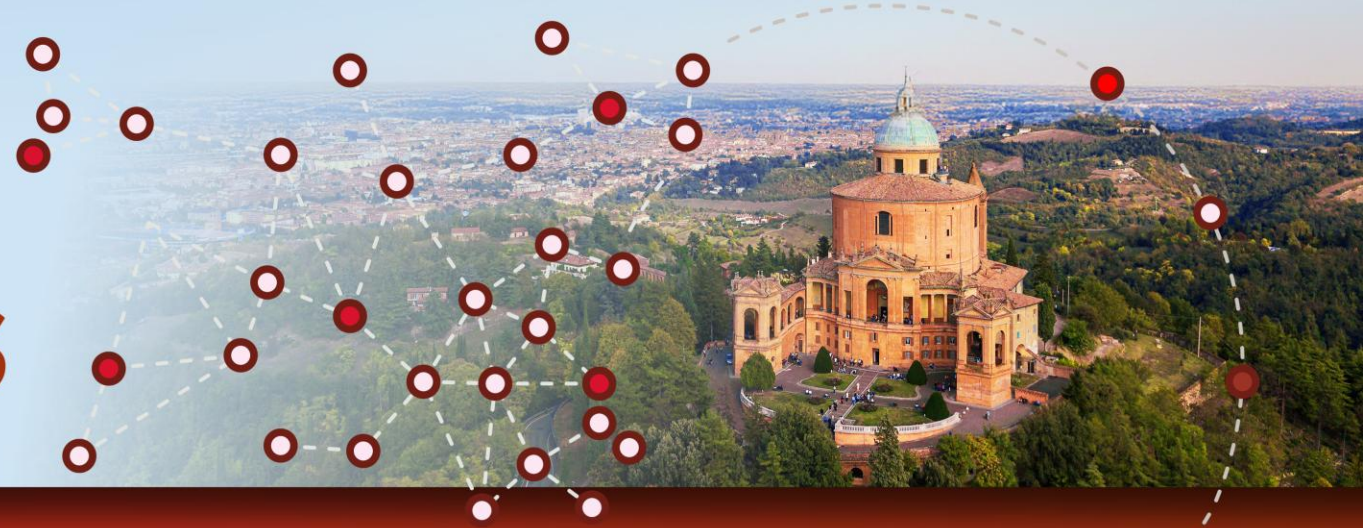
1ST INTERNATIONAL CONFERENCE ON

Ph+ Leukemias



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

New immunotherapy strategies in Ph+ ALL

Federico Lussana

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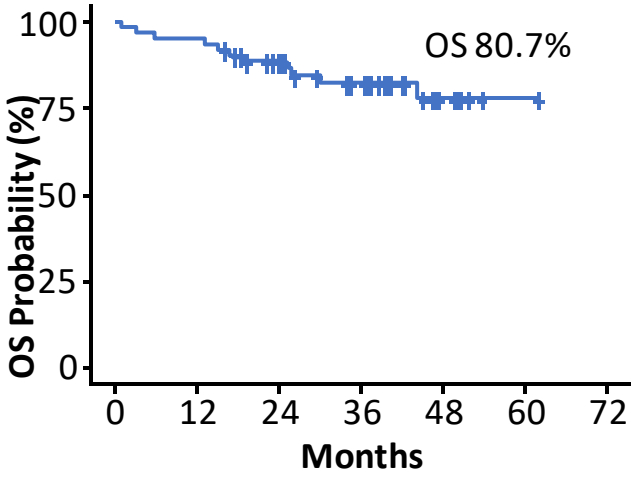
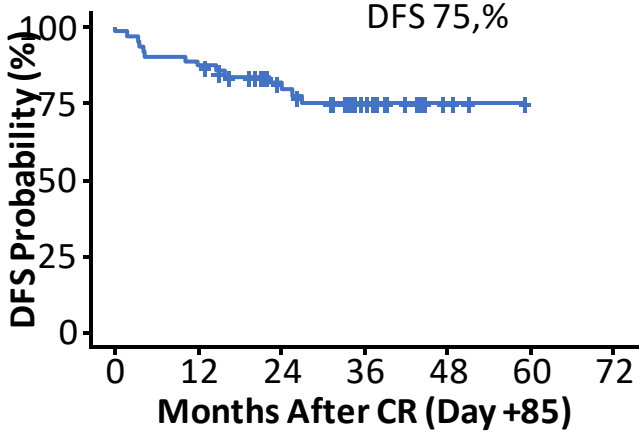
Disclosures Federico Lussana

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x	x	
Amgen					x	x	
Clinigen						x	
Incyte					x		
Jazz Pharmaceuticals					x		
Pfizer					x	x	

Efficacy of a chemo-free induction-consolidation strategy in Ph+ ALL

GIMEMA D-ALBA trial

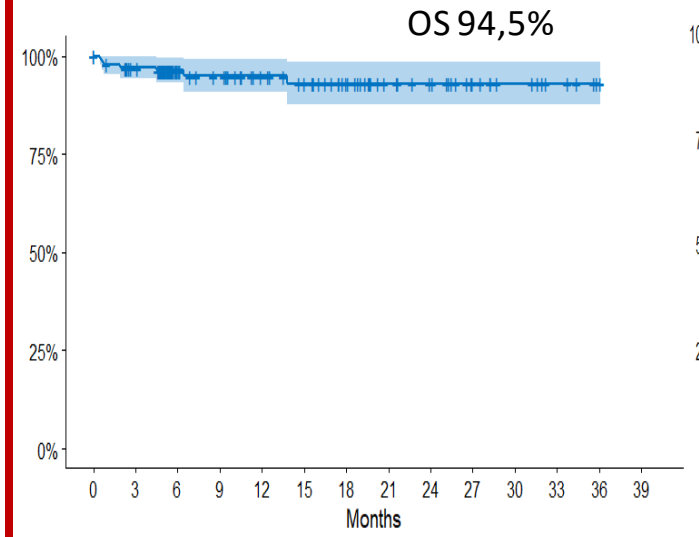


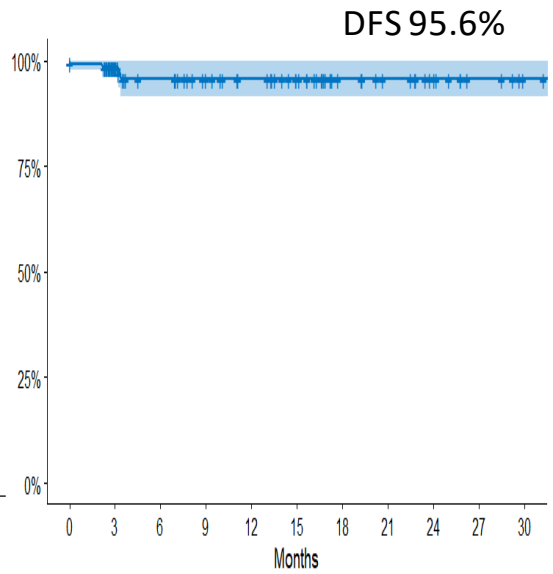


- Median FU: 53 months
- Primary endpoint: MRD negativity after 2 Blinatumomab cycles

Foà R et al. NEJM 2020 &. *J Clin Oncol.* **2024**;42:881-885.

GIMEMA ALL 2820 trial





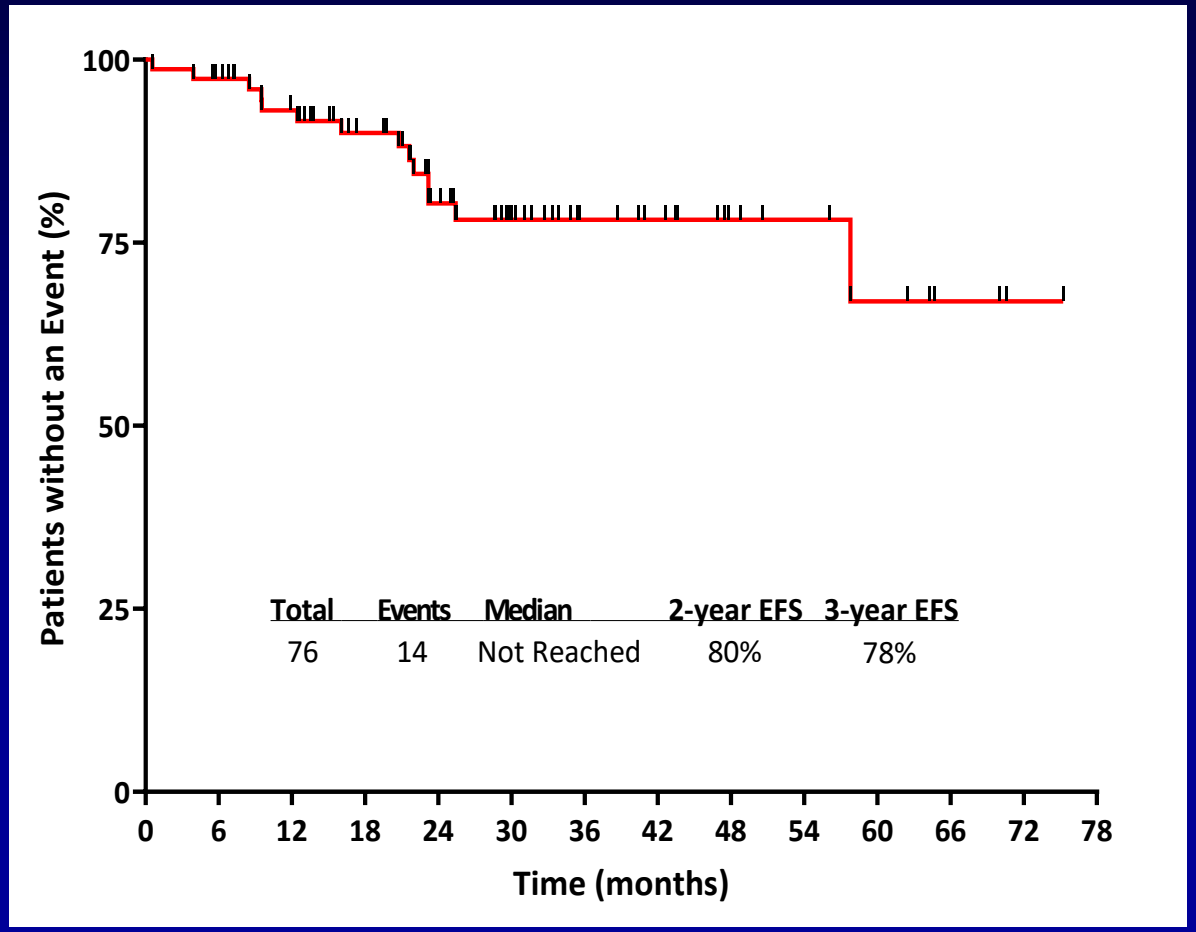
- Median FU: 8.5 months
- Primary endpoint: MRD negativity after 2 Blinatumomab cycles

Chiaretti et al, abs 835, ASH 2024

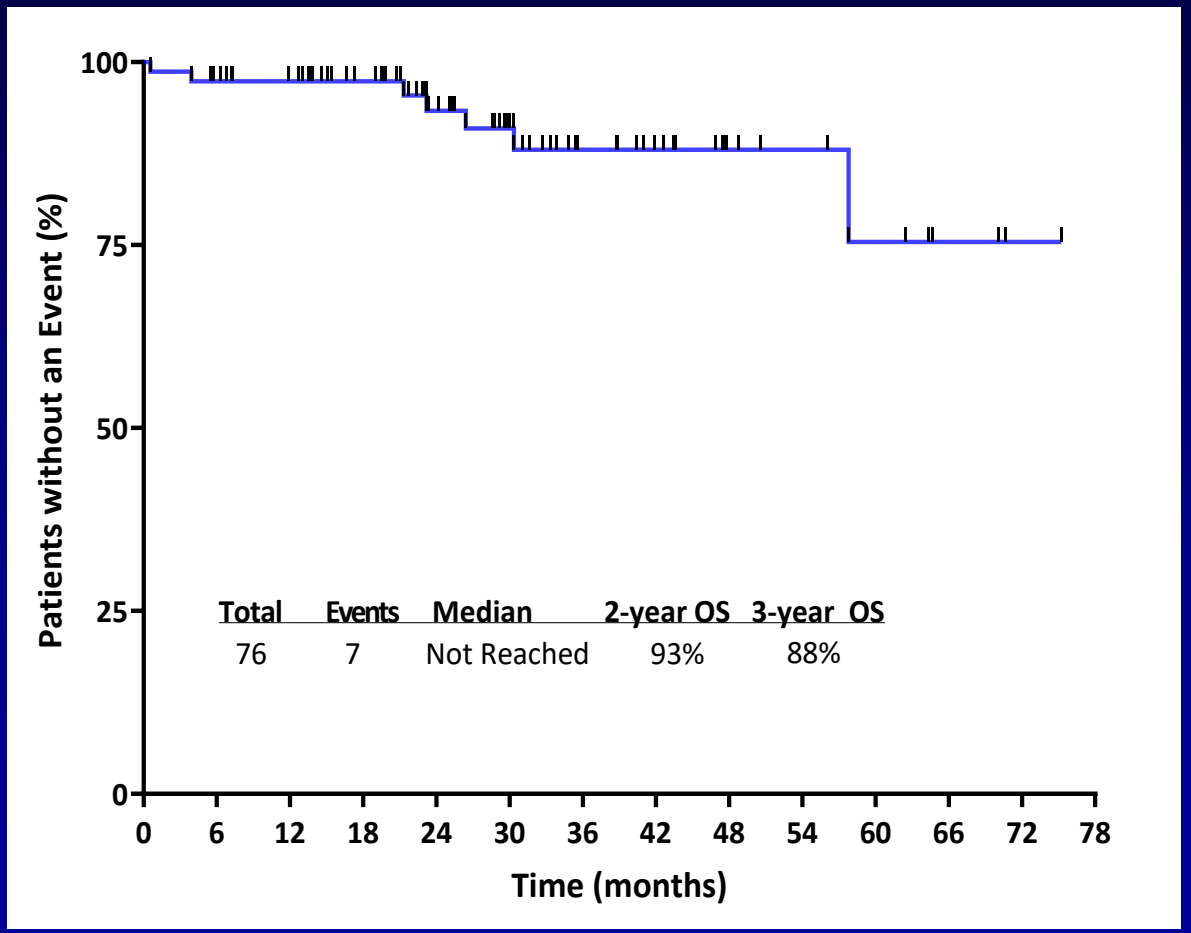
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 29 months (range, 5-75 months)

Event-Free Survival

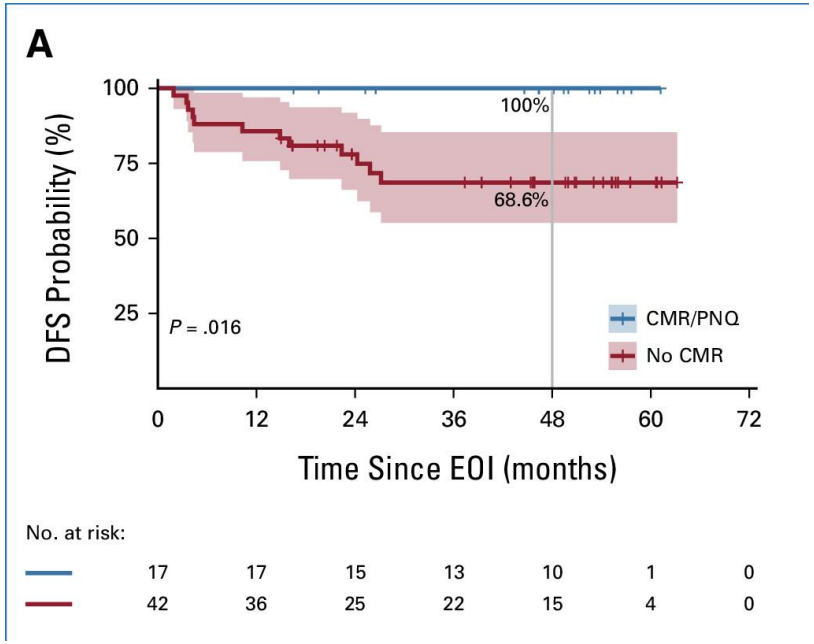


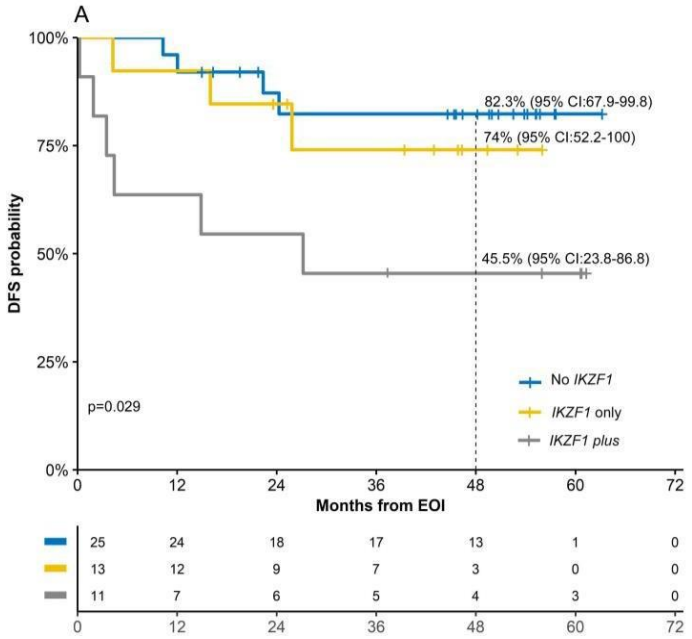
Overall Survival

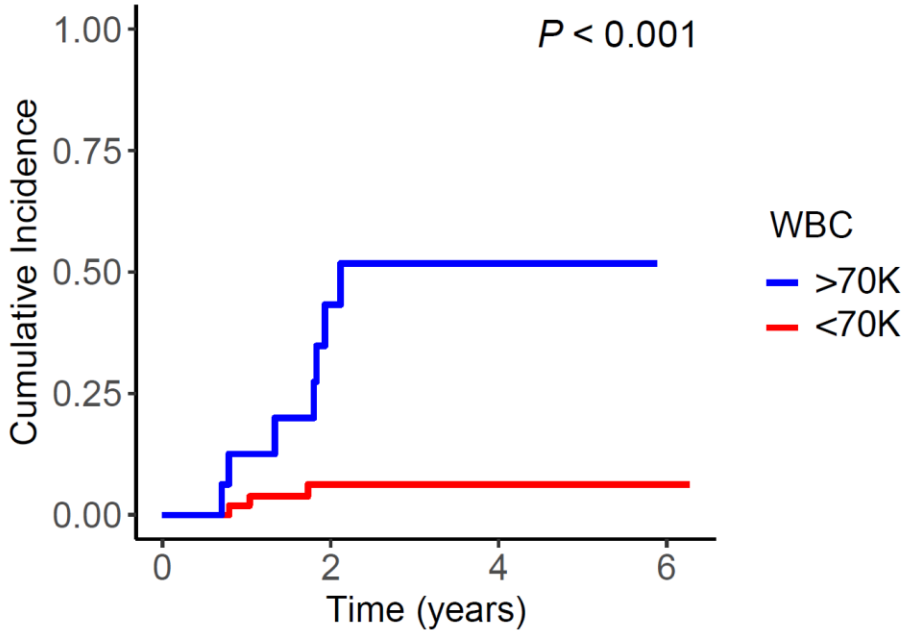


Kantarjian H et al, JCO 2024

Special concerns for patients receiving chemo-free strategies







- MRD
- *IKZF1*^{plus}
- WBC >70K
- CNS disease

Foà R et al. NEJM 2020 &. *J Clin Oncol.* **2024**;42:881-885; Kantarjian H et al, JCO 2024

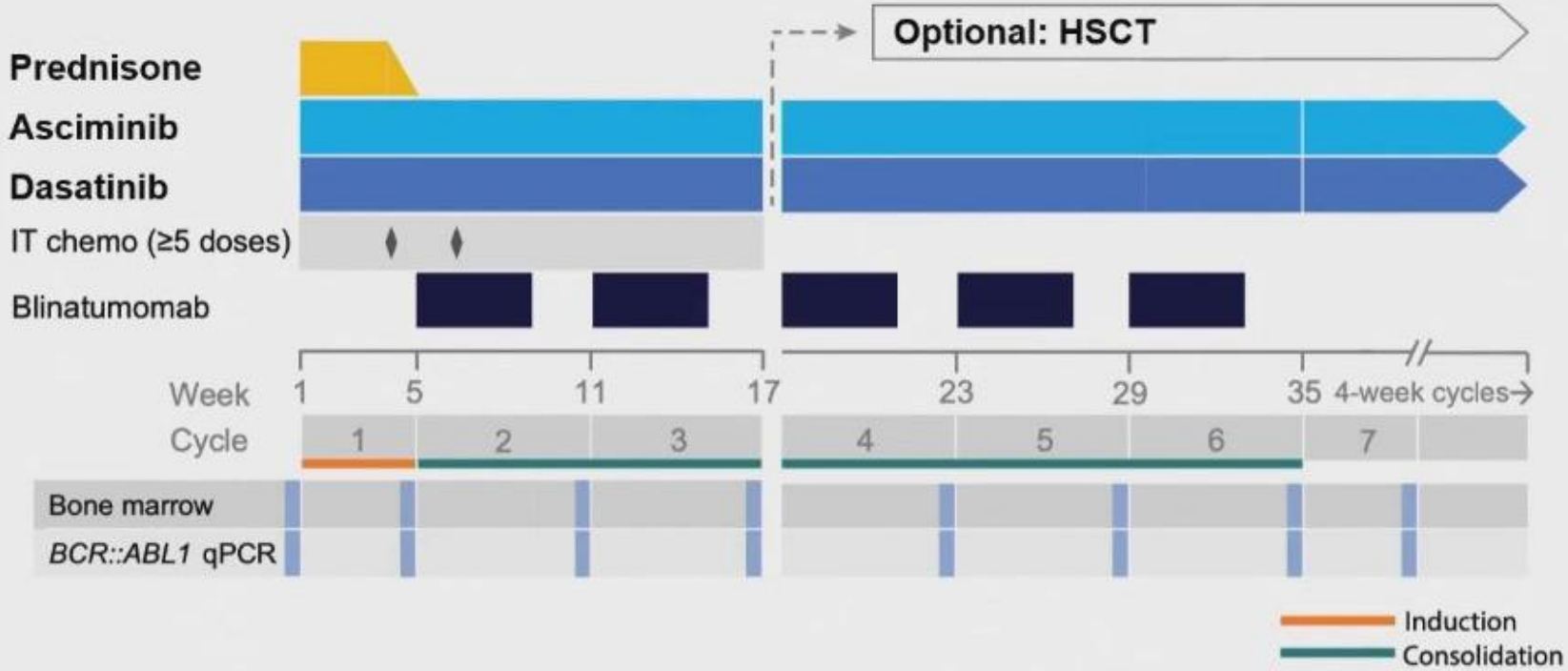
Can new immunotherapies improve these results?

1. Combining new TKIs with immunotherapies
2. New CD19 BITEs
3. CAR-T cells used upfront and new constructs

A phase I study of asciminib in combination with dasatinib, prednisone, and blinatumomab for Ph+ ALL in adults

Eligibility
≥ 18 years
Ph+ acute leukemia
Newly diagnosed

DLT definition
CTCAE v 5 non-heme toxicity gr 3+ during first combination cycle



Induction (28 days)
Asciminib 80 mg daily
Dasatinib 140 mg daily
Prednisone 60 mg/m^2 days 1-24

Consolidation
Asciminib 80 mg daily
Dasatinib 140 mg daily
Blinatumomab 28 mcg/day days 1-28/42-day cycle x 5

Maintenance
Asciminib 80 mg daily
Dasatinib 140 mg daily

Patients' characteristics

- Cohort enrolled 08/2023 – 09/2024 (data cut-off 04/02/25)

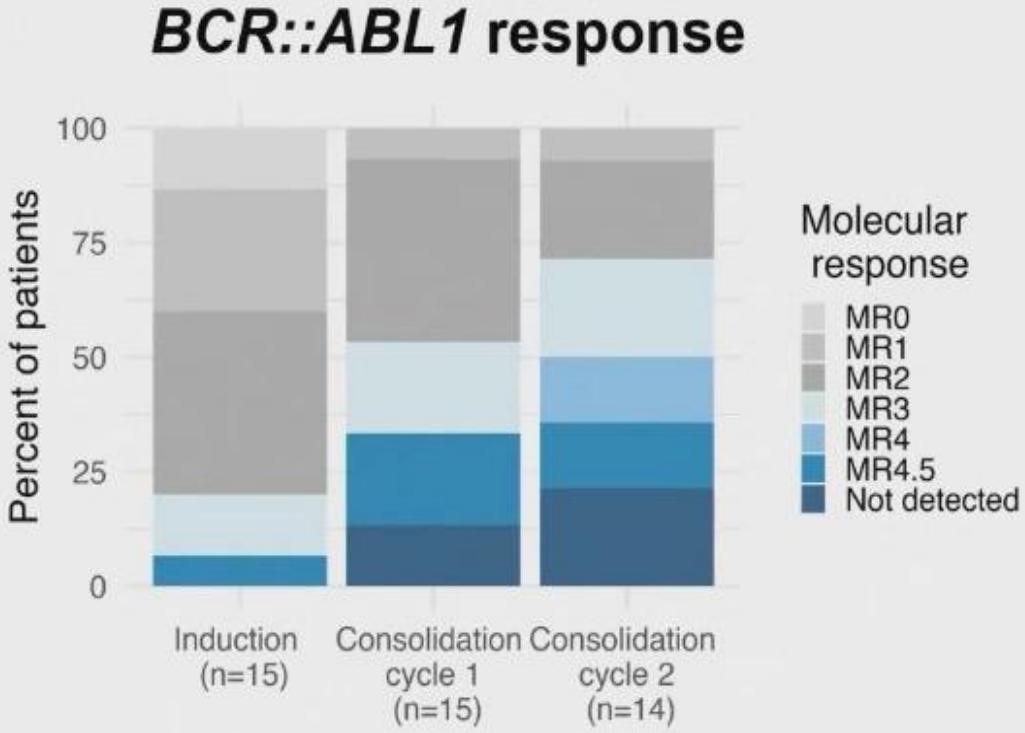
	Overall (n=15)
Age (years); median [min, max]	62 (25, 83)
≥ 60 years	**13 (87%)**
Sex	
Male	9 (60%)
Female	6 (40%)
Race	
White	13 (86.7%)
Black	1 (6.7%)
Other	1 (6.7%)
Ethnicity	
Non-Hispanic	14 (93.3%)
Hispanic	1 (6.7%)

	Overall (n=15)
Diagnosis	
De novo ALL	13 (86.7%)
CML blast crisis	2 (13.3%)
***BCR::ABL1* isoform**	
p190	11 (73.3%)
p210	4 (26.7%)
***IKZF1* plus**	
No	9 (60.0%)
Yes	5 (33.3%)
Unknown	1 (6.7%)
WBC; median (min, max)	11.1 (1.5, 176)
≥ 50 K/μL	3 (20%)

Responses

	Induction (asciminib, dasatinib, prednisone)	Blinatumomab Cycle 1 (asciminib, dasatinib, blinatumomab)	Blinatumomab Cycle 2 (asciminib, dasatinib, blinatumomab)[&]
Hematologic CR	**100%** (15/15)	**100%** (15/15)	**100%** (14/14)
Cytogenetic CR	**86%** (12/14)[#]	**100%** (15/15)	**100%** (14/14)
Flow MRD Negativity ($<10^{-4}$)	**79%** (11/14)[$]	**100%** (15/15)	**100%** (14/14)
***BCR::ABL1 MRD* response**			
MR1	**87%** (13/15)	**100%** (15/15)	**100%** (14/14)
MR2	**60%** (9/15)	**93%** (14/15)	**93%** (13/14)
MR3	**20%** (3/15)	**53%** (8/15)	**71%** (10/14)
MR4	**7%** (1/15)	**40%** (5/15)	**50%** (7/14)
MR4.5	**7%** (1/15)	**40%** (5/15)	**36%** (5/14)
Not detected	**0%** (0/15)	**13%** (2/15)	**21%** (3/14)
IGH NGS response*			
$<10^{-4}$	**67%** (6/9)[%]	**92%** (12/13)	**100%** (13/13)
$<10^{-6}$ (0-<1 transcripts)	**33%** (3/9)[%]	**77%** (10/13)	**85%** (11/13)

*clonoSeq assay, 2 of 15 patients not trackable by this assay; [%]4 patients not assessed after Induction
[#]failed karyotype; [$]missed assessment; [&]1 patient did not receive this cycle

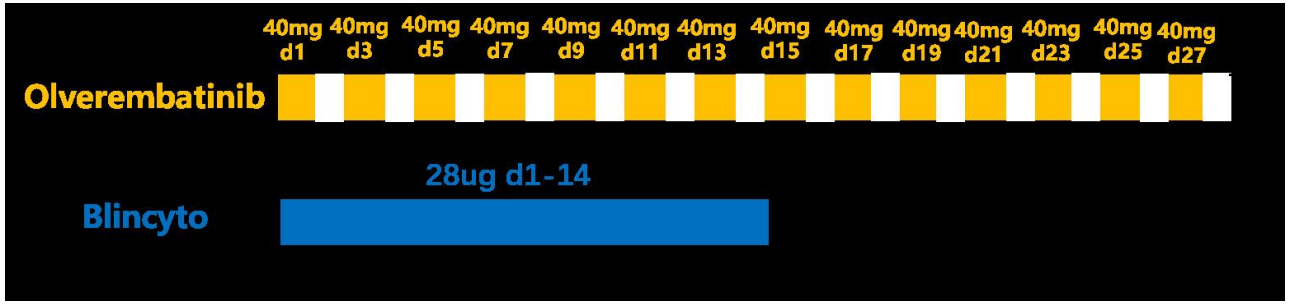


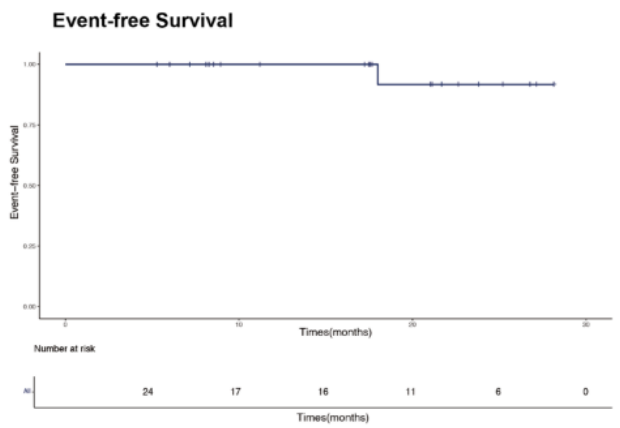
Central testing at Brigham and Women's Hospital Center for Advanced Molecular Diagnostics: *BCR::ABL1* mRNA RT-qPCR.

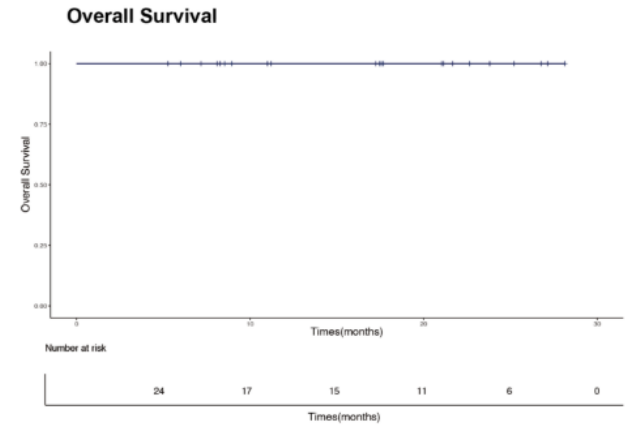
- p190 limit of detection = 0.001% (MR5)
- p210 limit of detection = 0.002% (MR4.7)

OLVEREMBATINIB AND BLINATUMOMAB FOR THE FRONTLINE TREATMENT OF Ph-POS OR Ph-LIKE ALL

- 24 patients (19 with Ph-positive ALL and 5 with ABL-class Ph-like ALL)
- Patients received olverembatinib (40mg once every other day) and blinatumomab (administered for 2 weeks followed by a two-week break)
- All patients (100%) achieved CR following one cycle of treatment.
- At 18 months, the OS rate was 100%, and the EFS rate was 91.6%.
- No dose interruptions or cardiovascular toxicities were observed.



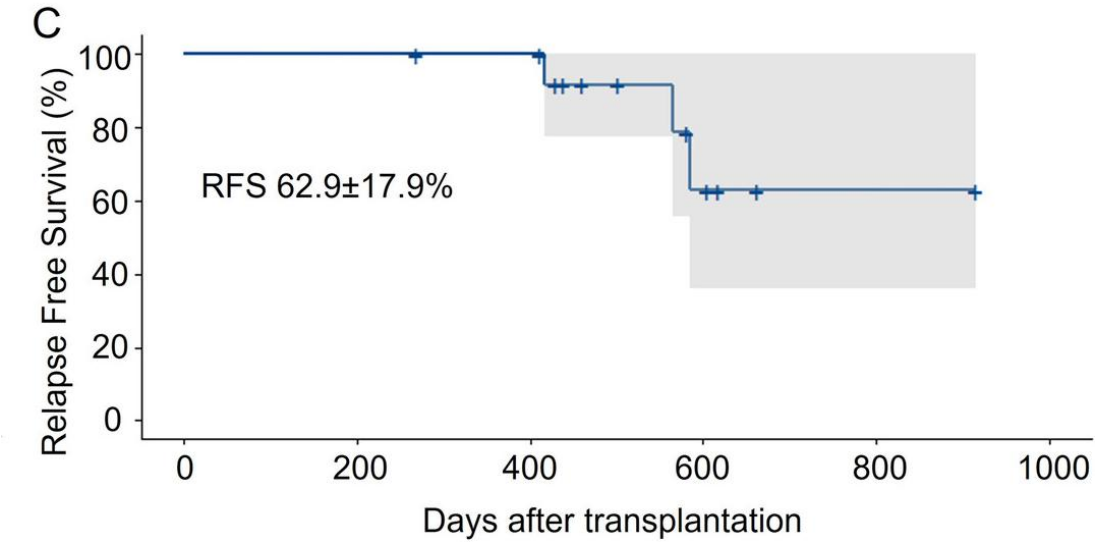


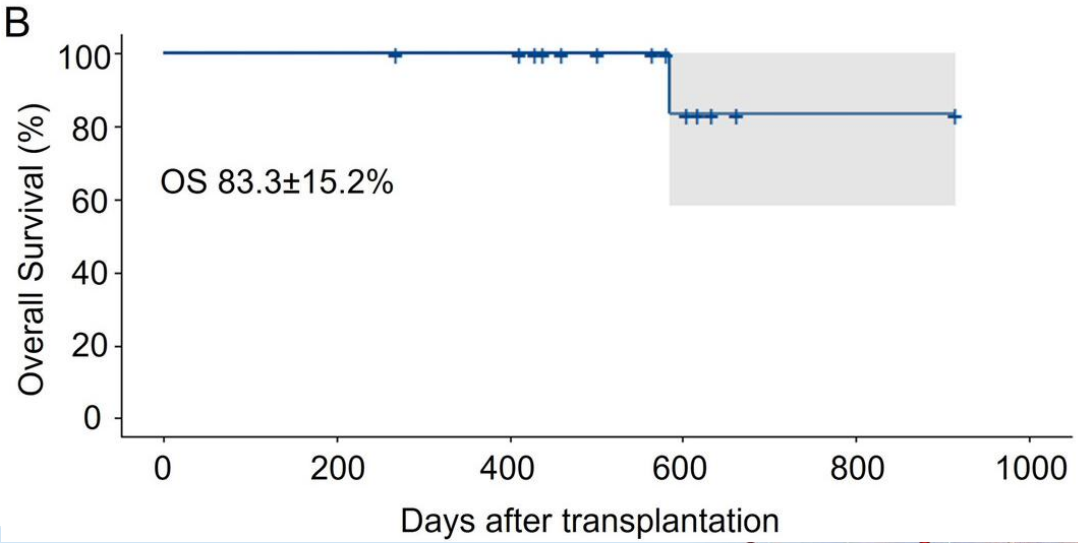


EHA Library. Xu X. 06/14/2025; 4160443; PS1367

Olverembatinib in Combination With Inotuzumab Ozogamicin for the Treatment of Adult Ph+ ALL Patients With R/R Disease or Persistent MRD

- Phase 2 study of 14 patients, 5 had hematological relapse and 9 MRD pos
- Therapy: olverembatinib (40 mg QOD, d1-28) combined with INO (0.6 mg/m2, d1, d8 per 28-day cycle)
- Enrolled patients received a maximum of two treatment cycles before proceeding to HSCT
- 2-year OS rate and RFS rate were 83.3% ± 15.2% and 62.9% ± 17.9%, respectively
- 9 patients (64.3%) successfully underwent bridged HSCT with no cases of VOD and a 100-day post-transplantation mortality of 0%.



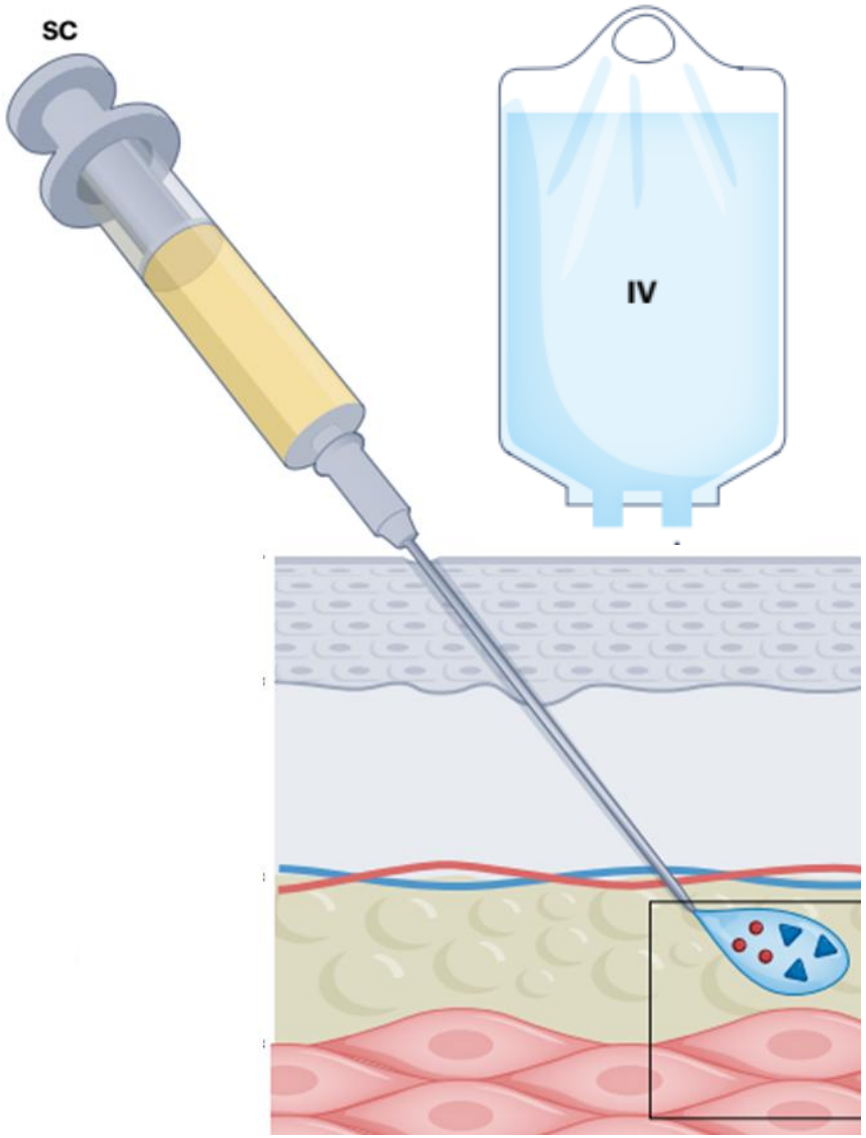


Zhang X et al. American J Hematol, 2025,

New immunotherapy strategies:

1. Combining new TKIs with immunotherapies
2. **New CD19 BITEs**
3. CAR-T cells used upfront and new constructs

Subcutaneous (SC) Administration of Blinatumomab



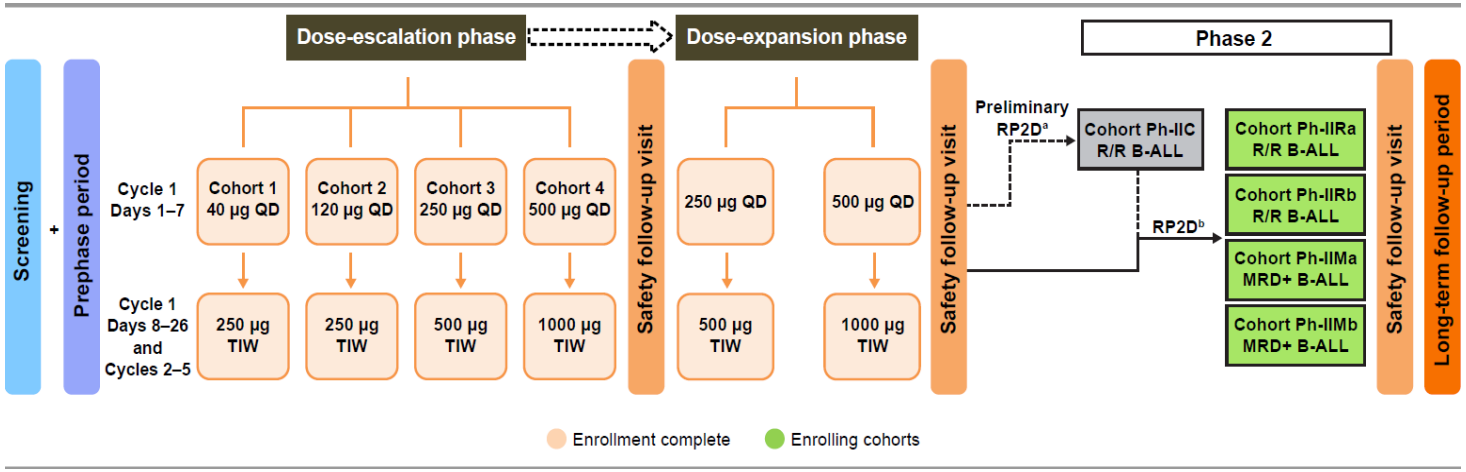
Blinatumomab as a continuous IV infusion is a standard treatment regimen utilized in patients with R/R B-ALL

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

Subcutaneous blinatumomab in R/R B-ALL

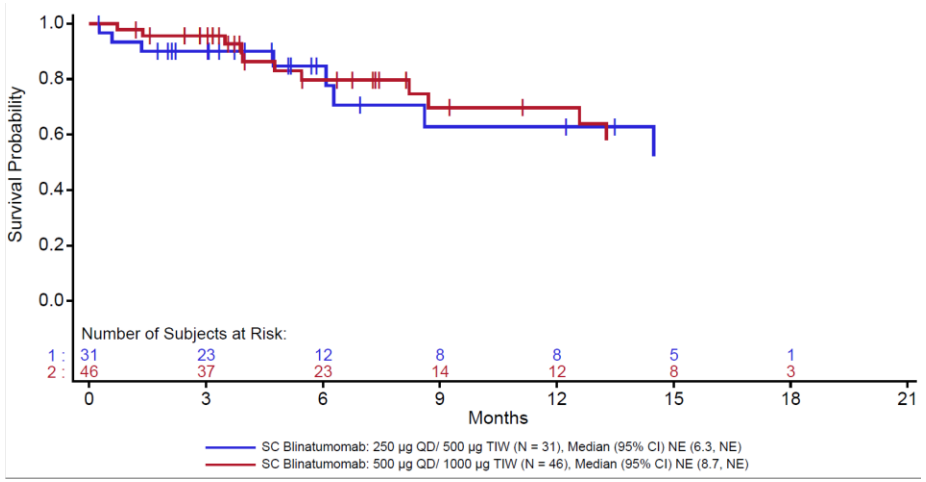


Jabbour E et al. Lancet Haematol 2025

Characteristics	250/500 µg group (N = 36)	500/1000 µg group (N = 52)
Male sex — n (%)	22 (61)	33 (63)
Age — years		
Mean	46 (19-78)	50 (19-76)
B-ALL Ph+, n (%)	7 (19)	8 (15)
Extramedullary disease, n(%)		
Yes	1 (3%)	3 (6%)
Prior therapy, n (%)		
Blinatumomab	8 (22)	9 (17)
CAR-T	7 (19)	7 (13)
HSCT	11 (31)	14 (27)
Inotuzumab	11 (31)	18 (35)

Subcutaneous blinatumomab: responses and outcomes

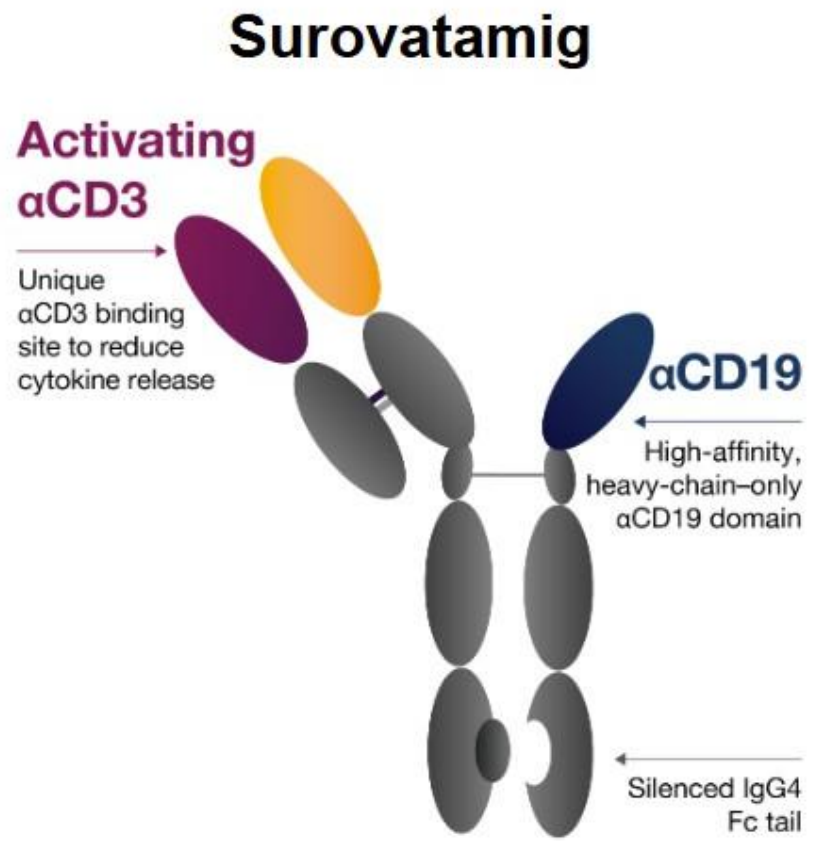
	250µg/500µg cohort N=36	500µg/1000 µg cohort N=52	Total N=88
Response within 2 cycles			
CR/CRh	27 (75%)	41 (79%)	68 (77%)
CR/CRh, MRD<10^{-4}	24/27 (89%)	38/41 (93%)	62/68 (91%)
CR/CRh/CRi	32 (89%)	48 (92%)	80 (91%)
CR/CRh/Cri, MRD<10^{-4}	29/32 (91%)	43/48 (90%)	72/80 (90%)



Jabbour E et al. Lancet Haematol 2025

Surovatamig

- Surovatamig, previously known as AZD0486, is a novel IgG4 fully human CD19×CD3 bispecific T-cell engager[1] designed for low-affinity CD3 binding to reduce cytokine release from T-cell activation while preserving T-cell cytotoxicity against malignant B cells
- A phase 1, FIH trial in patients with B-NHL (NCT04594642) demonstrated activity and tolerability of surovatamig in R/R FL and DLBCL[2,3]
- Here, we present the preliminary results from a dose-escalation study of surovatamig in patients with R/R B-ALL (SYRUS; NCT06137118)



B-ALL, B-cell acute lymphoblastic leukemia; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FC, fragment crystallizable; FIH, first-in-human; FL, follicular lymphoma; IgG, immunoglobulin G; R/R, relapsed/refractory.

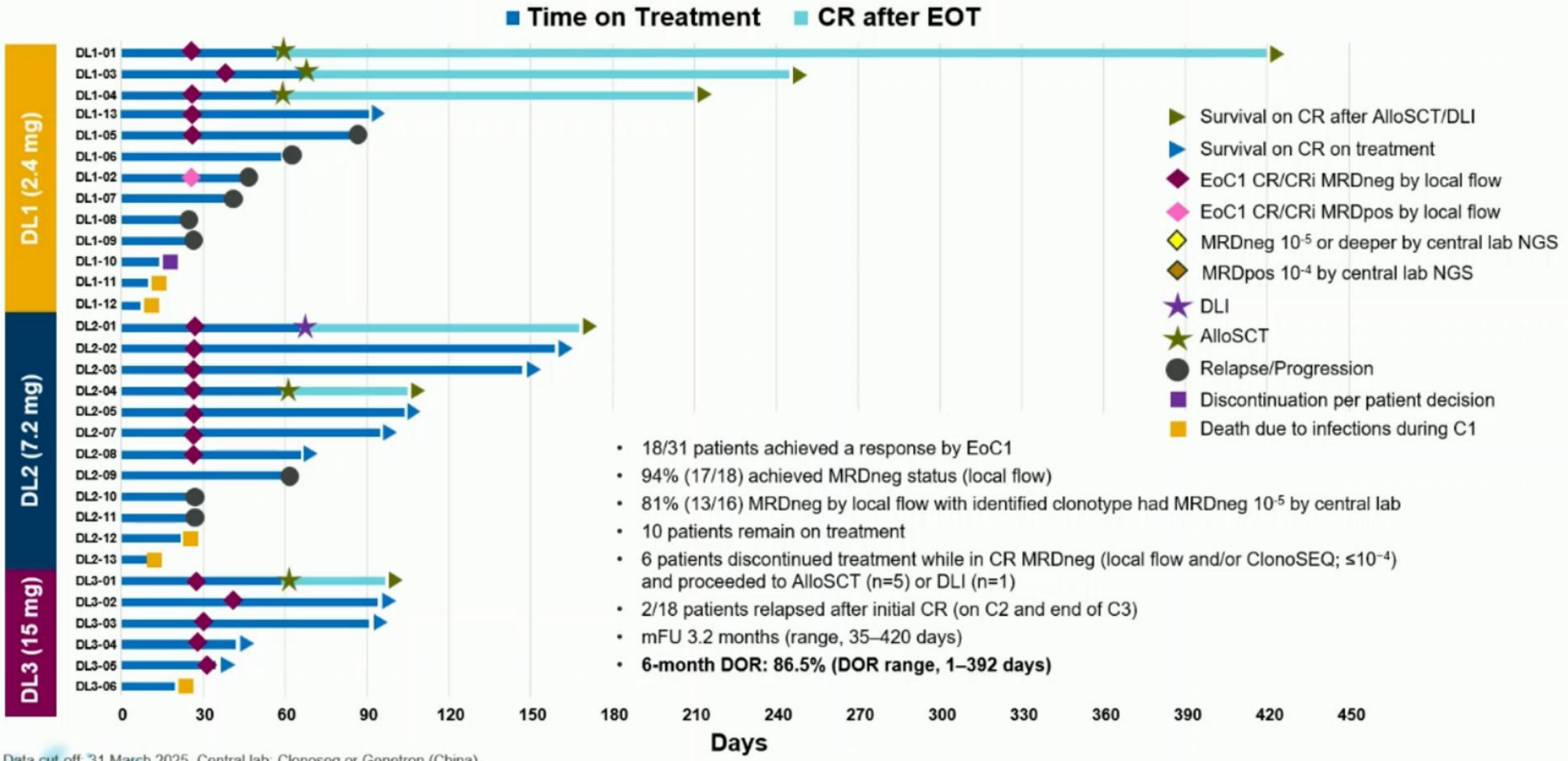
1. Malik-Chaudhry HK, et al. *MAbs*. 2021;313:1890411. 2. Hou JZ, et al. *Blood*. 2024;144(Suppl 1):341. 3. Gaballa S, et al. *Blood*. 2024;144(Suppl 1):868.

Patients Enrolled in SYRUS Were Heavily Pre-treated, Many With Prior CD19 Therapy Exposure

Characteristic	Total (N=31) n (%)
Age, median (range), y	56 (17–75)
Female	13 (42)
Ph (+)	6 (19)
Median (range) prior therapies	3 (2–9)
Prior CD19 targeted therapy exposure	19 (61)
Blinatumomab-exposed	16 (52)
CAR-T-exposed	11 (35)
Double-exposed	8 (26)
Allo-SCT	10 (32)
Mean (range) bone marrow blasts	61% (5%–97%)
≥50% bone marrow blasts	21 (68)

Values are n (%) unless otherwise specified.
Allo-SCT, allogeneic stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy; Ph (+), Philadelphia chromosome positive; y, years.

Response Assessment at End of C1



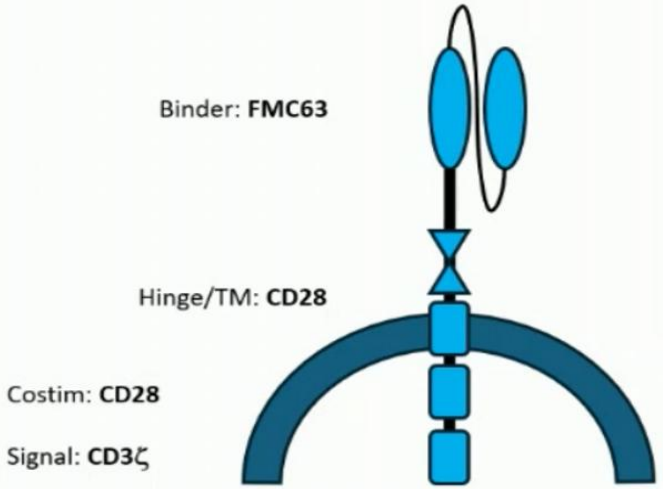
- 18/31 patients achieved a response by EoC1
- 94% (17/18) achieved MRDneg status (local flow)
- 81% (13/16) MRDneg by local flow with identified clonotype had MRDneg 10^{-5} by central lab
- 10 patients remain on treatment
- 6 patients discontinued treatment while in CR MRDneg (local flow and/or ClonoSEQ; $\leq 10^{-4}$) and proceeded to AlloSCT (n=5) or DLI (n=1)
- 2/18 patients relapsed after initial CR (on C2 and end of C3)
- mFU 3.2 months (range, 35–420 days)
- **6-month DOR: 86.5% (DOR range, 1–392 days)**

Data cut-off: 31 March 2025. Central lab: Clonoseq or Genetron (China).
AlloSCT, allogeneic stem cell transplant; C, cycle; CR, complete response; CRi, complete response with incomplete count recovery; DL, dosing level; DLI, donor lymphocyte infusion; DOR, duration of response; EoC1, end of cycle 1; EOT, end of treatment; mFU, median follow-up; MRDneg/MRDpos, minimal residual disease negative/positive.

1. Combining new TKIs with immunotherapies
2. New CD19 BITEs
3. **CAR-T cells used upfront and new constructs**

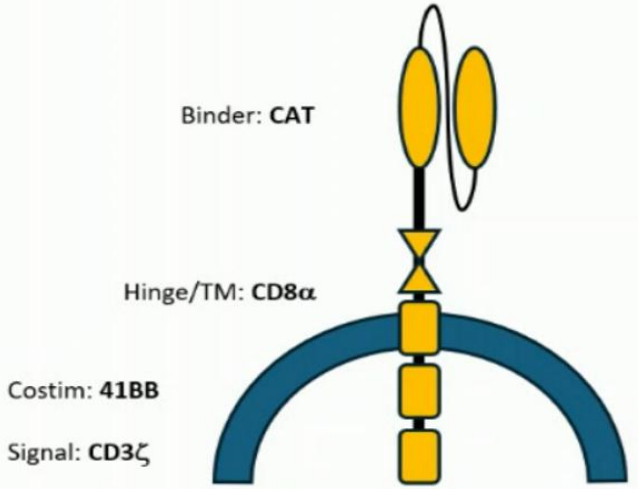
CAR-T cell therapy in adult B-ALL

Brexucabtagene Autoleucel



Manufacturing: 13d (92%)
Infused: 77%
LD: Flu 25x3, Cy 900x1
Cell Dose: $1x10^6$/kg

Obecabtagene Autoleucel



Manufacturing: 21d (95%)
Infused: 80%
LD: Flu 30x4, Cy 500x2
Cell Dose: $410x10^6$ (split dose)

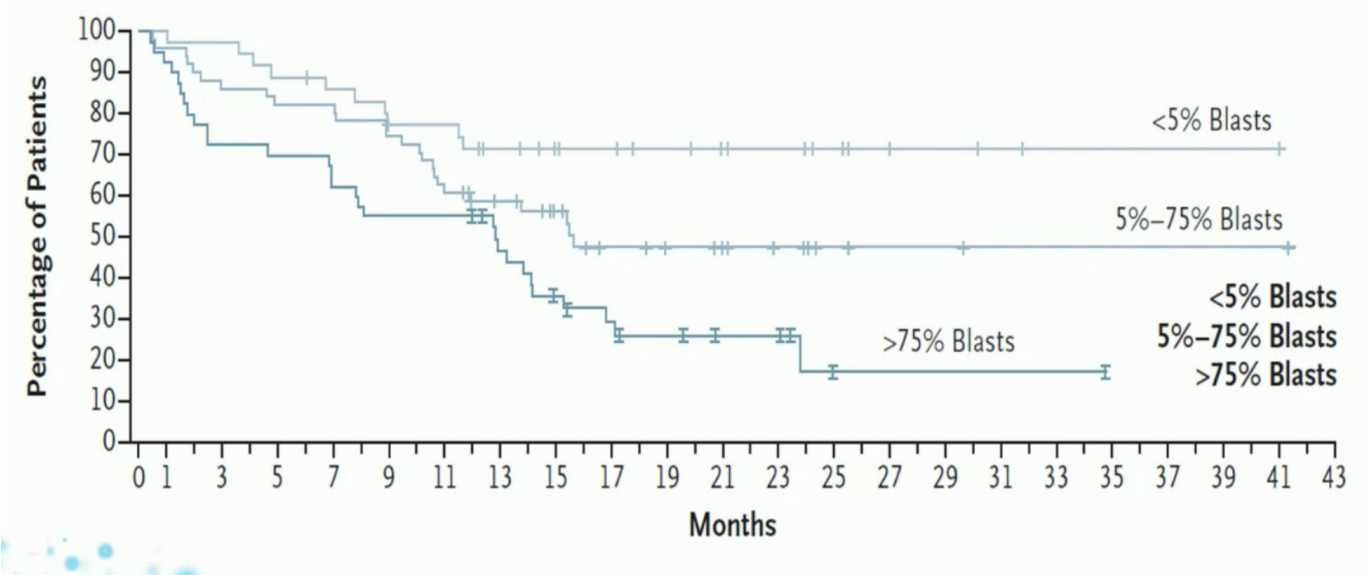
Main clinical outcomes after blinatumomab or inotuzumab ozogamicin or brexu-cel or obe-cel in Relapsed/Refractory Adult BCP-ALL

Study	CR/CRi	Duration of Remission (months)	Progression or Event or Relapse Free Survival (months)	Median Overall Survival (months)
INOvate (Inotuzumab arm)	80.7%	4.6	Median PFS: 5 months	7,7
Tower (blina arm)	34%	7.2	EFS at 6 months: 31%	7,7
Zuma-3	71%	12·8	Median RFS: 11.6 months	18,2
Felix	77%	21.2	Median EFS: 11.9 months	15,6

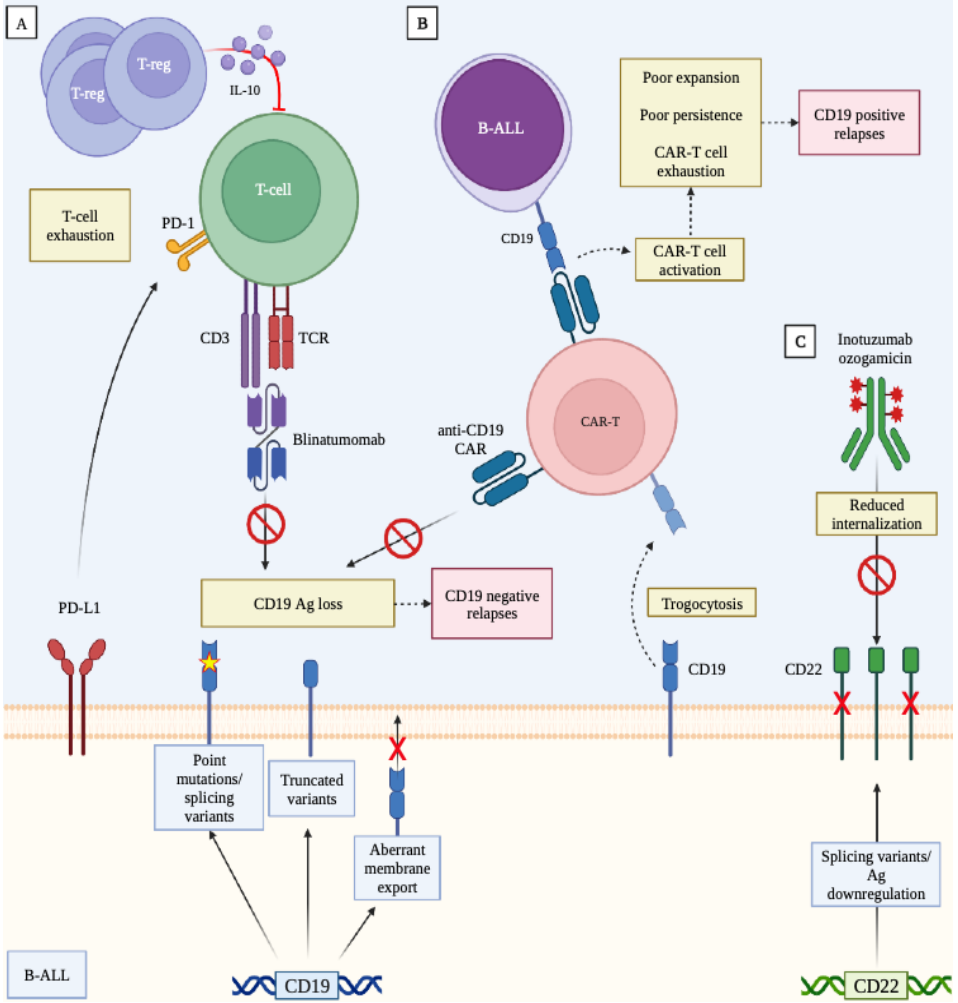
Kantakjian H et al.: N Engl J Med 2016;375:740-53. DOI: 10.1056/NEJMoa1509277
Kantarjian H et al.: N Engl J Med 2017;376:836-47. DOI: 10.1056/NEJMoa1609783
Shah BD, et al. Lancet 2021;398:491-502
Roddie C et al. N Engl J Med 2024;391:2219-2230

Mechanisms of resistance to the CAR-T

- Low tumor burden impact on OS
- Immune escape, primarily antigen loss
- T-Cell exhaustion

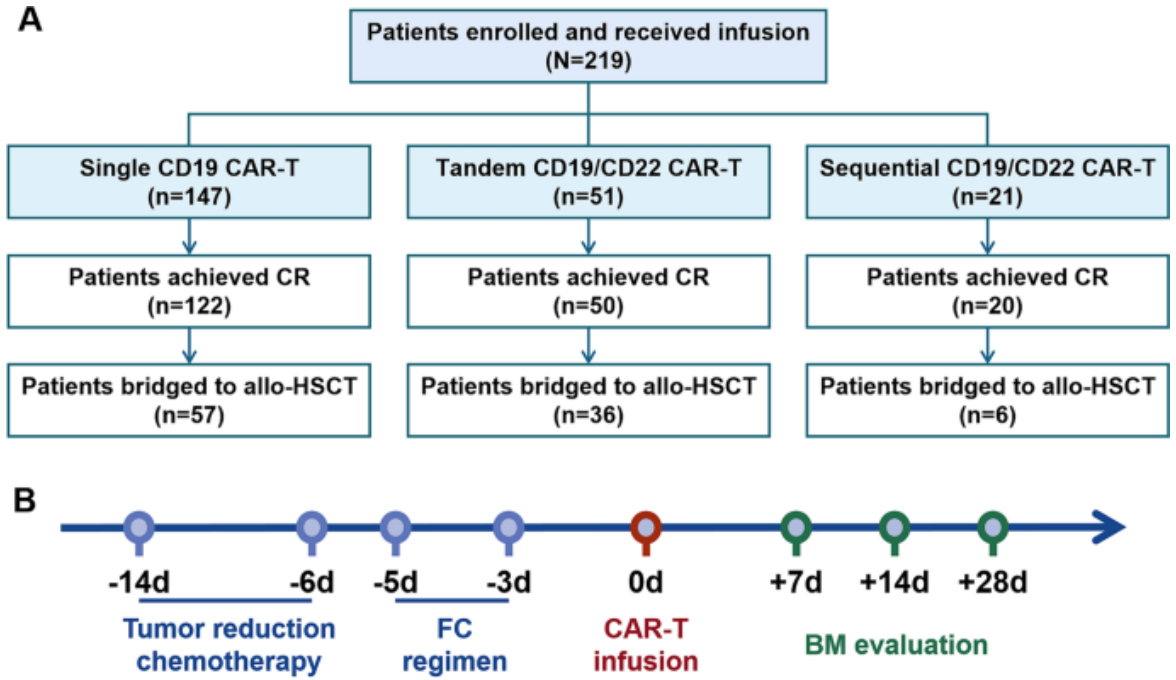


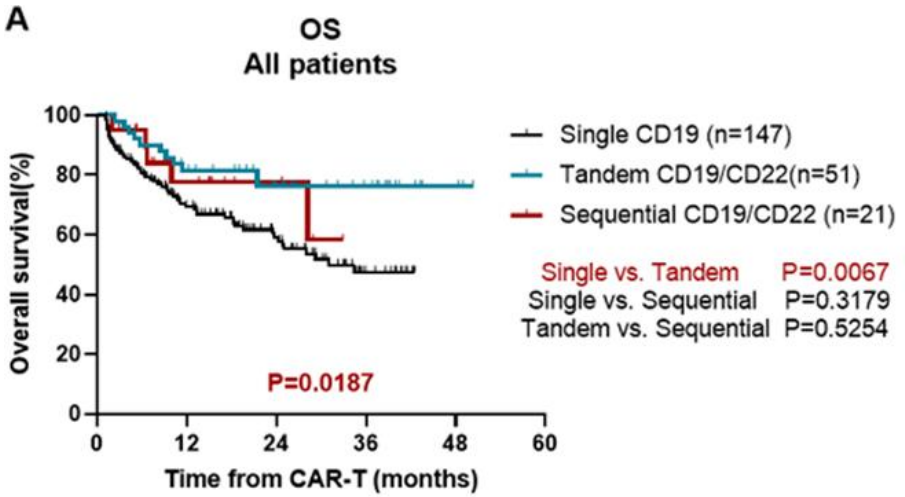
Roddie C et al. NEJMs 2024

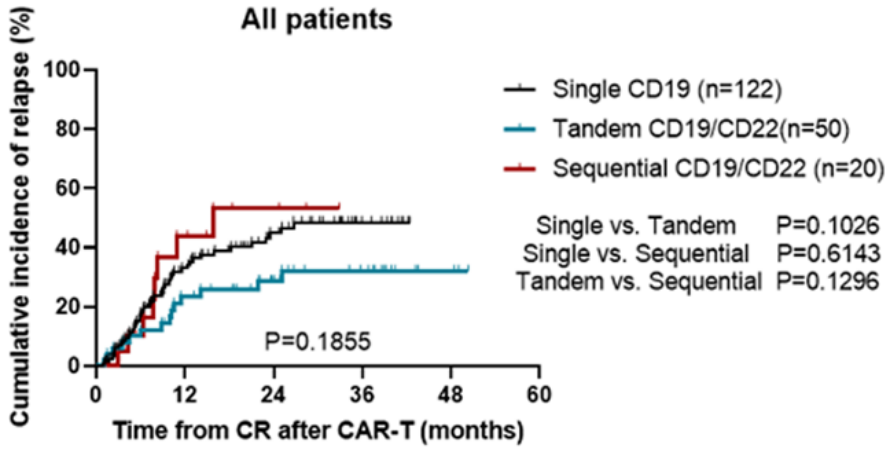


Lussana F et al. Cancers 2023

Single-target (CD19) or dual-target (tandem or sequential CD19/CD22) CAR T-cell therapy?

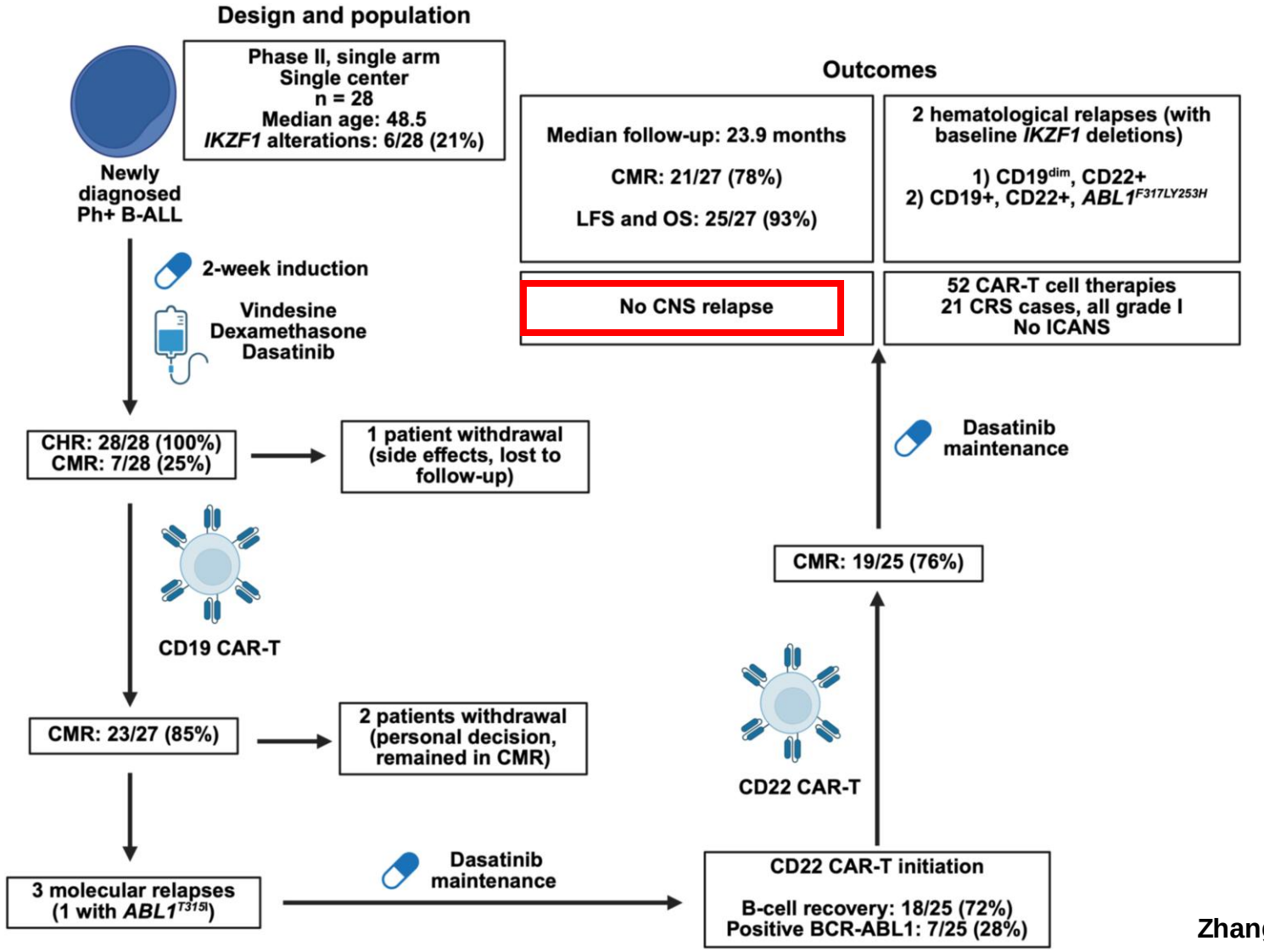






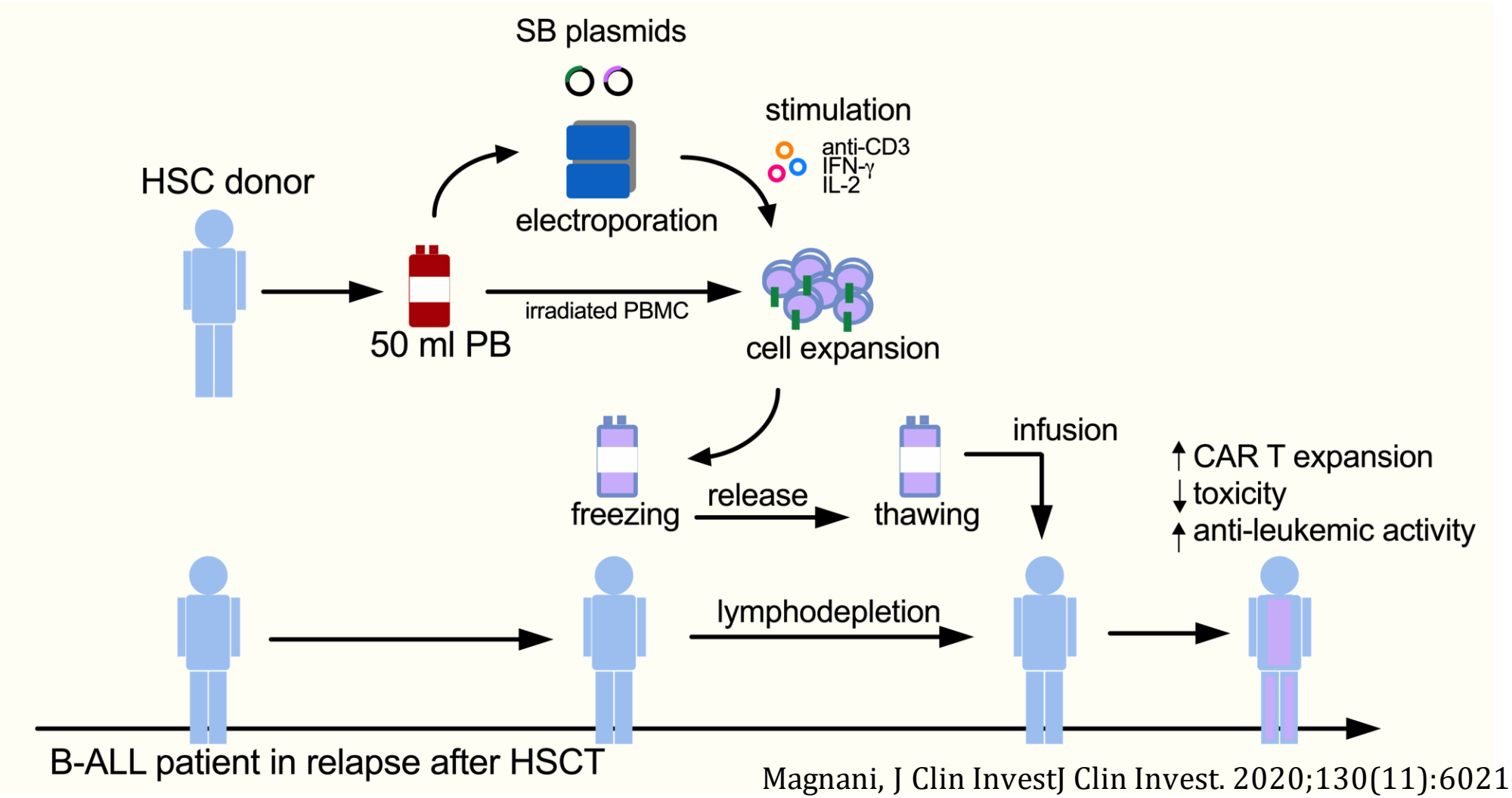
Liu S. et al. Blood Cancer Journal 2023

Dasatinib+CAR-T newly diagnosed Ph+ALL



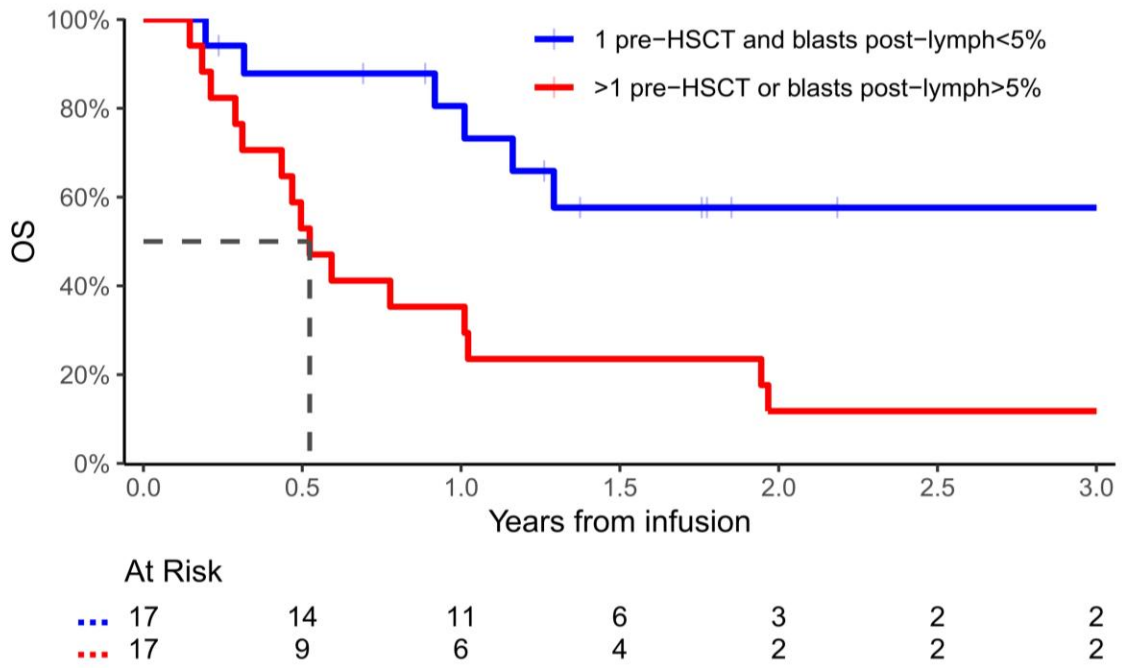
Zhang M et al. JAMA Oncology 2025

A non-viral platform to generate allogeneic CAR-T cells

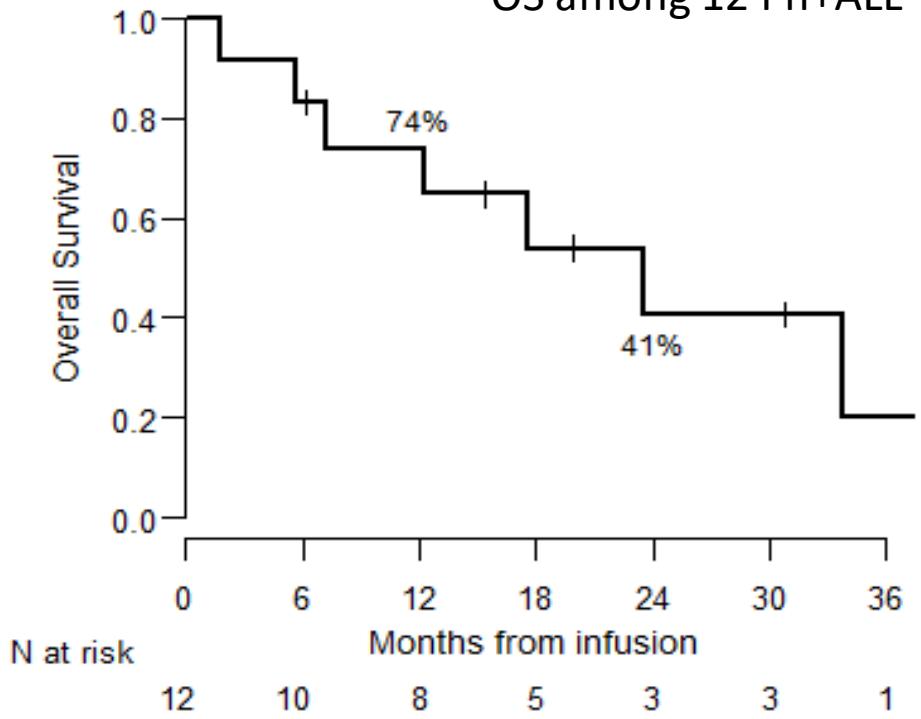


Magnani, J Clin InvestJ Clin Invest. 2020;130(11):6021-6033
Lussana F et al. Blood Cancer Jpiurnal 2025

Allogeneic CAR-T: the efficacy of anti CD19 CARCIK



OS among 12 Ph+ALL



Lussana F, et al. *Blood Cancer Journal*, 2025

Conclusions

- New immunotherapies continue to revolutionize Ph+ ALL treatment

- The future of Ph+ ALL therapy is **BRIGHT**
  - Upfront immunotherapy for all patients
  - Minimizing cytotoxic chemotherapy and reducing the need for alloHSCT consolidation

- The optimal timing and sequencing of CAR-T cell therapy in the context of modern treatment options for Ph+ ALL remains an area of active investigation

- The global implementation of these therapies faces challenges
  - Limited worldwide access/COST
  - Long-term data and more patients are critical to understand the curative potential of new approaches compared to other more sustainable strategies
  - Unclear long-term toxicities

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