

# Capecitabine oral chemotherapy with radium-223 in breast cancer patients with bone metastases (CARBON)

<b>Submission date</b> 17/02/2016	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 17/02/2016	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 06/03/2024	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-capecitabine-and-radium-223-for-advanced-breast-cancer-carbon>

## Contact information

### Type(s)

Public

### Contact name

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### Contact details

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## Additional identifiers

### EudraCT/CTIS number

2015-003979-29

### IRAS number

### ClinicalTrials.gov number

Nil known

## Secondary identifying numbers

CPMS 20654

# Study information

## Scientific Title

A randomized phase IB/IIA study of CApecitabine plus Radium-223 (Xofigo) in breast cancer patients with BONE metastases (CARBON): an open-label interventional study

## Acronym

CARBON

## Study objectives

In advanced breast cancer, most patients with bone involvement also have metastases in other organs. Thus, a bone-targeted treatment alone is unlikely to be relevant to the majority of patients. Combination strategies with established systemic breast cancer treatments are needed. This is an open-label study which comprises an initial safety phase to establish the feasibility and safety of combining radium-223 at the licensed dose and to the same maximum recommended total dose, but given on a 6 weekly schedule to enable combination with oral capecitabine administered with the usual two weeks on and one week off treatment schedule. The safety phase, if treatment proves to be safe and feasible, will be followed by a randomised extension phase to further characterise the safety profile and provide preliminary information on efficacy.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

London - Fulham Research Ethics Committee, 03/02/2016, ref: 16/LO/0052

## Study design

Interventional; Design type: Treatment

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Other

## Study type(s)

Treatment

## Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

## Health condition(s) or problem(s) studied

Topic: Cancer; Subtopic: Breast Cancer; Disease: Bone, Breast

## **Interventions**

Patients in the initial safety phase will receive capecitabine plus radium-223. Patients in the randomised extension phase will be randomised to receive either oral capecitabine alone or capecitabine plus radium-223 (added 07/03/2016).

Usual hospital stock of capecitabine 500mg and 150mg tablets will be used and supplied as trial specific stock according to standard operating procedures within the treating centre. Patients should swallow capecitabine tablets with water 30 min after a meal twice a day. Standard care should be followed regarding missed and vomited doses

Radium-223 50 kBq/kg b.w (55 kBq/kg after implementation of NIST update) will be administered as a slow i.v. injection 6 times at 6 weekly intervals. This treatment can be administered on an outpatient basis. It will be administered on day 1 of each alternate cycle (cycles 2, 4, 6, 8, 10 and 12). A cycle is 21 days in accordance with the standard administration of capecitabine.

Follow Up Length: 12 month(s)

## **Intervention Type**

Mixed

## **Primary outcome measure**

As of 07/03/2016:

Initial safety phase

1. Dose limiting toxicities

Randomised extension phase

1. Frequency of CTC grade III-IV toxicities with a focus on diarrhoea as the primary dose limiting toxicity

2. Decrease in uNTX from baseline to end of cycle 5 (approximately 15 weeks post trial entry).

For patients who progress prior to the end of cycle 5, the decrease in uNTX from baseline to their end of study treatment visit will be used.

Previous primary outcome measures:

To evaluate the safety and toxicity of the combination of radium-223 and capecitabine

## **Secondary outcome measures**

As of 07/03/2016:

1. Safety endpoints

1.1. Adverse events (AEs) and serum biochemistry and haematology abnormalities graded according to the Common Toxicity Criteria for Adverse Events (CTC) version 4.03

1.2. Serious adverse events

1.3. Dose delays and reductions due to toxicity

2. Efficacy endpoints

2.1. Changes from baseline in serum bone turnover markers (B-ALP, uNTX, P1NP, CTX and 1CTP) throughout the study period

2.2. Time to occurrence of 1st symptomatic skeletal event (SSE). This is time from registration / randomisation to 1ST SSE. Patients who do not experience an SSE by the time of final analysis will be censored at the last time known to have not experienced as SSE, study withdrawal, start

of new treatment or death

2.3. Time to progression of bone disease based on unequivocal progression of existing bone lesions or appearance of one or more new osteolytic bone lesions. This is time from registration / randomisation to progression in bone. Patients who do not progress in bone by time of final analysis will be censored at the last time known to have not progressed in bone, study withdrawal, start of new treatment or death

2.4. Time to progression of extraskkeletal disease. This is time from registration / randomisation to progression in extraskkeletal non bony sites. Patients who do not progress outside bone by time of final analysis will be censored at the last time known to have not progressed outside bone, study withdrawal, start of new treatment or death

3. Clinical benefit endpoints

3.1. Pain scores using the Brief Pain Inventory (BPI)

3.2. Quality of life using the EORTC BM-22 bone metastases module

Previous secondary outcome measures:

To evaluate the effect of radium-223 on other bone turnover markers (P1NP, CTX, 1CTP, B-ALP)

### **Overall study start date**

01/03/2015

### **Completion date**

02/08/2021

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria, as of 19/03/2018:

1. Female patients with histological evidence of primary breast cancer
2. Bone metastases (with or without soft tissue, lymph node or visceral metastases; brain metastases allowed if stable and untreated for = 8 weeks)
3. = 2 bone lesions confirmed on imaging (plain radiographs, CT or MRI)
4. Systemic chemotherapy with capecitabine is felt to be appropriate by the treating physician due to recent progression of metastatic disease
5. Received = 2 lines of chemotherapy in the metastatic setting. Prior cytotoxic therapy must have been completed = 28 days prior to initiation of study treatment
6. Patient has been on bone targeted therapy (bisphosphonate or denosumab) for at least 6 weeks prior to start of study treatment and no change to bone targeted therapy is expected during the treatment phase of the study.
7. ECOG performance status 0-2
8. Life expectancy = 6 months
9. Laboratory requirements:
  - 9.1. WBC =  $3.0 \times 10^9$  /l 3000/mm<sup>3</sup>
  - 9.2. ANC =  $1.5 \times 10^9$  /l 1500/mm<sup>3</sup>
  - 9.3. Platelet count =  $100 \times 10^9$  /l
  - 9.4. Haemoglobin = 10.0g/dL
  - 9.5. Total bilirubin level = 1.5 times ULN in treating institution
  - 9.6. AST and ALT = 3 times ULN in treating institution
  - 9.7. Calculated creatinine clearance or estimated GFR > 50mls/min (Cockcroft and Gault or Wright formula may be used according to local practice)
10. Patient must be willing and able to comply with the protocol, including follow-up visits and investigations and use effective contraception if relevant throughout the study and for at least 6

months after treatment completion

11. Must be fully informed about the study and has signed the informed consent form

12. Age at least 18 years

Previous inclusion criteria:

1. Female patients with histological evidence of primary breast cancer

2. Bone metastases (with or without soft tissue, lymph node or visceral metastases; brain metastases allowed if stable and untreated for = 8 weeks)

3. = 2 bone lesions confirmed on imaging (plain radiographs, CT or MRI)

4. Systemic chemotherapy with capecitabine is felt to be appropriate by the treating physician due to recent progression of metastatic disease

5. Received = 2 lines of chemotherapy in the metastatic setting. Prior cytotoxic therapy must have been completed = 28 days prior to initiation of study treatment

6. Patient has been on bone targeted therapy (bisphosphonate or denosumab) for at least 3 months prior to start of study treatment and no change to bone targeted therapy is expected during the treatment phase of the study

7. ECOG performance status 0-2

8. Life expectancy = 6 months

9. Laboratory requirements:

9.1. WBC =  $3.0 \times 10^9$  /l 3000/mm<sup>3</sup>

9.2. ANC =  $1.5 \times 10^9$  /l 1500/mm<sup>3</sup>

9.3. Platelet count =  $100 \times 10^9$  /l

9.4. Haemoglobin = 10.0g/dL

9.5. Total bilirubin level = 1.5 times ULN in treating institution

9.6. AST and ALT = 3 times ULN in treating institution

9.7. Calculated creatinine clearance or estimated GFR > 50mls/min (Cockcroft and Gault or Wright formula may be used according to local practice)

10. Patient must be willing and able to comply with the protocol, including follow-up visits and investigations and use effective contraception if relevant throughout the study and for at least 6 months after treatment completion

11. Must be fully informed about the study and has signed the informed consent form

12. Age at least 18 years

### **Participant type(s)**

Patient

### **Age group**

Adult

### **Lower age limit**

18 Years

### **Sex**

Female

### **Target number of participants**

Planned Sample Size: 48; UK Sample Size: 48; Description: The sample size for the initial safety phase will require a minimum of 6 and a maximum of 12 evaluable patients. This is based on the number of patients experiencing dose-limiting toxicities. A modified 3+3 approach has been

used to ensure an acceptable toxicity rate, and enable dose reduction if unacceptable toxicity is observed, prior to moving to a randomised extension phase. Up to 36 treated patients will be randomised on a 1:2 basis in the randomised extension phase at the RD.

### **Total final enrolment**

34

### **Key exclusion criteria**

1. Received an investigational drug within 4 weeks prior to the first study treatment
2. Received external beam radiotherapy within 4 weeks prior to the first study treatment
3. Presence of imminent or established spinal cord compression based on clinical findings and/or MRI
4. Presence of other currently active (diagnosis within the last 5 years) malignancy (except treated non-melanoma skin cancer (basal or squamous), carcinoma in situ of cervix and superficial bladder cancers).
5. Patients who have had severe and unexpected reactions to fluoropyrimidine therapy or have been diagnosed with dihydropyrimidine dehydrogenase deficiency
6. Received a blood transfusion or Use of erythropoietin within 4 weeks of study treatment
7. Pregnant or breast-feeding women.
8. Treatment with sorivudine or its chemically related analogues, such as brivudine
9. Treatment with phenytoin or warfarin
10. Patients with any other serious illness or medical condition, such as, but not limited to:
  - 10.1. Any uncontrolled infection
  - 10.2. Clinical heart failure (NYHA Heart Failure Class III or IV)
  - 10.3. Active Crohn's disease or ulcerative colitis
  - 10.4. Bone marrow myelodysplasia
  - 10.5. Uncontrolled coronary artery disease
  - 10.6. Active peptic ulcers
  - 10.7. Malabsorption
11. Any exclusions as per the Xofigo or Capecitabine SmPC

### **Date of first enrolment**

28/09/2016

### **Date of final enrolment**

20/03/2019

## **Locations**

### **Countries of recruitment**

England

United Kingdom

### **Study participating centre**

**St James' University Hospital**

NHS Trust

The Leeds Teaching Hospitals NHS Trust

Beckett Street

Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**

**Weston Park Hospital**

Sheffield Teaching Hospitals NHS FT  
Whitham Road  
Sheffield  
United Kingdom  
S10 2SJ

**Study participating centre**

**Manchester Cancer Research Centre**

The Christie NHS Foundation Trust  
Wilmslow Road  
Manchester  
United Kingdom  
M20 4QL

**Study participating centre**

**Clatterbridge Centre for Oncology NHS Foundation Trust**

Clatterbridge Road  
Bebington  
Wirral  
Liverpool  
United Kingdom  
CH63 4JY

## **Sponsor information**

**Organisation**

Sheffield Teaching Hospitals NHS Trust

**Sponsor details**

Royal Hallamshire Hospital  
Glossop Road  
Sheffield  
England  
United Kingdom  
S10 2JF

**Sponsor type**

Hospital/treatment centre

**ROR**

<https://ror.org/018hjpz25>

## **Funder(s)**

**Funder type**

Industry

**Funder Name**

Bayer HealthCare

**Alternative Name(s)**

BHC

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

Germany

**Funder Name**

Yorkshire Cancer Research

**Alternative Name(s)****Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

## **Results and Publications**

**Publication and dissemination plan**



The publication policy is to be defined by the Trial Management Group and reviewed by the Safety Review Committee, but will include the Chief Investigator and study statistician as a minimum with additional authors included according to ICMJE criteria. Publication of emerging safety data in the form of abstracts for oral or poster presentation, or journal letters is permitted. However no formal manuscript publication is permitted until the final analysis of the primary endpoint trial data has been completed. The release of any data prior to this must be approved by the independent members of the Safety Review Committee. All publications must have the approval of the Chief Investigator. Draft manuscripts and abstracts will be made available to Bayer and YCR prior to submission for comment. The decision to publish and final responsibility for the content will rest with the Chief Investigator and the Trial Management Group.

### **Intention to publish date**

31/08/2020

### **Individual participant data (IPD) sharing plan**

Not provided at time of registration

### **IPD sharing plan summary**

Not expected to be made available

### **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol article</a>	protocol	15/01/2020	17/01/2020	Yes	No
<a href="#">Basic results</a>		22/07/2022	22/07/2022	No	No
<a href="#">HRA research summary</a>			26/07/2023	No	No
<a href="#">Results article</a>		24/06/2022	06/03/2024	Yes	No