ISRCTN55804223 https://doi.org/10.1186/ISRCTN55804223

NEPTUNE: Determining the safety and assessing the effectiveness of combining avelumab and radium-223 in patients with breast cancer which has spread to the bones

Submission date
25/11/2019

Recruitment status
Stopped

Registration date
02/12/2019

Overall study status
Stopped

Last Edited
09/01/2025

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mr Jamie Oughton

Contact details
CTRU Neptune Study
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 (0)113 343 9077
medctnep@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2018-003620-37

Protocol serial number

CPMS: 39382

Study information

Scientific Title
NEPTUNE: Enhancement of immuNothEraPy combining avelumab and repeaT doses of radiUm-223 in ER+ve, HER2-ve metastatic breast caNcEr

Acronym
NEPTUNE

Study objectives
NEPTUNE is a study of patients with breast cancer that has spread to their bones. It will look at the safety and efficacy of treatment with avelumab and radium-223. All of the participants will be female patients attending selected NHS hospitals who have already had at least two different treatments for their cancer after it has spread to their bones.

About 70% of patients with advanced breast cancer will have the cancer spread to their bones, and the current treatments for these patients have relatively modest benefits and can cause a lot of side effects. If this trial finds this new treatment combination is effective, it may give these patients another treatment option that could have more benefits or less side effects.

These treatments have not been used together or on breast cancer patients before, but there is evidence that both radium-223 and avelumab are effective at treating other cancers. Avelumab helps the immune system fight the cancer and radium-223 binds to bones and kills cancer cells.

This study has two parts, or phases and participants will only take part in one phase. The first phase is a safety phase, where 6 patients will be recruited and treated with both avelumab and radium-223. They will be monitored closely to ensure the dosages of the drugs are safe and do not produce significant side effects. If the dosages are safe, there will then be an expansion phase, where 36 patients will be recruited and randomly allocated to receive either avelumab alone or avelumab and radium-223 together. The expansion phase will show researchers whether using radium-223 has an effect on the response of the cancer to avelumab.

The treatment will last up to 26 weeks, with avelumab being given once every two weeks and radium-223 being given once every 4 weeks.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 31/10/2019, South Central – Hampshire B Research Ethics Committee (Level 3 Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; Tel: +44 (0)20 7104 8057; Email: nrescommittee.southcentral-hampshireb@nhs.net), REC Ref: 19/SC/0536

Study design
Randomised; Interventional; Design type: Treatment, Drug, Immunotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Breast cancer

Interventions
This is a multi-centre, open-label, phase Ib/IIa, proof of concept study with a randomised expansion phase in eligible patients with ER+ve, HER2-ve breast cancer patients with bone metastasis and measurable metastatic disease at other sites. The trial aims to investigate the safety and preliminary efficacy of avelumab (13 x 2-weekly IV) combined with radium-223 (6 x 4-weekly IV). Up to 42 patients are expected to be recruited across both phases of the trial, 6 in the initial safety phase and a further 36 in the randomised expansion phase. A number of baseline assessments need to be conducted prior to the first administration of trial treatment. These include: a physical examination, a CT/MRI, a planar bone scintigraphy/SPECT +/-CT, blood & urine sampling, a Quality of Life Questionnaire, and metastatic tumour biopsy sampling (where this has not already been taken as part of standard care).

As these drugs have never previously been used in breast cancer patients in combination, an initial safety phase is required. This safety phase consists of 6 treatment cycles, each of 28 days in duration. During the safety phase all patients will be given avelumab at 10 mg/kg (the standard approved dose in non-breast cancers) on days 1 & 15 of each cycle and radium-223 at 55 kBq/kg (the standard approved dose in prostate cancer) at day 1 of each cycle to establish safety. During the initial safety phase, the first patient will be recruited and observed for the dose-limiting toxicity (DLT) reporting period, prior to any further participants being recruited. Follow Safety Review Committee (SRC) approval a further two patients will be recruited to the first cohort and observed for the DLT reporting period also. The SRC will meet after each cohort of three patients in order to review safety data. In the unlikely event that there are safety issues at these doses, the SRC may recommend a further cohort of up to six patients be recruited to the initial safety phase, with a modified treatment regime.

Once safety has been confirmed, this will be followed by a Phase IIa expansion phase which will assess efficacy based on overall response rate (ORR). The expansion phase also consists of six treatment cycles, each of 28 days in duration. Patients in this phase will be randomly allocated (2:1) to either avelumab plus radium-223 at the confirmed safe dose or to a calibration arm (avelumab only) to provide concurrent efficacy and safety data for interpretation purposes only. During the randomised expansion phase, the SRC will meet every 3 months. Endpoint data will be collected at regular intervals during treatment and follow-up throughout phases Ib and IIa of the trial. This will be achieved by conducting the following trial procedures: physical examinations, blood & urine sampling, vital signs, Quality of Life Questionnaires, CT/MRIs, planar bone scintigraphy/SPECT +/-CTs, and safety event reporting.

Once the treatment phase is complete, participants will be followed-up until one of the following occurs: disease progression, the commencement of a new anti-cancer treatment, or the end of the current trial. The trial duration is expected to be approximately 36 months from opening to recruitment to end of follow-up; 24 months for recruitment and 12 months follow-up.

Intervention Type
Drug

Phase

Phase I/II

Drug/device/biological/vaccine name(s)
Avelumab, radium-223

Primary outcome(s)
Phase Ib initial safety phase:
The number of dose-limiting toxicities (DLTs) observed during the DLT period. This will confirm the safety of radium-223 in combination with avelumab

Randomised expansion phase:
Objective response rate (ORR), calculated as the proportion of participants achieving at least a partial response (according to RECIST 1.1 (to include bone response)) within 24 weeks of cycle 1 day 1

Key secondary outcome(s))
Secondary outcome measures:
1. Safety and toxicity assessed by the occurrence of:
1.1. AEs & SAEs over the course of the study, recorded at the following timepoints: 7 days prior to day 1 of each treatment cycle, 7 days prior to day 15 of each treatment cycle, 30 days post treatment, and 90 days post treatment
1.2. SARs, SUSARs, ARs over the course of the study, recorded within 24 hours of the event occurring from baseline until disease progression, new anti-cancer treatment, or end of trial (whichever occurs first).
2. Tumour response according to RECIST 1.1 and where appropriate immune-RECIST (iRECIST), including maximum objective response of measurable non-osseous lesions, assessed within 24 weeks of cycle 1 day 1
3. Time to progression of bone disease, based on either unequivocal progression of existing bone lesion(s) or appearance of one or more new osteolytic bone lesions
4. Time to first documented disease progression either clinical or radiological
5. Disease control rate and duration of clinical benefit
6. Treatment compliance as assessed by dose omissions/delays, recorded at each treatment visit throughout the treatment phase.
7. Bone turnover markers in serum (PINP) and urine (uNTX:creatinine ratio) measured using the concentrations of serum PINP and a ratio between concentrations of urinary NTX and creatinine, respectively, at baseline and prior to cycle 4
8. Time to occurrence of first SSE (symptomatic skeletal-related event)
9. Quality of life measured using EORTC QLQ-C30 and QLQ-BM22 at the following timepoints: prior to treatment allocation (if randomised) and within 14 days prior to starting treatment, at day 15 of treatment cycles 2, 4, and 6, and at 12-weekly follow-up visits until disease progression, new anti-cancer treatment, or end of trial (whichever occurs first).

Exploratory translational outcome measures:
1. PD-L1 expression in primary breast tumour tissue (collected from an archival sample) and metastatic tumour tissue (optional if not standard of care); sample collected within 7 days prior to starting treatment) and measured using histochemical analysis
2. PD-L1 expression of circulating tumour cells in blood measured using histochemical analysis of samples taken at baseline and end of treatment timepoints
3. Cell-free ctDNA in blood measured using DNA analysis prior to cycle 4
4. Immune markers in blood including T cell subsets measured using immune marker concentrations in blood samples in blood taken at the following timepoints: within 7 days prior

to starting treatment, 7 days prior to day 1 of treatment cycles 2 & 4, and at day 29 of treatment cycle 6 (+14 days if required)

Completion date
01/06/2027

Eligibility

Key inclusion criteria
1. Female patients > = 18 years, with histological evidence of ER+ve, HER2-ve primary breast cancer
2. Radiological evidence of bone metastasis (with or without metastasis at other sites) to include plain radiograph, bone scan, CT or MRI and assessed according to RECIST v1.1, with at least 2 bone metastatic lesions on screening investigations performed at least 6 weeks prior to confirmation of eligibility
3. Measurable disease by RECIST 1.1 (including bone scans – see above)
4. 2-5 prior chemotherapy treatments for advanced disease, including an anthracycline and a taxane, unless contraindicated or patient has declined previous treatment or alternative treatment.
5. ECOG Performance Status 0, 1 or 2.
6. Life expectancy > 6 months
7. Adequate haematological, renal and hepatic function and bone marrow function. Laboratory requirements within 14 days prior to confirmation of eligibility and start of trial treatment as follows;
7.1. Neutrophil count > = 1.5 x10^9/L
7.2. Platelet count > = 100 x10^9/L
7.3. Haemoglobin > = 9.0 g/dL
7.4. Total bilirubin level < = 1.5 xULN in treating institution (or < = 3.0 xULN for patients with Gilbert's syndrome)
7.5. AST or ALT < = 3 xULN in treating institution
7.6. Calculated creatinine clearance or estimated GFR > 40mls/min (Cockcroft and Gault or Wright formula may be used according to local practice)
8. Patient on bone targeted therapy (e.g. bisphosphonates or denosumab) for > 6 weeks before confirmation of eligibility and starting treatment. No change to bone targeted therapy anticipated during study
9. Able to provide an archival primary tumour biopsy for assay of PD-1 expression (Please note that for Phase IIa participants only, provision of a biopsy from a metastatic lesion if already available, or optional provision of a new metastatic biopsy)
10. Patient must be fully informed about the study and has signed the informed consent form.
11. Patient must be willing and able to comply with the protocol, have mental capacity and (if relevant) use effective contraception throughout treatment and for 6 months after treatment completion.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
0

Key exclusion criteria
1. 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).
2. External beam radiotherapy within 4 weeks of confirmation of eligibility and starting treatment.
3. Past medical history of autoimmune disorders or organ transplant including but not limited to myasthenia gravis,myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, poorly controlled type 1 diabetes, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
4. Previous treatment with immune checkpoint inhibitors
5. Active hepatitis B or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. Testing must be performed within 12 months prior to confirmation of eligibility.
6. HIV positive tested within 12 months prior to confirmation of eligibility.
7. Active tuberculosis based on clinical findings.
8. Receipt of an active live vaccine within 4 weeks of confirmation of eligibility and starting treatment.
9. Treatment with systemic immune stimulants or suppressors (including systemic steroids) within 2 weeks of confirmation of eligibility and starting treatment.
10. Requirement for ongoing steroids in the context of active/symptomatic brain /leptomeningeal metastases.
11. Presence of imminent or established spinal cord compression based on clinical findings and /or MRI
12. Known history of clinically significant cardiac disease as documented in the medical records
13. Positive pregnancy test at eligibility assessment for women of childbearing potential or breast-feeding women
14. Known hypersensitivity to any of the excipients of avelumab or radium-223 as documented in the medical records
15. Inability to tolerate antihistamine or antipyretic (e.g. paracetamol) as documented in the medical records
16. Coagulation dysfunction that is deemed by the investigator to be likely to interfere with trial treatment as identified by clotting panel (APTT and INR) within 12 months prior to confirmation of eligibility.
17. Thyroid dysfunction that is deemed by the investigator to be likely to interfere with trial treatment as identified by TSH, free T3 and free T4 within 6 months prior to confirmation of eligibility. Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible.

18. Erythropoietin treatment within the 4 weeks prior to confirmation of eligibility and start of treatment

Date of first enrolment
19/10/2020

Date of final enrolment
19/10/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB

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

Study participating centre
University Hospitals Of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Road
Bebington
United Kingdom
CH63 4JY

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Charity

Funder Name
Breast Cancer Now; Grant Codes: 201 TNovCCl 073

Alternative Name(s)
BCN

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Yorkshire Cancer Research

Alternative Name(s)
YCR

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No