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CAR-T cells for children, teenagers and young adults with sarcoma

Submission date
09/10/2024

Recruitment status
Recruiting

Registration date
16/12/2024

Overall study status
Ongoing

Last Edited
18/11/2026

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
Rhabdomyosarcoma (RMS), Ewing sarcoma (ES) and desmoplastic small round cell tumour (DSRCT) are cancers known as sarcomas. They develop in bones or surrounding soft tissue such as muscle. For some patients chemotherapy, radiotherapy and surgery can control and sometimes cure their disease. However, there are patients whose disease returns or does not respond to treatment and their outcome is often poor. Chimeric antigen receptor (CAR) T cells are blood cells genetically engineered to recognise and kill tumour cells. Lasting tumour clearance has been achieved in leukaemia and CAR T products have been approved for use as part of standard treatment for some blood cancers. Early clinical trial data indicate that CAR T cells may also work in non-blood cancers. Currently, there are no CAR T cells approved for sarcoma. CAR T cells that are reprogrammed to recognise a specific target (B7H3) on the sarcoma cells have been developed. MIGHTY aims to test whether giving these CAR T cells to patients with RMS, ES or DSRCT is safe and what dose to use. MIGHTY has been developed by clinicians, scientists and patient advocates brought together by the NextGen Cancer Grand Challenge Initiative. It is one of three studies in the UK and the US assessing the safety of CAR T cells in solid tumours in children, teenagers and young adults.

Who can participate?
Patients aged ≥ 1 and ≤ 24 years old with a tissue diagnosis of RMS, ES or DSRCT sarcomas expressing B7H3

What does the study involve?
T cells are collected from the patient's blood to make the CAR T cells. The CAR gene is put into the T cells so they find and attack the sarcoma. Patients have 2 chemotherapy drugs to make space for the CAR T cells. The CAR T cells are then given into a vein. Patients are monitored in the hospital for at least 2 weeks. MRI/CT scans are used to look at the effect on the tumour.

What are the possible benefits and risks of participating?
It is hoped that the CAR T cells may be able to control the trial patient's sarcoma, however, there may be no benefit as the CAR T cells may not work as desired. The data obtained from this study

will help develop better CAR T cells targeting RMS, ES and DSRCT. If the results are promising, the CAR T cells will be tested in a larger study to confirm whether they can be used to treat these diseases.

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 study is the CRUK and UCL Cancer Trials Centre

When is the study starting and how long is it expected to run for?
October 2024 to December 2033, with recruitment planned between January 2025-January 2027

Who is funding the study?
1. Cancer Research UK
2. National Cancer Institute
3. The Mark Foundation

Who is the main contact?
ctc.mighty@ucl.ac.uk

Plain English summary under review with external organisation

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1009001

Central Portfolio Management System (CPMS)
60914

Protocol serial number
UCL/150859

Study information

Scientific Title

Multi-modular chimeric antigen receptor T cells targeting B7-H3 in Children, Teenage & Young adult sarcoma

Acronym
MIGHTY

Study objectives
To determine the safety and tolerability of hBRCA84D CAR T cells in patients with r/r RMS, ES or DSRCT after one or multiple previous lines of treatment.
To determine the feasibility of generating the ATIMP and administering hBRCA84D CAR T cells to patients with relapsed/refractory (r/r) RMS, ES or DSRCT after one or multiple previous lines of treatment.

To evaluate efficacy of hBRCA84D CAR T cells in patients with r/r RMS, ES and DSCRT after one or multiple previous lines of treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/12/2024, West London & GTAC REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 207 104 8098; westlondon.rec@hra.nhs.uk), ref: 24/LO/0701

Primary study design
Interventional

Study design
Randomized controlled trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Medical condition: Rhabdomyosarcoma (RMS), Ewing sarcoma (ES) and Desmoplastic small round cell tumour (DSRCT).
Medical condition in lay language: Sarcoma
Therapeutic areas: Diseases [C] - Cancer [C04]

Interventions
All trial patients undergo the following:

1. Leukapheresis: following registration, patients will undergo an unstimulated leukapheresis which will be sent to The 'Centre for Cell, Gene & Tissue Therapeutics' (CCGTT) at the Royal Free Hospital for the manufacture of the hBRCA84D CAR T cells
2. Lymphodepletion: before hBRCA84D CAR T cell infusion patients will receive fludarabine 30 mg/m2 (on days -6 to -3) and cyclophosphamide 500 mg/m2 (on days -4 to-3).
3. hBRCA84D CAR T cell infusion: on day 0, patients will receive an intravenous infusion of CAR T cells at a dose assigned by TMG/CTC according to the 3+3 design. hBRCA84D CAR T cells are autologous T cells engineered to target a specific protein (B7-H3) on the sarcoma cells. The following dose levels will be tested:

• Dose Level 1: 30 x 106 CAR T cells/m2
• Dose Level 2: 100 x 106 CAR T cells/m2

All patients undergo 1 year of regular follow-up, then annual follow-up until 15 years after the last ATIMP infusion.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
hBRCA84D CAR T cells [Autologous hBRCA84D CAR T cells]

Primary outcome(s)
1. Safety: toxicity of hBRCA84D CAR T cells as assessed by the incidence of grade 3-5 toxicity causally related to the ATIMP (particularly severe cytokine release syndrome and severe neurotoxicity) occurring within 28 days of hBRCA84D CAR T cell infusion
2. Feasibility of generation of the ATIMP as evaluated by the number of therapeutic products generated and the number of ATIMPs infused after successful manufacture

Key secondary outcome(s)
1. Objective response rate based on cross-sectional imaging after intravenous (iv) administration of hBRCA84D CAR T cells from any time point following CAR T infusion
2. Clinical outcomes including Progression Free Survival (PFS) and Time to Progression (TTP) after iv administration of hBRCA84D CAR T cells (PFS – time from CAR T infusion to progression or death, TTP – time from first response (≥MR) until progression)
3. Overall survival after iv administration of hBRCA84D CAR T cells (time from CAR T infusion to death by any cause)

Completion date
31/12/2033

Eligibility

Key inclusion criteria
1. Age ≥ 1 and ≤ 24 years
2. Tissue diagnosis of Rhabdomyosarcoma, Ewing sarcoma or Desmoplastic small round cell tumour
3. Expression of B7-H3 in the tumour
4. Relapsed or refractory disease after one or multiple lines of previous treatment
5. Measurable disease by cross-sectional imaging. Patients with only bone marrow detectable disease (bone marrow aspirate or trephine) are NOT eligible for the study
6. At least 3 weeks or 5 half-lives, whichever is shorter, after treatment with agents on other early phases clinical trial
7. Performance status: Karnofsky (age ≥ 10 years) or Lansky (age < 10) score ≥ 50%. Patients who are unable to walk because of paralysis, but who can sit upright unassisted in a wheelchair, will be considered ambulatory to assess performance score
8. Creatinine ≤1.5 ULN for age, if higher, an estimated (calculated) creatinine clearance must be ≥ 60 ml/min/1.73 m2

9. Left ventricular ejection fraction ≥50%
10. Absolute lymphocyte count ≥ 0.25 x 109/L
11. Women of childbearing potential must have a negative pregnancy test and agree to comply with the pregnancy reporting requirements of the protocol (if applicable)
12. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
1 Years

Upper age limit
24 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Patients with only bone marrow detectable disease in the absence of measurable disease by cross-sectional imaging
2. Patients with active, inoperative CNS disease including leptomeningeal disease
3. Active hepatitis B, C or HIV infection
4. Inability to tolerate leukapheresis
5. Clinically significant systemic illness or medical condition (e.g., significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the judgement of the investigator is likely to interfere with the assessment of safety or efficacy of the investigational regimen and its requirements
6. Any contraindication to lymphodepletion or the use of Cyclophosphamide or Fludarabine as per the local SmPC
7. Any contraindication to the use of Anticoagulant Citrate Dextrose Solution
8. Known allergy to albumin, EDTA or DMSO
9. Primary immunodeficiency or history of autoimmune disease (e.g., Crohn’s, rheumatoid arthritis, systemic lupus) requiring systemic immunosuppression /systemic disease-modifying agents within the last 2 years
10. Prior treatment with investigational or approved gene therapy or cell therapy products
11. Life expectancy <3 months
12. Systemic corticosteroid therapy ≥ 0.05 mg/kg dexamethasone daily (or equivalent) at the time of hBRCA84D CAR T cell infusion
13. Women who are pregnant or breastfeeding

Exclusion criteria for hBRCA84D CAR T cell infusion
1. Uncontrolled fungal, bacterial, viral, or other infection
Previously diagnosed infection for which the patient continues to receive antimicrobial therapy is permitted if responding to treatment and clinically stable at the time of scheduled hBRCA84D CAR T cell infusion
2. Systemic corticosteroid therapy ≥ 0.05 mg/kg dexamethasone daily (or equivalent) at the time of hBRCA84D CAR T cell infusion.

Date of first enrolment
15/08/2025

Date of final enrolment
31/01/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospitals
250 Euston Road
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Study participating centre
Great Ormond Street Hospital for Children
Great Ormond Street
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Sponsor information

Organisation
Cancer Research UK & UCL Cancer Trials Centre

Funder(s)

Funder type
Research organisation

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
National Cancer Institute

Alternative Name(s)
National Cancer Institute at the National Institutes of Health, Instituto Nacional del Cáncer, Instituto Nacional del Cáncer de los Institutos Nacionales de la Salud, NCI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Funder Name
The Mark Foundation

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Grace Luff, ctc.mighty@ucl.ac.uk. All of the following information will be

available upon study completion: the type of data that will be shared, when the data will become available and for how long, by what access criteria data will be shared including with whom, for what types of analyses, and by what mechanism, whether consent from participants was obtained, comments on data anonymisation, any ethical or legal restrictions, any other comments.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			18/11/2026	No	No
Study website		11/11/2025	11/11/2025	No	Yes