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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 November 2016 | AM1611/21<br>Addition of exclusion criteria.<br>Addition of tumour tissue collection.<br>Amendment to footnote on contraception. |
| 02 March 2017 | AM1702/57<br>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<br>Clarification of number of KORTUC injections (6 Fr).<br>Change to stopping rules and withdrawal criteria.<br>Change to inclusion criterion (minimum tumour size). |
| 12 April 2017 | AM1707/42<br>Change to stopping rules. |
| 26 October 2017 | AM1710/48<br>Change to eligibility criteria (allowing concomitant Herceptin and Pentuzumab). |
| 28 December 2017 | AM1711/83<br>Change to eligibility criteria (allowing concomitant Denosumab).<br>Clarification of number of KORTUC injections (18 Fr)<br>List of AEs not to be reported to Sponsor. |
| 25 January 2019 | AM1901/71<br>Change of Sponsor from The Royal Marsden NHS Foundation Trust to The Institute of Cancer Research. |
| 25 February 2019 | AM1902/43<br>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