Clinical trial results:
Phase I 'run in' study followed by randomised phase II trial testing intra-tumoural hydrogen peroxide as a radiation sensitizer in patients with locally advanced/recurrent breast cancer in terms of toxicity and tumour response

Summary

EudraCT number	2016-000833-40
Trial protocol	GB
Global end of trial date	12 November 2020

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	CCR4502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02757651
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicaTrials.gov: NCT02757651

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	123 Old Brompton Road, London, United Kingdom, SW7 3RP
Public contact	Research Coordinator, The Institute of Cancer Research, 0044 020 8661 3460, lone.gothard@icr.ac.uk
Scientific contact	Research Coordinator, The Institute of Cancer Research, 0044 020 8661 3460, lone.gothard@icr.ac.uk

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	15 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2020
Global end of trial reached?	Yes
Global end of trial date	12 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I
Objective:
To confirm safety reported in Japanese studies.
Endpoint:
Patient reported maximum intra-tumoural pain intensity over duration of treatment.

Phase II is currently underway under protocol CCR5119 / EudraCT 2019-001709-25

Protection of trial subjects:

Subjects were monitored closely for pain and skin toxicity and medication and advice provided as required.

Background therapy:

N/a

Evidence for comparator:

N/a

Actual start date of recruitment	01 October 2016
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: 12
Worldwide total number of subjects	12
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	6
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited between 8-Feb-2017 and 13-Jun-2018. 13 subjects were consented, but 1/13 withdrew due to clinical deterioration prior to any treatment and was not included in the analysis.

Pre-assignment

Screening details:

Screening data was not collected for patients approached but not entered into the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Daily radiotherapy

Arm description:

49.5 Gy in 18 daily fractions of radiotherapy + twice weekly H2O2 injections starting week 2

Arm type	Experimental
Investigational medicinal product name	H2O2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intratumoral use

Dosage and administration details:

A slow-release 0.5% H2O2 solution created by mixing 0.4ml of 3% H2O2 with 2.0ml OSTENIL (sodium hyaluronate)

Arm title	Twice weekly radiotherapy

Arm description:

36 Gy in 6 fractions of radiotherapy + twice weekly H2O2 injections starting week 2

Arm type	Experimental
Investigational medicinal product name	H2O2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intratumoral use

Dosage and administration details:

A slow-release 0.5% H2O2 solution created by mixing 0.4ml of 3% H2O2 with 2.0ml OSTENIL (sodium hyaluronate)

Number of subjects in period 1	Daily radiotherapy	Twice weekly radiotherapy
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	12	12	
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	6	6	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	10	10	
Male	2	2	

Subject analysis sets

Subject analysis set title	All subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All 12 subjects analysed as part of this phase 1 safety study

Reporting group values	All subjects		
Number of subjects	12		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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 65-84 years	6		
85 years and over	2		

Gender categorical Units: Subjects			
Female	10		
Male	2		

End points

End points reporting groups

Reporting group title	Daily radiotherapy
Reporting group description:	
49.5 Gy in 18 daily fractions of radiotherapy + twice weekly H2O2 injections starting week 2	
Reporting group title	Twice weekly radiotherapy
Reporting group description:	
36 Gy in 6 fractions of radiotherapy + twice weekly H2O2 injections starting week 2	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All 12 subjects analysed as part of this phase 1 safety study	

Primary: Patient reported maximum intra-tumoural pain intensity over duration of treatment

End point title	Patient reported maximum intra-tumoural pain intensity over duration of treatment
End point description:	
The maximum intra-tumoural pain intensity taken from the pain questionnaire provided to patients before and 0-24 hours after each KORTUC injection. The maximum intensity for all patients were then presented as proportions and frequencies	
End point type	Primary
End point timeframe:	
Duration of treatment	

End point values	Daily radiotherapy	Twice weekly radiotherapy	All subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	12	
Units: Pain intensity				
number (not applicable)	6	6	12	

Statistical analyses

Statistical analysis title	Summary of pain intensity
Statistical analysis description:	
Description of patient reported maximum intra-tumoural pain intensity over duration of treatment	
Comparison groups	Daily radiotherapy v Twice weekly radiotherapy v All subjects
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Descriptive analysis
Parameter estimate	Median and IQR
Point estimate	3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	4

Notes:

[1] - Descriptive analysis

Secondary: Skin toxicity

End point title	Skin toxicity

End point description:

Proportion of patients with grade ≥3 acute skin toxicity at any time from start of radiotherapy to 4 weeks after completion

End point type	Secondary

End point timeframe:

From start of radiotherapy to 4 weeks post radiotherapy

End point values	Daily radiotherapy	Twice weekly radiotherapy	All subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	12	
Units: Grade 3 or more Toxicity				
Tox Grade < 3	5	6	11	
Tox Grade >=3	1	0	1	

Statistical analyses

Statistical analysis title	Proportion of patients with grade≥3 acute skin tox

Statistical analysis description:

Proportion of patients with grade ≥3 acute skin toxicity at any time from start of radiotherapy to 4 weeks after completion

Comparison groups	Daily radiotherapy v Twice weekly radiotherapy v All subjects
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Descriptive analysis
Parameter estimate	Proportion
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	38.5

Notes:

[2] - Descriptive analysis

Secondary: Tumour response

End point title	Tumour response
End point description:	
Tumour response 3, 6, 9 and 12 months post- radiotherapy according to RECIST 1.1 criteria	
End point type	Secondary
End point timeframe:	
3 - 12 months post radiotherapy	

End point values	Daily radiotherapy	Twice weekly radiotherapy	All subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	6	12	
Units: Best response				
CR	1	0	1	
PR	4	6	10	
SD	0	0	0	
PD	1	0	1	

Statistical analyses

Statistical analysis title	Best response
Statistical analysis description:	
Best tumour response 3, 6, 9 and 12 months post-radiotherapy according to RECIST 1.1 criteria	
Comparison groups	Daily radiotherapy v Twice weekly radiotherapy v All subjects
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Descriptive analysis
Parameter estimate	Proportion
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	38.5

Notes:

[3] - Overall best tumour response

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of consent to 24 months post radiotherapy (90 days to 24 months post radiotherapy: SAR or SUSAR only).

Adverse event reporting additional description:

The active monitoring period was defined as date of consent to 90 days after the last exposure to radiotherapy. Following this, any SAR or SUSAR were also recorded to the end of trial participation at 24 months post radiotherapy.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.02

Reporting groups

Reporting group title	All subjects

Reporting group description:

All 12 subjects included in the analysis.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 12 (8.33%)		
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	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Hypomagnesium			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Low potassium			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Mild hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Mild hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Normocytic anaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Mild hyponatraemia			

subjects affected / exposed occurrences (all) Suspected fall subjects affected / exposed occurrences (all) Temperature spike subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Vascular disorders Varicose veins subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oral thrush subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all)	 5 / 12 (41.67%) 5 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2		
Respiratory, thoracic and mediastinal disorders Dry cough subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

Pleural effusion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders Arm lymphoedema subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Chronic kidney disease - fluid overload subjects affected / exposed occurrences (all) UTI subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Infections and infestations Sepsis subjects affected / exposed occurrences (all) Shivery subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2016	AM1611/21 Addition of exclusion criteria. Addition of tumour tissue collection. Amendment to footnote on contraception.
02 March 2017	AM1702/57 Error. The protocol was always intended for men as well as women and the title and inclusion criteria have now been corrected accordingly.
12 April 2017	AM1704/08 Clarification of number of KORTUC injections (6 Fr). Change to stopping rules and withdrawal criteria. Change to inclusion criterion (minimum tumour size).
12 April 2017	AM1707/42 Change to stopping rules.
26 October 2017	AM1710/48 Change to eligibility criteria (allowing concomitant Herceptin and Pentuzumab).
28 December 2017	AM1711/83 Change to eligibility criteria (allowing concomitant Denosumab). Clarification of number of KORTUC injections (18 Fr) List of AEs not to be reported to Sponsor.
25 January 2019	AM1901/71 Change of Sponsor from The Royal Marsden NHS Foundation Trust to The Institute of Cancer Research.
25 February 2019	AM1902/43 Addition of 3 time points for the secondary endpoint of tumour control in phase I.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32585332