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Fulvestrant and vandetanib in advanced aromatase inhibitor resistant breast cancer

Submission date 11/11/2015	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 11/11/2015	**Overall study status** Completed	
Last Edited 28/02/2024	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-vandetanib-and-fulvestrant-and-for-breast-cancer-that-has-become-resistant-to-hormone-therapy-furva

Study website
https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/furva

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2014-001208-23

IRAS number

ClinicalTrials.gov number
NCT02530411

Secondary identifying numbers
18232

Study information

Scientific Title
A randomised, double blind, placebo controlled, phase II study of fulvestrant with or without the addition of vandetanib as treatment for patients with metastatic breast cancer resistant to aromatase inhibitor therapy

Acronym
FURVA

Study objectives
The aim of this study is to establish whether the combination of vandetanib and fulvestrant will improve clinical outcome in patients with endocrine resistant advanced breast cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/12/2014, Wales Research Ethics Committee 3 (The Caerphilly Suite, Holiday Inn Cardiff North M4/J32, Merthyr Road, Coryton, Cardiff, CF15 7LH, United Kingdom; +44 2922 941107; Wales.REC3@wales.nhs.uk), ref: 14/WA/1219

Study design
Randomised double-blind placebo controlled phase II study

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
Metastatic breast cancer

Interventions
Participants are randomly allocated to one of two study arms. Participants in both arms will receive up to 16 x 28 day cycles of treatment over a total duration of 64 weeks.

Intervention arm: Participants will receive Fulvestrant at 500mg IM on Day 1 and Day 15 of Cycle 1 then on Day 1 only of each subsequent cycle, and Vandetanib 300 mg po daily from Day 1 of Cycle 1 onwards.

Control arm: Participants receive Fulvestrant at 500mg IM on Day 1 and Day 15 of Cycle 1 then on Day 1 only of each subsequent cycle, and Placebo po daily from Day 1 Cycle 1 onwards.

Patients in both trial arms will be assessed on weeks 4, 8, 12, 16, 20, 24 of treatment and then every 12 weeks up to and including week 60. Treatment and assessment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death. Patients that have not progressed by week 60 can remain on trial therapy indefinitely at the discretion of the local Principal Investigator.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Fulvestrant, vandetanib

Primary outcome measure
Progression-free survival is assessed using RECIST V1.1 criteria over an estimated period of up to 45 months.

Secondary outcome measures
1. Clinical Benefit Rate (proportion patients with no disease progression after 6 months treatment) is measured when all participants have completed a minimum 12 months follow-up
2. Influence of RET signalling pathway expression on vandetanib activity is analysed when archival tumour tissue samples have been collected from all consenting patients
3. Feasibility of use of the trial drug regime measured by dose delays/reductions and withdrawals after 20 and 40 patients have completed at least one cycle of treatment
4. Objective Response Rate is determined by measuring disease progression assessed via RECIST V1.1 when all participants have completed a minimum 12 month follow up
5. Overall Survival is assessed over an estimated period of up to 45 months
6. Safety and tolerability of the trial drug regime is measured by SAEs (composite outcome measure) after 20 and 40 patients have completed at least one cycle of treatment

Overall study start date
01/10/2014

Completion date
31/12/2021

Eligibility

Key inclusion criteria

1. Adult female patients aged 18 years or over
2. Post-menopausal patients. Post-menopausal can be defined as either of the following criteria:
2.1. Amenorrhoeic throughout AND after therapy with a third generation AI, without a GnRH analogue (eg. goserelin) AND screening FSH and estradiol in institutional post-menopausal ranges
OR
2.2. Treatment of early or metastatic breast cancer with a third generation AI and GnRH analogue, with discontinuation of the GnRH analogue for at least 6 months AND no resumption of menstruation AND screening FSH and estradiol in institutional postmenopausal ranges
3. Minimum life expectancy of 12 weeks
4. Histological confirmation of ER+ve breast cancer on primary tumour at diagnosis or on biopsy of a metastasis. ER is considered positive if =10% of tumour cells stain positive for ER (whatever the intensity of staining). If no percentage score is available then a Quick (Allred) Score of =4/8 will be considered ER positive
5. Histological confirmation of HER2 negative breast cancer on primary tumour at diagnosis or on biopsy of a metastasis. HER2 is considered negative by IHC if scored 0 or 1+ by Herceptest or similar assay. If HER2 is scored 2+ or 2+/3+ by IHC then HER2 gene amplification must be assessed by FISH/CISH/DDISH and the ratio of HER2 to EP17 probes must be <2.0
6. Clinical or histological confirmation of metastatic or locally advanced disease not amenable to curative surgical resection
7. ECOG performance status 0 to 2 with no deterioration over the previous 2 weeks
8. Measurable or non-measurable disease
9. Patient has adequate bone marrow and organ function as defined by the following:
9.1. Absolute Neutrophil Count (ANC) = 1.0 x 109/L
9.2. Platelets (plts) = 100 x 109/L
9.3. Haemoglobin (Hgb) = 9 g/dl (Note: any blood transfusion must be >14 days prior to the determination of haemoglobin)
9.4. Prothrombin time (seconds) INR= 1.5 x ULN
9.5. Potassium, calcium (corrected for serum albumin) and magnesium within normal limits (WNL) for the institution
9.6. Serum creatinine = 1.5xULN
9.7. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) = 2.5xULN (or < 5.0 x ULN if liver metastases are present)
9.8. Total bilirubin =1.5 times ULN
10. Progressive disease whilst receiving a third generation aromatase inhibitor (exemestane, anastrazole or letrozole)
for locally advanced or metastatic BC or relapsed with metastatic disease whilst receiving a third generation AI in the adjuvant setting. The AI does not need to be the last treatment immediately prior to recruitment
11. Radiological or objective clinical evidence of recurrence or progression on or after the last systemic therapy prior to enrollment
12. No more than 3 prior lines of endocrine therapy for ABC. If an attempt to downstage a locally advanced tumour with endocrine therapy was made in the absence of MBC, and the tumour operated upon, then this does not count as a line of therapy for ABC. In contrast, if the tumour remained inoperable then this treatment should be included as a line of therapy for ABC
13. No more than 1 line of cytotoxic chemotherapy for ABC (see inclusion criterion 11 12 for note on definition of lines of therapy)
14. Suitable for further endocrine therapy according to the treating clinician

15. Availability of archival tumour sample or fresh biopsy for exploratory analysis
16. Provision of informed consent prior to any study specific procedures
17. Normal cardiac function

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 160; UK Sample Size: 160

Total final enrolment
165

Key exclusion criteria
1. Previous treatment with fulvestrant or inhibitors of the RET pathway
2. Last dose chemotherapy, immunotherapy targeted therapy, biological therapy or tumour embolisation less than 21days (less than 6 weeks for nitrosurea or mitomycin C) prior to the first dose of study treatment. Note: endocrine (hormone) therapy is not considered a targeted or biological therapy for the purposes of this study. Denosumab and bisphosphonate treatment are accepted concomitant medications as long as they are started at least 14 days prior to study drug commencement.
3. Last dose of palliative radiotherapy less than 7 days prior to the first dose of study treatment
4. Rapidly progressive visceral disease not suitable for further endocrine therapy
5. Spinal cord compression or brain/meningeal metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks before starting study treatment
6. Any of the following cardiac criteria:
6.1. Significant cardiac event (e.g., myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease =2 within 12 weeks before randomisation (see Appendix 2), or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia
6.2. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE v 4.03 Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.
6.3. Congenital long QT syndrome
6.4. History of QT prolongation associated with other medications that required discontinuation of that medication
6.5. QTcB >480msec on screening ECG (Note: The screening ECG must be repeated three times 5 minutes apart. The average QTc from the three screening ECGs must be = 480 ms in order for the patient to be eligible for the study). If the average QTc is >480ms, the ECGs may be repeated at least 24 hours later, and the average must be =480 ms
7. Patients with the following electrolyte values (the rational is due to the increased risk of

prolonged QTc):
7.1. Potassium <4.0 mmol/L despite supplementation, or above the CTCAE Grade 1 upper limit, at the time of randomisation
7.2. Magnesium below the normal range despite supplementation, or above the CTCAE Grade 1 upper limit, at the time of randomisation
7.3. Calcium (ionised or serum) below the normal range despite supplementation, or above the Grade 1 upper limit, at the time of randomisation. If serum calcium is used, correction should be applied to account for hypoalbuminemia, if present, where the corrected serum calcium (mg/dL) is equal to measured serum Ca (mg/dL) + 0.8 x (4 serum albumin g/dL)
8. Creatinine clearance <30 ml/min (calculated by CockcroftGault formula, see Appendix 4). Patients with creatinine clearance <50 mL/min will start at a permanently reduced vandetanib dose of 200 mg
9. Major surgery (excluding placement of vascular access) within 4 weeks before the first dose of study treatment
10. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
11. With the exception of alopecia, any unresolved toxicities from previous therapy greater than CTCAE grade 1 at the time of starting study treatment
12. Elevated Alkaline phosphatase (ALP) in the absence of bone metastasis. If the patient has elevated ALP in the presence of bone metastasis and liver function is otherwise considered adequate in the investigator's judgement, then the patient is not excluded
13. History of hypersensitivity to active or inactive excipients of vandetanib or fulvestrant
14. Evidence of dementia, altered mental status or any psychiatric condition that would prohibit understanding or rendering of informed consent
15. Participation in another clinical study with an investigational product (IP) during the last 30 days
16. Inability or unwillingness to comply with study procedures, including the inability to take regular oral medication

Date of first enrolment
20/04/2015

Date of final enrolment
30/10/2017

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre

Velindre Cancer Centre
Velindre Road
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Royal United Hospital
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Royal Cornwall Hospital
2 Penventinnie Lane
Treliske
Truro
United Kingdom
TR1 3LQ

Study participating centre
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Weston General Hospital
Grange Road
Weston-super-Mare
United Kingdom
BS23 4TQ

Study participating centre
Peterborough Hospital
Edith Cavell Campus
Peterborough City Hospital
Bretton Gate
Peterborough

United Kingdom
PE3 9GZ

Study participating centre
Hinchingbrooke Hospital
Hinchingbrooke Park
Hinchingbrooke
Huntingdon
United Kingdom
PE29 6NT

Study participating centre
Colchester General Hospital
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Kidderminster Hospital
Bewdley Road
Kidderminster
United Kingdom
DY11 6R

Study participating centre
Worcestershire Royal Hospital
Charles Hastings Way
Worcester
United Kingdom
WR5 1DD

Study participating centre
Alexandra Hospital
Woodrow Drive
Redditch
United Kingdom
B98 7UB

Study participating centre
Queens Hospital
Belvedere Road
Burton-on-Trent
United Kingdom
DE13 0RB

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
Gloucester Royal Hospital
Great Western Road
Gloucester
United Kingdom
GL1 3NN

Study participating centre
Cheltenham General Hospital
Sandford Road
Cheltenham
United Kingdom
GL53 7AN

Study participating centre
City Hospital Birmingham
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
Musgrove Park Hospital
Parkfield Drive
Taunton
United Kingdom
TA1 5DA

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Poole Hospital
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre
Bristol Haematology and Oncology Centre
Horfield Road
Bristol
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BS2 8ED

Study participating centre
Centre for Trials Research - Cancer Division
6th Floor, Neuadd Meirionnydd
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4YS

Sponsor information

Organisation
Velindre NHS Trust

Sponsor details
Velindre Hospital
Velindre Road
Cardiff

Wales
United Kingdom
CF14 2TL

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05ntqkc30

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Data from all sites will be analysed when all participants have completed a minimum 12 months follow-up and at least 98 disease progression events are observed and published as soon as possible afterwards. The data will be disseminated via peer reviewed scientific journals, internal report, conference presentation, publication on website, and submission to regulatory authorities.

2017 NCRI Cancer Conference abstract in: http://abstracts.ncri.org.uk/abstract/fulvestrant-vandetanib-in-advanced-aromatase-inhibitor-resistant-breast-cancer/

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Stored in non-publicly available repository, Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Results article		14/09/2023	28/02/2024	Yes	No