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

Summary

EudraCT number	2018-004314-17
Trial protocol	GB
Global end of trial date	28 April 2023

Results information

Result version number	v1
This version publication date	30 June 2024
First version publication date	30 June 2024
Summary attachment (see zip file)	CAPER Statistical Analysis Report Version 1.0 (CAPER Final Analysis Report V1.0 20240501.pdf)

Trial information

Trial identification

Sponsor protocol code	CFTSp148

Additional study identifiers

ISRCTN number	ISRCTN95900287
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	550 Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	Dr Clare Griffin, Research Integrity and Governance Manager, The Christie NHS Foundation Trust, clare.griffin1@nhs.net
Scientific contact	Dr Clare Griffin, Research Integrity and Governance Manager, The Christie NHS Foundation Trust, clare.griffin1@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2023
Global end of trial reached?	Yes
Global end of trial date	28 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether the combination of oral metronomic (low doses of drug taken more often) cyclophosphamide and pembrolizumab will lead to objective tumour responses (a measurable shrinking of the tumour) in metastatic clear cell renal carcinoma (cancer of kidney cells that have spread to other parts of the body) patients who have previously progressed on immuno-oncology therapy (therapy that stimulates the immune system to fight cancer).

Protection of trial subjects:

Central and site monitoring is conducted to ensure protection of patients participating in the trial, and that trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	5

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Start of screening is defined as when a patient has been provided with the PIS and ICF and has had a discussion with their clinical care team regarding their treatment and the possibility of entry into a trial requiring additional tests.

Period 1

Period 1 title	Main Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Cyclophosphamide and Pembrolizumab

Arm description:

Cyclophosphamide
• Oral tablet
• 50mg once daily (OD) dosing (metronomic schedule)
• 21-day run-in period prior to commencing pembrolizumab
• Continuous dosing in 21-day cycles throughout (Q3W)
Pembrolizumab
• IV infusion
• 200mg flat dosing Q3W
• Commenced at C2D1 (following cyclophosphamide run-in)
• Continuous dosing Q3W throughout

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

• Oral tablet
• 50mg once daily (OD) dosing (metronomic schedule)
• 21-day run-in period prior to commencing pembrolizumab
• Continuous dosing in 21-day cycles throughout (Q3W)

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

• IV infusion
• 200mg flat dosing Q3W
• Commenced at C2D1 (following cyclophosphamide run-in)
• Continuous dosing Q3W throughout

Number of subjects in period 1	Cyclophosphamide and Pembrolizumab
Started	9
Completed	0
Not completed	9
Disease Progression	9

Baseline characteristics

Reporting groups

Reporting group title	Main Trial

Reporting group description: -

Reporting group values	Main Trial	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	64.1		
standard deviation	± 9	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	7	7	
Ethnicity Units: Subjects			
White British	7	7	
Any other white background	1	1	
Asian or Asian British: Indian	1	1	
Smoking Status Units: Subjects			
Current Smoker	1	1	
Ex-smoker	6	6	
Never Smoked	2	2	
Alcohol status Units: Subjects			
Regular	2	2	
Sporadic	4	4	
None	3	3	
ECOG performance Units: Subjects			
Zero	6	6	
One	3	3	
Protein			

Units: Subjects			
Negative	9	9	
Glucose Units: Subjects			
Negative	6	6	
Positive	3	3	
Blood Units: Subjects			
Negative	4	4	
Trace	4	4	
Positive	1	1	
Presence of sarcomatoid component Units: Subjects			
Yes	1	1	
No	7	7	
Missing	1	1	
Current TNM Stage Units: Subjects			
TX/NX/M1	1	1	
TX/N0/M1	2	2	
TX/N1/M1	2	2	
T1/N0/M1	1	1	
T3/NX/M1	1	1	
T4/N0/M1	1	1	
T4/N1/M1	1	1	
Fuhrman Grade Units: Subjects			
Two	1	1	
Three	3	3	
Four	4	4	
Missing	1	1	
IMDC prognostic group classification Units: Subjects			
Zero	2	2	
One	2	2	
Two	4	4	
Three	1	1	
Surgery for RCC Units: Subjects			
Yes	7	7	
No	2	2	
Radiotherapy for RCC Units: Subjects			
Yes	1	1	
No	8	8	
Systemic therapy for RCC Units: Subjects			
Yes	9	9	
Nitrites Units: Subjects			
Negative	9	9	

Number of years smoking			
This is only for the seven people that smoked.			
Units: Years			
arithmetic mean	21.1		
standard deviation	± 14.2	-	
Number of cigarettes per day			
This is for the seven smokers			
Units: Cigarettes			
arithmetic mean	12.4		
standard deviation	± 9.9	-	
Height			
Units: cm			
arithmetic mean	169.8		
standard deviation	± 9.8	-	
Weight			
Units: kg			
arithmetic mean	84.5		
standard deviation	± 19.2	-	
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	132.7		
standard deviation	± 8	-	
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	75.1		
standard deviation	± 5.8	-	
Temperature			
Units: degrees Celsius			
arithmetic mean	36.5		
standard deviation	± 0.5	-	
Respiratory rate			
Units: breaths per minute			
arithmetic mean	15.9		
standard deviation	± 2.3	-	
Pulse rate			
Units: beats per minute			
arithmetic mean	81		
standard deviation	± 9.8	-	
Oxygen saturation			
Units: percentage			
arithmetic mean	97.3		
standard deviation	± 1.5	-	
Haemoglobin			
Units: g/L			
arithmetic mean	135.3		
standard deviation	± 7.5	-	
White blood cell count			
Units: x10^9/L			
arithmetic mean	9.5		
standard deviation	± 1.5	-	
Platelets			
Units: x10^9/L			

arithmetic mean	295.4		
standard deviation	± 79.3	-	
Red blood cell count			
Units: x10^9/L			
arithmetic mean	4.9		
standard deviation	± 0.4	-	
Haematocrit			
Units: L/L			
arithmetic mean	0.4		
standard deviation	± 0	-	
Prothrombin time			
Units: seconds			
arithmetic mean	11.7		
standard deviation	± 0.9	-	
Absolute neutrophil count			
Units: x10^9/L			
arithmetic mean	6.8		
standard deviation	± 1.4	-	
Eosinophils			
Units: x10^9/L			
arithmetic mean	0.2		
standard deviation	± 0.1	-	
Basophils			
Units: x10^9/L			
arithmetic mean	0		
standard deviation	± 0	-	
Lymphocytes			
Units: x10^9/L			
arithmetic mean	1.8		
standard deviation	± 0.4	-	
Monocyte levels			
Units: x10^9/L			
arithmetic mean	0.5		
standard deviation	± 0.2	-	
INR			
Units: INR			
arithmetic mean	1.0		
standard deviation	± 0.1	-	
Sodium			
Units: mmol/L			
arithmetic mean	136.9		
standard deviation	± 2	-	
Potassium			
Units: mmol/L			
arithmetic mean	4.6		
standard deviation	± 0.4	-	
Urea			
Units: mmol/L			
arithmetic mean	6.5		
standard deviation	± 3	-	
Creatinine			
Units: µmol/L			

arithmetic mean	98.4		
standard deviation	± 22.7	-	
GFR			
Units: ml/min			
arithmetic mean	68		
standard deviation	± 21.5	-	
Alkaline phosphatase			
Units: IU/L			
arithmetic mean	98.9		
standard deviation	± 23.4	-	
Bilirubin			
Units: µmol/L			
arithmetic mean	7.4		
standard deviation	± 4	-	
Calcium – unadjusted			
Units: mmol/L			
arithmetic mean	2.4		
standard deviation	± 0.2	-	
Magnesium			
Units: mmol/L			
arithmetic mean	0.8		
standard deviation	± 0.1	-	
Phosphate			
Units: mmol/L			
arithmetic mean	1.1		
standard deviation	± 0.2	-	
Alanine aminotransferase			
Units: ul/L			
arithmetic mean	25.2		
standard deviation	± 17.6	-	
Lactate dehydrogenase			
Units: IU/L			
arithmetic mean	183.1		
standard deviation	± 31.9	-	
Total protein			
Units: g/L			
arithmetic mean	70.1		
standard deviation	± 3.1	-	
Albumin			
Units: g/L			
arithmetic mean	42.2		
standard deviation	± 3.6	-	
Glucose			
Units: mmol/L			
arithmetic mean	9.2		
standard deviation	± 5.8	-	
Free T4			
Units: mmol/L			
arithmetic mean	16.4		
standard deviation	± 3.1	-	
Thyroid stimulating hormone			
Units: mIU/L			

arithmetic mean	2.6		
standard deviation	± 1.4	-	
Specific gravity			
Units: Specific gravity			
arithmetic mean	114.2		
standard deviation	± 339.7	-	
pH			
Units: pH			
arithmetic mean	6		
standard deviation	± 0.6	-	
Time from initial diagnosis to registration			
Units: days			
arithmetic mean	2589.6		
standard deviation	± 1630.3	-	
Time from metastatic disease confirmation to registration			
Units: days			
arithmetic mean	1728.9		
standard deviation	± 1344.8	-	
Sum of lesion diameter			
Units: mm			
arithmetic mean	94.7		
standard deviation	± 58.5	-	
Activated Partial Thromboplastin Time			
Units: Seconds			
arithmetic mean	26.9		
standard deviation	± 3.5	-	

End points

End points reporting groups

Reporting group title	Cyclophosphamide and Pembrolizumab

Reporting group description:

Cyclophosphamide
• Oral tablet
• 50mg once daily (OD) dosing (metronomic schedule)
• 21-day run-in period prior to commencing pembrolizumab
• Continuous dosing in 21-day cycles throughout (Q3W)
Pembrolizumab
• IV infusion
• 200mg flat dosing Q3W
• Commenced at C2D1 (following cyclophosphamide run-in)
• Continuous dosing Q3W throughout

Primary: Object response as per RECIST

End point title	Object response as per RECIST[1]

End point description:

End point type	Primary

End point timeframe:

The primary endpoint of the trial is ORR according to RECIST version 1.1 from baseline until end of study or death, and will be calculated using the best response achieved during study treatment for each participant.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the trial being stopped early, there was no statistical analyses conducted.

End point values	Cyclophosphamide and Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Participants				
Progressive Disease	3			
Stable Disease	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

PFS, measured from the time of first treatment to the time of first documented progression or the

censor date in months

End point values	Cyclophosphamide and Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Months				
median (confidence interval 95%)	3.9 (1.2 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

12 month survival probability is reported as the median survival time could not be calculated.

End point type	Secondary

End point timeframe:

OS, defined as the time from first treatment to death by any cause in months

End point values	Cyclophosphamide and Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Probability				
number (confidence interval 95%)	0.9 (0.4 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety and tolerability of the combination of cyclophosphamide and pembrolizumab, reported following the CTCAE version 5 guidelines

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Safety

Reporting group description:

Participants had to have had at least once dose of medication.

Serious adverse events	Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Investigations			
Biopsy			

subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2		
Nervous system disorders Hemiparesis subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 4 / 9 (44.44%) 5 1 / 9 (11.11%) 1		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Frequent bowel movements subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1 4 / 9 (44.44%) 5		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

Musculoskelatal pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
COVID-19			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Onychomycosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypocalcaemia			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2021	This version was no approved by the MHRA Main changes were: - Clarification on End of Trial Definition in line with LCTC protocol template - Update to inclusion criterion 12: male participants contraception/abstinence timeframe from 180 days to 210 days; and inclusion criterion 13: female participants contraception/abstinence timeframe from 180 days to 150 days - Update to Exclusion criterion 14 with inclusion of interstitial lung disease to align with MSD protocol template - Update to male participants contraception/abstinence timeframe from 180 days to 210 days; and female participants contraception/abstinence timeframe from 180 days to 150 days - Update to dose modification guidance for pembrolizumab for immune-related AEs to align with MSD protocol template - Update to dose modification & toxicity management table for pembrolizumab for immune-related AEs to align with MSD protocol - Update to table to clarify what constitutes an SAE in line with regulatory definitions and funder AESI - Clarification on archiving responsibilities of sites and organisations involved in the study
17 November 2021	- Update to inclusion criterion 13: female participants contraception/abstinence timeframe from 150 days to 180 days - Update to female participants contraception/abstinence timeframe from 150 days to 180 days
16 December 2021	Main changes were - - Update to inclusion criterion 3: clarification on previous IO therapies patients can have received - Update to exclusion criterion 1: clarification on previous IO therapies patients can have received - Update on exclusion criterion 3: clarification to allow prior use of pembrolizumab for the CAPER study as per inclusion criterion 3 - Clarification that investigator can perform physical examinations if clinically indicated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 April 2023	The sponsor and CI have taken the decision to terminate the trial early due to poor recruitment and lack of funding.	-

Notes:

Limitations and caveats

None reported