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A trial to see the effect of cyclophosphamide and pembrolizumab on cancer in the kidney that has spread further into the body

Submission date
27/01/2020

Recruitment status
No longer recruiting

Registration date
07/02/2020

Overall study status
Completed

Last Edited
11/12/2025

Condition category
Cancer

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

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-cyclophosphamide-and-pembrolizumab-for-kidney-cancer-caper

Background and study aims
This study will investigate if adding an additional drug (cyclophosphamide) to an immunotherapy drug (pembrolizumab) increases the response of cancer to immunotherapy. The study will be looking at patients with metastatic clear cell renal cell carcinoma (a type of kidney cancer that has spread to other parts of the body) for which there are no standard existing chemotherapies available and who have had previous treatment with immunotherapy which has not been effective. Immunotherapy is a type of cancer treatment that boosts the body's natural defences to fight cancer. Every cancer has a slightly different environment in which the tumour exists this includes the surrounding blood vessels, immune cells and signalling molecules. This environment affects the way our body responds to cancer treatment and how well it works at reducing cancer growth and spread. The study aims to see if adding cyclophosphamide can alter the tumour environment and lead to a better response to the pembrolizumab.

Who can participate?
Patients aged over 18 with metastatic clear cell renal cell carcinoma

What does the study involve?
Participants take cyclophosphamide 50 mg tablets once a day for 21 days before adding intravenous (given directly into your blood through a drip) pembrolizumab treatment one day every 3 weeks. Participants continue both treatments until there are signs that cancer is growing and treatment is no longer working. Treatment is also stopped if patients have too many side effects; a maximum 24 months of treatment; or the tumour has shown a good response. Participants are scanned every 9 weeks and also have additional blood and biopsies taken to assess response.

What are the possible benefits and risks of participating?
It is hoped that the study treatments will help to stop cancer from growing or spreading.

However, this cannot be guaranteed. The information from this study may help to improve our understanding of how cyclophosphamide influences the immune system around renal cancers, which may help to develop new tests or medications to help other patients with renal cancer in the future. Participants are required to make additional visits to the hospital. Some of the additional tests and procedures may have possible side effects, risks and discomforts. Participants may experience none, some or all. During the study they will have to have blood taken, have CT scans (and for some patients MRI scans), and have samples of cancer removed for testing. These are standard and routine procedures and the study doctor will be able to explain these in detail and any risks and/or side effects associated. During blood tests participants may experience a scratching sensation as the needle goes in. They may also experience some bruising. CT scans use ionising radiation to form images of the body and provide other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chance of this happening is extremely small. Some people feel a bit claustrophobic when they are having an MRI scan. The possible risks associated with collection of tumour tissue samples will depend on the part of the body where the biopsy will be performed. Before a biopsy is taken participants will be given a local anaesthetic to numb the area to be biopsied. If they feel any discomfort following the biopsy the doctor may recommend painkillers. Rarely, a patient who has had a biopsy may experience infection and/or bleeding. Before undergoing a biopsy the doctor will consider the risk of developing any problems. If the risk is deemed significant the participant will not undergo this procedure and will not be able to take part in the study.

Where is the study run from?
1. The Royal Marsden NHS Foundation Trust (UK)
2. NHS Lothian (UK)
3. Cambridge University Hospitals NHS Foundation Trust (UK)
4. The Christie NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2018 to July 2023

Who is funding the study?
Merck Sharp and Dohme (UK)

Who is the main contact?
Dr Tom Waddell
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Contact information

Type(s)
Scientific

Contact name
Dr Tom Waddell

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-004314-17

Integrated Research Application System (IRAS)
209375

ClinicalTrials.gov (NCT)
NCT04262427

Central Portfolio Management System (CPMS)
42424

Study information

Scientific Title
The CAPER study: A Phase Ib clinical trial of Cyclophosphamide And PEmbrolizumab in metastatic Renal cell carcinoma (CAPER Trial)

Acronym
CAPER

Study objectives
The CAPER trial will investigate if adding an additional drug (cyclophosphamide) to an immunotherapy drug (pembrolizumab) increases the response of cancer to the immunotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/12/2019, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8012; Email: nrescommittee.northwest-haydock@nhs.net), ref: 19/NW/0705

Study design
Non-randomized; Interventional; Design type: Treatment, Drug, Immunotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Metastatic renal cell carcinoma

Interventions

Patient recruitment is expected to begin within 1 month of receiving approvals from the required regulatory authorities (HRA approval). Recruitment is expected to take 24 months and all patients are expected to have finished participation in the study within 12 months of this. Therefore it is expected the last patient, the last visit will be within 3 years of opening the first site. Analysis and interpretation of findings will take place within a year of this, therefore the results of the trial are expected within 4 years. 21 patients with metastatic renal cancer will be recruited to the trial.

Participants will be identified by their clinical team (or identified to a research nurse) and approached for the trial. All patients who take part in the trial will be used for the final analysis unless they have a deviation related to compliance with the trial treatment.

Patients will be required to go through a screening process to confirm eligibility and sign an informed consent form. Most screening tests are part of standard care and would have already been done and would not be considered as extra. These include: physical examination, demographics (checking age, sex, race etc.), medical history (what conditions the patient currently has and has had in the past), measuring height and weight, checking vital signs, reviewing any medication the patient is currently taking, and blood tests. As part of screening, patients will need to have a scan to measure their tumour (unless their last scan was within 4 weeks). This will be the baseline measurement for the primary endpoint.

Patients will receive 21 days of oral cyclophosphamide initially, and will then continue this treatment alongside an intravenous drip treatment every 21 days called Pembrolizumab which is a type of immunotherapy. Patients will have 3 tissue samples taken from their cancer at screening, cycle 2 and cycle 4 to try and assess the effects of drugs on the ‘good’ and ‘bad’ immune cells. They will also have additional blood samples collected prior to each treatment for the same reason.

The maximum amount of time that a patient could be on the study drugs is 102 weeks (this would be 34 cycles). Not all patients are expected to stay on the drugs for the full 34 cycles. The most common reason for a patient stopping the study treatment will be because of the cancer growing. It is expected that most patients will only stay on the drug for 6 cycles (18 weeks).

If the patient has disease progression they will stop taking the study drugs and will be followed up for survival.

If the patient stops taking the study drugs for any reason other than disease progression (cancer growing) e.g. severe treatment-related side effects, they will still need to come to the hospital for a follow-up to check their wellbeing. This visit will be 30 days after they finish treatment.

They will then have a visit every 9 weeks after this which will include a scan of their tumour to see whether it has grown. If they start a new anti-cancer therapy or their tumour has grown they will stop having the study scans. A phone call will be made every 12 weeks to check up on patient health and survival, however, this check may be done by the nurse looking at patient notes. These checks will continue until the end of participation in the trial or the end of the trial.

Based on the primary endpoint of overall response rate (ORR), it is planned to recruit a total of 21 eligible patients with the following statistical rationale:
Null hypothesis (H0): 0-1 out of 21 patients will respond to cyclophosphamide and

pembrolizumab (ORR <5%).
Alternative hypothesis (H1): At least 3 out of 21 patients will respond to cyclophosphamide and pembrolizumab (ORR target 20%).

If the alternative hypothesis is met then this would confirm the combination as being worthy of further evaluation.

This endpoint results from a direct anti-tumour effect of therapy, with associated tumour shrinkage. Given that the trial population will have already failed IO therapy, any tumour shrinkage seen with the combination of cyclophosphamide and pembrolizumab would support the immunomodulatory hypothesis, and provide an encouraging readout warranting further evaluation of this combination.
An interim analysis is planned to take place after the 12th patient has gone into follow-up following growth in their tumour. If none of the 12 patients has any evidence of anti-tumour response the trial will be terminated.

The trial is open-label with objective endpoints relating to RECIST v1.1 measurements, time to progression and overall survival, therefore there is little room for researcher bias.
The patient information sheet, informed consent form and protocol have been reviewed by patient representatives specifically looking at the screening process and trial schedule for patient burden and comprehension of the trial documents.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Cyclophosphamide, pembrolizumab

Primary outcome(s)
Objective Response Rate (ORR): occurrence of complete response or partial response as defined by RECIST v1.1 at any point in follow-up until end of study or death. Objective response is defined as occurrence of complete (CR) or partial responders (PR) as defined by the RECIST version 1.1 at any point in follow-up to death or end of study. Deaths before assessment, non-assessable or missing values will be counted as non-response. Best Objective Response is the highest value achieved for each patient and will be used for the primary outcome analysis. Time frame: from baseline up to 2 years, first documented progression or death

Key secondary outcome(s))
1. Progression-Free Survival (PFS): PFS events are defined as either disease progression or death from any cause. The event date used for analysis will be the first occurrence of either disease progression or death and the analysis will use the following formula:
Progression-free survival (months) = (exit date - date of first treatment)/30.4
Time frame: from the time of first treatment up to 2 years, the time of first documented progression, the censor date in months or death
2. Overall Survival (OS): OS events are defined as death from any cause. The event date used for analysis will be the confirmed date of death and the analysis will use the following formula:
Overall Survival (months) = (Exit date - date of first treatment)/30.4
Time frame: from first treatment up to 2 years or death by any cause in months

3. Incidence of treatment-emergent adverse events as assessed by occurrence of serious adverse events and adverse events of grade 3 severity and above. The number of patients reporting Serious Adverse Events (SAEs) and Grade 3 or higher toxicity will be summarised overall and by preferred term (if severity is missing, the worst case will be assumed).
Time frame: from commencement of treatment to 30 days post cessation of treatment

Completion date
11/07/2023

Eligibility

Key inclusion criteria
1. Histological confirmation of renal cell carcinoma (RCC) of predominantly (>50%) clear cell type
2. Presence of metastatic / locally advanced inoperable disease
3. Current evidence of disease progression on IO therapy as determined by CT / MRI imaging performed within 28 days prior to the first dose of study drug. Last dose of IO therapy must have been administered within 42 days prior to the first dose of study drug. IO therapy may consist of either:
3.1. First-line Ipilimumab / Nivolumab combination OR
3.2. Second / Third-line single-agent Nivolumab OR
3.3. Other PD-1 / PD-L1 / anti-CTLA-4 therapy within a clinical trial
4. Measurable disease according to RECIST version 1.1 criteria
5. Site(s) of disease which are easily accessible and suitable for repeated biopsies (bone metastases are not suitable as a biopsy site)
6. Provision of archival tumour tissue sample (formalin-fixed, paraffin-embedded (FFPE) tissue blocks) and a newly obtained core or excisional biopsy of a tumour lesion not previously irradiated
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study drug
8. Age > 18 years
9. Have adequate organ function as defined in Table 2 in the protocol (page 35). Specimens must be collected within 10 days prior to the start of study treatment
10. Able to take oral medications
11. Life expectancy of > 6 months in the opinion of the investigator
12. Male participants must agree to use a form of contraception as detailed in Appendix 3 of the protocol during the treatment period and for at least 180 days after the last dose of study treatment and refrain from donating sperm during this period
13. Female participants are eligible to participate if they are not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
13.1. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
OR
13.2. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 180 days after the last dose of study treatment.
14. The participant provides written informed consent for the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
9

Key exclusion criteria
1. Treatment with more than one prior line of IO therapy (including previous standard of care and trial treatments)
2. High burden / symptomatic disease which in the opinion of the treating investigator requires TKI / alternative therapeutic approach
3. Prior treatment with either pembrolizumab or cyclophosphamide
4. Known severe hypersensitivity (>= Grade 3) to pembrolizumab, cyclophosphamide and/or any of their excipients
5. Prior intolerance to IO therapy (any > Grade 2 toxicity which required permanent IO treatment discontinuation)
6. Ongoing AEs due to previous therapies or surgery which have not resolved to < = Grade 1 or baseline. Participants with < = Grade 2 neuropathy may be eligible
7. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
8. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
9. Known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial transitional cell carcinoma of the bladder/urothelial tract, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded
10. Prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<= 2 weeks of radiotherapy) to non-CNS disease
11. Live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chickenpox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed
12. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate

as long as it has been 4 weeks after the last dose of the previous investigational agent
13. Known previous or current CNS metastases and/or carcinomatous meningitis
14. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
15. Active infection requiring systemic therapy or has had requirement for antibiotics within 14 days prior to first dose of study treatment
16. Known history of Human Immunodeficiency Virus (HIV). Note: no testing for HIV is required
17. Known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA positive) infection. Note: no testing for Hepatitis B and Hepatitis C is required
18. Known history of active TB (Bacillus Tuberculosis). Note: no testing for TB is required
19. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
20. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial
21. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment. Note: WOCBP must have a negative urine pregnancy test within 72 hours prior to trial entry. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication

Date of first enrolment
28/04/2021

Date of final enrolment
21/10/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
The Royal Marsden NHS Foundation Trust
Renal and Melanoma Unit
Orchard House
Downs Road
Sutton
England
SW2 5PT

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
Scotland
EH1 3EG

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

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

Sponsor information

Organisation
Christie Hospital NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Other unpublished results	version 1.0	01/05/2024	20/06/2024	No	No
Plain English results			11/12/2025	No	Yes
Protocol file	version 3.0	11/12/2019	04/08/2021	No	No
Study website		11/11/2025	11/11/2025	No	Yes