2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

This activity is jointly provided by Partners for Advancing Clinical Education and Bio Ascend

CD19 Targeting in B-ALL: When to Use CAR T-Cells vs T-Cell Engagers.

Martha Arellano, MD

Professor and Associate Director, Hematology

Program Director, Hematology & Medical Oncology Fellowship

Winship Cancer Institute of Emory University

July 24, 2025

Disclosures

Consultant/Advisor/Speaker: SYNDAX Pharmaceuticals

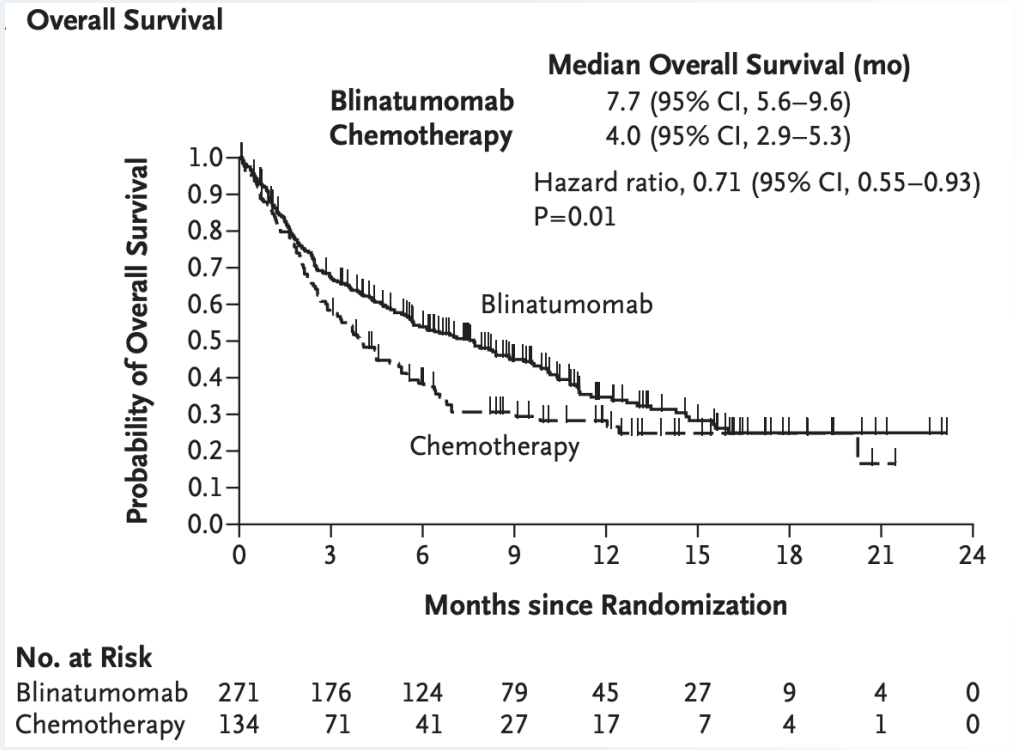
CD19 Targeting in B-ALL: When to Use CAR T-Cells vs T-Cell Engagers.

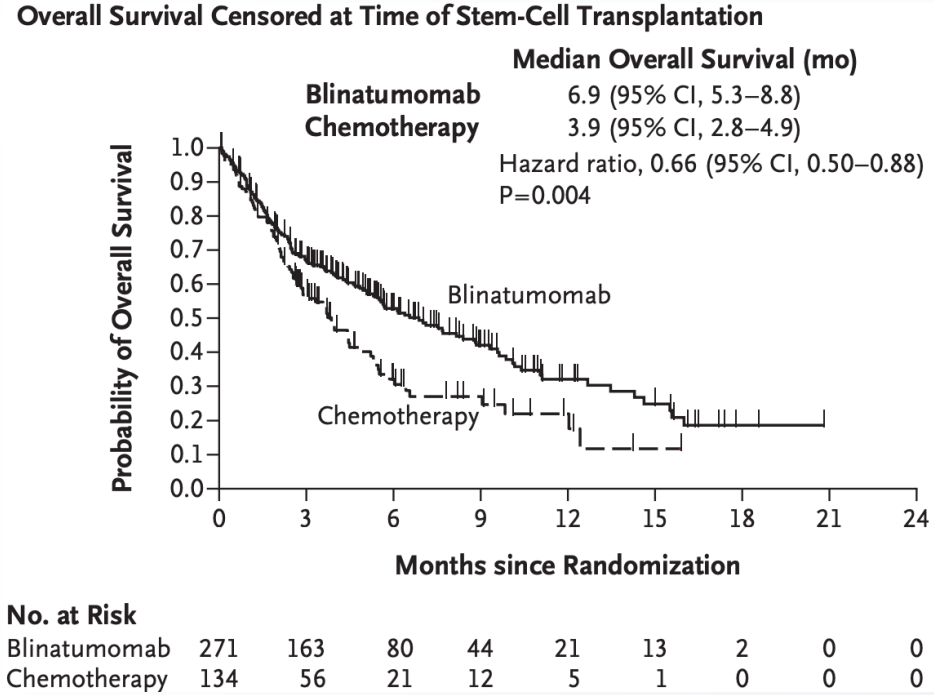
Objectives:

- Optimal timing for use of T-cell engagers in B-ALL
- CAR T-cells in the R/R setting
- Moving CAR T-cells to earlier lines of therapy?

Blinatumomab for Advanced B-cell ALL

- Multi-institutional phase 3 trial, randomly assigned adults with R/R B-cell ALL, in a 2:1 ratio, to blinatumomab or standard-of-care chemotherapy.
- Primary end point was overall survival.
- Full FDA approval in 2017 for R/R B-ALL

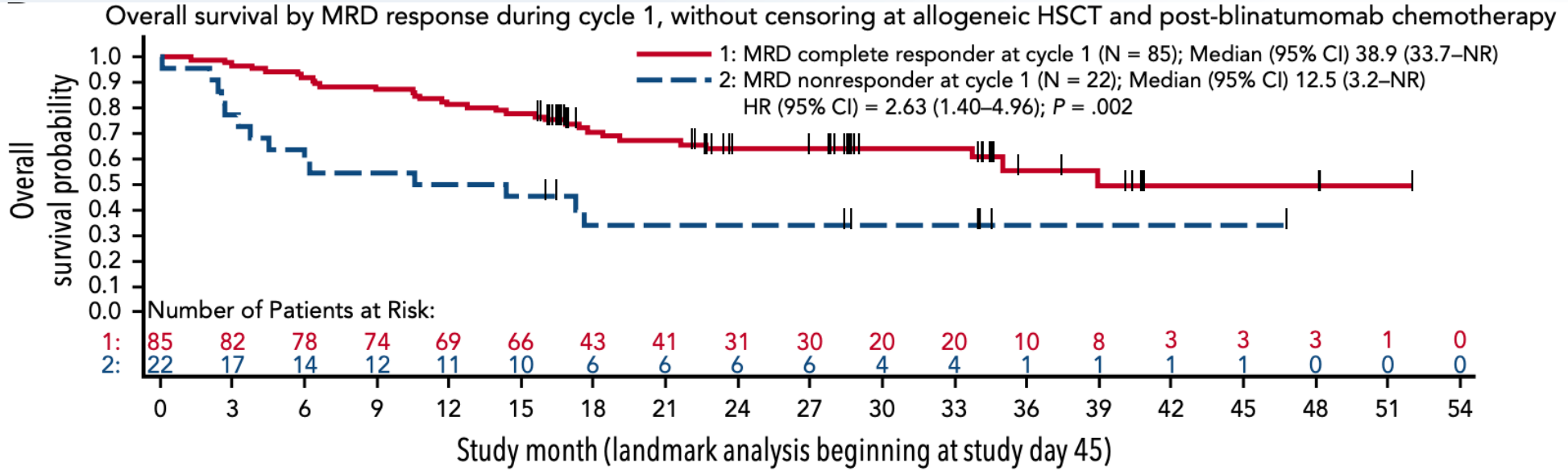




Kantarjian H, Stein A, Gökbuget N, Fielding AK..., Topp MS. N Engl J Med. 2017 Mar 2;376(9):836-847. doi: 10.1056/NEJMoa1609783. PMID: 28249141; PMCID: PMC5881572.

If Blinatumomab works late in B-ALL why not use it earlier in the disease??

Blinatumomab for ALL in MRD-Positive Complete Remission



- ✓ Undetectable MRD in 81.4% with sensitivity of 0.01% for 6 pts and ≥0.005% for 80 pts.

After cycle 1 →	Complete MRD Response	No Complete MRD Response	P-value
OS	38.9 mos.	12.5 mos.	0.002
RFS	23.6 mos.	5.7 mos.	0.002

Accelerated approval March 2018

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

If Blinatumomab works late in B-ALL why not use it earlier in the disease??

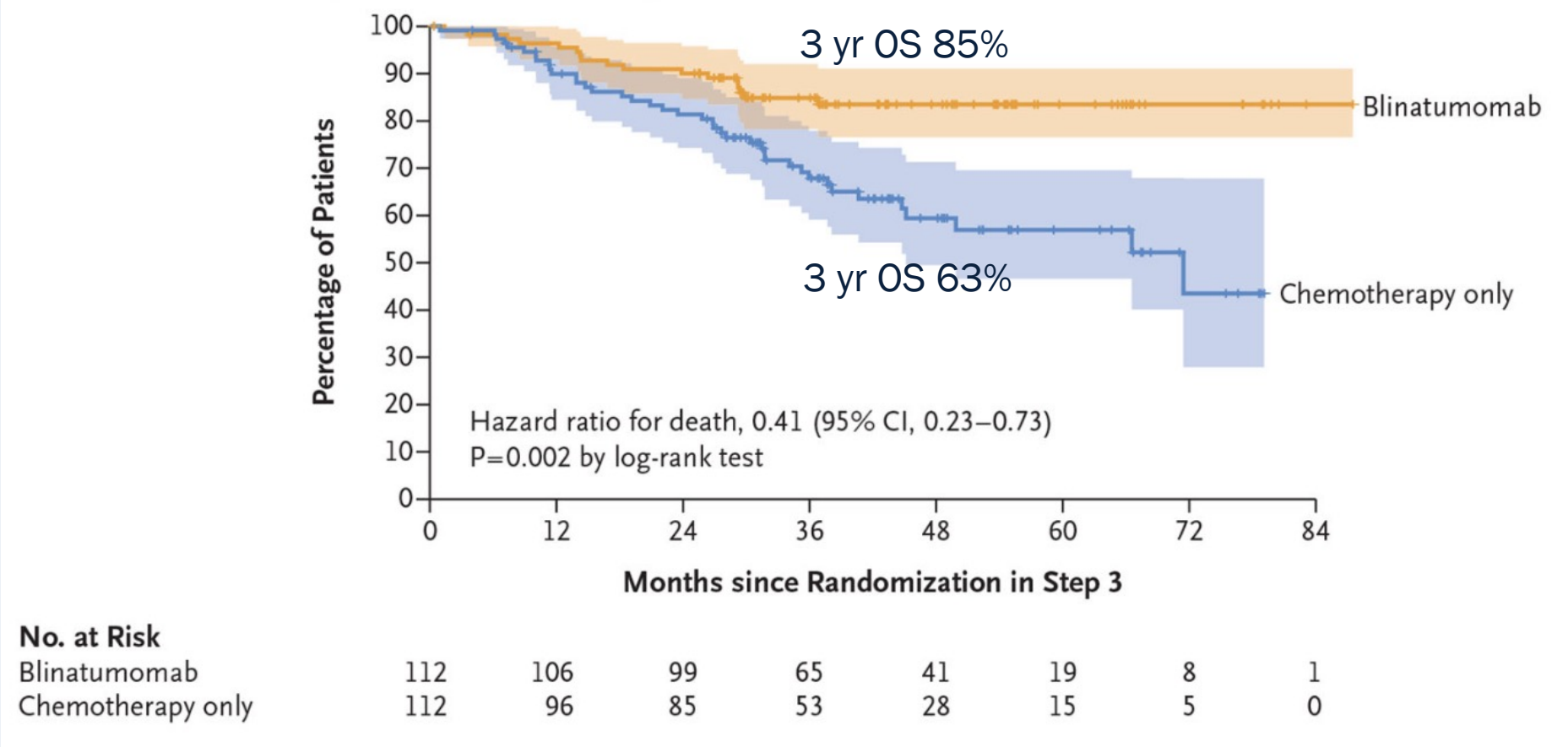
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

- Randomized, Phase III trial in pts. age 30-70 with Ph-negative B-ALL in MRD-negative CR (< 0.01% by flow cytometry in marrow) following induction and intensification
- Treatment arms balanced for patient and disease characteristics

<table>
<tr><td colspan="2">Induction cycle 1</td></tr>
<tr><td colspan="2">Induction cycle 2</td></tr>
<tr><td colspan="2">Intensification</td></tr>
<tr><td colspan="2">MRD assessment
Randomize 1:1 Blinatumomab vs. Chemotherapy-only
Consolidation (N= 112 in each arm)</td></tr>
<tr><td>Blina x 2 cycles</td><td rowspan="5">Chemo x 4 cycles</td></tr>
<tr><td>Chemo x 3 cycles</td></tr>
<tr><td>Blina x 1 cycle</td></tr>
<tr><td>Chemo x 1 cycle</td></tr>
<tr><td>Blina x 1 cycle</td></tr>
<tr><td colspan="2">Maintenance x 2.5 years from start of Intensification</td></tr>
</table>

Litzow MR, Sun Z, Mattison RJ..., Tallman MS. NEJM. 2024 Jul 25;391(4):320-333. doi: 10.1056/NEJMoa2312948. PMID: 39047240; PMCID: PMC11334054.

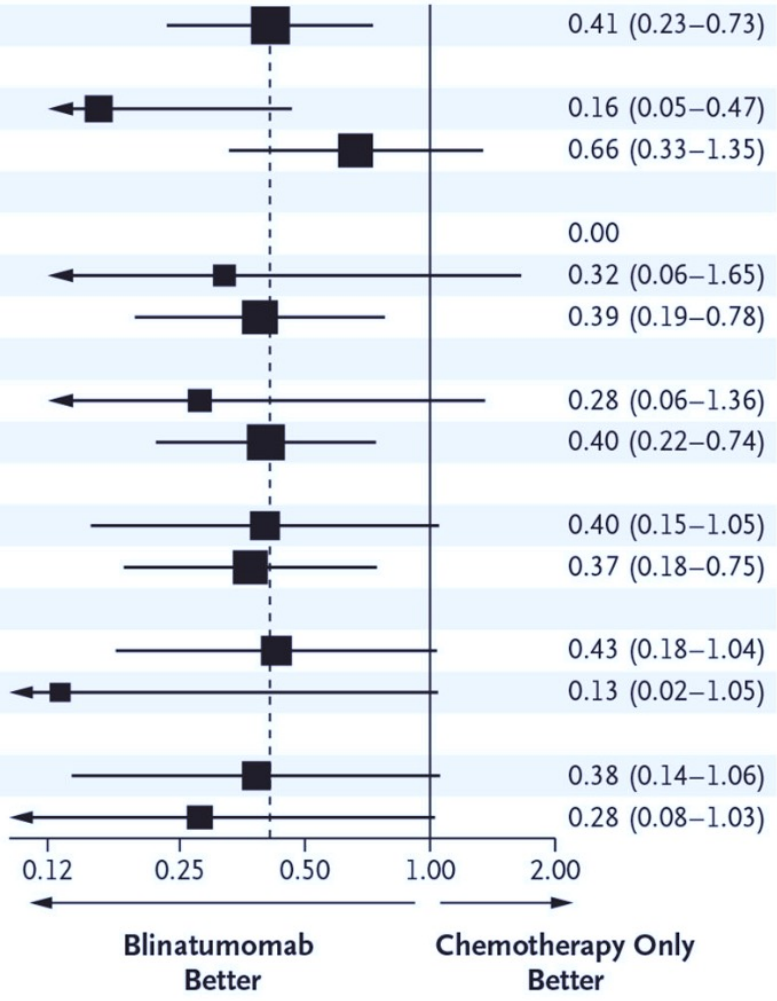
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults
Overall Survival



Litzow MR, Sun Z, Mattison RJ..., Tallman MS. NEJM. 2024 Jul 25;391(4):320-333. doi: 10.1056/NEJMoa2312948. PMID: 39047240; PMCID: PMC11334054.

Blinatumomab for MRD-Negative ALL in Adults

Subgroup	Blinatumomab	Chemotherapy Only	Hazard Ratio for Death (95% CI)
	no. of deaths/total no.		
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, Sun Z, Mattison RJ..., Tallman MS. NEJM. 2024 Jul 25;391(4):320-333. doi: 10.1056/NEJMoa2312948. PMID: 39047240; PMCID: PMC11334054.

Blinatumomab for MRD-Negative ALL in Adults - Toxicity

- Treatment-related non-hematologic toxicity:
  - Blina arm: 43% Gr. 3, 14% Gr. 4, and 2% Gr. 5
  - Chemo arm: 36% Gr. 3, 15% Gr. 4, and 1% Gr. 5 group (P = 0.87).

- Treatment-related neurologic or psychiatric adverse events:
  - 23% Gr. $\geq$ 3, compared with 5% in the chemotherapy-only group (P<0.001).

Summary:

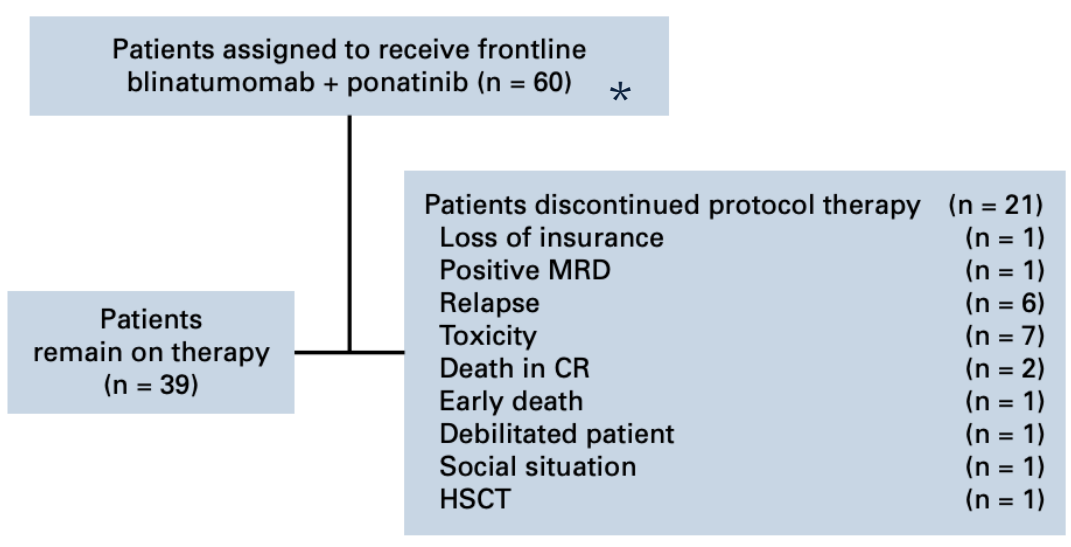
- Significant OS benefit among patients aged 30-70 years with B-ALL in MRD-negative CR who received blinatumomab plus chemotherapy in consolidation, compared with chemotherapy only.

- **FDA approved for pts. with CD19 Ph-neg B-ALL in consolidation phase of multi-phase chemotherapy on June 14, 2024**

Litzow MR, Sun Z, Mattison RJ..., Tallman MS. NEJM. 2024 Jul 25;391(4):320-333. doi: 10.1056/NEJMoa2312948. PMID: 39047240; PMCID: PMC11334054.

Blinatumomab and Ponatinib for Philadelphia Chromosome (+) ALL

- Blinatumomab 9 mg/d continuous intravenous (CIV) on days 1-4 of cycle 1, increased to 28 mg/d CIV on days 5-28 on a 4-week-on, 2-week off schedule, for up to 5 cycles.
- Ponatinib starts at 30 mg/d during induction and for at least 5 years. Dose reduced to 15 mg/d upon achieving CMR.
- Twelve to 15 doses of intrathecal chemotherapy (IT)



*

- 39 patients had newly diagnosed, untreated disease.
- 21 pts were in CR after 1-2 courses of chemotherapy within median duration of chemo and prior TKI of 49 days, and 6 pts in CMR at start of trial.

Hagop Kantarjian et al. *JCO* **42**, 4246-4251(2024).DOI:10.1200/JCO.24.00272

Blinatumomab and Ponatinib for Philadelphia Chromosome (+) ALL, Efficacy and Toxicity

Parameter	n/N (%)
Overall response rate[a]	
CR	37/39 (95)
CRi	1/39 (2)
Early death	1/39 (3)
CMR[b]	
After cycle 1	36/54 (67)
Overall	45/54 (83)
MRD negativity by NGS/ClonoSEQ	
After cycle 1	10/22 (45)
Overall	44/45 (98)
EFS	
3-year rate, % (95% CI)	77 (60 to 87)
No. of events	10 (17)
OS	
3-year rate, % (95% CI)	91 (76 to 97)
No. of events	4 (7)

97%

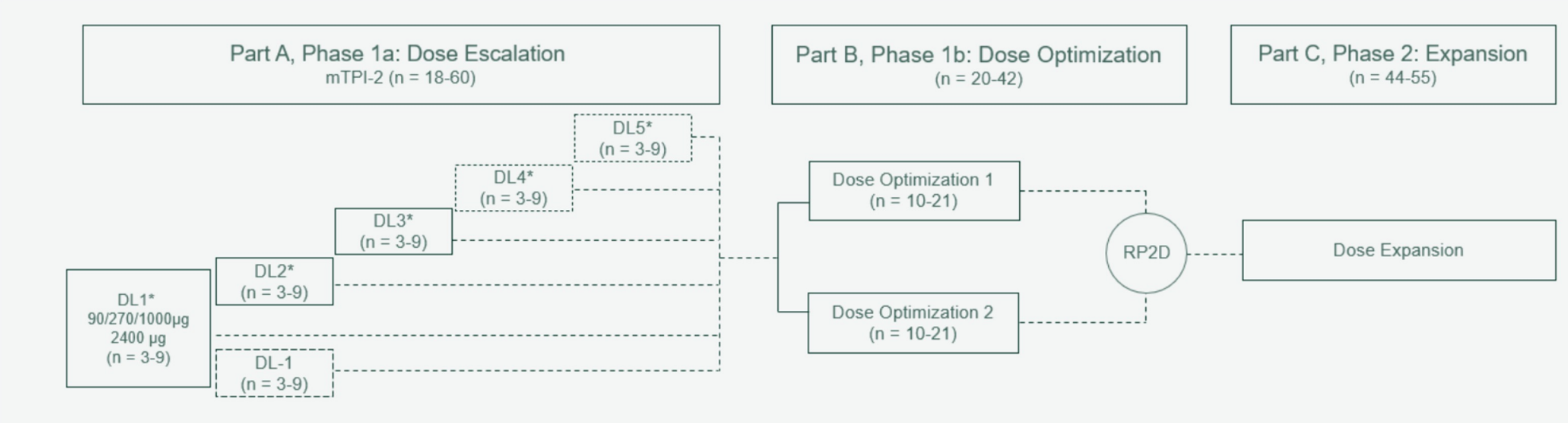
- CRS (all grade 1-2) observed in 7 pts (12%) all previously untreated (n = 39).
- Neurotoxicity included grade 1- 2 tremors in 6 (10%) pts, peripheral neuropathy/ paresthesia in 8 (13%), and grade 1 dizziness in 1 (2%).
- Resulting in blinatumomab dose reduction in 2 pts (gr 2 tremor, N=1 and gr 1 dizziness, N=1).
- 15% of pts discontinued ponatinib and 5% discontinued blinatumomab due to side effects.
- Rapid ponatinib dose reduction to 15 mg/d was associated with a favorable safety profile and a low rate of arterial occlusive events.

CMR, complete molecular response; CR, complete remission; CRi, CR with incomplete hematologic recovery; EFS, eventfree survival; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival, CRS= cytokine release syndrome.

Hagop Kantarjian et al. *JCO* **42**, 4246-4251(2024).DOI:10.1200/JCO.24.00272

A Phase 1/2 Study to Evaluate the Safety and Efficacy of AZD0486 in Adolescent and Adult Participants with Relapsed or Refractory B-Cell ALL

- AZD0486 is a fully human bispecific monoclonal IgG4 antibody that has shown activity across a range of in vitro and in vivo models of CD19-expressing tumor cells and initial clinical activity in pts with R/R B-NHL
- Low affinity C3 moiety may reduce cytokine release syndrome
- Longer half-life, allowing dosing every 2-4 weeks after a ramp up dose.



FDA Approved CAR T Cells for Acute Lymphoblastic Leukemia

CAR T-cell product	Patients infused (N)	Median age yrs (range)	CR/CRi (%)	Indication	Approval date
tisa-cel	75	11 (3-23)	61 (81%)	CD19+ R/R B-ALL, Up to 25 years of age	August 30, 2017
brexu-cel	55	40 (28-52)	39 (70.9%)	CD19+ R/R B-ALL, adult	October 1, 2021
obe-cel	127	50 (20-81)	72/97 (77%)	CD19+ R/R B-ALL, adult	November 8, 2024

- CR= complete remission; CRi= complete remission with incomplete hematologic recovery.

C. Roddie et al. N Engl J Med 2024;391:2219-2230, Maude et al. N Engl J Med 2018;378:439-48, B Shah, et al. The Lancet. V. 398, issue 10299. P491-502August 07, 2021

(PF374) 5-year Survival Outcomes of Pts. with R/R B-cell ALL Treated with Brexucabtagene Autoleucel (Brexu-cel) in Zuma-3

- As of July 23, 2024, median follow-up time in Phase 1 and 2 in pts ≥18 y (N=78) was 65.7 mo (range, 56.7-94.3).

Group	Median OS (95% CI)	5-y OS Rate (95% CI)
All subjects (n= 78)	25.6 mo. (16.2-60.4)	40% (28.4-51.3)
Responders (CR/CRi; n=57)	60.4 mo. (23.2–NE)	
Responders with CR (n=47)	Not reached (34.1–NE)	
Responders with subsequent allogeneic HSCT (N= 14)	50.2 mo (10.2-NE)	42% (16.4-65.4)
Responders without subsequent allogeneic HSCT (N= 44)	60.4 mo (23.2-NE)	52% (35.8-66.5)

- In the pivotal trial, grade ≥ 3 cytokine release syndrome occurred in 13 (24%) patients and grade ≥ 3 neurological events in 14 (25%) patients.

NE= not evaluable

Olalekan Oluwole , et al. EHA 2025. HemaSphere 2025;9(S1)

(PF374) 5-year Survival Outcomes of Pts. with R/R B-cell ALL Treated with Brexucabtagene Autoleucel (Brexu-cel) in Zuma-3

- 5-year overall survival (OS) based on prior treatments

Prior Treatment	With Treatment (n)	5-year OS Rate (95% CI)	Without Treatment (n)	5-year OS Rate (95% CI)
Blinatumomab	38	25% (12.1–40.4)	40	54% (36.3–68.5)
Inotuzumab	17	21% (5.2–43.9)	61	45% (31.1–57.4)
AlloSCT	29	36% (17.1–55.3)	49	42% (26.9–55.5)

- At data cutoff, 44 of 78 pts (56%) had died; 20 pts (26%) alive; 14 pts (18%) lost to follow-up or withdrew consent.
- Estimated 60-mo cumulative incidences of death due to progressive disease (PD) and non-PD reasons were 34% (95% CI, 23.5-45.2) and 26% (95% CI, 16.0-36.7), respectively.

Olalekan Oluwole , et al. EHA 2025. HemaSphere 2025;9(S1)

Obecabtagene Autoleucel (obe-cel) in Adults with B-Cell ALL

- Autologous 41BB-ζ anti-CD19 CAR T-cell therapy which uses an intermediate-affinity CAR to reduce toxic effects and improve persistence.
- Phase 1b–2 multicenter study in adults (≥18 y/o) with R/R B-cell ALL. Cohort 2A (pts. with morphologic disease); cohort 2B (pts. with measurable residual disease).
- Primary end point: overall remission (complete remission or complete remission with incomplete hematologic recovery) in cohort 2A.
- Secondary end points: event-free survival, overall survival, and safety.

Claire Roddie, M.D., Karamjeet S. Sandhu..., and Elias Jabbour, M.D.. **N Engl J Med 2024;391:2219-2230. DOI: 10.1056/NEJMoa2406526**

Obecabtagene Autoleucel in Adults with B-Cell ALL

Total patients enrolled	153
Patients who received obe-cel	127 (83%)
Cohort 2A	94 patients (Median follow-up: 20.3 mo)
Overall remission rate	77% (95% CI, 67–85); P<0.001
Complete remission (CR)	55% (95% CI, 45–66); P<0.001
CR with incomplete hematologic recovery	21% (95% CI, 14–31)
Event-Free Survival (n=127)	Median: 11.9 mo (95% CI, 8.0–22.1)
6-month EFS	65.4%
12-month EFS	49.5%
Overall Survival (n=127)	Median: 15.6 mo (95% CI, 12.9–NE)
6-month OS	80.3%
12-month OS	61.1%
Grade ≥3 Cytokine Release Syndrome (CRS)	2.4%
Grade ≥3 ICANS	7.1%

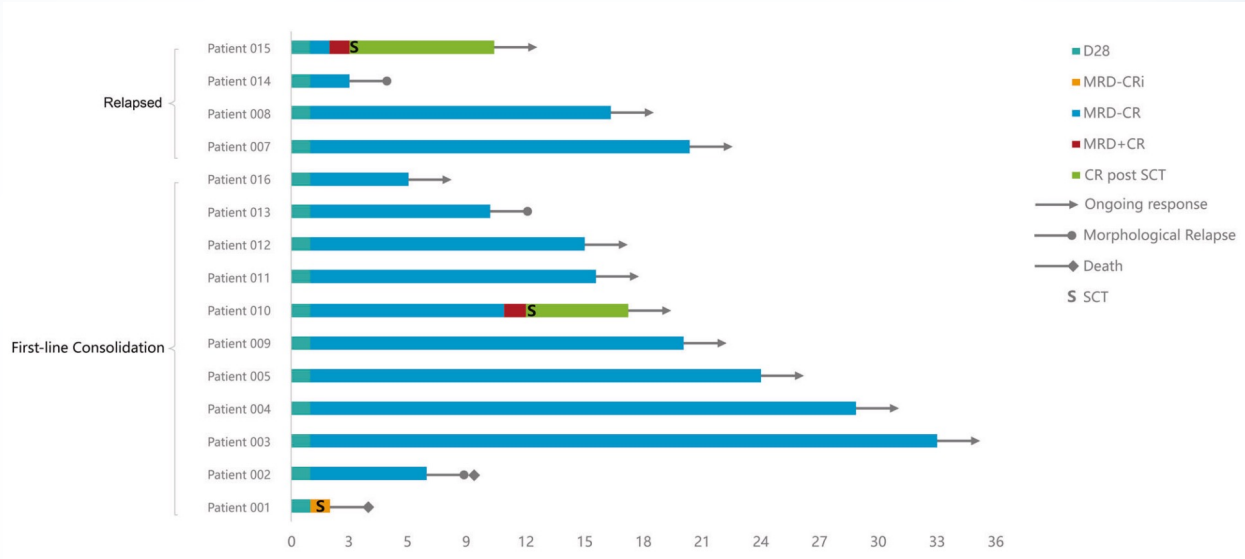
- FDA approved for pts. with R/R B-ALL on Nov 8, 2024.

Claire Roddie, M.D., Karamjeet S. Sandhu..., and Elias Jabbour, M.D.. **N Engl J Med 2024;391:2219-2230. DOI: 10.1056/NEJMoa2406526**

Early activity on CD19/CD22 bispecific CAR-T cells for MRD-positive B cell acute lymphoblastic leukemia: a phase I clinical study

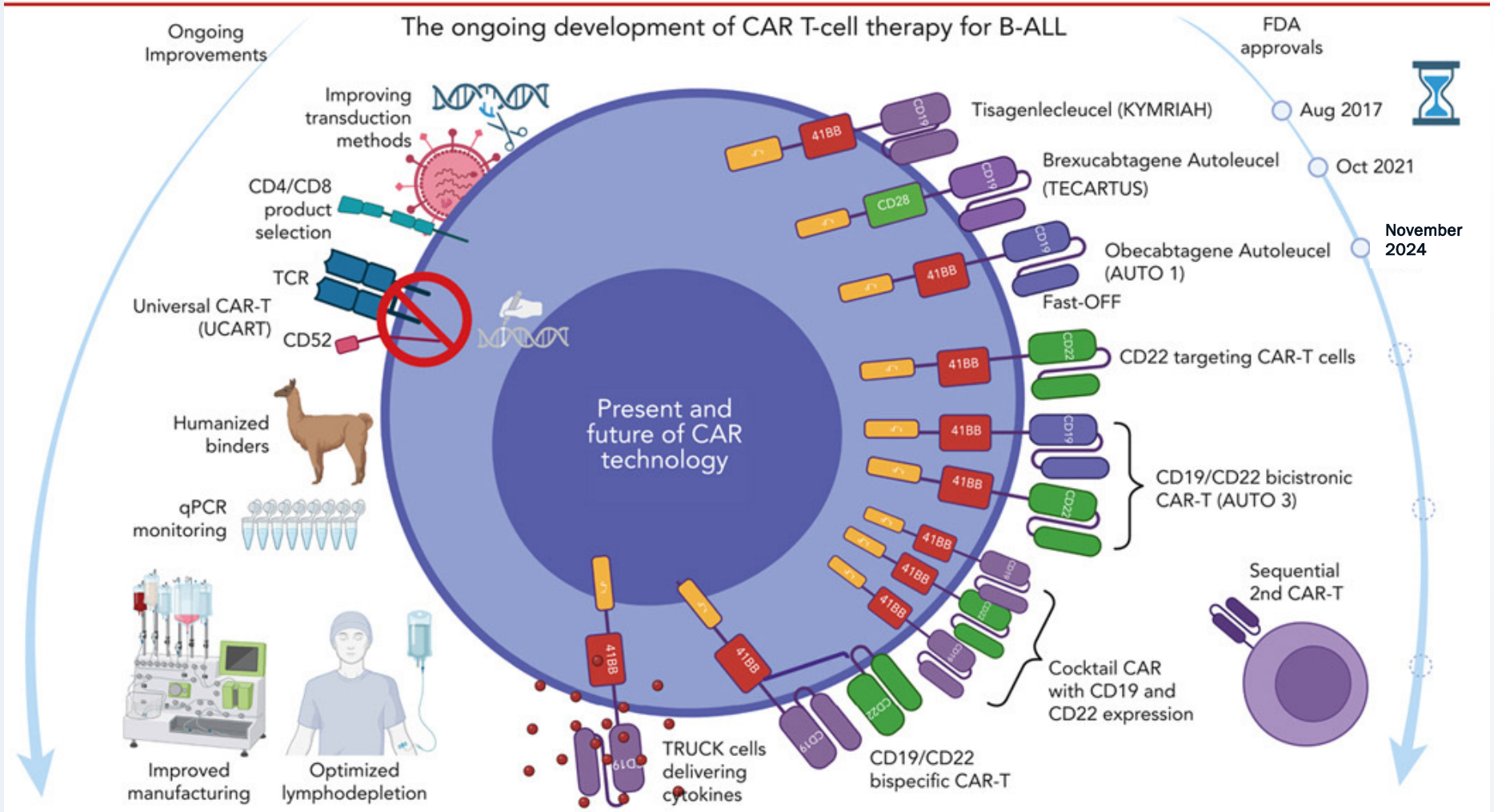
Table 1. Patient characteristics.

Baseline characteristics	All patients evaluable ($N = 15$)	First-line consolidation ($N = 11$)	Relapsed group ($N = 4$)	*P*
Median age, years (range)	51 (23–70)	45 (23–70)	54.5 (31–61)	0.447
Age ≥ 35 years, *n* (%)	10(66.7%)	7(63.6%)	3(75%)	0.68
Male, *n* (%)	6 (40%)	5 (45.5%)	1 (25%)	0.348
ECOG performance status score of 0–1, *n* (%)	15 (100%)	11 (100%)	4 (100%)	>0.99
Median time since diagnosis, months (range)	6.5 (1–41.5)	6.5 (3–18)	7 (1–41.5)	0.851
Median Cycle Number of chemotherapy, *n* (range)	4(3–8)	4(3–5)	3.5 (3–8)	0.949
Ph-positive	7(46.7%)	3(27.3%)	4(100%)	0.026
Disease burden				
Before lymphodepletion				
MRD ≥ 10^{-2}	2(13.3%)	1(9.1%)	1(25%)	0.4
MRD ≥ 10^{-3}–<10^{-2}	5(33.3%)	3(27.3%)	2(50%)	
MRD ≥ 10^{-4}–<10^{-3}	8(53.3%)	7(63.6%)	1(25%)	
Before infusion				
MRD ≥ 10^{-2}	3(21.4%)	1(9.1%)	2(50%)	0.183
MRD ≥ 10^{-3}–<10^{-2}	5(35.7%)	5(45.5%)	0	
MRD ≥ 10^{-4}–<10^{-3}	1(7.1%)	1(9.1%)	0	
MRD Negative	5(35.7%)	3(27.3%)	2(50%)	
Follow-up time	15.5(2.5–33)	15.5(2.5–33)	15.25(10.5–20.5)	0.949



Jiahua Niu, et al. Blood Cancer Journal (2023) 13:44 ; https://doi.org/ 10.1038/s41408-023-00813-x

The Present and Future for CAR T-Cell Therapy in Adult B-Cell Acute Lymphoblastic Leukemia (B-ALL)



- Dual targeting, CD19/CD22
- Allogeneic CAR T cells
- mRNA–lipid nanoparticle injection that induces CAR expression inside pts. own T cells
- Armored CAR-T secreting TIM-3-Fc decoy
- Epigenetic predictors for CD19 CAR-T effectiveness

Ramporas and Roddie. https://doi.org/10.1182/blood.2023022922

SUMMARY

- Blinatumomab is standard of care for patients with B-ALL in MRD-negative CR
- TNB-486 (AZD0486): A next-gen IgG4 fully human CD19xCD3 bispecific T-cell engager aiming to reduce cytokine release syndrome (CRS) due to its low-affinity CD3 moiety and may offer a more practical infusion schedule
- Emerging data appears to support moving CAR T cells to earlier lines of therapy in certain patients
- Next generation CAR T cells promising

Q&A