CAR-T cells e anticorpi monoclonali bispecifici:

indicazioni e prospettive di impiego in ematologia e reumatologia

Ferrara - 30 Ottobre 2024 Hotel Ferrara

CAR-T cells: dati recenti ed esperienza italiana

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Disclosures of Alice Di Rocco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche			X		x	X	
Incyte			X		X		
Kite/Gilead					X	X	
Abbvie			X		X	X	
Takeda			X		X	X	
Eli-Lilly					X		
Novartis					X	X	
BMS					X		
Recordati rare disease					X		
Jannsen			X		X		

Agenda

- Efficacy outcomes of CART19 in R/R B-ALL
  - Adolescents and young adults → Tisa cel (4-1BB)
  - Adults → Brexu cel (CD28)
- Effect of CD19 expression and blinatumomab
- The evolving role of allo-SCT in the era of CAR-T cells
- Limits to durable remissions after CAR T cell therapy

Relapsed/refractory B-cell ALL in pediatric and young adult patients

- B-cell acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children
- Despite current treatment options, **~15% pediatric and young adult** patients with ALL experience relapsed/ refractory (r/r)disease
  - Median overall survival is 3 to 9 months
- Unmet medical need for novel treatment options for pediatric and young adult patients with r/r ALL to provide
  - Deep and durable remission
  - Curative treatment opportunities
  - Improved quality of life

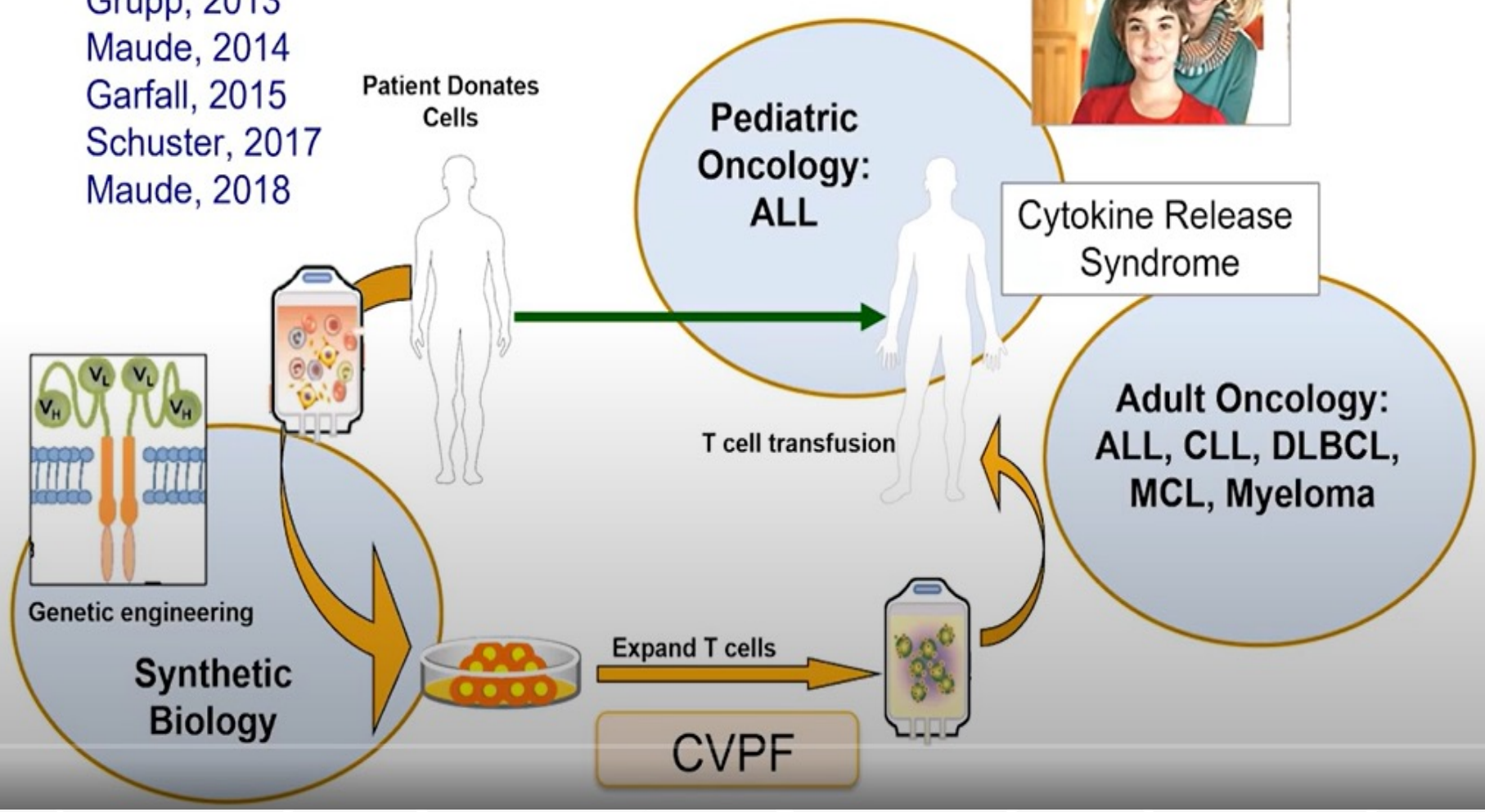
Pui CH, et al. *J Clin Oncol*. 2011;29(5):551-565.

The NEW ENGLAND JOURNAL of MEDICINE

Porter, 2011
Grupp, 2013
Maude, 2014
Garfall, 2015
Schuster, 2017
Maude, 2018

July 31, 2010
1st CART19 Infusion

The New York Times



The NEW ENGLAND JOURNAL of MEDICINE

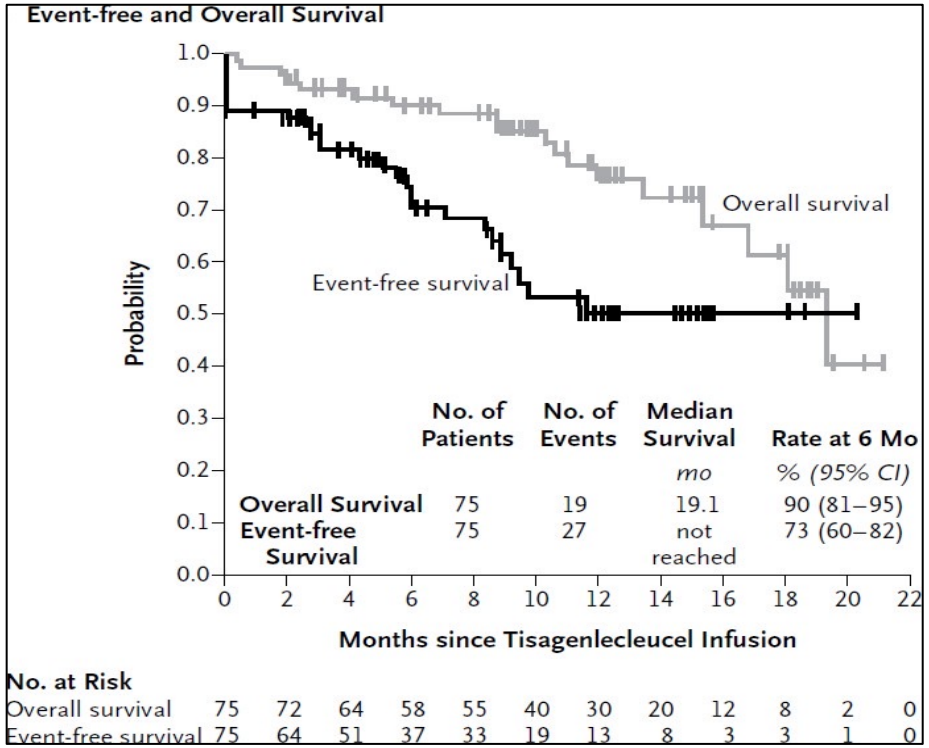
ORIGINAL ARTICLE

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

ELIANA study

- 97 patients enrolled, 79 treated
- 43% grade 3-4 CRS
- 47% PICU for CRS (13% ventilated, 25% inotropes)
- 40% neurotoxicity, but mostly mind
- 82% → CR/Cri, all MRD negative; 66% in intention to treat analysis
- 1 year EFS at 50%, no relapse after this

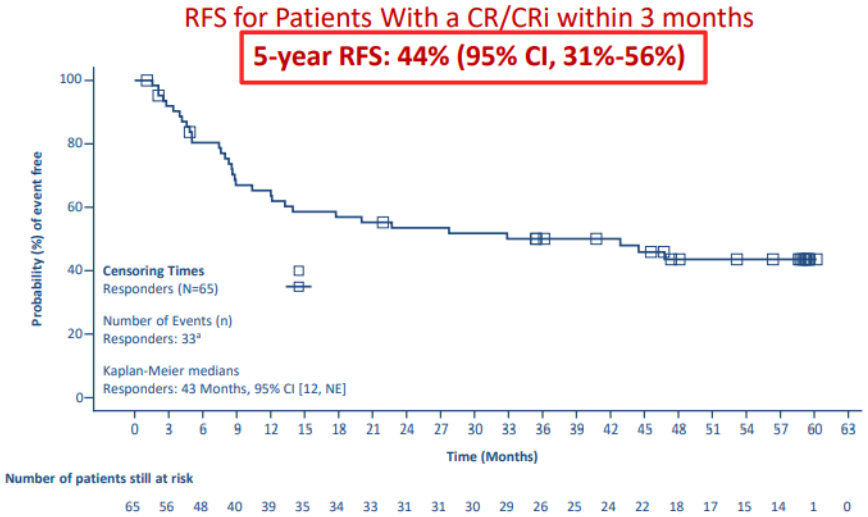
- **FDA approval for R/R paediatric ALL: August 2017**



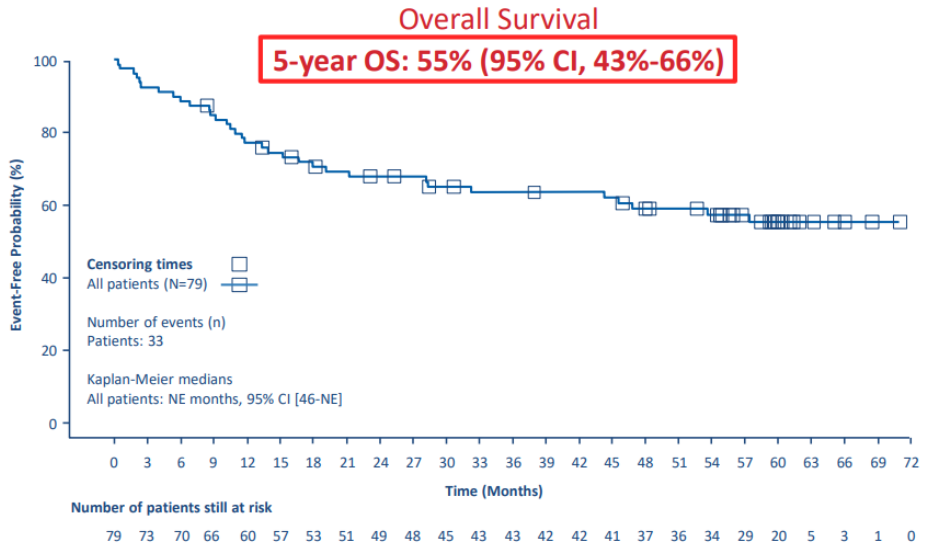
N Engl J Med 2018;378:439-48

ELIANA STUDY: UPDATED FOLLOW UP

Median RFS Was 43 Months



Median OS Was Not Reached

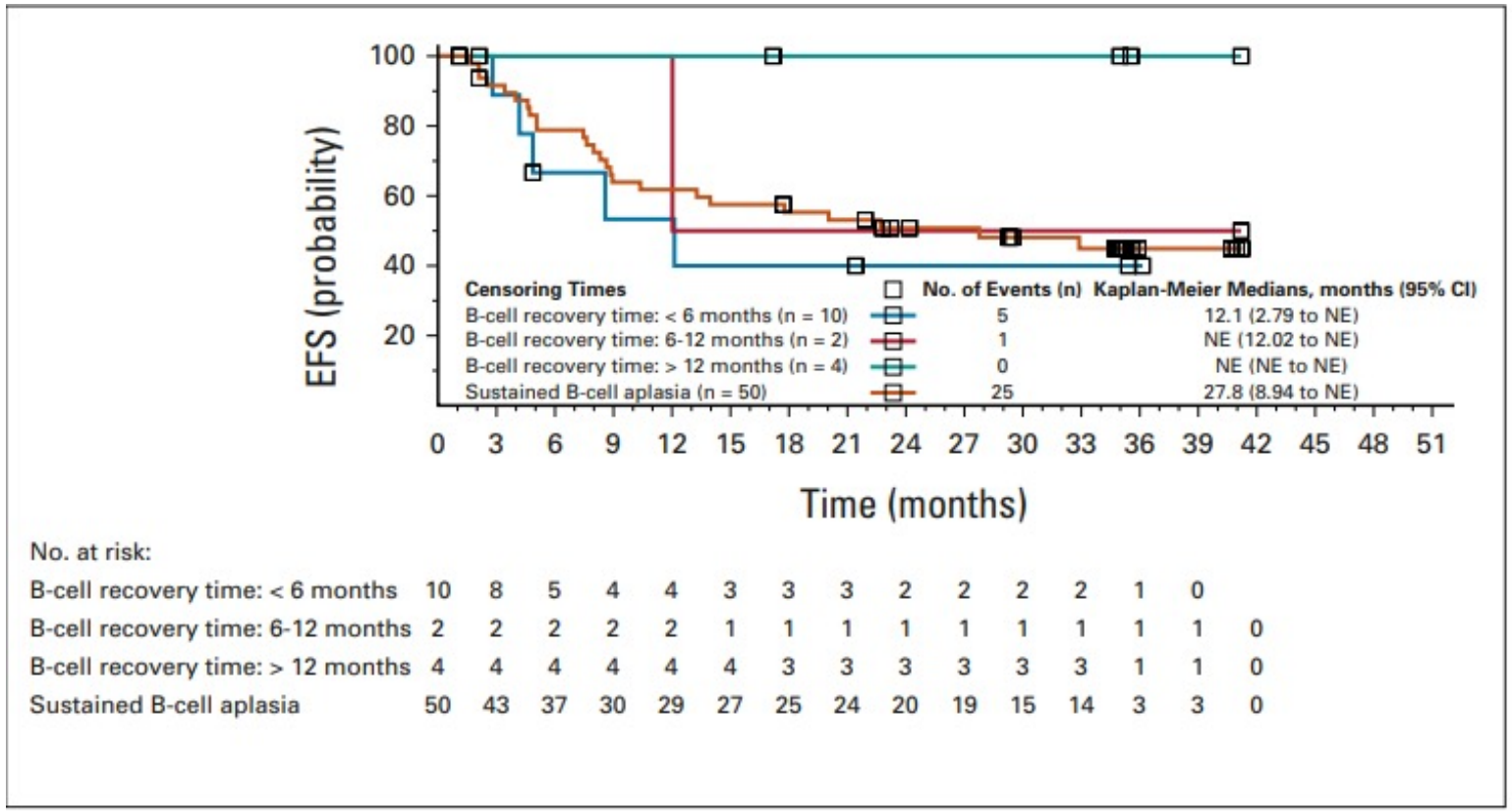


- Median EFS of 15 months
- Most relapses occurring within the first 18 months
- Post tisa-cel infusion, 25% of patients underwent Allo SCT

	Patients Who Achieved Remission N=69
No. of patients who received post infusion alloSCT, n (%)[a]	17 (25)
AlloSCT in remission	10 (14)
AlloSCT after relapse	7 (10)

Rives S. EHA22, Oral S112

B-Cell Recovery and Chimeric Antigen Receptor Persistence



Median time to B-cell recovery among responders was 35.3 months

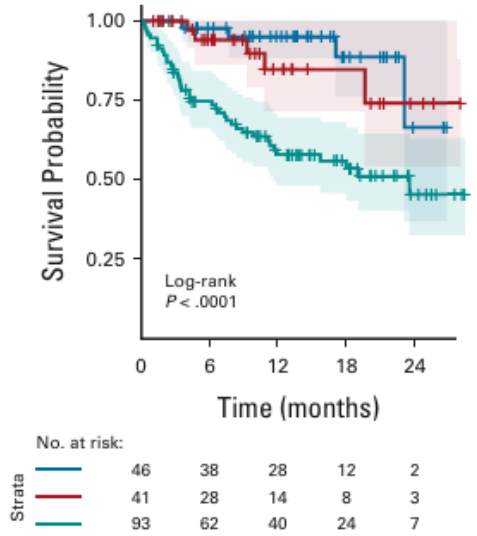
The probability of persistent B-cell aplasia at 12 and 24 months after infusion was 71% (95% CI, 57.4 to 81.5) and 59%

B-cell recovery within the first 6 months after infusion predicts risk of relapse

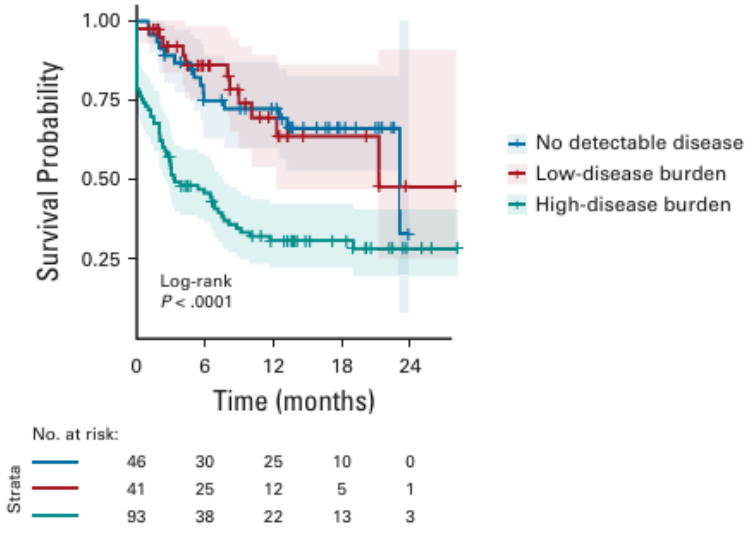
Laetsch et al. JCO 2022

US REAL WORLD: TISA CEL

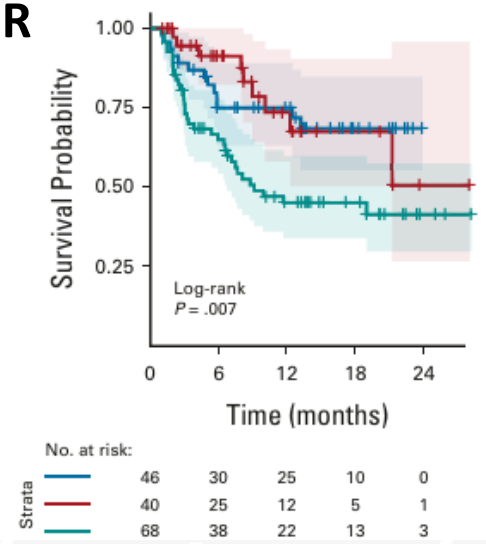
OS



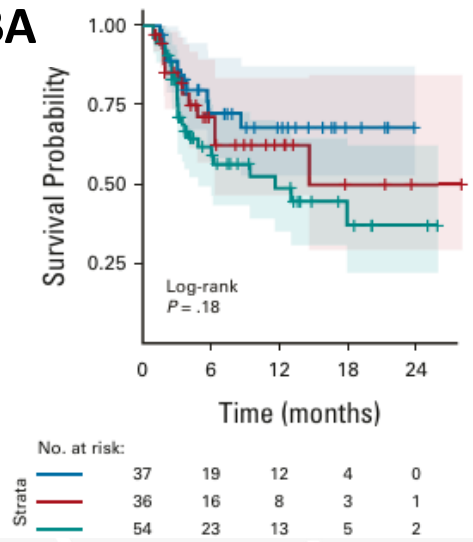
EFS



DOR



DBA



200 patients, 92.5% (185) of patients were infused

- ✓ CR rate was 85%
- ✓ 12month OS was 72%.
- ✓ 12-month EFS was 50%

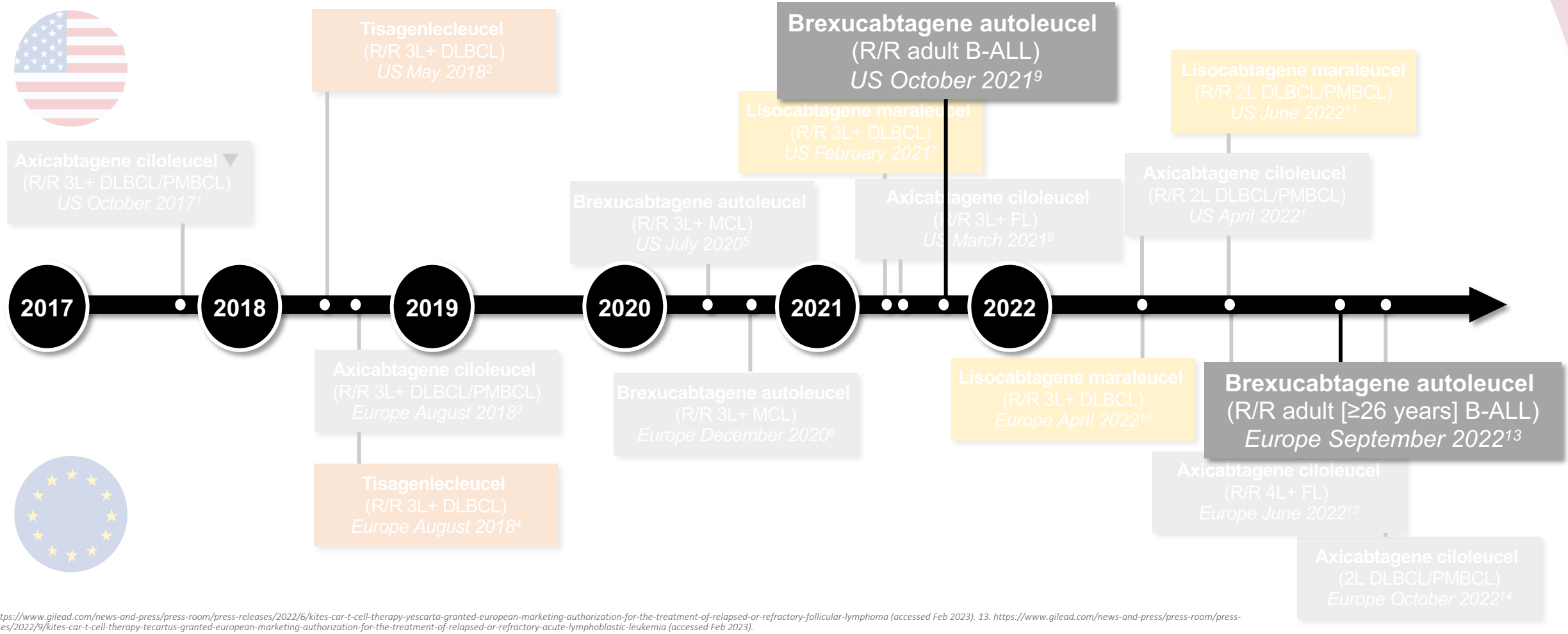
CRS G >3 in 21%
ICANS G > 3 in 7%

Overall comparable response, OS, and EFS rates with ELIANA study

OS, EFS and DOR were lower among patients with High tumor burden at 6 and 12months

Schultz et al. JCO 2021

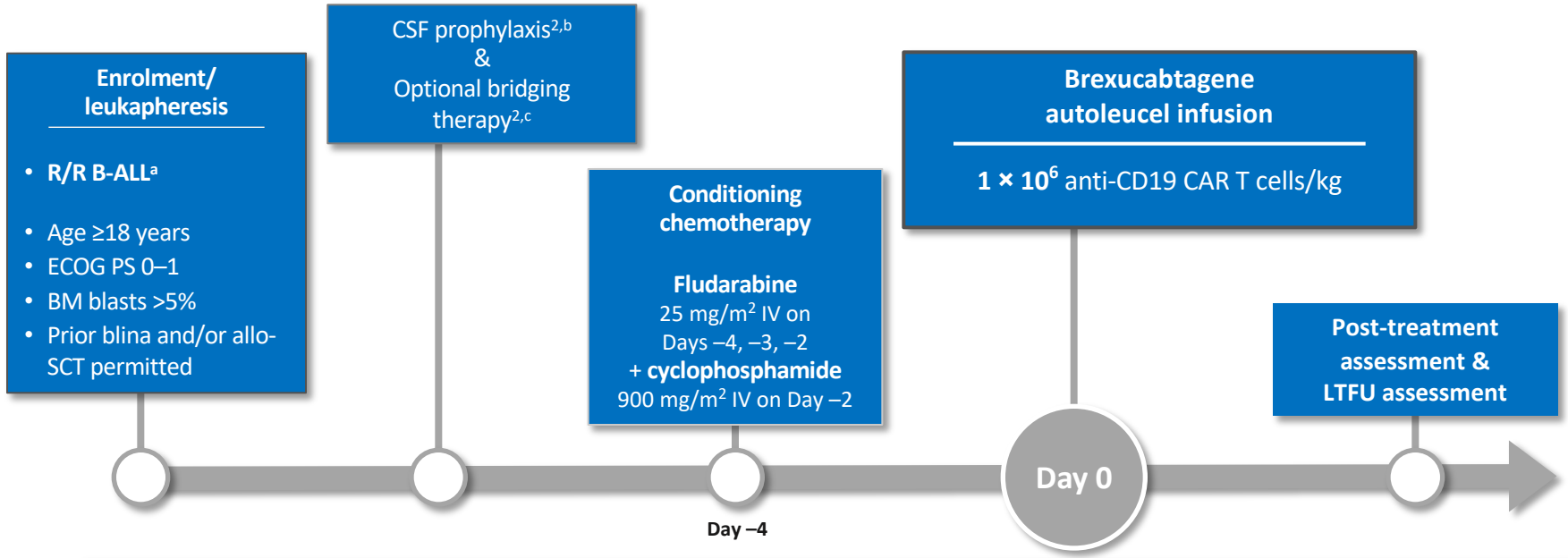
Brexu-cel is the first and only CAR T approved for the treatment of adult ALL (age ≥26 years)



12. https://www.gilead.com/news-and-press/press-room/press-releases/2022/6/kites-car-t-cell-therapy-yescarta-granted-european-marketing-authorization-for-the-treatment-of-relapsed-or-refractory-follicular-lymphoma (accessed Feb 2023). 13. https://www.gilead.com/news-and-press/press-room/press-releases/2022/9/kites-car-t-cell-therapy-tecartus-granted-european-marketing-authorization-for-the-treatment-of-relapsed-or-refractory-acute-lymphoblastic-leukemia (accessed Feb 2023).
14. https://www.gilead.com/news-and-press/press-room/press-releases/2022/10/kites-yescarta-first-car-t-cell-therapy-to-receive-european-marketing-authorization-for-use-in-second-line-diffuse-large-b-cell-lymphoma-and-high-gra (accessed Feb 2023).

CAR-T: ZUMA-3 trial

Phase 2, open-label, multicentre study evaluating the efficacy and safety profile of brexucabtagene autoleucel in adults with R/R B-ALL (N=71)[1]



Primary endpoint

- Overall CR rate (CR + CRi) by central assessment

Key secondary endpoints

- DoR
- RFS
- Subsequent allo-SCT
- OS
- MRD negativity rate
- Safety

Patient disposition:	Enrolled & underwent leukapheresis **N=71**	Conditioning chemotherapy **n=57**	Received brexucabtagene autoleucel **n=55**	ITT analysis set (n=71) Safety analysis set (n=55) **mITT analysis set in treated patients (n=55)**

Drop-out rate: 22%

1. Shah BD, et al. Lancet 2021; 398:491–502 (incl. suppl.). 2. Shah BD, et al. ASCO 2022 (Abstract 7010, poster).

ZUMA-3: Patients' features

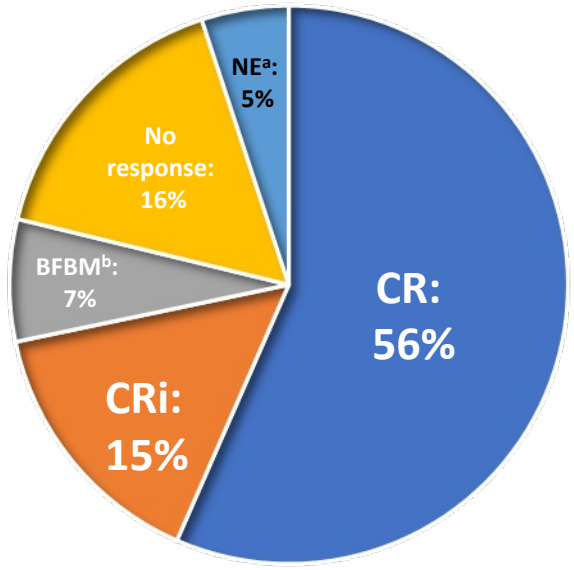
Baseline characteristics[1,2]	Patients treated with brexucabtagene autoleucel (n=55)[1]
Age, median (range), years	40 (19–84)[2]
Male, n (%)	33 (60)
ECOG PS of 1, n (%)	39 (71)
Philadelphia chromosome positive, n (%)	15 (27)
CNS-1 disease at baseline, n (%)[a]	55 (100)
Number of prior therapies, median (range)	2 (1–8)[2]
≥3 prior lines of therapy, n (%)	**26 (47)**
Prior blinatumomab, n (%)	**25 (45)**
Prior inotuzumab ozogamicin, n (%)	**12 (22)**
Prior allo-SCT, n (%)	**23 (42)**
Primary refractory, n (%)	18 (33)
R/R to ≥2 prior systemic therapy lines, n (%)	43 (78)
First relapse with remission ≤12 months, n (%)	16 (29)
R/R post allo-SCT,[b] n (%)	24 (44)
BM blasts at screening, median (range), %	**65 (5–100)[2]**
BM blasts at preconditioning after bridging chemotherapy, median (range), %[c]	**59 (0–98)[2]**

1. Shah BD, et al. Lancet 2021; 398:491–502 (incl. suppl.). 2. Shah BD, et al. ASCO 2022 (Abstract 7010; poster).

ZUMA-3: Responses

mFU 38.8 months[2]

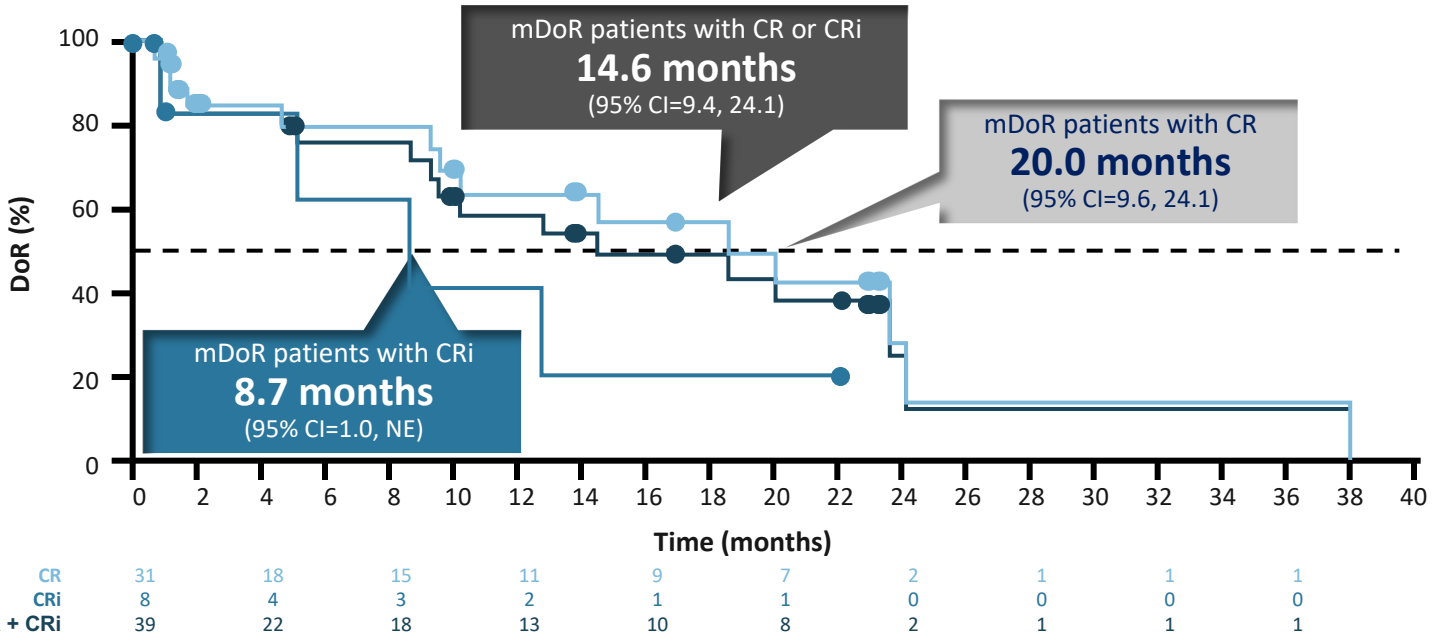
Primary endpoint: CR/CRi (n=55)[1,2]



CR/CRi: 71%

(95% CI=57, 82; p<0.0001)[3]

Duration of response censored at subsequent allo-SCT (n=55)[2]



Of the 39 patients with CR or CRi, 10 received subsequent allo-SCT while in remission, 4 of these patients have died as of data cut-off

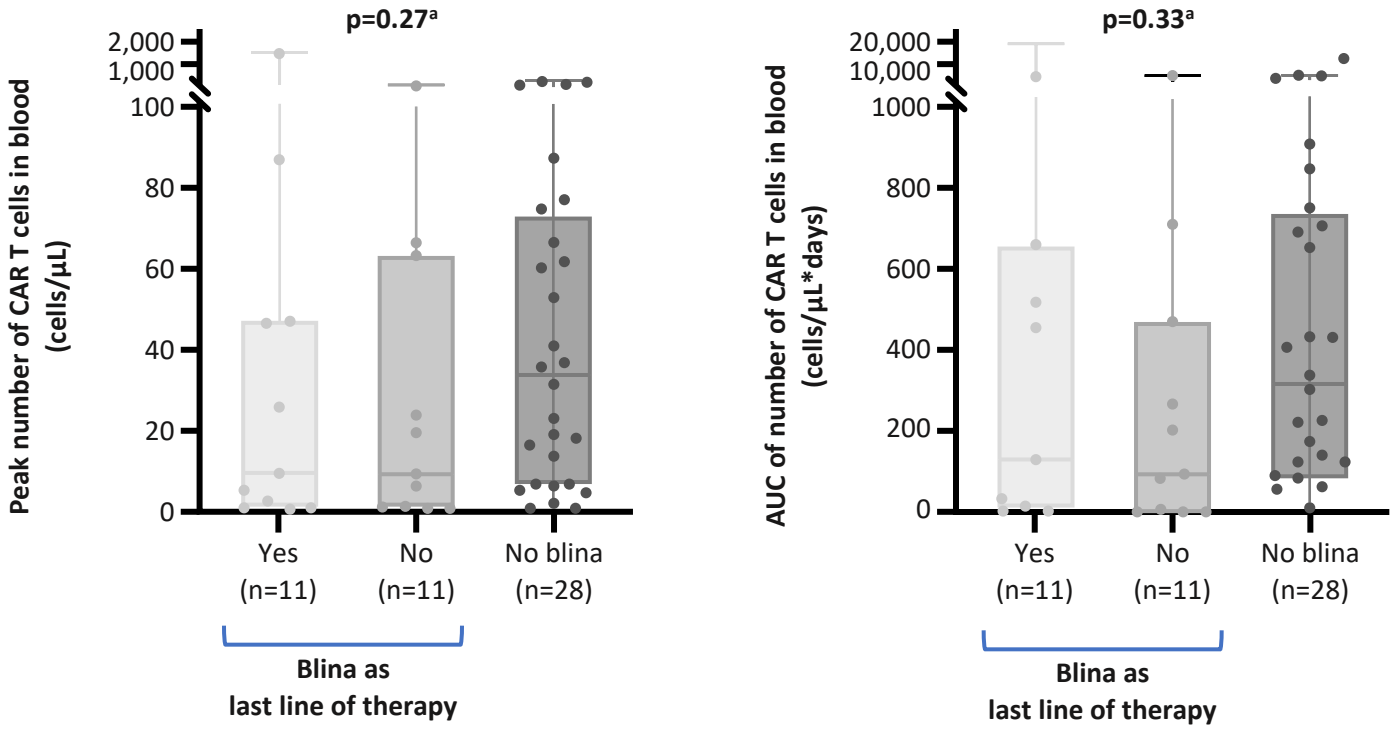
Median time to first CR/CRi was 1.1 months (IQR 1.0–1.9); 97% of patients achieving CR or CRi were MRD negative[3,c]

1. Shah BD, et al. Hematol Oncol 2022; 15:170. 2. Hadjivassileva T, et al. EHA-EBMT 2023 (Abstract 34; poster). 3. Shah BD, et al. Lancet 2021; 398:491–502 (incl. suppl.).

ZUMA-3: CAR T-cell expansion in patients with or without prior blinatumomab exposure

mFU 26.8 months

Peak and AUC CAR T-cell levels by last prior therapy as blinatumomab in Phase 2-treated patients (N=55)



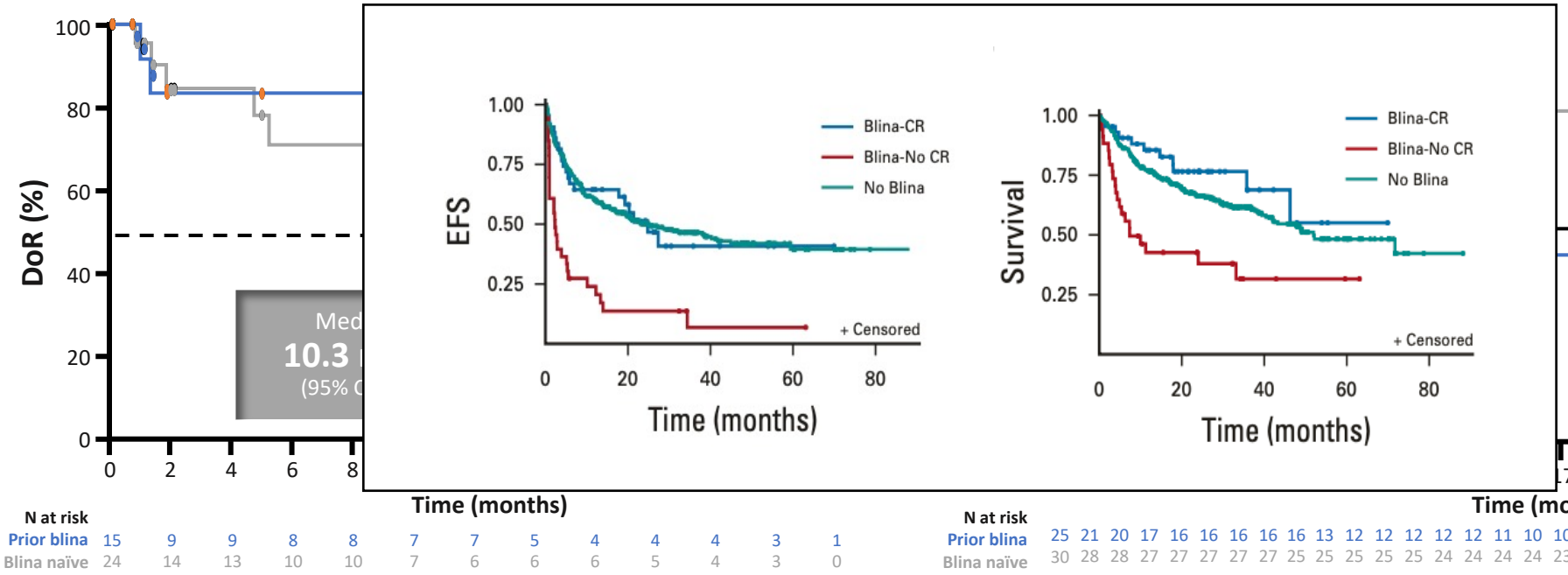
Median peak CAR T-cell expansion trended lower in patients with prior blinatumomab exposure vs. those without; differences were not statistically significant, potentially due to small sample size

ª p value is calculated by Kruskal-Wallis test.
AUC = area under the curve; Blina = blinatumomab.
Shah BD, et al. EHA 2022 (Abstract P356; poster).

ZUMA-3:DOR and OS in Blinatumomab experienced or naïve cases

mFU 26.8 months

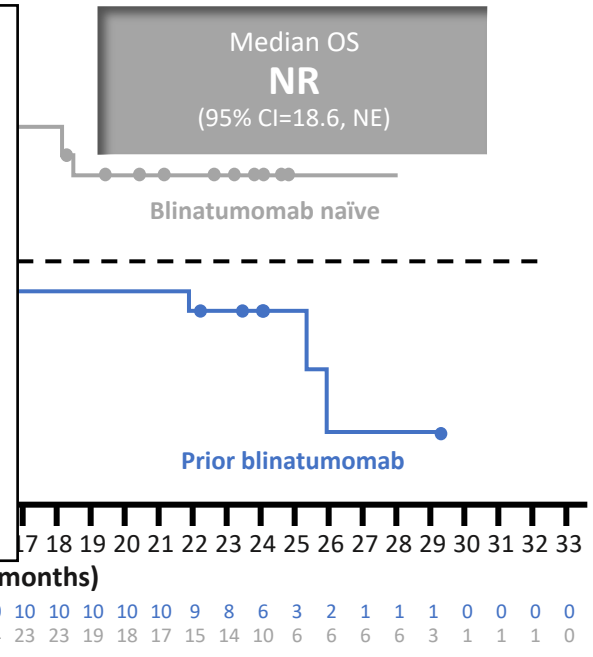
Duration of remission (patients with CR/CRi)[1,a]



Time (months)

N at risk													
Prior blina	15	9	9	8	8	7	7	5	4	4	4	3	1
Blina naïve	24	14	13	10	10	7	6	6	6	5	4	3	0

Overall survival by prior blinatumomab exposure (N=55)[1]



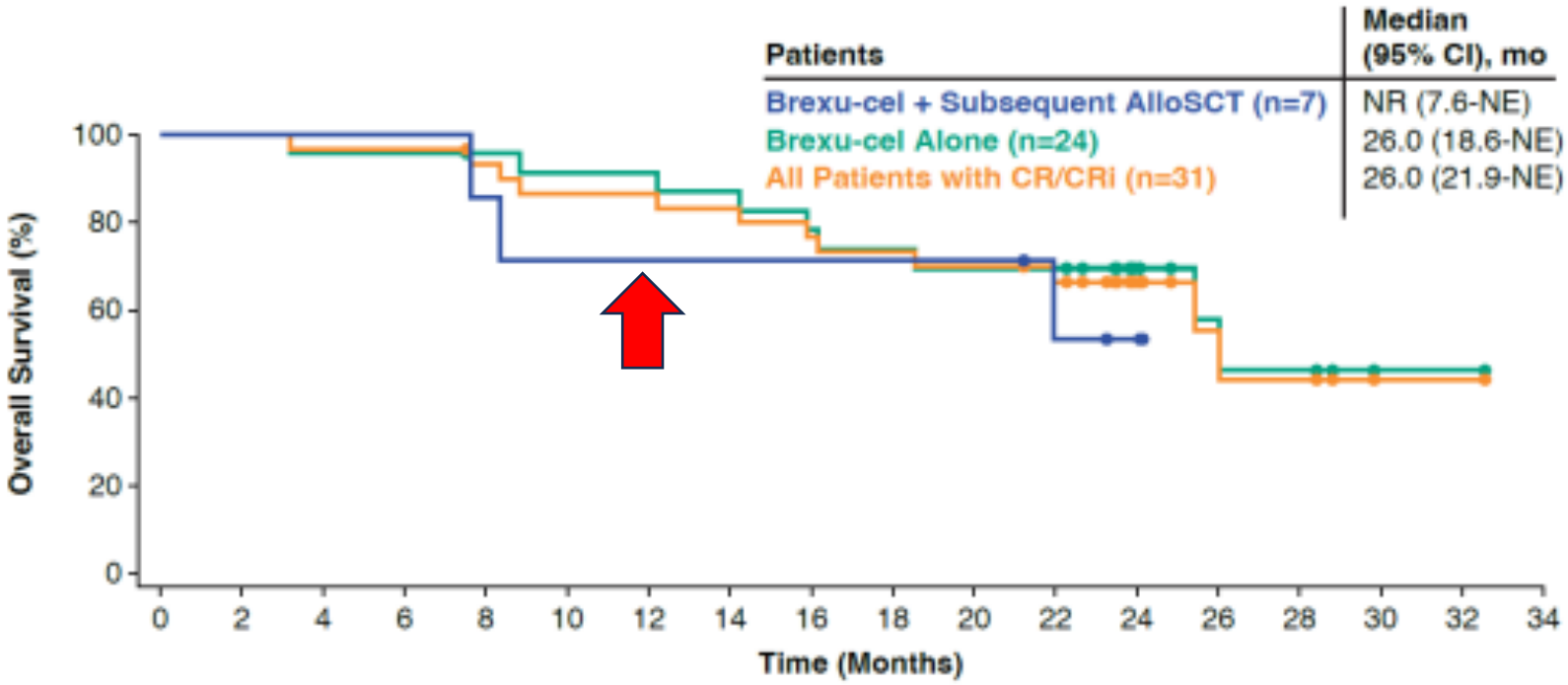
N at risk																															
Prior blina	25	21	20	17	16	16	16	16	16	13	12	12	12	12	12	11	10	10	10	10	10	10	9	8	6	3	2	1	1	1	0	0	0	0
Blina naïve	30	28	28	27	27	27	27	27	25	25	25	25	25	24	24	24	24	23	23	19	18	17	15	14	10	6	6	6	6	3	1	1	1	0

Median OS was higher in blinatumomab-naïve vs. blinatumomab-exposed patients[1]

Non-response to blinatumomab may be suggestive of non-response to CAR T; however, factors such as prior therapies may impact outcomes[2,b]

Shah B, et al. EHA 2022 (Abstract P356; poster). 2. Myers RM, et al. J Clin Oncol 2021; 40:932–944.

CAR-T for >26 years old patients: role of allo-SCT

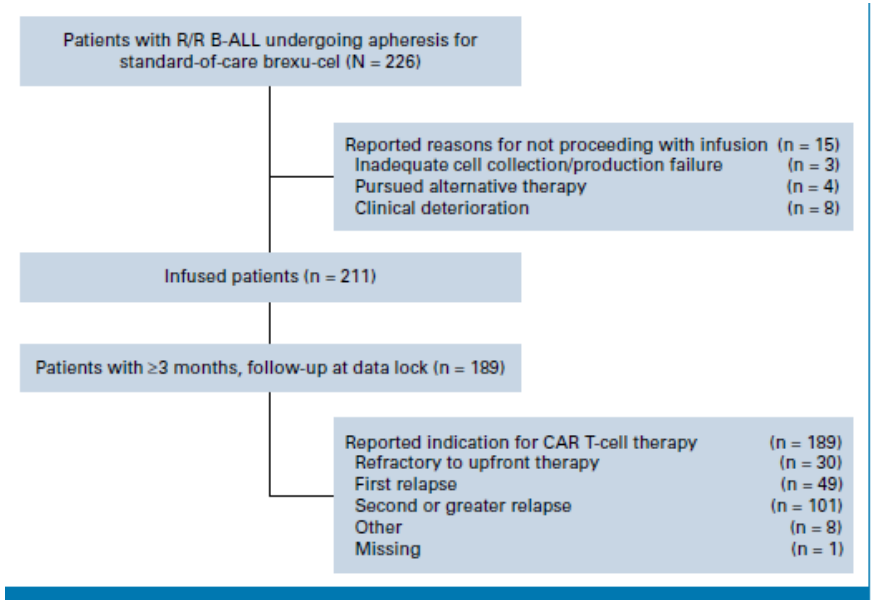


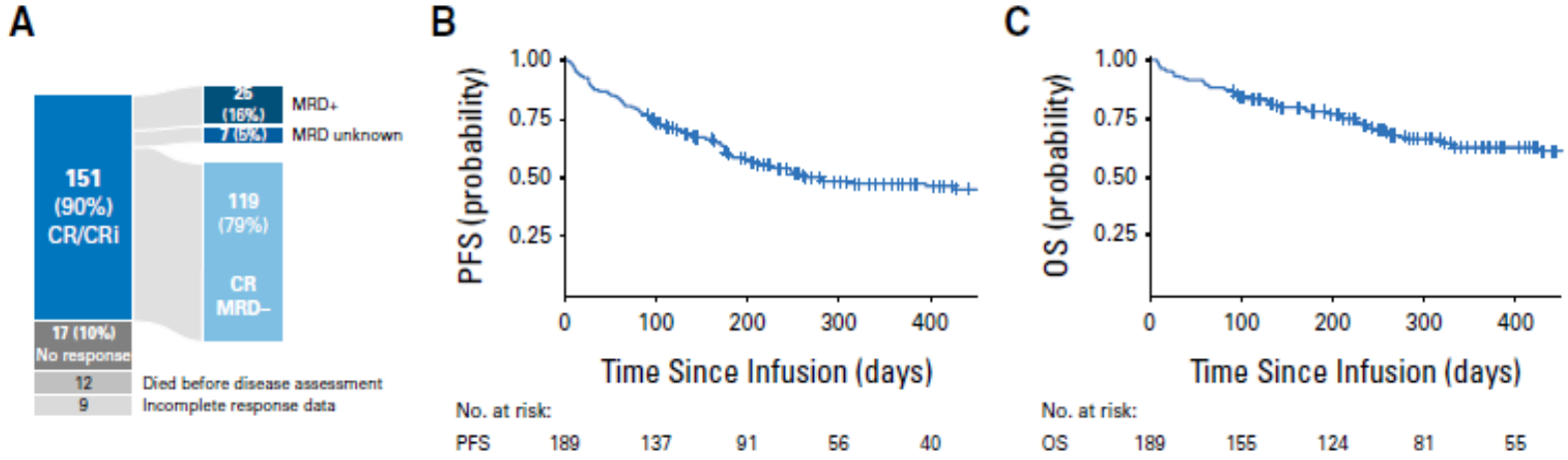
Toxicity

	Any grade	Grade 3/4	Grade 5
Any adverse event	43 (100)	32 (74)	9 (21)
Pyrexia	42 (98)	15 (35)	0 (0)
Hypotension	27 (63)	14 (33)	0 (0)
Anemia	22 (51)	21 (49)	0 (0)
Nausea	17 (40)	0 (0)	0 (0)
Sinus tachycardia	15 (35)	3 (7)	0 (0)
Headache	15 (35)	0 (0)	0 (0)
Chills	12 (28)	0 (0)	0 (0)
Platelet count decreased	13 (30)	12 (28)	0 (0)
Hypoxia	13 (30)	8 (19)	0 (0)
Fatigue	13 (30)	0 (0)	0 (0)
Hypokalemia	11 (26)	3 (7)	0 (0)
Hypophosphatemia	11 (26)	8 (19)	0 (0)
Neutrophil count decreased	12 (28)	12 (28)	0 (0)
Tremor	11 (26)	1 (2)	0 (0)
White blood cell count decreased	11 (26)	10 (23)	0 (0)
Confusional state	10 (23)	1 (2)	0 (0)
Diarrhea	10 (23)	2 (5)	0 (0)
Hypomagnesemia	10 (23)	0 (0)	0 (0)
Tachycardia	9 (21)	0 (0)	0 (0)
Encephalopathy	9 (21)	3 (7)	0 (0)
Cytokine release syndrome[a]	37 (86)	10 (23)	0 (0)
Neurological events[b]	25 (58)	8 (19)	1 (2)

Minnema MC, et al. Leuk Lymphoma. 2024;65(10):1438-1447.

Outcomes After Brexucabtagene Autoleucel Administered as a Standard Therapy for Adults With Relapsed/Refractory B-Cell ALL





- ✓ 31 US centers; from October 2021 to October 2023
- ✓ median age was 46 years (range, 18-81)

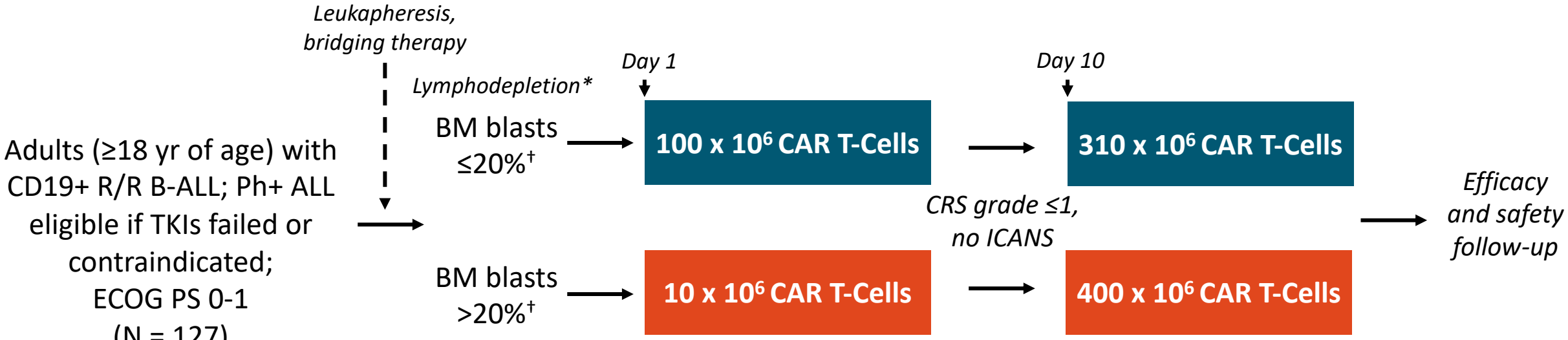
Median of 11.4 months of follow-up
12 month PFS was 48%, median PFS was 9.5months.
OS was 63% at 12month; NR

- ✓ CRS in 84% / **G3-4 (11%)**
- ✓ ICANS in 56% / **G3-4 (31%)**

Roloff et al. JCO2024

Obecabtagene Autoleucel (obe-cel, AUTO1) for R/R B-ALL: FELIX Phase Ib/II Study

- Open-label, single-arm phase Ib/II study
- AUTO1 construct was designed with 4-1BB and a fast off rate (low affinity anti CD-19 CART)



Cohort A: ≥5% BM blasts (n = 107); cohort B: MRD+ (n = 13); cohort C: isolated EMD (n = 7).
*4 doses of fludarabine 30 mg/m^2 + 2 doses of cyclophosphamide 500 mg/m^2. †Tumor burden–guided split dosing.

- **Primary endpoints:** safety in phase I; ORR, MRD-negative remission in phase II
- **Secondary endpoints:** MRD-negative CR, CR rate, DoR, PFS, OS, safety, CAR T-cell expansion and persistence in phase II

Jabbour. ASCO 2024. Abstr 6504. NCT04404660.

FELIX: Baseline Characteristics

Characteristic	Cohort IIA, ≥5% BM Blasts (n = 94)	Total (N = 127)
Median age, yr (range)	50 (20-81)	47 (20-81)
Male/female, %	47/47	66/61
Hispanic or Latino, n (%)	29 (30.9)	38 (29.9)
Ph+, n (%)	25 (26.6)	36 (28.3)
Complex karyotype, n (%)	37 (39.4)	51 (40.2)
Median prior lines of therapy (range)	2 (1-6)	2 (1-6)
No. prior lines, n (%) • 3 • ≥4	 17 (18.1) 12 (12.8)	 26 (20.5) 19 (15.0)
Prior treatment, n (%) • Blinatumomab • Inotuzumab • Blinatumomab and inotuzumab • Allogeneic SCT	 33 (35.1) 30 (31.9) 15 (16.0) 36 (38.3)	 53 (41.7) 40 (31.5) 21 (16.5) 56 (44.1)
Median BM blasts at screening, % (range)	58.9 (6-100)	40.0 (0-100)
EMD at screening, n (%)	19 (20.2)	29 (22.8)

Jabbour. ASCO 2024. Abstr 6504.

FELIX: Remissions and Survival

Outcome	N = 127
CR/CRi, n (%)	99 (78)
Patients with CR/CRi	**n = 99**
Ongoing remission without SCT or other subsequent treatment, %	40
Subsequent SCT in remission with negative MRD, %	18
Initiated new cancer treatment, %	5
Relapsed or died, %	36

Survival	SCT Censoring	No SCT Censoring
Median EFS, mo (95% CI)	11.9 (7.98-22.11)*	9.0 (6.57-14.32)
12-mo EFS, % (95% CI)	49.5 (39.6-58.6)	44.0 (35.2-52.5)
Median OS, mo (95% CI)	23.8 (12.91-NE)	15.6 (12.91-NE)*
12-mo OS, % (95% CI)	63.7 (53.7-72.0)	61.1 (52.0-69.0)

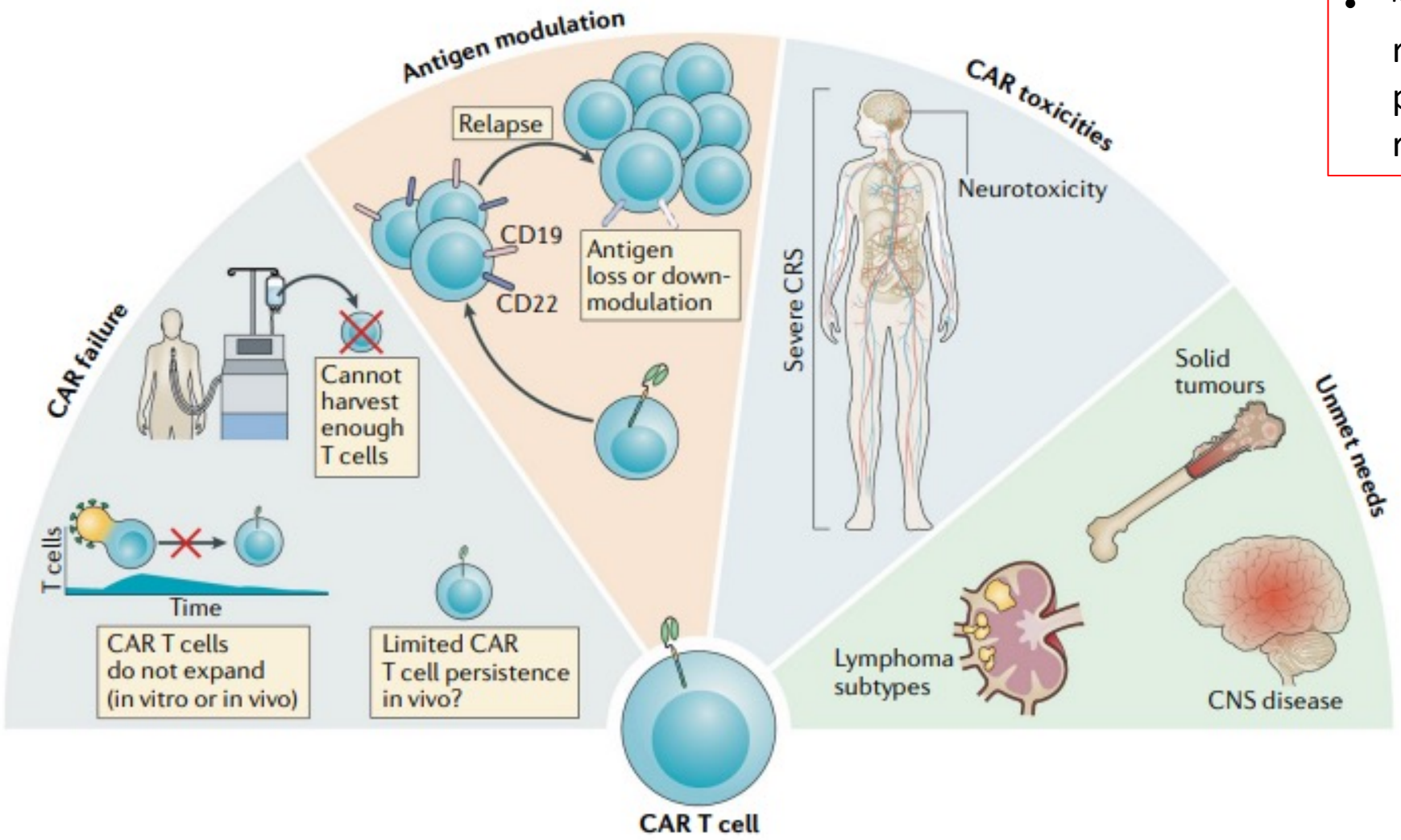
*Main analysis.

- Of 18 patients who had SCT while in remission, all MRD negative
  - 10 (55.6%) of these had ongoing CAR T-cell persistence before SCT

Median follow-up: 21.5 mo (range: 8.6-41.4).
Data cutoff: February 7, 2024.

Jabbour. ASCO 2024. Abstr 6504.

Limitations to durable remissions after CAR T cell therapy



- ~50% of patients have disease relapse. Furthermore, some patients develop CD19 loss at relapse.

Novel investigations:

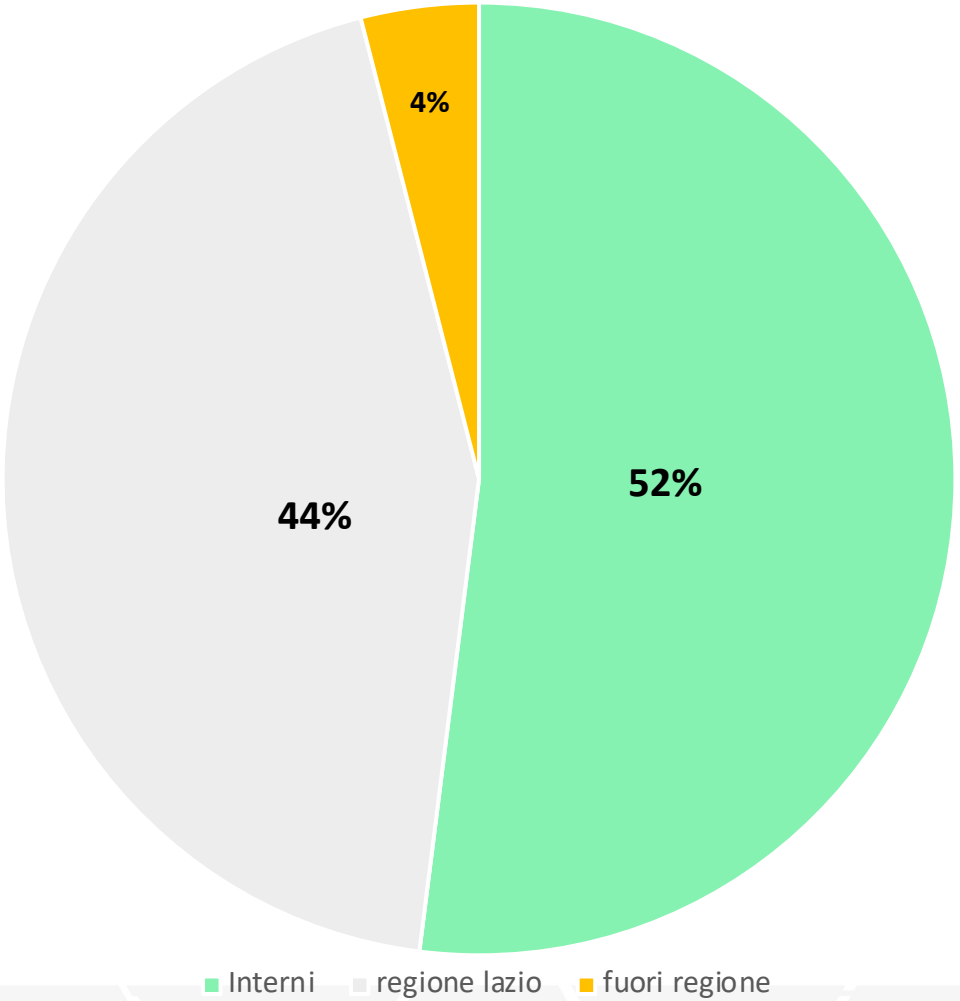
✓ Targets beyond CD19

✓ Allogeneic CARs

Shah N et. al. Nature rev. 2019

Provenienza dei pazienti avviati al percorso CAR-T

(totali 79: infusi 69 (88%), non infusi 12)



Pazienti eleggibili R/R B-ALL proposti per aferesi N=11

N=1 deterioramento clinico per PD

Pazienti che hanno eseguito aferesi N= 10

n=2 infezione/shock settico
n= 1 deterioramento condizioni generali
n= 1 manufacturing failure
n= 1 ongoing

Pazienti infusi N= 5

Pazienti trattati con CAR-T @ Policlinico Umberto I

Indicazione	Nov 2019	2020	2021	2022	2023	2024 (sett)
Leucemia Linfoblastica Acuta	**1**	**1**		**-**	**1**	**2**
Linfoma grandi cellule B (LBCL) R/R III linea	1	6	8	10	8	5
LBCL II linea (refrattario/<12 mesi)	NA	NA	NA	NA	-	4
Linfoma a grandi cellule primitivo del mediastino (PMBCL) R/R	-	-	1	6	4	3
Linfoma a cellule mantellari R/R	NA	NA	NA	NA	3	1
Linfoma Follicolare R/R	NA	NA	NA	NA		2
Totale CAR-T INFUSE (69)	**2**	**7**	**9**	**16**	**16**	**19**

3 centri CAR-T in regione Lazio: Ospedale Bambin Gesù, Policlinico Gemelli, **Policlinico Umberto I**

Conclusions

- ✓ Treatment with CART19 yields high and durable response rates for adult and pediatric patients with r/r ALL.
- ✓ The toxicities associated with CAR T cells are manageable and most institutions have developed clinical practice algorithms to manage these toxicities.
- ✓ The role of allo-SCT after CAR T-cell treatment remains not clear.
- ✓ The field of CAR T-cell therapy continues to evolve with several novel constructs, novel targets, allogeneic CARs to minimize CD19+ and CD19– relapses and prevent or mitigate tox icity

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EMATOLOGIA

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Grazie per l'attenzione