An Open-Label, Multi-Centre Phase I/IIa Study Evaluating the Safety and Clinical Activity of Clonal Neoantigen Reactive T cells in Patients with Advanced Non-Small Cell Lung Cancer (CHIRON)

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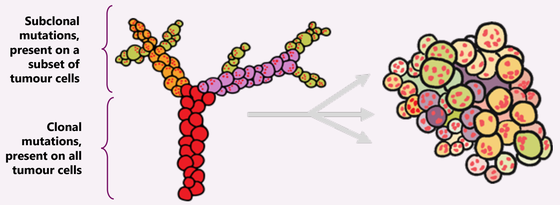
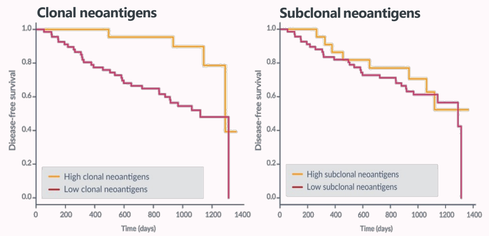
Background

Lung cancer is the most common cause of cancer-related death worldwide with over 1.6 million deaths per year. Non-small cell lung cancer (NSCLC) accounts for 80% of cases, the majority of which are adenocarcinomas. 75% of patients present with inoperable tumours and/or with distant metastatic spread, **with 5-year survival for stage IV disease as low as 5%**[1]. Treatment options include chemotherapy, targeted therapies for specific mutations, and - increasingly - immune checkpoint inhibitors (CPI). **Adoptive cell therapies (ACT) can produce durable responses in pre-treated NSCLC**. Evidence also suggests potential benefit of **combining ACT with CPIs, even after acquired resistance**[2]. Efforts to improve efficacy include the expansion of T cells able to recognise patient-specific clonal tumour neoantigens. **Clonal tumour neoantigens arise early in cancer evolution** and represent a subset of patient-specific mutations present in all cancer cells[3].



Developing ACTs that target clonal neoantigens represents a personalised approach to treating all cancer cells concurrently, minimising the risk of tumour escape and reducing potential for off-target toxicities. Insights gained from applying **a bioinformatic platform** that identifies clonal neoantigens **(developed using UK TRACERx study data)** to matched tumour and blood samples from NSCLC patients – as part of a tissue acquisition study (NCT03517917) – has **enabled the manufacture of a personalised clonal neoantigen T cell (cNeT) product**, which is now in clinical development (ATL001).

Rationale

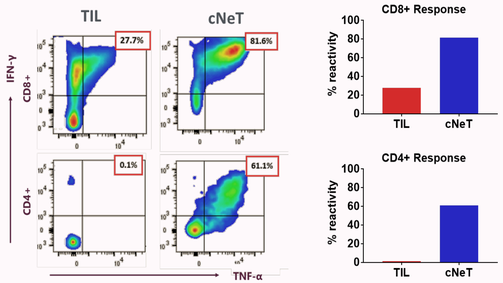


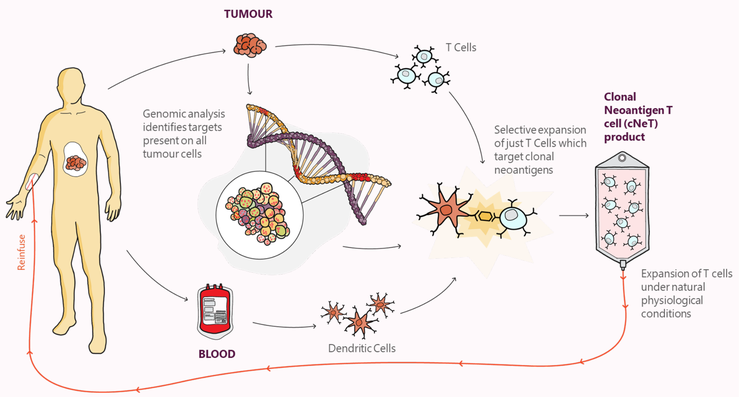
Clonality is the driver of disease free survival

- NSCLC patients with **high clonal neoantigen burden** have an **improved disease free survival**[4]
- This is not seen in patients with high sub-clonal neoantigen burden

Checkpoint inhibitor response is correlated with clonality

- **Sensitivity to PD-1** and CTLA-4 blockade is enhanced in tumours **enriched for clonal neoantigens**





Manufacturing

- Product contains **both cytotoxic (CD8+) and helper T cells (CD4+)** which can directly target tumour cells[5-7] and are critical for durable responses[8-9]

Superior Potency

- In response to clonal neoantigens, cNeT secrete significantly **higher amounts (>5X) of effector cytokines** compared to TIL[10]
- Compared to TIL, cNeT have a **less exhausted phenotype** which should enable **greater in vivo proliferation and improved anti-tumour activity**[11-12]

A patient specific product

- The cNeT product contains **multiple** clonally reactive T cell populations that are **unique** to each patient and reduce the risk of relapse through tumour escape

Key Study Objectives

Primary: To assess the **safety and tolerability** of ATL001 as a monotherapy and in combination with pembrolizumab

Secondary: To evaluate the **clinical efficacy of ATL001** treatment as a monotherapy and in combination with pembrolizumab

Exploratory:

- To evaluate the **persistence, phenotype and functionality of cNeT** and to explore possible relationships with clinical outcomes
- To evaluate **potential biomarkers of clinical activity** and factors affecting response
- To evaluate the **manufacturing rate** and factors that may affect the quality of ATL001
- To evaluate the **utility of a bespoke plasma ctDNA assay**

Entry Criteria

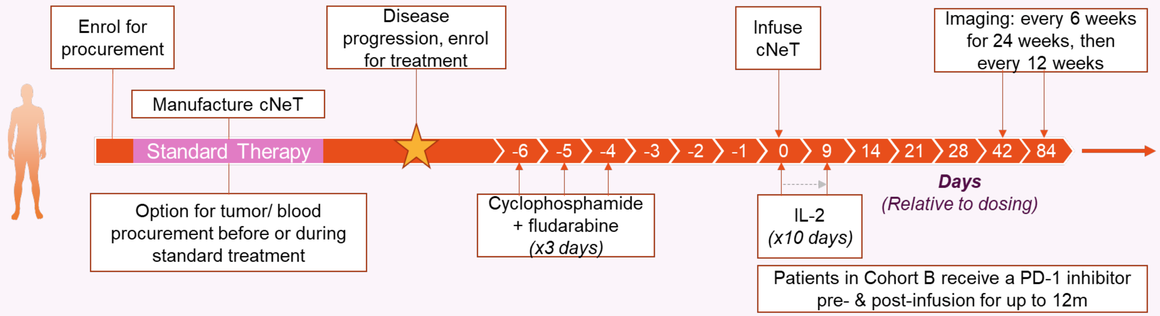
Key inclusion criteria include:

- Treatment with at **least one prior systemic therapy** (inclusive of a checkpoint inhibitor)
- Eastern Cooperative Oncology Group **(ECOG) Status 0-1**
- Patients with advanced stage (IIIB/IV) disease who have **accessible sites of disease** suitable for collection of adequate tissue for ATL001 manufacture

Key exclusion criteria include:

- Patients requiring **regular treatment with steroids** at a dose higher than prednisolone 10 mg/day (or equivalent)
- Patients who have **previously received any investigational cell or gene therapies**

Study Design



The CHIRON Study (NCT04032847), is a first-in-human, open-label multi-centre phase I/IIa study to characterise the safety and clinical activity of ATL001 administered intravenously in up to 40 adults with advanced unresectable or metastatic NSCLC

- Following consent and screening, patients enter the study for **procurement of tumour tissue and blood** to manufacture ATL001
- Tissue may be **procured during treatment with standard systemic therapies**
- Patients in **Cohort A** receive cyclophosphamide/fludarabine on days -6 to -4, followed by a **single dose of ATL001** and **10 daily doses of subcutaneous IL-2**
- Patients in **Cohort B** will additionally receive one dose of **pembrolizumab** before receiving ATL001, then restart pembrolizumab 2 weeks after receiving ATL001 and **continue for up to 12 months**

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