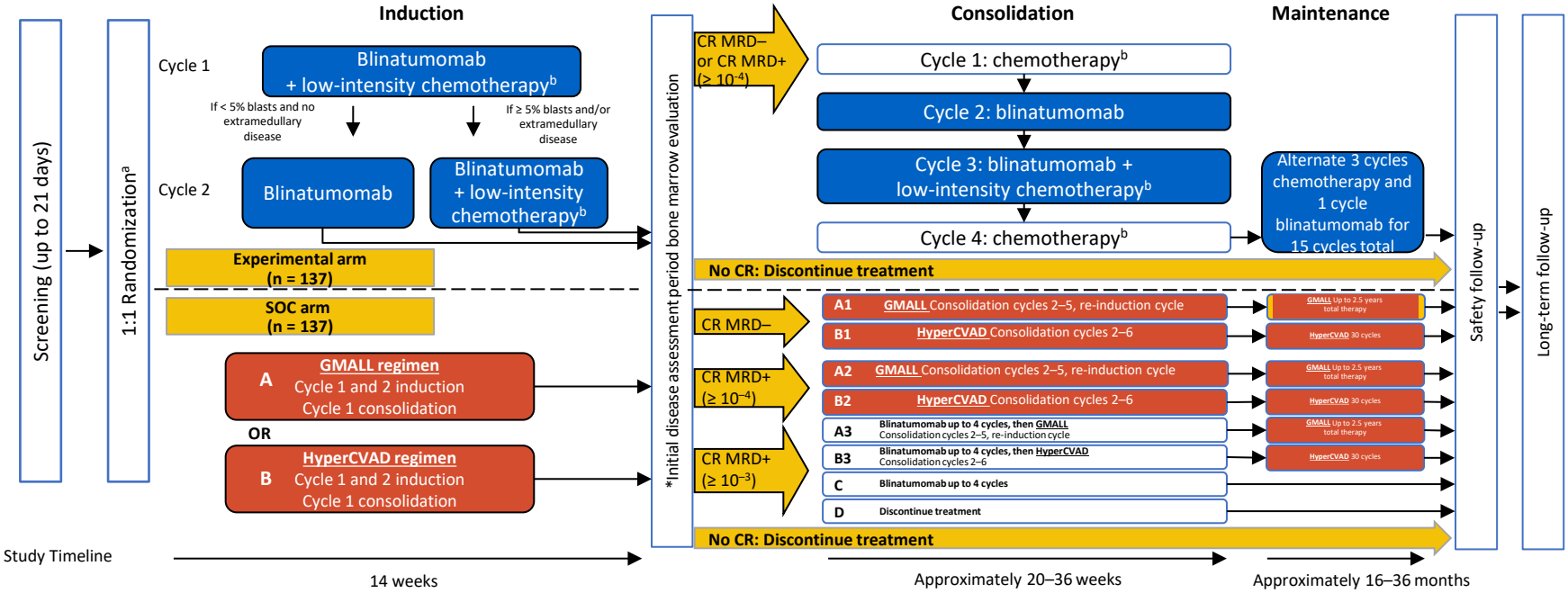
- Safety run-in: CR, MRD, RFS
- Phase 3: CR, MRD, RFS, safety, global health status

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. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, and virtual. Poster 2732.

Golden Gate study design



The GOLDEN GATE study: a 76 years-old lady enrolled into the experimental arm

- Sept 2024: diagnosis of Ph negative B-ALL with *BCR-ABL* like features (complex karyotype, deletion of ABL2 and CRFL2 rearrangement in FISH)
- Comorbidities:
  - cerebral vasculopathy
  - arterial hypertension
- Enrolled in Golden Gate trial experimental arm
- Sept-Oct 24 Induction-1 (low dose chemo+blina)

  Klebsiella pneumoniae KPC+ and E. coli ESBL+ sepsis

  CRS G2, ICANS G1, Steroid-related diabetes
- Nov-Dec 24 Induction-2 (blina)

Dec 2024: initial disease assesment:
CR with **MRD negativity** on PB and PNQ on BM

- Dec-Jan 2024: Consolidation-1 (iv MTX)
  - G3 ESBL+ E. coli sepsis
- Feb-Mar 25: Consolidation-2 (blina)

Disease assesment post Cons-2:
CR with MRD negativity

- Mar-Apr 25 Consolidation-3 (low dose chemo+blina)
- Consolidation-4 (iv MTX) ongoing

The GOLDEN GATE study: a 67 years-old gentleman enrolled into the experimental arm

- July 2024: diagnosis of Ph negative B-ALL NOS per WHO 2022 (EGIL B-II, CD20 negative)
- Comorbidities:
  - arterial hypertension
  - benign prostatic hypertrophy
- Enrolled in Golden Gate trial, standard arm (**GMALL**) Sept-Oct 24 Induction-1 (low dose chemo+blina)

11/06/24

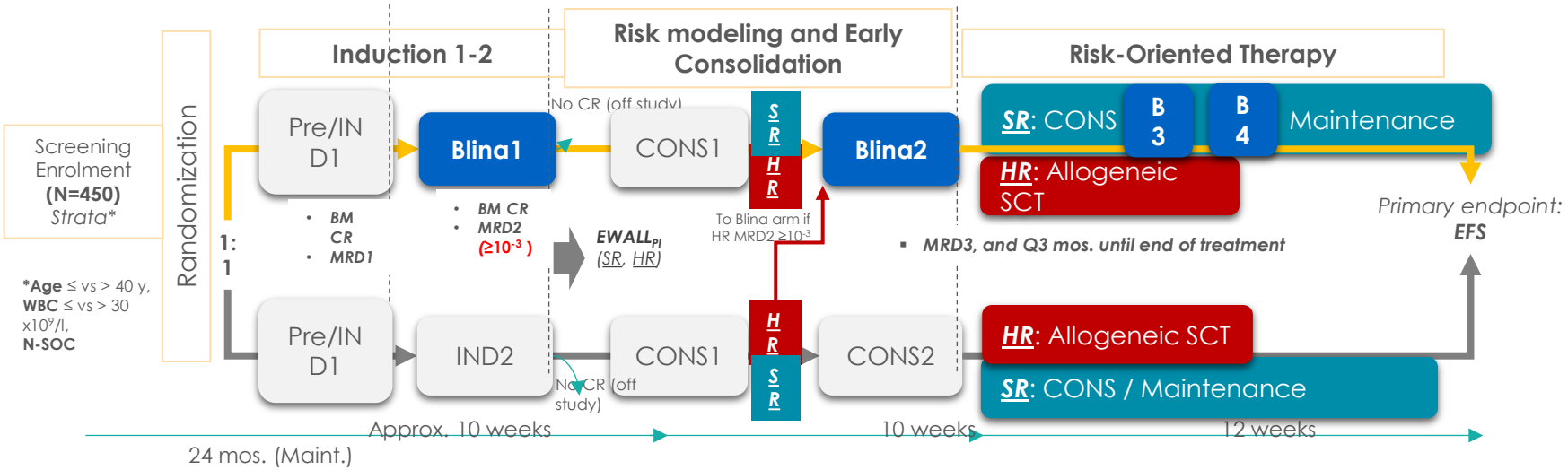
initial disease assesment

CR with **MRD positivity 10^-4** on PB and BM

Crossover to blinatumomab 4 cycles

- 2 ESBL+ E. coli sepsis, perianal abscess requiring surgery)
- Very slow hematological recovery
- No MUD or MMUD available for allogeneic transplant
- Post Ind-1 assessment: CR with MRD positivity (10^-3)

ACADEMIA TRIAL: International, multicenter, randomized Phase 3 trial with Blinatumomab SC in frontline



1° endpoint	Key 2° endpoints	Population
EFS: time from randomization (enrollment) until treatment failure defined as no CR/CRi or MRD ≥ 10-4 after Induction 2, molecular relapse ≥ 10-3, relapse, death for any cause whichever is earlier	• OS • QOL • other efficacy endoints • Safety	**Adults 18-55 years with ND B-ALL Ph-** Simple size: **450 pts** (225 per Arm)
4 Countries and groups involved: GIMEMA – Italy, HOVON – Netherlands, PETHEMA- Spain and NCRI AALL - Uk		

Poster Presentation (ASH) Meeting December 2023; San Diego, USA. (Chiaretti et al)

Conclusions

- Immunotherapy of ALL is changing the therapeutic landscape of adult ALL
- Targeting MRD is crucial for optimizing the therapeutic strategy, to avoid transplant when not necessary as well as to maximize its therapeutic value
- The front-line use of blinatumomab will decrease indication to transplant but transplant remains the consolidation treatment of choice for HR patients
- The SC formulation of blinatumomab has different pharmacokinetic and pharmacodynamic properties which favor higher rates of response

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