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A CAR T study for paediatric-type diffuse high-grade gliomas including diffuse midline glioma

Submission date
08/05/2024

Recruitment status
Recruiting

Registration date
11/07/2024

Overall study status
Ongoing

Last Edited
04/04/2025

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
Of childhood brain tumours, about 10% are high-grade gliomas. Paediatric high-grade gliomas (pHGG) account for 40% of deaths due to brain tumours in children. Treatment is limited with surgery only possible if the tumour is not in delicate parts of the brain. Radiotherapy can stop tumour growth but tumour will inevitably grow again.
Chimeric antigen receptor (CAR) T cells are blood cells genetically engineered to recognize and kill tumour cells. Sustained complete remissions have been achieved in leukaemia and encouraging results in non-blood cancers are emerging. Early clinical data suggests CAR T therapy can be effective in glioma. Researchers have developed CAR T cells that recognize IL13RA2 (Interleukin 13 receptor subunit alpha 2) present on glioma cells. The CAR T cells have been engineered to secrete interleukin15 to help the CAR T cells persist in the body. The study aims to test whether giving CAR T cells to pHGG patients is safe, what is the best dose and the optimal way to give the cells.

Who can participate?
Patients aged between 2 and 16 years with pHGG

What does the study involve?
T cells are collected from the participant's blood to make the CAR T cells. New genes are put into the T cells so they recognise and kill the glioma cells and help the CAR T cells persist in the body to stop tumour regrowth. To allow careful monitoring, participants have an Ommaya Reservoir placed under the skin of the scalp so the pressure in the brain can be measured. They are given two chemotherapy drugs to help the CAR T cells persist in the body. The CAR T cells are given into the vein. Participants are closely monitored in hospital for at least 2 weeks. MRI scans are used to look at the effect on the tumour. If the tumour is still present 1 month after the CAR T cells and the cells did not cause severe side effects, a 2nd CAR T cell dose may be given via the Ommaya reservoir into the fluid around the brain.

What are the possible benefits and risks of participating?
There may be no benefit in taking part in this study. If the CAR T cells 'work', which is not yet known, this may help decrease the pHGG tumour or stop it from growing. The information collected may help improve our knowledge of treating pHGG, which may benefit the treatment

of patients with high-grade glioma in the future.
Leukapheresis is required to obtain participants' T cells (a type of white blood cell) 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 at the insertion site. Pain medication and application of a pressure dressing may be used. The small risk of fainting is prevented by having the participant sit or lie down during the procedure. Muscle cramps are prevented by giving calcium supplements if needed.
Fludarabine and cyclophosphamide are used as a standard regimen to prepare 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 have anti-emetic prophylaxis and transfusion support as needed.
Participants will have an Ommaya reservoir placed before lymphodepletion in order to monitor, and if necessary treat, raised intracranial pressure (ICP). The researchers will also test if delivery of CAR T cells with an Ommaya reservoir is safe and benefits participants whose disease persists or regrows after CAR T cells are given into a vein.
An Ommaya reservoir is a catheter placed in one of the fluid-filled spaces in the brain (ventricle) attached to a reservoir implanted under the scalp. Insertion is a surgical procedure performed under general anaesthesia. The risk of serious complications due to implanting this device is <2%. Complications include infection, bleeding or swelling in the brain causing loss of function, such as weakness, pain, numbness, speech, swallowing or visual problems, difficulties with memory and cognition, and epilepsy. This is usually temporary and mild but can be serious and sustained in rare cases.
The Ommaya reservoir will be inserted by an experienced neurosurgeon. Antibiotics will be given to prevent infection. Post-procedure observation is at least 6 hours and supportive care will be provided as required if a complication occurs. Infusion of CAR T cells via the Ommaya reservoir will be performed by a practitioner experienced in the administration of medications via this device. Participants will be closely monitored for 4 hours after infusion and then daily for at least 14 days in hospital.
Cytokine release syndrome (CRS) is characterised by fever, hypotension, and in severe cases hypoxia and/or neurological disturbance. 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 on the intensive care unit.
Immune effector cell-associated neurotoxicity syndrome (ICANS) is a type of neurotoxicity which 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.
Neurotoxicity can occur due to activation of CAR T cells and associated swelling at the tumour site when - as in pHGG - the tumour is located in the brain or spine (tumour inflammation associated neurotoxicity or TIAN). TIAN can result in transient worsening of pre-existing neurological symptoms (e.g. cranial nerve deficits or ataxia in brainstem tumours; or back pain in spinal cord tumours). In severe cases, TIAN can cause raised ICP resulting in headache and vomiting or, impending herniation syndromes which are life-threatening and need urgent intervention. Participants with spinal cord tumours may develop urinary retention or reduced power or sensation in extremities.
Participants will have daily assessments including neurological examination for at least 14 days

after CAR T cell administration, with increased frequency as clinically indicated. Patients with spinal cord tumours will be monitored daily for spinal cord dysfunction. The Ommaya reservoir allows regular measurement of ICP to ensure early detection of raised ICP and drainage of CSF to rapidly normalise ICP. Management also includes Anakinra and corticosteroids. With the listed monitoring and management of TIAN, experience to date in patients with DMG treated with CAR T cells indicates that symptoms of TIAN are transient and fully reversible.

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?
May 2024 to December 2041

Who is funding the study?
1. Jon Moulton Charity Trust (UK)
2. Abbie's Army (UK)

Who is the main contact?
GLIMPS Trial Manager, ctc.glimps@ucl.ac.uk

Plain English summary under review with external organisation

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008429

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
UCL/150463, IRAS 1008429

Study information

Scientific Title
Glioma targeting IL13RA2/IL-15 multi-modular CAR T cell paediatric study

Acronym
GLIMPS

Study objectives
Primary objectives:
1. To determine the feasibility of generating the ATIMP and administering IL-15/06B5 CAR T cells to patients with paediatric-type diffuse high-grade glioma (pHGG) after the completion of standard-of-care treatment.
2. To determine the safety and tolerability of IL-15/06B5 CAR T cells in patients with pHGG following completion of standard of care treatment, firstly as an intravenous (IV) agent (Theme 1) and in the event of non-response or partial response following IV, as an intracerebroventricular (ICV) agent (Theme 2).

Secondary objectives:
To evaluate the efficacy of IL-15/06B5 CAR T cells in patients with pHGG following completion of standard-of-care treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/07/2024, London - West London GTAC REC (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8098; westlondon.rec@hra.nhs.uk), ref: 24/LO/0303

Study design
Non-randomized study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Paediatric-type diffuse high-grade glioma (pHGG)

Interventions
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 manufacture of the IL-15/06B5 CAR T cells
2. Ommaya reservoir (or similar catheter) insertion: Patients will have an intracerebroventricular catheter (Ommaya catheter or similar catheter) placed following enrolment and prior to IL-15 /06B5 CAR T cell infusion to allow monitoring, and treatment if necessary, of increased intracranial pressure (ICP) (both on theme 1 and 2) and, if eligible, for IL-15/06B5 CAR T cell administration (on theme 2).
3. Lymphodepletion*: prior to the 1st IV 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).
A decision on whether the patient will have a repeat lymphodepletion prior to the intracerebroventricular CAR T cell infusion will be made by the Site investigator and TMG following a patient review
4. IL-15/06B5 CAR T cell infusion:

Theme 1 (intravenously): infusion of CAR T cells at a dose assigned to the patient by TMG/CTC. The following dose levels will be tested:
Dose Level 1: 10 x 10e6 CAR T cells/m2
Dose Level 2: 30 x 10e6 CAR T cells/m2
Dose Level 3: 100 x 10e6 CAR T cells/m2

Patients who have no/partial response (or disease relapse beyond day 28 after initial CR) in the absence of significant and/or persistent toxicity following IV administration of IL-15/06B5 CAR T cells (Theme 1) may be eligible for a second dose of IL-15/06B5 CAR T cells on Theme 2.

Theme 2 (intracerebroventricularly): infusion of 10 x 10e6 CAR T cells via an Ommaya reservoir (or similar catheter) following lymphodepletion (if applicable) as described above.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Dose response

Phase
Phase I

Drug/device/biological/vaccine name(s)
Autologous IL-15/06B5 CAR T cells

Primary outcome measure
1. Safety: toxicity of IL-15/06B5 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 IL-15/06B5 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 (as an intravenous agent (Theme 1) and as an intracerebroventricular agent (Theme 2) after successful manufacture. Measured 28 days after the ATIMP infusion.

Secondary outcome measures
Measured 1 year after ATIMP infusion:
1. Overall survival (OS): the proportion of patients alive at 1 year will be tabulated. If numbers are sufficient, overall survival will also be analysed using Kaplan-Meier survival analyses. Survival times will be measured from the date of IL15/06B5 CAR T infusion until the date of death from any cause.
2. Progression Free Survival (PFS): the proportion of patients alive and progression-free at 1 year will be tabulated. Progression-free survival will be analysed using Kaplan-Meier survival analyses with the median survival time reported. Survival times will be measured from the date of the IL15 /06B5 CAR T infusion until the date of progression or death.
3. Time to Progression (TTP): TTP will be summarised as a median and range. If numbers are sufficient, this will also be analysed using Kaplan-Meier survival analyses with the duration calculated as the time from first response (≥PR) until progression.
4. Best objective response rate (ORR): this will be taken as the best response as defined by both iRANO and RAPNO criteria observed at any time point following CAR T infusion. The number and proportion of patients achieving a response ≥PR will be presented for all patients as well as by dose level.

Overall study start date
02/05/2024

Completion date
31/12/2041

Eligibility

Key inclusion criteria
1. Age ≥2 and ≤16 years
2. Tissue diagnosis of paediatric-type diffuse high-grade glioma
3. Expression of IL-13RA2 in the tumour
4. Radiographically evident tumour
5. At least 6 weeks following completion of standard of care treatment.
6. At least 3 weeks or 5 half-lives, whichever is shorter, after treatment with chemotherapy or other agents on other early phase clinical trial
7. Performance status: Karnofsky (age ≥10 years) or Lansky (age <10) score ≥40% allowing for

stable neurological deficit due to pHGG
8. Absolute neutrophil count ≥1.0 x 10e9/L and platelet count ≥50 x 10e9/L
9. Total bilirubin <1.5 ULN and ALT <2.5 ULN
10. Serum creatine <1.5 ULN for age, if higher, an estimated (calculated) creatinine clearance must be ≥60 ml/min/1.73m²
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

Age group
Child

Lower age limit
2 Years

Upper age limit
16 Years

Sex
Both

Target number of participants
12

Key exclusion criteria
1. Systemic corticosteroid therapy ≥0.05 mg/kg dexamethasone daily (or equivalent) at the time of IL-15/06B5 CAR T cell infusion
2. Asthma or atopic dermatitis requiring inhaled steroids or topical steroids respectively
3. Tissue diagnosis of Infant-type hemispheric glioma
4. Tumour involvement of the thalamus or cerebellar vermis or hemispheres (pontocerebellar peduncle involvement is allowed)
5. Clinical or radiological evidence of significant and rapid tumour progression
6. Active hepatitis B, C or HIV infection
7. Active helminth or parasite infection
8. Inability to tolerate leukapheresis
9. Pre-existing significant neurological disorder not related to pHGG
10. 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
11. Any contraindication to lymphodepletion or to the use of Cyclophosphamide or Fludarabine as per the local SmPC
12. Any contraindication to the use of Anticoagulant Citrate Dextrose Solution
13. Any contraindication to Ommaya reservoir (or similar catheter) insertion
14. Known allergy to albumin, DMSO or EDTA
15. Primary immunodeficiency or history of autoimmune disease (e.g., Crohn’s, rheumatoid arthritis, systemic lupus) or inflammatory bowel disease requiring systemic immunosuppression /systemic disease-modifying agents within the last 2 years

16. Prior treatment with investigational or approved gene therapy or cell therapy products
17. Life expectancy <3 months
18. Women who are pregnant or breastfeeding

Exclusion criteria for IL-15/06B5 CAR T cell infusion (IV Theme 1 and ICV Theme 2):
1. Uncontrolled fungal, bacterial, viral, or other infection.
2. Previously diagnosed infection for which the patient continues to receive antimicrobial therapy is permitted (with the exception of ongoing treatment for helminth of parasite infection) if responding to treatment and clinically stable at the time of scheduled IL-15/06B5 CAR T cell infusion.
3. Systemic corticosteroid therapy ≥ 0.05 mg/kg dexamethasone daily (or equivalent) at the time of IL-15/06B5 CAR T cell infusion

Additional exclusion criteria for dose 2 IL-15/06B5 CAR T cell infusion (ICV – Theme 2):
1. Presence of grade 4 neurotoxicity (ICANS and/or TIAN) following infusion of Theme 1 dose
2. Presence of grade 1, 2 or 3 neurotoxicity (ICANS and/or TIAN) following the infusion of Theme 1 (Dose 1/IV IL-15/06B5 CAR T cell dose) that has not fully resolved prior to proposed administration of Theme 2 (Dose 2/ICV IL-15/06B5 CAR T cell dose), or if the investigators consider that the risk/benefit balance does not support proceeding with Theme 2 (Dose 2/ICV)
3. Presence of grade 4 CRS following infusion of Theme 1 (Dose 1/IV IL-15/06B5 CAR T cell dose)
4. Presence of grade 1, 2 or 3 CRS following infusion of Theme 1 (Dose 1/IV IL-15/06B5 CAR T cell dose) that has not fully resolved prior to proposed administration of Theme 2 (Dose 2/ICV IL-15/06B5 CAR T cell dose), or if the investigators consider that the risk/benefit balance does not support proceeding with Theme 2 (Dose 2/ICV)

Date of first enrolment
28/02/2025

Date of final enrolment
28/02/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Great Ormond Street Hospital for Children
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Sponsor information

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Sponsor type
University/education

Website
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ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Jon Moulton Charity Trust

Alternative Name(s)
The Jon Moulton Charity Trust

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Funder Name
Abbie's Army

Results and Publications

Publication and dissemination plan

1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Other

Pseudonymised trial data will be published as part of the trial publication in a peer-reviewed scientific journal. Trial data will also be included in the accompanying documents for any conference where final trial results are presented. A lay summary of results will be made available to participants via clinicians and the Cancer Research UK website.

Intention to publish date

31/12/2034

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