Early Proof of Concept of Safety and Clinical Activity of Clonal Neoantigen Reactive T Cells (cNeT)

Judith Cave[1], Alastair Greystoke[2], Ruth Plummer[2], James Spicer[3], Fiona Thistlewaite[4], Samra Turajlic[5], Andrew Craig[6], Katy Newton[6], Matilde Saggese[6], Sergio A. Quezada[6], Karl S. Peggs[6], Martin Forster[7]

[1]University Hospital Southampton NHS Foundation Trust, Southampton, UK, [2]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, [3] Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK [4]The Christie NHS Foundation Trust, Manchester, UK, [5]Royal Marsden NHS Foundation Trust, London, UK
[6]Achilles Therapeutics UK Ltd, London, UK, [7]University College London Hospitals NHS Foundation, London, UK

For further information on Achilles Therapeutics' clinical trials, please contact the VP Medical Director- Dr Matilde Saggese - at **M.Saggese@achillestx.com**

179P

Background

In NSCLC and melanoma, checkpoint inhibitors (CPI) are included in first line therapy. Most patients, however, exhibit partial or complete resistance with time. There is a significant unmet need in patients in the post-checkpoint setting. Tumour infiltrating T lymphocyte (TIL) therapies have activity in a variety of malignancies, although a lack of understanding of the active component limits product optimisation and impedes potency assay development. The requirement for high doses of lymphodepleting chemotherapy and IL-2 also limits application to fitter patients which is particularly restrictive in NSCLC.

We have initiated trials evaluating T cells reactive against clonal neoantigens (cNeT) in advanced, heavily pre-treated patients with NSCLC (CHIRON, NCT04032847) and melanoma (THETIS, NCT03997474). Clonal neoantigen mutations develop early in tumour ontology and are present in all tumour cells in contrast to subclonal mutations which occur later and are present in only subsets of tumour cells. ***Since neoantigens are not present on normal tissues, the chances of on-target off-tumour toxicities are limited.*** Our manufacturing process uses dendritic cell co-culture with low doses of IL-2 resulting in greater IL-2 responsiveness and allowing us to utilize lower dose lymphodepletion and IL-2, ***in order to limit associated toxicities and broaden applicability.*** The use of highly selective proprietary clonal neoantigen directed therapy therefore ***promises to address some of the current limitations with TIL therapies.***

Methods

CHIRON: All patients had advanced or metastatic Stage III-IV NSCLC and had received prior anti-PD(L)1 treatment.

THETIS: All patients had recurrent or metastatic malignant melanoma and had received prior anti-PD(L)1 treatment.

Inclusion criteria: Key inclusion criteria (non-exhaustive) across both studies include 1) >18 years old, 2) histologically confirmed diagnosis, 3) medically fit for procurement, 4) ECOG 0-1, 5) adequate organ function determined by full blood count, clotting, liver function tests, GFR, 6) accessible lesion 7) anticipated life expectancy >6 months.

Study-specific exclusions: In CHIRON, never smokers and patients with EGFR/ALK/Ros-1 mutations were excluded. In THETIS acral, uveal and mucosal melanomas were excluded.

Exclusion criteria across both studies: Key exclusions (non-exhaustive) include 1) known untreated/symptomatic/progressing CNS metastases, 2) Hep B/C, HIV, syphilis or HTLVI/II, 3) active autoimmune disease requiring immunosuppressants, 4) regular steroid treatment >10mg prednisolone/day, 5) history of immune-mediated CNS toxicity that was caused by immunotherapy, 6) concurrent cancer, 7) confirmed history of allergy to amphotericin b, penicillin or streptomycin

Pre-conditioning: Patients underwent low-dose lymphodepletion (fludarabine 30mg/m^2 iv & cyclophosphamide 300mg/m^2 iv) on days -6, -5 and -4 prior to infusion.

IL-2: Patients received 10 daily doses of IL-2 1M IU/m^2 subcutaneously.

No. of patients: 13 patients (7 in CHIRON, 6 in THETIS) were dosed at time of safety data cut-off (Sept 7th 2022). The 14th patient (CHIRON C-28) was dosed after this date and prior to submission of abstract and thus included in the efficacy dataset, but not safety.

Results

Fourteen patients dosed (including three on VELOS™ Process 2)

Median cNeT dosed administered across the 14 patients was 18M cNeT, with median clonal reactivity of 16% (18M/16% and 29M/33% in CHIRON & THETIS respectively). The median age was 56, nine were male and patients had a median of two prior lines of systemic anti-cancer therapy. Three patients in CHIRON were dosed on VELOS Process 2, these products had a median cNeT dose of 78M. Patients had a median of: LDH 281 µmol/L, two metastases, sum of target lesion diameter of 112mm and 10 months on CPI prior to dosing.

cNeT is well tolerated

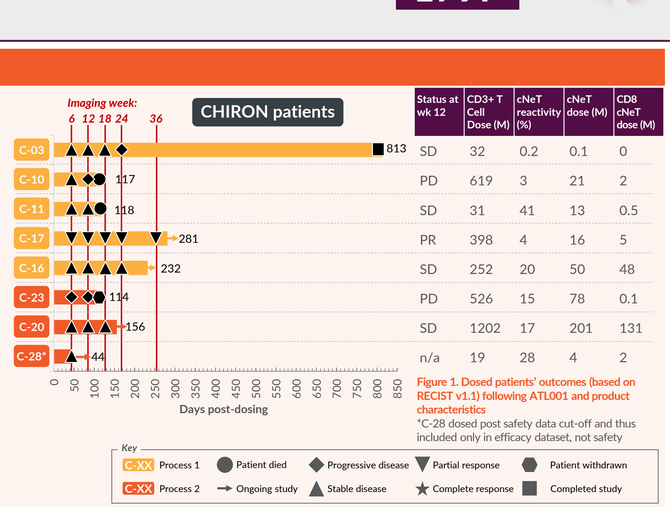
There were 25 treatment-emergent adverse events (AEs) with lymphopenia and neutropenia the most common (15 NSCLC, 10 melanoma respectively). There were four serious TEAEs. One cNeT related SAE (ICANS) and three episodes of cytokine release syndrome (G≤2) were reported (all responsive to standard management with steroids/tocilizumab). IL-2 was well tolerated. 10/13 patients received the full 10-day IL-2 course, with 124 of 130 doses delivered in total. To date seven patients have died on study, all related to disease progression (two NSCLC, five melanoma).

n=13: No of patients *(%)*				
	Related to:	TEAEs	Serious TEAEs	TEAEs with CTCAE ≥G3	TEAEs leading to death
# of pts	Any component of study treatment	11 *(83)*	3 *(23)*	8 *(62)*	0 *(0)*
# of events	Lympho-depletion	10 *(77)*	1 *(8)*	8 *(62)*	0 *(0)*
	ATL001	8 *(62)*	2 *(15)*	2 *(15)*	0 *(0)*
	IL-2	7 *(54)*	1 *(8)*	2 *(15)*	0 *(0)*

Table 1. Safety summary

Treatment emergent adverse events (TEAEs) defined as AE that started after ATL001 infusion and before earliest of date of infusion + 182 days or date of PD based on site assessment according to RECIST v1.1. Coded using the MedDRA Dictionary, version 24.1. Data cut-off 07/09/2022. Excludes patient C-28 who was dosed after safety data cut-off.

n=13: No of patients *(%)*	
Summary of TEAEs	# *(%)*
Gastrointestinal	11 *(85)*
Blood and lymphatic system	10 *(77)*
- *Neutropenia*	7 *(54)*
- *Febrile Neutropenia*	3 *(23)*
- *Anaemia*	2 *(15)*
Investigations	9 *(69)*
General & administration site conditions	8 *(62)*
Metabolism & nutrition	8 *(62)*
Nervous system	7 *(54)*
- *Encephalopathy*	1 *(8)*
- *ICANS*	1 *(8)*
Infections & infestations	5 *(39)*
Skin & subcutaneous tissue	5 *(39)*
Musculoskeletal & connective tissue	4 *(31)*
Psychiatric	4 *(31)*
Immune system	3 *(23)*
- CRS	3 *(23)*
Resp., thoracic & mediastinal	3 *(23)*



Status at wk 12	CD3+ T Cell Dose (M)	cNeT reactivity (%)	cNeT dose (M)	CD8 cNeT dose (M)
SD	32	0.2	0.1	0
PD	619	3	21	2
SD	31	41	13	0.5
PR	398	4	16	5
SD	252	20	50	48
PD	526	15	78	0.1
SD	1202	17	201	131
n/a	19	28	4	2

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

*C-28 dosed post safety data cut-off and thus included only in efficacy dataset, not safety

Efficacy: best responses of 1 x PR, 9 x SD and 4 x PD

CHIRON: In the NSCLC study we have observed best responses of one partial response (PR), six stable diseases (SD) and one progressive disease (PD). There was overall durable clinical benefit at 12 weeks in 5/7 evaluable patients (71%), and 4/7 at 18 weeks (57%). The partial responder showed total target lesion reduction of 56% at week 36 (Fig. 2). T cell engraftment and cytokine profiles are supportive of cNeT driving anti-tumour activity in the PR (Figures 3-5).

THETIS: Of six melanoma patients dosed best responses were three SD, three PD.

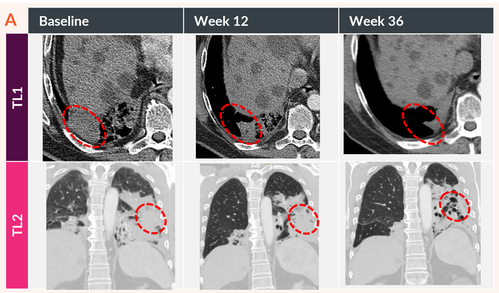


Figure 2. NSCLC Patient C-17: 56% total tumour reduction at week 36

Imaging shows initial response detected at 6 weeks deepening over time with persistent partial response at latest follow up (36 weeks post infusion)

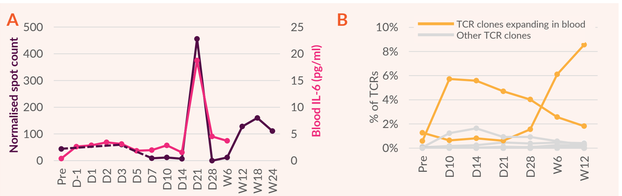


Figure 4. Early engraftment of cytokine-secreting cNeT coupled to durable expansion of infused clones in C-17

(A) ELISpot analysis using patient-specific clonal neoantigen peptides allows detection of cytokine-producing T cells in blood. The peak at day 21 is coincident with a peak in serum IL-6 levels. Together these point to high levels of cytokine secreting cNeT in blood. The overall levels of IL-6 and other cytokines were low, correlating with a lack of CRS and toxicity. (B) TCRseq allows tracking of infused cells irrespective of cytokine secretion, demonstrating both early and late expansion to high levels of different infused clones that had expanded during dendritic cell co-culture in response to clonal neoantigen stimulation.

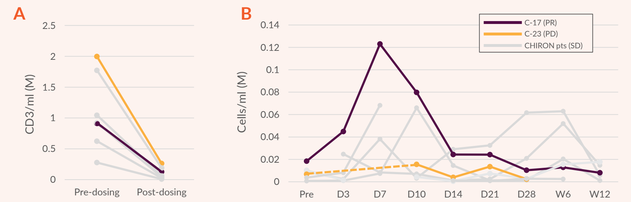


Figure 3. Effective lymphodepletion and high levels of proliferating CD8+ T cells in the patient with partial response

(A) Effective lymphodepletion was observed in all patients despite lower doses of lymphodepleting chemotherapy. (B) Phenotyping the cells in blood post-dosing shows expansion of a CD8+Ki67+ cell type in patient C-17 (purple line), whereas a patient with progressive disease (yellow line) has very few. A similar pattern was observed for CD8+ Granzyme B+ cells, not shown. These populations have previously been associated with clinical response to CPI[1] and therefore suggest anti-tumour reactivity.

Figure 5. Product characterisation at the single cell level demonstrates phenotypic features that may correlate with response:

(A) Cells from the product were stimulated with clonal neoantigen peptides. Expression of markers known to correlate with activation, trafficking and exhaustion can then be compared between patients, identifying specific features that correlate with clinical endpoints. (B) Using known T cell gene signatures, single cell RNAseq analysis of the C-17 product reveals clusters of cells that have features of various pathways including tissue migration and cytolytic function.

Conclusions

- Encouraging safety and tolerability has been demonstrated for cNeT, with potential for deep and durable clinical responses in solid tumours with low doses of cNeT and reduced dose lymphodepletion and IL-2.
- 77% of patients received the full course of IL-2, and 95% of doses were delivered in total
- Early proof of concept has been demonstrated in NSCLC with a disease control at 12+ weeks observed in 5 of 7 evaluable patients (71%), including one PR (36+weeks).
- For the patient with PR, T cell engraftment and cytokine profiles were supportive of cNeT driving anti-tumour activity. In-depth characterisation of the cNeT product suggests the active component is polyfunctional in nature.
- Due to the lower dose lymphodepletion and IL-2 (vs. other TIL therapies) there is potential for wider applicability of cNeT including in an ambulatory setting.
- These data support the expansion in enrollment of subjects in ongoing Phase 1/IIa studies.
- Ongoing use of proprietary translational platforms will allow further understanding of parameters associated with clinical response and inform development of the VELOS™ process as well as forming the foundation of a potency assay.

References
1. Machiraju et al, Oncoimmunology 2021

Disclosures
MF has received honoraria from Achilles for advisory services

Scan to view online