CAR-T Cells for T Cell Lymphomas

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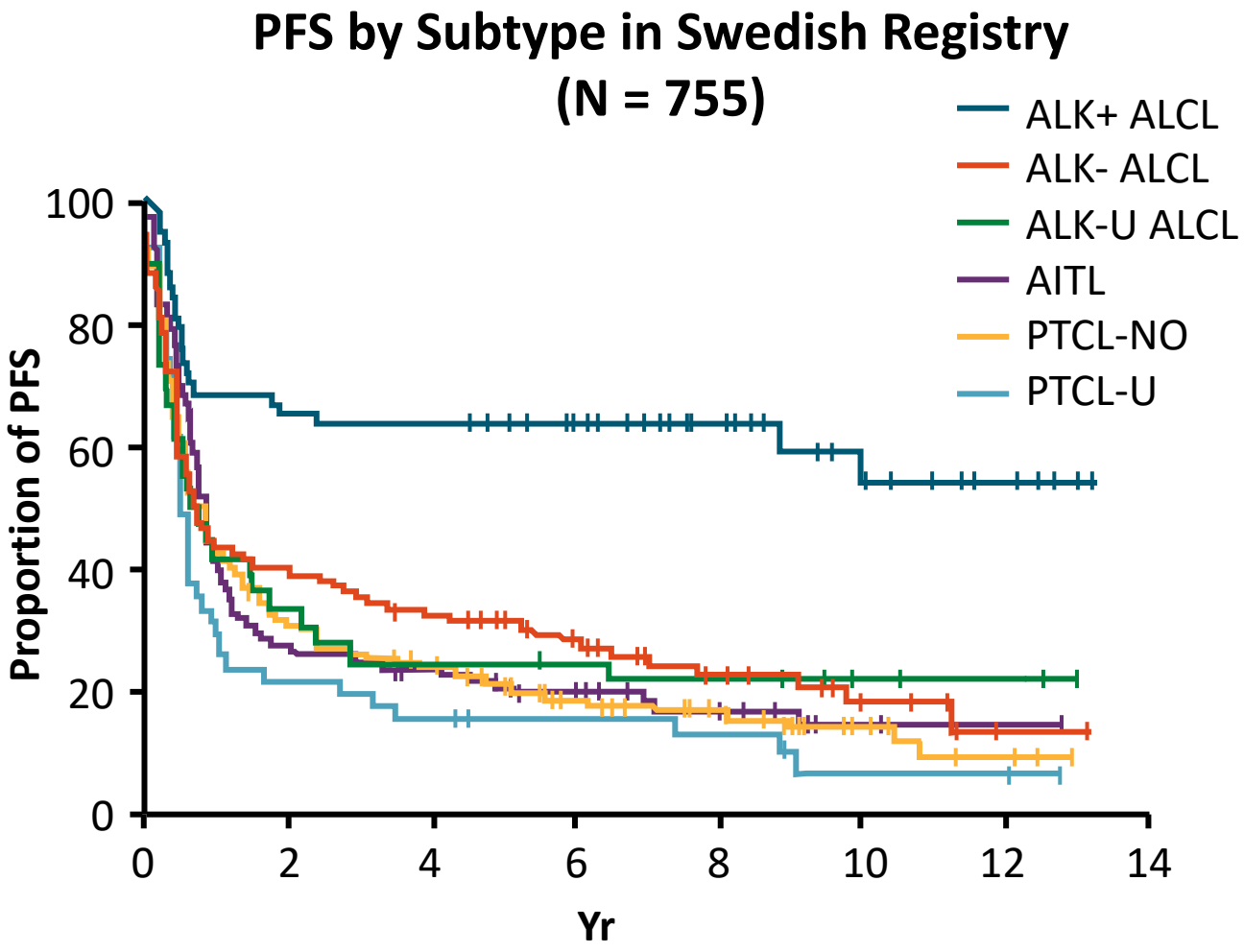
Disclosures

- UCL Business – patents
- Autolus – research funding, stock

Poor outcomes of T cell lymphomas



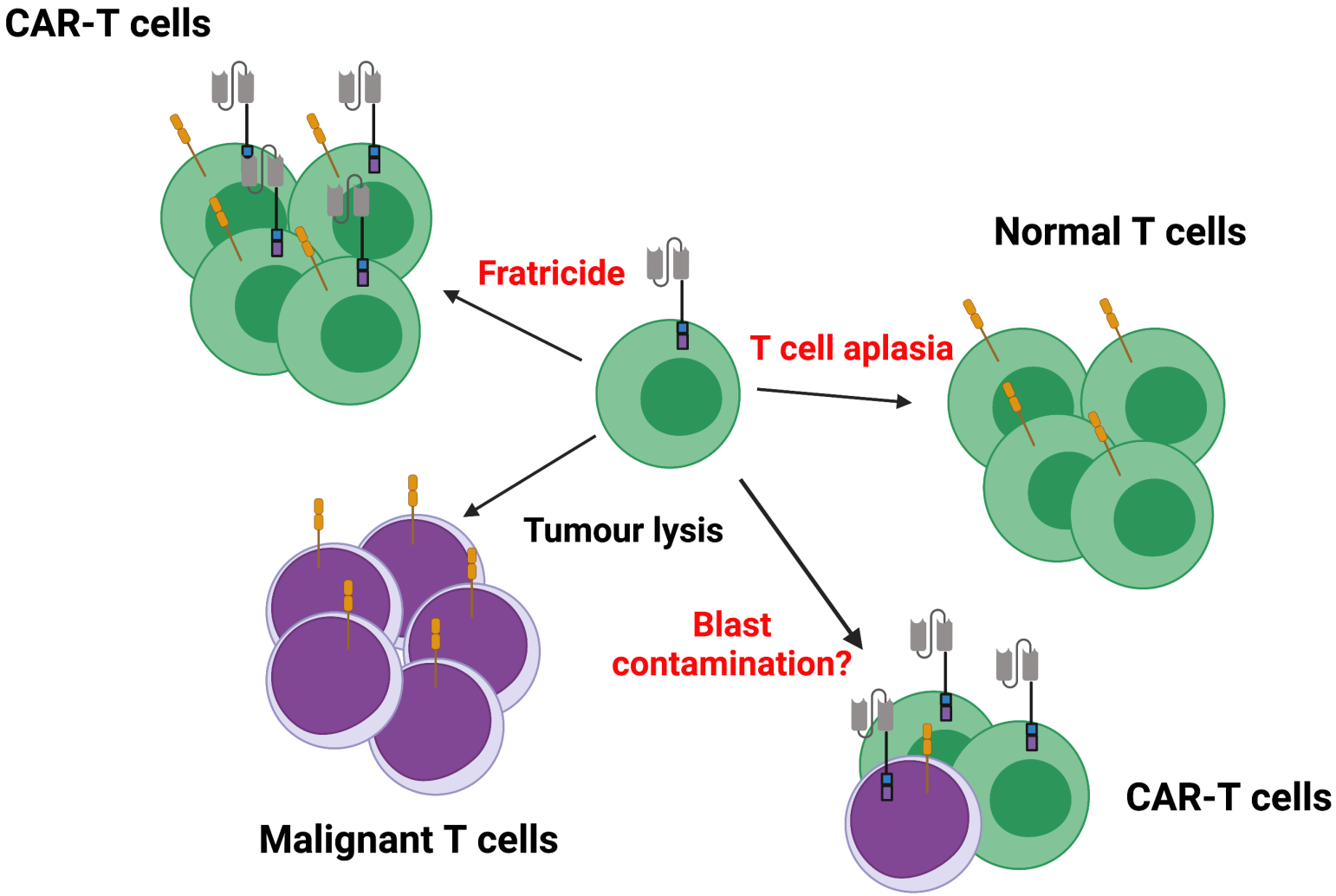
Rate, %	AITL	PTCL NOS	EATL	TCL U
5-yr OS	31.6	28.1	20.4	24.6
5-yr PFS	20.4	21.3	17.6	15.1

Ellin. Blood. 2014; 124:1570.

Slide credit: clinicaloptions.com

Challenges of Targeting T Cell Malignancies

Shared antigens between tumour and normal T cells

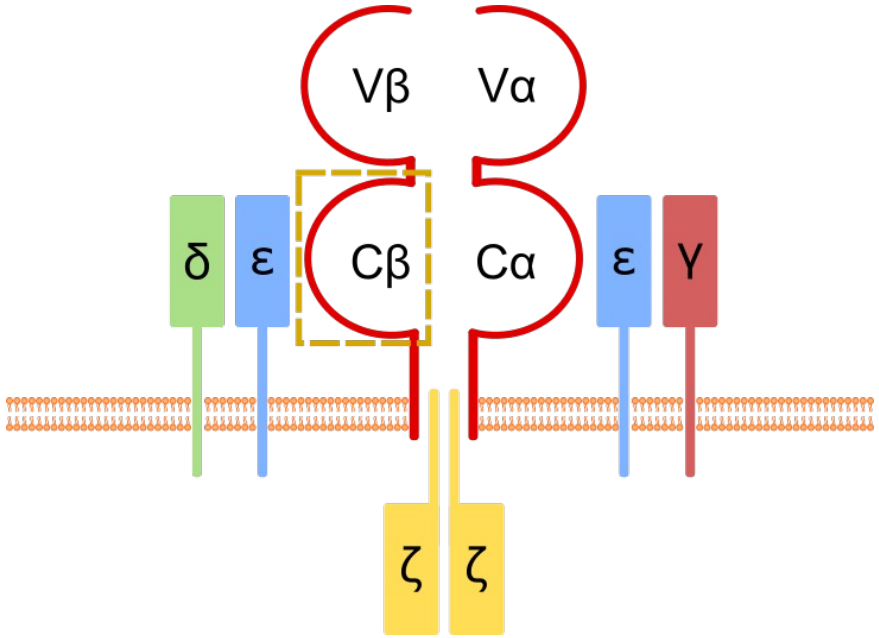


Ideal target: highly and specifically expressed on malignant and not normal T cells

What is a Good CAR Target in PTCL?

Antigen	PTCL No.	PTCL Positive (%)	AILD No.	AILD Positive (%)
Human TCR βF1	133	97	30	94
CD2	136	70	41	100
CD3	144	86	40	95
CD4	135	46	38	42
CD8	129	15	34	32
CD5	137	20	36	19
CD7	141	19	41	24
CD10	143	1	43	39
CD15	140	4	43	2
CD30	145	3	42	0
CD56	140	6	40	3
CD57	143	10	42	5
TIA-1	138	27	41	34
GB	140	2	40	0
ALK-C	143	0	41	0
EBER	132	5	39	3
Mib-1 high	138	11	40	5
CD20	141	1	42	0
CD79a	142	0	36	0

Went *et al*. *J Clin Oncol* (2006); **24**:2472-2479

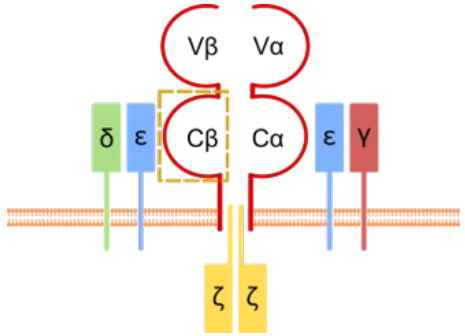


In ALCL – CD30

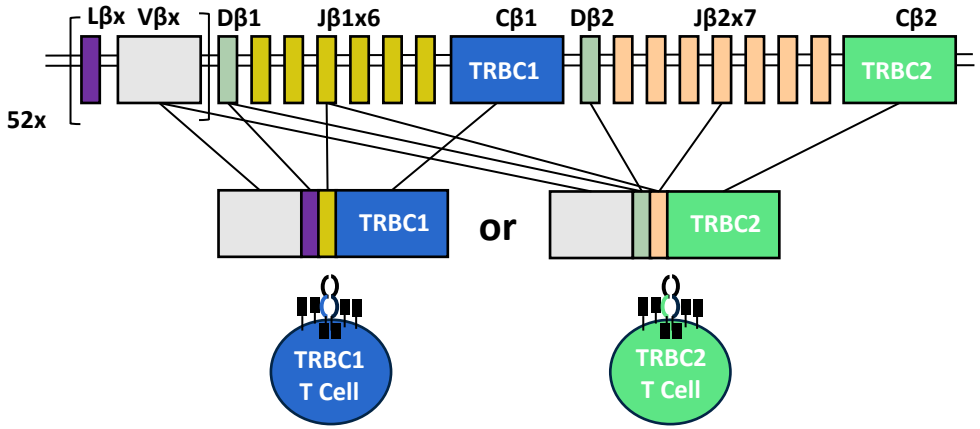
Mature T cells express either TRBC1 or TRBC2

- T cell lymphomas are clonal and also express TRBC1 or TRBC2

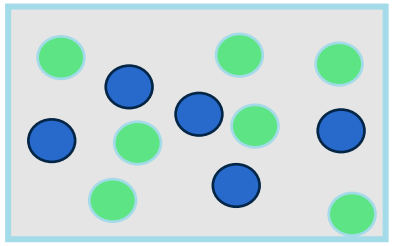
Structure of the T Cell Receptor or TCR



Duplication of β chain constant region gene



Healthy T Cells

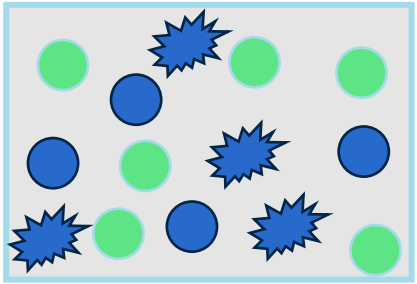


Contain mixture of

TRBC1+ cells

TRBC2+ cells

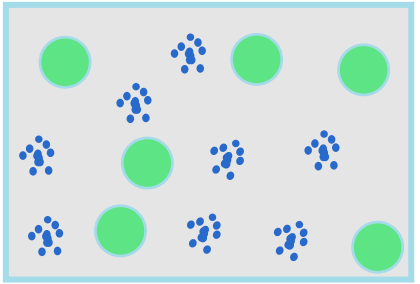
TRBC1+ T cell lymphoma



TRBC1+ tumour cell

TRBC1 CAR

TRBC2+ normal T cells retained
(immunity maintained)

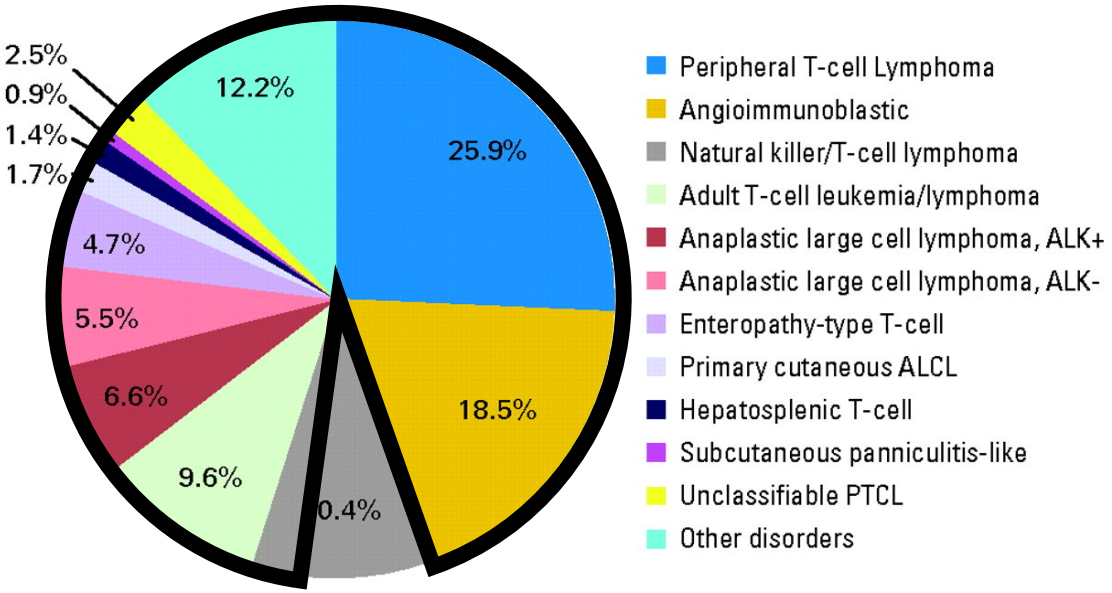


TRBC1+ cells killed
(tumour & healthy)

Maciocia et al., Nature Medicine, 2017

TRBC1/TRBC2 targeting applicable to ~90% of TCL

- Distribution of cases by subtype



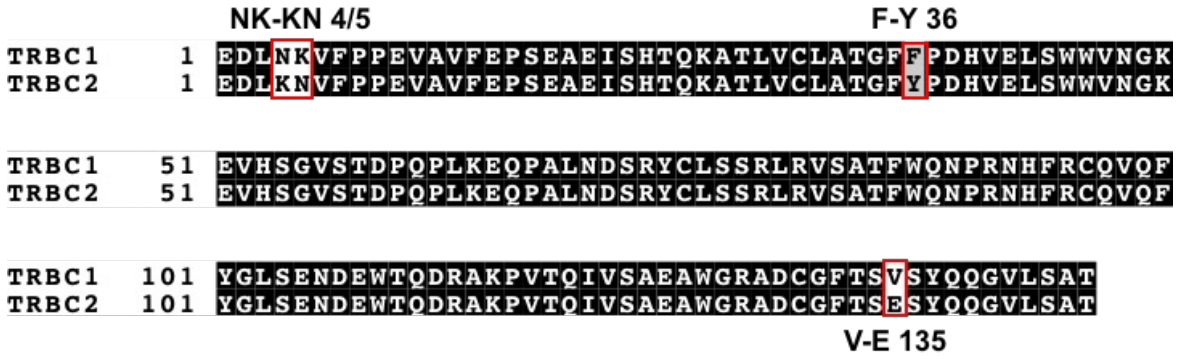
Subtypes that are TRBC1 or TRBC2 positive

- High and homogeneous expression of TRBC1 or TRBC2 is seen in the majority of TCL subsets - 95% of cases
- TRBC1 and TRBC2 will not be expressed in NK cell lymphomas or rare gamma delta t-cell lymphomas

Source: International T-Cell Lymphoma Project published in Journal of Clinical Oncology 2008 264124-4130

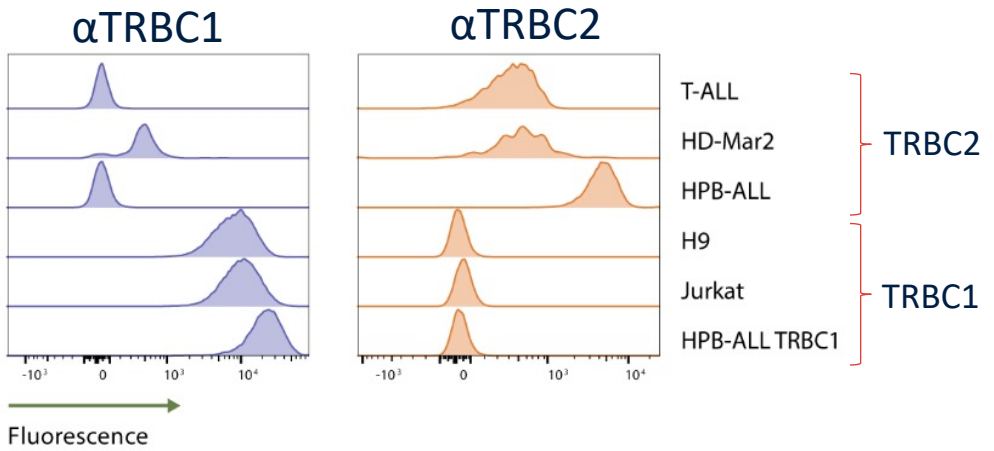
Development of TRBC1 and TRBC2 selective antibodies

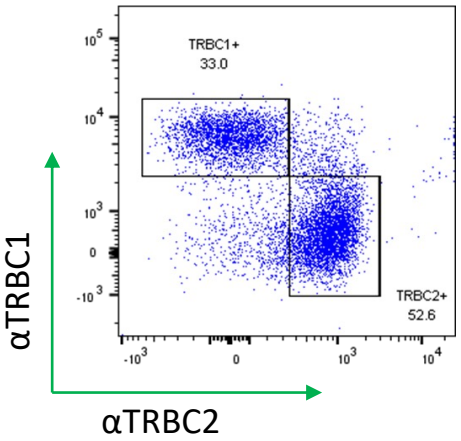
- TRBC1 and TRBC2 proteins are very similar
- Antibodies are designed to selective target the NK-KN inversion at position 4/5

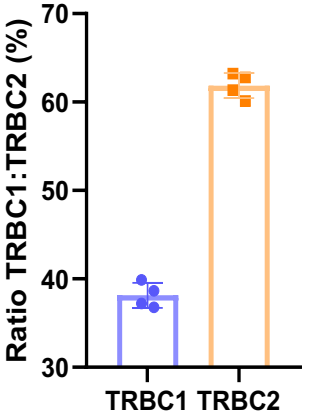


Maciocia et al., Nature Medicine, 2017 and Ferrari et al., Bioxrviv 2022

- TRBC1 and TRBC2 discrimination on tumour cell lines and in healthy peripheral blood T cells

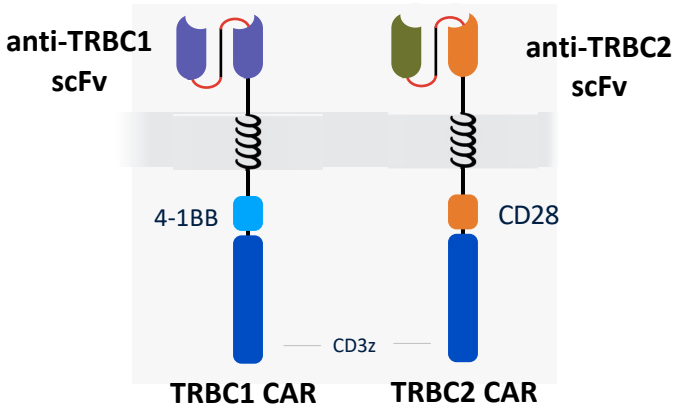


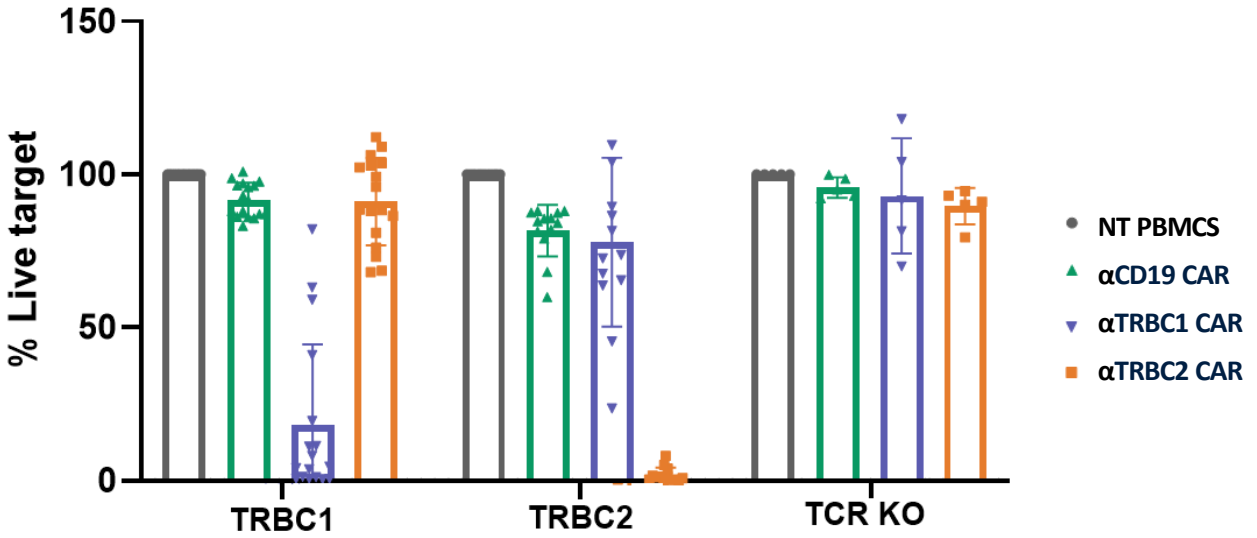




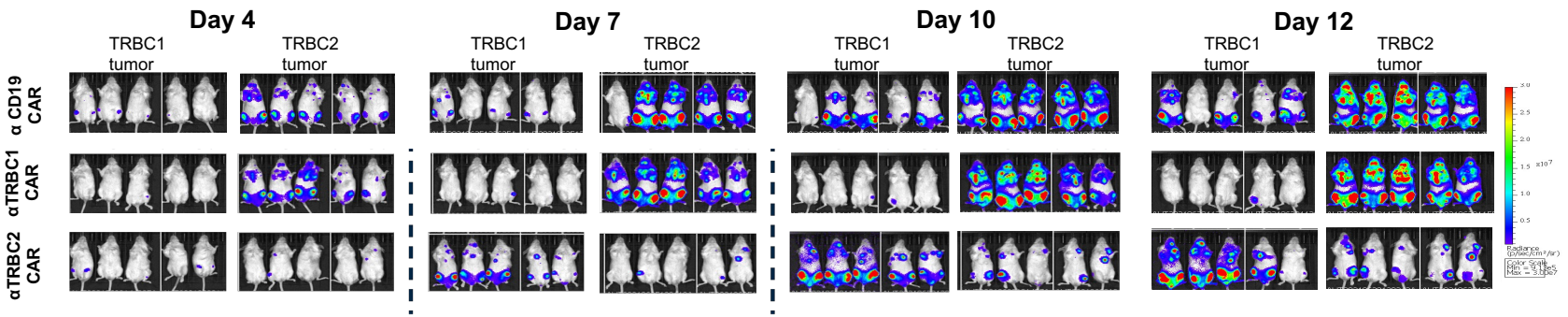
Development of αTRBC1 and αTRBC2 CAR T cells

- Demonstration of in vitro and in vivo selectivity and activity against TRBC1 and TRBC2 target cells





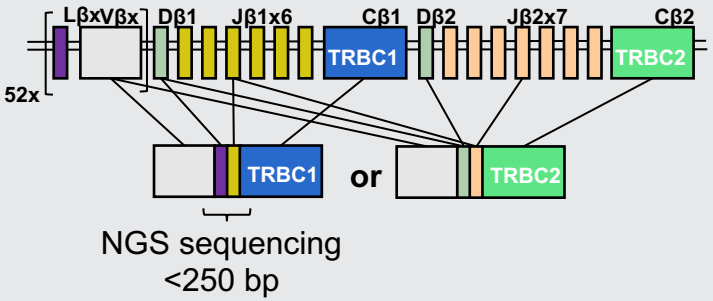
1:16 E:T ratio, 72h timepoint, n = 17 for TRBC1 and TRBC2+ targets, n = 5 for TCR KO targets



Ferrari et al., Bioxrviv 2022

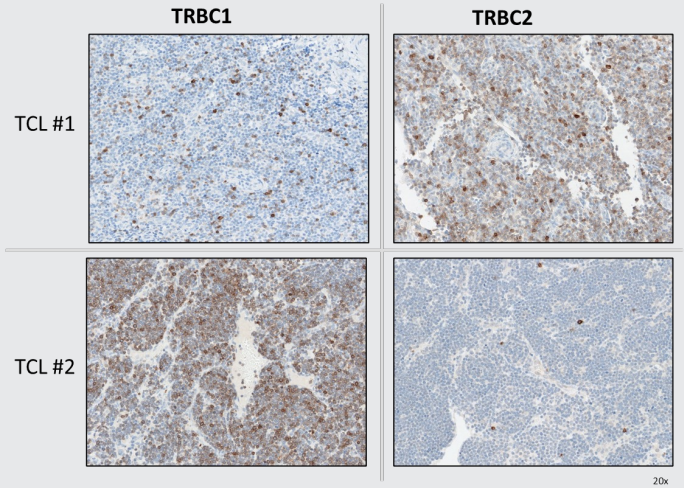
TRBC1/ TRBC2 Assessment

Next Generation Sequencing



- T cell clonality NGS assay currently used in AUTO4 Phase 1

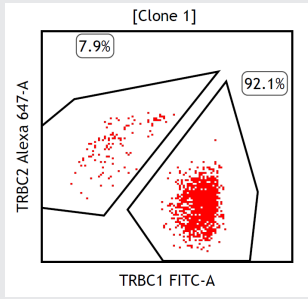
Immunohistochemistry



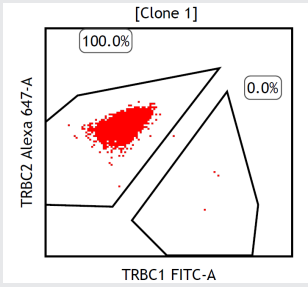
Teresa Marafioti

- FFPE specific antibodies can discriminate between TRBC1 and TRBC2 patient tumors

Flow Cytometry



TRBC1 positive T-cell Prolymphocytic Leukemia



TRBC2 positive small Sezary cell cutaneous T-Cell Lymphoma

- Flow specific antibodies can discriminate between TRBC1 and TRBC2 in patient tumors

Clinical Data to Date

CLINICAL STUDIES IN T CELL MALIGNANCIES

Target	Target KO?	NCT	Design	Sponsor	Location	Opened
CD5	No	NCT03081910	Retro, 28z	Baylor College Medicine	Houston, USA	Mar-17
CD7	CRISPR/Cas9	NCT03690011	Retro, 28z	Baylor College Medicine	Houston, USA	Mar-19
	No (NK cells)	NCT02742727	Allo NK cells - retro, 28-41bbz	PersonGen BioTherapeutics	Suzhou, China	Mar-16
	No	NCT04033302	Lenti, 4-1BBz	Shenzhen Geno-Immune Medical Institute	Shenzen, China	Aug-19
	?	NCT04004637	?	PersonGen BioTherapeutics	Suzhou, China	Jul-19
CD4	No	NCT03829540	Lenti, 28-41bbz	iCell Gene Therapeutics	New York, USA	Feb-19
CD30	No	NCT04008394	Lenti, 3rd generation	Wuhan Union Hospital	Wuhan, China	Jul-19
	No	NCT03602157	Retro, 28z, co-express CCR4	University North Carolina	North Carolina, USA	Dec-18
	No	NCT03049449	Retro, 28z	NCI	NCI, USA	Mar-17
	No	NCT02917083	Retro, 28z	Baylor College Medicine	Houston, USA	Sep-16
	No	NCT02274584	Retro, 28z	Peking University	Florida, USA + Bejing, China	Mar-14
TRBC1	Selected TRBC2	NCT03590574	Retro, 41bbz	Autolus	London, UK	Jul-18

Now >50 recruiting studies on clinicaltrials.gov – further targets = CD37, CD38, CD70

BAYLOR CD5 STUDY (ASH 2022)

- 10 patients
- Autologous retro 28-zeta CAR
- No CD5 KO
- 10, 50 or 100 million cells/ m2

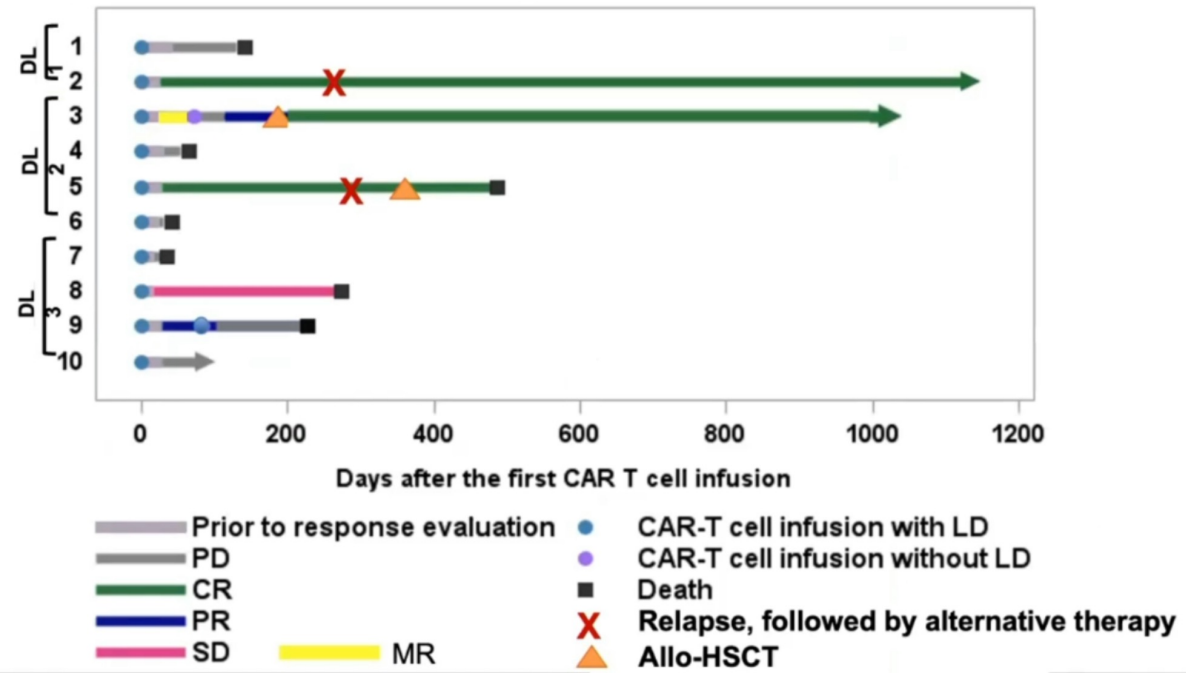
- 4/10 responded, 2 patients CR

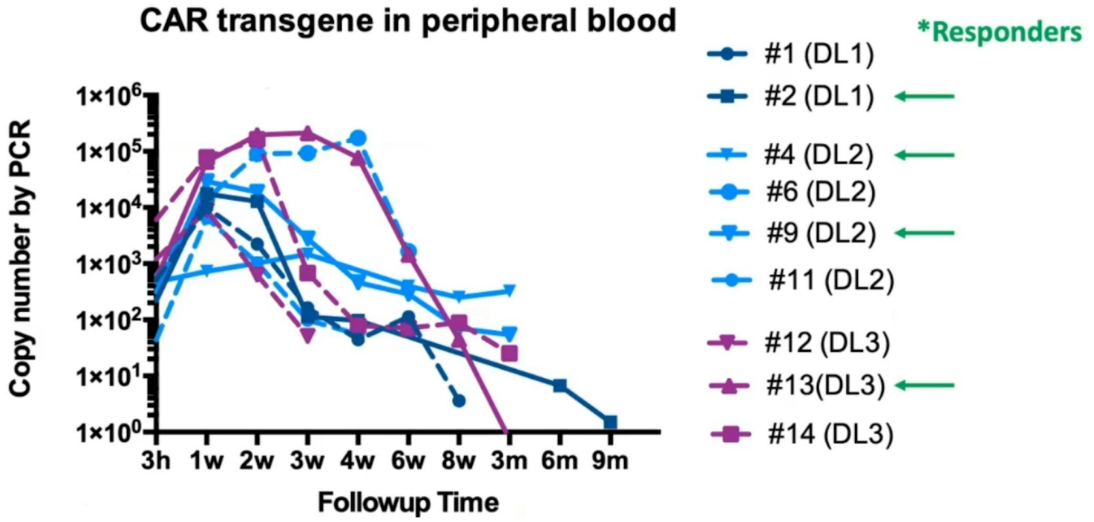
- No CD5 aplasia

- Minimal toxicity

- ? better responses with shortened manufacture

- Limited efficacy in T-ALL (new data to be updated)





CRISPR Therapeutics CD70 - EHA 2022

- **Allogeneic CRISPR-Cas9 edited T cells (CTX130)**
  - Triple-edited – TCR, B2M, CD70

- **17 patients infused, mixture of histologies**

Data cutoff date: 26 April 2022

Best overall response, n (%)

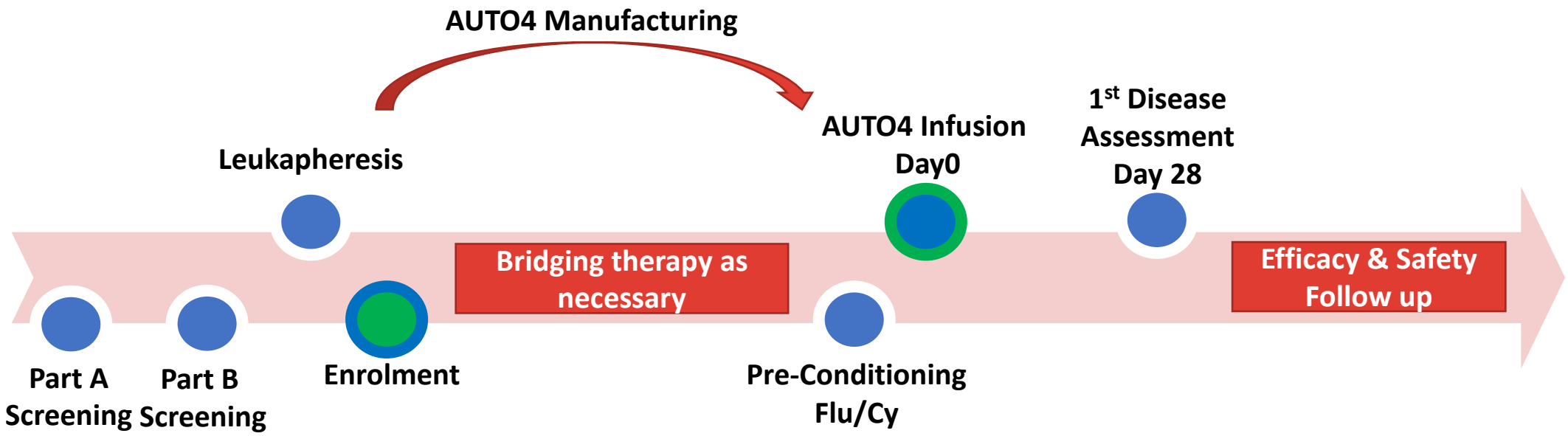
Cell dose (CAR+ T cells)	DL1 $3x10^7$ N=4	DL2 $1x10^8$ N=4	DL3 $3x10^8$ N=5	DL4 $9x10^8$ N=5	DL≥3 N=10
Overall Response Rate (ORR)	2 (50)	0	3 (60)	4 (80)	7 (70)
CR	1 (25)	0	2 (40)*	1 (20)	3 (30)
PR	1 (25)	0	1 (20)	3 (60)	4 (40)
Disease Control Rate (DCR = CR + PR + SD)	3 (75)	1 (25)	5 (100)	4 (80)	9 (90)

	PTCL		CTCL	
	DL≥3 N=5	Total N=8	DL≥3 N=5	Total N=10
ORR	4 (80)	5 (63)	3 (60)	4 (40)
CR	2 (40)	3 (38)	1 (20)	1 (10)
PR	2 (40)	2 (25)	2 (40)	3 (30)
DCR	4 (80)	5 (63)	5 (100)	8 (80)

*1 patient in DL3 who initially achieved a PR was re-infused at DL4 following a change to SD and achieved a CR at DL4.
CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; DCR, disease control rate; DL, dose level; ORR, overall response rate; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease.

Presented at the European Hematology Association Annual Meeting. 11 June 2022

AUTO4 Study design



- Part A: Lymphoma tissue screening for TRBC1 or TRBC2 expression using NGS
- Part B: Study screening for patients determined to have TRBC1+ Lymphoma

Baseline Characteristics

	Total (N=10)
Age, median (range)	55 (34 – 63)
Median prior lines of treatment (range)	3 (1 – 5)
Stage of Lymphoma at screening • I/II • III/IV	 2 (20%) 8 (80%)
Lymphoma Subtype, n (%) • Peripheral T-cell lymphoma NOS • Anaplastic large cell lymphoma, ALK-negative • Angioimmunoblastic T cell lymphoma (AITL)	 5 (50%) 1 (10%) 4 (40%)
Prior Autologous Stem Cell Transplant, n (%)	3 (30%)
ECOG 0/1, n (%)	3 (30%), 7 (70%)
Bridging therapy YES, n (%)	7 (70%)

Data Cut-off: 26 April 2022

Key Safety Data

	Cohort 1 $25x10^6$ cells (N = 3)	Cohort 2 $75x10^6$ cells (N = 2)	Cohort 3 $225x10^6$ cells (N = 1)	Cohort 4 $450x10^6$ cells (N = 4)	Total (N = 10)
Dose Limiting Toxicity (DLT)	0	0	0	0	0
Grade 3 or 4 TEAE within 60 days	3 (100%)	2 (100%)	1 (100%)	4 (100%)	10 (100%)
Neutropenia	3 (100%)	2 (100%)	0	3 (75%)	8 (80%)
Infections and Infestations	0	0	0	0	0
Serious TEAE	2 (67%)	0	0	2 (50%)	4 (40%)
Any grade CRS	0	0	0	4 (100%)	4 (40%)
Grade 3 CRS	0	0	0	1 (25%)	1 (10%)
Any grade ICANS	0	0	0	0	0

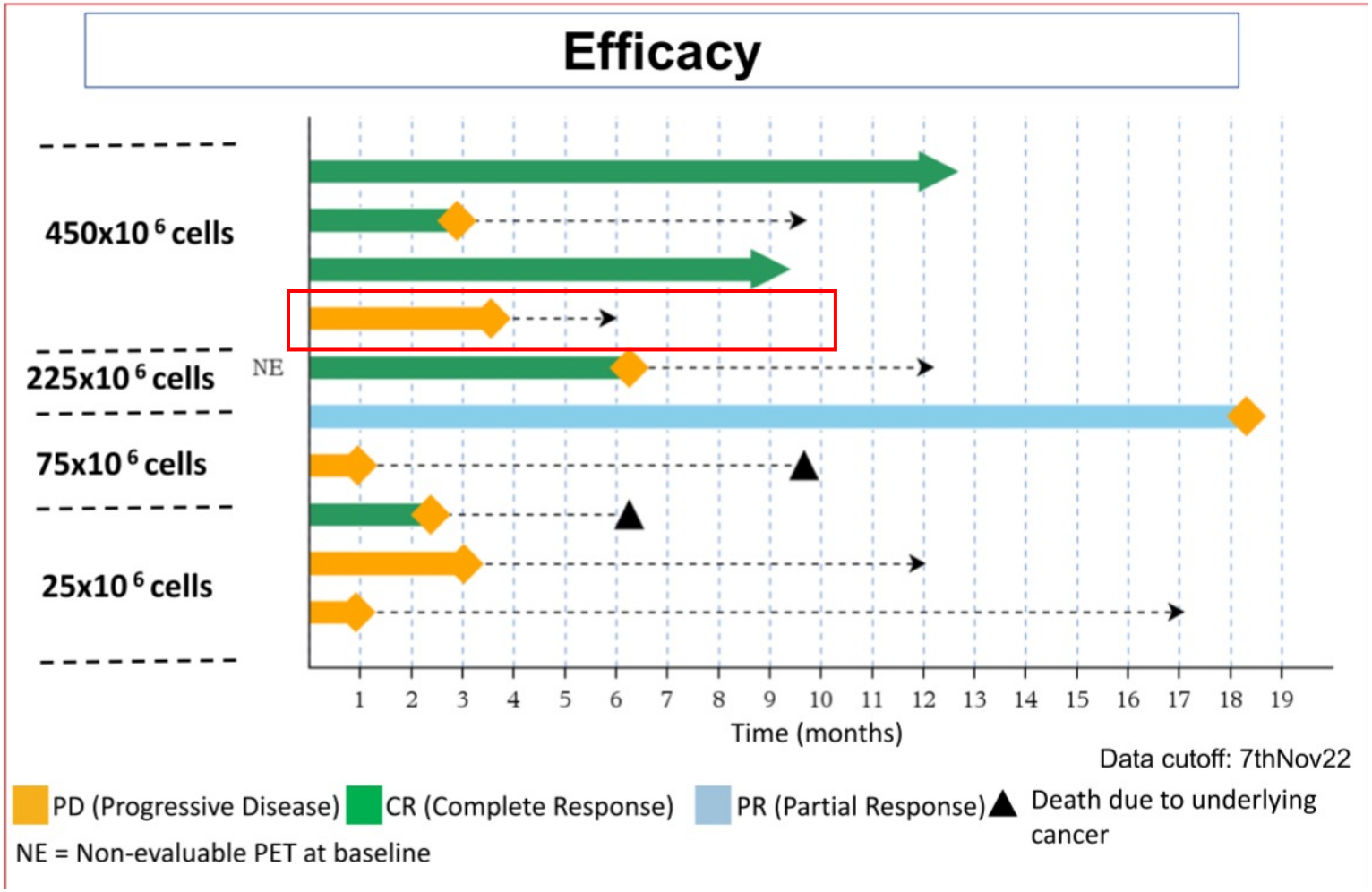
Safety set is all infused (n=10)

TEAE - Treatment-emergent adverse events; CRS - cytokine release syndrome; ICANS - Immune Effect Cell-Associated Neurotoxicity Syndrome

Data Cutoff: 26 April 2022

Initial data encouraging

- All patients treated at highest dose level had a complete metabolic response

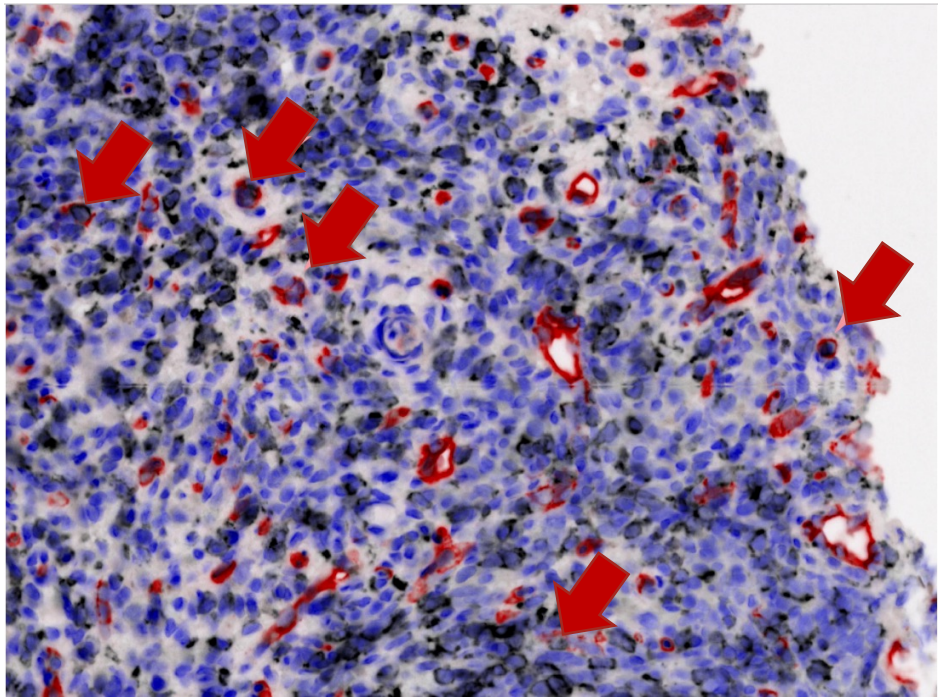


All patients at 450M dose attained CR, 3/4 persisting at 10, 14, 16 months

Efficacy assessments were performed by the Investigators according to the Lugano Classification.
† Evaluable Set consists of patients who have received an infusion of AUTO4 treatment and completed the Day 28 evaluation.
All patients had relapsed/refractory disease at time of Part B screening and enrolment.
* Patient was PET-negative at the start of pre-conditioning therapy.

CAR T cells detected in lymph node but not in peripheral blood

- CAR T cells detected in a lymph node biopsy of a patient who achieved complete remission
  - Approx 2% nucleated cells in lymph node are CAR T cells (n=1)[1]
- No CAR T expansion detected by PCR or flow in peripheral blood



Double staining for CAR T cell (red) and CD3 (black) x40 IHC view (deconvoluted)[1]

CAR T cell – double stained for CAR and CD3

[1]Professor Teresa Marafioti, personal communication

Data Cutoff: 26 April 2022

FUTURE PERSPECTIVES

- AUTO4 – modified manufacturing process, re-entered accelerated dose escalation
- Clinical data updates in next year in PTCL
  - CD5/ TRBC1/ CD30?
- AUTO5 (TRBC2) - TBC
- Highly promising data with CD7 in T-ALL
  - ? long term remissions/ ? Infections etc

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- Patients

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Autolus