AUTO-4, a TRBC1-TARGETING CAR-T in Relapsed/Refractory T cell lymphoma

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Disclosures

- Consulting/Advisory Role: Roche, Takeda, Celgene, Atara, Gilead, KITE, Janssen, Incyte
- Speakers’ Bureau: Roche, Takeda, KITE, Gilead, Incyte
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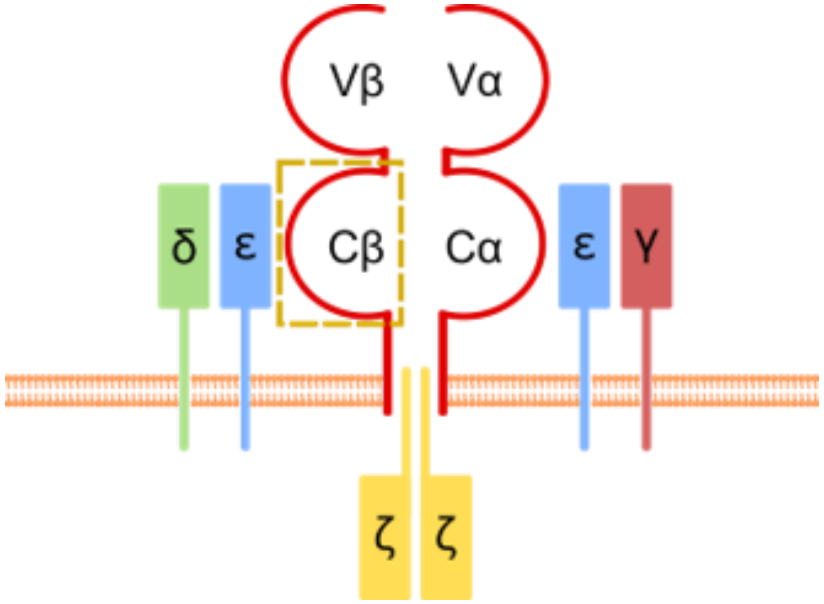
Peripheral T-Cell Lymphoma: No Standard of Care After First Relapse

- T cell lymphoma is an aggressive disease with a very poor prognosis
- Many T cell lymphoma patients are refractory/relapse following first-line treatment (68%)[3]
- Standard of care variable, often based on high-dose chemotherapy and stem cell transplants
  - Median 5 yrs OS: 32% [1]
- Relapsed/refractory patients have a worse prognosis
  - Median PFS approximately 3 months/ Median OS < 6 months [2,3]
- T cell lymphoma has not benefited from advances in immunotherapy to date
  - Pan T-cell depletion highly toxic; Few/no tumour-specific antigen targets

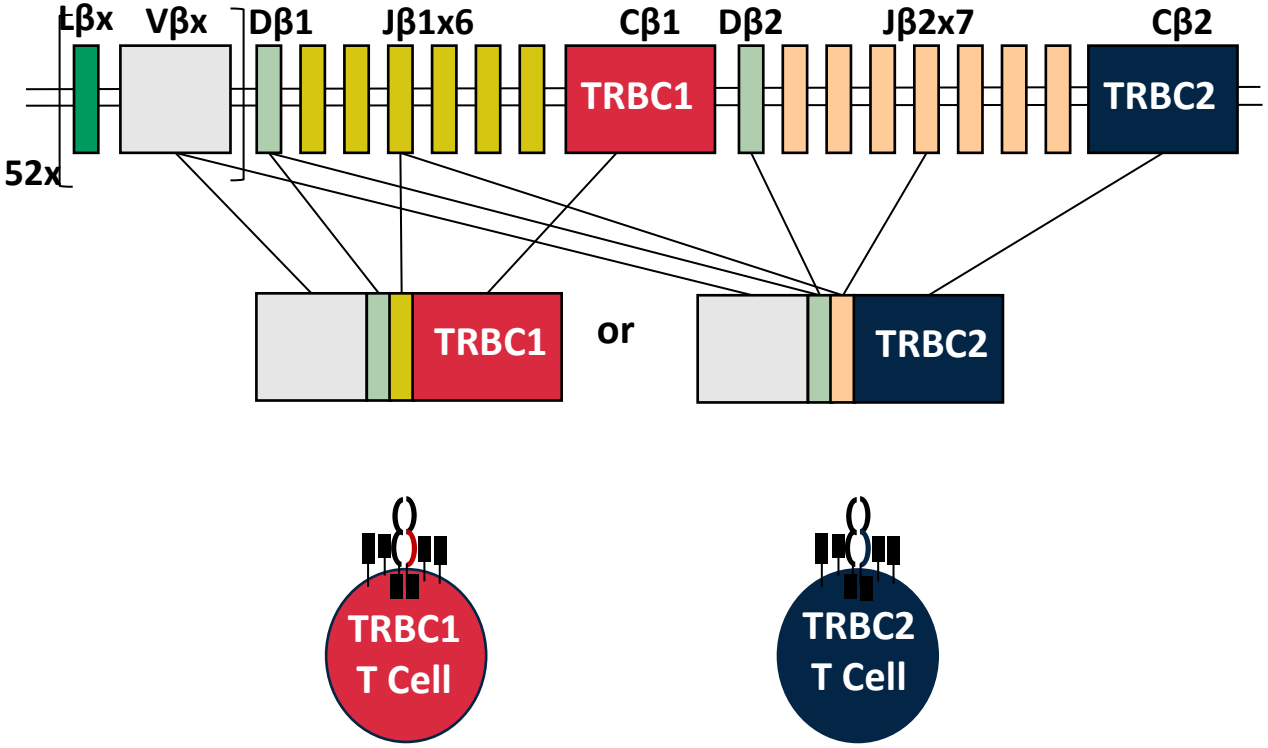
[1] Weisenburger et al, Blood 2011; [2]Mak et al, JCO 2013; [3]Bellei M et al, Haematologica 2018

Mature T Cells express either TRBC1 or TRBC2

TCR Structure

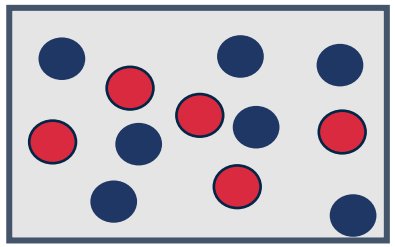


Duplication of β chain constant region gene



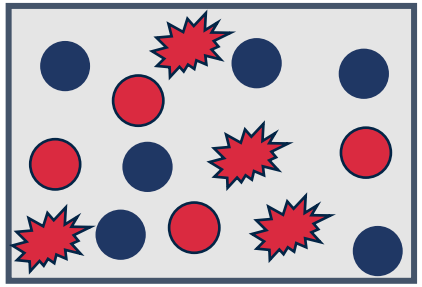
T cell lymphomas are clonal and express either TRBC1 or TRBC2

Healthy T Cells



Contains mixture of
TRBC1+ cells
TRBC2+ cells

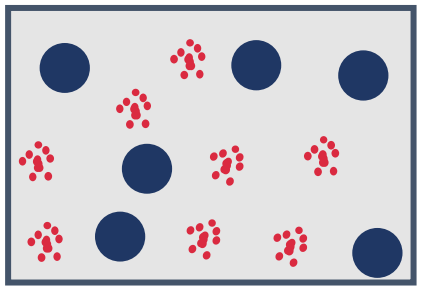
TRBC1+
T cell lymphoma



TRBC1+ tumour cell

TRBC1 CAR

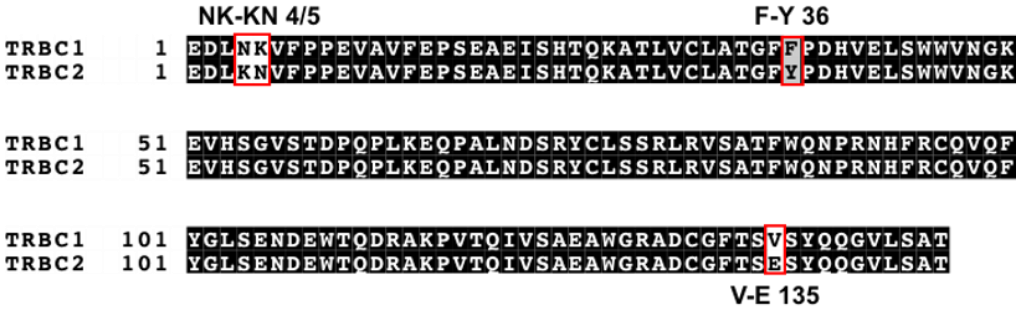
TRBC1+ cells killed
(tumour & healthy)



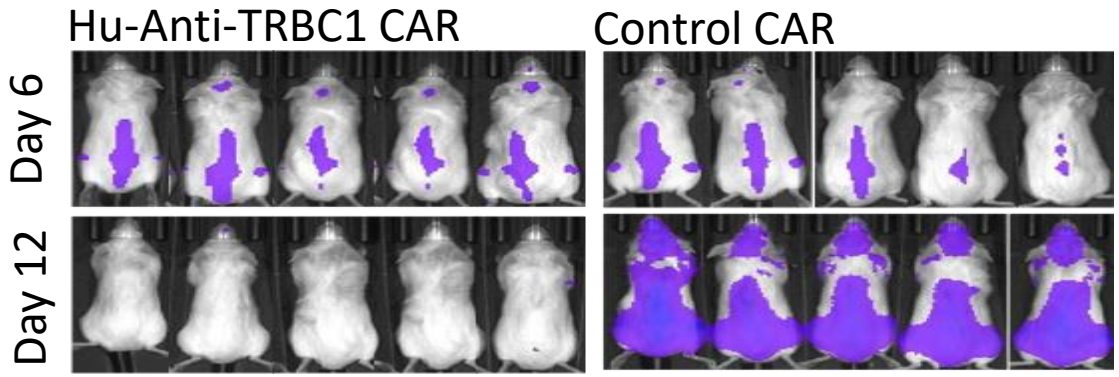
TRBC2+ normal T cells retained - immunity maintained

AUTO4: a CAR targeting TRBC1

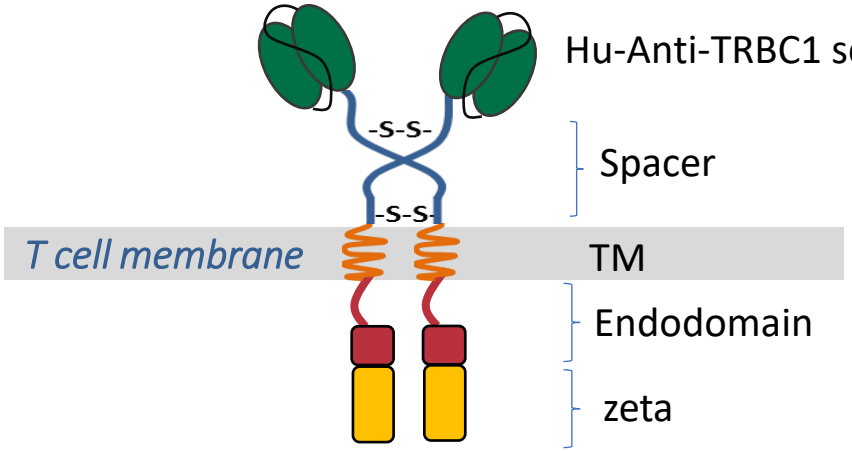
- TRBC1 and TRBC2 very similar



- Selectivity, *in vitro* and *in vivo* activity[1]



- AUTO4: CAR targeting TRBC1 with >10,000 selectivity over TRBC2[1]



[1] Maciocia *et al.*, Nat Med 2017

Phase I/II Study Evaluating AUTO4 in Patients With TRBC1 Positive PTCL: LibraT1

Key Inclusion

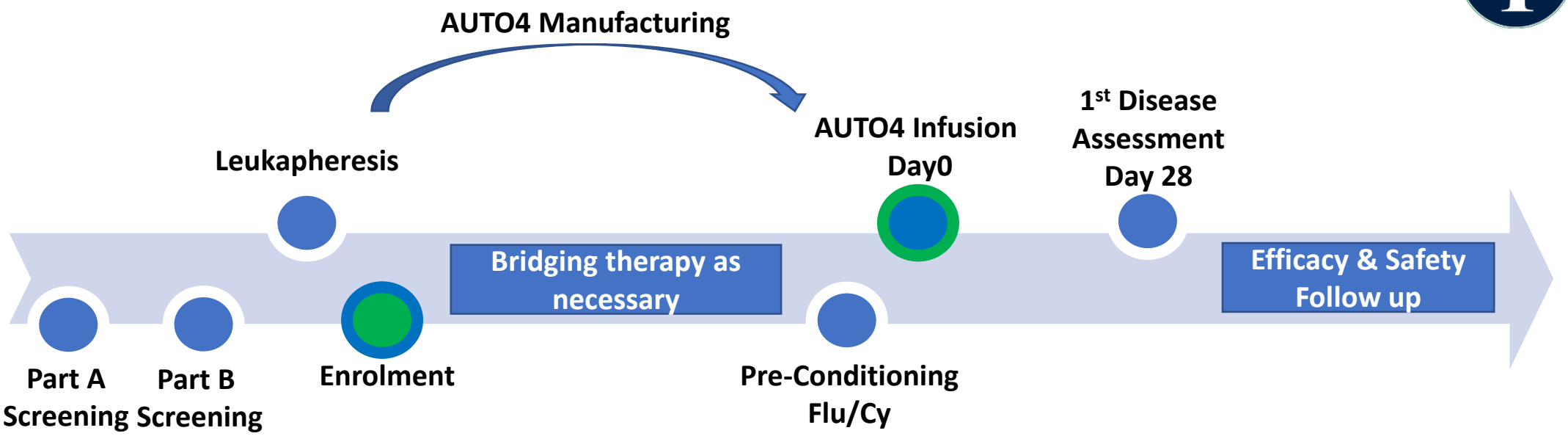
- ≥18 years of age
- ECOG 0-1
- Confirmed diagnosis of PTCL-NOS, AITL, or ALCL
- Confirmed TRBC1+ tumour – confirmed using a NGS assay
- Relapsed/refractory disease following at least 1 line of therapy

Key Exclusion

- Patients with T-cell leukaemia
- Active or past history of CNS involvement by malignancy
- Prior allogeneic haematopoietic stem cell transplant

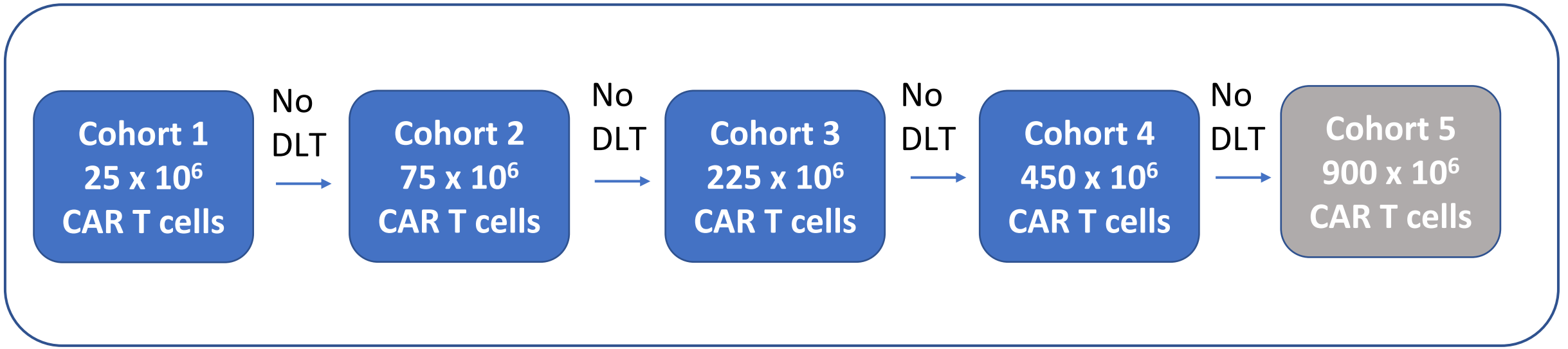
PTCL-NOS, Peripheral T-cell lymphoma, not otherwise specified; AITL, Angioimmunoblastic T-cell lymphoma; ALCL, Anaplastic large cell lymphoma; CNS, central nerve system; NGS, next-generation sequencing.

Study Design



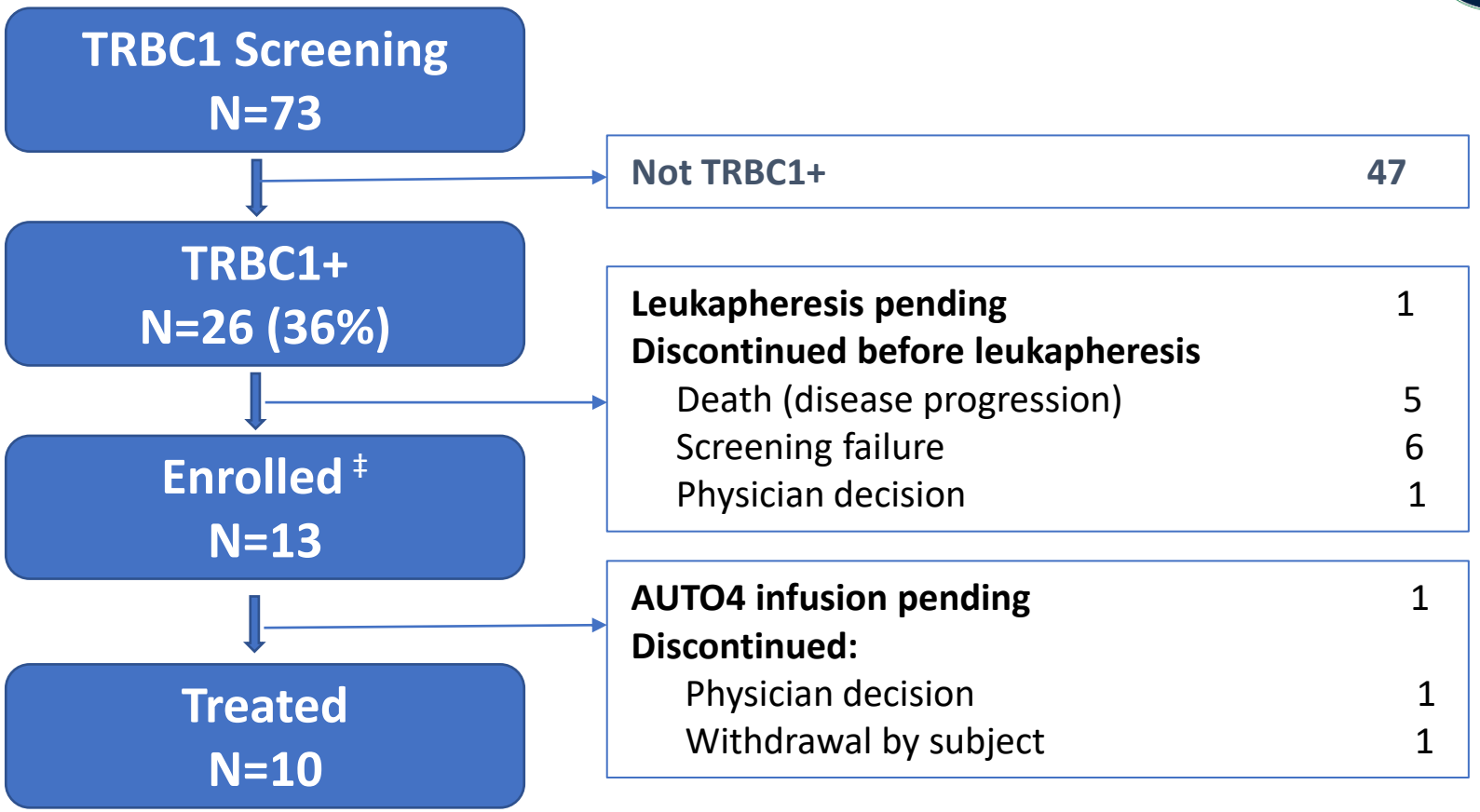
- Part A: Lymphoma tissue screening for TRBC1 or TRBC2 expression using NGS
- Part B: Study screening for patients determined to have TRBC1+ lymphoma

Phase I Dose Escalation of AUTO4



- Pre-conditioning: FLU 30 mg/m^2 IV (Days -6, -5, -4, -3) & CY 500 mg/m^2 IV (Days -6, -5)
- Accelerated escalation: Cohort 2 and 3 may dose <3 patients if there are no DLTs and no CAR T expansion.

Patient Disposition



Safety set: all infused, n=10
Efficacy set: ≥1mth follow up, n=9

Data Cutoff: 26APR2022

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 Cutoff: 26APR2022

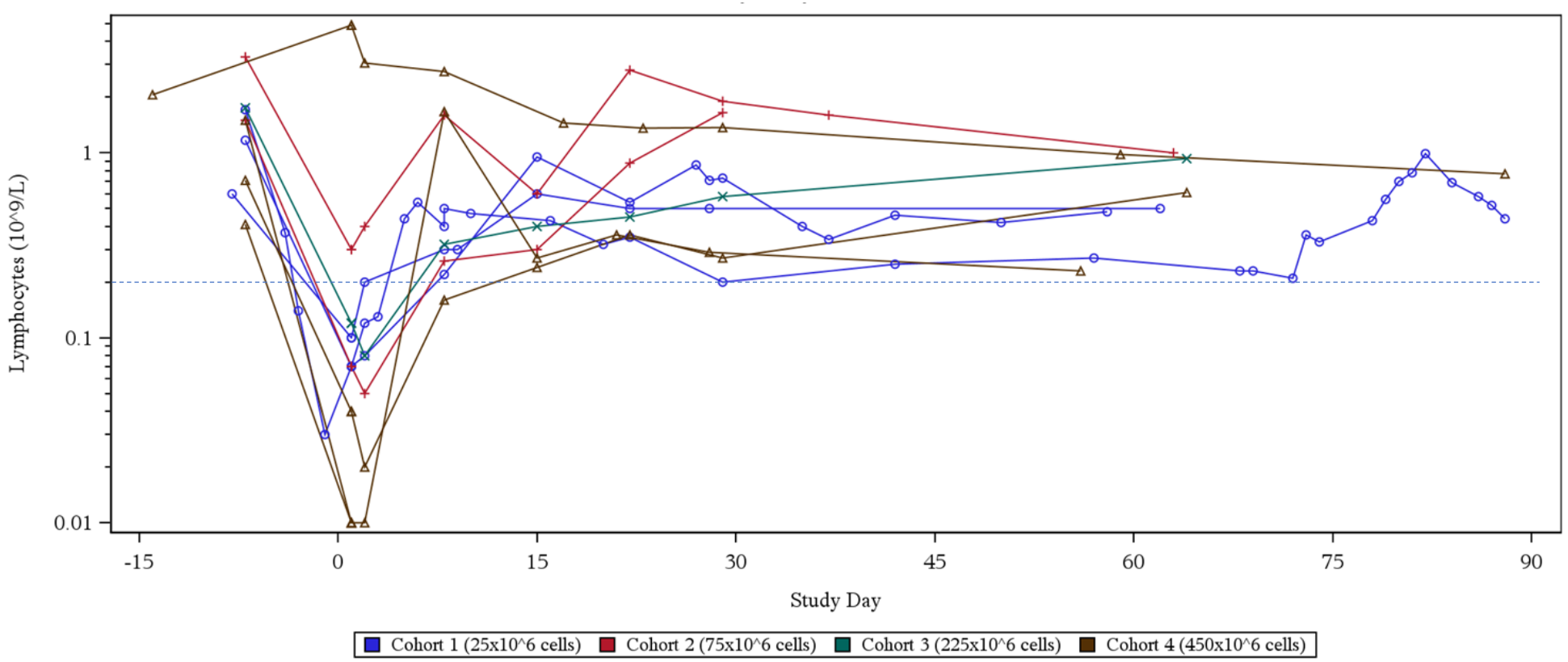
Key Safety Data

	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

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

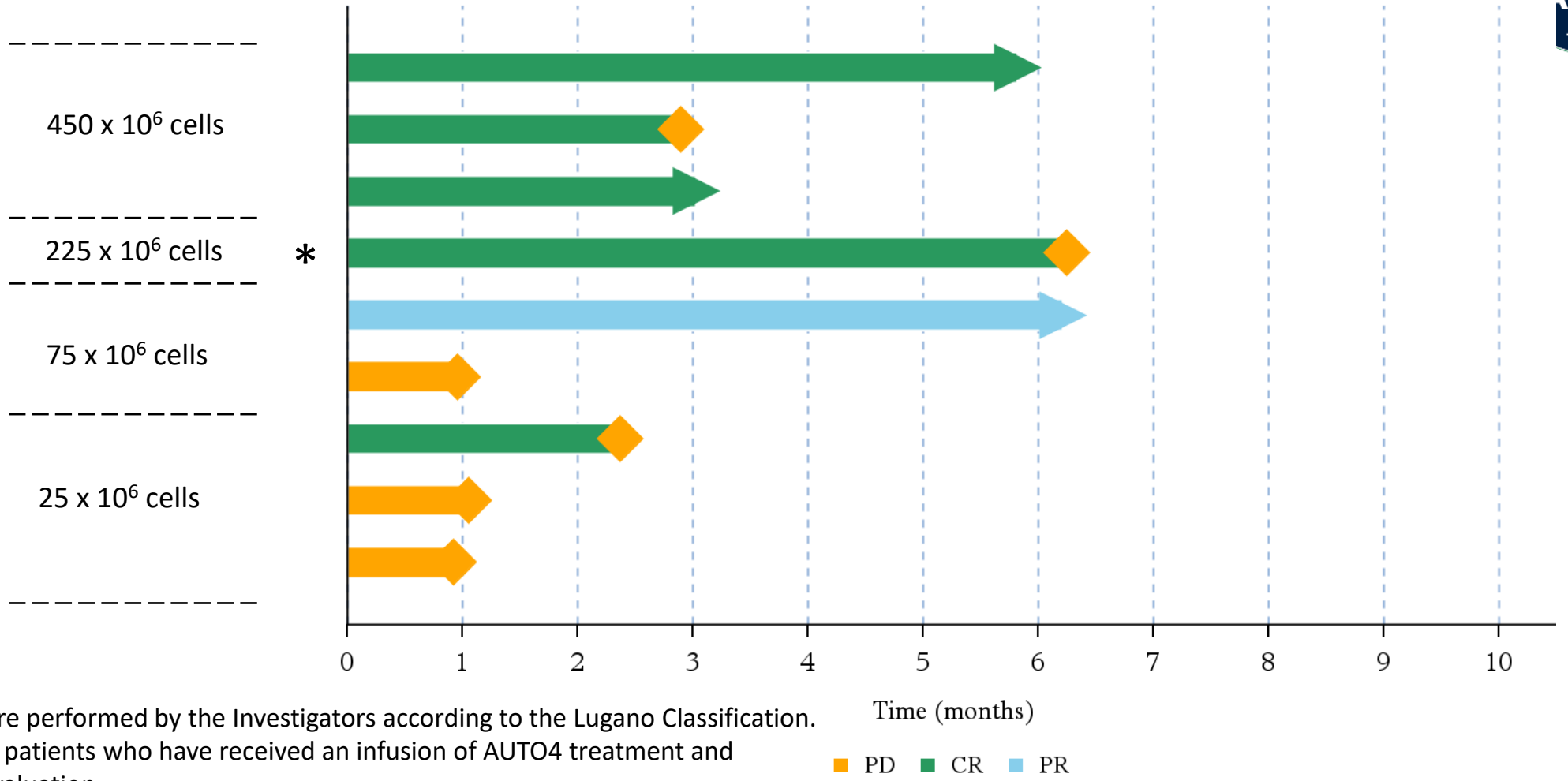
Data Cutoff: 26APR2022

Recovery following transient lymphopaenia after Flu/Cy and AUTO4



Data Cutoff: 26APR2022

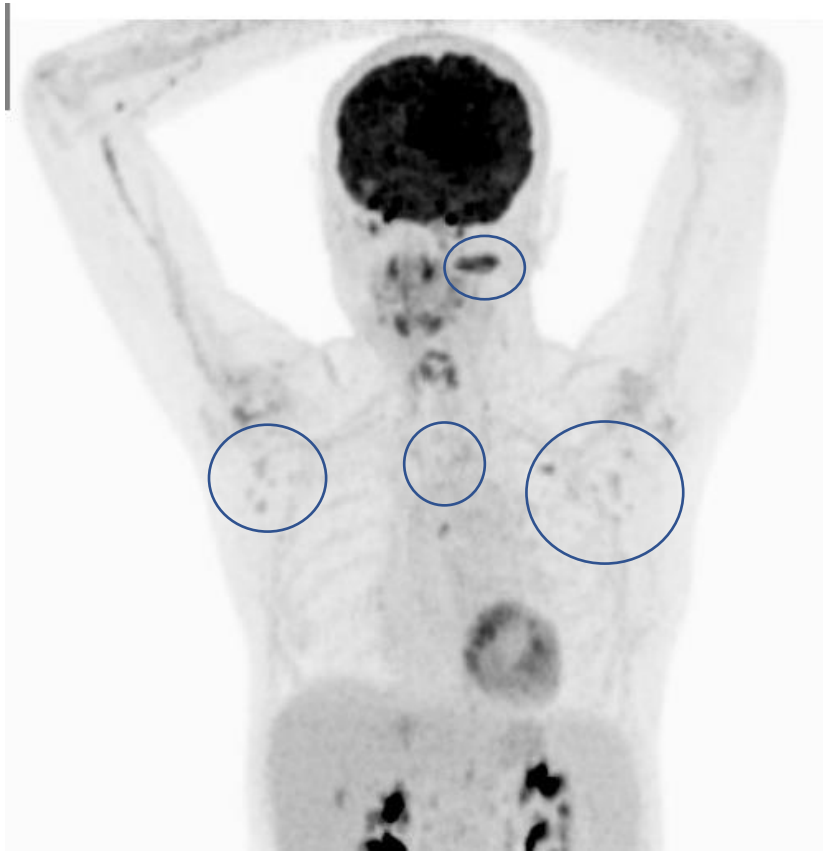
Efficacy



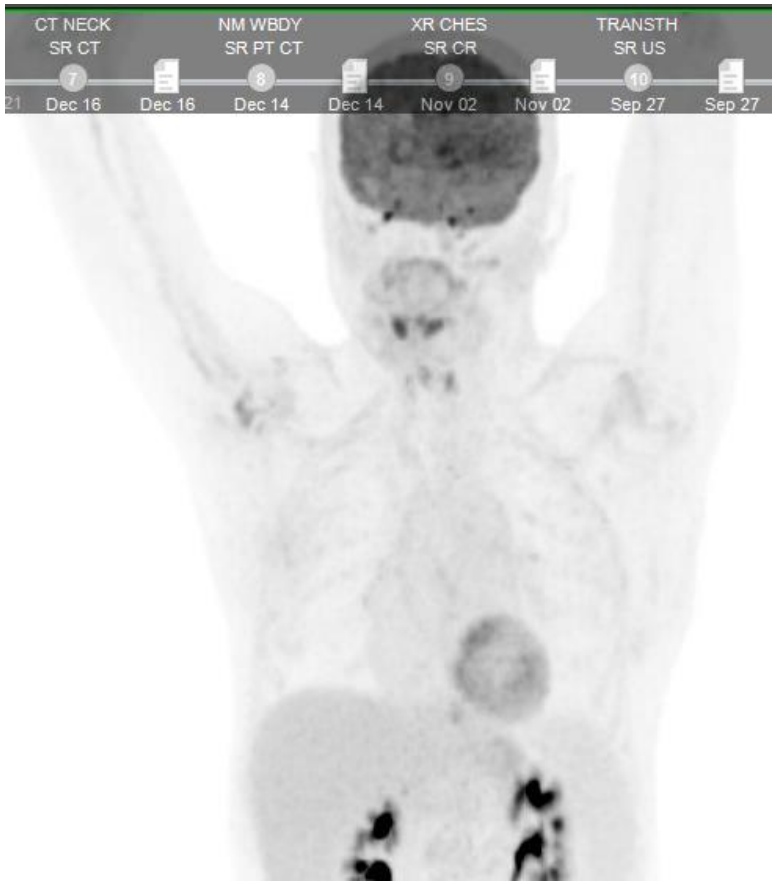
Efficacy assessments were performed by the Investigators according to the Lugano Classification.
Evaluable Set consists of patients who have received an infusion of AUTO4 treatment and completed the Day 28 evaluation.
All patients had relapsed/refractory disease at time of Part B screening and enrolment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

Data Cutoff: 26APR2022

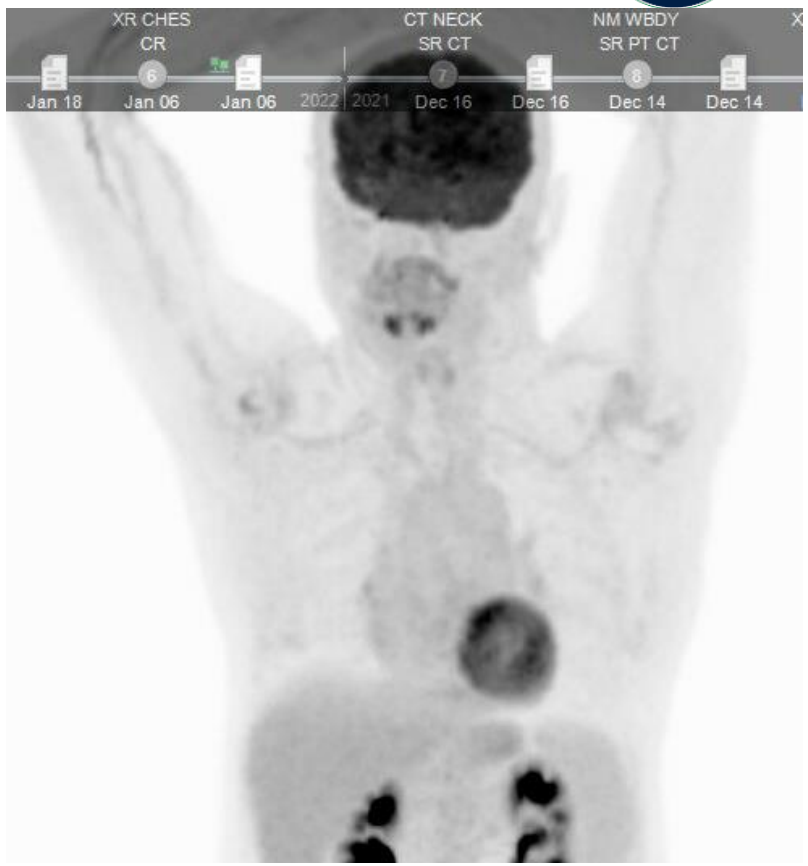
PET scans for patient given 450 x 10^6 CAR T cells



Baseline



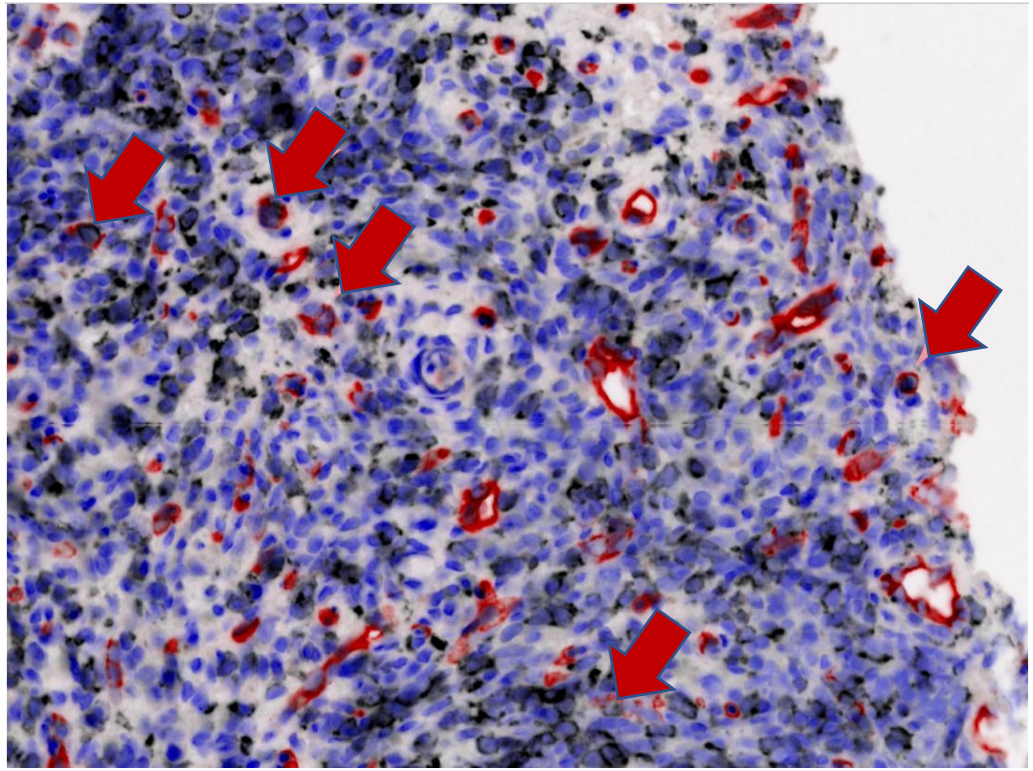
Day 28 post-infusion



6 months post-infusion

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

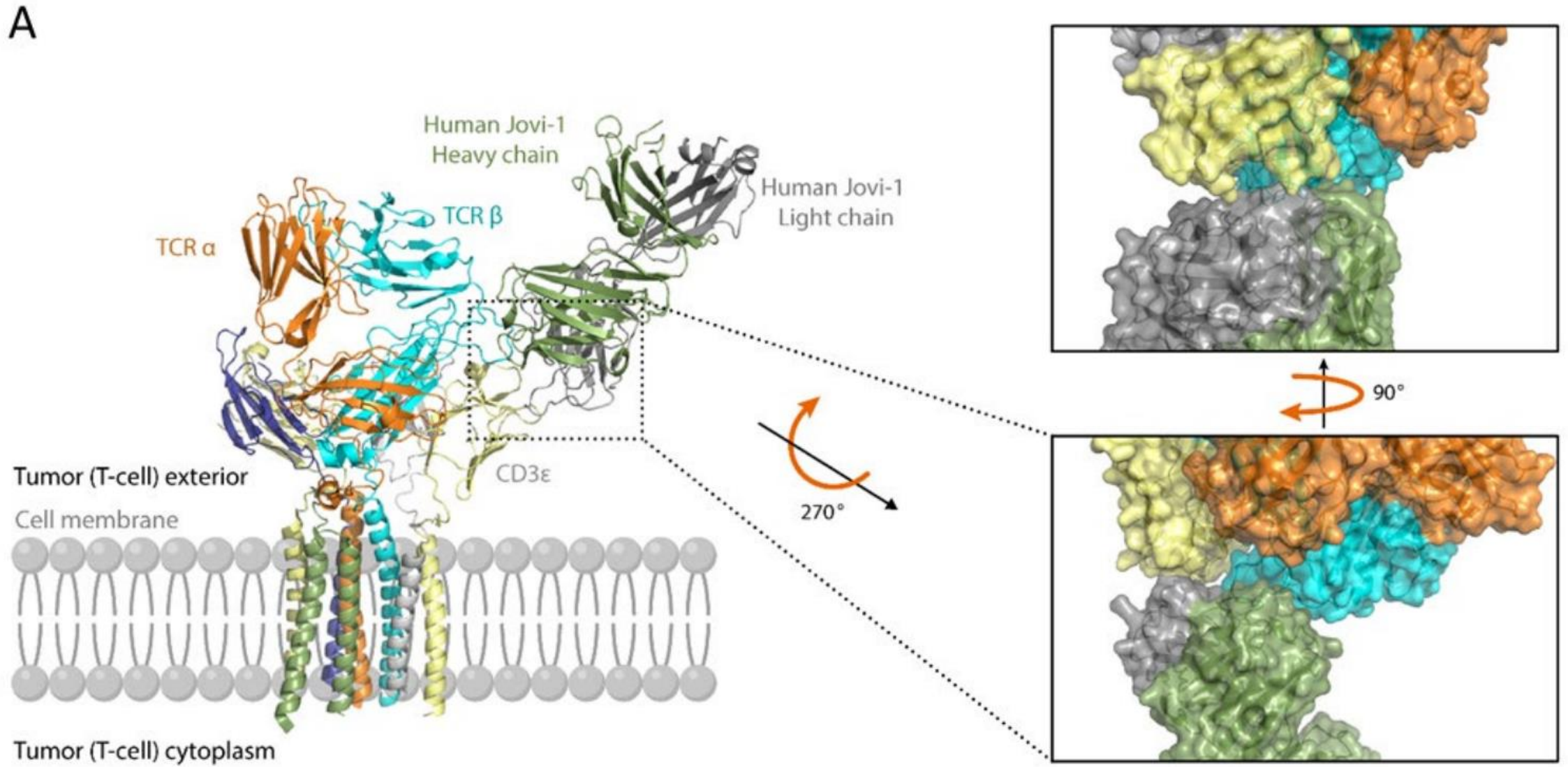
Summary

- AUTO4 treatment generally well tolerated
- Early efficacy is encouraging
- Longer follow-up ongoing
- CAR T-cells detected in lymph node
  - but no expansion observed in peripheral blood
- Change in manufacturing approach
- Study ongoing, with additional patients due to be treated to define recommended phase II dose

Can we extend this approach to patients with TRBC2 positive tumours?

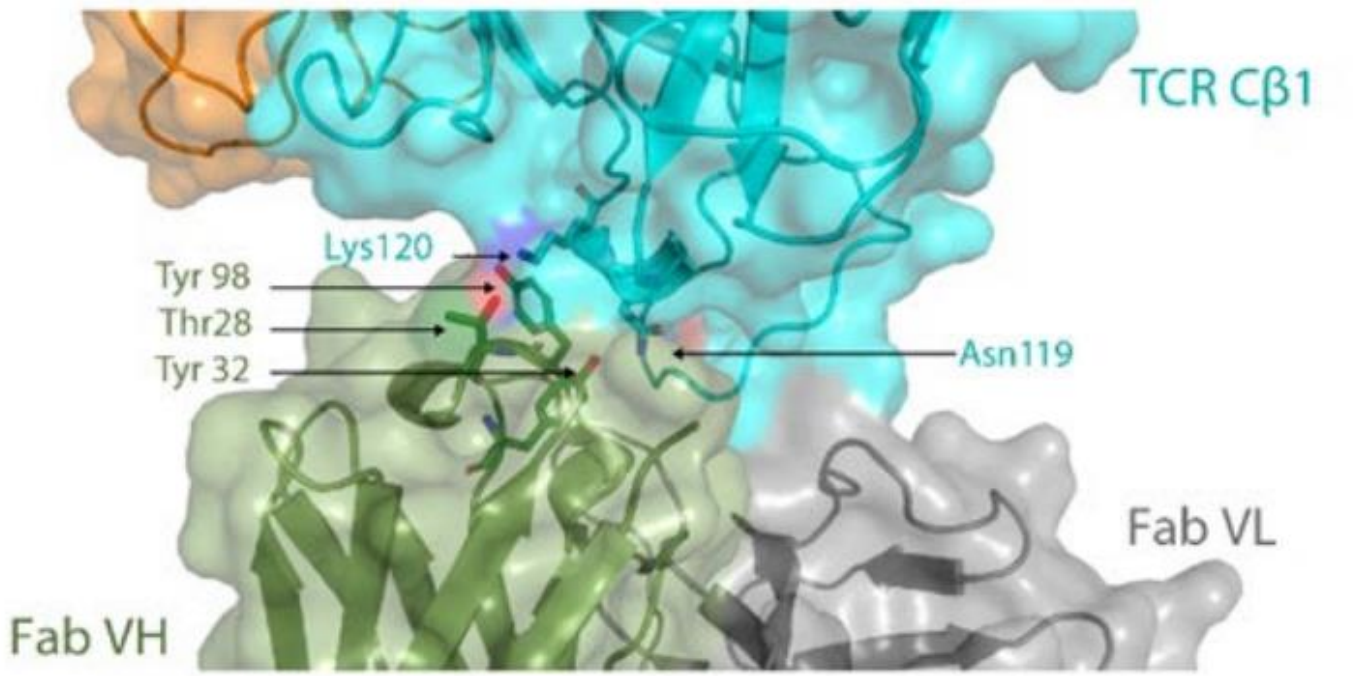
ie a capacity to treat ALL patients with relapsed/refractory T cell lymphoma

Structure of TRBC1 antibody binding to the TCR



Ferrari et al, Research Square, https://doi.org/10.21203/rs.3.rs-1475171/v1

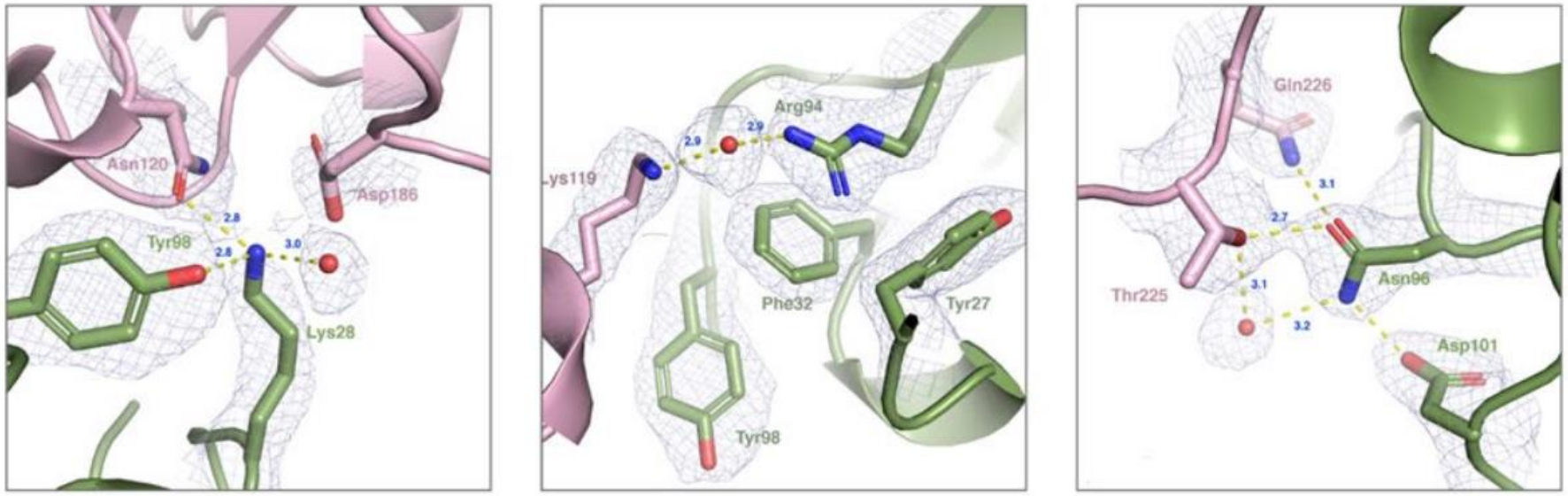
Crystal Structure of a TRBC1 Antibody in Complex with TCR

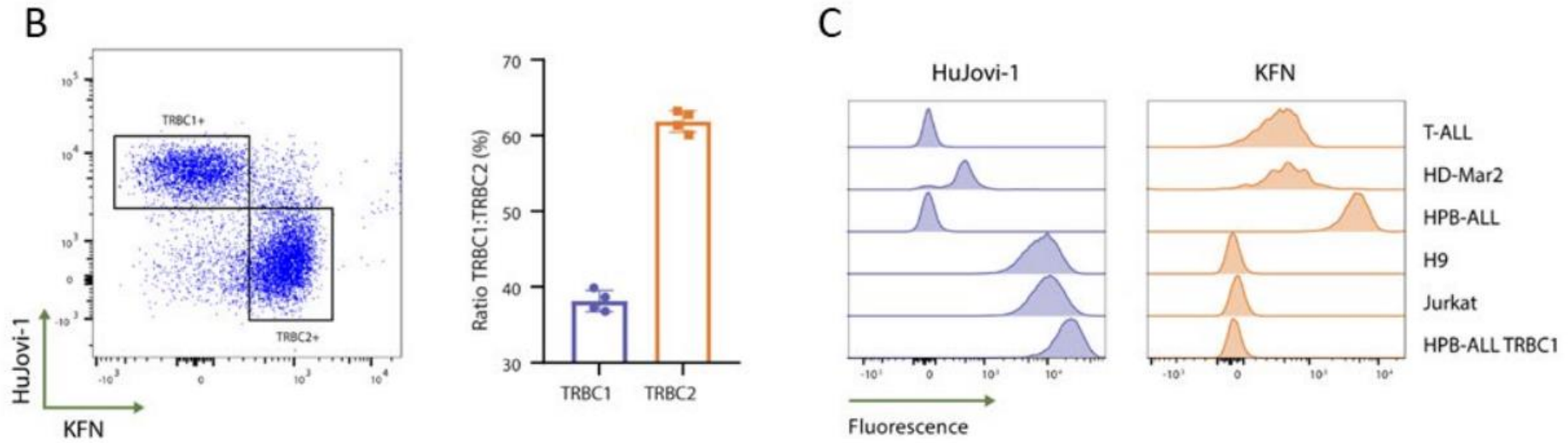


NK-KN 4/5

TRBC1	1	EDLNKVFPPEVAVFE
TRBC2	1	EDLKNVFPPEVAVFE

Converting JOVI-1 to a TRBC2 antibody: in silico design + phage display

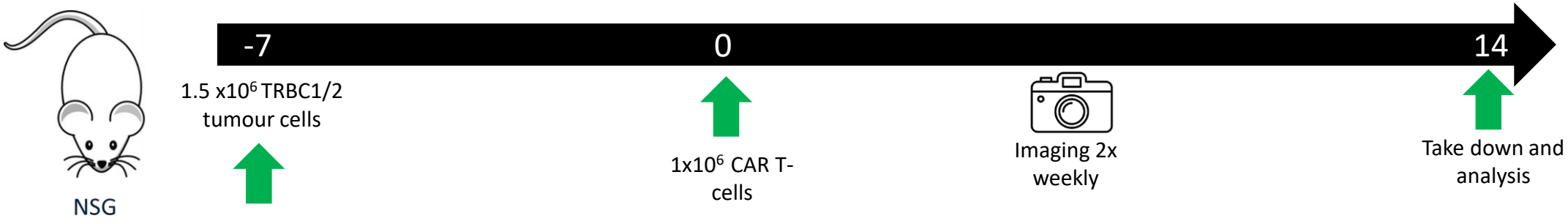


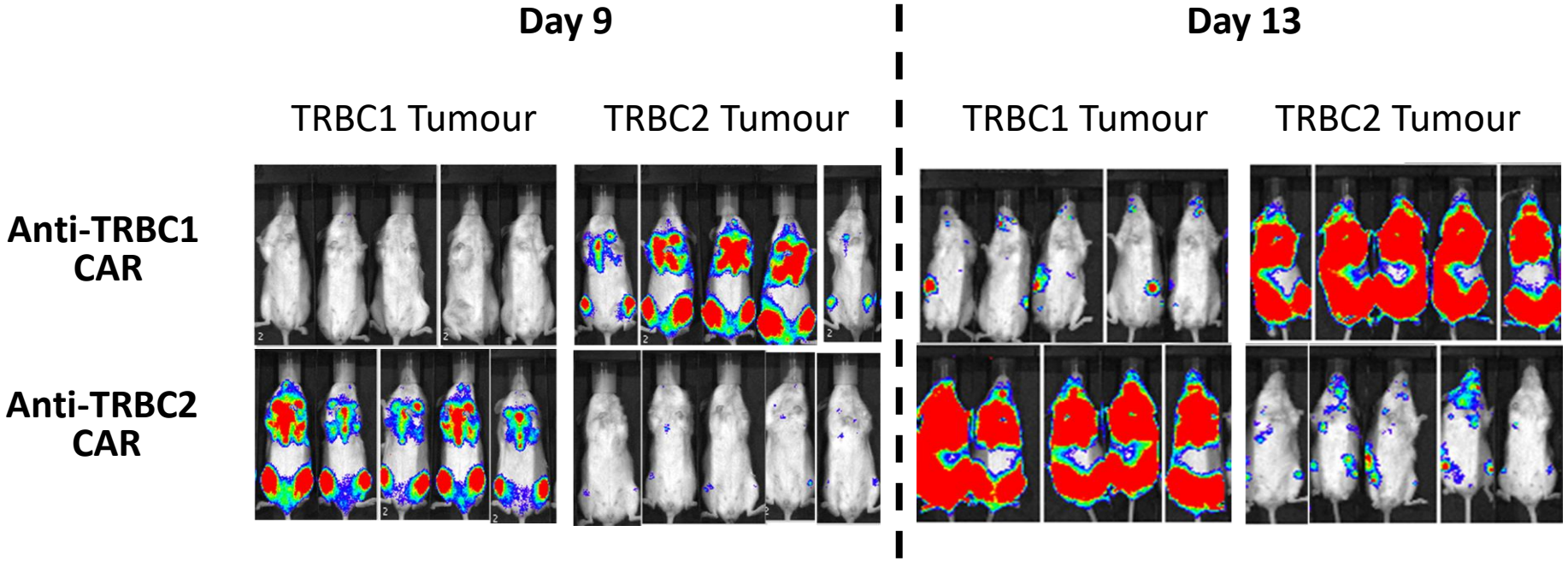


Maciocia P, Pule M *et al*

TRBC2 *in-vivo* CAR Activity

aTRBC2 CARs clear tumour in NSG model

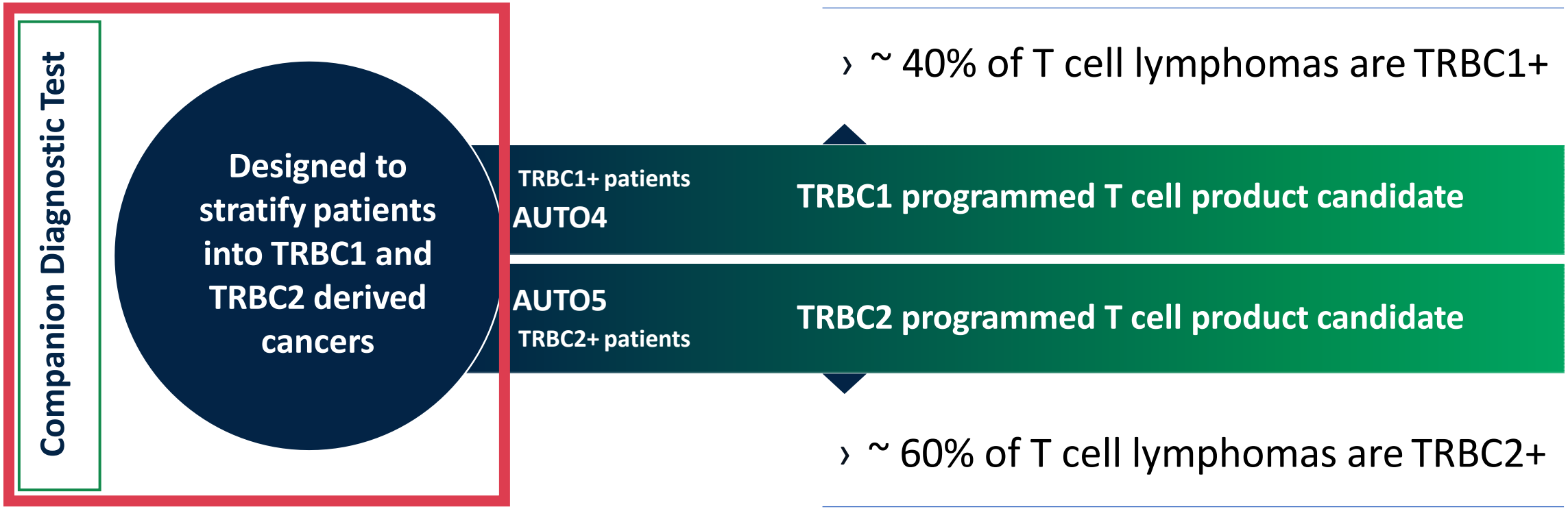




Maciocia P, Pule M *et al*

Addressing T cell lymphomas

Three key elements - AUTO4, AUTO5 and a companion diagnostic test



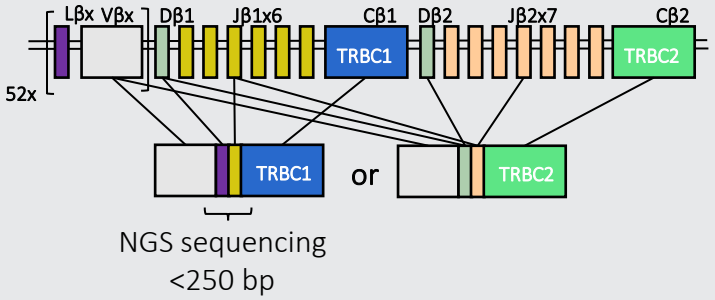
› ~ 40% of T cell lymphomas are TRBC1+

› ~ 60% of T cell lymphomas are TRBC2+

Companion Diagnostic

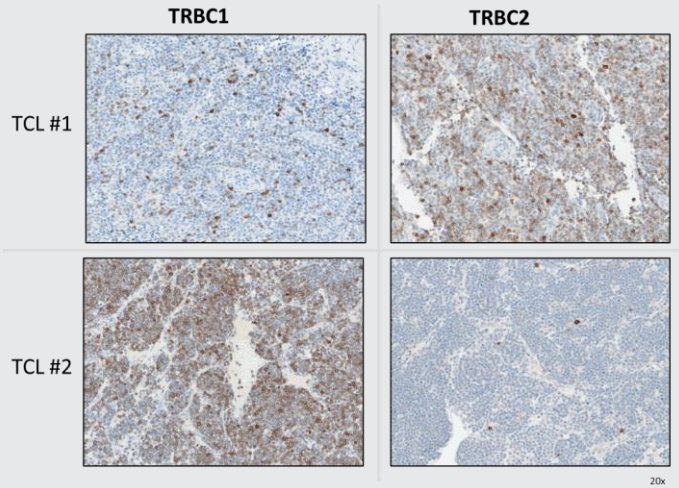
- Multiple approaches de-risked for development

• Next Generation Sequencing



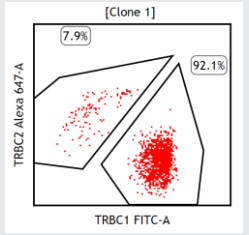
- T cell clonality NGS assay currently used in AUTO4 Phase 1

• Immunohistochemistry

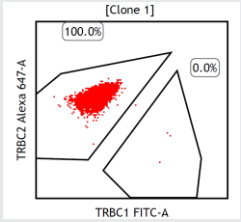


- FFPE specific antibodies can discriminate between TRBC1 and TRBC2 patient tumors

• 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

Conclusions

- Early efficacy of AUTO-4, a TRBC1-targeted CAR-T is encouraging
- Change in manufacturing approach: improve persistence?
  - Is this ‘necessary’?
- Recommended phase II dose to be defined
- Extend approach to patients with TRBC2 positive tumours

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