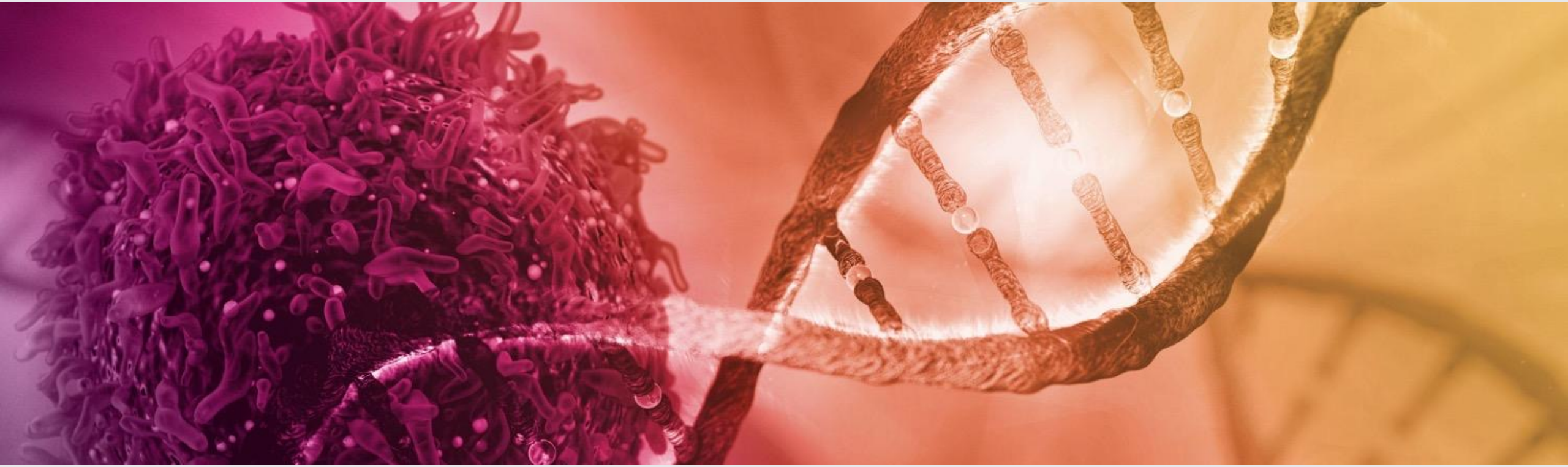


Achilles Therapeutics

Seeking Efficacy in Solid Tumours Through Precision Targeting

April 2024

Forward-Looking Statements

This presentation contains “forward-looking statements,” including statements regarding the proposed development plans and timelines for the Company’s product candidates and the success, cost and timing of its research activities and clinical trials. Forward-looking statements can generally be identified by the use of words such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “forecast,” “intend,” “may,” “plan,” “project,” “potential,” “seek,” “should,” “think,” “will,” “would” and similar expressions, or they may use future dates.

Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. These and other risks which may impact management's expectations are described in greater detail under the heading "Risk Factors" in the Company's quarterly report or Annual Report on Form 20-F and in any subsequent periodic or current report that the Company files with the SEC.

All forward-looking statements reflect the Company's estimates only as of the date of this presentation (unless another date is indicated) and should not be relied upon as reflecting the Company's views, expectations or beliefs at any date subsequent to the date of this presentation.

Working to transform the treatment of solid tumors with precision T cell therapy

Company founded
2016

Nasdaq IPO: ACHL
2021

Early clinical proof of concept
2022

Clinical update
Q1 2024

Clinical update
H2 2024

Global Headquarters
London, UK

Two active clinical programs with near-term clinical milestones

Emerging PoC for cNeT in NSCLC

$132M[1] cash supports operations through 2025

~180 employees

Catapult Cell and Gene Therapy Centre
Stevenage, UK

1. As of Dec 31, 2023

Clinical-stage precision targeting for solid tumors using clonal neoantigen-reactive T cells (cNeT)

Clinical data continue to support clonal neoantigens as critical targets in solid tumor immunotherapy

Neoantigens have been correlated with clinical benefit across multiple therapeutic modalities including checkpoint inhibitors, mRNA vaccines and TIL therapy

Clinical update on 18 patients with improved manufacturing process (~10-fold dose increase)

Favorable tolerability profile but no new objective responses observed. Updated clinical study incorporates enhanced conditioning to drive improved cNeT engraftment and clinical activity

Translational science providing critical mechanistic insight for TIL based and related therapies

Building a deep understanding of factors that can impact clinical activity focused on T cell engraftment and persistence, markers of cell function and impact of immune evasion at the antigen level

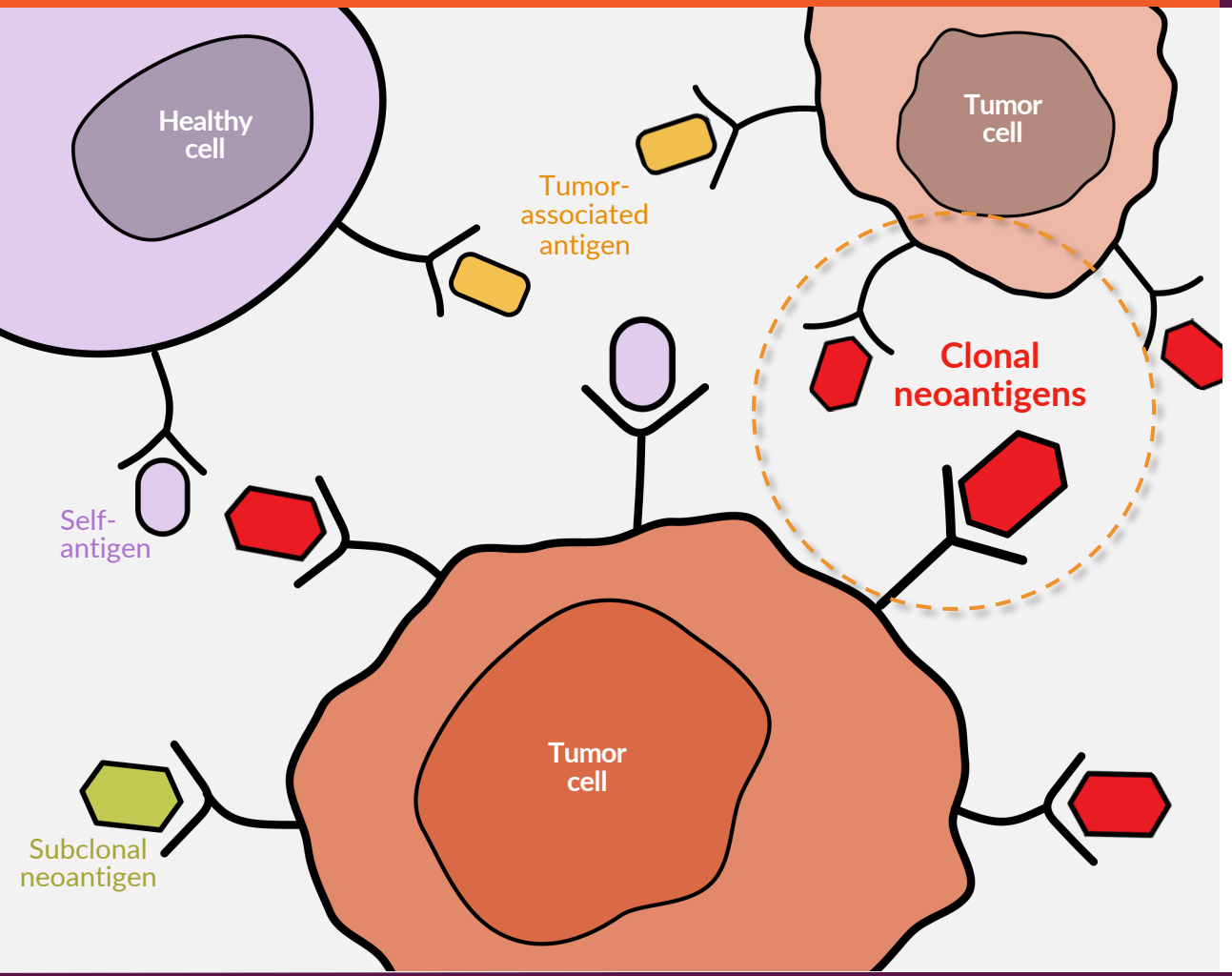
Second clinical update to follow in H2 2024 with meaningful enhanced conditioning cohort

Strong cash position supports all planned operations through 2025

Cash runway of $132M as of December 31, 2023

Clonal neoantigens: A critical and clinically validated target class in solid tumour immunotherapy

Clonals are the only known target present on all tumor cells & absent from healthy tissue



Multiple clinical modalities validate neoantigens but only clonals drive overall survival

Neoantigen-reactive T cells correlated with **improved outcomes** in **checkpoint inhibitor (CPI) and TIL** therapy[1-3]

mRNA vaccines targeting neoantigens have demonstrated **recurrence-free survival benefit** vs anti-PD-1 alone[4]

Tumor heterogeneity and sub-clonal neoantigens **impair response** to **CPI**[5-7]

Only clonal neoantigens are correlated with **overall survival** in **CPI therapy**[8-10]

1. *Litchfield et al. Cell 2021*
2. *Lauss et al. Nat Commun. 2017 Nov 23;8(1):1738*
3. *Kristensen et al. J Clin Invest. 2022 Jan 18;132(2):e150535*
4. *https://clinicaltrials.gov/ct2/show/NCT03897881*
5. *Wolf et al. Cell 2019*
6. *Wescott et al. Nat Gen 2023*
6. *Reading et al. Nat Gen 2023*
7. *Rizvi et al. 2015 Cancer Immuno 348(6230):124-8*
8. *McGranahan et al. 2016 Science 351:1463-1469*
9. *Litchfield et al. Cell 2021*

PELEUS™: A patent protected world-leading AI-platform for identifying the most potent and immunogenic targets

Superior clonal calling: only platform to use multi-region analysis proven to overcome limitations of traditional VAF based methods[1]

Most immunogenic targets: our proprietary and validated "neoRanker" AI-technology can identify >70% of all T cell reactivities in just 30 antigens (at least twice as good as current deep-learning tools)

Mitigates immune evasion:[2] PELEUS prioritizes antigens not impacted by immune evasion mechanisms (i.e. loss of HLA heterozygosity)

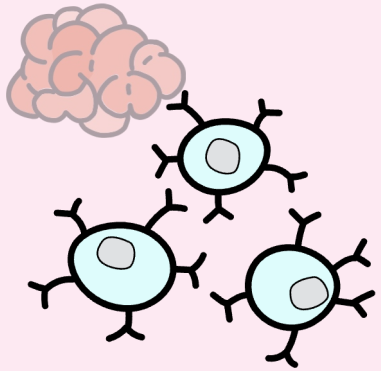
1. Jamal-Hanjani *et al* 2017
2. McGranahan *et al* 2017

Clonal neoantigens can be targeted with a number of therapeutic modalities

Current Achilles approach

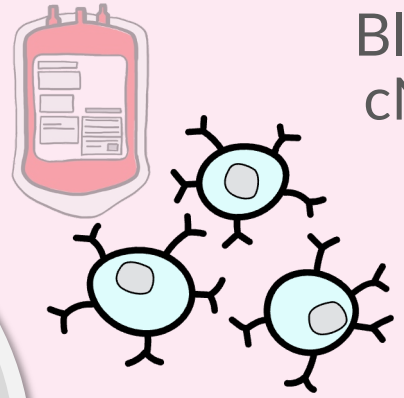
Alternative modalities

TIL-based cNeT

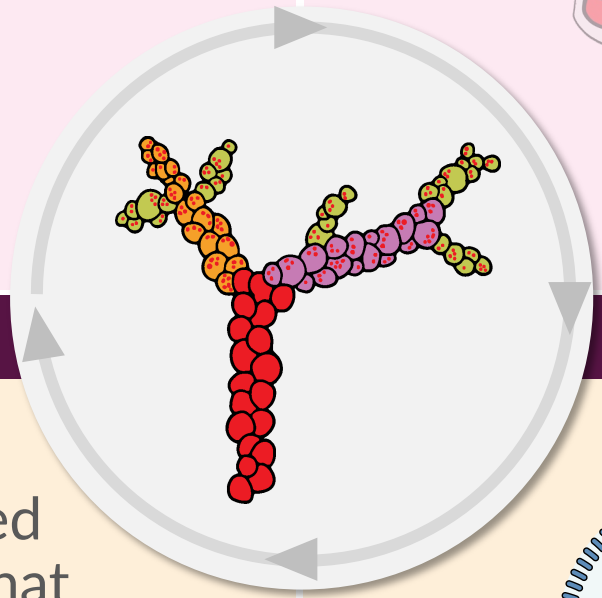


TIL-based therapy is clinically validated across multiple solid tumor settings

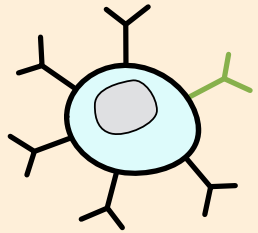
Blood-based cNeT



Blood as source of cNeT, without the need for surgery

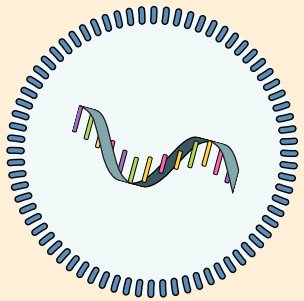


TCR-therapy



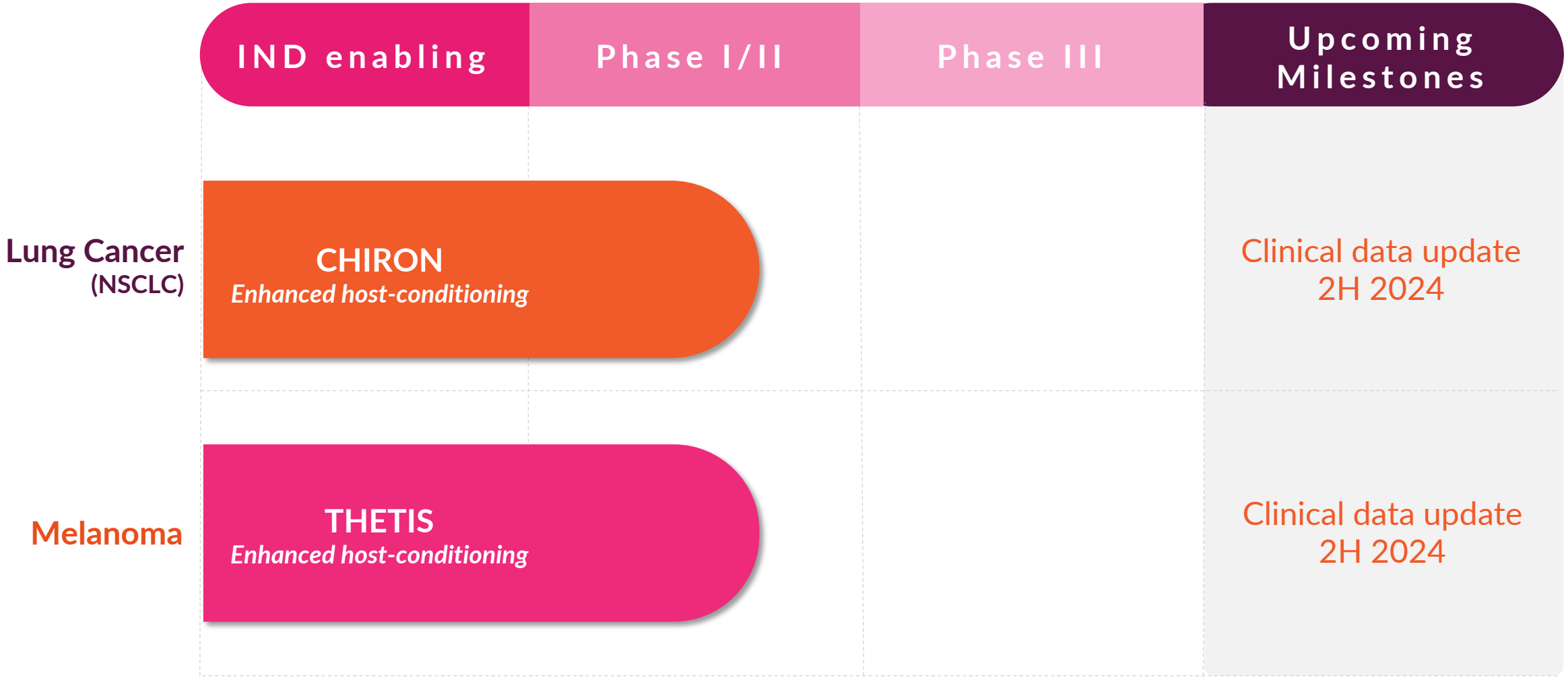
T cells engineered with receptors that target “off-the-shelf” shared neoantigens

Clonal neoantigen vaccines



mRNA vaccines using highly immunogenic clonal neoantigens to improve efficacy

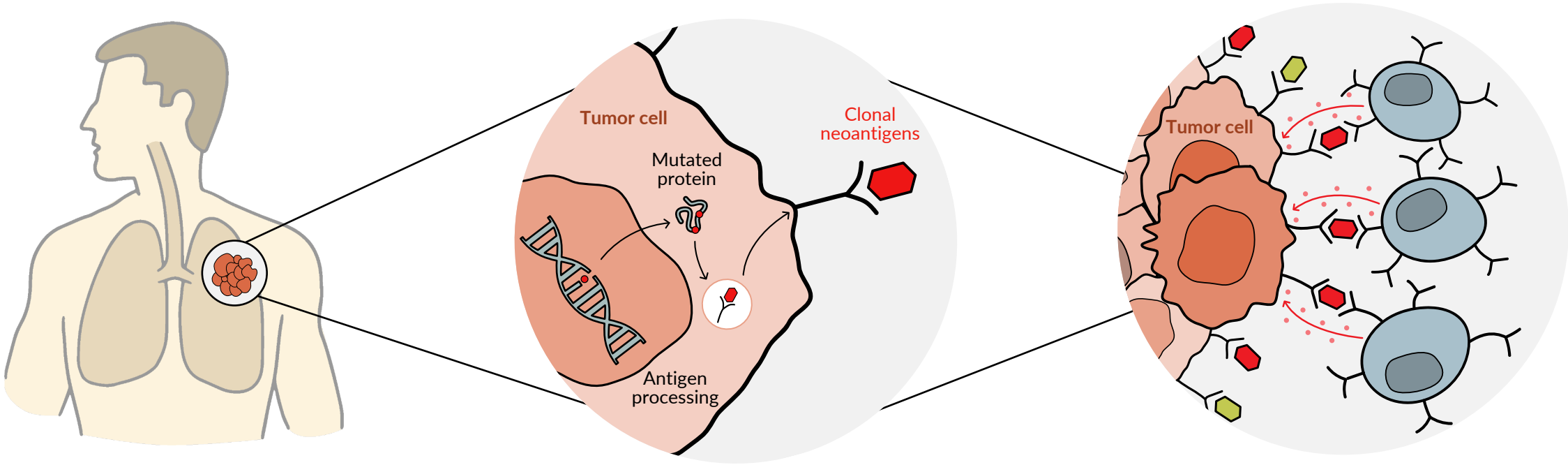
Differentiated pipeline of precision T cell therapies across multiple solid tumors



Several lines of clinical evidence support neoantigen reactive T cells driving efficacy in TIL Tx

TIL-based studies have demonstrated impressive clinical responses in multiple solid tumor settings[1-3]

Improved clinical outcomes in TIL therapy are correlated with high **neoantigen load** and the presence of **neoantigen reactive T cells**[4-8]



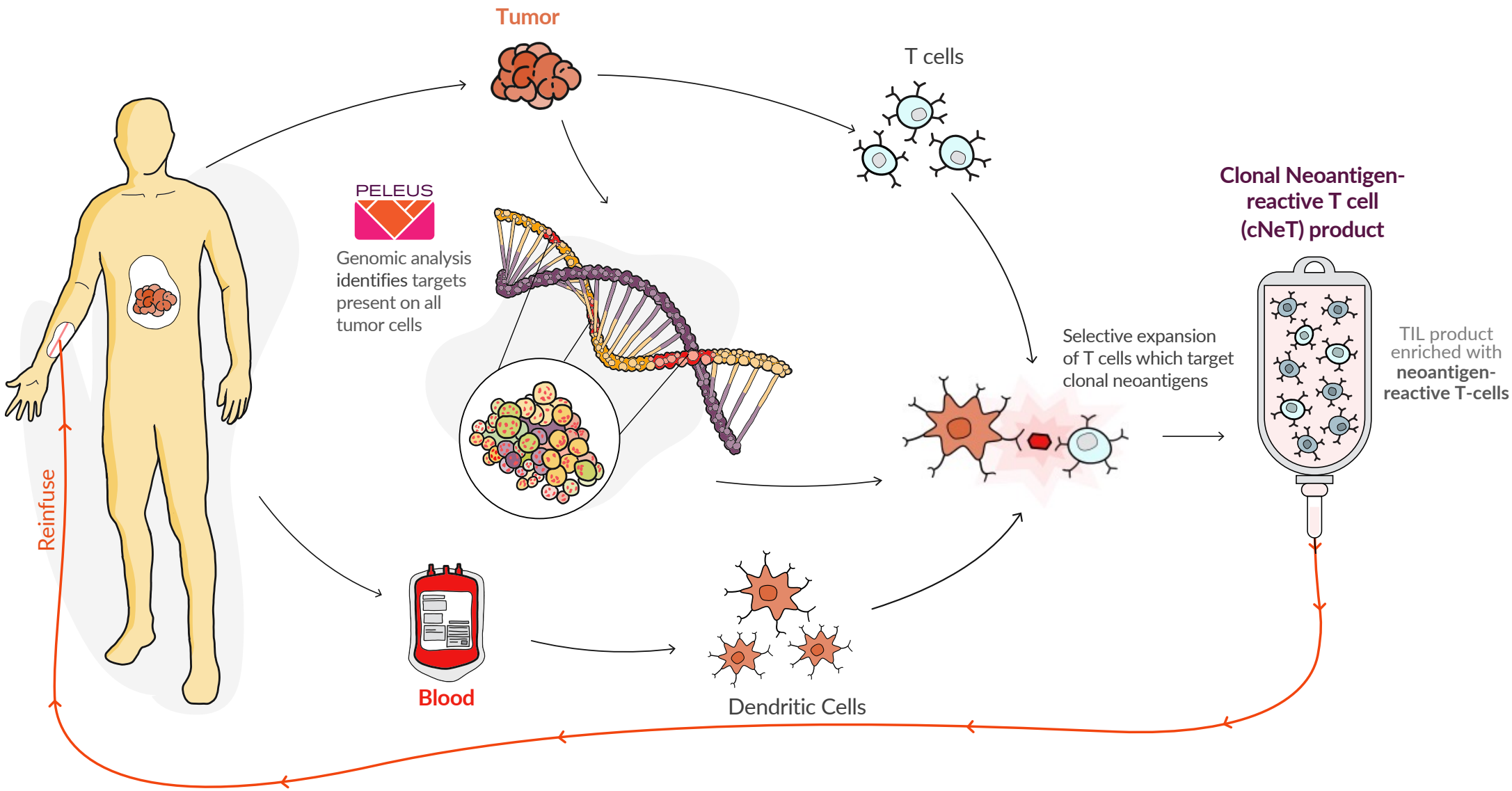
Achilles' approach **enriches for the active component of TIL therapy** (neoantigen reactive T cells) and seeks to improve activity by targeting **the most immunogenic clonal neoantigens**

1. Chesney et al. Journal for ImmunoTherapy of Cancer 2022;
2. IOVANCE Cohort 3B;
3 IOVANCE ASCO abstract May 2019

4. Tran et al. N Engl J Med 2016;
5. Zacharakis et al. Nat Med 24 2018;
6. Lauss et al. Nat Commun. 2017
7. Kristensen et al. J Clin Invest. 2022
8. Levi et al. Clin. Cancer Res. 2022

Achilles process delivers precision clonal neoantigen targeting T cell therapy (cNeT)

Cutting edge personalized genomics and machine learning enable targeting of all cancer cells



Updated programs in advanced NSCLC and metastatic melanoma

CHIRON
Advanced NSCLC

NSCLC, Stage III-Stage IV (*n=40*, open label)

Cohort A – Monotherapy (enhanced lymphodepletion[1] and low dose IL-2)

Cohort C – Monotherapy (enhanced lymphodepletion[1] and high dose IL-2[2])

All NSCLC patients receive enhanced lymphodepletion (Flu/Cy)[1]

THETIS*
Advanced Melanoma

Melanoma, metastatic malignant (*n=40*, open-label)

Cohort A – Monotherapy (low dose IL-2)

Cohort C – Monotherapy (high dose IL-2)[2]

Evaluating safety, tolerability, clinical activity (RECIST) and biomarkers of clinical activity

Ongoing in UK, Europe and US

* Cohort B Combination of cNeT with PD-1 inhibitor

1 Fludarabine (Flu) and Cyclophosphamide (Cy) doses aligned with standard TIL with dose escalation from intermediate (*n=3*) to full dose
2 IL-2 dose and regime aligned with standard TIL

Summary

Interim clinical update on 18 patients

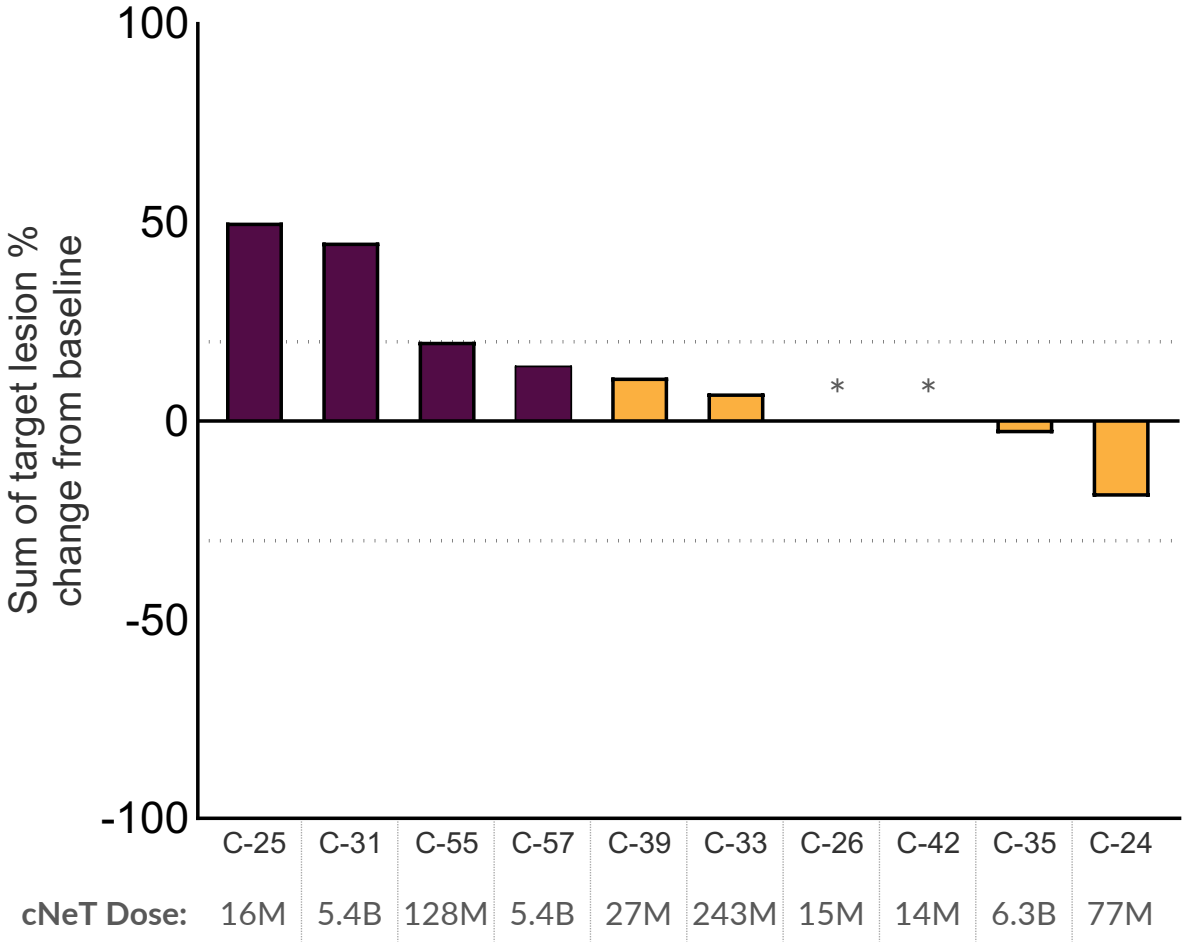
- **We have dosed 18 new patients since last update with a median cNeT dose of 172M**
  - 15 patients were dosed using low intensity lymphodepletion and IL-2 (host conditioning)
  - Favourable safety profile, similar to standard TIL
  - 25% of high dose (>100M cNeT) patients demonstrated some tumor reduction but we did not observe any new objective responses
- **We observed early peaks of cNeT post infusion but limited persistence beyond 28 days**
  - Clinical study protocols have been updated to include enhanced host conditioning (EHC) aligned to standard TIL to drive improved cNeT persistence and clinical activity
- **Three patients dosed to date with enhanced host-conditioning (EHC) showing significantly improved cNeT engraftment kinetics**
  - All three patients showed significantly improved cNeT engraftment and persistent engraftment in the two evaluable patients
  - Best response observed for NSCLC patient (C-66) with stable disease (-14% tumor volume) at week 6
- **Meaningful clinical update with enhanced host conditioning planned for H2 2024**

Clinical update in NSCLC and melanoma

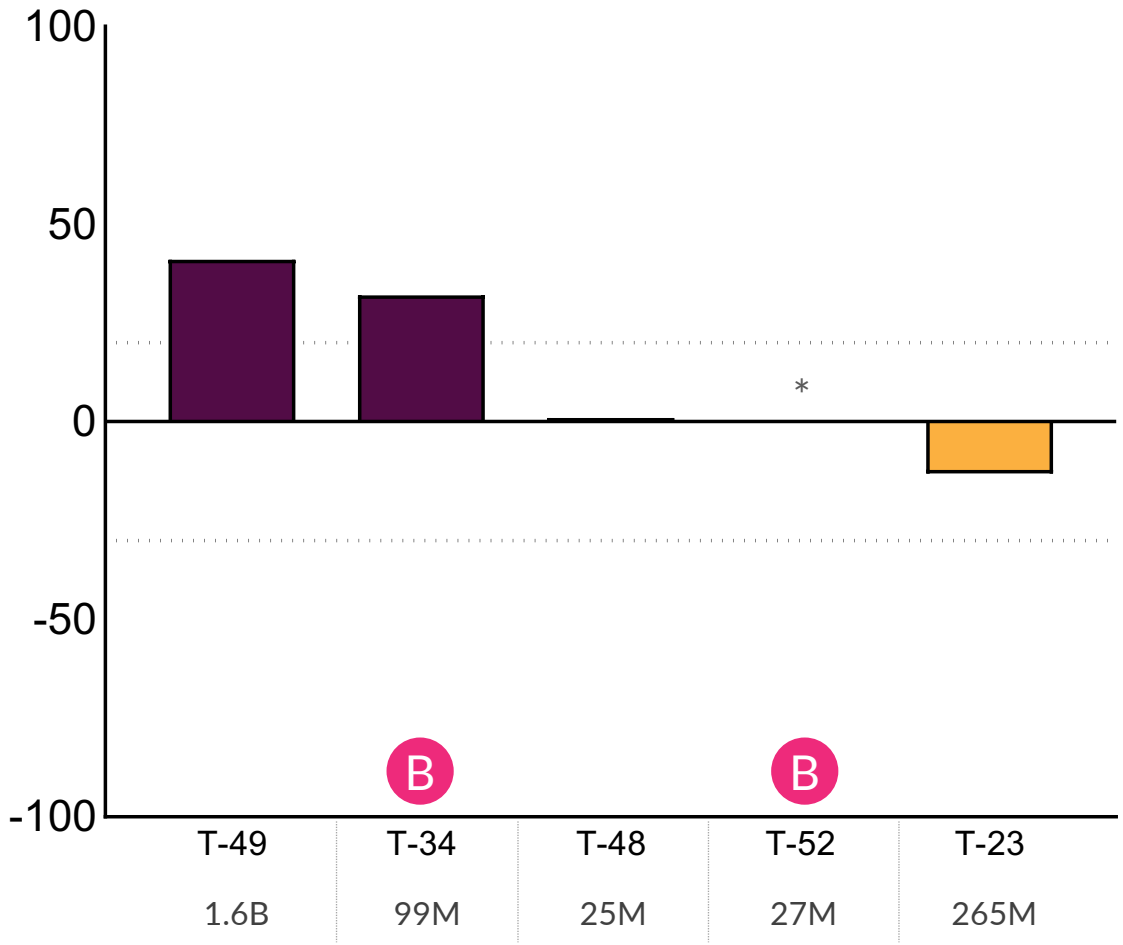
15 (of 18) patients were dosed using low intensity host conditioning

Key
- Stable disease
- Progressive disease
- B Cohort B (+ CPI)

CHIRON
Best response to cNeT (n=10)

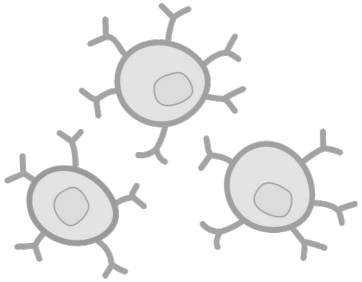
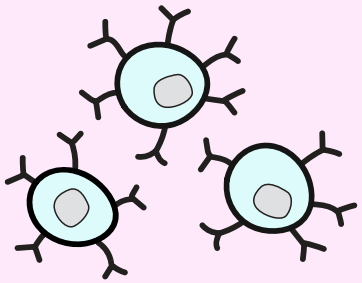


THETIS
Best response to cNeT (n=5)



**Patients confirmed PD but unevaluable target lesions*

Achilles translational science platform enables detailed mechanistic comparison to recently approved standard TIL therapy

	Cell dose	Function	Host conditioning	Mechanism
TIL Tx 	Stochastic expansion (clonal and subclonal) with median **reactive doses** estimated at **210-420 M** cells[1]	TIL therapies express key markers of tumor migration and anti-tumor activity[2]	Industry standard host conditioning able to deliver durable tumor-reactive T cell engraftment[3,4]	Unable to characterize and track tumor-reactive component of product
 cNeT	Median cNeT dose of **172 M** for last 18 patients dosed and **611 M** in last 10 products manufactured	Highly functional, expressing markers of **activation, tumor migration** and **anti-tumor activity**	Trial protocol now updated to evaluate **enhanced lymphodepletion and IL-2** aligned to standard TIL	**We measure active component** in product characterization and patient tracking to **deconvolute mechanism of action**

1. Based on Achilles data (*n=10*) TIL for TIL reactivity (1-2%) and median total T cell dose of 21.1 B (AMTAGIV label); 2. *Anderson et al., Clin Cancer Res. 2016; 3. Kristensen et al., J Clin Invest. 2022; 4. Creelan et al. Nat Med. 2021*

cNeT are functional and active, consistent with reported TIL data

Activation and anti-tumour activity

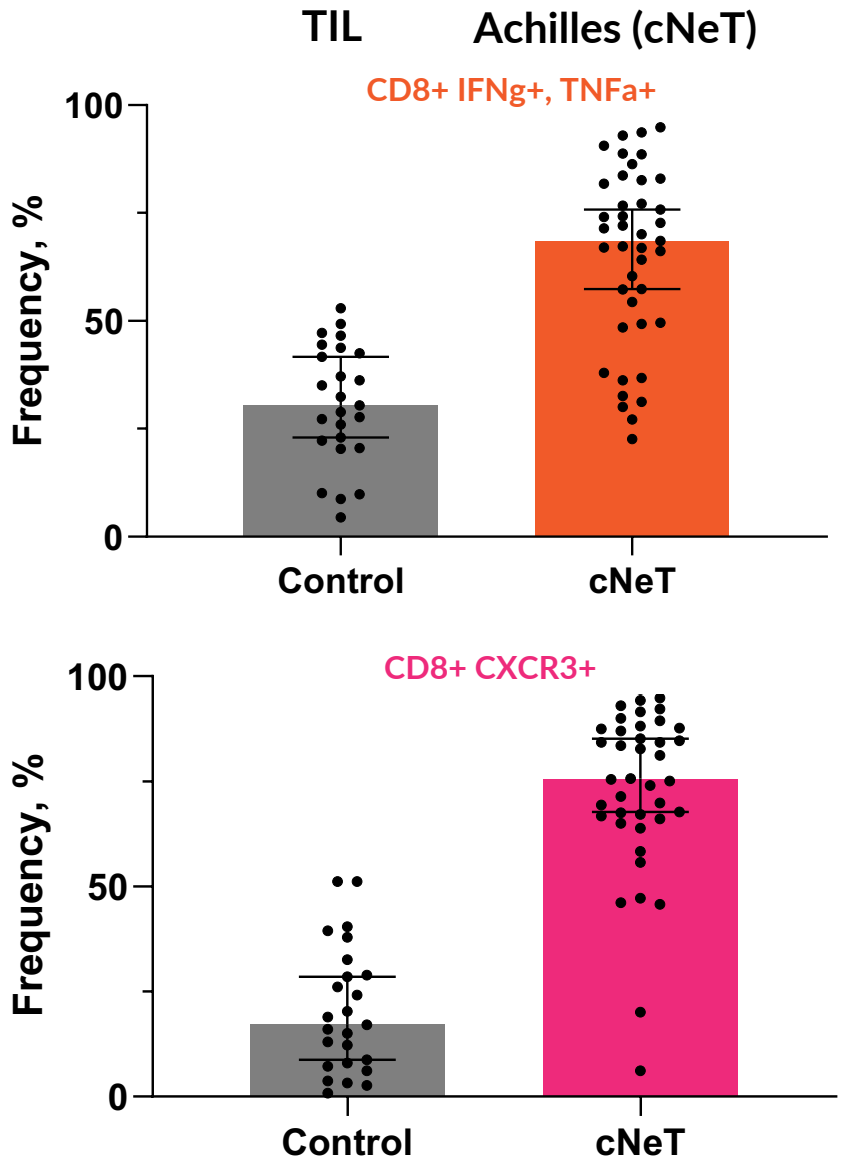
- Anti-tumor activity markers (TNFa/IFNg) highly expressed
- TIGIT highly expressed and low levels of exhaustion marker PD-1 correlated with TIL response[1]

Tumor migration

- High expression of tumor migration marker CXCR3

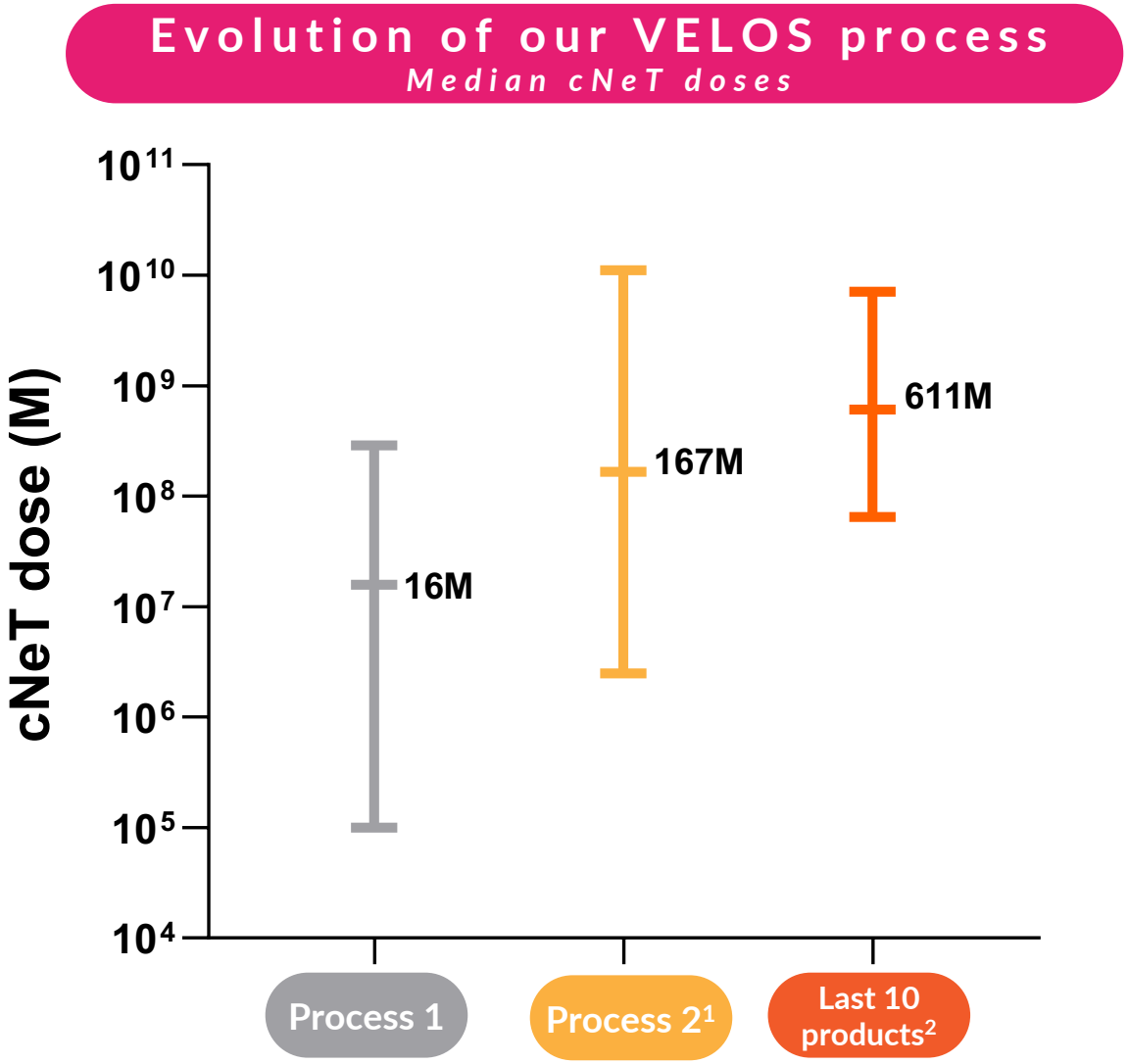
Memory phenotype

- High proportion of effector memory T cells, as seen in standard TIL[1]
- Expression profile consistent with a less terminally differentiated cell type (e.g., high CD27[2])



[1]Yuhas et al, ASCO 2023 poster

VELOS Process 2 is delivering significantly higher cNeT doses



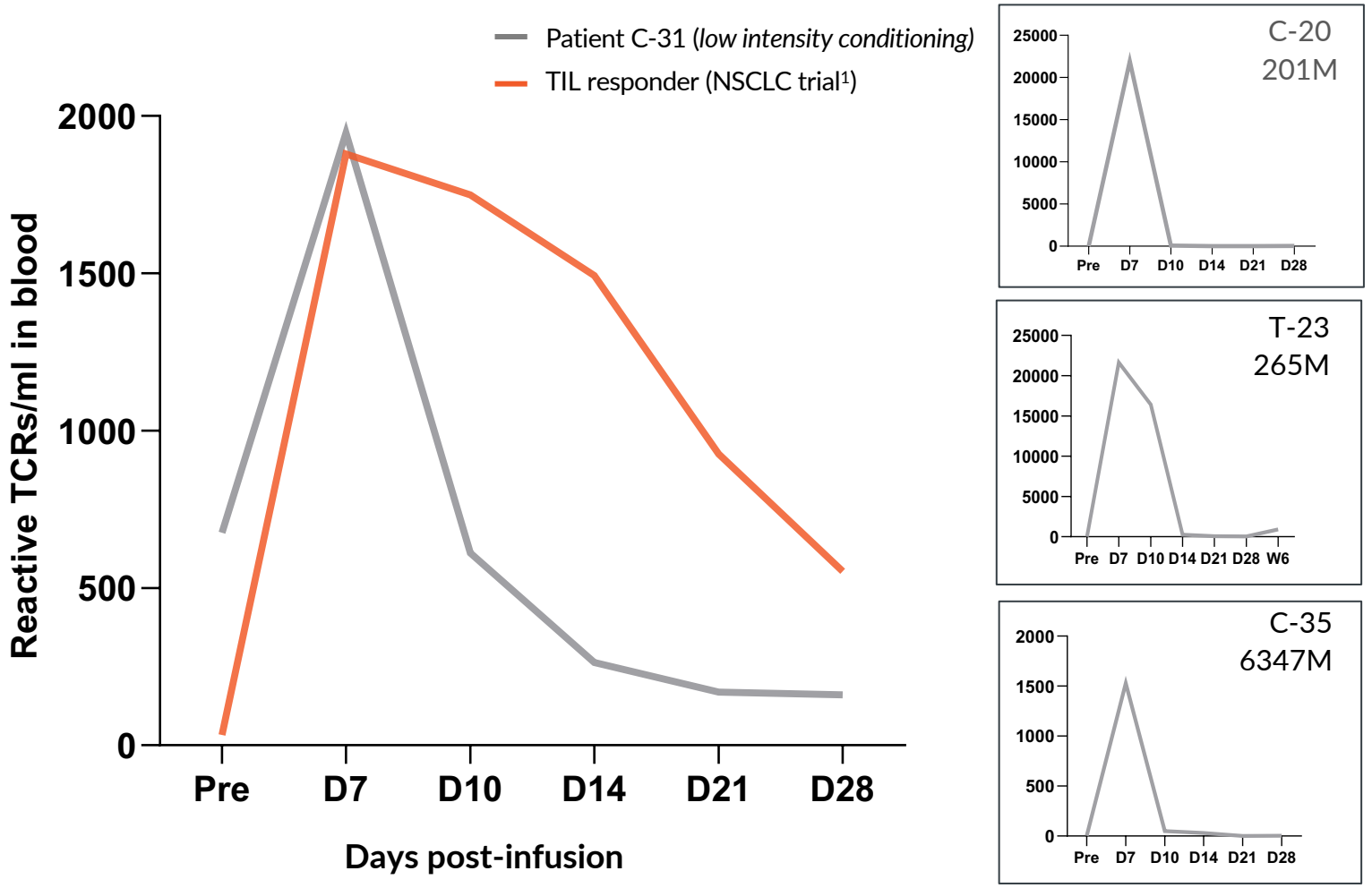
- Over **10-fold improvement in cNeT doses** across Process 1 to Process 2
- Optimisation of T cell extraction conditions and implementation of automated cell harvesting delivering significant improvements in cNeT yields

[1] *Process 2 performance in 2023* [2]*Last 10 products manufactured and ready for dosing as of 25/3*

Lack of cNeT persistence observed when using low intensity host conditioning

Persistence of neoantigen reactive T cells post-dosing

Patient C31, 5.4 B cNeT, *Single reactive TCR clone*



- **Early peaks** of cNeTs detected post dosing at levels comparable to those observed in standard TIL therapy where objective responses have been observed[1,2]
- However, subsequent and **rapid cNeT decay** suggest lack of persistence likely leading to lack of clinical activity

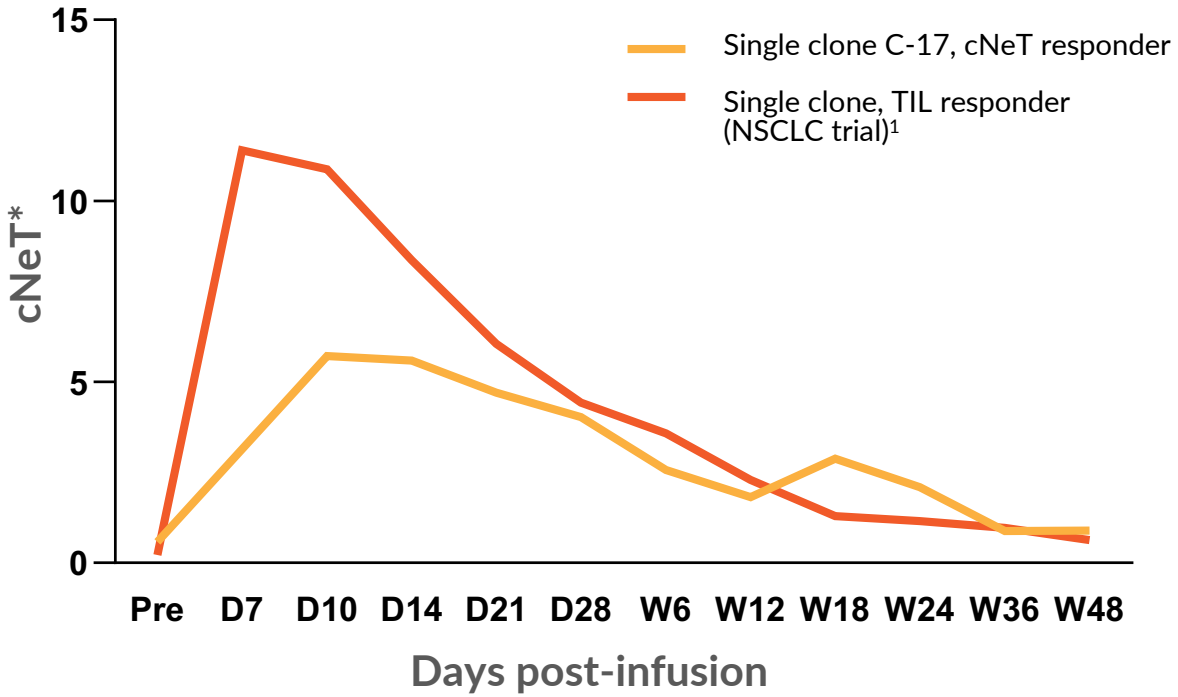
**Single reactive clones with highest TCR levels at D7*

1. *Reconstructed from Creelan et al. Nat Med vol27, 1410–1418 (2021)*
2. *Kristensen et al. J Clin Invest.;132(2):e150535 (2022)*

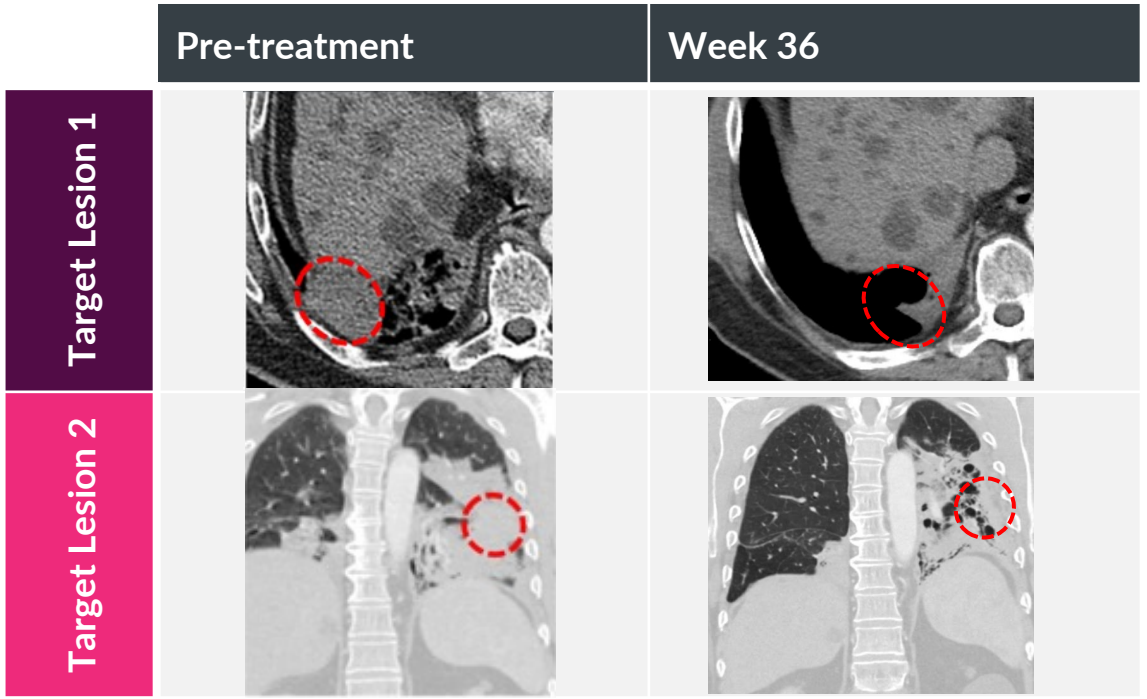
Sustained persistence of reactive TCR clones associated with partial response seen in patient C-17 and standard TIL studies

C-17: Detection of T cell receptors

Sum of Neo-Ag reactive TCRs, TCR/mL
Low intensity conditioning



cNeTs persisted beyond 6 months - longer than any other cNeT patient and similar to kinetics seen in standard TIL studies



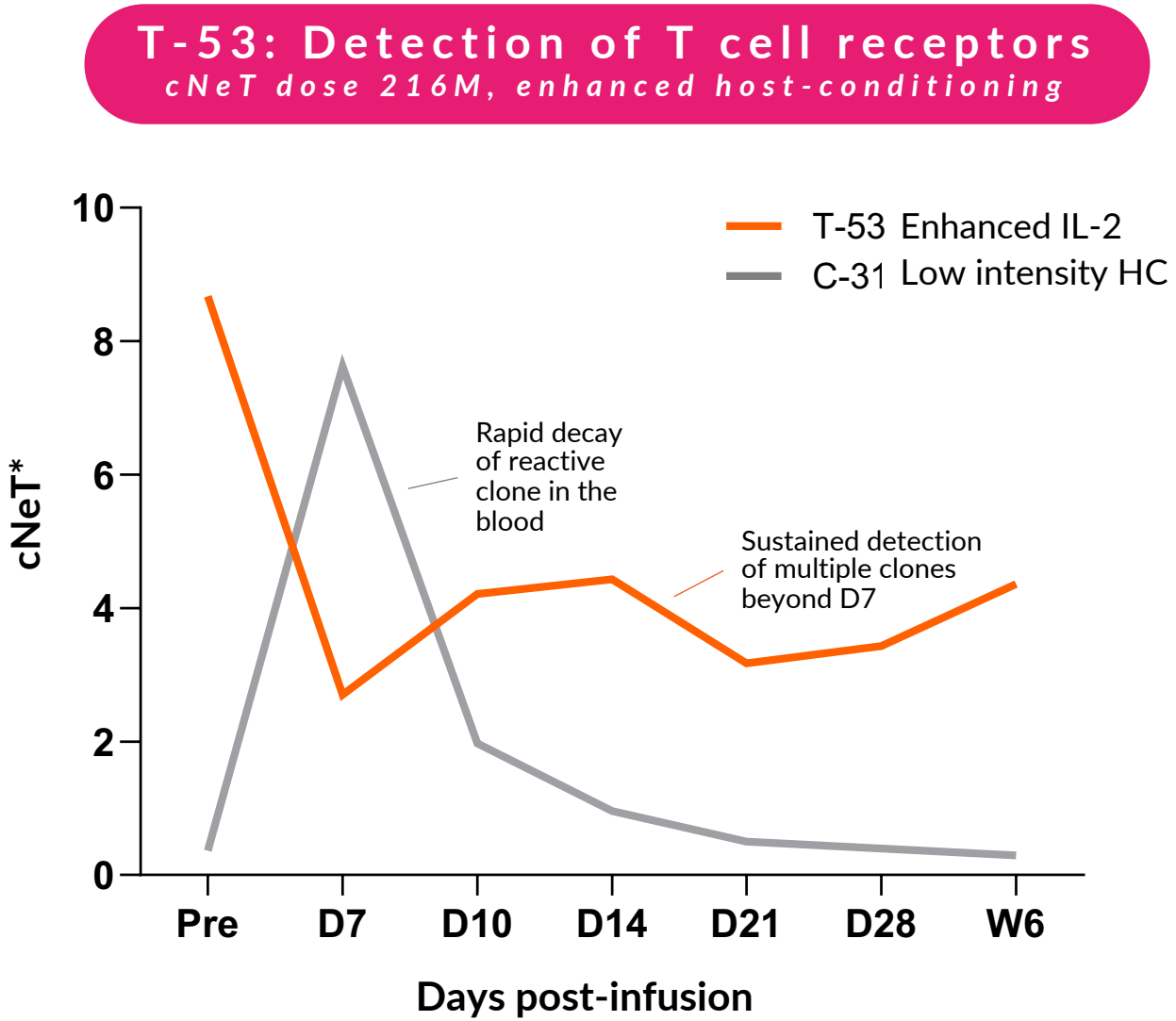
Total target lesion **reduction of 56%** at week 36

Immune evasion not detected: No HLA allele loss with even distribution of peptides across alleles

*Sum of NeoAg-specific TCR/mL (x10^3)

1. Creelan et al. Nat Med vol27, 1410–1418 (2021)

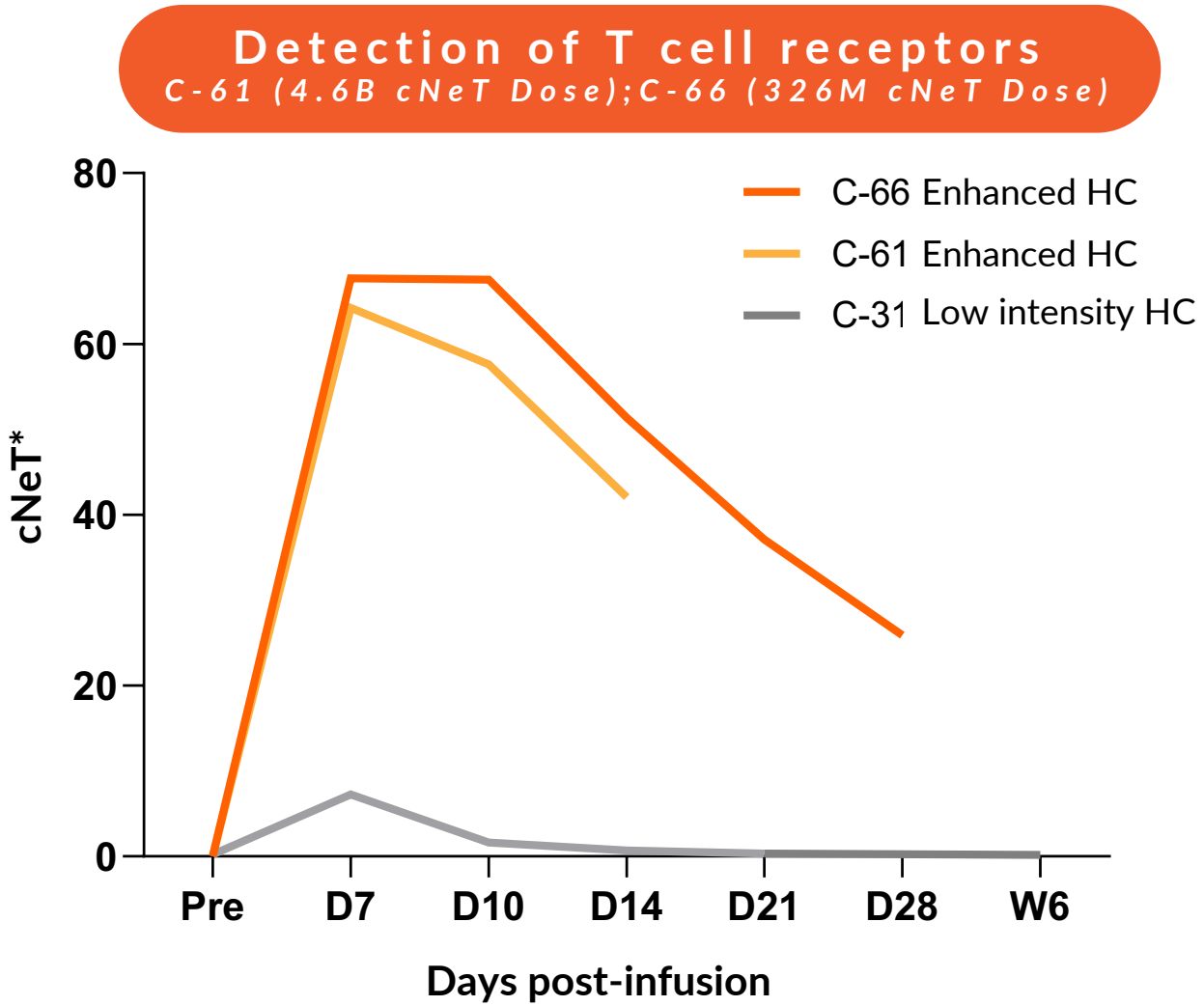
First melanoma patient dosed following enhanced conditioning demonstrated improved cNeT persistence with clinical activity likely impacted by immune evasion



- Significantly improved cNeT persistence compared to low intensity conditioning; cNeTs account for ~4% of all the T cell receptors detected in the blood beyond 28 days
- Progressive disease at Week 6: reduction in size of some of the target lesions (-4% overall) but progression observed in non-target lesions
- Tumor exhibited high immune evasion with loss of expression of three different HLA molecules
- The clonal neoantigen targeted by $CD8^+$ cNeTs was predicted to be presented by one of the lost HLA molecules, likely preventing tumor recognition by $CD8^+$ cNeTs

*Sum of NeoAg-specific TCR (% of sample)

NSCLC patients (C-61 and C66) showed significant improvement in cNeT persistence with enhanced host conditioning (enhanced lymphodepletion and IL-2)



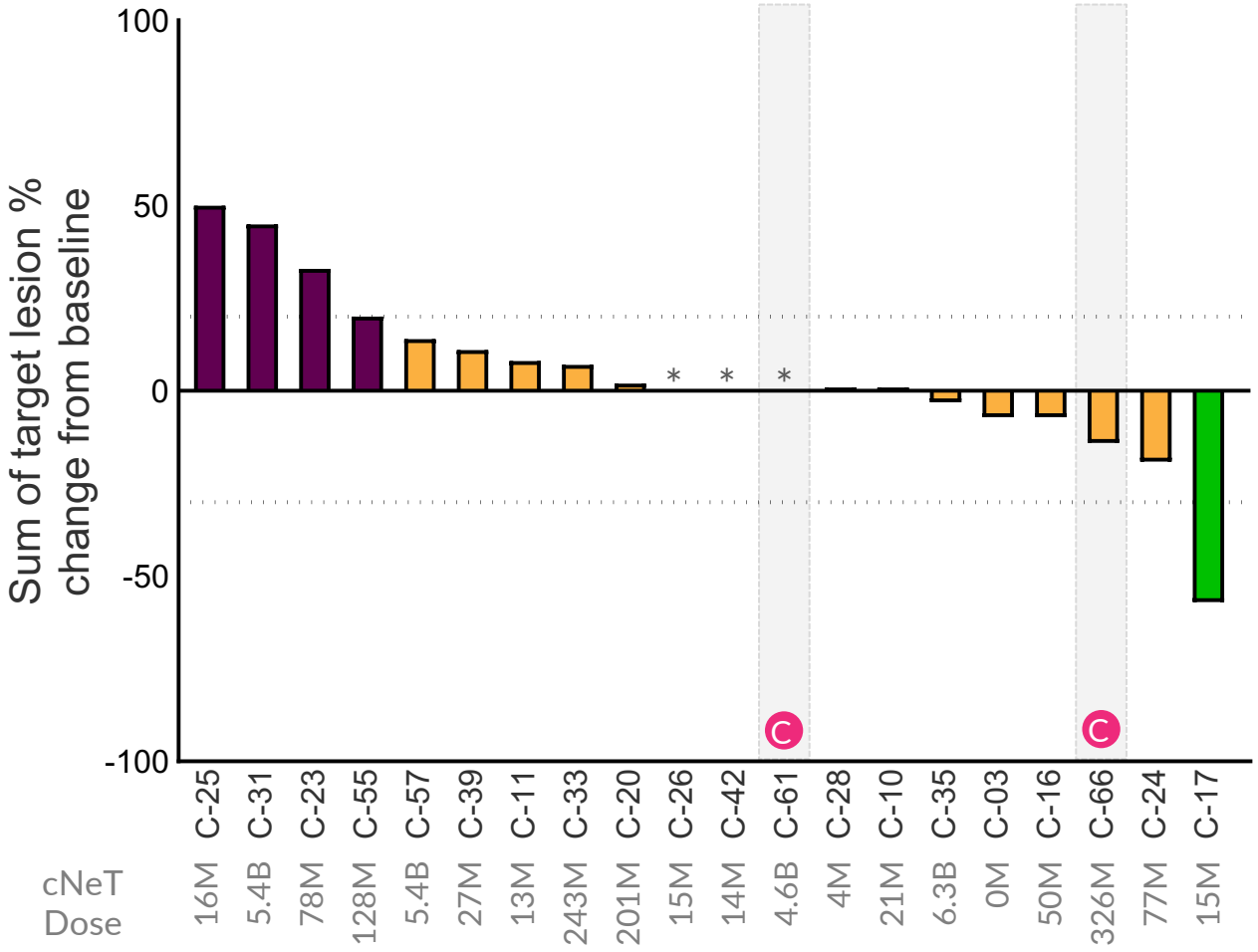
- Patient C-66 and C-61 show significant early peaks (>60% of all T cell receptors detected) with sustained detection of cNeTs in blood post dosing
- Data from both patients consistent with improved engraftment driven by the enhanced conditioning
- C-66 had stable disease at week 6, with reduction in tumor volume (-14%) and low immune evasion of targeted clonal neoantigens
- C-61 experienced progressive disease at week 4 and withdrew from the study

*Sum of NeoAg-specific TCR (% of sample)

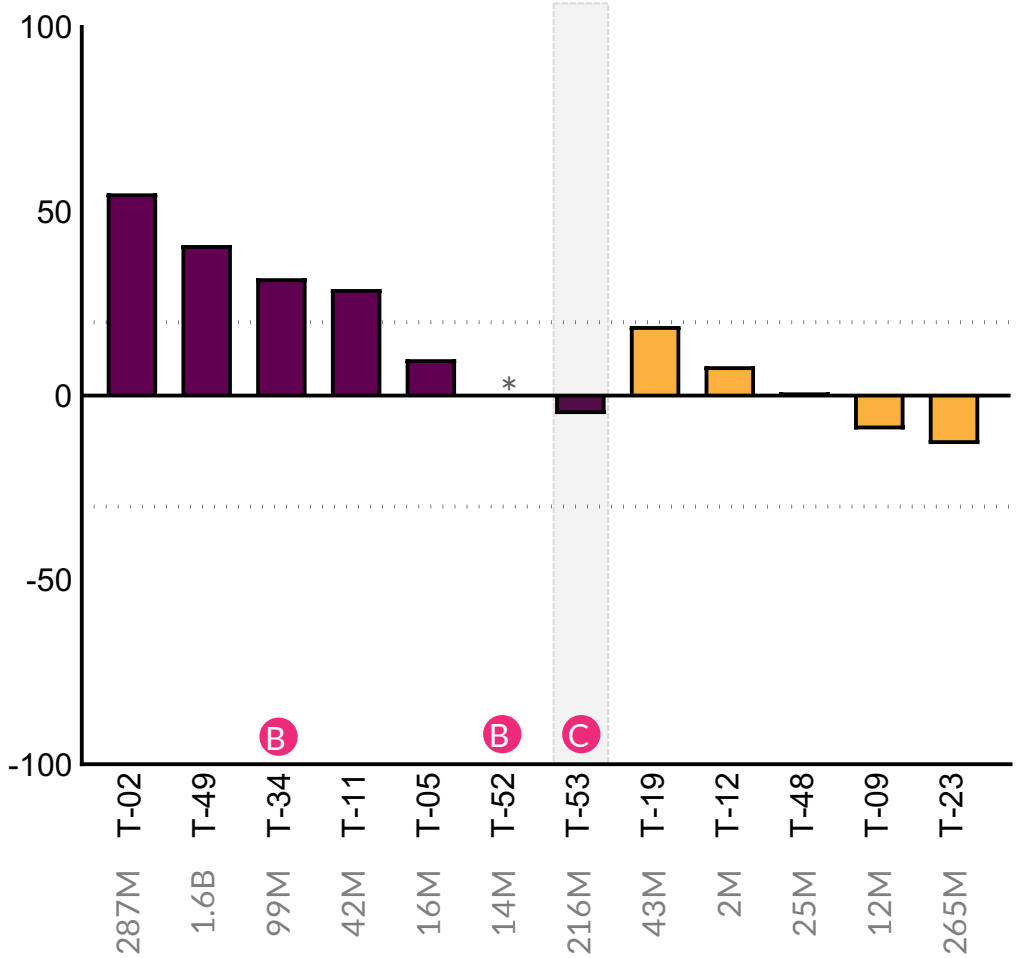
All Patients Dosed (n=32)

Key
- Partial response
- Stable disease
- Progressive disease
- B Cohort B (+ CPI)
- C Cohort C *(+ enhanced host-conditioning)*

CHIRON
Best response to cNeT (n=20)



THETIS
Best response to cNeT (n=12)



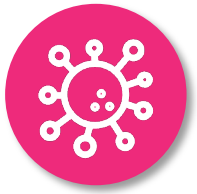
**Patients confirmed PD but unevaluable target lesions (n=4)*

Key mechanistic learnings for cNeT (and related therapies)

Safety

- Tolerability in line with standard TIL therapies with majority of adverse events related to the host conditioning
- No observed impact of cNeT dose on tolerability

Engraftment & persistence



- Optimized host conditioning key to enable T cell persistence; elevated product doses (>100 M) and cell phenotype cannot compensate for low intensity conditioning
- IL-2 and lymphodepletion are likely to independently contribute to T cell persistence; Achilles' data in 2H 2024 aim to evaluate parameters independently to inform optimal regime

Immune evasion

- Almost half of all NSCLC patients will have some level of HLA loss and ~16% will have lost at least three different HLA molecules[1]
- Achilles' approach is focused on targeting antigens for which there are retained HLA molecules which can be used to prioritize antigens for cNeT therapy
- In addition, immune evasion status can be used to select targets in neoantigen vaccines where antigen cargo is limited and screen patients in TCR-T approaches

[1]Achilles analysis of NSCLC patients (*n=421 tumour samples*)

Focus for CHIRON and THETIS data readouts in 2024

Clinical	**Meaningful clinical update in H2 2024 with cNeT monotherapy (NSCLC & melanoma) with enhanced host conditioning**
	Aiming to demonstrate improved cNeT persistence and clinical activity with optimized dose, functionality and host conditioning
Translational	**Leverage world-class translational science platform to link cNeT dose, persistence and immune evasion with clinical activity**
Process	**Optimized Process 2 delivering significant improvement with median cNeT dose of 611 M for last 10 products manufactured**
	Continue PELEUS™ and process development to optimize dose, immunogenicity ranking and tracking of immune evasion status