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A Phase I/IIa trial of BT1718 in patients with advanced solid tumours.

Submission date
13/12/2023

Recruitment status
No longer recruiting

Registration date
18/12/2023

Overall study status
Completed

Last Edited
30/10/2024

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Researchers are looking for new ways to treat people with advanced solid tumours when standard treatments have stopped working. In this trial, they are looking at BT1718. MT1 MMP is a protein. It breaks down other proteins that surround a cell. Cancer cells have higher levels of MT1 MMP than normal cells. This can cause cancer to grow and spread. So, researchers are looking at ways to stop this happening. They think having BT1718 might help. BT1718 is a type of targeted treatment called a small molecule drug. It recognises and attaches itself to the MT1 MMP protein. This causes the cancer cells to die. As cancer cells have more MT1 MMP on their surface than normal cells, healthy cells are less affected. The main aims of the trial are to find out the best dose of BT1718; what happens to the drug in the body; how well treatment works; and more about the side effects. This trial is in two phases. Phase I looked at the best dose of BT1718. Phase II tested this dose in a larger number of people.

Who can participate?
The trial has now closed to recruitment. People with advanced cancer who were at least 16 years old could take part. Part of Phase II of the trial included a group of people with non-small cell lung cancer.

What does the study involve?
This is a phase I/II trial. In phase I, the first few people taking part had a low dose of BT1718. The next few people had a higher dose if they didn't have any serious side effects. And so on, until they found the best dose. We call this a dose-escalation trial. In phase II, the same dose was tested on a larger number of people. Different groups of people joined this part including a group of people with non-small cell lung cancer (researchers call this a basket cohort).

You have BT1718 as a drip into a vein or you might have it through a small syringe connected to a pump. It takes about 60 minutes each time. You have treatment in cycles. Each 4-week period is a cycle of treatment.

For each cycle in phase II, you have:
BT1718 once a week for the first 3 weeks and a week without treatment

You see the doctor at each hospital visit for a quick check-up before treatment. At each visit, you have some blood tests and a heart trace.

You might have treatment for up to 2 years if it is working and the side effects aren't too bad.

Research samples
You give some extra blood samples before, during and after treatment. The researchers will ask if they can take some extra tissue samples before and after treatment. The researchers will look at the samples to:
Measure the levels of BT1718 in your blood
Predict who will benefit from treatment
Find biomarkers

Hospital Visits
You see a doctor and have some tests before you can join the trial. These include:
A physical examination
Heart trace (ECG)
A test to see how well your kidneys work
Blood tests
A CT scan or MRI scan

To join phase II, the trial team will do some tests on a sample of tissue (biopsy) you gave when you were diagnosed. Or you might need to give another sample if there isn't one available.

You have your treatment at the hospital. You might stay overnight so the trial team can keep an eye on you and check for any side effects. The trial team will tell you more about how often you stay overnight.

You have a CT scan or MRI scan every 8 weeks. You stop treatment if your cancer has continued to grow. Your doctor will discuss other treatment options with you.

When you finish treatment, you have a check-up 1 month later. The trial team continue to follow you up every 3 months at routine clinic appointments or they might phone you or check your medical records to see how you are getting on.

What are the possible benefits and risks of participating?
Side effects
BT1718 is a new drug, so there might be side effects we don't know about yet. The trial team will give you a phone number to call them if you are worried about anything.

The possible side effects could include:
A drop in the number of blood cells causing an increased risk of infection, breathlessness, bruising and bleeding
A skin reaction where the nurse injects the drug into a vein causing pain and swelling
Liver changes
Kidney changes
Nerve changes such as pins and needles in the hands or feet or weakness in the arms or legs
Feeling or being sick
Low or high blood pressure causing dizziness or headaches
Dry mouth
Feeling tired

There is a chance that exposure to sunlight could cause skin side effects while you are having treatment. You should avoid going out in the sun too much. You should cover up and use sun cream with a high sun protection factor (SPF 30).

Where is the study run from?
The trial is Sponsored by the Cancer Research UK Centre for Drug Development, based in London, UK.

When is the study starting and how long is it expected to run for?
The study started recruiting in January 2018 and completed in November 2023

Who is funding the study?
Cancer Research UK

Who is the main contact?
Cancer Research UK Centre for Drug Development, regulatory@cancer.org.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-bt1718-for-advanced-cancer

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03486730

Clinical Trials Information System (CTIS)
2016-004633-24

Integrated Research Application System (IRAS)
228376

Central Portfolio Management System (CPMS)
36506

Protocol serial number
CRUKD/17/009

Study information

Scientific Title
A Cancer Research UK Phase I/IIa clinical trial of BT1718, (A Bicycle drug conjugate) given intravenously in patients with advanced solid tumours

Study objectives
1. Dose escalation phase: To propose a recommended Phase II dose (RP2D) for evaluation by establishing the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), of BT1718 given in patients with advanced solid tumours, at one or more dosing schedules.
2. Dose escalation and expansion phase: To assess the safety and toxicity profile of BT1718 in patients with advanced solid tumours.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 08/12/2017, London - Chelsea REC (Bristol HRA Centre, Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, United Kingdom; +44 (0)207 1048150; chelsea.rec@hra.nhs.uk), ref: 17/LO/1862

Study design
Multi-centre first in human (FIH) Phase I/IIa open-label dose-escalation trial with an expansion phase

Primary study design
Interventional

Study type(s)
Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Treatment of patients with advanced solid tumours

Interventions
Dose escalation will consist of Stages 1 and 2.
Stage 1 patients will receive BT1718 intravenously twice a week (Days: 1,4,8,11,15,18) for 3 out of 4 weeks. The starting dose will be 0.6mg/m2. Single patient cohorts will be explored, but it will change to 3 to 6 patient cohorts.
Stage 2 patients will receive BT1718 intravenously once weekly (Days: 1,8,15) for 3 out of 4 weeks. This stage will have 3 to 6 patient cohorts until the recommended dose is established.
The expansion phase will consist of two or more expansion cohorts to include tumour types known to commonly over-express MT1-MMP and where MT1-MMP overexpression is confirmed during prospective and retrospective (in appropriate patients) selection at enrolment. A squamous NSCLC and basket cohort will include approximately 16 patients with high MT1-MMP levels. In the expansion cohorts, BT1718 will be administered intravenously at the once-weekly RP2D established in Phase I, Stage 2.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
BT1718

Primary outcome(s)
1. Maximum dose at which no more than one out of six patients at the same dose level experiences a probable or highly probable BT1718-related dose-limiting toxicity (DLT) measured using data recorded in the study case report forms (CRF) when sufficient patients have had the opportunity to complete 1 Cycle (28 days)
2. Determination of the frequency and causality of each adverse event (AE) to BT1718 and grade severity according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.02 measured using data recorded in the study CRF when sufficient patients have had the opportunity to complete 1 Cycle (28 days)

Key secondary outcome(s))
1. Maximum observed plasma concentration (Cmax), area under curve (AUC), terminal elimination half-life (t½), and other pharmacokinetic (PK) parameters of BT1718 in plasma, both as an intact and cleaved molecule measured using standard PK methods in up to 24 timepoints from the first dose of BT1718 over the first two cycles (i.e. Cycle 1 and Cycle 2). Each Cycle is 28 days.
2. Anti-tumour response, according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1, measured using computerised tomography (CT) or magnetic resonance imaging (MRI) scans at database lock - 4 weeks after the last patient last visit
3. Estimate progression-free survival measured using data recorded in the study CRF; evaluation will be at database lock - 4 weeks after the last patient last visit
4. Estimate progression-free survival rate measured using data recorded in the study CRF at six months
5. Estimate overall survival measured using data recorded in the study CRF; evaluation will be at database lock - 4 weeks after the last patient last visit
6. Estimate duration of response measured using data recorded in the study CRF; evaluation will be at database lock - 4 weeks after the last patient last visit

Completion date
20/11/2023

Eligibility

Key inclusion criteria
1. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up
2. Phase I, dose-escalation phase (Stages 1 and 2):
2.1. Histologically or cytologically proven advanced solid tumour, refractory to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the patient.
Phase IIa, expansion phase:
2.2. Histologically or cytologically proven advanced solid tumour of particular interest based on pre-clinical and clinical data, refractory to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the patient. Phase IIa expansion cohorts will be:
2.2.3. Squamous NSCLC cohort - retrospective MT1-MMP testing.
2.2.4. Basket cohort (advanced solid tumours, excluding patients eligible for one of the other recruiting expansion cohorts) - high MT1-MMP expression by IHC assay using archival tumour sample (mandatory fresh tumour samples for those patients without available archival tumour samples or additional analysis is deemed necessary). Retrospective testing may be permitted for tumour types estimated to have high MT1-MMP positivity rates as per the Laboratory manual.
2.2.5. Additional expansion cohort(s) of squamous oesophageal cancer if confirmed as recruiting by the Sponsor.
2.3. At least one measurable lesion according to RECIST criteria Version 1.1, that has had objective radiological progression on or after the last therapy.
2.4. Consent for pre-treatment and post-treatment fresh tumour biopsy sample in a minimum of eight patients in the squamous NSCLC cohort, squamous oesophageal cohort (if confirmed as recruiting by the Sponsor) and all patients in the basket cohort (except patients with a very high MT1-MMP H-score if agreed with the Sponsor and PI as defined in the Laboratory Manual).
2.5. Consent for pre-treatment and post-treatment non-tumour samples (optional) for patients

having a pre and post-treatment tumour biopsy.
2.6. Consent for pre and post-treatment skin punch biopsy (optional).
3. Life expectancy of at least 12 weeks.
4. World Health Organisation (WHO) performance status of 0 - 1.
5. Haematological and biochemical indices within the ranges shown below. These measurements should be performed to confirm the patient's eligibility.
Haemoglobin (Hb): ≥90.0 g/L, or ≥100.0 g/L if transfusion within last four weeks
Absolute neutrophil count (ANC): ≥1.5 x 10^9/L
Platelet count: ≥100 x 10^9/L
Bilirubin: ≤1.5 x upper limit of normal (ULN). NB: >1.5 ULN, acceptable if conjugated bilirubin is ≤1.5x ULN
Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT): ≤2.5 x ULN (or ≤5 x ULN if has liver metastases)
Renal function
Either:
Serum creatinine: ≤1.5 x ULN
Or:
Calculated creatinine clearance (using the Wright or Cockcroft & Gault [C&G] formula): GFR ≥50 mL/min (uncorrected value)
Or:
Isotope clearance measurement: GFR ≥50 mL/min (corrected value)
6. 16 years or over at the time consent is given
7. Consent to access and analyse any available archival tissue.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Sex
All

Total final enrolment
66

Key exclusion criteria
1. Radiotherapy (except for palliative reasons), systemic anti-cancer therapy (except life-long hormone suppression such as LHRH agents in prostate cancer) or investigational medicinal products during the previous four weeks (six weeks for nitrosoureas, mitomycin-C) before treatment (or first dose of immunotherapy during the previous 12 weeks).
2. Prior bone marrow transplant, myeloablative conditioning, or extensive radiotherapy to greater than 25% of bone marrow, within the previous eight weeks of the first BT1718 dose.
3. Ongoing toxic manifestations of previous treatments greater than NCI CTCAE Grade 1. Exceptions to this are alopecia, amenorrhea/oligospermia and any other ongoing toxic

manifestation which in the opinion of the Investigator and the Medical Advisor should not exclude the patient.
4. Any CNS metastases (unless had local therapy and are asymptomatic and radiologically stable off steroids for the last four weeks).
5. Current or prior malignancy which could affect compliance with the protocol or interpretation of results. Patients with curatively-treated non-melanoma skin cancer, non-muscle-invasive bladder cancer, or carcinomas-in-situ are generally eligible.
6. Female patients who can become pregnant (or are already pregnant or lactating). However, those patients who have a negative serum or urine pregnancy test before enrolment and agree to use two forms of contraception (one effective form plus a barrier method) [oral, injected or implanted hormonal contraception and condom; intra-uterine device and condom; diaphragm with a spermicidal gel and condom] or agree to sexual abstinence, effective from the first administration of BT1718, throughout the trial and for six months afterwards are considered eligible.
7. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using a barrier method of contraception [condom plus spermicide] or to sexual abstinence effective from the first administration of BT1718, throughout the trial and for six months afterwards. Men with partners of child-bearing potential must also be willing to ensure that their partner uses an effective method of contraception for the same duration for example, hormonal contraception, intrauterine device, diaphragm with spermicidal gel or sexual abstinence). Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure of the foetus or neonate.
8. Surgery from which the patient has not yet recovered.
9. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.
10. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
11. Patients with significant cardiovascular disease are excluded as defined by:
11.1. Current congestive heart failure requiring therapy (NYHA III or IV) or known LVEF <40% (moderate to severe)
11.2. History of unstable angina pectoris or myocardial infarction up to six months before trial entry, or of current poorly controlled angina (symptoms weekly or more)
11.3. Presence of symptomatic or severe valvular heart disease (severe by local echographic criteria or AHA/ACC Stage C or D)
11.4. History of a clinically significant cardiac arrhythmia up to six months before trial entry (asymptomatic atrial fibrillation or asymptomatic first-degree heart block are permitted)
12. Previous known allergy to one of the constituents or excipients of BT1718.
13. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I/IIa study of BT1718. Participation in an observational trial or interventional clinical trial which does not involve administration of an IMP and which would not place an unacceptable burden on the patient in the opinion of the Investigator and Medical Advisor would be acceptable.
14. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

Date of first enrolment
24/01/2018

Date of final enrolment
30/12/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

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

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre

University College London Hospitals NHS Foundation Trust
235 Euston Road, Bloomsbury
London
United Kingdom
NW1 2BU

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham NHS Foundation Trust
Birmingham
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B15 2TH

Sponsor information

Organisation
Cancer Research UK

ROR
https://ror.org/054225q67

Funder(s)

Funder type
Charity

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

Results and Publications

Individual participant data (IPD) sharing plan

A summary of the clinical trial results will be uploaded to an established public register. Individual deidentified participant data that underlie the results reported on the established public register (text, figures, tables and supplementary information) 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. Data sharing requests should be sent to: drugdev@cancer.org.uk.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0	08/10/2024	15/10/2024	No	No
Participant information sheet	version 11.0	20/06/2022	18/12/2023	No	Yes
Plain English results			30/10/2024	No	Yes
Protocol file	version 10.0	14/10/2022	18/10/2024	No	No
Statistical Analysis Plan	version 4.0	06/02/2024	18/10/2024	No	No