

# Fulvestrant and vandetanib in advanced aromatase inhibitor resistant breast cancer

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|--|---|---|
| <b>Submission date</b><br>11/11/2015   | <b>Recruitment status</b><br>No longer recruiting | <input type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol            |
| <b>Registration date</b><br>11/11/2015 | <b>Overall study status</b><br>Completed          | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results |
| <b>Last Edited</b><br>28/02/2024       | <b>Condition category</b><br>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-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

### Contact name

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### Contact details

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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  $\geq 10\%$  of tumour cells stain positive for ER (whatever the intensity of staining). If no percentage score is available then a Quick (Allred) Score of  $\geq 4/8$  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) =  $1.0 \times 10^9/L$
  - 9.2. Platelets (plt) =  $100 \times 10^9/L$
  - 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 =  $1.5 \times ULN$
  - 9.5. Potassium, calcium (corrected for serum albumin) and magnesium within normal limits (WNL) for the institution
  - 9.6. Serum creatinine =  $1.5 \times ULN$
  - 9.7. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) =  $2.5 \times ULN$  (or  $< 5.0 \times ULN$  if liver metastases are present)
  - 9.8. Total bilirubin =  $1.5 \times ULN$
10. Progressive disease whilst receiving a third generation aromatase inhibitor (exemestane, anastrozole 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 21 days (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 >480 msec 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 >480 ms, 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 rationale 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  
United Kingdom  
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? |
|--------------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">HRA research summary</a> |         |              | 28/06/2023 | No             | No              |
| <a href="#">Results article</a>      |         | 14/09/2023   | 28/02/2024 | Yes            | No              |