ISRCTN49320109 https://doi.org/10.1186/ISRCTN49320109

A CAR T trial for amyloid light chain amyloidosis (AL Amyloid)

Submission date
13/02/2025

Recruitment status
Recruiting

Registration date
06/05/2025

Overall study status
Ongoing

Last Edited
01/07/2025

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?
'Amyloidosis' is a term used for a group of conditions where an abnormal protein, called amyloid, accumulates in the tissues. Tissues affected can include kidneys, heart, liver, nerves or digestive system, and two or more organs can be affected at the same time.
Light chain amyloidosis (AL amyloid) is a subtype of amyloidosis that happens when plasma cells in the bone marrow change. Normally the plasma cells make proteins, called antibodies that fight infections. Abnormal plasma cells make extra pieces of antibodies called 'light chain' that circulate in the blood and can deposit in organs, as amyloid protein fibrils, throughout the body causing damage.
Treatment of AL amyloidosis may include chemotherapy (to kill the abnormal cells), proteasome inhibitors (a type of chemotherapy to stop the abnormal proteins in the cell from breaking down and thus killing the cell), immunomodulatory drugs (to help the immune system work better) and antibodies (that target specific proteins (like CD38) to reduce the production of abnormal proteins). Some patients may also have an autologous stem cell transplant.
However, there are patients whose disease returns (called relapse) or does not respond to treatment (called refractory disease). For these patients, further treatment is required.
New treatments (called immunotherapy) have been developed in recent years. They aim to improve the body own immune system to fight cancer. One type is Chimeric Antigen Receptor (CAR) T cell immunotherapy. It uses 'T cells' (a type of white blood cell that are part of the immune system that fight infections and protects you from disease
We have developed 2 types of CAR T cells that we expect to recognise specific targets present on the plasma cells that make the abnormal light chain protein in AL amyloid. The 1st type of the CAR T cells targets a protein called BCMA (we call them D8 CAR T cells). The 2nd type of the CAR T cells targets BCMA and a different protein, called CD19 (we call these D8/CAT CAR T cells).
We will make these CAR T cells by taking some of the participant's T cells and modifying them in a laboratory. We will reprogramme the T cells by inserting new gene(s) into them which enables the T cells to recognise BCMA or both BCMA and CD19 so they can target the cancer cells when given back to participants.

Who can participate?
Patients over the age of 18 who have been diagnosed with AL Amyloid and have received at least 1 line of treatment.

What does the study involve?
T cells are collected from the patient's blood to make the CAR T cells (a process known as leucapheresis). The CAR gene is put into the T cells so they find and attack the AL Amyloid. Patients have 2 chemotherapy drugs to make space for the CAR T cells (known as lymphodepletion). The CAR T cells are then given into a vein. Patients are monitored in the hospital for at least 2 weeks.

What are the possible benefits and risks of participating
It is hoped that the CAR T cells may be able to control the trial participants's AL Amyloid, however, there may be no benefit as the CAR T cells may not work as desired.

Leukapheresis is required to collect participants' T cells (a type of white blood cells) from the blood for the manufacture of CAR T cells. The T cells are collected using a catheter inserted into a large vein. 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 participant sit or lie down during the procedure. Anti-coagulants used during the cell collection procedure can reduce the calcium levels in the blood. This can cause tingling/numbness or muscle cramps. This will be prevented by giving calcium supplements if needed.

Fludarabine and cyclophosphamide are used as a standard regimen for preparation for CAR T cell administration referred to as lymphodepletion. Common side effects of fludarabine are lymphopenia and infection. Neurotoxicity is generally only observed in higher doses.

Cyclophosphamide can cause irritation and bleeding from the bladder. To minimize this risk, it is administered with excess fluids and mesna. Cyclophosphamide may cause transient nausea and cytopenias. Participants will have anti-emetic prophylaxis and transfusion support as needed.

Cytokine release syndrome (CRS) is characterised by fever, hypotension, and in severe cases hypoxia and/or other organ dysfunction (liver, renal, cardiac). Severe CRS requires high-dependency supportive care and is usually self-limiting but may be fatal. Treatment with Tocilizumab is highly effective. Other agents are available for the management of CRS that is unresponsive to Tocilizumab.

Participants will be monitored for at least 14 days post CAR T cell infusion with daily review /regular blood tests. Participants developing CRS will receive supportive care including intravenous fluids, supplementary oxygen and if needed ventilatory/inotropic support in the intensive care unit.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a type of neurotoxicity which - like CRS - can occur in participants after receiving CAR T cells. It is of variable severity, mild and reversible in most cases. Severe cases present with aphasia, obtundation, delirium and seizures. In rare cases, fatalities have been reported. Participants will receive supportive treatment with anticonvulsants, corticosteroids, and if required intensive care including sedation and ventilation.

Participants will have daily assessments including neurological examination for at least 14 days post CAR T cell administration, with increased frequency as clinically indicated.

Where is the study run from?
The sponsor of the trial is University College London and is being run by Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) (UK)

When is the study starting and how long is it expected to run for?
February 2025 to January 2034

Who is funding the study?
Autolus (a UK biopharmaceutical company developing T cell therapies for cancer)

Who is the main contact?
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Type(s)
Public, Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1010908

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
UCL/173497, CPMS 65942

Study information

Scientific Title
BCMA/CD19 targeting CAR T cell for AL Amyloid: Phase 1 trial assessing the treatment of AL Amyloid (relapsed/refractory to previous therapy) with CAR T cells

Acronym
ALARIC

Study objectives
Primary objective:
To determine the safety and tolerability of a novel BCMA CAR (D8) alone and of CAR T cells engineered to co-express BCMA CAR and a CD19 CAR (CAT) in patients with relapsed/refractory AL Amyloid.

Secondary objective:
To evaluate efficacy of a novel BCMA CAR (D8) alone and of CAR T cells engineered to co-express BCMA CAR and a CD19 CAR (CAT) in patients with relapsed/refractory AL Amyloid.

Ethics approval required
Ethics approval required

Ethics approval(s)
notYetSubmitted, London - West London GTAC, ref: 25/LO/0139

Study design
Interventional non randomized

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
AL Amyloid

Interventions
There are 2 cohorts in this trial:
Cohort 1 – D8 CAR T cells (CAR T cells targeting BCMA).
Cohort 2 – D8/ CAT CAR T cells (CAR T cells targeting both BCMA and CD19)

Both cohorts have 2 dose levels: 50 x 10^6 and 150 x 10^6

When the trial opens, patients will be recruited into the lower dose of cohort 1 (D8 CAR T cells, dose level 50 x 10^6). If the dose level is found to be safe by TMG review of safety data, recruitment will begin to the higher dose of cohort 1 (D8 CAR T cells, dose 150 x 10^6) and

cohort 2 lower dose (D8/CAT CAR T cells, dose level 50 x 10^6) in parallel. Allocations to the cohort will alternate beginning with the D8 higher dose. Recruitment to the higher dose of cohort 2 (D8/CAT CAR T cells, dose level 150 x 10^6) can only begin once the lower dose has been found to be safe by TMG review of safety data.

All trial patients will undergo the following procedures:
Leucapheresis – following registration patients will undergo unstimulated leucapheresis which will be sent to the 'centre for cell, gene and tissue' (CCGTT) at the Royal Free Hospital for manufacture of the CAR T cells
Lymphodepletion – before cell infusion patients will receive fludarabine and cyclophosphamide (between days -5 and -3)
Infusion: on day 0 patients will receive an intravenous infusion of CAR T cells from allocated cohort and dose level.
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
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
D8 CAR T Cells [autologous T cells transduced with the lentiviral pCCL.EGF1α..D8Fab-41BBz vector], D8/CAT CAR T cells [autologous patient-derived T cells dually transduced with the lentiviral pCCL.EGF1α..D8Fab-41BBz and pCCL.PGK.CD19CAT-41BBz vectors]

Primary outcome(s)
Safety: toxicity of D8 or D8/CAT CAR T cells as assessed by the incidence of grade 3-5 toxicity causally related to the ATIMP (particularly severe cytokine release syndrome, neurotoxicity) occurring within 28 days of CAR T cell infusion

Key secondary outcome(s))
Up to 2 years (unless noted otherwise):
1. Best objective response rate (as defined by ISA criteria)
2. Overall rate of CR, CR rate at 1 month and 3 months
3. Time to first and best sFLC response
4. Time to sFLC-CR
5. Overall rate of MRD-negative(10-5) response
6. Rate of CR with MRD-negativity at 12 ± 3 months
7. Duration of response in patients achieving ≥PR
8. PFS
9. OS
10. Time to new treatment or death
11. EFS (new treatment, progression or death as events)
12. Organ response at 6 and 12 months
13. Incidence and severity of adverse events
14. Occurrence of neurotoxicity, early and late, considered related to CAR T cells
15. Incidence & duration of hypogammaglobulinaemia (all cohorts) and B-cell aplasia (cohort 2)

Completion date
31/01/2034

Eligibility

Key inclusion criteria
1. Age ≥ 18 years old
2. Histopathological diagnosis of amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens AND confirmation of AL derived amyloid deposits by at least one of the following:
2.1. Immunohistochemistry or
2.2. Mass spectrometry or
2.3. Characteristic electron microscopy appearance or
2.4. Hereditary amyloidosis ruled out by appropriate genetic screening
3. ECOG performance status 0-2
4. Measurable disease defined by at least one of the following:
4.1. Serum free light chain ≥50 mg/L and an abnormal K:L ratio
4.2. The difference between involved and uninvolved free light chains (dFLC) ≥50mg/L
4.3. The difference between involved and uninvolved serum free light chain is 20-50mg/L (termed low-dFLC), only if the patients had at diagnosis either iFLC of >50mg/L with abnormal ratio of dFLC>50mg/L
4.4. Serum monoclonal protein ≥5g/L
5. Patient must have adequate organ function, defined as follows:
5.1. Neutrophils >1x10^9/L
5.2. Haemoglobin >80mg/L
5.3. Platelets >50 x10^9/L
5.4. Lymphocytes >0.3 x10^9/L
5.5. eGFR >30ml/min
5.6. NT-proBNP <5000g/L
5.7. Systolic BP >100mmHg
6. At least 1 previous line of therapy and relapsed or <CR to last line
7. Patients must weigh >30 kg
8. Women of childbearing potential must have a negative pregnancy test and agree to comply with the pregnancy reporting requirements of the protocol (if applicable)
9. Provide written informed consent and be willing and able to comply with all study procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

1. Have any other form of amyloidosis other than AL amyloidosis
2. Have POEMS syndrome
3. Have systolic blood pressure < 100 mmHg or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of > 30 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
4. Receiving haemodialysis
5. Have had myocardial infarction, uncontrolled angina within 6 months prior to screening or percutaneous cardiac intervention with recent stent or coronary artery bypass grafting within 4 months prior to screening
6. LVEF is < 40% by echocardiogram at Screening
7. Have severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area < 1.0 cm^2) or severe congenital heart disease
8. Have history of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker/implantable cardioverter-defibrillator (ICD) is indicated but not placed. (Participants who do have a pacemaker or ICD are allowed in the study.). The following are acceptable:
8.1. First degree AV-block
8.2. Second degree AV-block Type 1 (Mobitz Type 1/Wenckebach type)
8.3. Right or left bundle branch block
8.4. Atrial fibrillation with a controlled ventricular rate. (An uncontrolled ventricular rate [i.e., > 110 beats per minute] determined by an average of three beats in lead II or representative beats in lead II is not allowed)
9. Corrected QT interval (QTc) > 500 ms on the screening electrocardiogram (ECG) in absence of bundle branch block or paced rhythm
10. Current unstable liver or biliary disease defined by the presence of ascites requiring paracentesis, encephalopathy, coagulopathy, or cirrhosis. Note: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement due to AL amyloidosis is acceptable if otherwise meets entry criteria
11. Prior treatment with investigational or approved gene therapy or cell therapy products
12. Oxygen saturation ≤ 90% on air
13. Patients with any major surgical intervention in the last 3 months (cement augmentation for vertebral collapse is permitted)
14. Patients with active gastrointestinal bleeding
15. Patients with active infectious bacterial or viral disease (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human T-lymphotropic virus or syphilis) requiring treatment
16. Known active central nervous system involvement of AL amyloid or multiple myeloma. History or presence of clinically relevant central nervous system pathology such as epilepsy*, paresis, aphasia, stroke within 3 months prior to enrolment, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, uncontrolled mental illness, or psychosis (*patients with well-controlled epilepsy with no seizures within the last 12 months, confirmed by treating neurologist will not be excluded)
17. Active autoimmune disease requiring immunosuppression
18. Patients receiving corticosteroids at a dose of > 5 mg prednisolone per day (or equivalent) that cannot be discontinued
19. Past or current history of other neoplasms (including lymphoma), except for:
19.1. Curatively treated non-melanoma skin cancer
19.2. Adequately treated in situ carcinoma of the cervix
19.3. Low-risk prostate cancer with Gleason score < 7 and prostate-specific antigen < 10 mg/mL
19.4. Other cancer curatively treated and with no evidence of disease for at least 2 years or malignancy that in the opinion of the Investigator, with concurrence with the TMG and UCL CTC,

is considered cured with minimal risk of recurrence
20. Received any radiotherapy within the last 7 days prior to lymphodepletion or leukapheresis. Localised radiation to a single site, e.g., for bone pain is permitted at any time
21. Patients that received any plasma cell directed therapy within the last 7 days prior to lymphodepletion or leukapheresis
22. Inability to tolerate leucapheresis
23. Life expectancy < 3 months
24. Women who are pregnant or breastfeeding
25. Known allergy to albumin or DMSO

Date of first enrolment
31/05/2025

Date of final enrolment
30/05/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospitals NHS Foundation Trust
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Study participating centre
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Sponsor information

Organisation
University College London Cancer Trials Centre

Funder(s)

Funder type
Industry

Funder Name
Autolus

Results and Publications

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

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