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A Phase I/II trial of UCB4594 in participants with advanced cancer

Submission date 17/10/2023	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 24/01/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 06/09/2024	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
This clinical trial is looking at UCB4594. This is the first time the drug is being tested in humans. UCB4594 is a type of drug called a monoclonal antibody. It has been designed to work by targeting a protein called HLA-G that is found in high levels on some cancer cells. By attaching itself to this protein it may help the immune system to attack and kill the cancer cells.
The four main aims of the clinical trial are to find out:
1. The best dose of UCB4594 that can be given safely to participants in the trial.
2. What the side effects of UCB4594 are and how they can be managed.
3. What happens to UCB4594 inside the body and how it affects cancer cells.
4. Whether UCB4594 can cause cancer to shrink.

Who can participate?
Patients aged 18 years and over with advanced solid tumours that do not respond to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the participant

What does the study involve?
This clinical trial is split into two phases.
Phase I is the ‘dose escalation’ phase. This is where small groups of participants receive UCB4594 at a certain dose level starting with a low dose level. After reviewing the results obtained at each dose level, it will be decided whether or how much to increase the dose for the next group of participants. This part of the study aims to find the best dose to give that does not cause too many side effects.
Phase II is the ‘dose expansion’ phase. This starts when the dose escalation phase has worked out the best dose of UCB4594 to give. In this part of the trial UCB4594 will be given alone or in combination with other anti-cancer drugs. This will allow us to find out more about how the drug is working and whether UCB4594 affects cancer.

What are the possible benefits and risks of participating?
UCB4594 is a new drug that has never been given to humans before. Possible risks and benefits

are based on laboratory tests and experience with similar drugs but there is not yet any information about the effects of UCB4594 in humans. Participants in the trial will be monitored closely to find out the effects of UCB4594.

Where is the study run from?
Cancer Research UK

When is the study starting and how long is it expected to run for?
October 2023 to November 2029

Who is funding the study?
Cancer Research UK

Who is the main contact?
Prof. Fiona Thistlethwaite, fiona.thistlethwaite@nhs.net

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-drug-called-ucb4594-for-cancer-that-has-spread

Contact information

Type(s)
Scientific, Principal Investigator

Contact name
Prof Fiona Thistlethwaite

Contact details
Wilmslow Road
Manchester
United Kingdom
M20 4BX
+44 (0)161 9187672
fiona.thistlethwaite@nhs.net

Type(s)
Scientific

Contact name
Mrs Karen Dyer

Contact details
Centre for Drug Development
2 Redman Place
London
United Kingdom
E20 1JQ

Type(s)
Scientific

Contact name
Dr David Gervais

Contact details
Centre for Drug Development
2 Redman Place
London
United Kingdom
E20 1JQ

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008098

ClinicalTrials.gov number
NCT06380816

Secondary identifying numbers
CRUKD/24/001, IRAS 1008098, CPMS 58100

Study information

Scientific Title
A Cancer Research UK Phase I/II trial to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of UCB4594 alone and in combination with anti-cancer treatments in participants with advanced malignancies

Study objectives
Primary objectives:
1. To find out the best dose or doses of UCB4594 that can be given safely to participants on its own and with other anti-cancer drugs
2. To assess how safe and tolerated the best dose or doses of UCB4594 identified are when UCB4594 is given to participants on its own or with other anti-cancer drugs for up to one year.

Secondary objectives:
1. To determine if there is any anti-cancer activity of UCB4594 in participants with advanced solid tumours, both on its own and with other anti-cancer drugs
2. To monitor levels of UCB4594 in the blood
3. To further assess the safety and tolerability profile of UCB4594 both on its own and in combination with other anti-cancer drugs

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 12/12/2023, North East – York Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 104 8079; york.rec@hra.nhs.uk), ref: 23/NE/0170

Study design
Multi-centre first-in-human non-randomized Phase I/II dose escalation and dose expansion trial

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
Advanced solid tumours

Interventions
Dose escalation phase: Participants will receive UCB4594 as an intravenous infusion once every 3 weeks. The dose administered will be between 3 mg and 1600 mg.

Expansion phase: Participants will receive UCB4594 as an intravenous infusion once every 3 weeks. The dose of UCB4594 as monotherapy and in combination with other anti-cancer treatments and the dose of the combination agents will be determined based on data from the dose escalation phase and the choice of combination agent.

All participants may receive UCB4594 for up to 18 cycles (~1 year) and will be followed up for up to 6 months after their last dose.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic, Dose response

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
UCB4594

Primary outcome measure

1. The recommended Phase 2 dose (RP2D) of UCB4594 will be determined both for UCB4594 on its own and with other anti-cancer drugs, based on the maximum tolerated dose or maximum administered dose (MTD/MAD) and all available safety, efficacy, pharmacokinetic (PK) and pharmacodynamic data (all modules – dose escalation [module A], monotherapy dose expansion [module B] and any combination modules [module C]). Evaluation of this endpoint will occur once all patients in each module (Module A, B or C) have completed the dose-limiting toxicity (DLT) assessment period (21 days) and all relevant data has been collected.
2. The frequency of adverse events (AEs) considered at least possibly related to UCB4594. AE data will be collected for UCB4594 (all modules) and in combination with other anti-cancer treatments (Module C), and the number of Grade 3, 4 and 5 AEs at least possibly related to UCB4594 (all modules) and with other anti-cancer treatments (Module C) for up to 18 cycles (~12 months) of dosing determined. AEs, including relatedness, seriousness and severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, will be assessed by the Investigator. Evaluation of this endpoint will occur once the last patient recruited overall has received up to 18 cycles (~12 months) of UCB4594.

Secondary outcome measures
1. Tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and immune RECIST (iRECIST) (all modules) and Overall Response Rate (ORR) (expansion phase; Modules B and C). ORR is defined as the proportion of participants who achieve complete response (CR/iCR) or partial response (PR/iPR) as the best overall response according to RECIST v1.1 and iRECIST. Response will be assessed at baseline, once every 6–9 weeks, and at End of Treatment.
2. The PK parameters of UCB4594 (including maximum concentration, minimum concentration, area under the curve, steady state volume of distribution, and clearance) (monotherapy modules; Modules A and B). UCB4594 concentrations will be measured in serum in samples collected from participants at up to 18 timepoints during Cycles 1 to 2, two timepoints for every subsequent cycle, and at the End of Treatment Visit for Module A (dose escalation); 2 samples will be taken for every cycle, and a further sample at the End of Treatment Visit for Module B (monotherapy expansion).
3. The frequency of AEs considered at least possibly related to UCB4594. The frequency of AEs will be assessed for UCB4594 (all modules) and/or with other anti-cancer treatments (Module C), and the number of Grade 3, 4 and 5 AEs at least possibly related to UCB4594 (all modules) and or other anti-cancer treatments (Module C) determined. AEs, including relatedness, seriousness and severity according to NCI CTCAE Version 5.0, will be assessed by the Investigator. AEs are collected from the date of informed consent until 6 months after the last dose of UCB4594.

Overall study start date
13/10/2023

Completion date
01/11/2029

Eligibility

Key inclusion criteria
1. Written (signed and dated) informed consent and capable of co-operating with IMP administration and follow-up.
2. Participant population: Histologically or cytologically proven advanced solid tumours (as specified below), refractory to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the participant. Module A (dose

escalation): Tumour types which have shown high levels of human leucocyte antigen (HLA)-G expression (as reported in the literature): head and neck squamous cell carcinoma, non-small cell lung cancer, colorectal cancer, triple-negative breast cancer, renal cell cancer (clear cell only), oesophago-gastric cancer (excluding gastrointestinal stromal tumour), cervical cancer, ovarian cancer, pancreatic cancer. N.B. Participants with small cell type cancers on histology/cytology are excluded. Pre-treatment biopsies are mandatory for all participants. Paired biopsies will be mandatory for participants from doses of 30 mg and higher. Participants must have disease amenable to biopsy (excluding bone metastases) as deemed safe by the Investigator.
3. Measurable disease, according to RECIST v1.1
4. Life expectancy of at least 12 weeks
5. Eastern Cooperative Oncology Group performance status of 0 or 1
6. Haematological and biochemical indices within defined ranges. These measurements should be performed to confirm the patient's eligibility to participate in the trial.
7. Aged 18 years or over at the time consent is given. Participants aged 16–17 years may be eligible for recruitment to the backfill cohorts in dose escalation once adequate safety and toxicity data have been established in participants aged 18 years or over. All relevant data will be reviewed and a decision on the inclusion of participants aged 16–17 years will be made by the Trial Management Group.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
167

Key exclusion criteria
1. Radiotherapy (except palliative), endocrine therapy (unless for non-malignant disease), chemotherapy, targeted therapy or immunotherapy, or any other investigational medicinal products (IMPs) during the previous 4 weeks or 5 half-lives (whichever is shorter) before the first dose of IMP
2. Ongoing toxicity of previous treatments >CTCAE Grade 1 (except alopecia of any grade, stable Grade 2 peripheral neuropathy or hormone-replacement therapy (HRT)-managed endocrine disorders)
3. Patients with rapidly progressing / symptomatically deteriorating brain/leptomeningeal metastases/untreated brain metastases are excluded. Patients with previously treated brain metastases are eligible if they haven't had a seizure or a clinically significant change in neurological status or required steroids in the last 2 weeks
4. Pregnant or breastfeeding female patients (or planning to breastfeed)
5. Women of childbearing potential. However, those not already pregnant or breastfeeding (or discontinue breastfeeding) and meet the following are eligible:
5.1. Have a negative serum pregnancy test within 7 days before enrolment and either:
5.2.1. Agree to a form of highly effective contraception plus a barrier method, or

5.2.2. Agree to sexual abstinence
Effective from the negative pregnancy test, throughout the trial and for 10 months after the last dose of UCB4594.
6. Male patients with partners of childbearing potential. However, patients who meet the following are eligible:
6.1. Agree to a barrier method of contraception or sexual abstinence
6.2. Males with pregnant or breastfeeding partners must use barrier method contraception to prevent exposure of the foetus or neonate
6.3. Non-vasectomised males must also ensure any partner of childbearing potential uses highly effective contraception or agrees to sexual abstinence
Effective from the date of the first dose of UCB4594, throughout the trial and for 5 months after the last dose of UCB4594
N.B. Males must refrain from donating sperm for the same period
7. Surgery from which the patient has not yet recovered
8. High medical risk because of non-malignant systemic disease, including serious or uncontrolled infection (requiring IV antibiotics) or unexplained fever >38°C within 2 weeks prior to the first dose of UCB4594
9. Known to be serologically positive for hepatitis B virus, hepatitis C virus or human immunodeficiency virus
10. Active or suspected autoimmune disease, or any history of autoimmune condition that required systemic corticosteroids or immunosuppressive agents. Patients who have ever had a transplant are excluded. This does not apply to patients with: vitiligo, alopecia, or type I diabetes mellitus, psoriasis not requiring chronic systemic immunosuppressive treatment within the past 2 years, stable autoimmune-mediated hypothyroidism on HRT, and Raynaud's syndrome
11. Are being treated with escalating or supraphysiologic doses of corticosteroids or immunosuppressive agents. Participants with immunotherapy-related hypophysitis adequately treated with physiologic doses of steroids are not excluded. Use of topical, ophthalmic, inhaled, intermittent steroid injections, and intranasal corticosteroids are permitted
12. Hypersensitivity to the ingredients/excipients (including polysorbate 80) in UCB4594
13. History of significant toxicities from treatment of immune checkpoint inhibitors (CPIs) that necessitated permanent discontinuation (Patients who started on combination CPI [e.g., ipilimumab/nivolumab] and had toxicity requiring discontinuation of one CPI [e.g., continued with nivolumab single agent] are not excluded)
14. History of Grade ≥3 infusion-related reaction to monoclonal antibodies or similar drugs
15. Prior treatment with HLA-G, immunoglobulin-like transcript (ILT)2 or ILT4-targeting drug
16. Live, attenuated vaccine within 28 days prior to the first dose of IMP
17. Increased risk due to tumour flare (e.g., an initial increase in tumour size that may lead to obstruction of airways, etc)
18. Significant active pulmonary disease or condition at screening, including:
18.1. Lymphangitis carcinomatosa
18.2. History of interstitial lung disease or pulmonary fibrosis
18.3. History of pulmonary inflammatory disease
19. Evidence of bleeding diathesis
20. Significant cardiovascular disease, defined as a history of: congestive heart failure requiring therapy or left ventricular ejection fraction <40%, unstable angina pectoris or myocardial infarction within 6 months prior to entry, or current poorly controlled angina (symptoms weekly or more), clinically significant cardiac arrhythmia within 6 months prior to entry (asymptomatic atrial fibrillation or asymptomatic first-degree heart block permitted), or myocarditis. Presence of symptomatic or severe valvular heart disease. Baseline QT interval corrected by Fridericia >450 msec for males and >470 msec for females on triplicate electrocardiogram is ineligible
21. Participant in or plans to join another interventional trial
22. Other current malignancies. Cancer survivors who have undergone potentially curative

therapy for prior malignancy with no evidence of disease for 3+ years are eligible
23. Any other condition that, in the Investigator's opinion, means the trial is not in the patient's best interest

Date of first enrolment
25/06/2024

Date of final enrolment
01/11/2028

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation
Cancer Research UK

Sponsor details
2 Redman Place
London
England
United Kingdom

E20 1JQ
+44 (0)20 34696878
regulatory@cancer.org.uk

Sponsor type
Charity

Website
http://www.cancerresearchuk.org/

ROR
https://ror.org/054225q67

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

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

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Submission to regulatory authorities

It is intended that the results of the trial will be published on a publicly accessible database (ISRCTN) and in peer-reviewed journals, at conferences and in press releases as appropriate. A lay summary of the results will also be published on patient-facing websites (such as the Cancer

Research UK website). Anonymised individual participant data may be shared with researchers whose proposed use of the data is approved by a review committee of the Sponsor. All requests made within 5 years from the end of the trial will be considered, and requests made subsequently will be considered where possible.

Intention to publish date
01/11/2030

Individual participant data (IPD) sharing plan
Data from this trial and the final clinical study protocol will be submitted to a public registry and will be available immediately following publication, with no end date. Individual deidentified participant data that underlie the results reported will be shared with researchers whose proposed use of the data is approved by a review committee of the Sponsor. All requests made within 5 years from the end of trial will be considered; requests made subsequently will be considered where possible. Requests should be submitted to drugdev@cancer.org.uk.

IPD sharing plan summary
Available on request