Chemo-Immunotherapy in Acute Lymphoblastic Leukemia

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2026 Princess Margaret Hematology Conference

UHN | Canada's #1 Hospital

Disclosure of Potential Conflicts of Interest

- Novartis: Speaker at educational events and invited speaker at regional consult meeting
- Servier: Participation in consultant meeting

These activities are not related to the content of this presentation.

Objectives

- Review the evolution of treatment in Acute Lymphoblastic Leukemia
- Discuss the rationale for immunotherapy in ALL
- Review approved immunotherapeutic approaches in B-ALL, including monoclonal antibodies, bispecific antibodies (BiTEs), and CAR-T cell therapy
- Highlight emerging strategies and future directions in ALL treatment

ALL – Outcomes

- **Estimated 5-year overall survival (OS)** approaches ~90% in children
- **Estimated 5-year OS** in adults is ~40–50%, with substantial variation by age, treatment, and risk factors

High frequency of the favorable cytogenetics

Higher risk leukemia genetics
Ph +

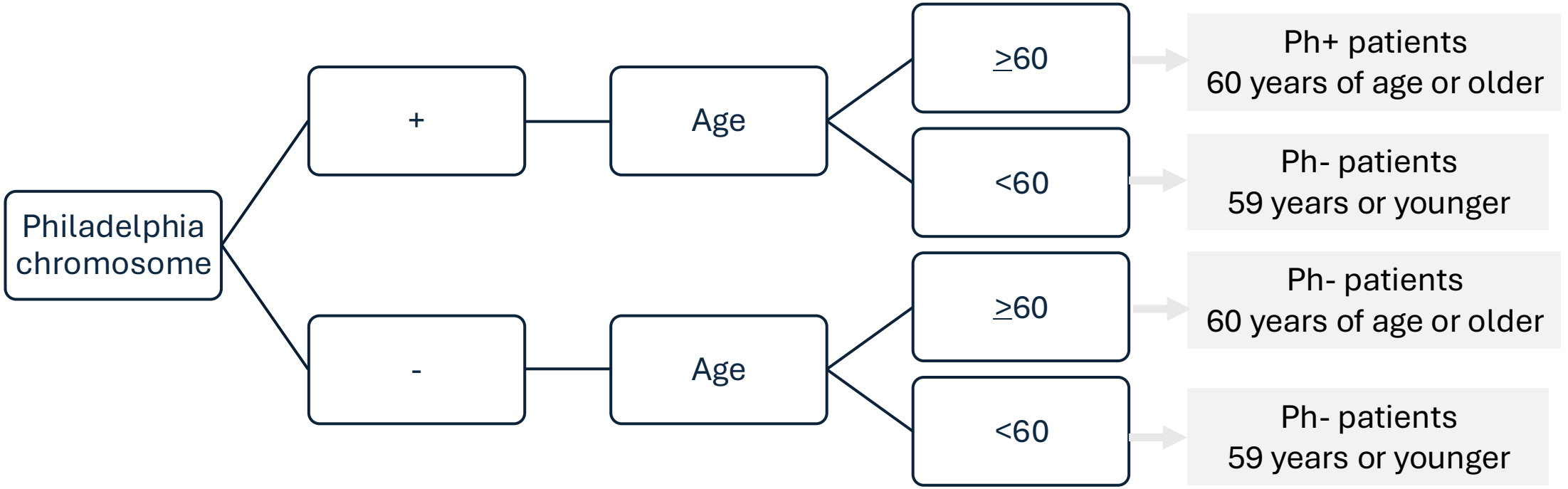
Less tolerance of intensive chemotherapy

more comorbidities and poorer performance status

Intensified treatment protocols

ALL – treatment -PMH

PMH
Canadian pediatric inspired protocol



Induction: inpatient → CNS phase (3-weeks) → Intensification (10/7 cycles q 3 weeks) → Maintenance (24 cycles q 3 weeks)

PMH ALL RWE -

Retrospective analysis	**373 newly diagnosed ALL > 30 years old**	**January 2002 January 2022**	**modified pediatric-inspired. Multiagent-multiphase**	**Ph-negative B-ALL; Ph-positive ALL T-ALL; Mixed-phenotype acute leukemia (MPAL)**

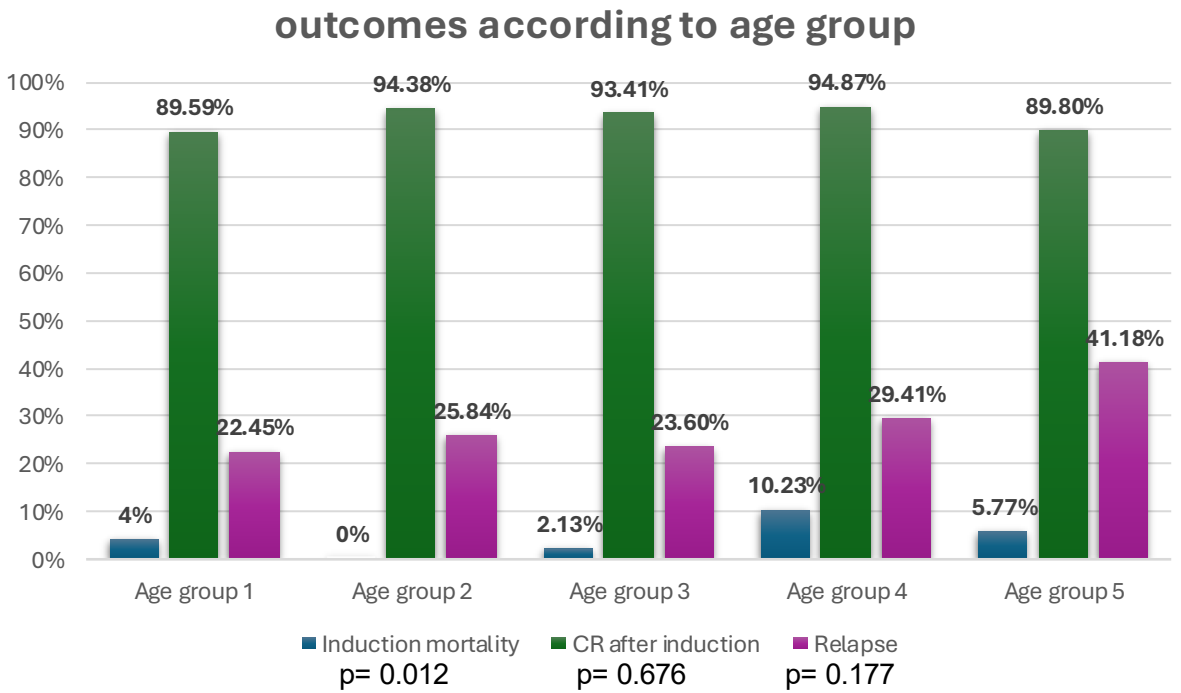
400 pts:
Induction-related mortality: 16 patients (4%)

Complete remission (CR) after induction: 330 patients (93%)

Relapse after achieving CR1: 101 patients (28%)

Median follow-up of 7 years

Group 1	30 to <40 years	N= 50
Group 2	40 to <50 years	N= 89
Group 3	50 to <60 years	N= 94
Group 4	60 to <70	N= 88
Group 5	>70	N = 52



Perusini MA, Andrews C, Eshetu AG, Gupta V, Maze D, Yee KWL, Bankar A, Davidson MB, Richard-Carpentier G, Chan SM, Schimmer AD, Sibai J, Alharbi S, Lucero JA, Linn SM, Minden MD, Schuh AC, Sibai H. Asparaginase completion among adults including older patients with acute lymphoblastic leukemia treated with a modified DFCI protocol. Leukemia. 2024 Apr;38(4):912-913. doi: 10.1038/s41375-024-02201-1. Epub 2024 Mar 2. PMID: 38431747.
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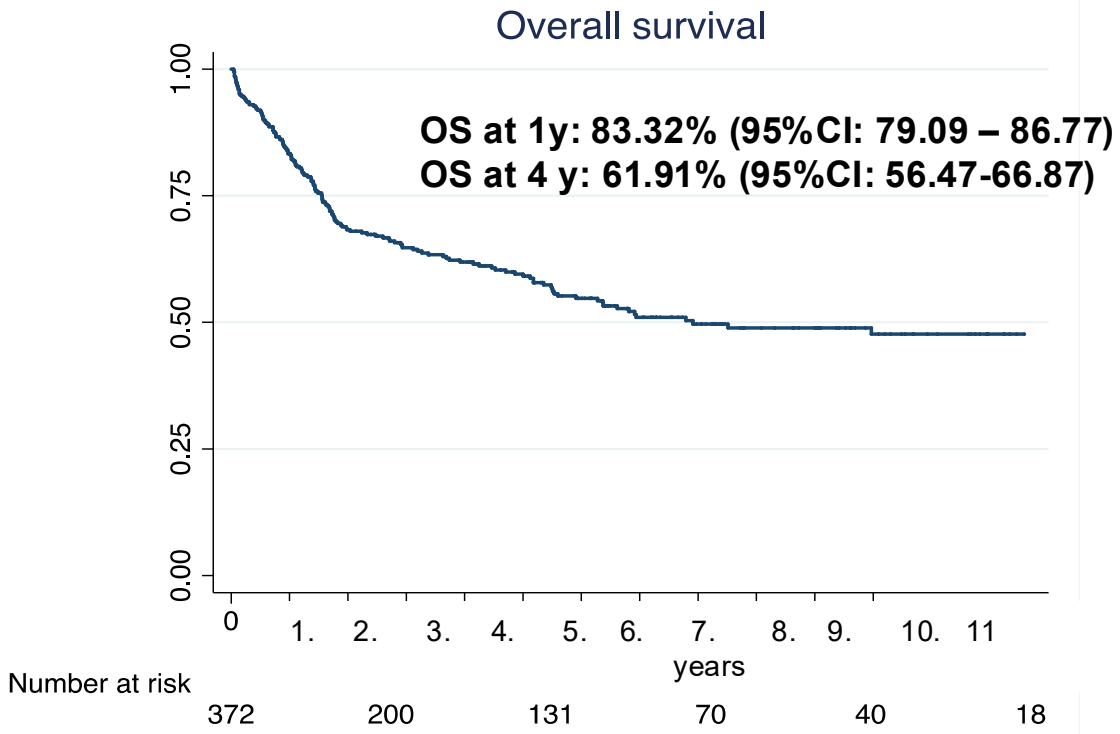
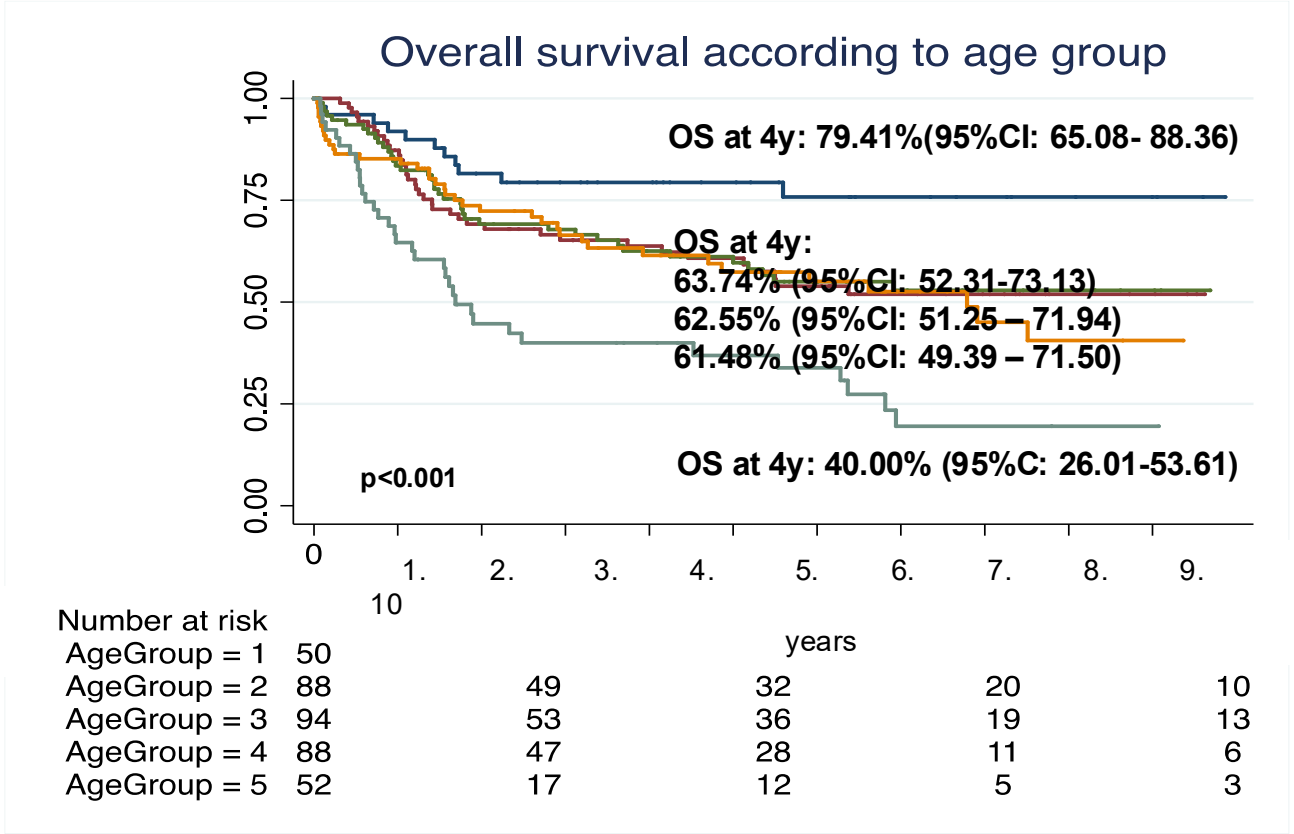
PMH – overall survival





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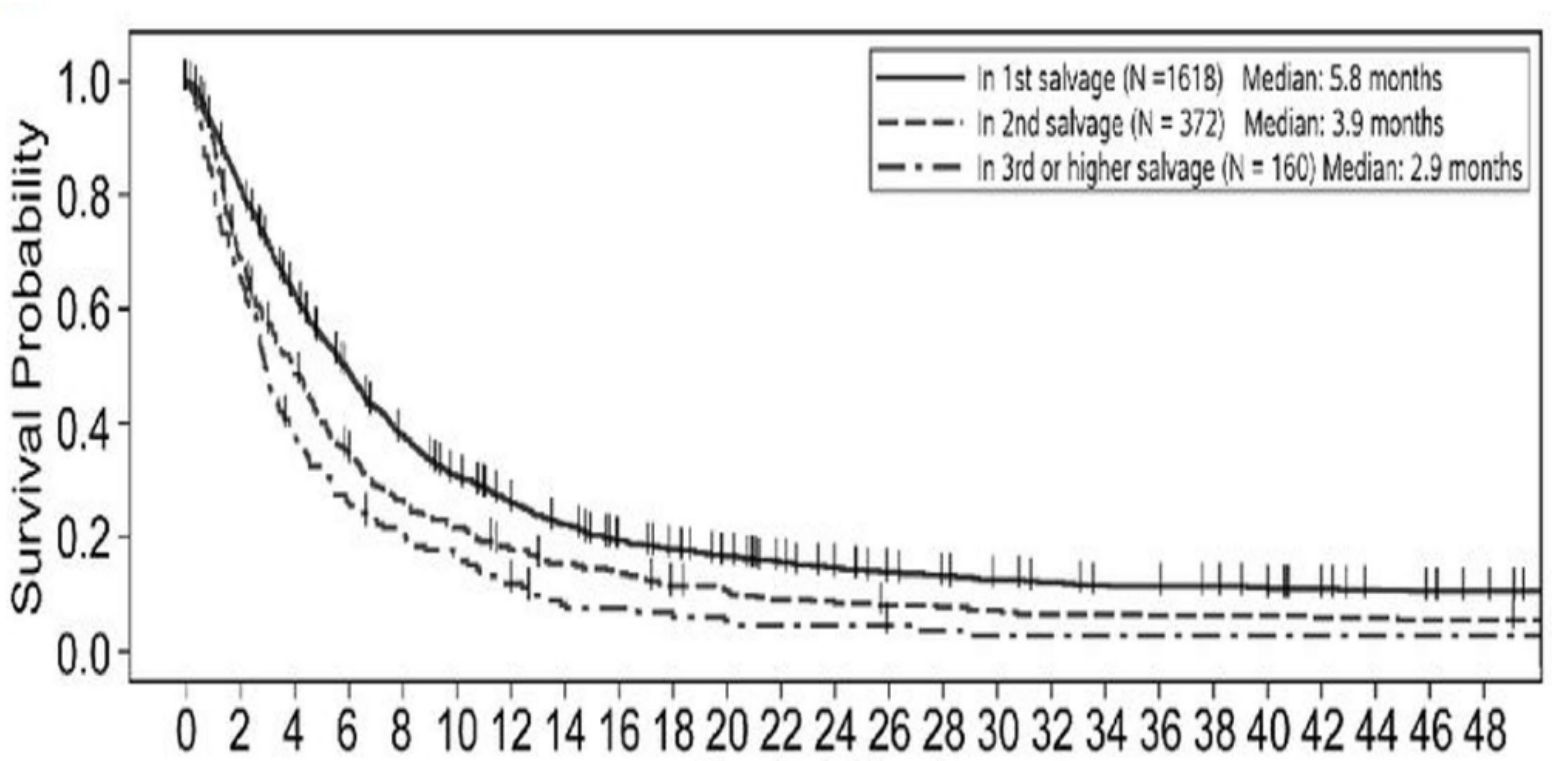
International Reference Analysis for Outcomes in Adults R/R B-ALL



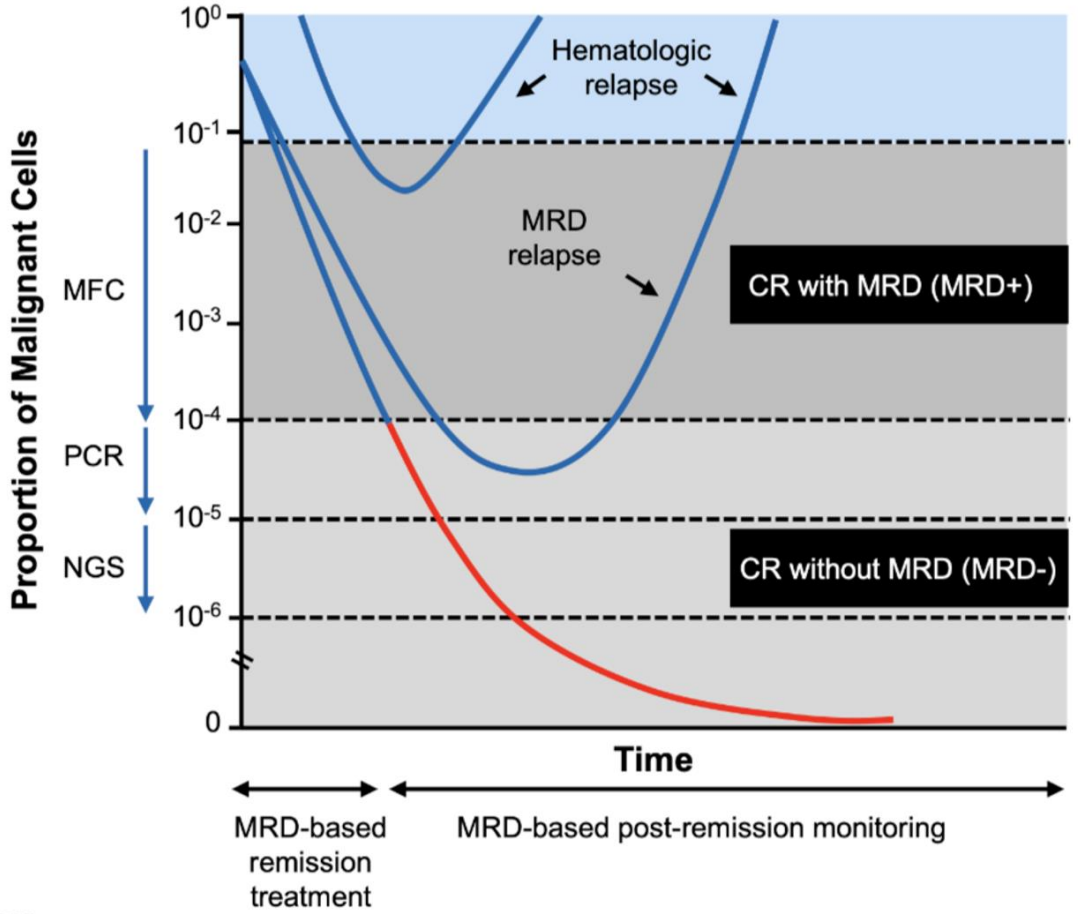
Gokbuget et al. Haematologica. 2016;101 (12): 1524-1533.

- 1960 Chemotherapy [1]
- 2000 TKI. Imatinib. [2,3]
- 2014 Blinatumomab [4]
- 2016 Rituximab [5]
- 2017 Inotuzumab [6] Tisa-Cel (Kymriah) [7]
- 2018 Nelarebine [8]
- 2021 Brexu-cel (Tecartus) [9] .....

1. *Haematologica 2016 Volume 101(12):1524-1533.* 2. *Oliver G. Ottmann, Barbara Wassmann; Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia. Hematology Am Soc Hematol Educ Program 2005; 2005 (1): 118–122.* 3: *Blood 2007;110:2309-15.* 4: *NEJM 2017;376:836-47.* 5: *Maury et al NEJM 2016:375:1044-53* 6: Kantarjian et al *NEJM 2016:375:740-53.* 7. *N Engl J Med. 2018 Feb 1;378(5):439-448. doi: 10.1056/NEJMoa1709866.* 8. *Journal of Clinical Oncology, 38(28), 3282-3293.* 9 *N Engl J Med 2018; 378:449-459*

MRD assessment is important in ALL

More robust remissions with MRD- status



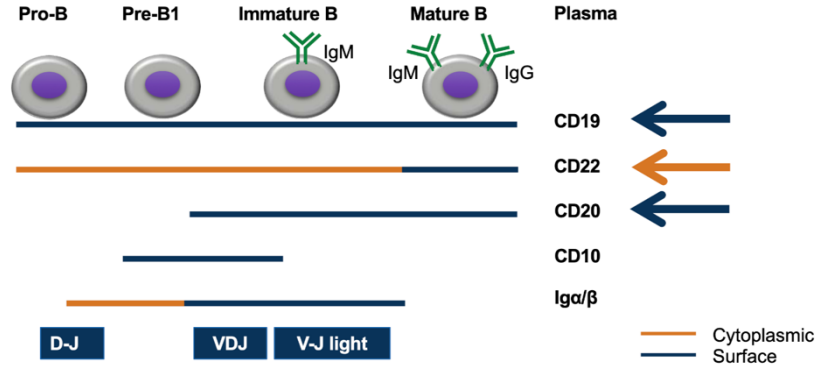
. Short N et al. *Am J Hematol*. 2019;94:257-265.

Why Immunotherapy?

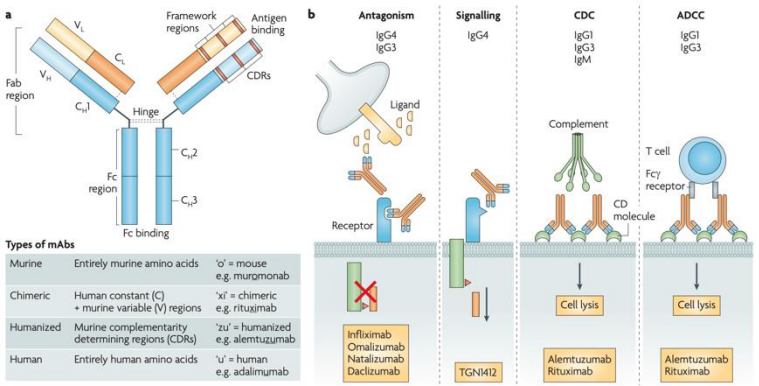
Addressing Unmet Needs in ALL and R/R ALL

- Improve outcomes across all patients, including high-risk subgroups and special populatoins
- Overcome relapse and resistance mechanisms
- Achieve deep responses with MRD eradication

Therapeutic Targets – B-ALL

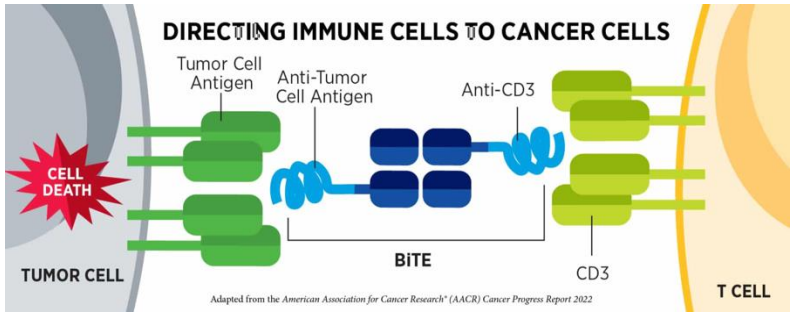


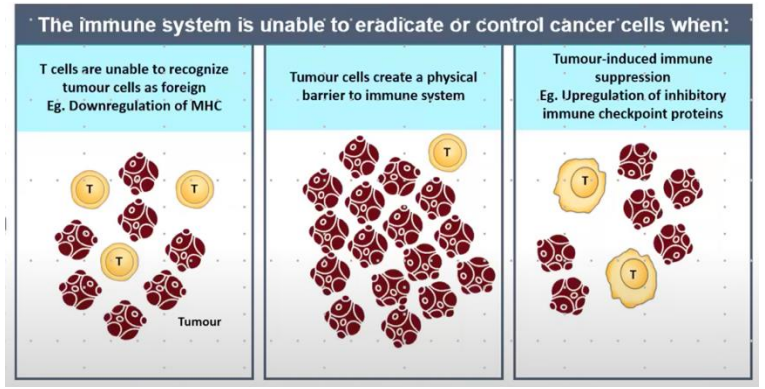
Monoclonal antibodies	Bispecific Antibodies (BiTEs)	CAR-T
Inotuzumab Ozogamicin (CD22)	Blinatumomab (CD19-CD3)	TISA-CEL BREXU-CEL



Types of mAbs

Murine	Entirely murine amino acids	'o' = mouse e.g. muromonab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. rituximab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtuzumab
Human	Entirely human amino acids	'u' = human e.g. adalimumab

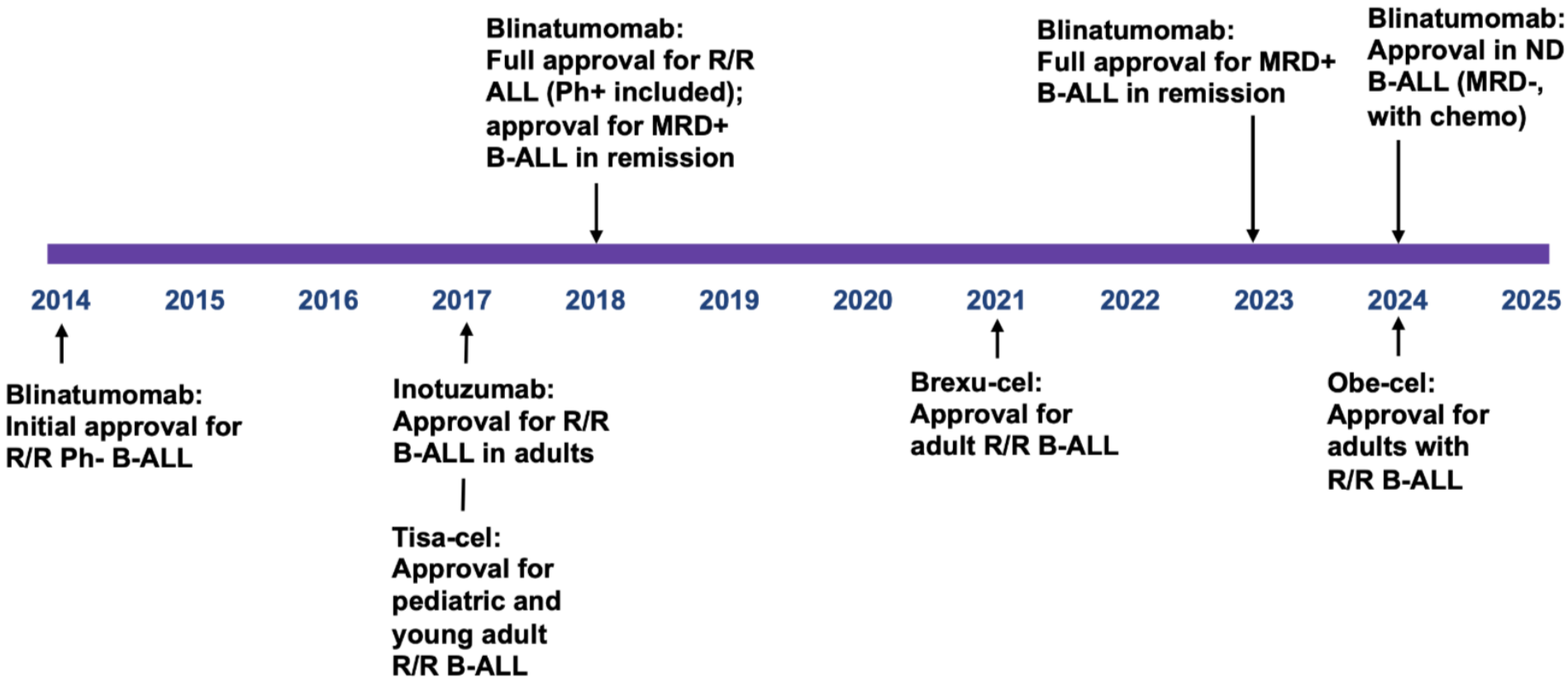




Murphy KM, *et al*. Janeway Immunobiology book; 2017

The safety and side effects of monoclonal antibodies Trevor T. Hansel*‡, Harald Kropshofer §, Thomas Singer §, Jane A. Mitchell‡ and Andrew J. T. George||

ALL- progress



Inotuzumab Ozogamicin

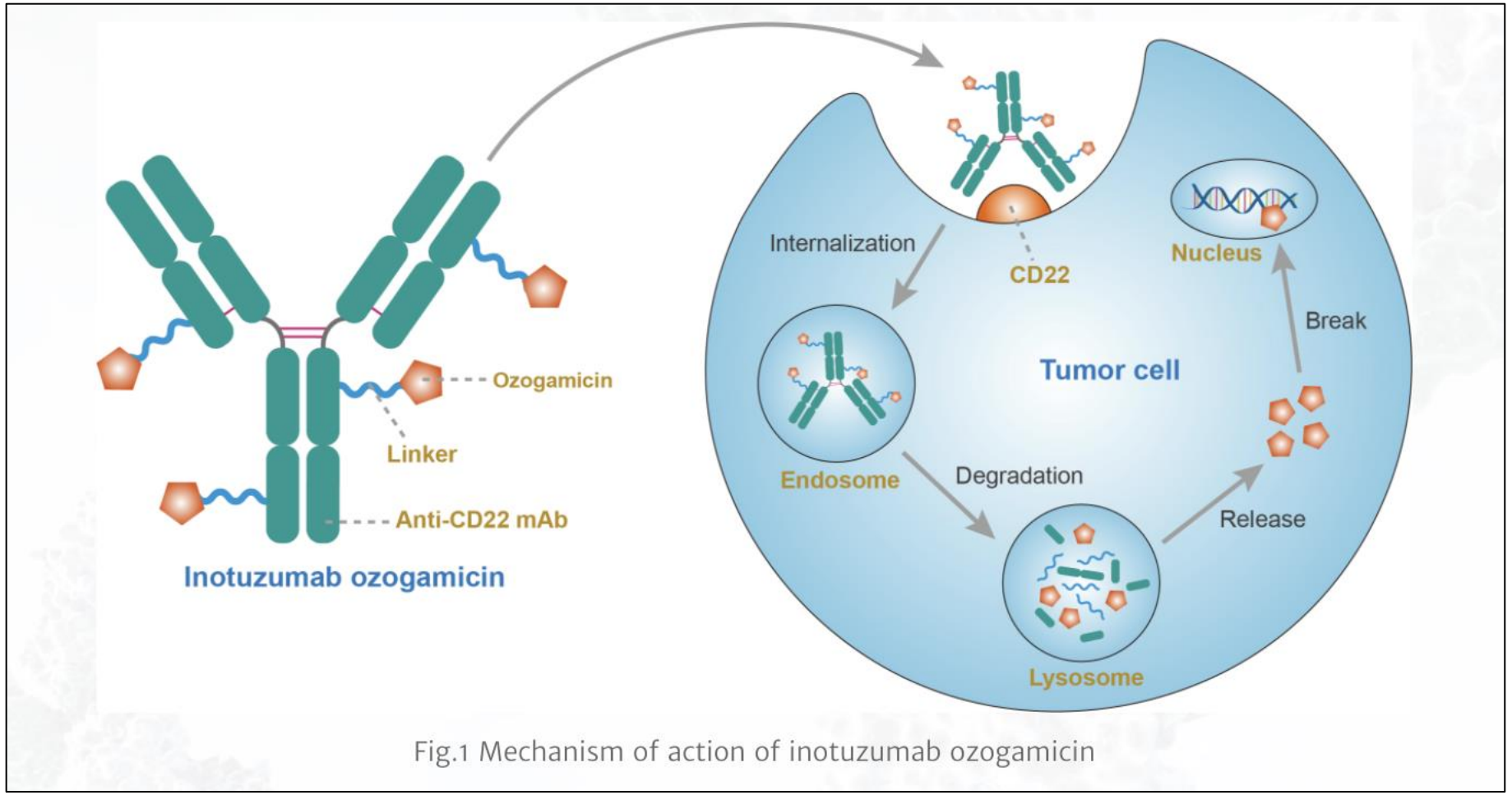


Fig.1 Mechanism of action of inotuzumab ozogamicin

Leukemia 2012; 26:255; 2

INO-VATE: Study design

- **Patients ≥18 years with R/R CD22+ ALL**
- **Due for Salvage 1 or 2 therapy**
- **Ph– or Ph+**

1:1 randomisation (N=326)

Stratifications:

- Duration of first remission ≥12 vs <12 months
- Salvage 1 vs 2
- Age <55 vs ≥55 years

Inotuzumab (n=164)

- Starting dose 1.8 mg/m^2/cycle
- 0.8 mg/m^2 on day 1; 0.5 mg/m^2 on days 8 and 15 of a 21–28 day cycle (≤6 cycles)

SOC (n=162)

- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC

≤4 cycles

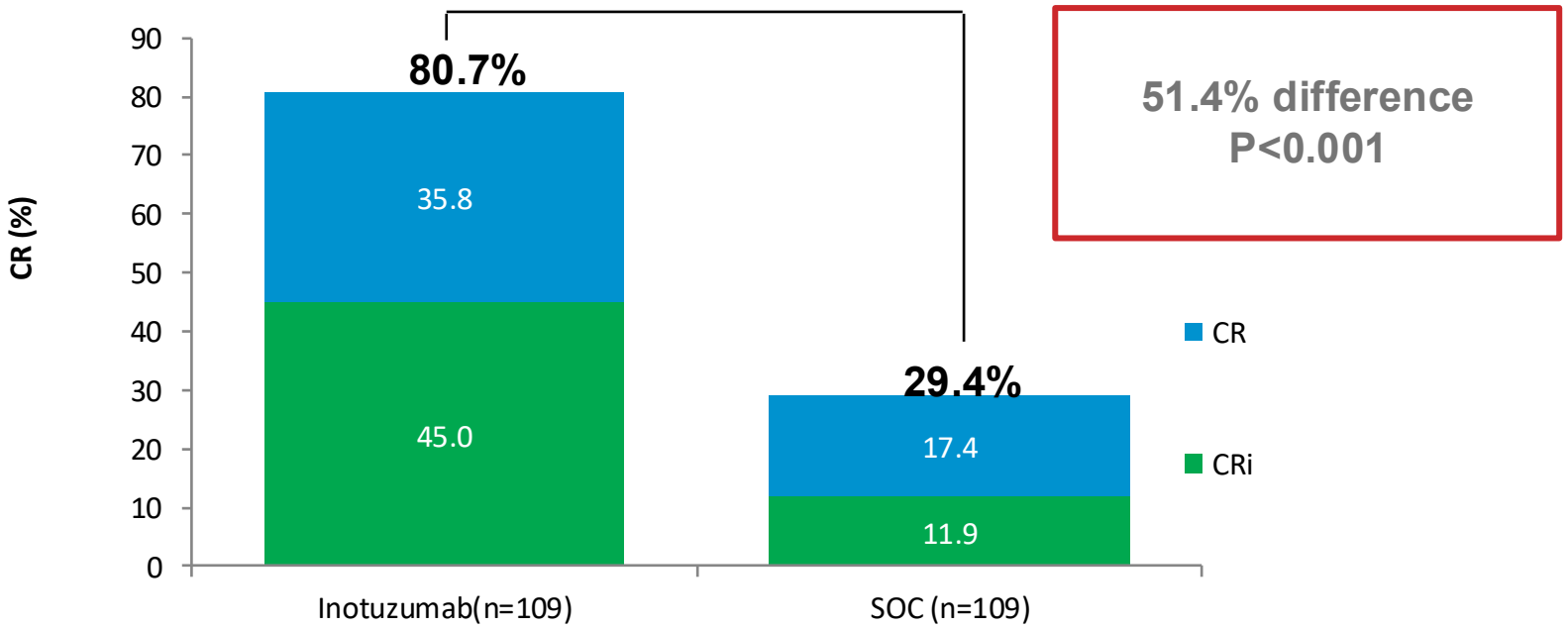
- There are two primary endpoints: **CR/CRi* and OS†**
- Key secondary endpoints: **PFS, remission duration, stem cell transplant rate, safety and MRD rate among responders, QoL**

*CR/CRi based on first 218 patients randomised; †OS assessed in all patients after ≥248 events.

Kantarjian HM et al. N Engl J Med 2016;375:740–53

INO-VATE: Treatment Response

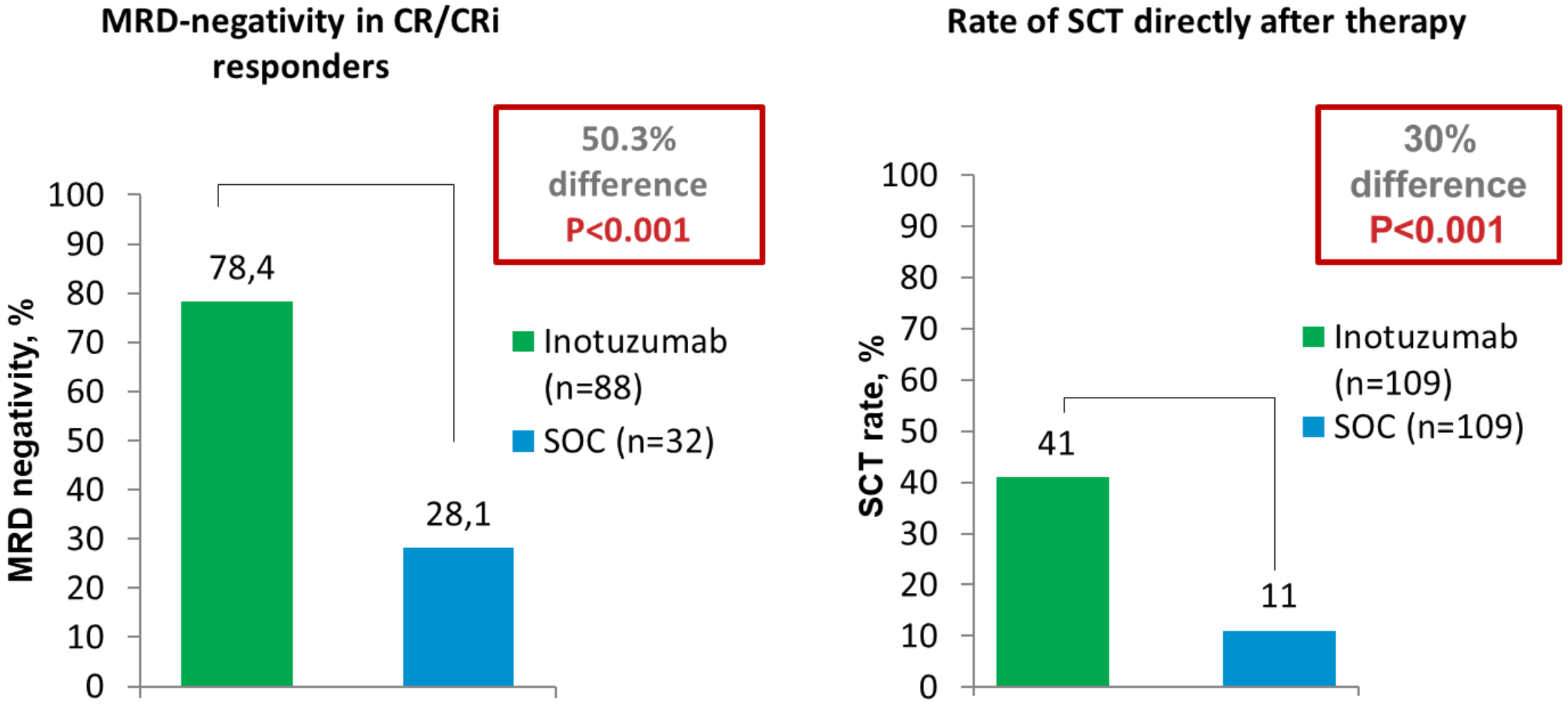
The CR/CRi rate was significantly higher in the inotuzumab arm than in the SOC arm (80.7% vs 29.4%; P<0.001)



- In both arms, most patients who achieved CR/CRi did so within the first cycle: 64/88 (73%) inotuzumab vs 29/32 (93%) SOC

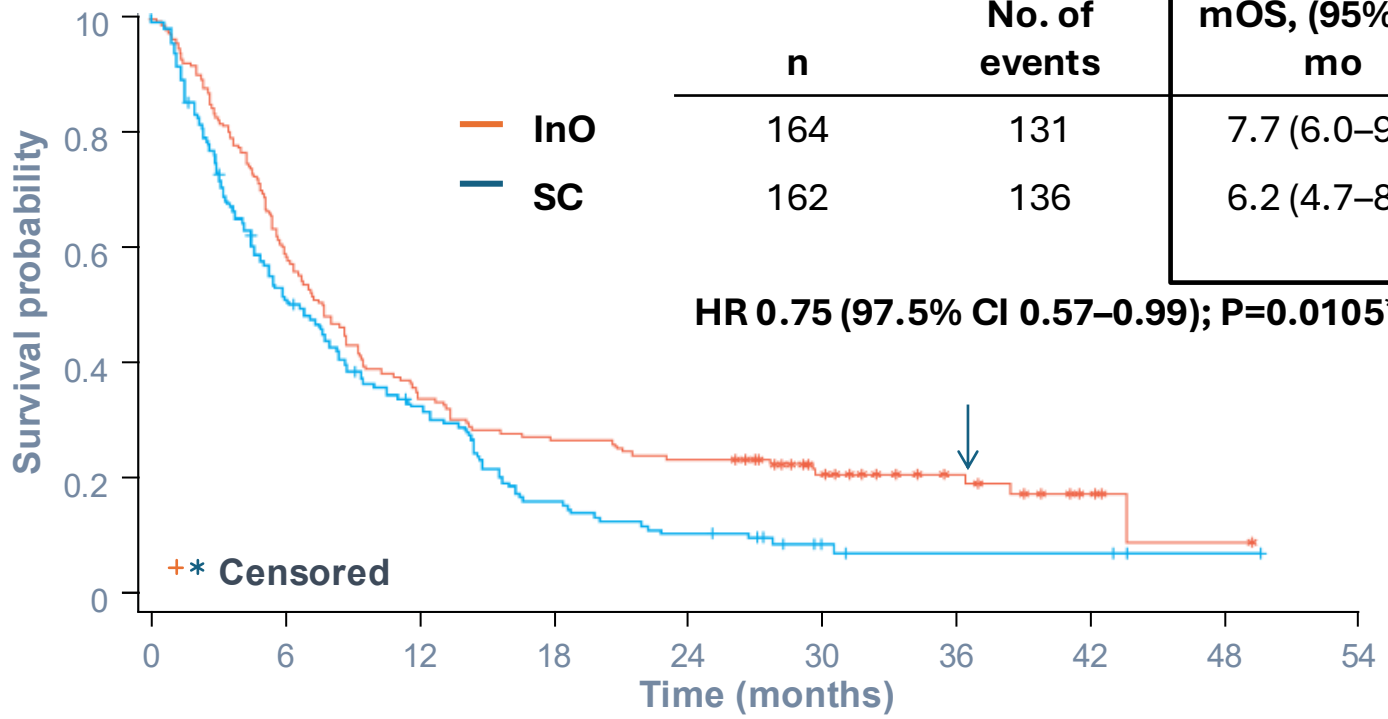
Kantarjian HM et al. N Engl J Med 2016;375:740–753

INO-VATE: MRD-negativity in responders and rate of SCT



Kantarjian HM et al. N Engl J Med 2016;375:740–753

INO-VATE long-term follow-up: Overall survival



	n	No. of events	mOS, (95% CI), mo	2y survival, (95% CI), %	3y survival, (95% CI), %
InO	164	131	7.7 (6.0–9.2)	22.8 (16.7–29.6)	**20.3** (14.4–27.0)
SC	162	136	6.2 (4.7–8.3)	10.0 (5.7–15.5) P=0.0004	**6.5** (2.9–12.3) P=0.0093

HR 0.75 (97.5% CI 0.57–0.99); P=0.0105*

Median duration of follow-up for all patients was 7.5 months (range 0.33–49.28) in the InO group, and 5.4 months (range 0.03–49.68) in the SC arm[2]

Adapted from: Kantarjian HM *et al.* 2019
Median follow-up time for all patients who were censored for OS: 29.6 months (range 1.7–49.7). *One-sided log-rank
CI, confidence interval; HR, hazard ratio; InO, inotuzumab ozogamicin; OS, overall survival; SC, standard chemotherapy
1. Kantarjian HM *et al. Cancer* 2019;125:2474–2487; 2. Pfizer data on file

INO-VATE: Safety

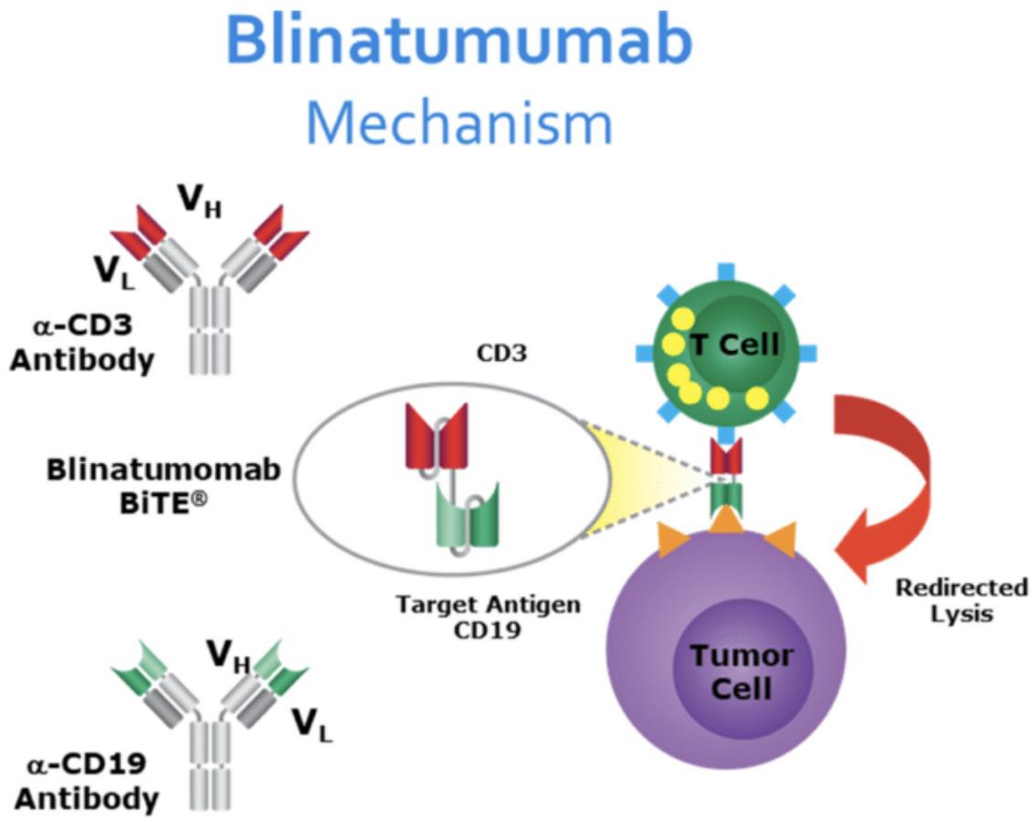
VOD incidence: **Inotuzumab 11% (n=15) vs SOC 1% (n=1)**

- 5 (3%) patients had VOD during study treatment
- 48/139 patients in inotuzumab arm underwent SCT
  - 10 patients developed VOD after transplantation
- Median (range) time to VOD after SCT: 16 (3–39) days

Multivariate analysis of factors associated with post-SCT VOD

Factor	OR (95% CI)	P-value
Alkylator conditioning (dual vs single)	5.6 (1.0–30.1)	0.004

BITE- Blinatumomab



Blinatumomab is a **bispecific T-cell engager antibody** designed to direct cytotoxic T-cells to CD19 expressing cancer cells

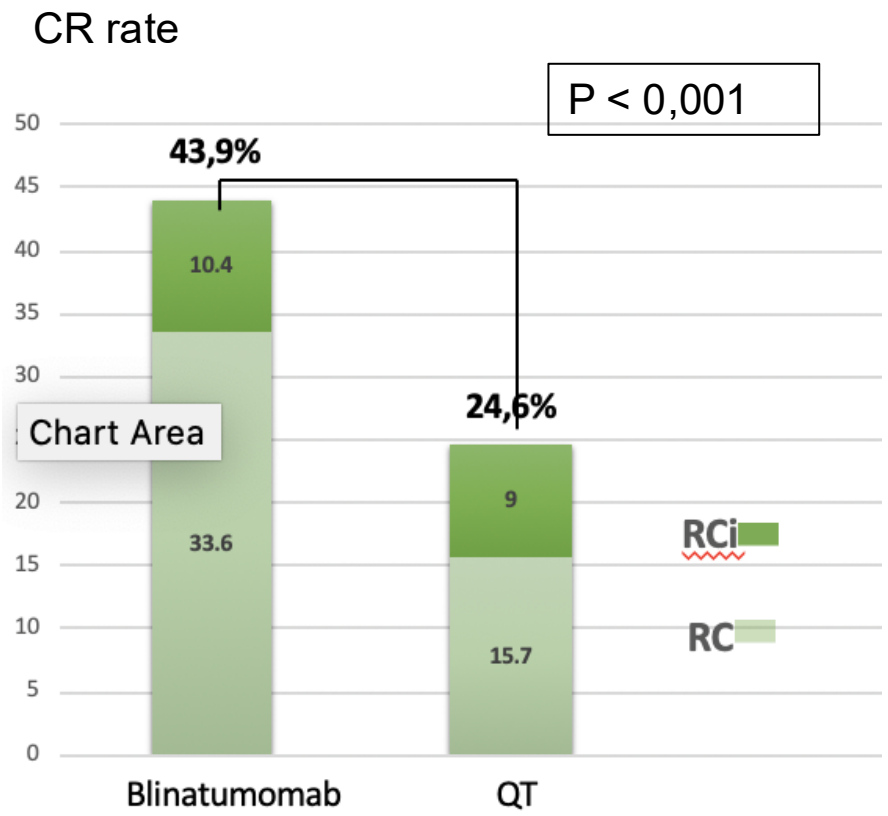
Approved
1- R/R B-ALL
2- MRD positive B-ALL post induction
3- Upfront in consolidation regardless of MRD

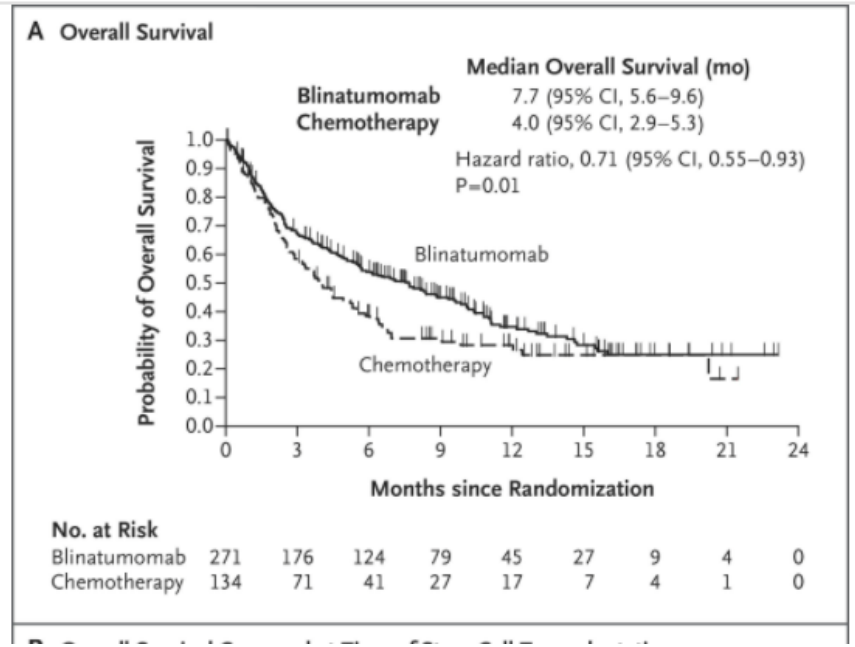
	Ph-Positive	Ph-Negative		Positive MRD
Parameter	Pivotal Phase II (ALCANTARA)	Confirmatory Phase II	Tower Phase III	BLAST Phase II
No. of Patients	45	189	271	116
CR/CRh/ CRi, %	36	43	45	NA
MRD* negativity, %	88	82	76	78
OS, median, mo	7.1	6.1	7.7	36

Kantarjian H, Jabbour E. Am Soc Clin Oncol Educ Book 2018;574–78.

TOWER TRIAL

TOWER trial : Use of Blinatumomab Improved CR rates and OS in Patients with R/R ALL





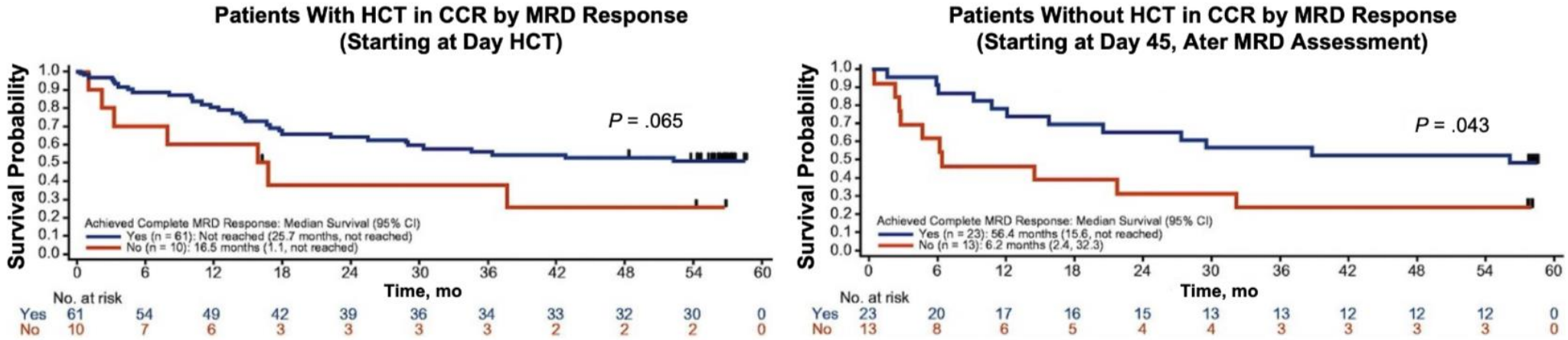
Kantarjian H et al. N Engl J Med 2017;376:836–837

BLAST TRIAL

BLAST: Final Analysis Suggests Complete MRD Response During Blinatumomab Treatment Can Lead to Long-Term Survival

Final Analysis[1]

- 5-y OS was 43%
- Estimated 5-y survival for complete MRD responders: 50%



~78% achieved **MRD negativity** after 1 cycle
Improved **relapse-free survival** in responders

Single-arm, phase II study
Blinatumomab in B-ALL patients in complete remission but **MRD-positive**

1. Gökbuget N et al. *Leuk Lymphoma*. 2020;61:2665-2673.

E1910: Randomized Phase 3 Trial Combining Blinatumomab With CT in Adult Frontline ALL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

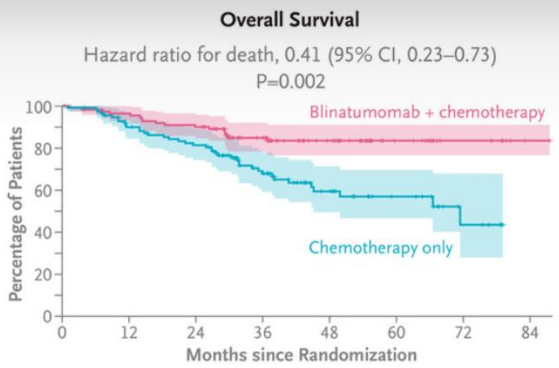
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

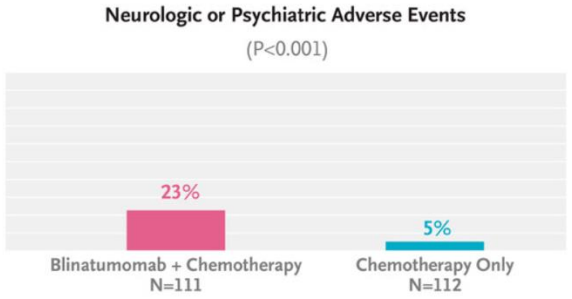
RESULTS

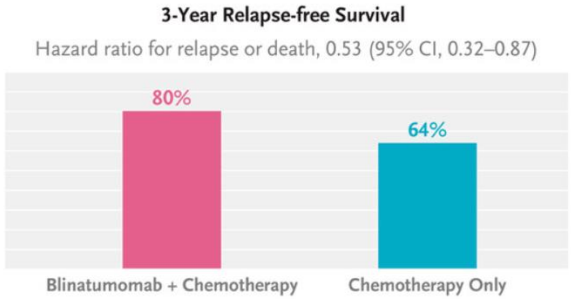
Blinatumomab plus chemotherapy significantly improved overall survival at 3 years, as compared with chemotherapy alone.

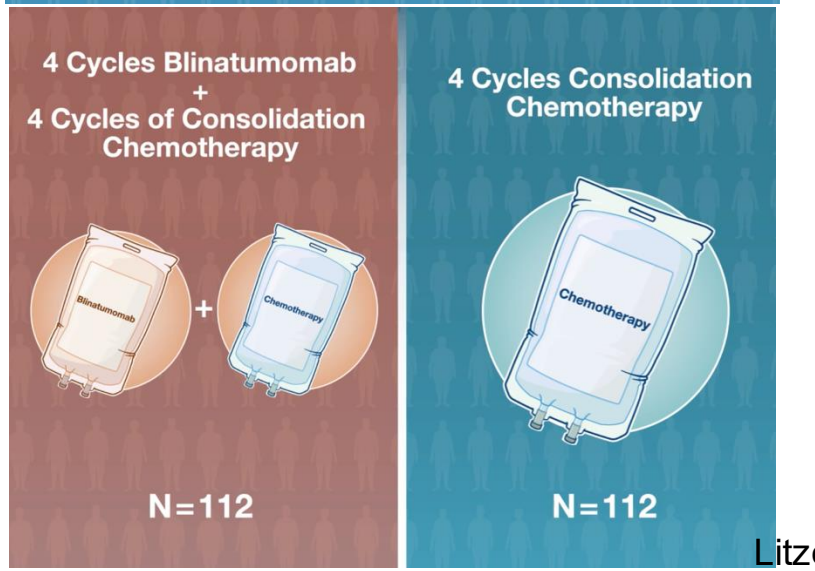
The blinatumomab group also saw a benefit in relapse-free survival at 3 years.

Grade 3–5 treatment-related neurologic or psychiatric adverse events were more common in the blinatumomab group.









Litzow M. et a

Blinatumomab Toxicities

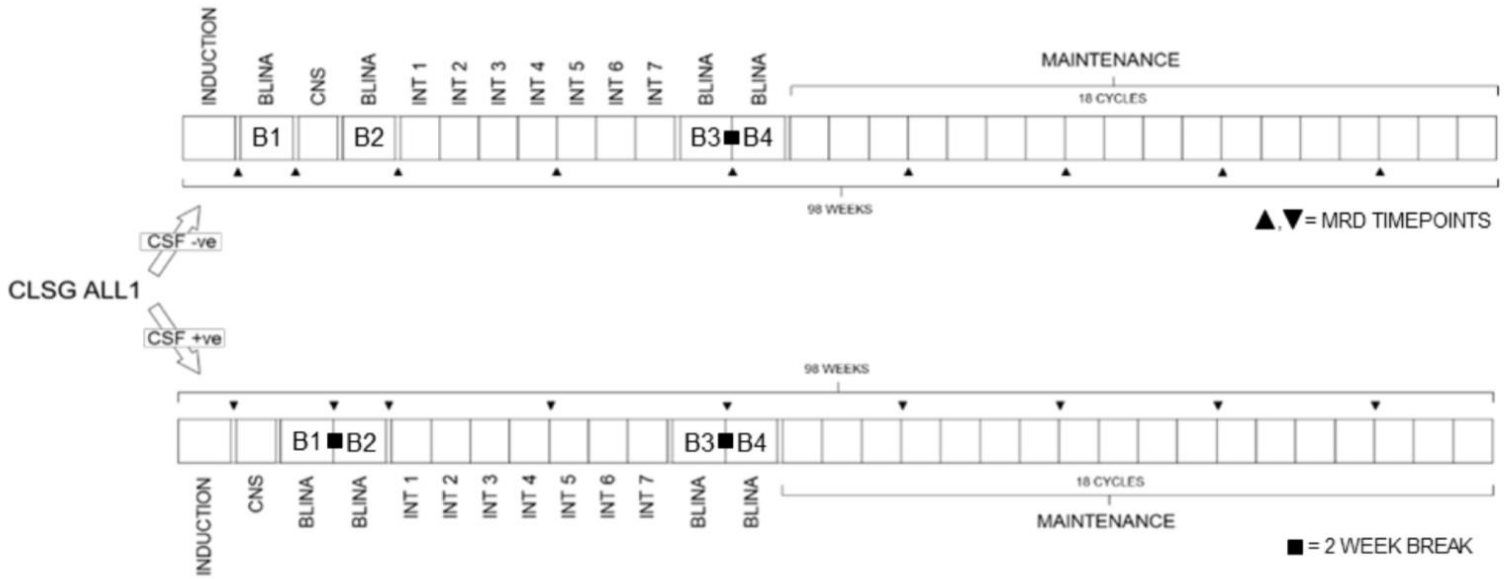
Adverse Event	TOWER (R/R ALL)	BLAST (MRD+ ALL)	ECOG E1910
CRS (any grade)	4.9%	2.0%	2.4%
CRS (Grade ≥3)	0.6%	0%	0%
Neurotoxicity (any grade)	9.4%	13%	7%
Neurotoxicity (Grade ≥3)	2.7%	2.0%	2.4%

Management of CRS and neurotoxicity involves early recognition, treatment interruption if severe, and supportive measures including corticosteroids (for neurotoxicity) and antipyretics or tocilizumab (for CRS).

Kantarjian H et al. N Engl J Med. 2017;376:836-847. 2 Gökbuget N et al. Blood. 2018;131:1522-1531. 3. Litzow M et al.

Blinatumomab integration to pediatric inspired protocol – CLSG-ALL protocol

Overall Protocol Schema:



Attenuated derivative of two PM-DFCI protocols (PM-DFCI <60, Ph-ve V.29; and PM-DFCI ≥60, Ph-ve v.23),

4 MRD-independent cycles of Blinatumomab added

Intensification cycles reduced to 7 (all age groups)

Intensification no longer includes Methotrexate (previously only for <60 years

maintenance is reduced to 18 cycles

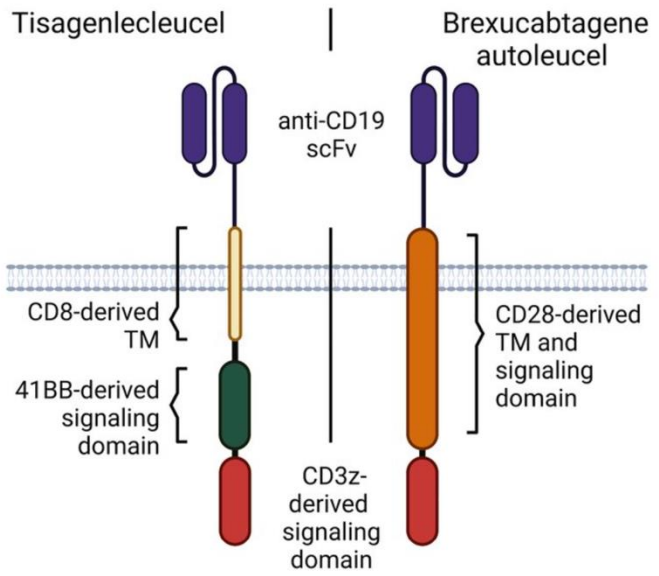
Rationale for Clinical Development of CAR T-Cell Therapy in ALL

- Despite blinatumomab and inotuzumab, median OS for R/R B-ALL remains low at 7-8 mo
- Blinatumomab and inotuzumab have less curative potential as monotherapy in R/R ALL
- <50% of the responding patients proceed to alloHSCT
- Blinatumomab is administered as continuous infusions over 4 wk
- Inotuzumab is associated with VOD/SOS

Kantarjian. NEJM. 2017;376:836. Kantarjian. NEJM. 2016;375:740.
Kantarjian. Cancer. 2019;125:2474. Shah. Lancet. 2021;398:491.

Approved CAR-T cells for R/R B-ALL

Tisagenlecleucel (Kymriah) (Approved Aug 2017)	**Brexucabtagene autoleucel (Tecartus)** (Approved Oct 2021)
Co-stim: 4-1BB	CD28
Age upto 25 yrs	Adult patients
Refractory or second or greater relapse	Relapsed or refractory
Fludarabine 30 mg/m2 x 4 days Cyclophosphamide 500 mg/m2 x 2 days	Fludarabine 25 mg/m2 x 3 days Cyclophosphamide 900 mg/m2 x 1 day
Cell dose: 0.1 to 2.5 x 10^8 CAR+ T cells	1 x 10^6 CAR+ T cells / kg



Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

The NEW ENGLAND JOURNAL of MEDICINE
Maude SL et al. N Engl J Med2018;378:439-448

ELIANA Study Design

Key Eligibility Criteria

• Inclusion:
- R/R B-cell ALL, aged 3-21 years
- Bone marrow with ≥ 5% lymphoblasts

• Exclusion:
- Isolated EMD relapse
- Prior CD19-directed or gene therapy

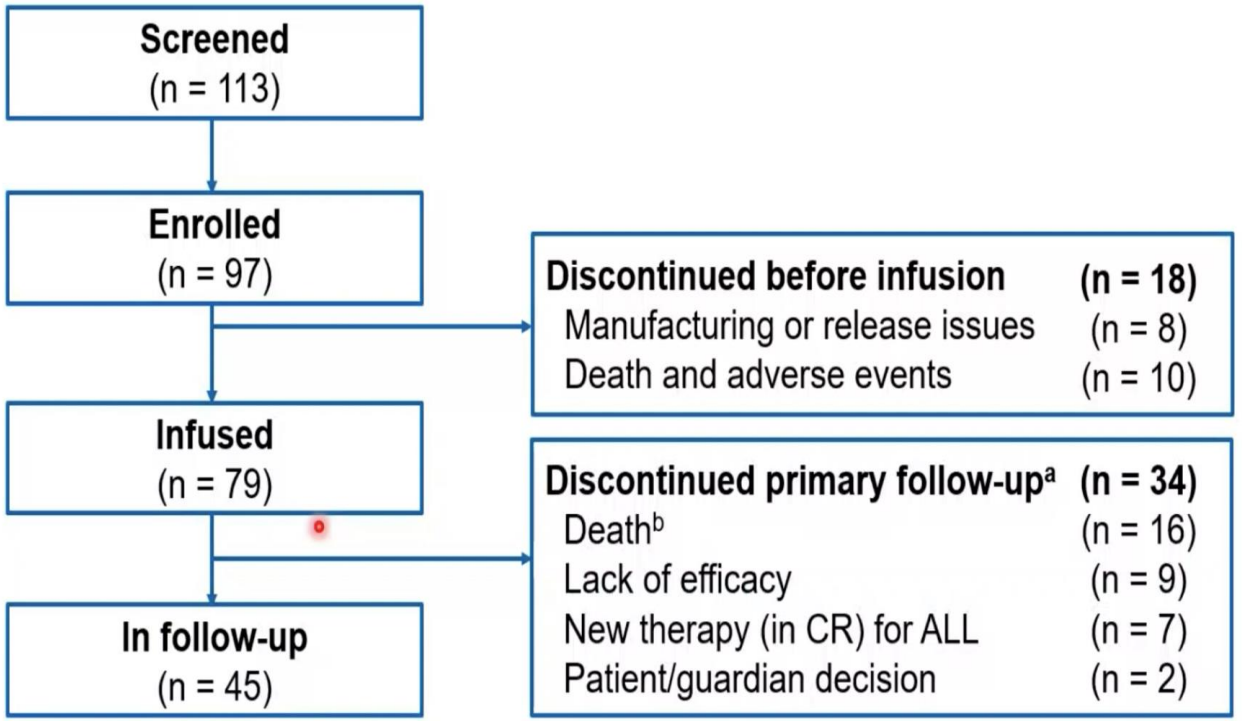
Endpoints

• Primary endpoint: Overall remission rate (CR + CRi) within 3 months
- 4-week maintenance of remission
- IRC assessment

Study Treatment

• Lymphodepleting chemotherapy prior to infusion
- Fludarabine 30 mq/m2 IV daily for 4 doses
- Cyclophosphamide 500 mg/m2 IV daily for 2 doses
- Tisagenlecleucel dose range (single infusion)
  0.2 to 5.0 × 106 cells/kg for patients≤50 kg
  0.1 to 2.5 × 108 cells for patients > 50 kg

Patient disposition and key baseline characteristics

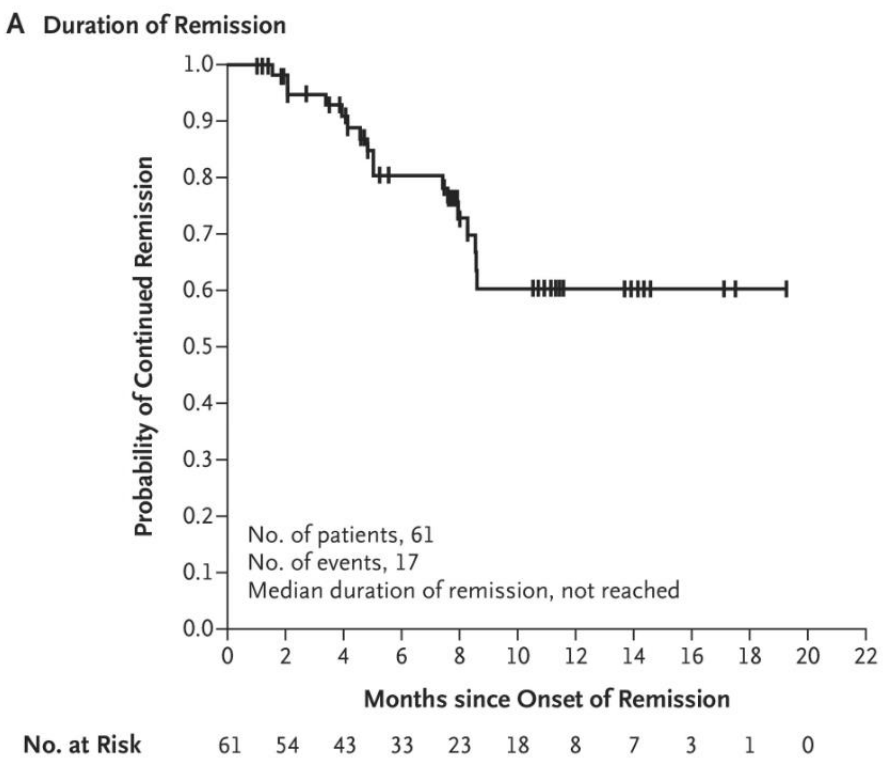


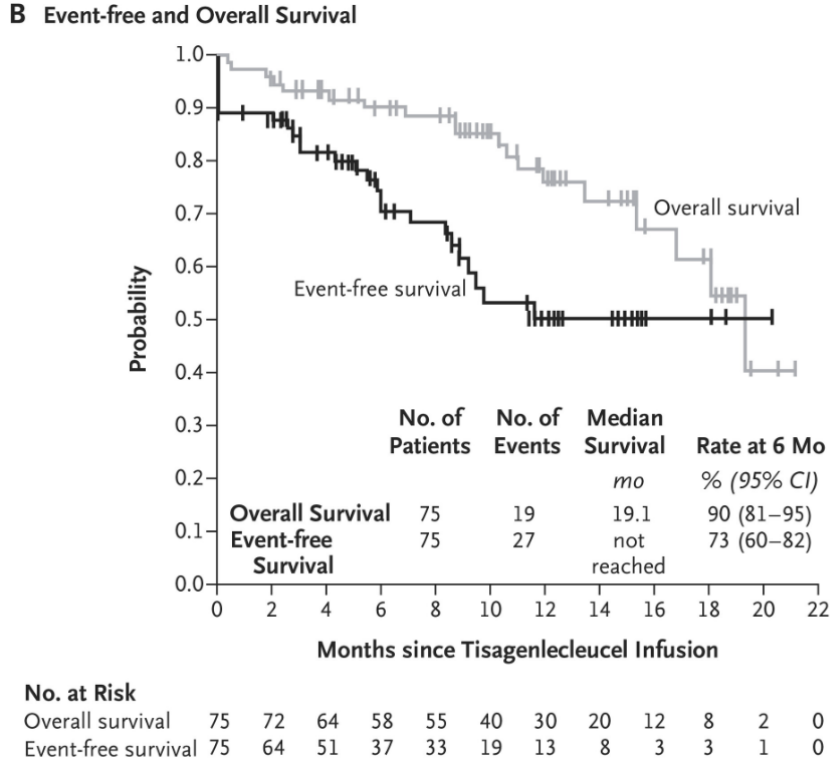
Median time from infusion to data cut-off (13 April 2018) was 24.2 months (range, 4.5-35.1 months)

	All Patients (N=79)
Median age (range), years	11 (3–24)
Male sex, n (%)	45 (57)
Prior alloSCT, n (%)	48 (61)
Lines of prior therapies, median (range)	3 (1–8)
Disease status – Primary refractory, n (%)	6 (8)
Morphologic BM blast count, median (range), %	74 (5–99)
CNS status classification, n (%)	
• CNS-1	67 (85)
• CNS-2	10 (13)
• CNS-3	1 (1)
• Unknown	1 (1)

Maude SL et al. N Engl J Med2018;378:439-448

Duration of Remission, Event-free Survival, and Overall Survival





Follow-up:13.1 months

CR + CRi 82% (65/79)

-98% (64/65) achieved MRD(-) BM

Note: Only patients who achieved CR or CRI were included. Time is relative to onset of remissior a The response was unknown in 6 patients While in remission. 8 patients went on to stem-cell transplantation
~ MRD negatlve = MRD < 0.01%, as assessed by fiow cytometry.
OR, complete remission; CRI, complete remisslon with incomplete blood count recovery; MRD, minimal residual disease, NE, not estimable

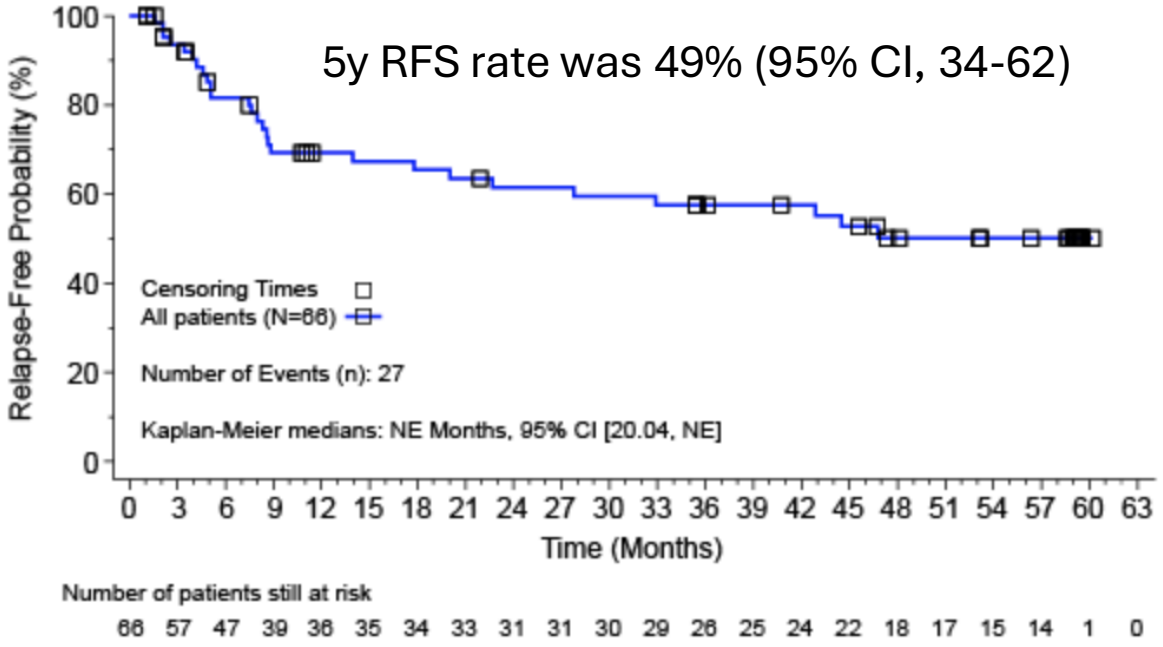
Maude SL et al. N Engl J Med2018;378:439-448

ELIANA – Long-term follow-up

S112 TISAGENLECLEUCEL IN PEDIATRIC AND YOUNG ADULT PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL): FINAL ANALYSES FROM THE ELIANA STUDY

Topic: 02. Acute lymphoblastic leukemia - Clinical

Figure. Relapse-Free Survival. Only patients who achieved BOR of CR or CRi are included. BOR, best overall response; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; NE, not estimable.



Continued durable efficacy without late adverse effects

	Patients Who Achieved Remission (N=69)
Received post-infusion alloSCT, n (%)	17 (25)
AlloSCT in remission	10 (14)
AlloSCT after relapse	7 (10)

Follow-up to 5.9 years

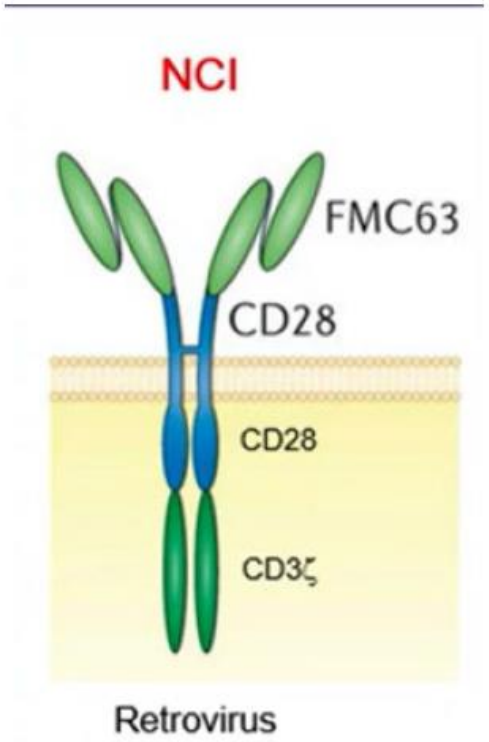
Presentation during EHA2022: Susana Rives

KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

Bijal D Shah, Armin Ghobadi, Olalekan O Oluwole, Aaron C Logan, Nicolas Boissel, Ryan D Cassaday, Thibaut Leguay, Michael R Bishop, Max S Topp, Dimitrios Tzachanis, Kristen M O'Dwyer, Martha L Arellano, Yi Lin, Maria R Baer, Gary J Schiller, Jae H Park, Marion Subklewe, Mehrdad Abedi, Monique C Minnema, William G Wierda, Daniel J DeAngelo, Patrick Stiff, Deepa Jeyakumar, Chaoling Feng, Jinghui Dong, Tong Shen, Francesca Milletti, John M Rossi, Remus Vezan, Behzad Kharabi Masouleh, Roch Houot

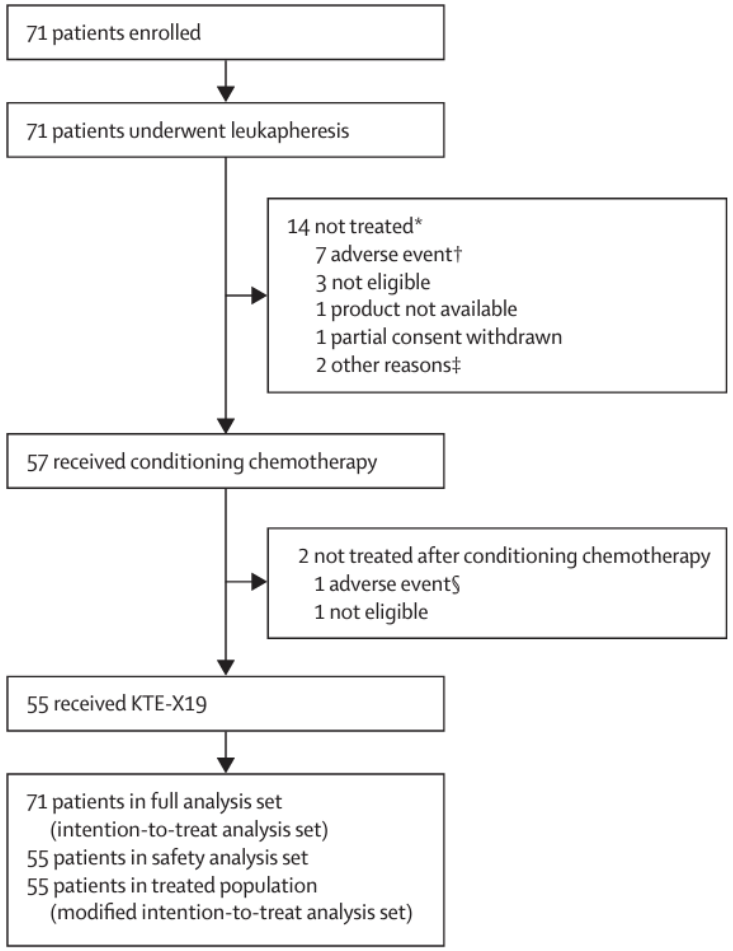
Autologous anti-CD 19 CAR-T
R/R B-ALL aged >18 yrs with 5% marrow blasrt

Lymphodepletion
Flu 25 mg/m2 (day -4,-3,-2_)
Cyclo 99 mg/m2 (day -2_
Dose = 1 million CAR-T/KG



Kite -> Gilead
KTE-C19 Axicabtagene
KTE-X19 Brexucabtagene

BREXU-CEL – ZUMA3 trial
KTE-X19 in Adult B-ALL (ZUMA-3)

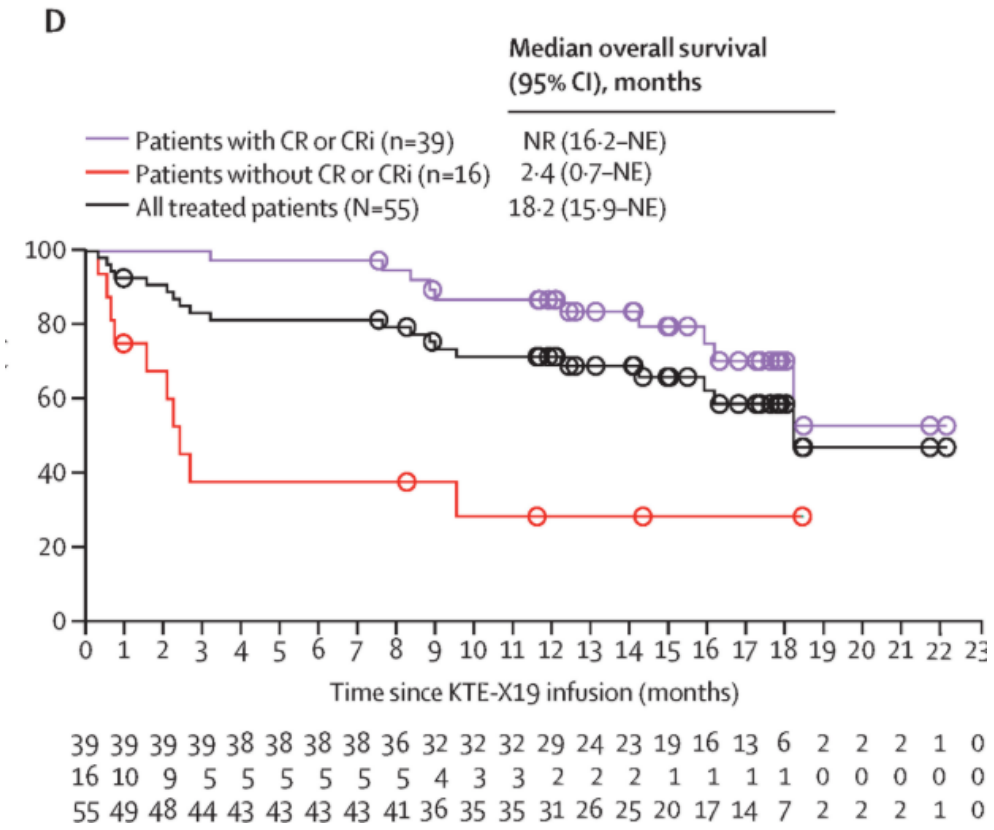


Phase 2 results of ZUMA-3
Multicenter, single-arm
Relapsed or refractory B-precursor acute lymphoblastic leukemia.
Aged 18 years or older, with ECOG of 0–1, and marrow blasts >5% blasts

Median age	40 years
Number of prior therapies	2
Prior blinatumomab	45%
Prior inotuzumab	22%
Prior allo-SCT	42%
Median pre-LD BM blasts	59%

Shah et al. Lancet. 2021 Aug 7;398(10299):491-502.

BREXU-CEL – ZUMA3 trial OUTCOMES



	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57–82, p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.

Table 2: **Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment**

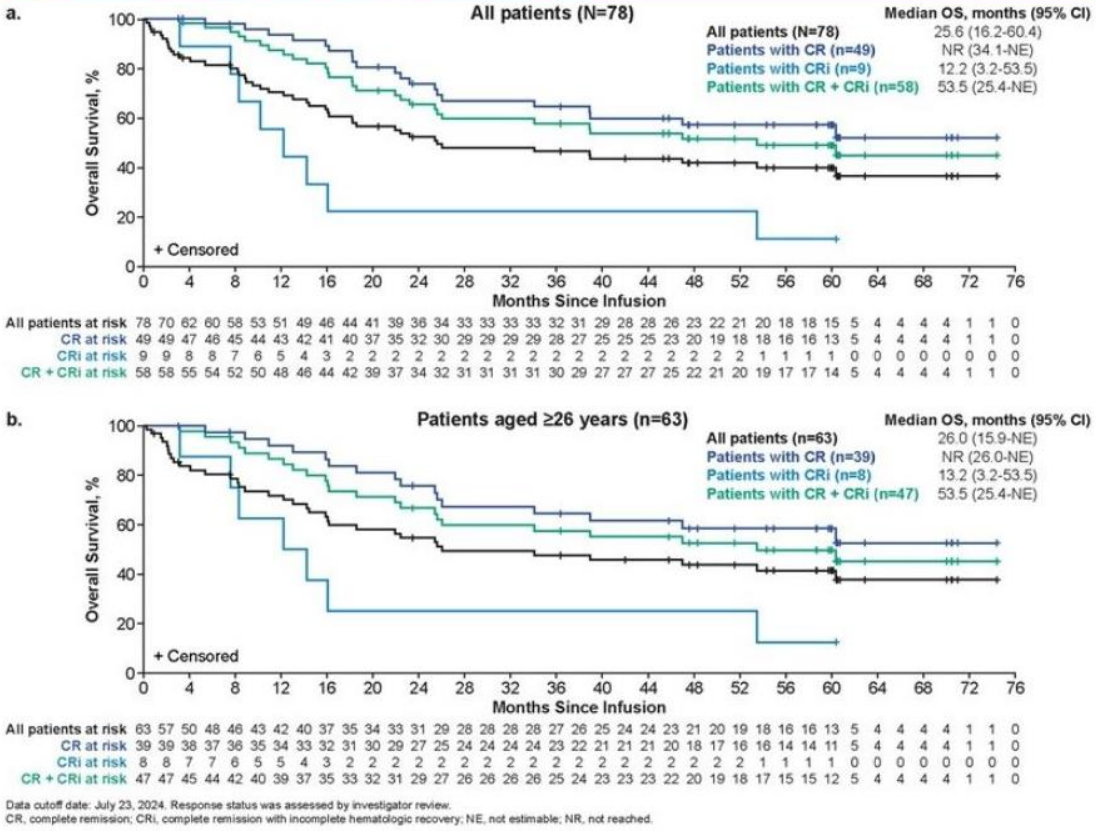
After a median follow-up of 16·4 months, median overall survival was 18·2m

The median duration of remission both with and without censoring patients at subsequent allo-SCT was 12·8 months (95% CI 8·7–not estimable with censoring, 9·4–not estimable without censoring

Shah et al. Lancet. 2021 Aug 7;398(10299):491-502.

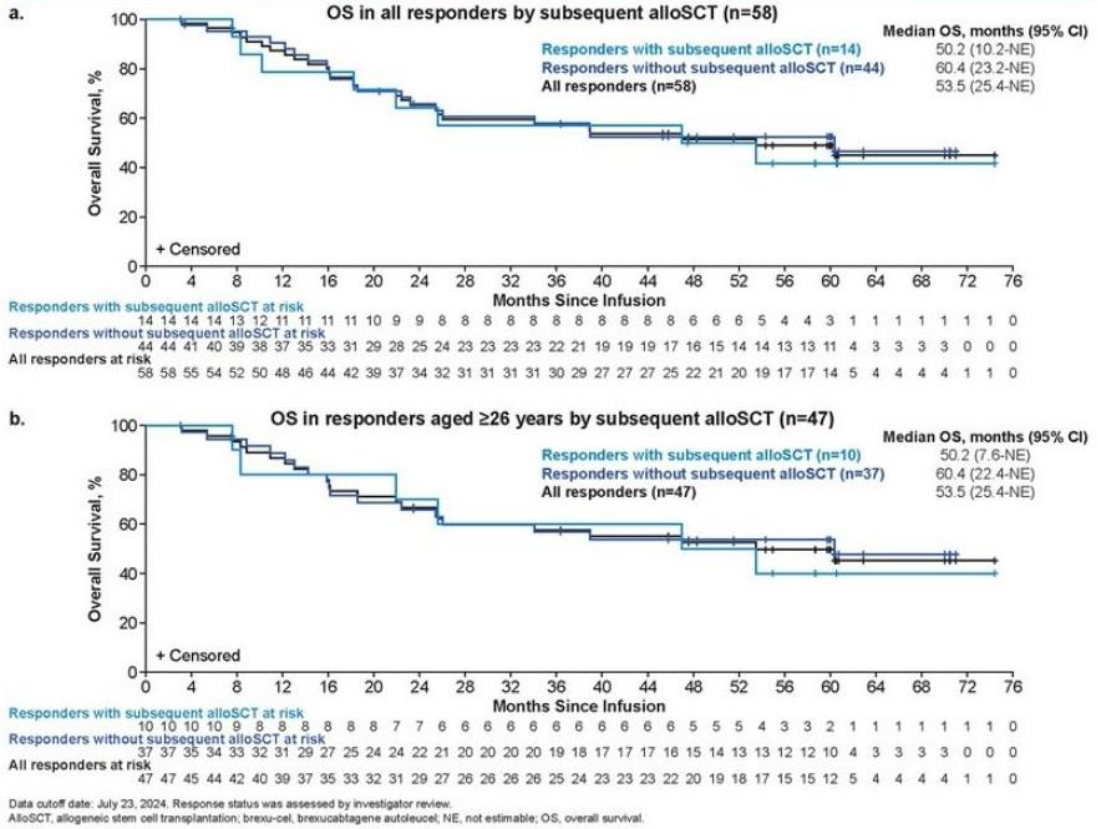
ZUMA-3 - FIVE-YEAR SURVIVAL OUTCOMES OF PATIENTS (PTS) WITH RELAPSED OR REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (R/R B-ALL) TREATED WITH BREXUCABTAGENE AUTOLEUCEL (BREXU-CEL) IN ZUMA-3

Figure 3. Overall Survival Update in ZUMA-3



Data cutoff date: July 23, 2024. Response status was assessed by investigator review.
CR, complete remission; CRi, complete remission with incomplete hematologic recovery; NE, not estimable; NR, not reached.

Figure 4. Overall Survival Update in ZUMA-3 by Subsequent AlloSCT



Data cutoff date: July 23, 2024. Response status was assessed by investigator review.
AlloSCT, allogeneic stem cell transplantation; brexu-cel, brexucabtagene autoleucel; NE, not estimable; OS, overall survival.

EHA 2025 (16-05-2025)- Olalekan Oluwole et al

ADVERSE EVENTS CAR-T CELLS

Parameter	**KTE-X19 (ZUMA-3)**	**Tisa-cel**
Median time to CRS onset	5 days	~3–4 days
Grade ≥3 CRS (%)	24%	~22–26%
Median time to ICANS onset	9 days	~6–9 days
Grade ≥3 ICANS (%)	25%	~10–12%
Neurotoxicity-related deaths	1 (brain herniation)	Rare
Median hospitalization (post infusion)	22 days	~2–3 weeks
Tocilizumab use (%)	80%	~60–70%
Steroid use (%)	75%	~40–50%
Vasopressor support (%)	40%	~20–30%

CAR-T in ALL: Key Unanswered Questions

- **Optimal Timing**
  - When to use CAR-T: earlier lines vs. after multiple relapses?
  - Role as bridge vs. definitive therapy
- **Impact of Prior Therapies**
  - Effect of prior blinatumomab (CD19 targeting) on CAR-T efficacy
  - Influence of prior inotuzumab on outcomes and toxicity
  - Antigen loss and resistance mechanisms
- **Need for Consolidation**
  - Is post–CAR-T allo-SCT necessary for durable remission?
- **Durability and Monitoring**
  - Predictors of long-term remission vs. relapse
  - Role of MRD and CAR-T persistence
- **Toxicity Optimization**
  - How to reduce CRS and ICANS without compromising efficacy

Future direction

- **Less toxicity**
- **More durable responses** – combinations
- **New and multiple targets**
- **Sequential treatment**
- **Earlier use of better therapies**

New Strategies Being Assessed With Implications for Treatment of R/R B-ALL

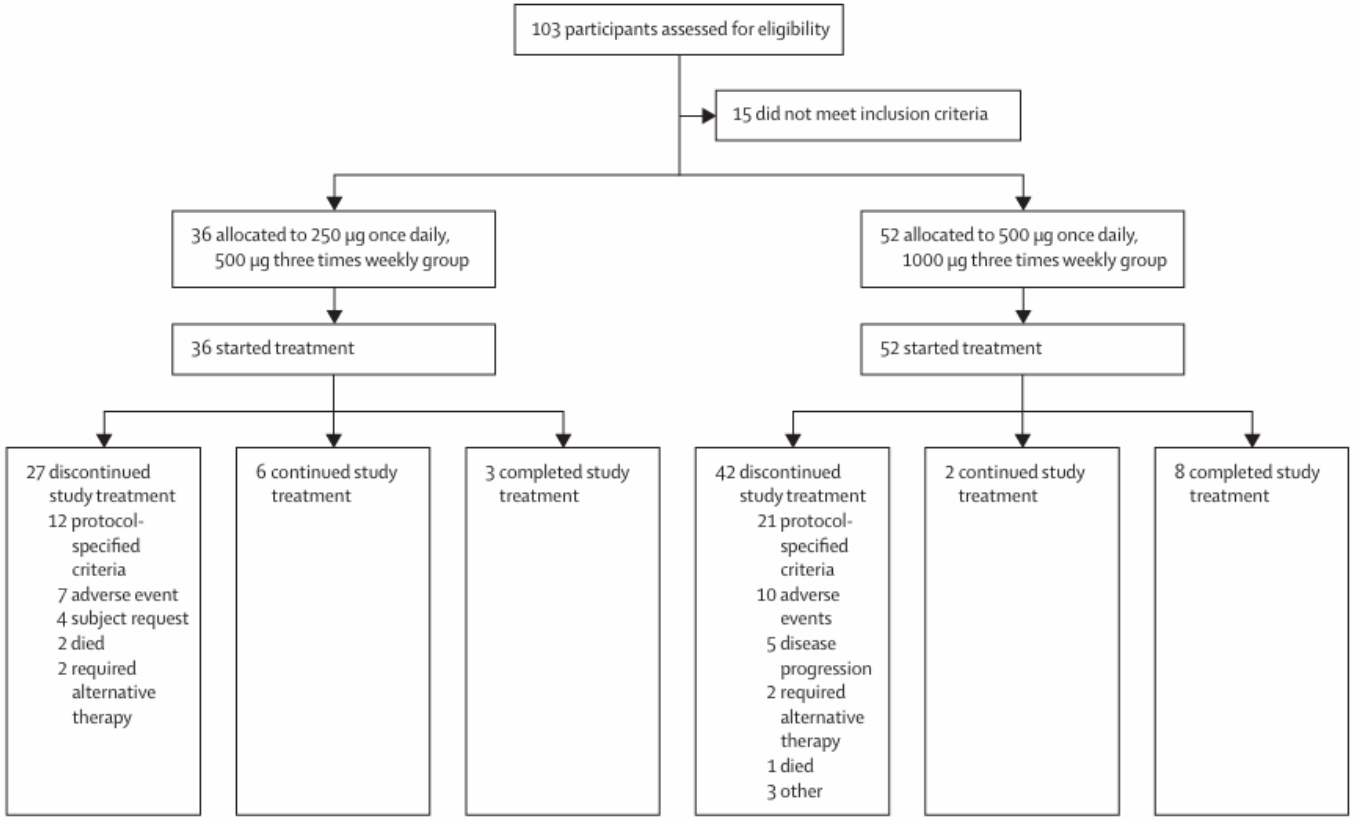
Bispecific Antibodies

- Subcutaneous Blinatumomab
- Emerging CD19 × CD3 agents
  - Surovatamig (SYRUS)
  - MK-1045 (CN201)
- Trispecific antibodies
  - CD19 × CD22 × CD3

CAR-T Cell Therapies

- CD19 CAR-T
  - OBE-CEL → Intermediate affinity CD19 binding with fast off-rate (↓ toxicity, ↑ engraftment & persistence)
- CD22 CAR-T
- Dual-target CAR-T (CD19/CD22)
- Allogeneic (ALLO) CAR-T cells

Subcutaneous blinatumomab in adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: post-hoc safety and activity analysis from a multicentre, single-arm, phase 1/2 trial



	250 µg/500 µg group (n=36)	500 µg/1000 µg group (n=52)
Sex*		
Male	22 (61%)	33 (63%)
Female	14 (39%)	19 (37%)
Age, years	46 (19–78)	50 (19–76)
Race†		
American Indian or Alaska Native	0	2 (4%)
Asian	0	6 (12%)
Black or African American	2 (6%)	1 (2%)
White	25 (69%)	31 (60%)
Other	9 (25%)	11 (21%)
Missing	0	1 (2%)
Hispanic or Latino ethnic group	15 (42%)	18 (35%)
B-ALL Philadelphia chromosome positive	7 (19%)	8 (15%)
Extramedullary disease		
Yes	1 (3%)	3 (6%)
Yes—CNS	0	2 (4%)
Yes—testis	0	0
Yes—other	1 (3%)	1 (2%)
No	35 (97%)	49 (94%)
Received previous anticancer therapy		
Blinatumomab	8 (22%)	9 (17%)
CAR T-cell therapy	7 (19%)	7 (13%)
HSCT	11 (31%)	14 (27%)
Inotuzumab ozogamicin	11 (31%)	18 (35%)
Criteria for entry to study		
Refractory to frontline therapy	17 (47%)	15 (29%)
Refractory to salvage therapy	4 (11%)	8 (15%)
First relapse with remission duration of <12 months	16 (44%)	24 (46%)
Untreated second or greater relapse	10 (28%)	12 (23%)
Relapse any time after allogeneic HSCT	11 (31%)	15 (29%)
Primary refractory at enrolment‡	5 (14%)	7 (13%)

Primary endopoint: CR / CRpH after 2 cycles
Pre phase: Dex (16%), dex + chemo (48%), chemo (14%)

Prof Elias Jabbour, M. The LaNCET: Published June 15, 2025

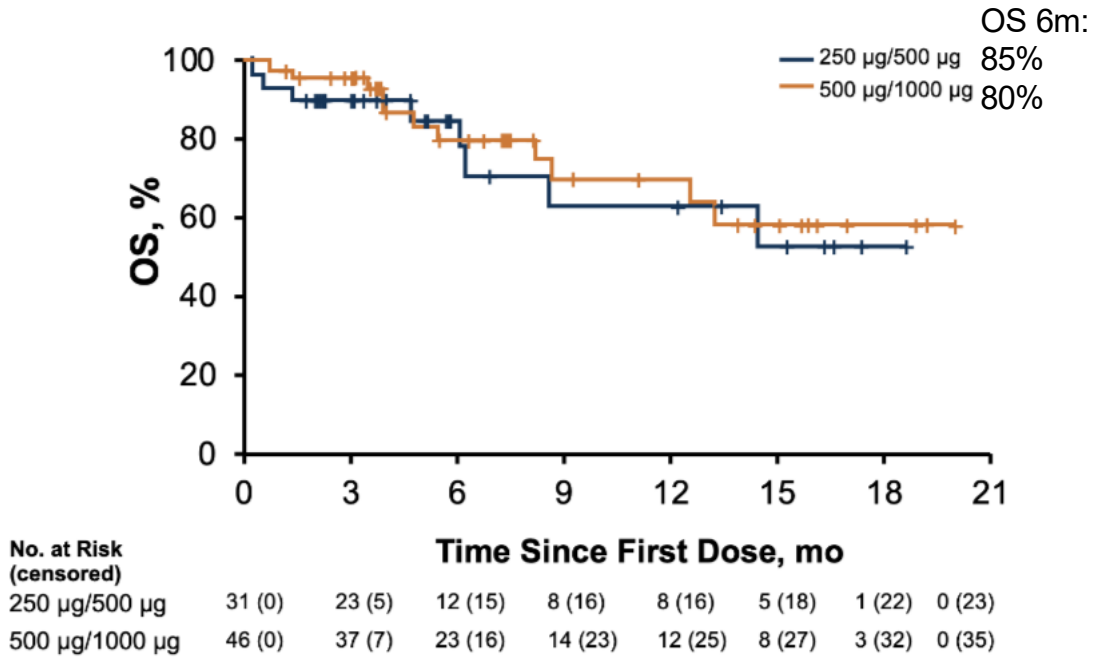
Subcutaneous Blinatumomab

SC blina	250/500 µg	500/1000 µg	All patients
	36	52	88
CR/CRh within 2 cycles, n (%)	27 (75%)	41 (79%)	68 (77%)
MRD <10⁻ among CR/CRh, n/ (%)	24/27 (89%)	38/41 (93%)	62/68 (91%)

Median follow-up: 5 months (iqr 3-9)

Adverse Event	Rate (%)
Neutropenia	22%
CRS	20%
ICANS	17%
Serious AEs	**80%** (mainly CRS, ICANS)

Parameter	Timing
CRS onset	~1 day
CRS resolution	~5 days
ICANS onset	2–4.5 days
ICANS resolution	6–12 days



250/500 µg selected as the recommended phase 2 dose

1. Jabbour E et al. Lancet Haematol. 2025;12:e529-e541

Efficacy of single-agent subcutaneous blinatumomab in adults with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL): Results from a phase 1/2 dose expansion study with extended follow-up

Efficacy outcomes with an additional 7 months of follow-up for all patients who were enrolled and received at least one dose of SC blinatumomab.

Efficacy & Survival (Extended Follow-up)
- Median follow-up: **11.4 vs 16.3 months** (250/500 vs 500/1000)
- **12-month OS:** 72.3% vs 67.4%
- **No new safety signals**

Outcomes by HSCT (CR/CRh responders)
- 12-month OS: **80.2% (HSCT)** vs **85.2% (no HSCT)**
- Alive at data cutoff: **78% (HSCT)** vs **76% (no HSCT)**

Conclusion
- **Durable remissions and OS across doses**
- **Consistent benefit regardless of HSCT**
- Supports **SC blinatumomab** as an effective option in R/R B-ALL

Elias Jabbour, ASH25

The NEW ENGLAND JOURNAL of MEDICINE

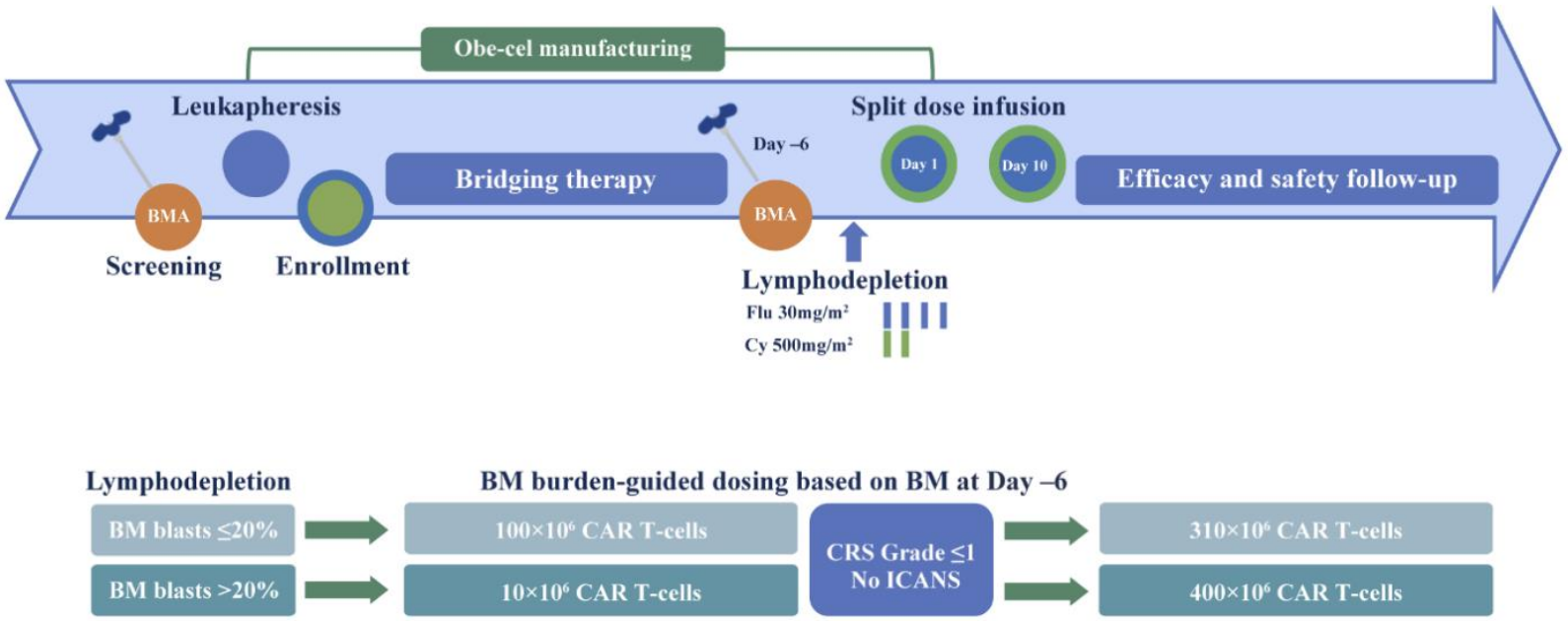
ORIGINAL ARTICLE

Obecabtagene Autoleucel in Adults with B-Cell Acute Lymphoblastic Leukemia

Claire Roddie, M.D., Karamjeet S. Sandhu, M.D., Eleni Tholouli, M.D.,

This article was published on November 27, 2024, at NEJM.org.

Figure S2. FELIX Ib/II Trial Design.



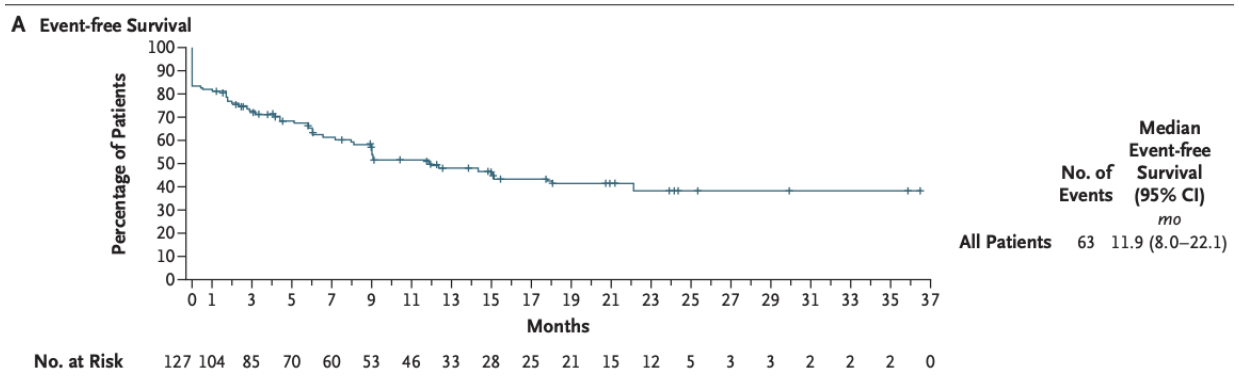
BM, bone marrow; BMA, bone marrow aspirate; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome.

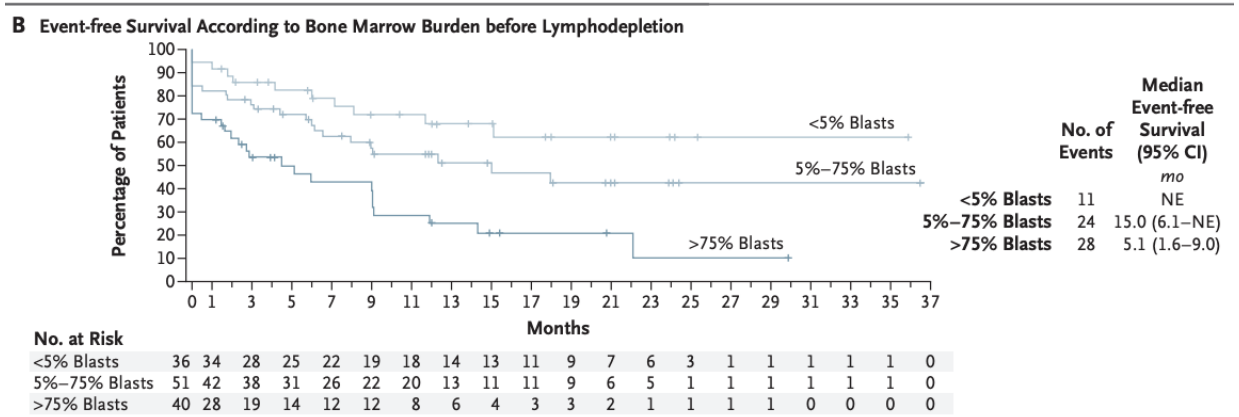
Patients aged ≥18 years with R/R B-ALL CAR-T products were generated via an automated process.

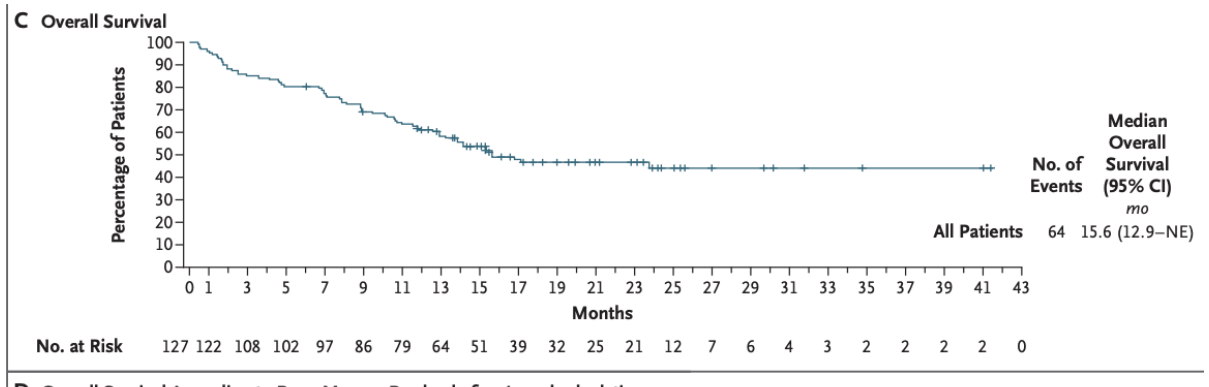
Patients received:
- bridging therapy (at the investigator's discretion- NO blinatumomab)
- lymphodepletion (fludarabine, 4×30mg/m2; cyclophosphamide, 2×500mg/m2).
- Obe-cel by split dose infusions on Days 1 and 10 based on pre-lymphodepletion leukemic burden at a target dose of 410×10*6 CAR-T cells.

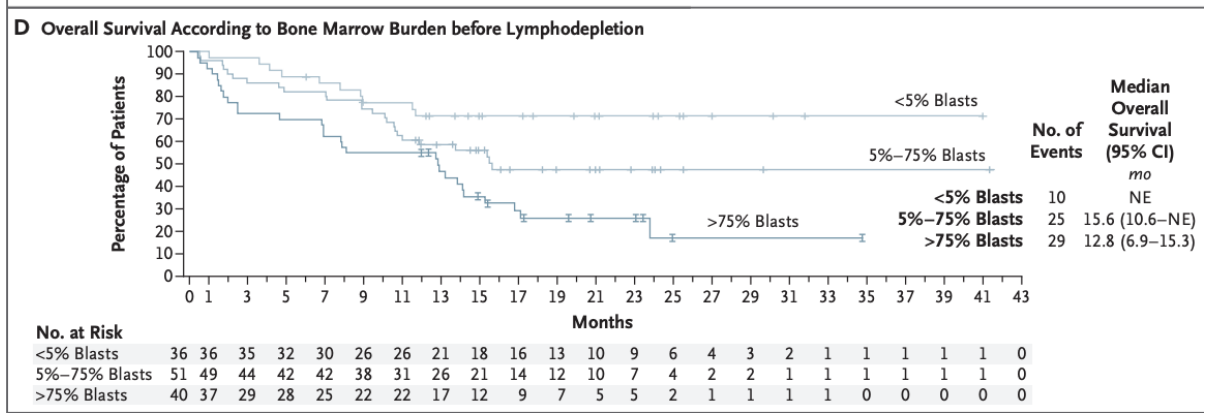
FELIX TRIAL - EFS - OS

- **Follow-up:** Median follow-up 20.3 months (cohort 2A); 21.5 months overall.
- **Remission (≥5% blasts):** 75% overall remission (68/91 patients).
- **MRD status:** 94% of responders with available data were MRD-negative after obe-cel.









Median EFS 11.9 months
Median OS 15.6 months

FELIX TRIAL : AEs

Parameter	KTE-X19 (ZUMA-3)	Tisa-cel	Obe-cel (FELIX)
Median time to CRS onset	5 days	~3–4 days	~8–9 days
Grade ≥3 CRS (%)	24%	~22–26%	~3–5%
Median time to ICANS onset	9 days	~6–9 days	~10–11 days
Grade ≥3 ICANS (%)	25%	~10–12%	~7–10%
Neurotoxicity-related deaths	1 (brain herniation)	Rare	Rare
Median hospitalization (post infusion)	22 days	~2–3 weeks	~2 weeks (shorter trend)
Tocilizumab use (%)	80%	~60–70%	~20–30%
Steroid use (%)	75%	~40–50%	~25–35%
Vasopressor support (%)	40%	~20–30%	<10%

Table 3. Summary of Adverse Events of Special Interest.*

Event	<5% Blasts (N=36)		5–75% Blasts (N=51)		>75% Blasts (N=40)		All the Patients Who Received Infusion (N=127)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)							
Cytokine release syndrome	17 (47)	0	36 (71)	2 (4)	34 (85)	1 (2)	87 (69)	3 (2)
ICANS	3 (8)	0	10 (20)	4 (8)	16 (40)	5 (12)	29 (23)	9 (7)
Febrile neutropenia	—	—	—	—	—	—	31 (24)	30 (24)
Infections and infestations	—	—	—	—	—	—	99 (78)	66 (52)

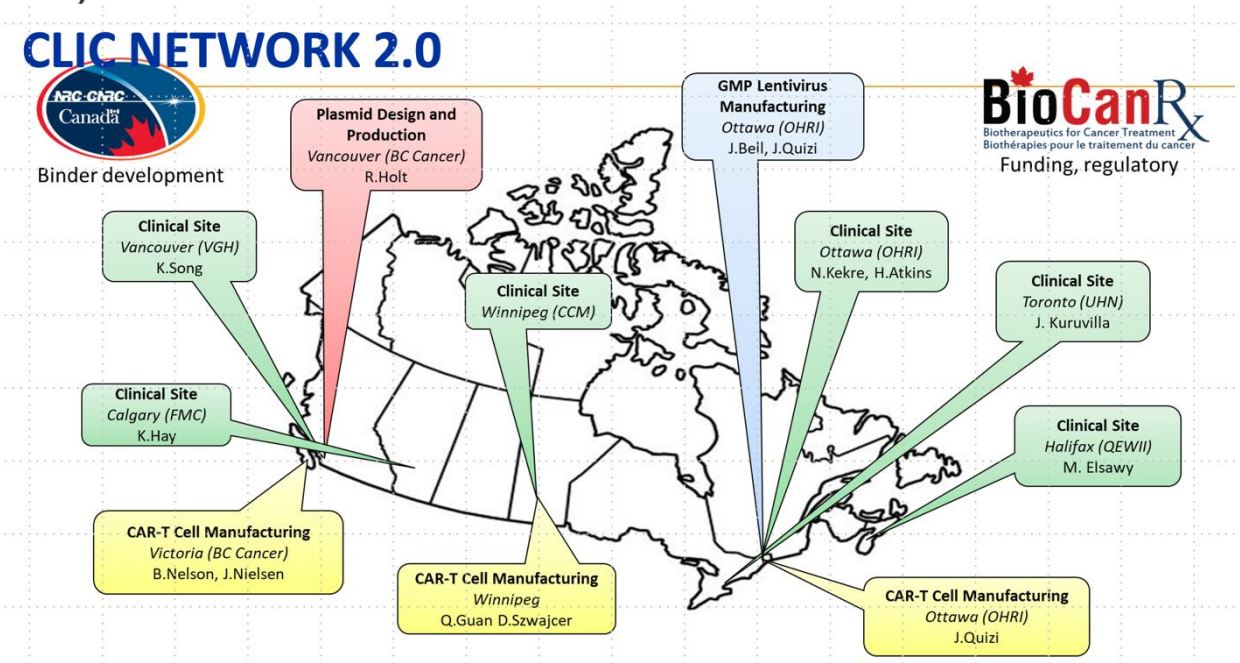
* Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS) are shown for all the patients who received at least one infusion of obe-cel and according to bone marrow burden before lymphodepletion. Febrile neutropenia and infections are shown for all the patients who received at least one infusion of obe-cel.

Hematologic recovery: Median time to neutrophil recovery was 21 days; platelet recovery also 21 days.
ICU admissions: 15.7% of patients required ICU care (median 5.5 days); one-third due to immunotoxicity (ICANS or CRS).
Treatment-related mortality: 2 deaths attributed to obe-cel (ARDS with ICANS; neutropenic sepsis).
Safety associations: Higher post-infusion markers were linked to increased CRS/ICANS, but not higher remission rates.
Comparative safety: markedly lower rates of severe CRS, severe ICANS, and vasopressor use compared with brexu-cel.

Ongoing Canadian Trial: CLIC-02: A Phase I Trial for the Treatment of Relapsed/Refractory B cell malignancies - NCT06208735

CLIC-01 Canadian-Led Immunotherapies in Cancer

- Novel CD22 CAR-T cell product, CLIC-2201, which contains a targeting moiety derived from a single domain llama-derived antibody, known as a VHH, against CD22.
- Second-generation CAR configuration; specifically, the gene contains the CD22-VHH targeting domain, a CD8 alpha hinge and transmembrane domain, a 4-1BB costimulatory domain, and a CD3 zeta signaling domain. Replication incompetent lentivirus containing the synthetic CAR gene was produced using the same lentiviral packaging system used in our previous CD19 CAR T-cell trial (CLIC-01).
- Primary Objective: To evaluate the safety and tolerability of CLIC-2201 and estimate the maximum tolerated dose (MTD) of CLIC-2201.



Sponsor Investigator: Dr. Kevin Hay
Participating sites:
Vancouver General Hospital: Dr. Hannah Cherniawsky
BC Children's Hospital: Dr. Amanda Li
The Ottawa Hospital: Dr. Natasha Kekre
Princess Margaret Cancer Centre: Dr. John Kuruvilla
The Hospital for Sick Children: Dr. Joerg Krueger
Tom Baker Cancer Centre: Dr. Robert Puckrin
Alberta Children's Hospital: Dr Victor Lewis

Take-Home Messages – Summary

Treatment of ALL is shifting from chemotherapy-based approaches to immunotherapy-driven strategies

Immunotherapy has significantly improved outcomes across disease settings (R/R, MRD+, and frontline)

Early integration and optimal sequencing of these therapies are key to maximizing benefit and remain an area of ongoing evolution

Thank you

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