Sensitive quantification and tracking of the active components of a clonal neoantigen T cell (cNeT) therapy: From manufacture to peripheral circulation

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Background

Ex-vivo expanded tumour infiltrating lymphocytes (TIL) show promise in delivering durable responses among several solid tumour indications.

However, characterising, quantifying and tracking the active component of TIL therapy remains challenging as the expansion process does not distinguish between tumour reactive and bystander T-cells. Achilles Therapeutics has developed ATL001, a patient-specific TIL-based product, manufactured using the VELOS™ process (Figure 1) that specifically targets clonal neoantigens present in all tumour cells within a patient.

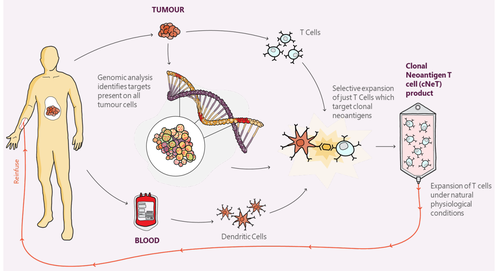
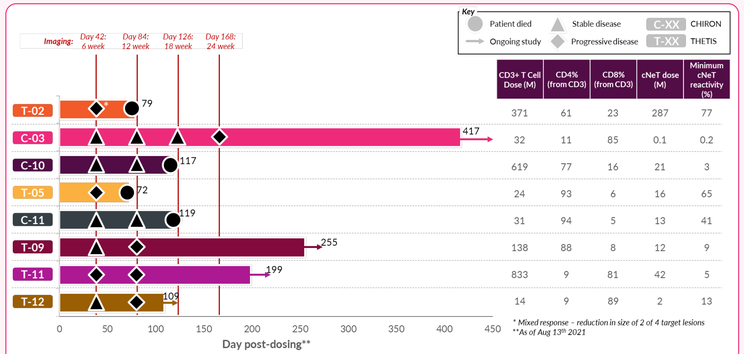


Figure 1. VELOS™ Process

Two Phase I/IIa clinical trials of ATL001 are ongoing in patients with advanced Non-Small Cell Lung Cancer, CHIRON (NCT04032847), and metastatic or recurrent melanoma, THETIS (NCT03997474).

Extensive product characterisation and immune-monitoring are performed through Achilles' manufacturing and translational science programme. This enables precise quantification and characterisation of the active component of this therapy – clonal neoantigen-reactive T cells (cNeT) during manufacture and following patient administration, offering unique insight into the mechanism of action of ATL001 and aiding the development of next generation processes.

Results



	CD3+ T Cell Dose (M)	CD4% (from CD3)	CD8% (from CD3)	cNeT dose (M)	Minimum cNeT reactivity (%)
T-02	371	61	23	287	77
C-03	32	11	85	0.1	0.2
C-10	619	77	16	21	3
T-05	24	93	6	16	65
C-11	31	94	5	13	41
T-09	138	88	8	12	9
T-11	833	9	81	42	5
T-12	14	9	89	2	13

Figure 2. Dosed patients outcomes (based on RECIST v1.1) following ATL001 and characteristics

Immuno-monitoring shows heterogenous response to Short- and Long master peptide pools (SMP, LMP) at Re-Screening (RS) and subsequent to dosing (D0)

T-02
- Large detectable reactivity at RS for SMP
- Steroids at D11 may have dampened down reactivity D14 onwards
- W6 SMP increase

T-05
- Increased reactivity after infusion peaks at D10 (cNeT/ml), declines to baseline levels at W6
- No data D14 and D21 due to remote visits
- Cells expanding *in vivo*

C-11
- Reactivity of LMP at baseline
- Reactivity for LMP increases post dosing and peaks D7
- SMP Reactivity at D28

T-11
- Clear SMP reactivity pre-dosing, some reactivity observed D14 to W6 post-dosing
- Low LMP reactivity pre-dosing but increasing reactivity from D14 to W6 post-dosing

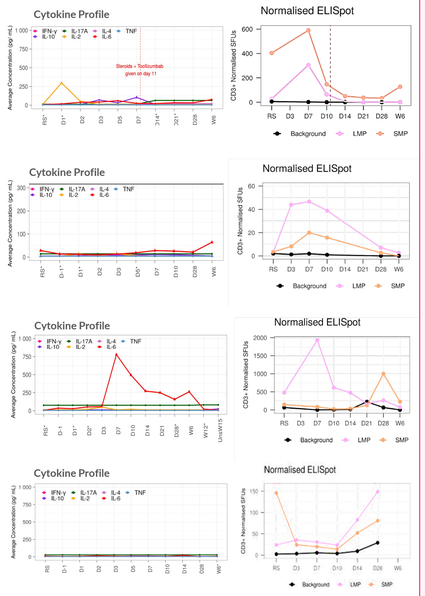


Figure 3. Normalised ELISpot results for dosed patients from baseline to 6 weeks post-dose

8 patients dosed to date

- 5 patients with melanoma (THETIS) and 3 patients with NSCLC (CHIRON) have received their ATL001 product
- The median age was 57 (range 30 – 71) and 6/8 patients were male
- The median number of previous lines of systemic anti-cancer treatment at ATL001 dosing was 2.5 (range 1 – 5)
- Median cNeT dose infused in this initial cohort was 14.2M (within a trial defined target range of 10-1000M)
- Unique single peptide reactivities were observed in 7 of 8 products (range 0 – 28, mean 8.6)
- cNeT were detected in 5/8 patients post dosing
- Best disease response was stable disease, with no objective radiological responses (RECIST v1.1) demonstrated to date from low doses of ATL001 generated using VELOS™ Process 1
- 4 patients remain in safety follow-up

Safety and tolerability

- In total, 34 ≥Grade 3 Adverse Events (AE) were recorded across the 8 dosed patients in THETIS and CHIRON
- 3 Adverse Events of Special Interest (AESI); three events of Cytokine Release Syndrome (CRS)
  - Two Grade 2 CRS events and one Grade 1
  - Events resolved in 3-8 days
- 2 neurological Suspected Unexpected Serious Adverse Reactions (SUSAR) were observed in two of the dosed patients:
  - Immune effector cell-associated neurotoxicity syndrome (ICANS) possibly related to ATL001
  - Encephalopathy – deemed unlikely related to ATL001 following IDSMC review

VELOS™ generates polyfunctional cNeT cells

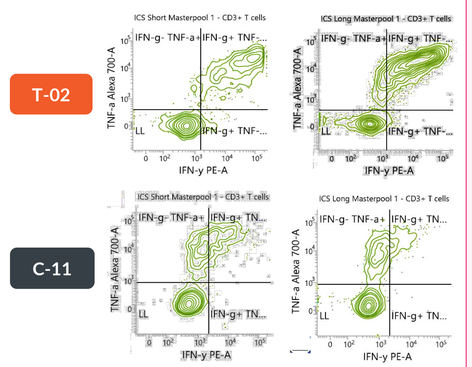


Figure 4. Gated CD3+-Overnight stimulation with neoantigen peptide pools

System Organ Class	Preferred Term	No. of AEs
Blood and lymphatic system disorders	Leukopenia	1
	Lymphopenia	2
	Neutropenia	4
	Anaemia	3
Gastrointestinal disorders	Diarrhoea	3
Infections and infestations	Cellulitis	1
	Infected seroma*	3
	Klebsiella sepsis	1
	Neutropenic sepsis	1
	Sepsis	1
	Urinary tract infection	1
Metabolism and nutrition disorders	Hypophosphataemia	2
Musculoskeletal and connective tissue disorders	Inguinal mass	1
	Musculoskeletal chest pain	1
Nervous system disorders	Neuralgia	1
	Neurotoxicity**	1
	Encephalopathy	1
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1
	Dyspnoea	2
	Hypoxia	1
	Pleural effusion	1
	Tachypnoea	1

Table 1. Adverse Events ≥Grade 3 (THETIS and CHIRON)
*The 3 events of infected seroma were all recorded within the same patient
**Neurotoxicity event attributed to Immune effector cell-associated neurotoxicity syndrome (ICANS)

Methods

ATL001 was manufactured using procured tumour and matched whole blood from 8 patients enrolled in the THETIS (n=5) and CHIRON (n=3) clinical trials.

Following administration of ATL001, peripheral blood samples were collected up to week 6.

- The active component of the product was detected via re-stimulation with clonal neoantigen peptide pools and evaluation of IFN-γ and/or TNF-α production.
- Deconvolution of individual reactivities was achieved via ELISPOT assays, normalised to T-cell component of PBMC.
- Immune reconstitution was evaluated by flow cytometry.
- cNeT expansion was evaluated by restimulation of isolated PBMCs with peptide pools and individual peptide reactivities (ELISPOT).

Future Directions

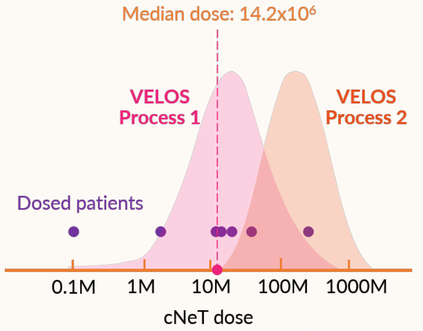


Figure 5. cNeT doses in dosed patients and projected dose range for VELOS™ Process 2

For more information of VELOS™ Process 2, please see SITC Poster Number: 193; presented by Joseph Robinson, PhD, Senior Scientist, Achilles Therapeutics

Conclusions

These data underscore our ability to sensitively detect, quantify and track the patient-specific cNeT component of ATL001 – during manufacture and post dosing. Our move to Process 2 allows dosing with higher cNeT numbers, up 1000M. As the dataset matures, these metrics of detection and expansion will be correlated with product, clinical and genomic characteristics to determine variables associated with peripheral cNeT dynamics and clinical response.