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CAR T cells for T cell cancers

Submission date
24/04/2025

Recruitment status
Recruiting

Registration date
16/07/2025

Overall study status
Ongoing

Last Edited
16/07/2025

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
T-cell Acute Lymphoblastic Leukaemia (T-ALL) and T-cell Lymphoblastic Lymphoma (T-LBL) are aggressive cancers that are hard to cure. Often, the cancer does not respond to treatment or comes back afterwards. For these patients, treatment options are limited and usually involve intensive chemotherapy followed by a stem cell transplant. However, chemotherapy often fails, and many patients are too unwell for a transplant. Even when possible, transplants carry serious risks and long-term side effects. There is an urgent need for safer, more effective therapies.
This study is testing a new product called CAR-T cells (short for Chimeric Antigen Receptor T cells) in patients with T-ALL or T-LBL whose disease has not responded to treatment or has returned after initial success. T cells are part of the immune system and help fight infections. In CAR-T therapy, we take a patient's own T cells and modify them in the lab so they can recognise and kill cancer cells. These reprogrammed cells are called CAR-T cells. CAR-T cells have already shown success in another type of leukaemia called B-ALL, leading to long-term remissions in many patients. There is growing evidence that CAR-T therapy may also work in T-ALL and T-LBL. In this study, we are developing a new type of CAR-T cell that targets a marker called CCR9, found on most cancerous T cells. We will collect T cells from each patient's blood, modify them to recognise CCR9, and then give them back to the patient. The main goals of the study are to find out if these new CAR T cells are safe and to determine the best dose. We plan to give the cells to 12 children (under 18) and 12 adults.

Who can participate?
Patients with relapsed or refractory T-ALL/T-LBL following at least one or two standard prior lines of combination cytotoxic therapy

What does the study involve?
Patients will receive a short course of chemotherapy before getting the CAR-T cells, which are given through a drip. They will stay in hospital for at least 2 weeks and be closely monitored. After leaving hospital, they will return for regular check-ups for two years, including blood tests, scans, and sometimes bone marrow tests.

What are the possible benefits and risks of participating?
Leukapheresis is required to collect the patient's T cells from the blood for the manufacture of CAR-T cells. The T cells are collected using a central line or a small plastic tube inserted into a large vein. Depending on the participant's age and health condition, they may have a general

anaesthetic or a local anaesthetic applied to the skin before the line insertion. Pain, bruising and a small amount of bleeding can occur around the insertion site. Pain medication and application of a pressure dressing will be used if needed. The small risk of fainting will be prevented by having the patient sit or lie down during the procedure. Muscle cramps can be prevented by taking calcium supplements if needed.
The chemotherapy proposed is based on the regimen used in the commercially available anti-CD19 CAR for B-ALL, tisagenlecleucel. This has also been the most-used regimen in studies of anti-CD7 CAR-T in T-ALL. Fludarabine is generally well tolerated: the most common side effects are lymphopenia and infection. Neurotoxicity can occur but this is generally only observed in higher doses. Cyclophosphamide can cause bleeding from the bladder. Cardiotoxicity can occur but is extremely rare at the proposed dose. Cyclophosphamide may cause transient nausea and cytopenias. Participants will be monitored, and appropriate supportive care will be instituted as necessary. Participants will be given anti-emetic prophylaxis, transfusion support and antibiotics as required as per standard institutional policy.
Cytokine release syndrome (CRS) occurs to some extent in most CAR-T cell therapies. In studies of CD7 targeting CAR T cells, the most widely studied antigen in T-ALL, 60-90% of patients treated developed CRS of any grade, but severe CRS only occurred in 10-18% of all patients and appeared to relate to disease burden. CRS is characterised by culture-negative fever and/or hypotension, hypoxia, and neurological disturbance and appears to be mediated by hypersecretion of pro-inflammatory cytokines, particularly IL-6 and IFN-γ. Severe CRS often requires high-dependency supportive care and is usually self-limiting but may be fatal. Diagnostic criteria for severe CRS have now been established, and treatment with the IL-6 receptor-blocking antibody tocilizumab appears to be highly effective. A number of other agents are clinically available to investigators for the management of CRS that is unresponsive to tocilizumab. Patients enrolled will need to be of relatively good health and thus likely to be able to withstand the potential toxicity of CAR-T cell therapy. Patients will be monitored for a period of 28 days after CARCCR9 T cell infusion with daily clinical review and blood tests, including C-reactive protein (CRP). In the event of a cytokine-driven serious adverse event (SAE) occurring, the trial site has facilities for resuscitation and intensive care. Patients developing CRS will receive supportive care including intravenous fluids, intravenous antibiotics (pending cultures), supplementary oxygen and if needed, ventilatory/inotropic support in the intensive care unit.
Neurotoxicity, termed Immune effector cell associated neurotoxicity syndrome (ICANS), is well described in patients treated with other CAR T cell therapies and is of variable severity. Severe ICANS has an approximate incidence of 1-21% in CD19-targeting CAR-T cell therapy. In T-ALL, rates of ICANS in CD7 CAR-T trials have been low (1-15%) and of low grade. Most neurotoxicity is mild and transient and resolves spontaneously, but more severe cases can present with aphasia, obtundation, delirium and seizures and may require supportive treatment with anticonvulsants, corticosteroids, and in some cases, sedation and ventilation. In rare cases fatalities have been reported. On FRACTALL, participants developing neurotoxicity will receive clinical investigations and supportive care as per standard institutional policy and all participants with neurotoxicity should be discussed with the CI and TMG. Decisions regarding corticosteroids or other immunosuppressive therapy should be discussed with the CI/TMG.
Lymphodepletion may cause a drop in blood cell count and recovery may be delayed by the CAR T cells. Participants will have blood counts monitored and will be given blood product transfusions and supportive medication if needed.
The low blood cell count may increase the chance of participants getting an infection. As a precaution, participants will be given antibiotics and antivirals. Participants will be monitored for signs of infection and given appropriate medication if needed.
Participants will be admitted to hospital or ambulatory care while having pre-conditioning lymphodepletion and for a minimum of 2 weeks following CARCCR9 T cell infusion. Afterwards, participants will have regular follow-up visits in clinic for 2 years. These visits are comparable to those following alternative therapies such as stem cell transplants.

Where is the study run from?
Cancer Research UK & University College London Cancer Trials Centre (UK)

When is the study starting and how long is it expected to run for?
April 2025 to December 2035

Who is funding the study?
1. Medical Research Council (UK)
2. Great Ormond Street Hospital Children's Charity (UK)

Who is the main contact?
FRACTALL Trial Manager, ctc.fractall@ucl.ac.uk

Plain English summary under review with external organisation

Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-003497-23

Integrated Research Application System (IRAS)
1007887

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
UCL/150854

Study information

Scientific Title
Fratricide-resistant autologous chimeric antigen receptor T cells targeting CCR9 for the treatment of T cell acute lymphoblastic leukaemia/ lymphoma

Acronym
FRACTALL

Study objectives
Primary objectives:
1. To determine the feasibility of semi-automated autologous CARCCR9 T cells manufacture in patients with r/r T-ALL/T-LBL, in the setting of a Phase I trial.
2. To determine the safety of autologous CARCCR9 T cells and to identify the recommended Phase II dose (R2PD) in these patients, we will determine the incidence/severity of general CAR T cell immune toxicity and determine if CCR9 CAR T cell targeting is associated with any specific toxicity.

Secondary objectives:
1. To determine the expansion and persistence of CARCCR9 T cells by PCR and flow cytometry.
2. To understand the potential efficacy of CARCCR9 T cells, including molecular response and durability of response over 12 months.

Ethics approval required
Ethics approval required

Ethics approval(s)
notYetSubmitted, London – West London & GTAC (United Kingdom), ref: 25/LO/0356

Study design
Non-randomized study

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Relapsed or refractory T-cell malignancies (T-ALL or T-LBL)

Interventions
Both cohorts (adult (≥18 years old) and paediatric:
1. Leukapheresis: following registration, patients will undergo an unstimulated leukapheresis which will be used for the manufacture of the CARCCR9 T cells
2. Lymphodepletion: patients will receive fludarabine 30 mg/m2 (on days -6 to -3) and cyclophosphamide 500 mg/m2 (on days -6 to -5)
3. CARCCR9 T cells: Intravenous infusion on Day 0 at a dose assigned according to the Continuous Reassessment Method design. The following dose levels will be tested:
Dose level 1: 0.5 x 10^6 CARCCR9 T cells/kg
Dose level 2: 1.0 x 10^6 CARCCR9 T cells/kg
Dose level 3: 2.0 x 10^6 CARCCR9 T cells/kg
4. Follow-up – patients remain in hospital for at least 2 weeks post-infusion and then are actively followed up for 2 years. Following this, patients are followed up annually until 15 years post-infusion.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
Autologous CARCCR9 T cells

Primary outcome(s)
1. Feasibility of generation of CARCCR9 T cells as evaluated by the number of therapeutic products generated.
2. Toxicity following CARCCR9 T cell administration as evaluated by the incidence of grade 3-5 toxicity causally related to the ATIMP occurring within 28 days of CAR T cell infusion.

Key secondary outcome(s))
Measured up to 2 years (unless noted otherwise):
1. Proportion of responders and depth of response over 12 months post-ATIMP infusion
2. Persistence and frequency of circulating CARCCR9 T cells in peripheral blood as assessed by flow cytometry and qPCR

3. Time to Disease Progression
4. Event-free survival at 1 and 2 years after immunotherapy with CARCCR9 T cells
5. Overall survival at 1 and 2 years after immunotherapy with CARCCR9 T cells
6. Quality of life of participants post CARCCR9 T cells assessed by the EORTC QLQ-C30 questionnaire

Exploratory endpoints - measured up to 2 years (unless noted otherwise):
1. Expansion and persistence of CARCCR9 T cells in bone marrow (BM) +/- cerebrospinal fluid (CSF), as assessed by immunophenotyping and qPCR
2. Cytokine response analysis up to day 28 post CARCCR9 T cells infusion
3. Analysis of peripheral blood T and NK cell number and function in patients up to 2 years post CARCCR9 T cells infusion

Completion date
31/12/2035

Eligibility

Key inclusion criteria
1. Relapsed or refractory T-ALL/T-LBL following at least:
1.1. Patients ≥18 years old: one standard prior line of combination cytotoxic therapy
1.2. Patients <18 years old: two standard prior lines of combination cytotoxic therapy
2. All disease types: CCR9-positive disease as assessed by flow cytometry
3. T-LBL patients only: Patients must have measurable disease which is CCR9-positive by standard flow cytometry tests (on tissue biopsy, blood, bone marrow, or malignant effusion)
4. Agreement to have a pregnancy test, use adequate contraception (if applicable)
5. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Sex
All

Key exclusion criteria
1. ECOG performance score >2 (patients aged ≥10 years old) OR Lanksy score ≤50% (patients aged <10 years old) (see Appendix 2)
2. Stem Cell Transplant patients only: active significant acute GvHD (overall Grade ≥ II, modified Glucksberg criteria) or moderate/severe chronic GvHD (NIH consensus criteria) requiring immunosuppressive therapy and/or systemic steroids (see Appendix 5)
3. Active CNS involvement of disease
4. Active hepatitis B, C or HIV infection
5. Oxygen saturation ≤90% on air
6. Bilirubin >3 x upper limit of normal
7. GFR <30 ml/min

8. Cardiac dysfunction as defined by:
8.1. Patients ≥18 years old: cardiac dysrhythmias (excluding well-controlled atrial fibrillation or other supraventricular tachycardia) or significant cardiac disease and left ventricular ejection fraction <40%
8.2. Patients <18 years old: Left ventricle shortening fraction <28% on echocardiogram
9. Patients receiving corticosteroids at a supraphysiological dose that cannot be discontinued
10. Known allergy to albumin, DMSO, PBS/EDTA (or any component of the ATIMP)
11. Any contraindications to lymphodepletion or to the use of cyclophosphamide or fludarabine as per local SmPC
12. Women who are pregnant or breastfeeding
13. Life expectancy <3 months
14. Fulminant or rapidly progressive disease

Date of first enrolment
31/07/2025

Date of final enrolment
30/09/2027

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Great Ormond Street Hospital Charity

Alternative Name(s)
Great Ormond Street Hospital Children's Charity, GOSH Charity, greatormondSt, GOSH

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes