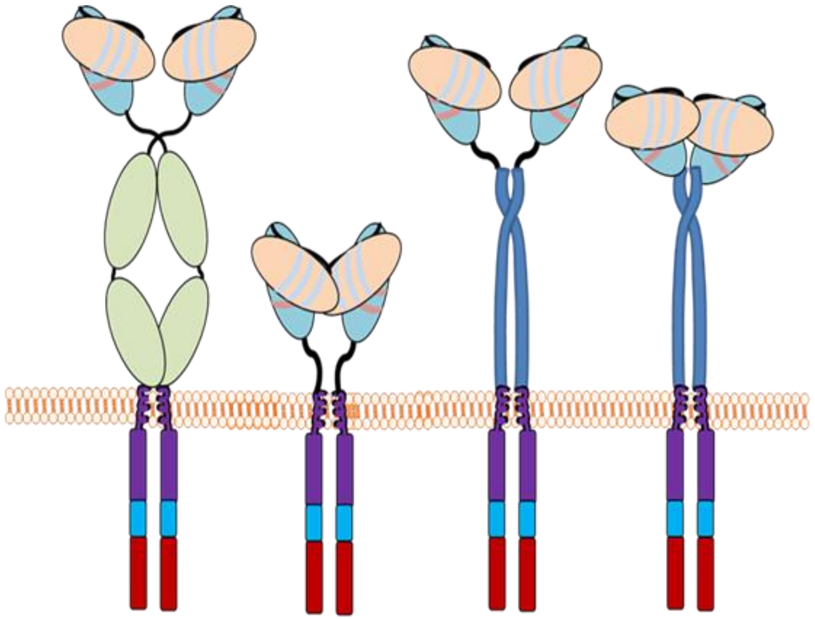
CAR T-Cell Therapy for B-ALL



The UCL CAR T-cell Program

BOLOGNA MEETING SEPTEMBER 2025

c.roddie@ucl.ac.uk

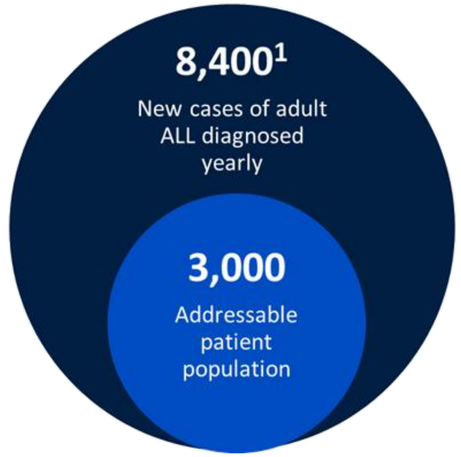
Discloures

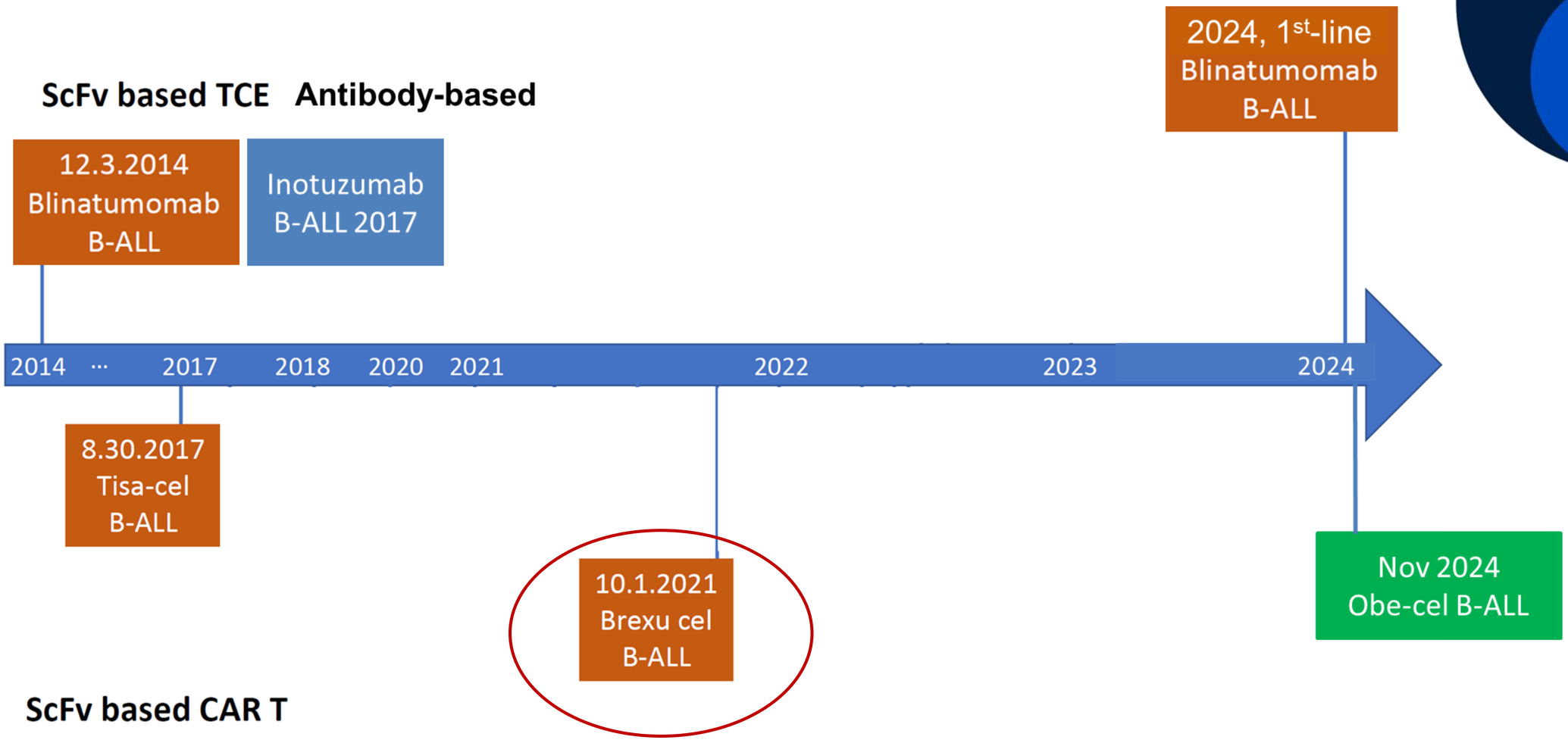
- Advisory Role Novartis, BMS, J+J, Kite/Gilead, Cellistic, Autolus, Miltenyi, Ascentage, BD

What can we currently access for B-ALL patients?

FDA approved immunotherapeutics…

- Adult B-ALL prognosis is poor; long-term remission rates limited to 30-40%
  - 50% of all adult patients will relapse, with 5-year OS 7% (Fielding et al., 2007)

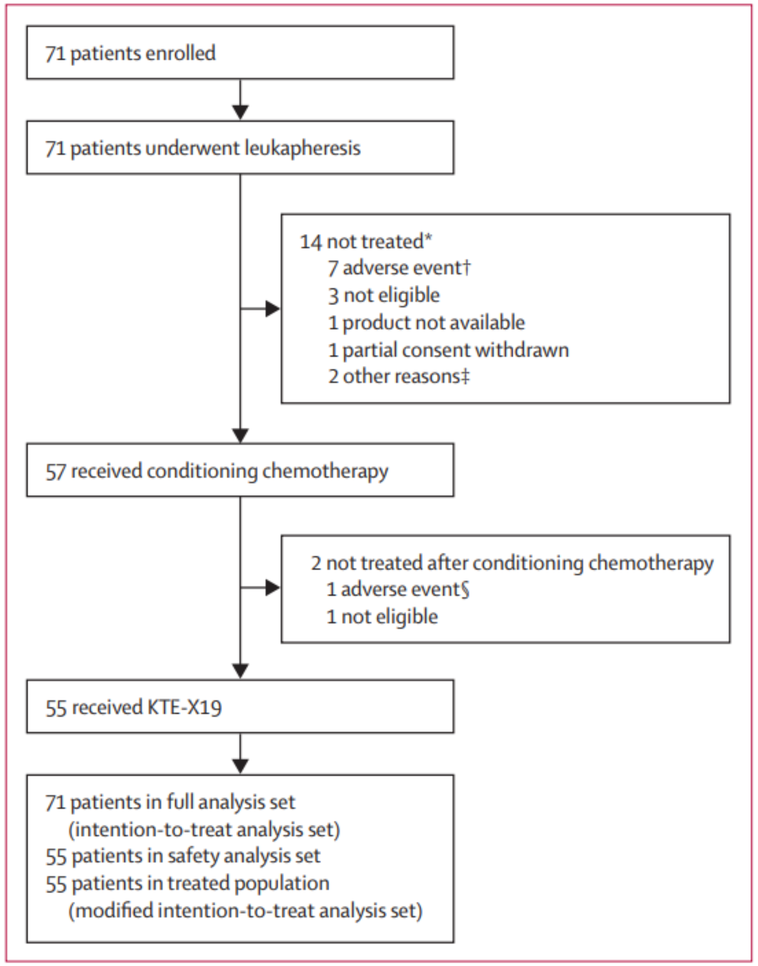




ZUMA-3: Brexu-cel for adult B-ALL

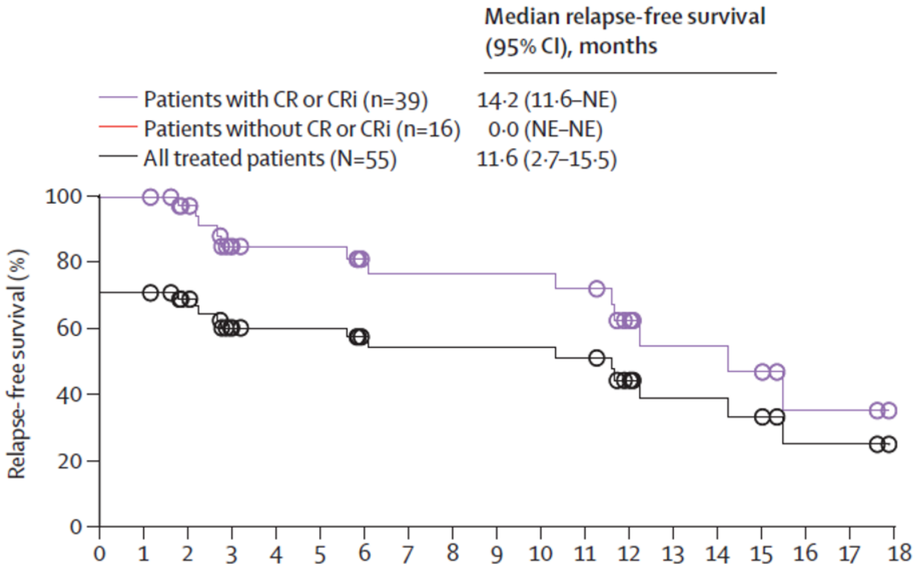
Trial flow, efficacy & toxicity treated patients (n=55)

Trial Flow[1,2]



Efficacy[1,2]

- Overall CR/CRi: 71%
  - Complete CR: 56%
- Median RFS (n=55): 11.6 months[1]
- Median OS (n=55): 26 months[2]



Toxicity[1,2]

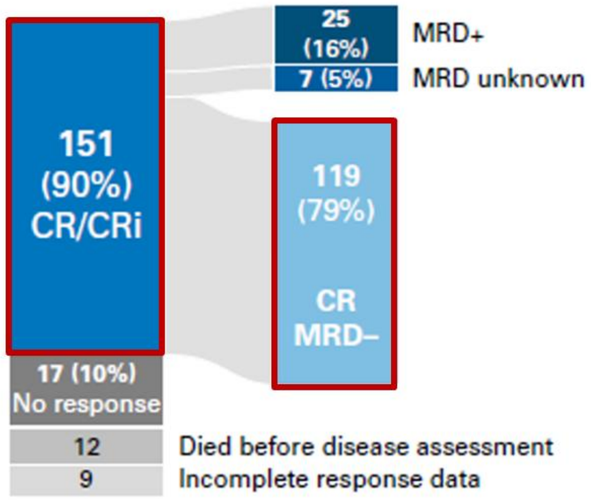
- Grade ≥3 CRS: 24%
- Grade ≥3 ICANS: 25%

1.Shah BD, et al. Lancet 2021;398:491–502. 2.Oluwole O, et al. ASH 2023.

ROCCA: RWE of brexu-cel in adult ALL

Response and Toxicity in 189 patients (follow up 11 months)

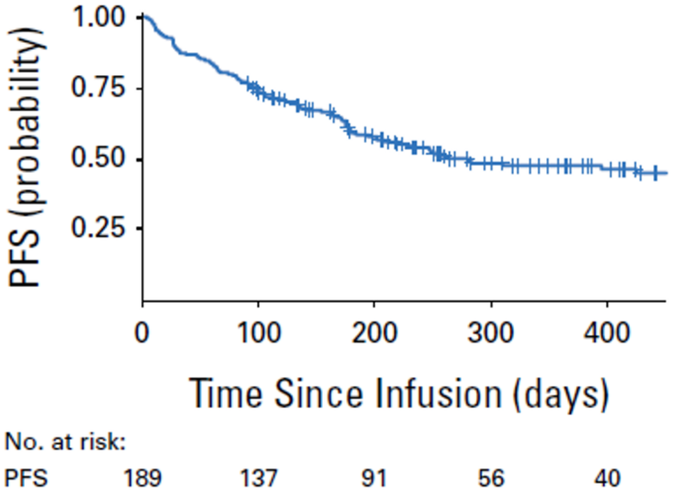
Response Rates



Toxicity

- G3-4 CRS in 11%
- G3-4 ICANS in 31%

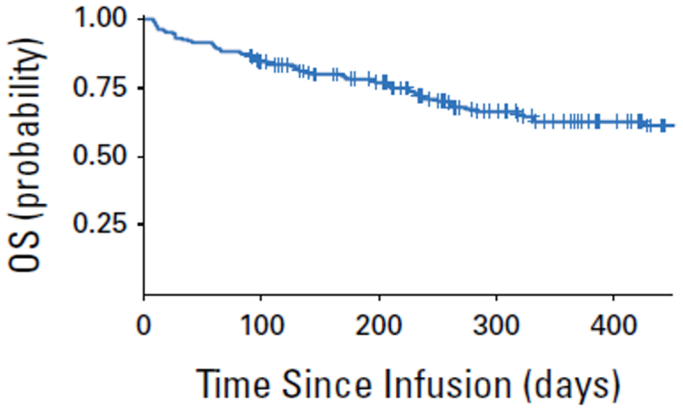
PFS (median 9.5m)



No. at risk:

PFS	189	137	91	56	40

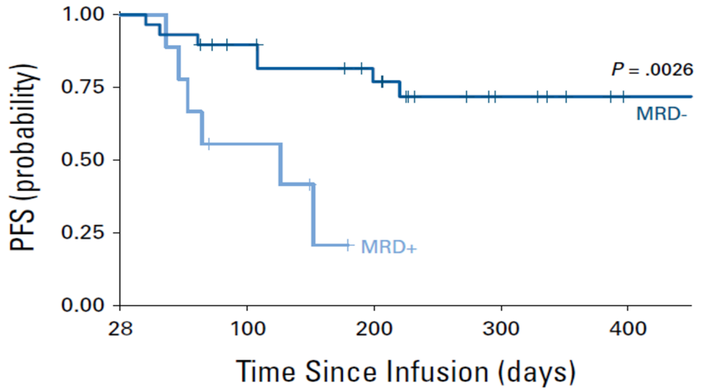
Overall Survival (not reached)



No. at risk:

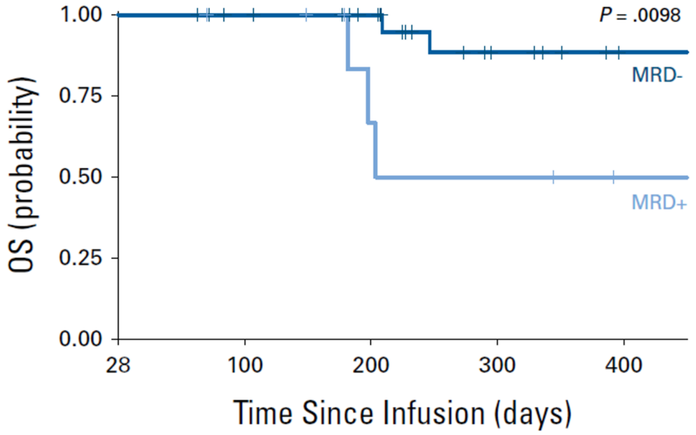
OS	189	155	124	81	55

Impact MRD-neg CR on PFS/OS



No. at risk:

MRD–	29	23	17	8	3
MRD+	9	4	0	0	0



No. at risk:

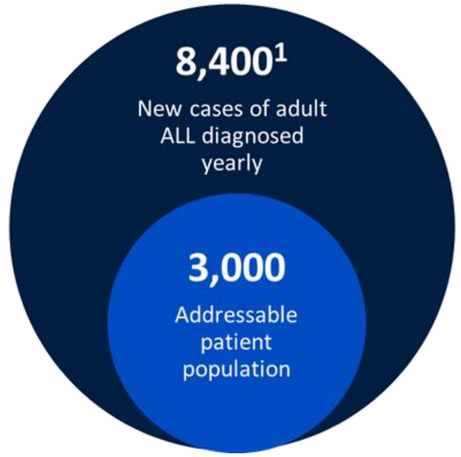
MRD–	29	26	22	11	6
MRD+	9	8	4	3	1

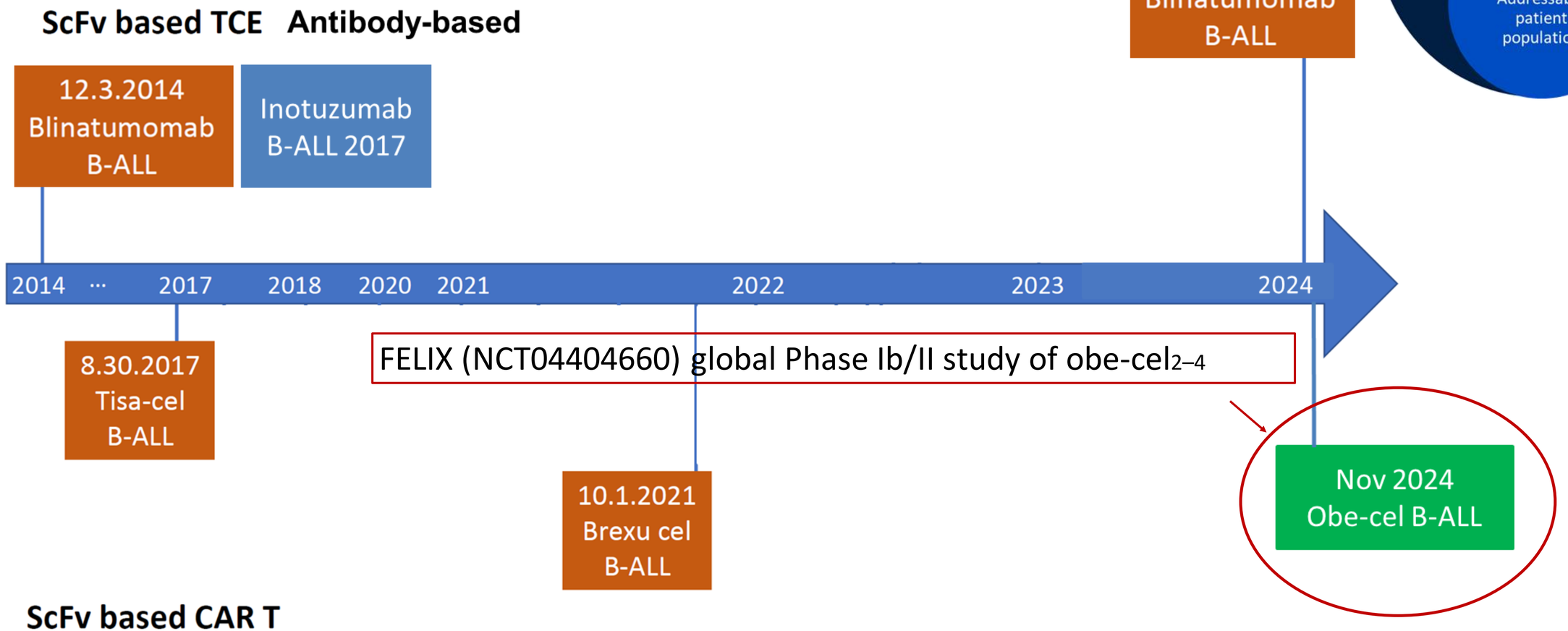
Roloff G, et al. JCO 2024

What can we currently access for B-ALL patients?

FDA approved immunotherapeutics…

- Adult B-ALL prognosis is poor; long-term remission rates limited to 30-40%
  - 50% of all adult patients will relapse, with 5-year OS 7% (Fielding et al., 2007)





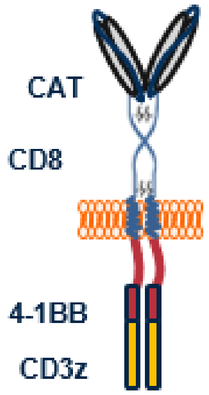
Improving Physiology: low-affinity CD19 CAR (AUTO1)

Key characteristics, compared with FMC63 (scFv, Kymriah)

AUTO1 (CAT) binder with lower affinity for CD19

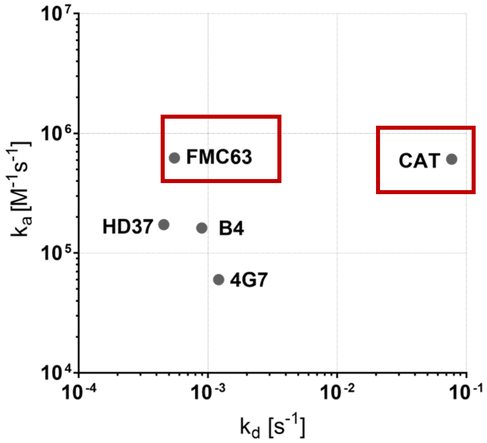
- Half-life of target interaction very short compared to FMC63 (eg Kymriah®) binder:

- Obe-cel = 9.8 seconds
- Kymriah = 21 minutes

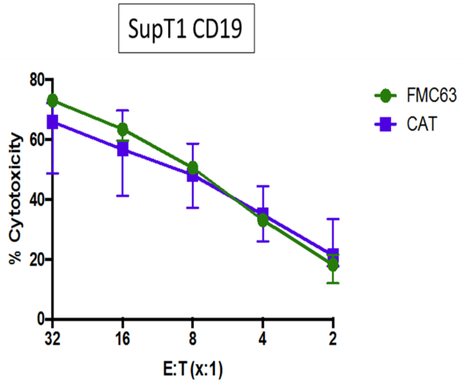


Fast off-rate (Biacore analysis)

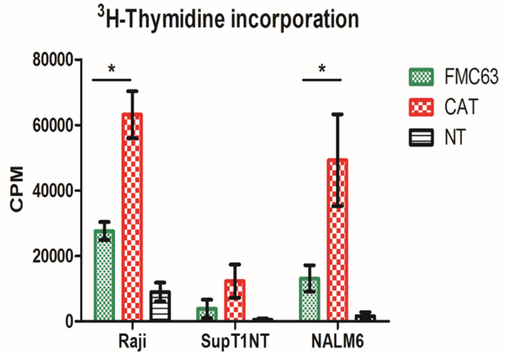
Hybridoma	K_d [sec^{-1}]	K_a [$M^{-1}s^{-1}$]	K_D [M]
HD37	4.55E-04	1.73E+05	2.63E-09
B4	8.96E-04	1.62E+05	5.52E-09
FMC63	5.50E-04	6.24E+05	8.81E-10
CAT	7.70E-02	6.09E+05	1.16E-07
4G7	1.21E-03	6.01E+04	2.01E-08



Enhanced cytotoxicity and Proliferation *in vitro*

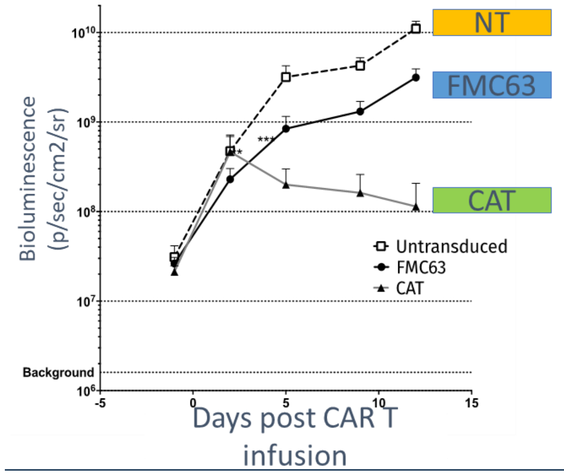


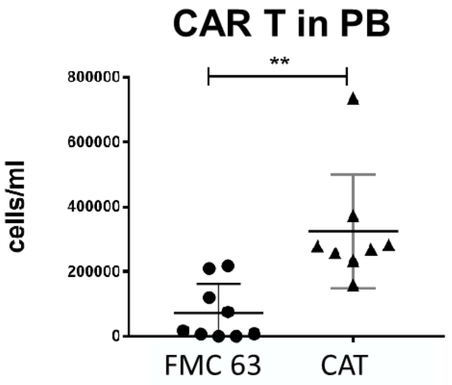
Equivalent cytotoxicity towards CD19+ targets in vitro cf FMC63



Superior proliferation with CD19+ targets in vitro cf FMC63

Enhanced cytotoxicity and proliferation *in vivo*

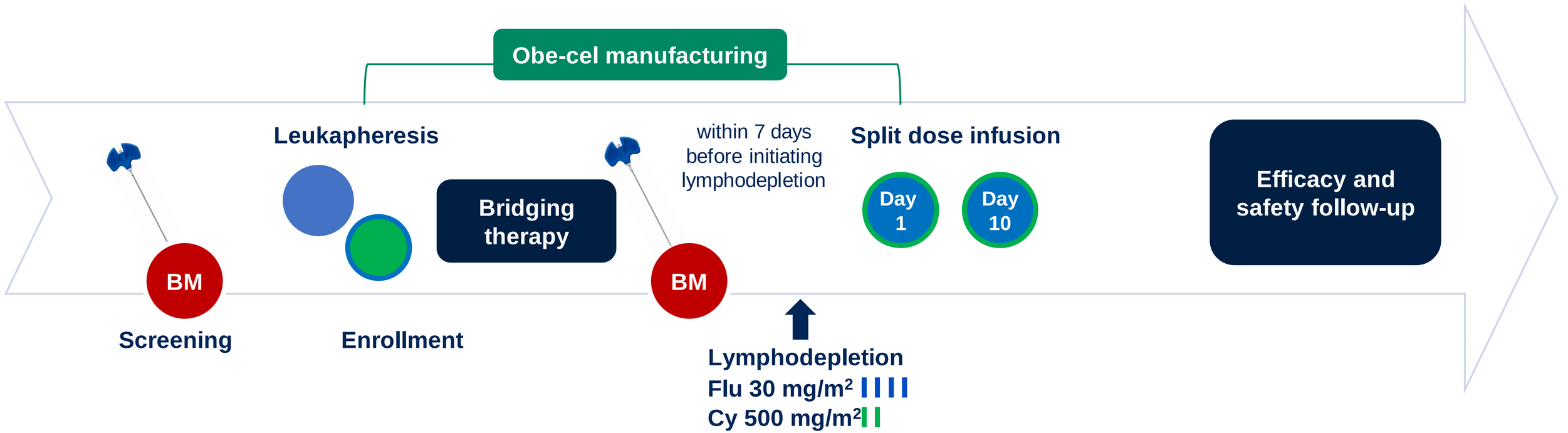




Ghorashian S et al, Nature Medicine 2019

Can CAR-T therapy be a definitive treatment for adult R/R B-ALL without allo-SCT?

Learnings from the FELIX study of Obecabtagene Autoleucel



Tumor burden-guided dosing

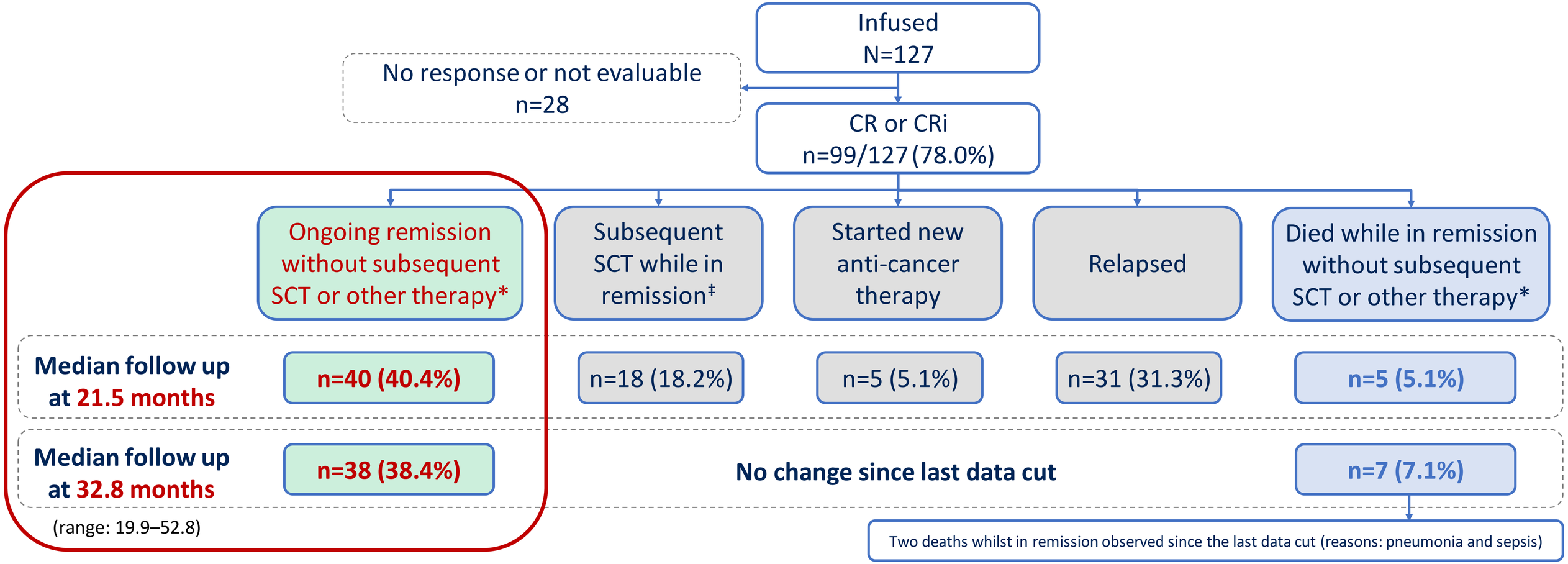
Lymphodepletion	Day 1: Dose 1		Day 10: Dose 2	
BM blasts ≤20%	100×10^6 CAR T-cells	CRS Grade ≤1 No ICANS*	310×10^6 CAR T-cells	Total target dose is always 410×10^6 CAR T-cells
BM blasts >20%	10×10^6 CAR T-cells		400×10^6 CAR T-cells	

*Patients with Grade 2 CRS and/or Grade 1 ICANS following the first dose received the second dose on Day 10 (±2 days) up to Day 21, only if CRS resolved to Grade ≤1 and ICANS completely resolved.

(NCT04404660)

Majority of FELIX responders show durable response

38.4% of responders in ongoing CR without allo-SCT at 3 years….

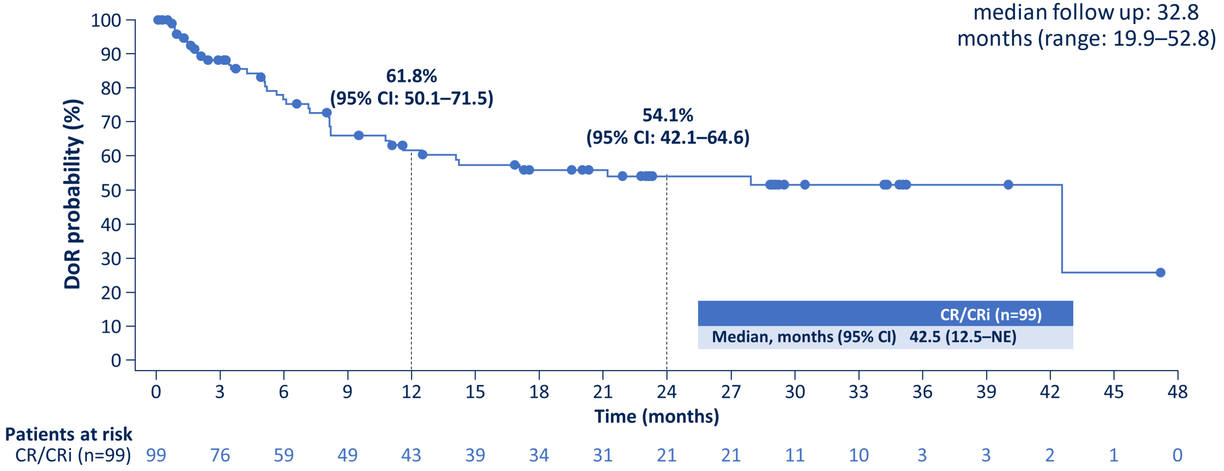


Current data cut: 18 Jan 2025. *Without non-protocol specified anti-cancer therapies, including SCT; maintenance tyrosine kinase inhibitors allowed per protocol after two months post obe-cel infusion in patients with Philadelphia chromosome-positive disease. ‡All patients who received consolidative SCT were in MRD-negative remission ($<10^{-4}$ leukemic cells) at the time of transplant. CR, complete remission; CRi, complete remission with incomplete hematologic recovery; MRD, measurable residual disease; obe-cel, obecabtagene autoleucel; SCT, stem cell transplant.

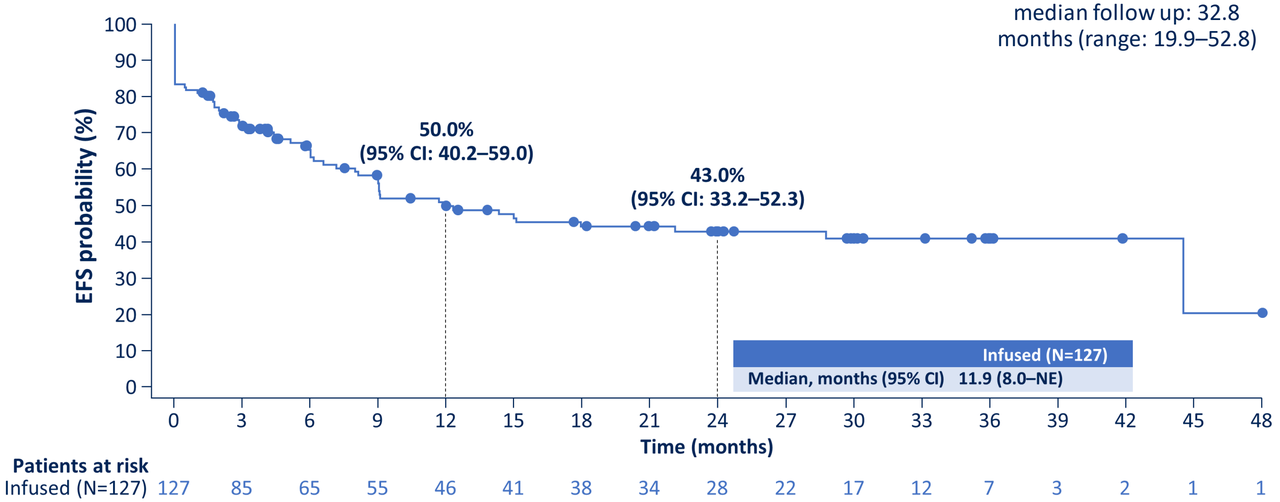
Durable outcomes reflected in updated survival curves

Median follow up of ~3 years

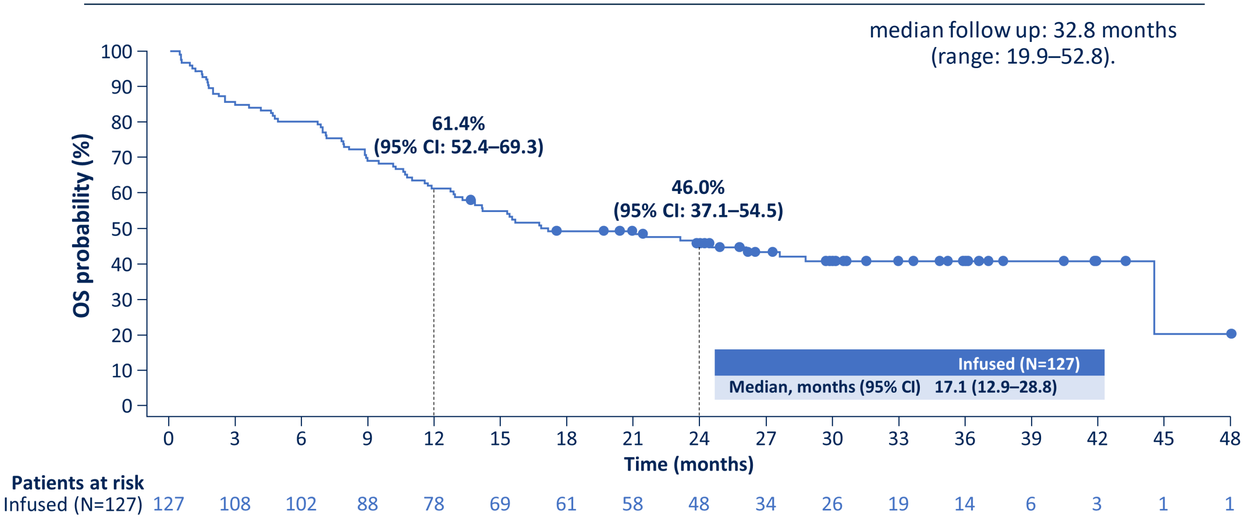
Duration of Remission **54.1% at 24m** *(allo-SCT censored)*



Event Free Survival **43% at 24m** *(allo-SCT censored)*



Overall Survival **46% at 24m** *(allo-SCT not censored)*



Nov 2024: Approved by the U.S. FDA

April 2025: Conditional marketing authorization by UK MHRA

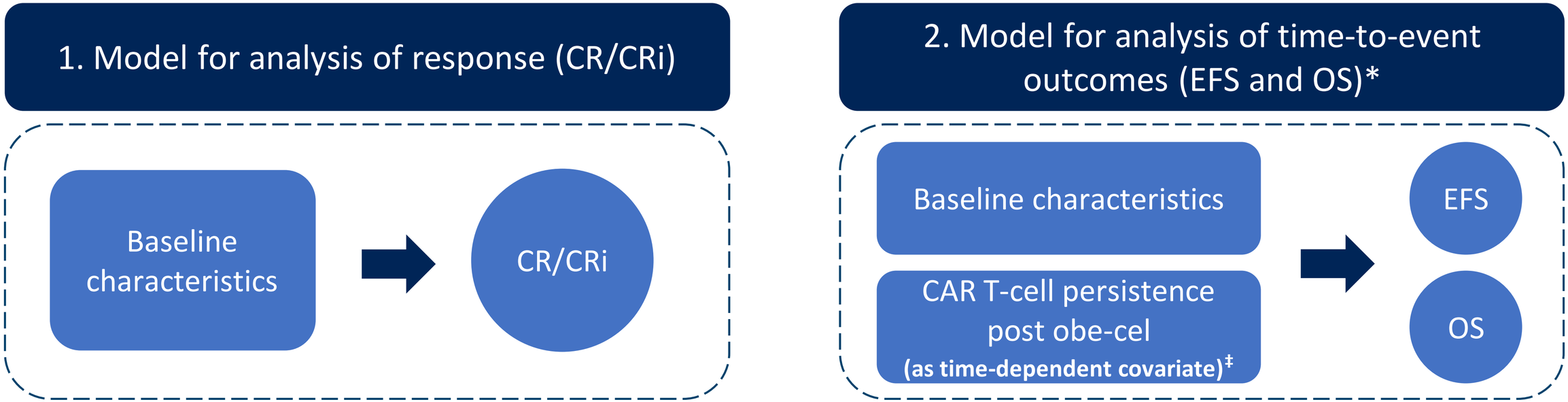
May 2025: Positive EMA CHMP opinion for adult R/R B-ALL

Park J, Roddie C et al, EHA, 2025

BUT…can we predict which patients will obtain long-term benefit?

MVAs were conducted using UVA-selected baseline characteristics

- A UVA on response, EFS, and OS was performed to pre-select baseline characteristics; those significant (p-value <0.1) in any of the three UVAs were fed into the MVA models below



- Stepwise variable selection was performed to identify the list of important factors in the final MVA model. Significance level for entry and stay was 0.25 and 0.2, respectively

*Deep MRD negative remission by NGS was not considered because of sample size limitation, as not all patients had NGS calibration. ‡Change in CAR T-cell persistence status (ongoing versus loss) over time, rather than at a specific timepoint, was analyzed. CAR, chimeric antigen receptor; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EFS, event-free survival; MRD, measurable residual disease; MVA, multivariate analysis; NGS, next-generation sequencing; obe-cel, obecabtagene autoleucel; OS, overall survival, UVA, univariate analysis.

Park J, Roddie C et al, EHA, 2025

UVA: Baseline characteristics selected for the MVA models

Better outcomes with less disease, less prior treatment, no EM disease

Characteristics with a UVA p-value <0.1	Associated with CR/CRi, EFS and/or OS			
	Better outcome (% of patients)		Worse outcome (% of patients)	
Age	≥55 years	(37.8%)	<55 years	(62.2%)
Ethnicity	Not Hispanic/Latino/unknown	(70.1%)	Hispanic or Latino	(29.9%)
Philadelphia chromosome	Ph+	(28.3%)	Ph–	(71.7%)
Prior lines of therapy	≤3	(85.0%)	>3	(15.0%)
Response to first-line therapy	Relapse after 12M	(27.6%)	R/R within 12M	(72.4%)
Refractory to last prior line of therapy	No	(48.0%)	Yes	(52.0%)
Prior allogeneic stem cell transplant	Yes	(44.1%)	No	(55.9%)
Prior inotuzumab ozogamicin*	No	(68.5%)	Yes	(31.5%)
Extramedullary disease at LD	Absent	(78.7%)	Present	(21.3%)
Bone marrow blasts at LD‡	<5%	(28.3%)	>75%	(31.5%)

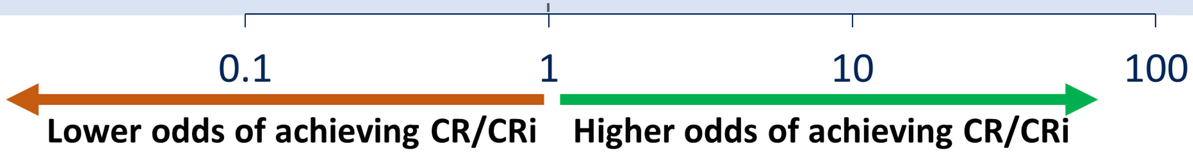
*Prior to screening; inotuzumab ozogamicin used as bridging therapy in FELIX was not included in these analyses. ‡Categorical variable with three groups. CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EFS, event-free survival; LD, lymphodepletion; M, months; MVA, multivariate analysis; OS, overall survival; Ph, Philadelphia chromosome; R/R, relapsed/refractory; UVA, univariate analysis.

Park J, Roddie C et al, EHA, 2025

Model 1: Can we predict who will achieve CR/CRi?

Ph+, earlier obe-cel use, less refractory disease, lower burden

Final model characteristics				Odds ratio (95% CI)*
Philadelphia chromosome	Ph–	vs	Ph+	6.0 (1.4–26.3)
Prior lines of therapy	>3	vs	≤3	3.8 (1.2–12.1)
Refractory to last prior line of therapy	Yes	vs	No	2.9 (1.1–8.0)
Extramedullary disease at LD	Present	vs	Absent	2.8 (1.0–7.8)
BM blasts at LD	>75%	vs	<5%	3.2 (0.9–11.6)
	≥5%–≤75%	vs	<5%	1.5 (0.4–5.6)
	>75%	vs	≥5%–≤75%	2.1 (0.7–6.3)



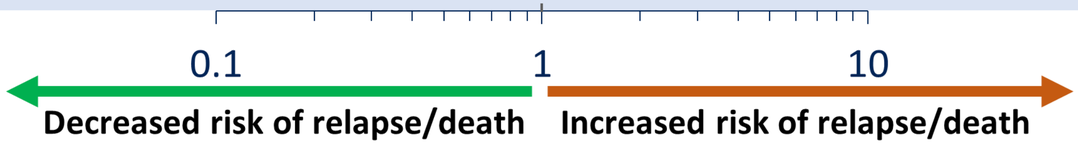
*A logistics regression analysis of patients achieving CR/CRi was performed against baseline characteristics. BM, bone marrow; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; LD, lymphodepletion; obe-cel, obecabtagene autoleucel; Ph, Philadelphia chromosome.

Park J, Roddie C et al, EHA, 2025

Model 2: Can we predict who will achieve prolonged EFS*?

Low BM blasts, prior SCT, ongoing persistence, and earlier obe-cel use

Final model characteristics				Hazard ratio (95% CI)‡
BM blasts at LD	<5%	vs	>75%	0.3 (0.1–0.6)
	<5%	vs	5%–≤75%	0.6 (0.3–1.2)
	≥5%–≤75%	vs	>75%	0.5 (0.3–0.9)
Prior SCT	Yes	vs	No	0.5 (0.3–0.8)
CAR T-cell persistence	Yes	vs	No	0.4 (0.2–0.9)
Prior lines of therapy	≤3	vs	>3	0.5 (0.3–1.0)
Philadelphia chromosome	Ph+	vs	Ph–	0.6 (0.3–1.1)



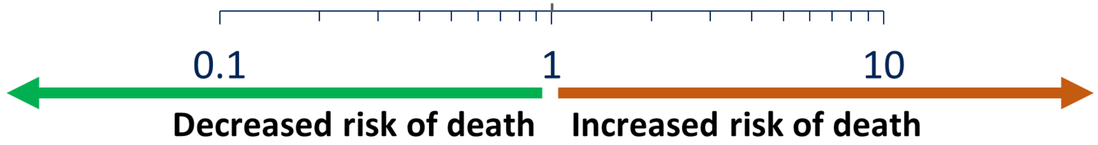
*EFS censoring for non-protocol anti-cancer therapies including consolidative SCT with disease assessment by independent response review committee. ‡A multivariate analysis Cox regression model was used to identify key factors for EFS using baseline characteristics and CAR T-cell persistence as a time-dependent covariate. BM, bone marrow; CAR, chimeric antigen receptor; CI, confidence interval; EFS, event-free survival; LD, lymphodepletion; SCT, stem cell transplant.

Park J, Roddie C et al, EHA, 2025

Model 2: Can we predict who will achieve prolonged OS*?

Low BM blasts, ongoing persistence and no prior InO

Final model characteristics				Hazard ratio (95% CI)‡
BM blasts at LD	<5%	vs	>75%	0.3 (0.1–0.5)
	<5%	vs	5%–≤75%	0.5 (0.2–1.0)
	≥5%–≤75%	vs	>75%	0.5 (0.3–0.9)
CAR T-cell persistence	Yes	vs	No	0.5 (0.3–0.9)
Prior InO§	No	vs	Yes	0.6 (0.3–0.9)
Philadelphia chromosome	Ph+	vs	Ph–	0.6 (0.3–1.0)

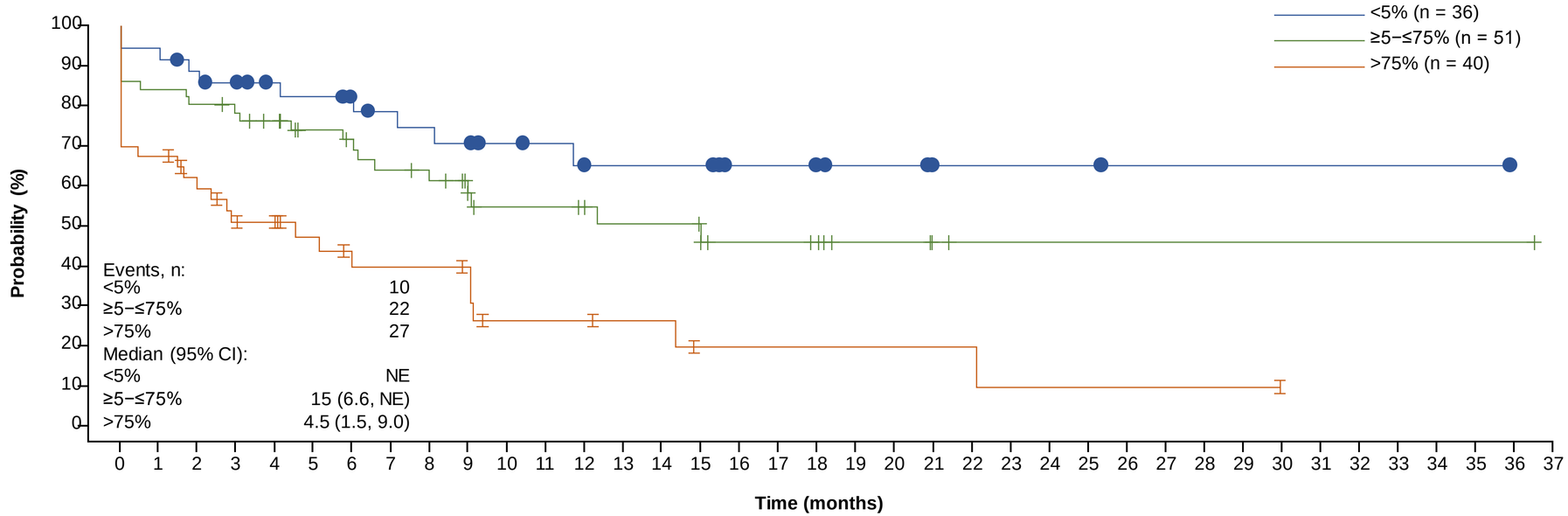


*OS without censoring for consolidative SCT. ‡A multivariate analysis Cox regression model was used to identify key factors for OS using baseline characteristics and CAR T-cell persistence as a time-dependent covariate. §Prior to screening; InO used as bridging therapy in FELIX was not included in these analyses. BM, bone marrow; CAR, chimeric antigen receptor; CI, confidence interval; InO, inotuzumab ozogamicin; LD, lymphodepletion; OS, overall survival; Ph, Philadelphia chromosome; SCT, stem cell transplant.

Park J, Roddie C et al, EHA, 2025

High leukemic burden pre-LD adversely impacts likelihood EFS*

Lower leukemic burden pre-LD is associated with better outcomes



Patients at risk

<5% (n = 36)	36	34	31	28	25	24	22	20	19	18	14	13	11	11	11	11	8	8	7	6	6	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0
≥5–≤75% (n = 51)	51	43	41	39	36	31	28	25	23	18	15	15	13	12	12	9	8	8	7	4	4	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
>75% (n = 40)	40	27	22	18	17	13	10	10	10	9	5	5	5	4	4	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	0	0	0	0	0	0	0

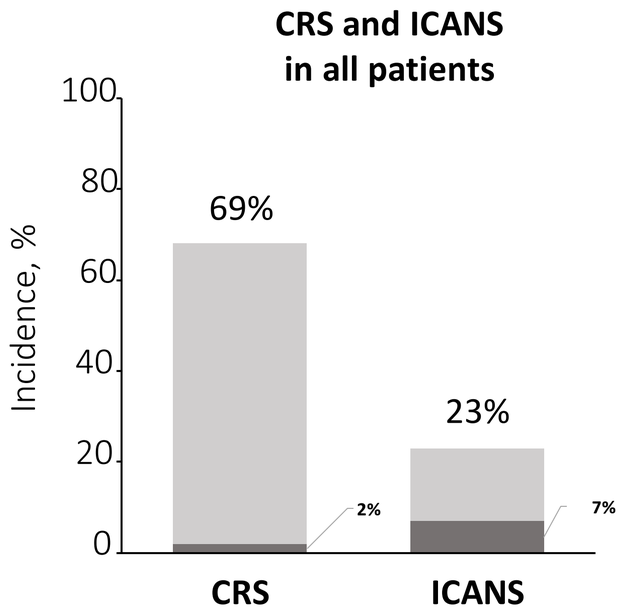
BM blasts % prior to lymphodepletion	<5% (n = 36)	≥5–≤75% (n = 51)	>75% (n = 40)
Median EFS (95% CI), months	**NE**	**15.0** (6.6, NE)	**4.5** (1.5, 9.0)
6-month EFS (95% CI), %	**83** (65, 92)	**72** (57, 82)	**40** (23, 56)
12-month EFS (95% CI), %	**65** (44, 80)	**55** (38, 69)	**27** (12, 44)

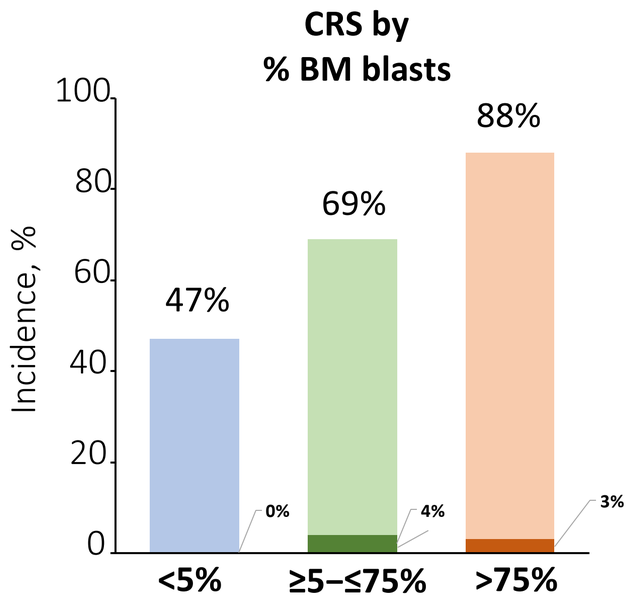
*Censoring new non-protocol anti-cancer therapies including SCT with disease assessment by IRRC (data cut-off date: September 13, 2023)

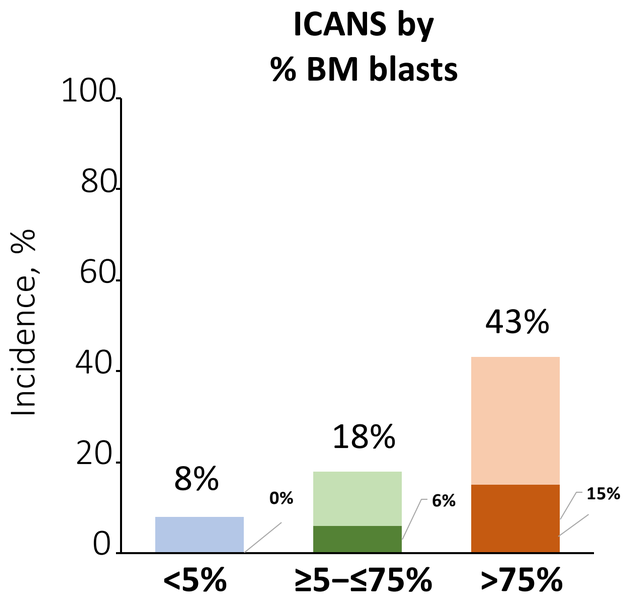
BM, bone marrow; CI, confidence interval; EFS, event-free survival; IRRC, Independent Response Review Committee; NE, not evaluable; SCT, stem cell transplant

FELIX: Low rates of Grade ≥3 CRS and/or ICANS were observed

Grade ≥3 events in high disease burden patients (>/=75% BM blasts)







Light colors = grade ≤2
Dark colors = grade ≥3

BM blasts % at lymphodepletion

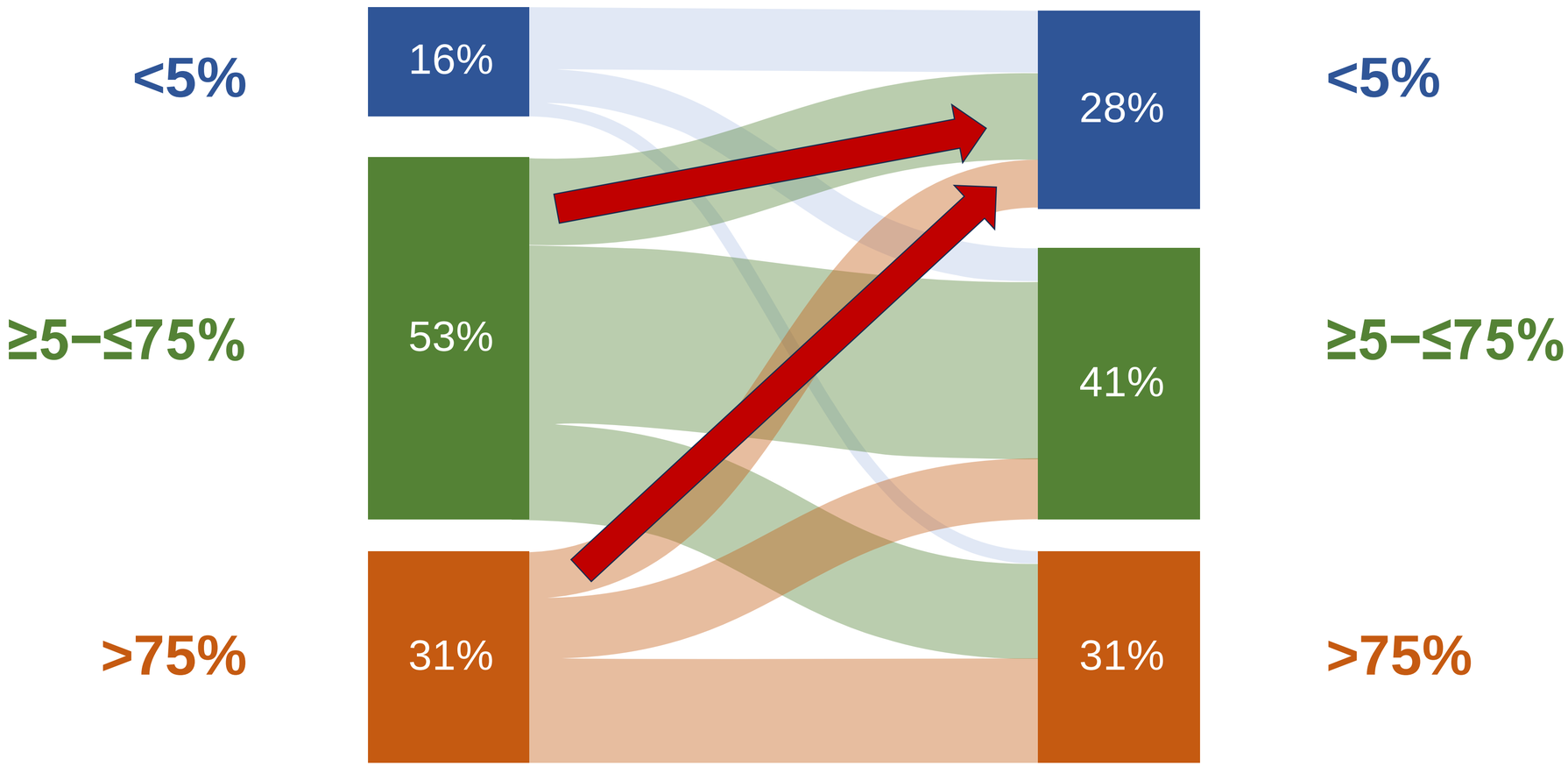
- No grade ≥3 CRS and/or ICANS were observed in patients with <5% BM blasts at lymphodepletion
- Vasopressors were used to treat CRS in 2.4% of patients

BM, bone marrow; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit

FELIX: Can we reduce the leukaemic burden with good bridging therapy?

Leukemic burden at screening is not predictive of burden pre-LD

118/127 (93%) patients received bridging therapy*



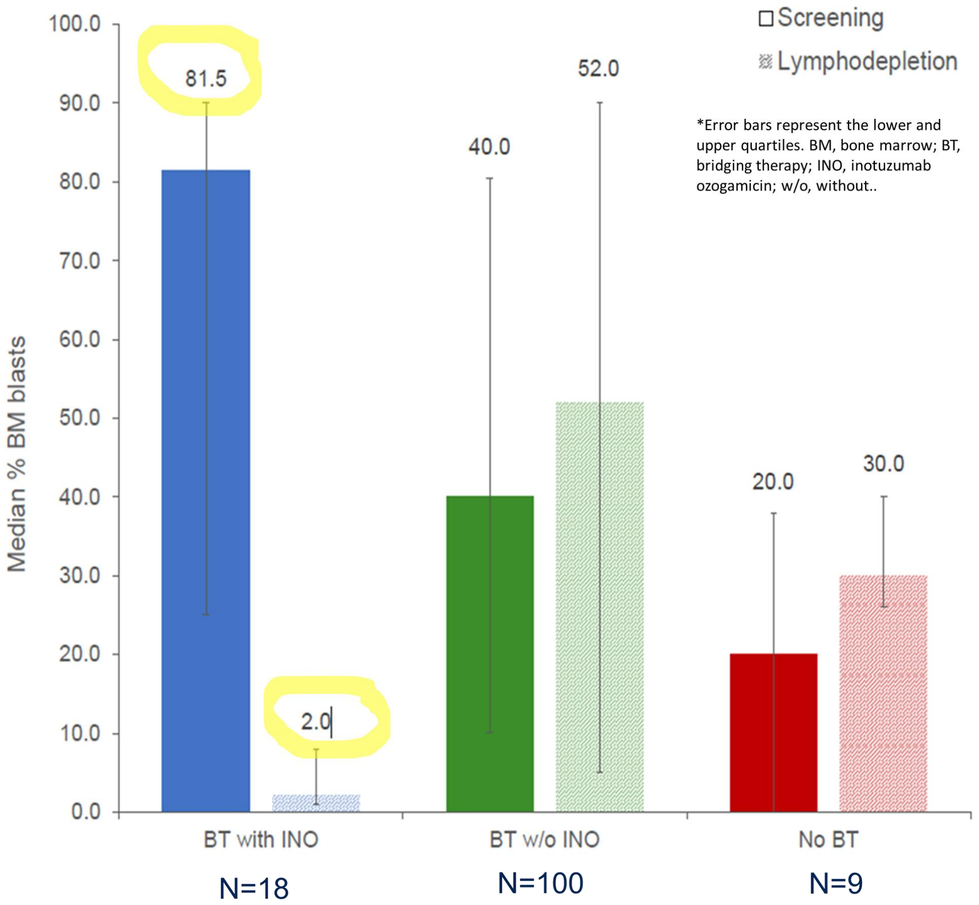
*Bridging therapy per physician's choice, including inotuzumab ozogamicin

BM, bone marrow

Can we reduce leukaemic burden pre-LD with good bridging therapy?

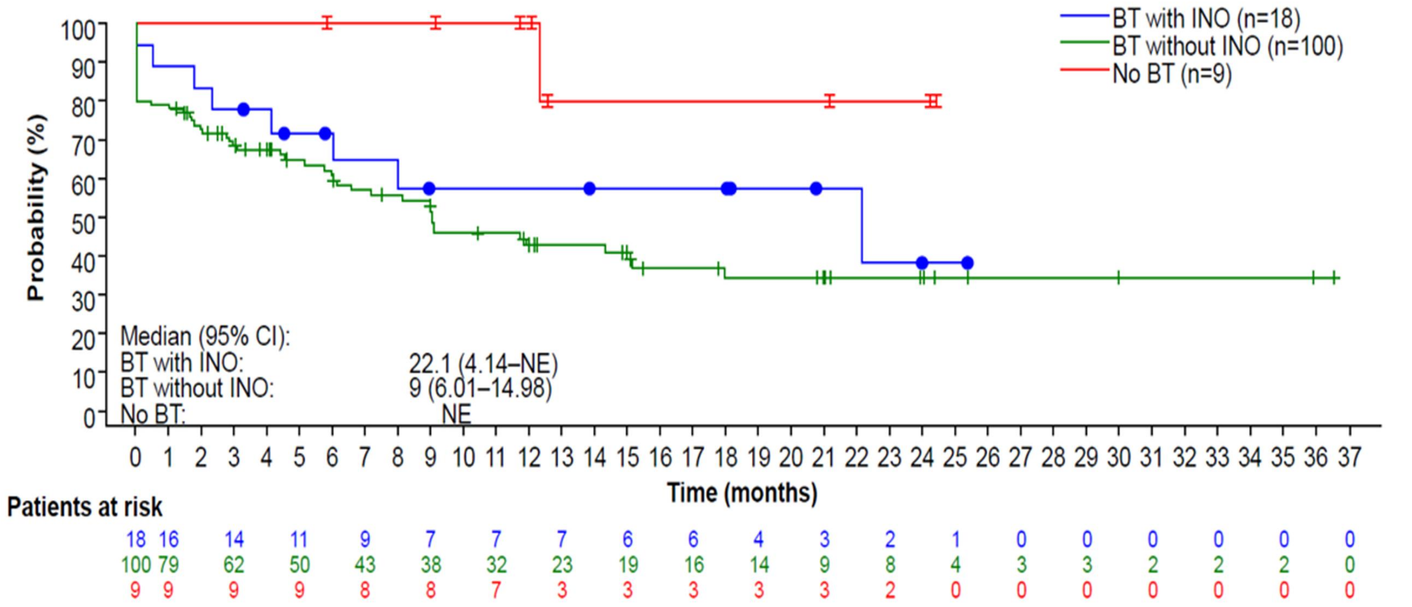
And can this improve the EFS associated with >75% blasts pre=LD?

On FELIX, IO was most effective at reducing BM blasts (82% to 2%)



*Error bars represent the lower and upper quartiles. BM, bone marrow; BT, bridging therapy; INO, inotuzumab ozogamicin; w/o, without..

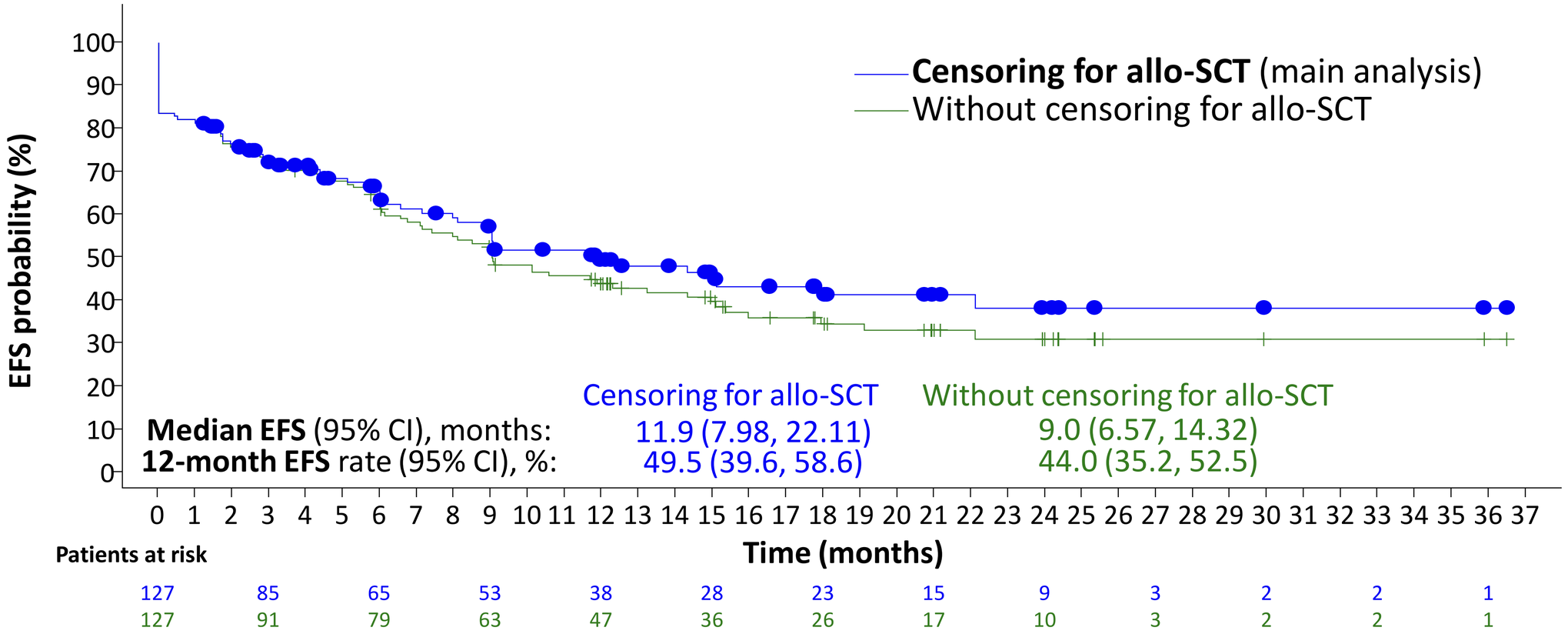
IO BT may improve EFS curve for high-risk patients (>75% blasts)



Park et al EHA 2024, ASH 2024

Does consolidation allo-SCT improve EFS post-CAR?

Potential long-term plateau from stand-alone treatment with obe-cel

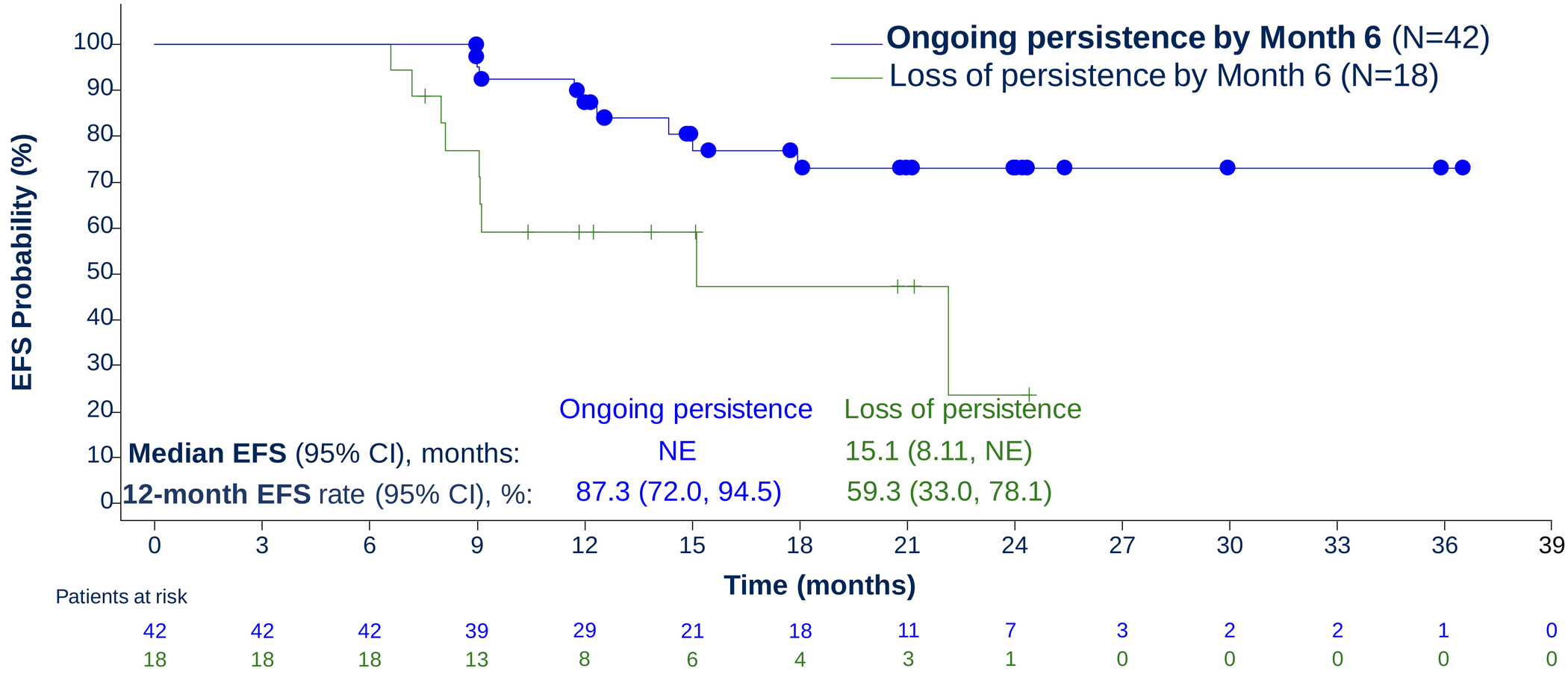


- All 18 patients who received allo-SCT in remission were MRD negative
- 10/18 (55.6%) had ongoing CAR T persistence prior to allo-SCT (n = 2 ongoing CR; n = 8 relapse/death)
- Characteristics similar between patients who did vs those who did not undergo consolidative allo-SCT

Roddie C, et al. EHA 2024. Abstract S114.

Can we predict who stays in remission and potentially avoid allo-SCT?

Landmark analysis of patients in ongoing CR at 6m by CAR marking



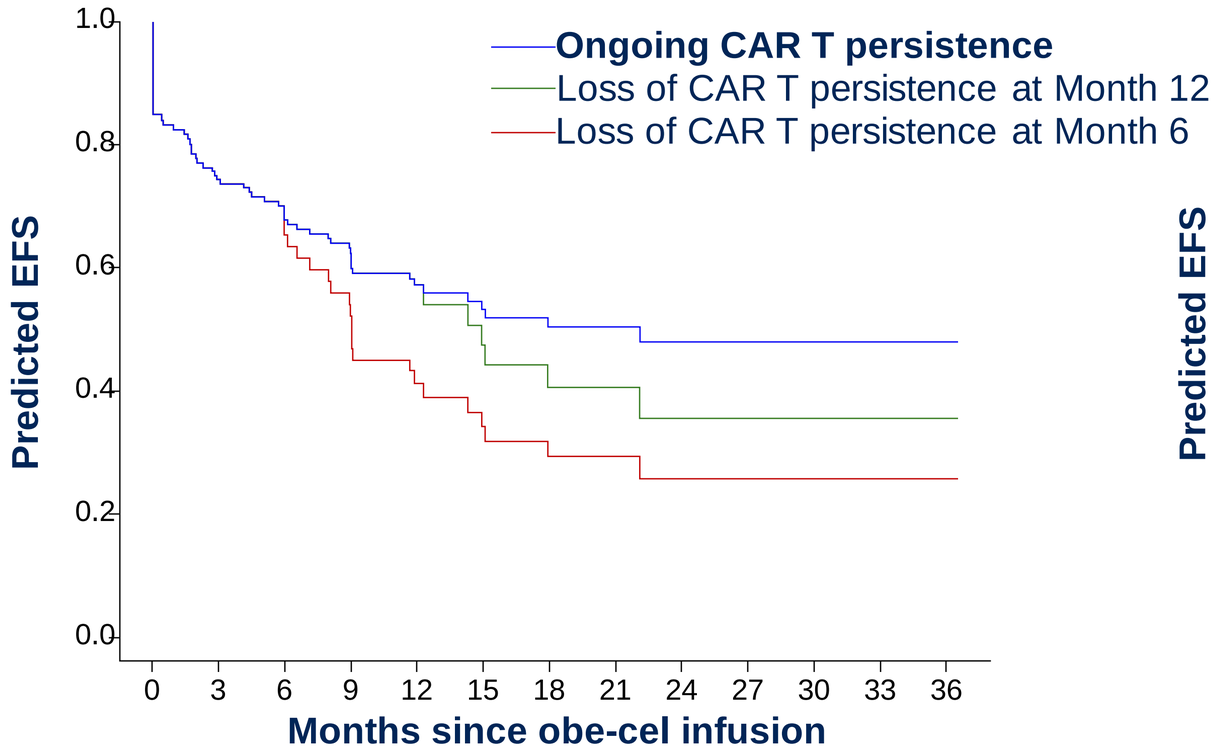
Ongoing CAR T persistence at 6 months associated w improved EFS

Roddie et al EHA 2024

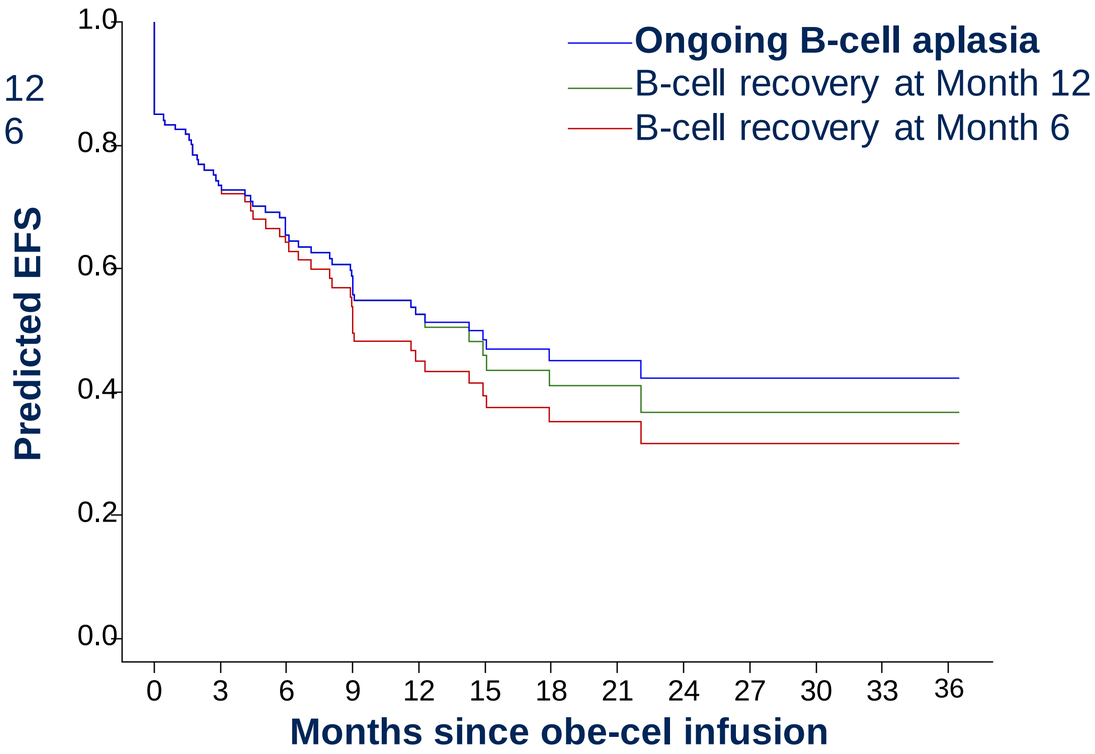
EFS, Event-free survival , SCT, Stem cell transplant

The importance of CAR T persistence re. prediction of relapse

Ongoing CAR T persistence + BCA correlates with long-term EFS



HR 2.7 (95% CI: 1.4, 5.3)



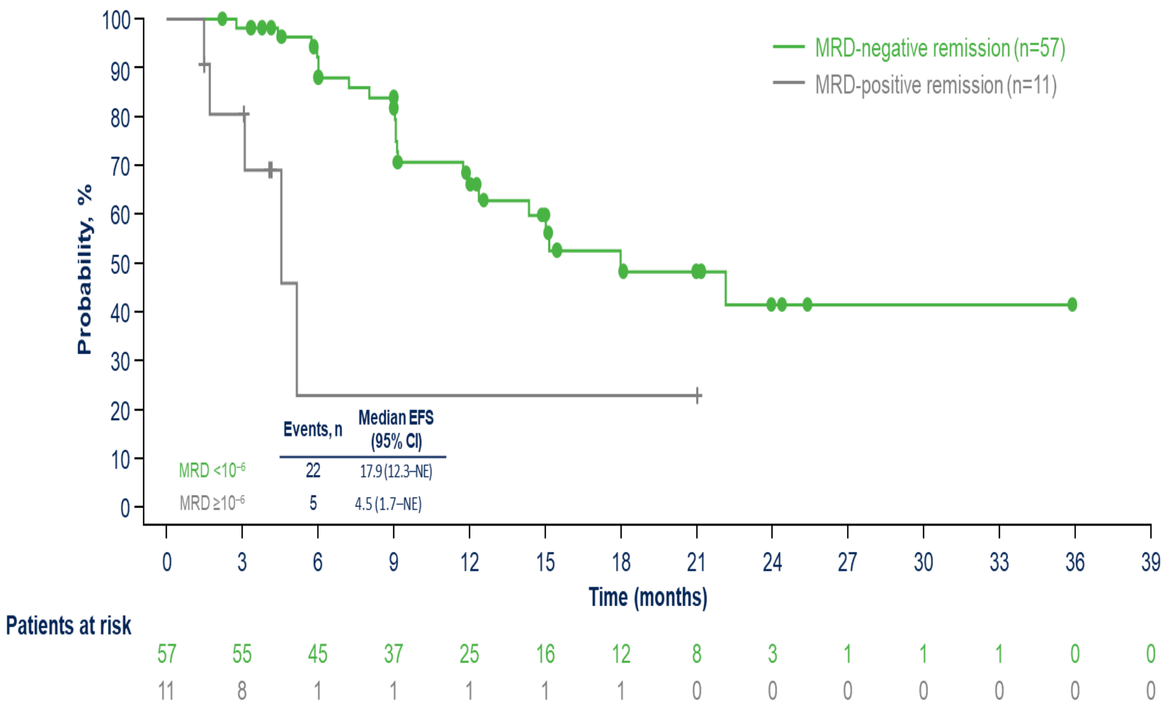
HR 1.7 (95% CI: 0.7, 3.8)

Roddie et al EHA 2024

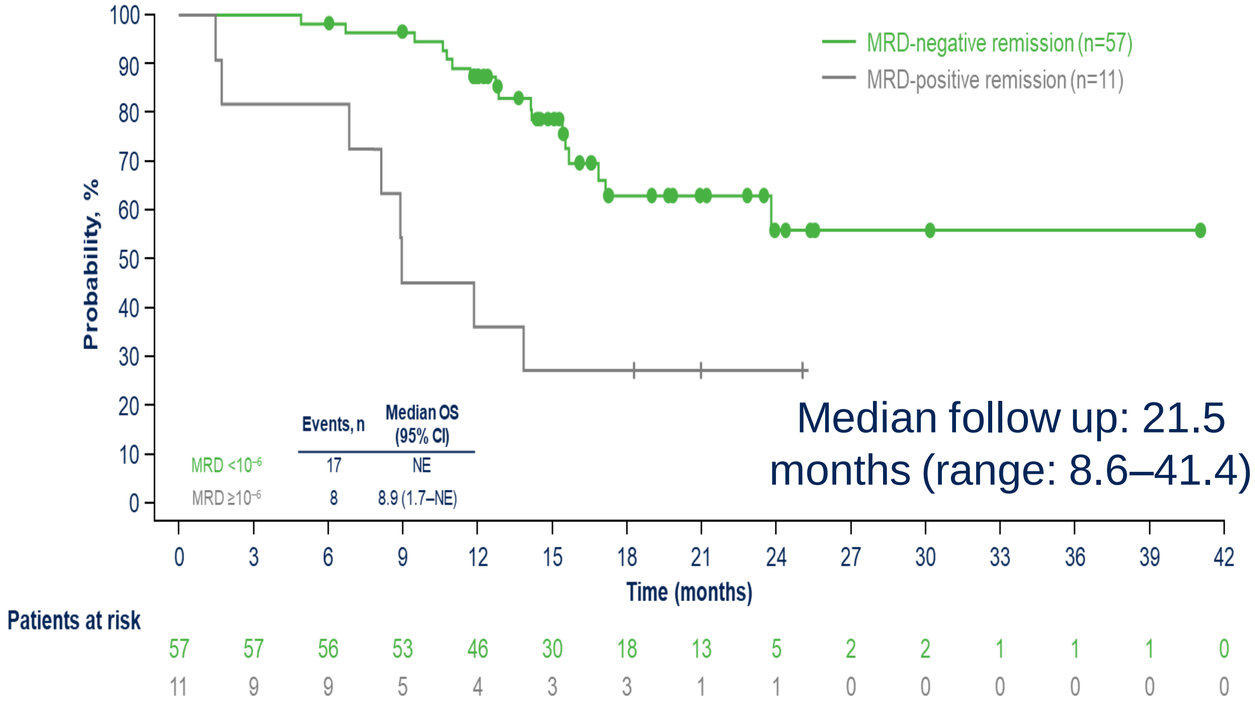
Impact central NGS MRD response (10^-6) by ClonoSEQ® on outcomes

84% of responders achieved <10–6 leukemic cells (MRD- remission)

EFS



OS



Median follow up: 21.5 months (range: 8.6–41.4)

Patients with MRD-negative remission had longer EFS and OS

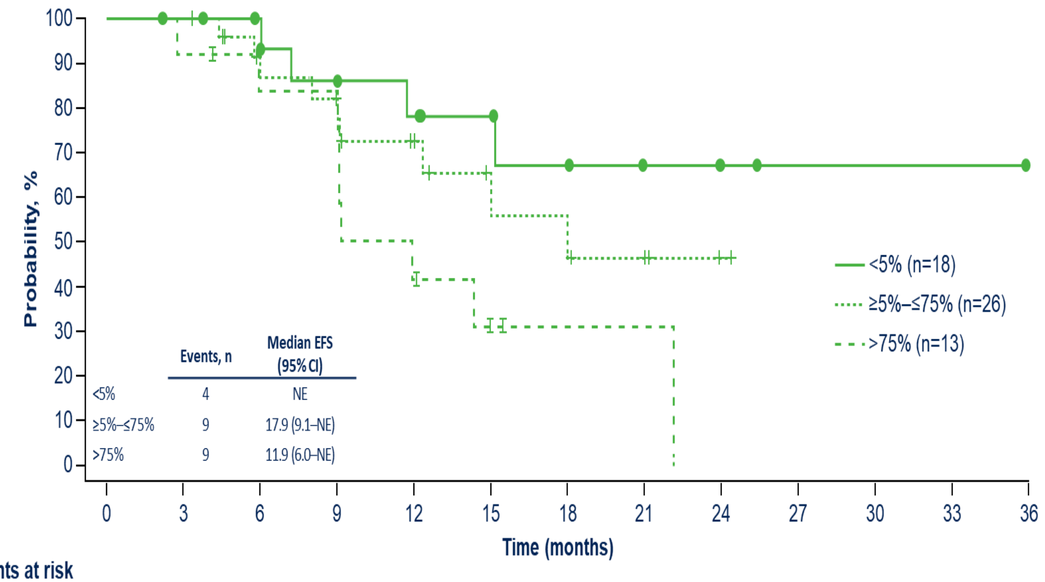
EFS censoring for non-protocol anti-cancer therapies including stem cell transplant with disease assessment by independent response review committee.

Jabbour et al ASH 2024

MRD-neg EFS stratified by pre-LD disease burden

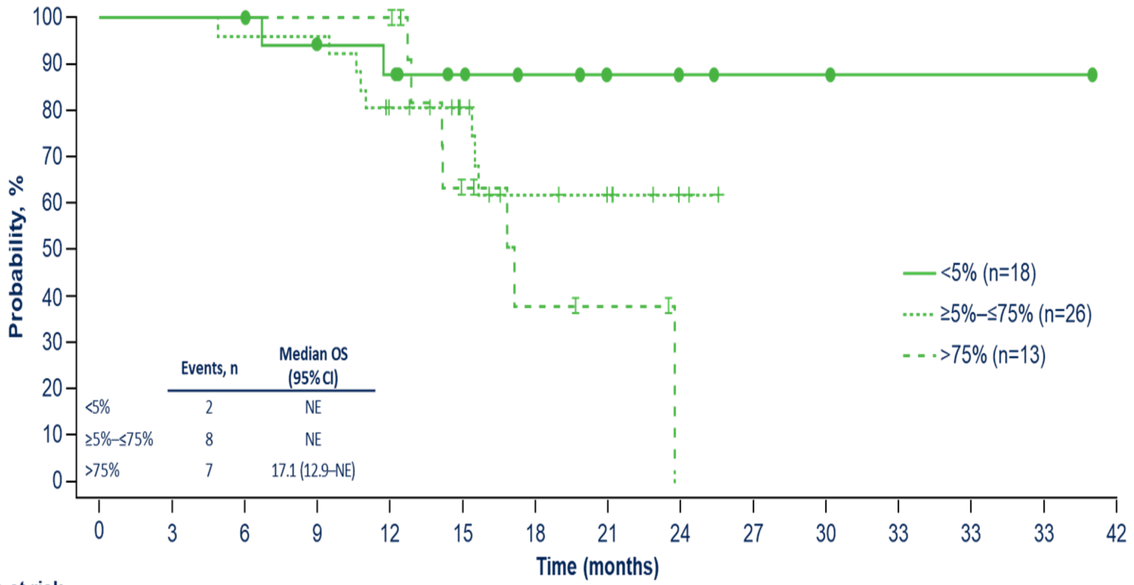
Lower tumor burden at LD correlates with largest benefit in EFS

EFS



Patients at risk														
MRD-negative remission n=57	<5%	18	17	15	11	10	8	6	4	2	1	1	1	0
	≥5%–≤75%	26	26	20	16	10	6	5	3	1	0	0	0	0
	>75%	13	12	10	10	5	2	1	1	0	0	0	0	0

OS



Patients at risk															
MRD-negative remission n=57	<5%	18	18	18	15	14	10	7	5	3	2	2	1	1	1	0
	≥5%–≤75%	26	26	25	25	19	14	8	6	2	0	0	0	0	0	0
	>75%	13	13	13	13	13	6	3	2	0	0	0	0	0	0	0

MRD-neg CR is associated with longer EFS and OS….BUT….
Largest EFS/OS benefit in low tumour burden pre-LD

EFS censoring for non-protocol anti-cancer therapies including stem cell transplant with disease assessment by independent response review committee.

Jabbour et al ASH 2024

Conclusions

Obe-cel may be considered a standard of care for adult R/R B-ALL

- At a median follow up of ~3 years, there is a sustained benefit for DoR, EFS, and OS
- 24-month DoR **54.1%** and EFS **43%** without consolidative SCT or other therapies
- *Potential for long-term plateau: for some patients obe-cel may be a stand-alone definitive therapy*

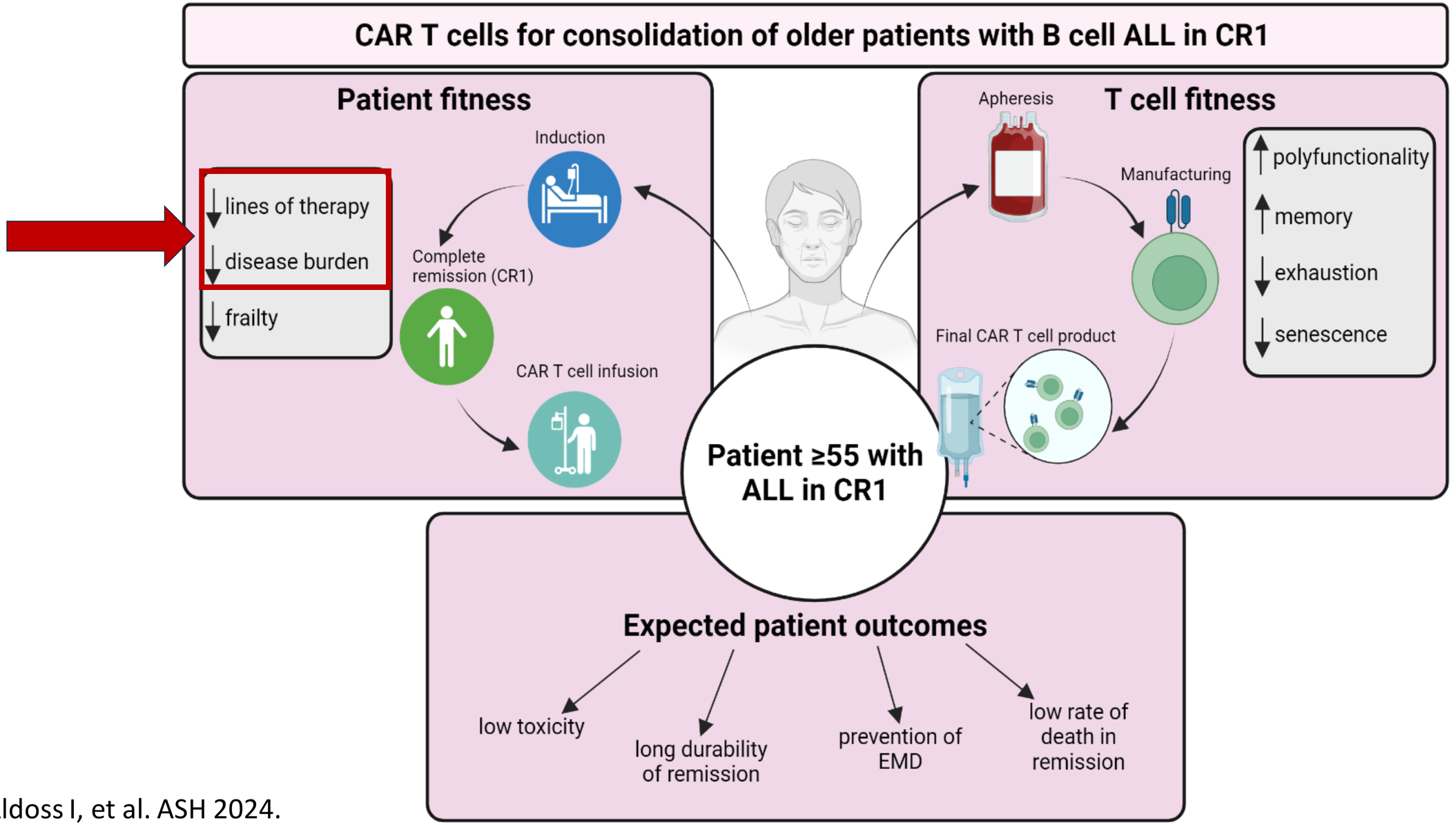
- Ph+ disease, earlier obe-cel use, and less refractory disease correlated with CR/CRi
- Lower disease burden pre-LD and CAR-T persistence independently associated with long-term survival

- Choice of BT prior to obe-cel, though influenced by clinical variables, may impact outcomes and studies comparing bridging with INO-containing therapies or chemotherapy are warranted.
- Baseline disease status remains the most important predictive factor…..

- Given better outcomes for low disease burden and less heavily pre-treated disease, **should we be using obe-cel as consolidation of low DB in earlier therapeutic lines?**

CD19CAR-T in older adults as a definitive consolidation in CR1 (NCT05707273)

Better patient fitness and T-cell fitness towards better outcomes….



Aldoss I, et al. ASH 2024.

CD19CAR-T in older adults as a definitive consolidation in CR1 (NCT05707273)

Eligibility/objectives and enrolment

Eligibility

- CD19+ B-ALL
- ≥ 55 years old
- ECOG <2
- Achieved CR1

➢No immediate plans for HCT

Exclusion

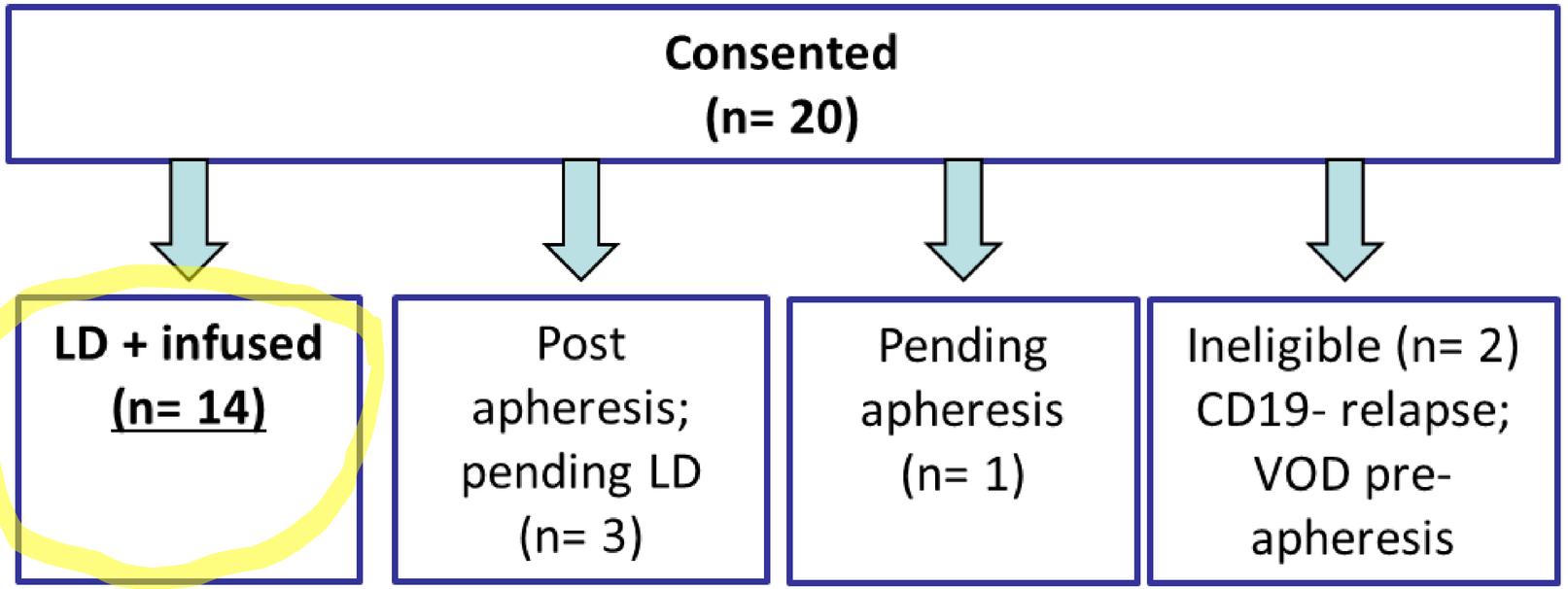
- Relapsed disease
- CNS pathology
- Active infection
- Steroids and IS

Primary objectives

- Safety
- RP2D

Secondary objectives

- Feasibility
- EFS,OS, QOL, T cell persistence



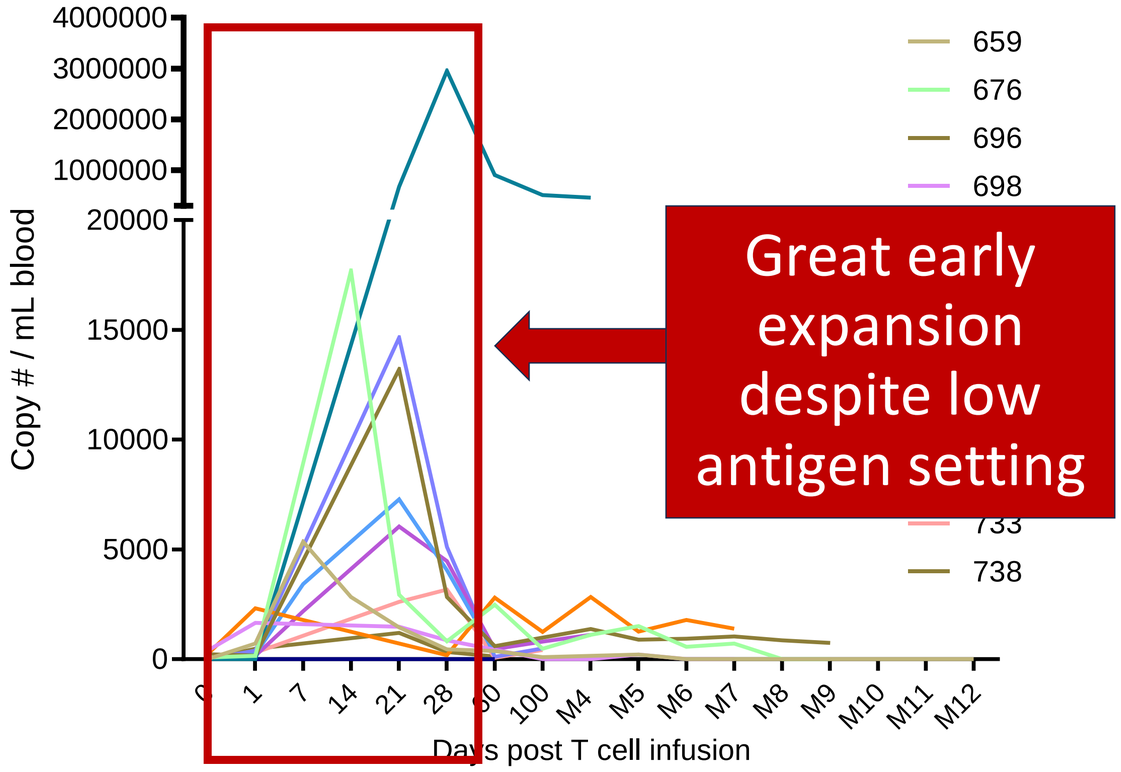
Aldoss I, et al. ASH 2024.

CD19CAR-T in older adults as a definitive consolidation in CR1 (NCT05707273)

Demographics, Toxicity, CAR-T engraftment (n=14 infused patients)

	N (%)
Median age (range), years	**68 (55-79)**
Gender	
Male	8 (57)
Female	6 (43)
Time from ALL diagnosis to consent (median, range), months	3.3 (1.8- 7.4)
Disease genetics	
Ph+	4
Ph-like	1
KMT2Ar	1
Hypodiploidy/*TP53m*	2
ZNF384::EP300	1
TCF3::PBX1	1
NOS	4
Prior blinatumomab	**11 (79)**
Prior inotuzumab	2 (14)

- No DLTs
- Grade 1 CRS= 64%
- Grade ≥2 CRS= 0
- Any grade ICANS= 0
- No deaths so far



Aldoss I, et al. ASH 2024.

CD19CAR-T in older adults as a definitive consolidation in CR1 (NCT05707273)

Efficacy at median F-U 244 days…12/14 (86%) patients in ongoing CR

Subject	Age/ sex	Cytogenetics/ molecular	Prior therapy	MRD pre-LD	CRS/ICANS	100 days	6 mo	9 mo	12 mo	15 mo	18 mo	F/U post CAR, days
1	66/F	*TCF::PBX1*	Chemo, blina	MRD-	**None**	NGS-	NGS-	NGS-	NGS-	NGS-	NGS-	576
2	64/M	*BCR::ABL, ASXL1, monosomy 7*	TKI + low dose chemo	ClonoSEQ detected	**None**	NGS-	PCR+, NGS+, MCF-	NA	NA	NA	NA	499
3	70/F	*FLT3, IKZF1, CDKN2A, XPO1*	Chemo + blina	MRD-	**G1 CRS**	NGS-	NGS-	NGS-	NGS-	Pending	Pending	378
4	55/M	*47,XY,+5*	Chemo	MRD-	**G1 CRS**	MCF-	MCF-	MCF-	Pending	Pending	Pending	322
5	75/M	*P2RY8::CRLF2*	Chemo + InO	MRD-	**G1 CRS**	NGS-	NGS-	MCF- /? NGS+	Pending	Pending	Pending	316
6	62/M	*IKZF2::ERBB4, CDKN2A loss, TP53m*	Chemo + blina	MRD-	**None**	NGS-	NGS-	NGS-	Pending	Pending	Pending	308
7	74/M	*BCR::ABL1*	TKI + chemo, blina + TKI	MRD-	**None**	MCF-	MCF-/PCR-	Pending	Pending	Pending	Pending	261
8	63/F	*BCR::ABL1, DNMT2A, IKZF1 onco iso*	TKI + chemo Blina + TKI	MRD-	**G1 CRS**	NGS-	NGS-	Pending	Pending	Pending	Pending	226
9	62/M	*BCR::ABL1*	TKI + chemo Blina + TKI	MRD-	**G1 CRS**	NGS-	NGS-	Pending	Pending	Pending	Pending	205
10	76/F	*KMT2A::AFF1*	Mini-CVD + InO, blina	MRD-	**G1 CRS**	NGS-	NGS-	Pending	Pending	Pending	Pending	196
11	79/M	*TP53m*	Chemo + Blina	MRD-	**G1 CRS**	NGS-	MRD-	Pending	Pending	Pending	Pending	177
12	72/F	*EP300::ZNF384*	Chemo + blina	MRD-	**None**	NGS-	Pending	Pending	Pending	Pending	Pending	140
13	59/F	*BCR::ABL1, ETV6, IKZF1 onco*	TKI + blina	MRD-	**G1 CRS**	NGS-	Pending	Pending	Pending	Pending	Pending	133
14	71/M	*NK*	Chemo + blina	MRD-	**G1 CRS**	MCF-	Pending	Pending	Pending	Pending	Pending	106

Aldoss I, et al. ASH 2024.

Conclusions

CD19CAR-T in adult B-ALL as first line consolidation

- CD19CAR T cells administered to older adults with B-ALL in CR1 is safe
- No ICANS or grade ≥2 CRS
- Older patients maintained their walking speed and cognitive function post infusion

- CD19CAR T cells expanded adequately in low antigen setting (clonoSEQ- state, B-cell aplasia)

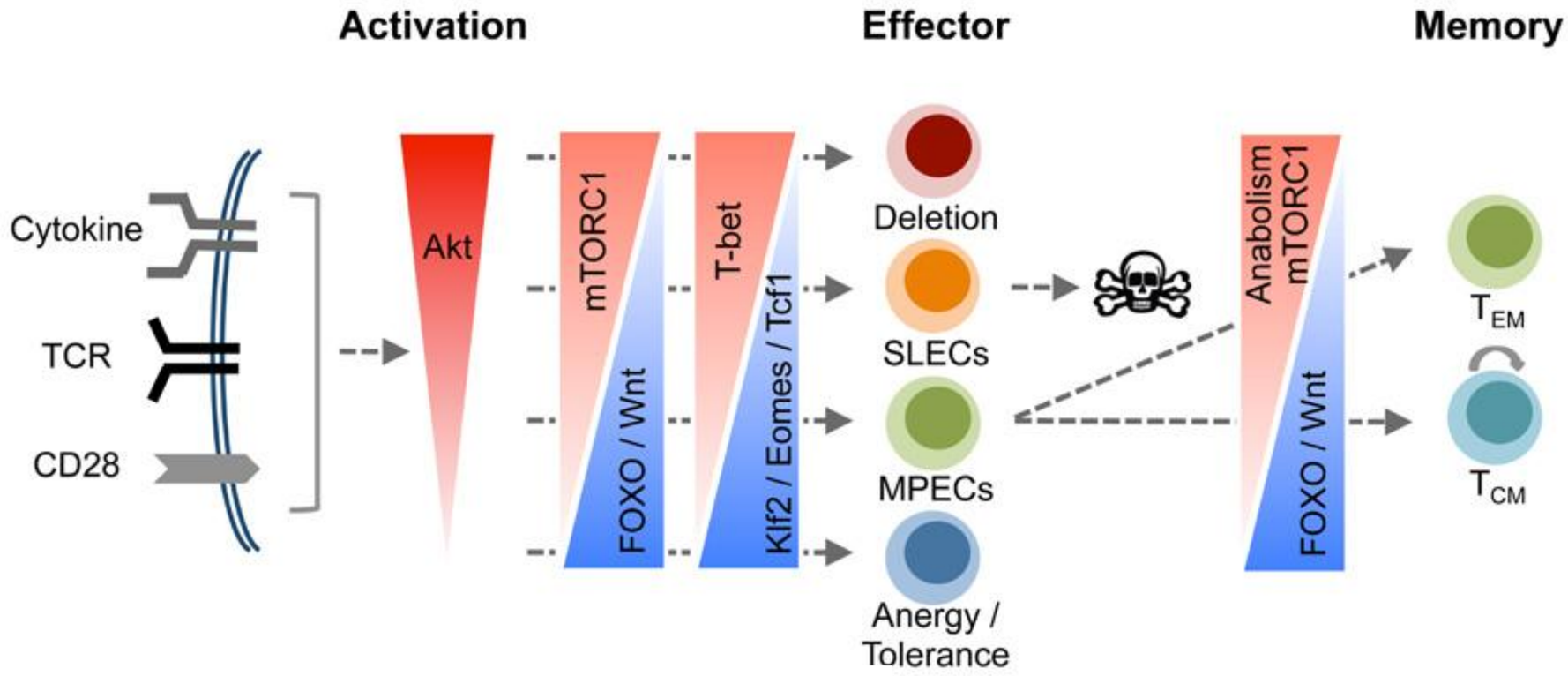
- Preliminary results indicate durable remission post infusion

- A confirmatory study to validate these results with commercially available CD19CAR is warranted
- It is intriguing to extend CR1 therapy to younger adults at high risk for treatment toxicity and failure

Aldoss I, et al. ASH 2024.

CD19+ relapse with loss of CAR persistence

Can optimised CAR-T manufacture overcome this issue?



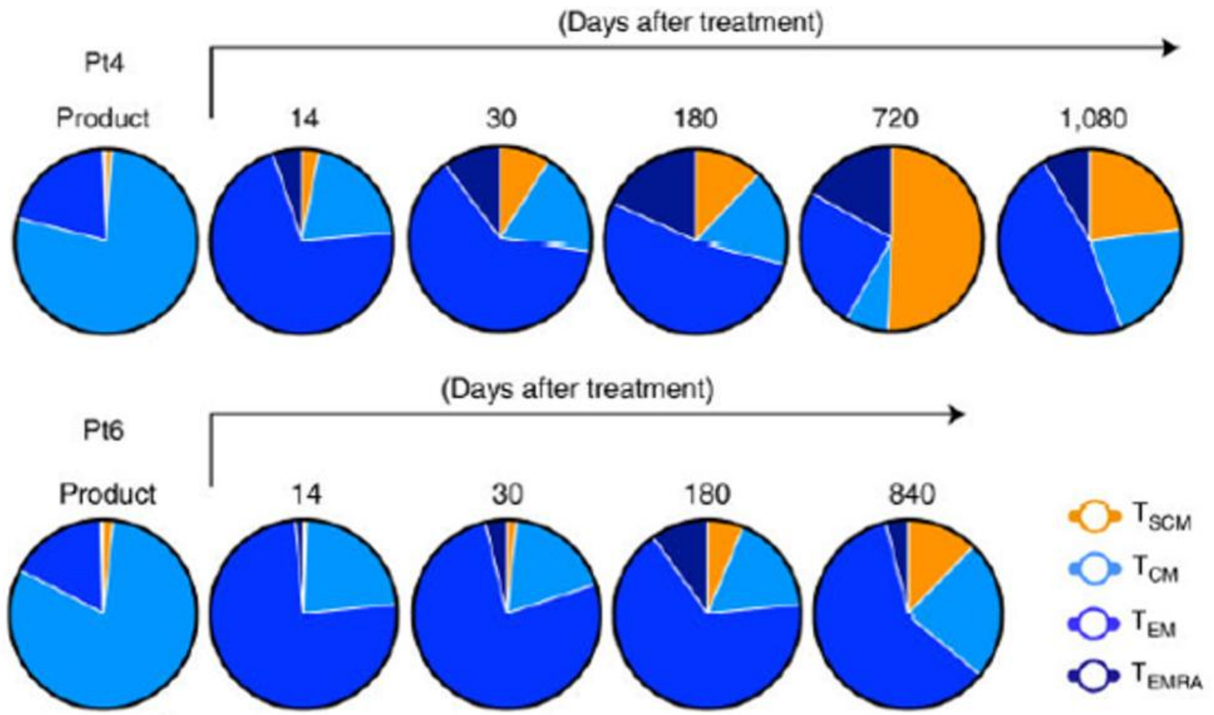
- **Shorter** Manufacture Process?
- Different **cytokine** combinations?
- **Pre-emptive harvest** for high risk disease?
- **PI3K or AKT inhibition?**

Suresh, M. et al, Frontiers Immunology 2013

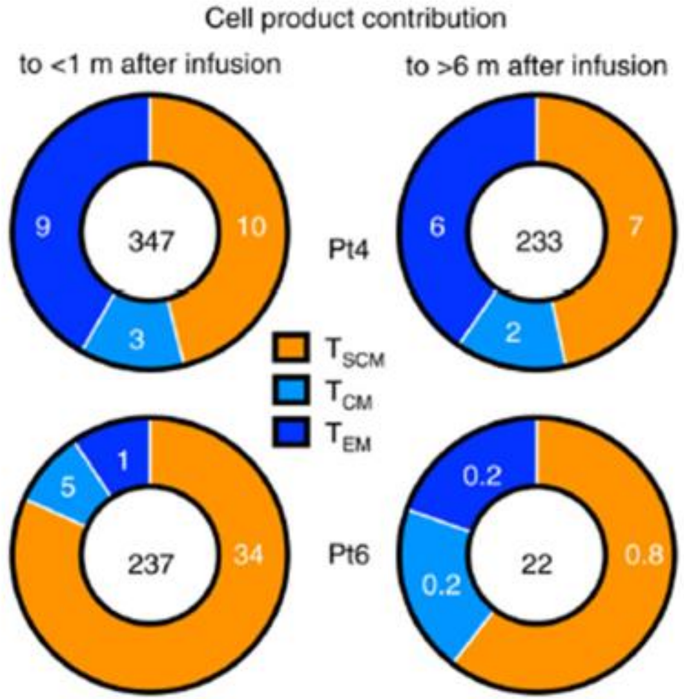
Which cells in the CAR-T product deliver tumour control & persistence?

Analysis of AUTO1 product/patient blood in long-term responders

Long-term responders: phenotyping product/blood (>D1000)



Integration site product and blood (to>6months)



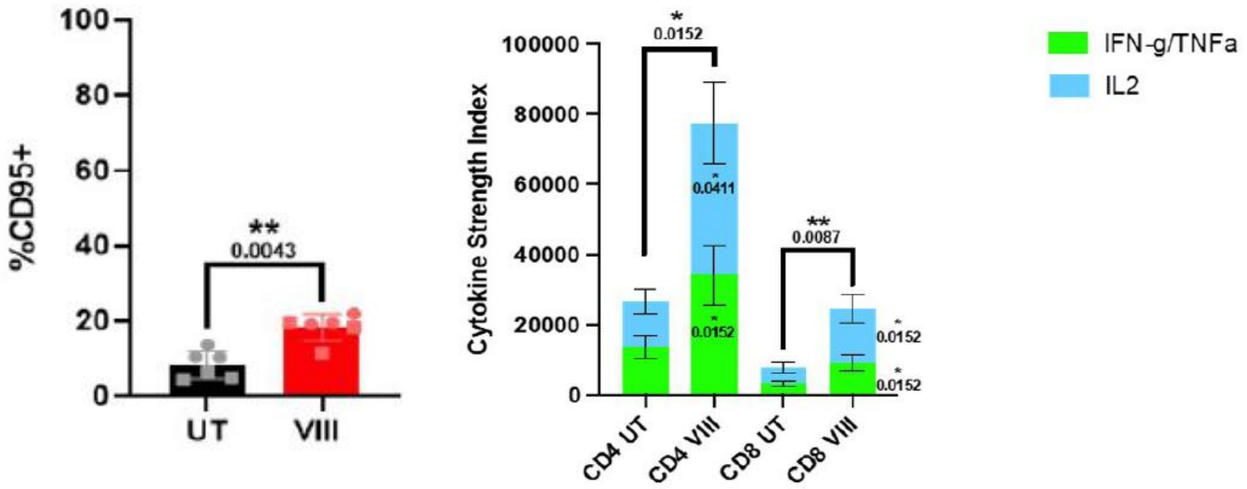
Need to explore and prioritise manufacturing protocols that generate CAR products enriched for Tscm populations

Biacso L et al., Nature Med, 2022

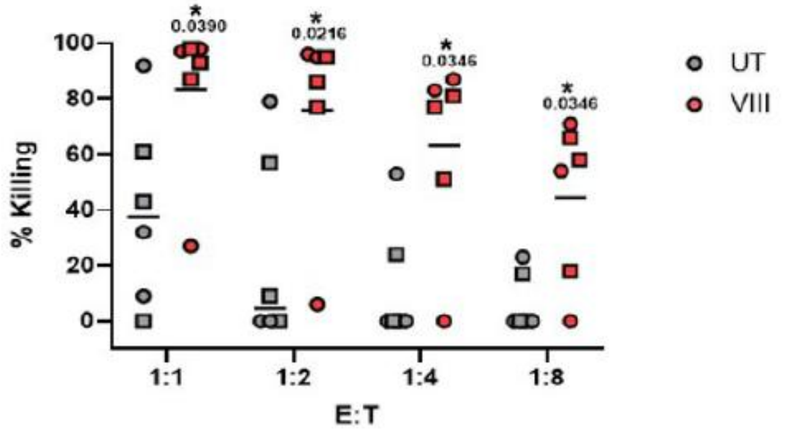
AKT inhibition generates Tscm-enriched, polyfunctional clinical CAR T-cells

AUTO1 trial patient products: AKTi exposed vs standard AUTO1 manufacture

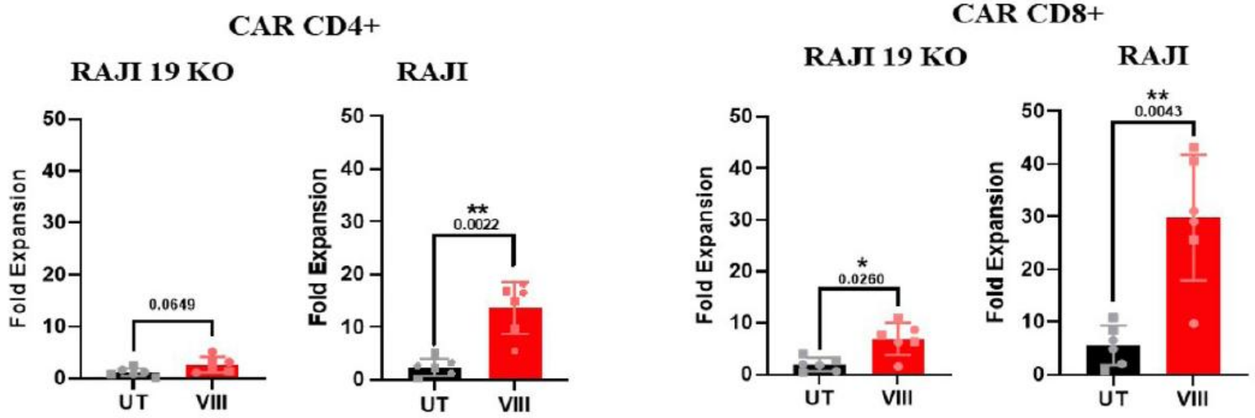
AKTi improves Tscm and cytokine secretion in patient products



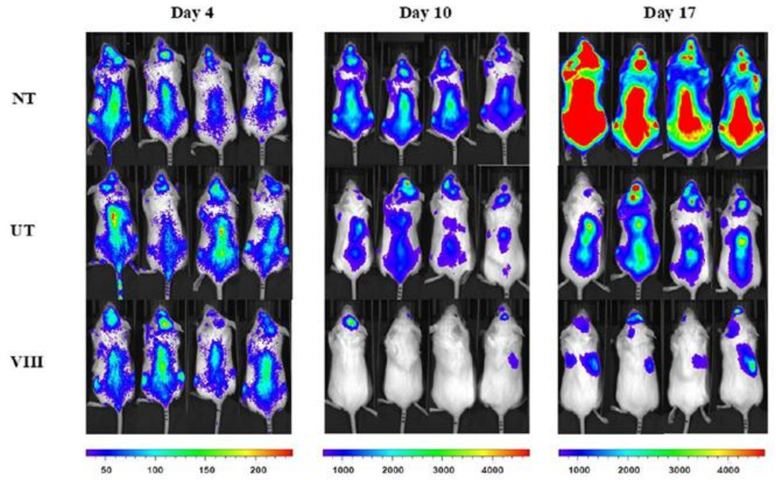
AKTi improves cytotoxicity in patient products



AKTi improves CAR proliferation in patient products



AKTi improves tumour eradication by patient products



Mehra V, Roddie C et al, JITC 2023

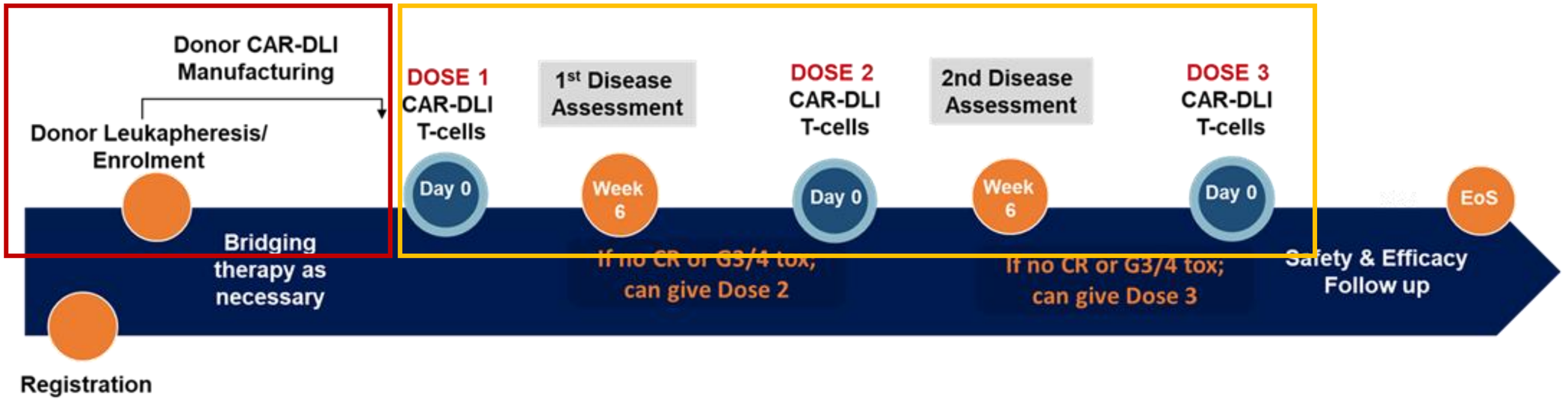
What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

The Phase I CARD study in r/r ALL post-allo-SCT (NCT02893189)

Is allo-SCT donor-derived CAR therapy feasible?

What is the role for Flu/Cy in matched allo CAR– more GvHD?

Is there a role for repeat CAR-T dosing in B-ALL?



Akin to DLI, dosing on CARD is:

- Delivered in an **escalating schedule**
- Based on CD3+ T-cell number/kg
  - 1 x 10^6/kg CD3+ T-cells
  - 3 x 10^6/kg CD3+ T-cells
  - 1 x 10^7/kg CD3+ T-cells
- **Minimum 8 weeks between CAR doses**

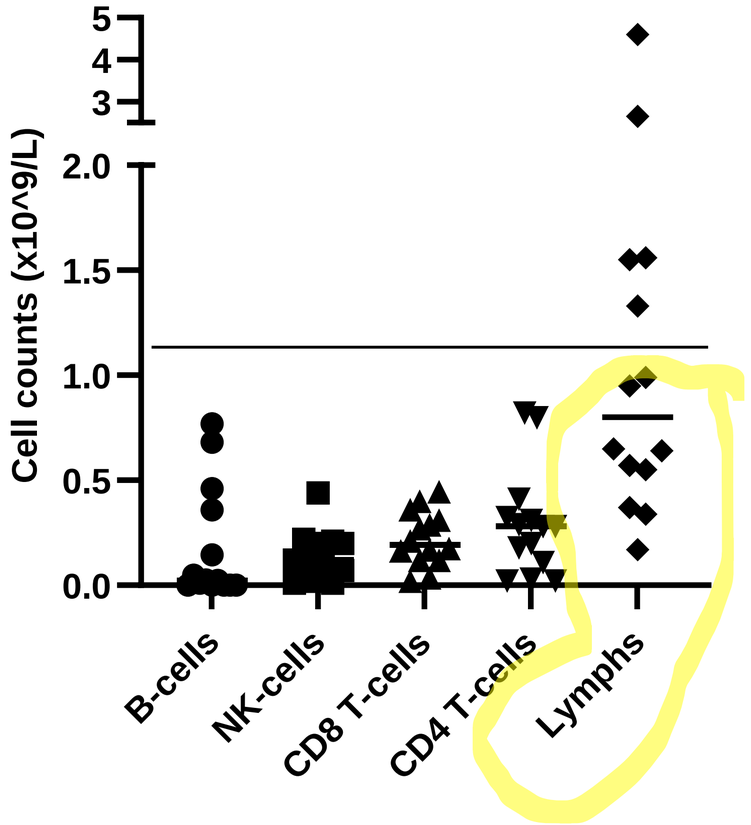
CAR-DLI-alone	NO LYMPHODEPLETION
CAR-DLI+LD	Flu. 30mg/kg for 3 days Cy. 300mg/m2 for 3 days

Roddie C, et al. Blood 2025.

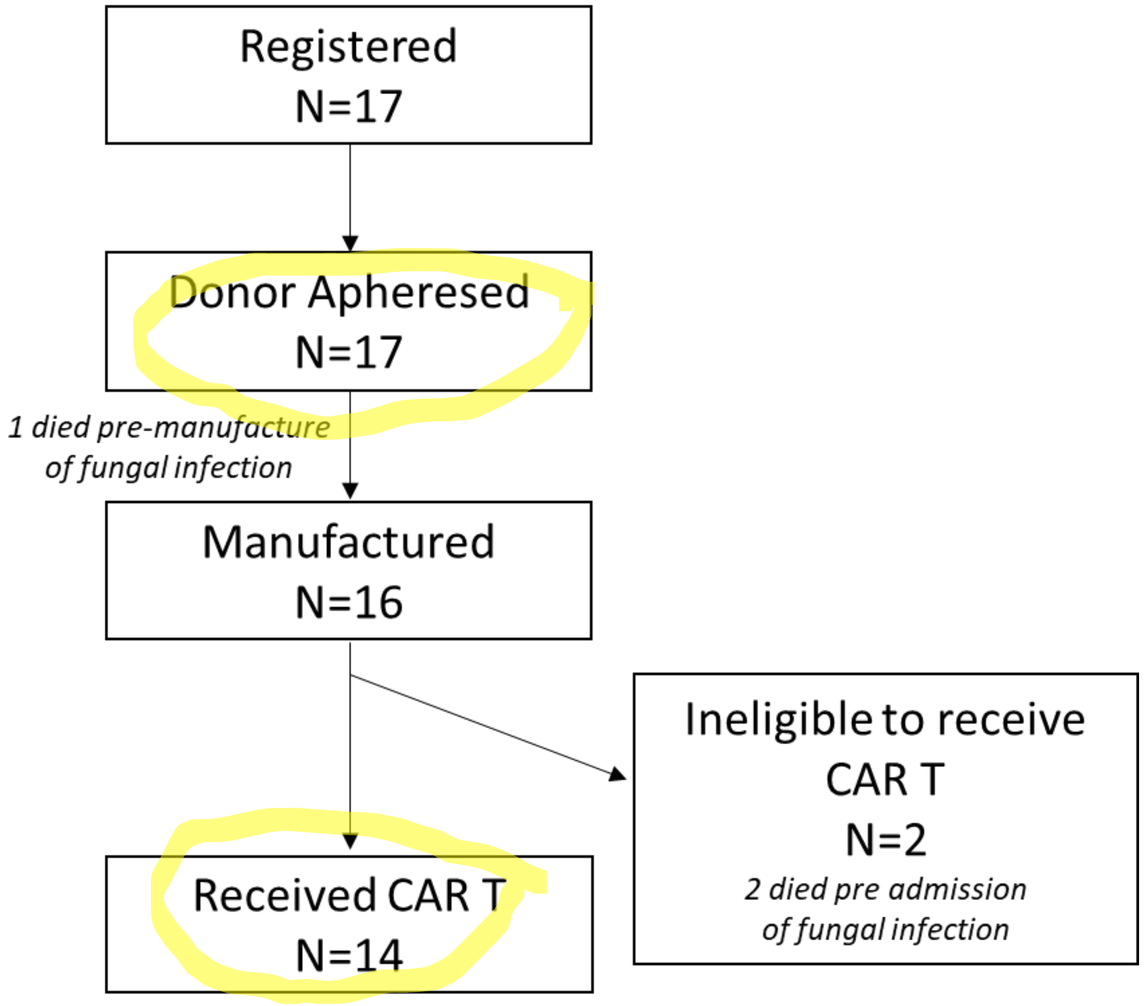
What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

The Phase I CARD study: recruitment and baseline lymphopenia

Most allo-SCT patients were lymphopenic at screening



17 patients screened & 17 donors harvested



Roddie C, et al. Blood 2025.

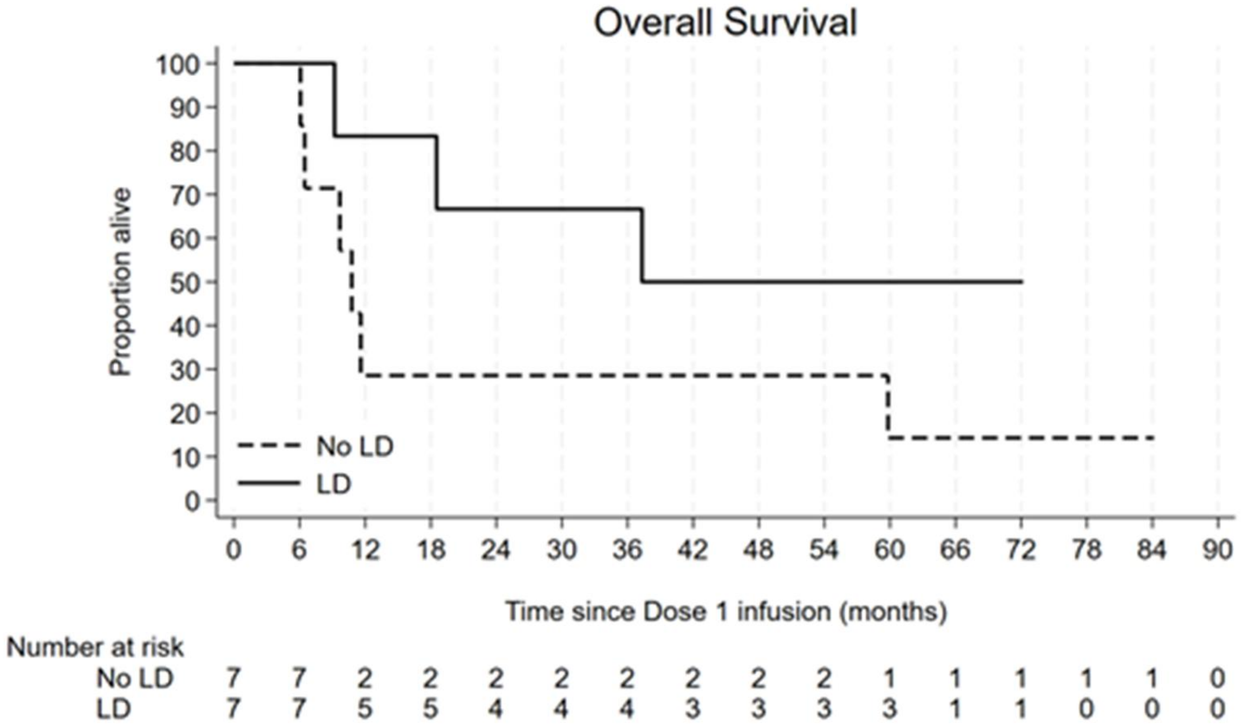
What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

Toxicity/GvHD minimal & Flu/Cy critical for overall survival (OS)

Toxicity minimal & only 2 cases of Grade 1 (skin) GvHD

Maximum grade CRS Dose 1 (ASTCT Criteria), n (%)	
CRS (any)	6/14 (43%)
Grade 2	2/ 14 (14%)
≥ Grade 3	1/14 (7%)
Maximum grade Neurotoxicity (ICANS)	
ICANS (any)	0/14 (0%)
Maximum grade GvHD	
GvHD (any)	2/14 (14%)
Grade 1	2/14 (14%)
≥ Grade 2	0/14 (0%)

Flu/Cy LD critical for OS

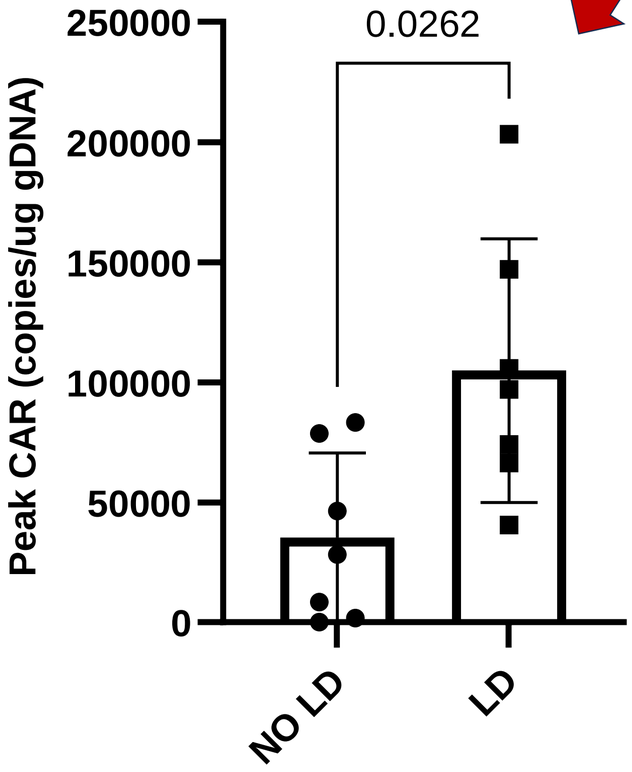


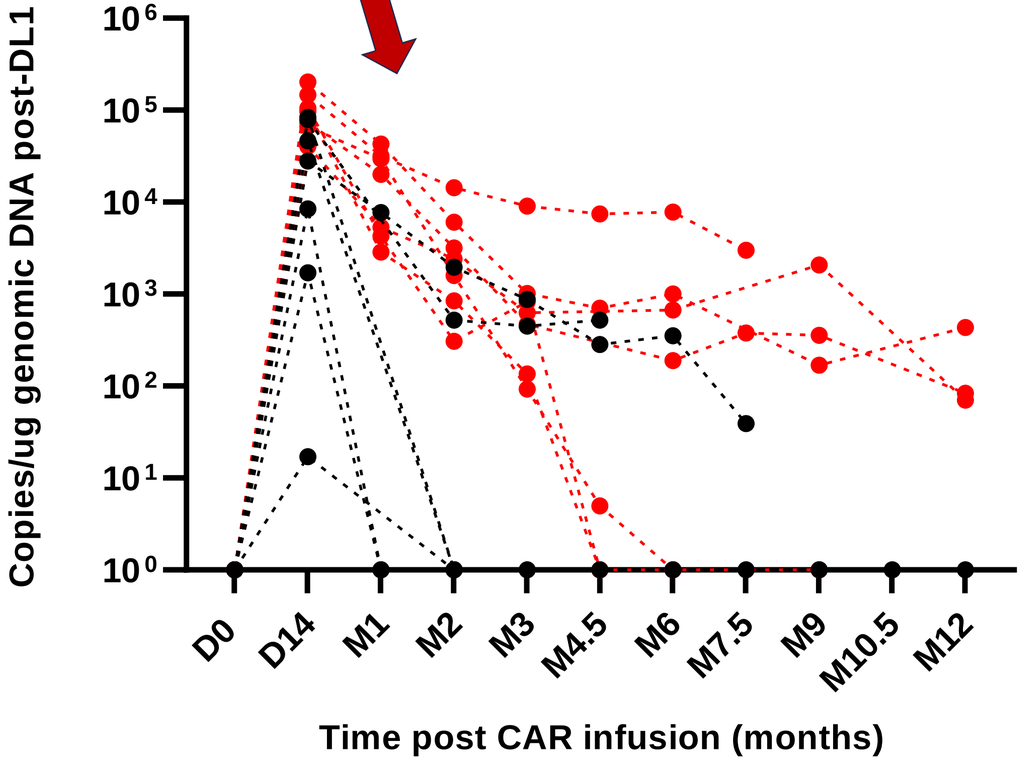
Roddie C, et al. Blood 2025.

What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

Why Flu/Cy LD associated with OS benefits in allo donor-derived CAR?

Flu/Cy critical for donor-CAR expansion and persistence



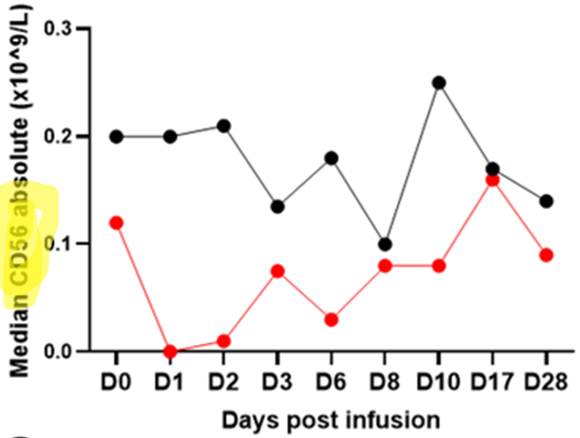


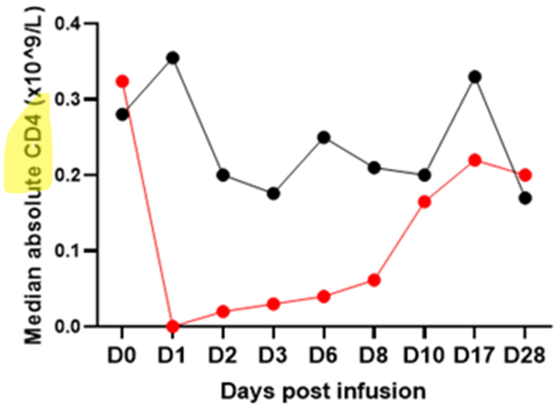
Roddie C, et al. Blood 2025.

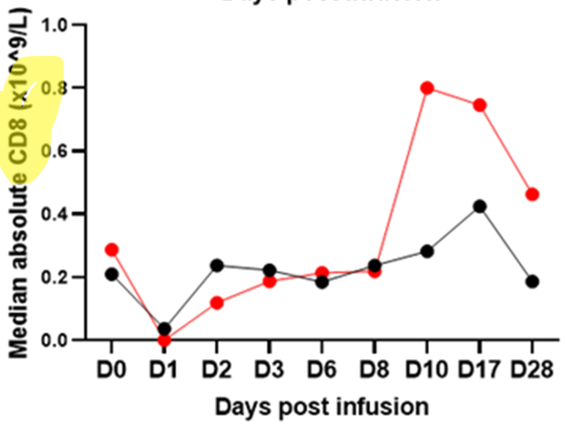
What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

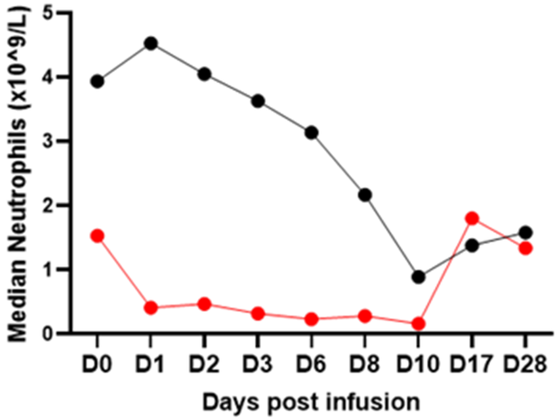
How does Flu/Cy support allo donor CAR expansion/persistence?

Fly/Cy LD depletes endogenous cytokine sinks

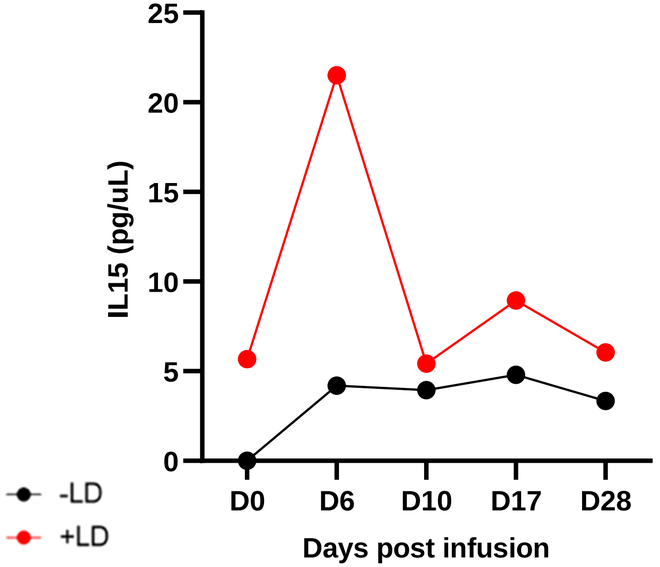


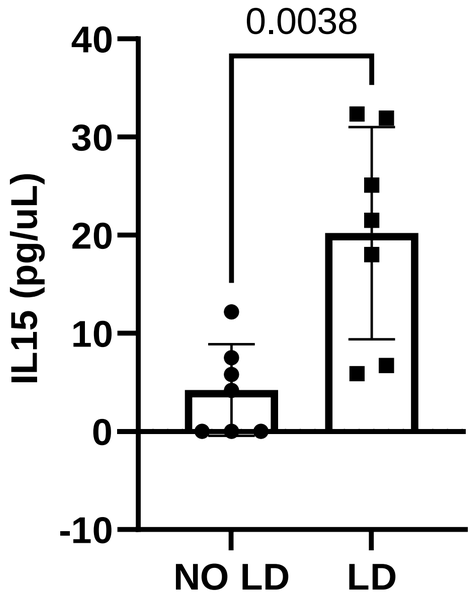






Fly/Cy LD creates early IL15 surge supporting CAR expansion



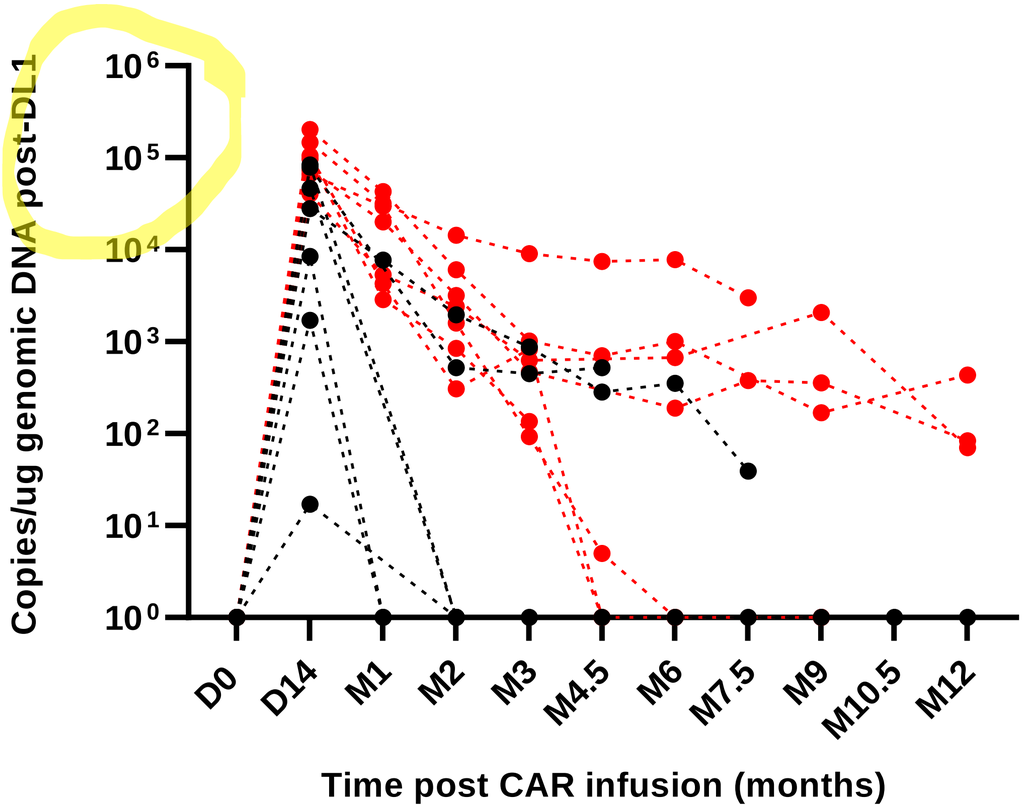


Roddie C, et al. Blood 2025.

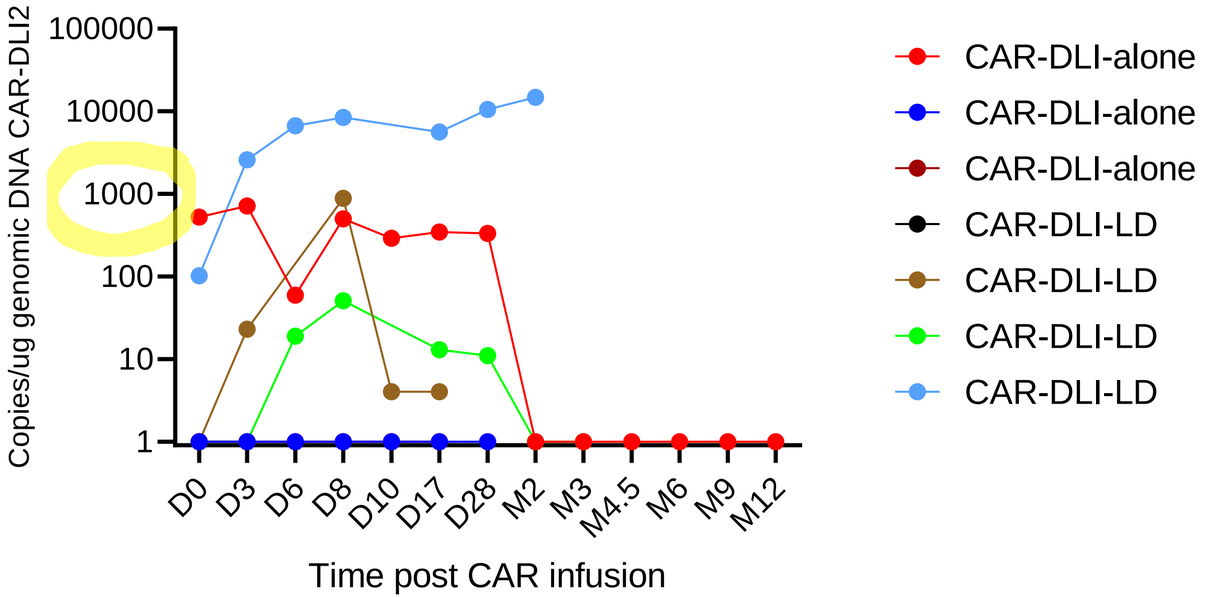
What about matched allogeneic donor CAR T-cells for a ‘fitter’ product?

What about repeat donor-derived allo CAR-T dosing?

CAR-T expansion by qPCR after Dose 1: ~100,000 copies



CAR-T expansion by qPCR after Dose 2: ~1-1000 copies



Minimal Toxicity, Minimal Engraftment, No Expansion, No Responses

Roddie C, et al. Blood 2025.

Conclusions

Strategies to improve CAR-T products for patients

- Tscm T-cells confer short and long term CAR-T activity – we should prioritise these populations for manufacturing

- Pharmacological modifications to CAR-T manufacture with T-cell signalling inhibition via AKT uncouples differentiation and expansion and gives more polyfunctional CAR products

- Donor-derived CAR T-cells following relapse post-allo SCT do not confer a high risk of GvHD and Flu/Cy LD is critical for CAR expansion, with no GvHD signal

- Repeat donor-derived CAR-T dosing was not successful on this study- need to explore alternative humanised binders and LD schedules

Acknowledgements

UCL Cancer Institute
Martin Pule
Paul Maciocia
Nicola Maciocia
Lydia Lee
Gordon Cheung
Marina Mitsikakou
Eftychia Charalambous
Harriet Roddy
Devika Singh
Gabriel Osborn
Simona Parinello
Alex Rampotas
Richard Jenner
Maria Hawkins
Isaac Gannon
Stephanie Ho
Elefteria Kateli
Mariana Viegas
Katie Smetanova
Abha Chipalkati
Jyoti Chhetri
Samira Ali
Patrycja Lewandoska

UCL CABI
Mark Lythgo
Tammy Kalber

UCLH
Maeve O'Reilly
Maise Al Bakir
Mike Northend
Kate Cwynarski
Amandeep Langotra
Clemency Every-Clayton
Maia Collins
Karl Peggs
Frederick VonBerg
Aisling Carr
Harpreet Hyare
Michael Kosmin

CCGTT
Juliana Dias
Giulia Agliardi
John Garcia
Mhairi Vaughan
Louisa Green
Evie Lewin
Eleanor Wooderson
Owen Bain
Silvia Rondelli
Noor Mujahid
Anthony Schillings
Anna Stockwell

UCL CTC
Bilyana Popova
Cathy McDowell
Amy Kirkwood
Sevi Galani
Andre Lopes
Memuna Rashid
William Wilson
Alex Day
Allan Hackshaw

GOSH
Sara Ghorashian
Persis Amrolia
Luca Biasco
Karin Straathof

Autolus
Leila Mekkaoui
James Sillibourne
Wolfram Brugger
Michael Zhang

UCL ECMC GCLP Lab
John Hartley
Helen Lowe
Victoria Spanswick
Yashma Pathak
Nas Mahmoud

City of Hope
Ibrahim Aldoss
Kharamjeet Sandhu
Steve Foreman

MD Anderson
Elias Jabbour
Hagop Kantarjan

Funded by NIHR

A huge thank you to patients and their families