

# Safety of AZD4547 in breast cancer patients

<b>Submission date</b> 27/04/2012	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 27/04/2012	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 26/10/2022	<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-of-azd4547-for-breast-cancer-that-is-oestrogen-receptor-positive-got-worse-despite-having-anastrozole-or-letrozole-radical>

## Contact information

### Type(s)

Scientific

### Contact name

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## Additional identifiers

### ClinicalTrials.gov (NCT)

NCT01791985

### Clinical Trials Information System (CTIS)

2011-000454-32

### Protocol serial number

## Study information

### Scientific Title

A phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 In Combination with either anastrozole or letrozole versus exemestane alone in ER positive breast cancer patients who are progressing on current treatment with Anastrozole or Letrozole

### Acronym

RADICAL

### Study objectives

1. To assess the safety and tolerability and determine the dose of AZD4547 to be used in combination with a standard dose of anastrozole/letrozole for the Phase IIa part of the study
2. To assess efficacy based on the change in tumour size at 12 weeks (or progression if prior to week 12) between treatments AZD4547 in combination with anastrozole/letrozole versus exemestane alone in patients who are progressing on treatment with either anastrozole or letrozole in the adjuvant or first line metastatic setting
3. To assess the pharmacokinetics (PK) of anastrozole/letrozole when given alone compared to in combination with AZD4547
4. To describe the PK of AZD4547 when given in combination with anastrozole/letrozole
5. To assess the efficacy based on the change in tumour size at other time points (6 weeks, 20 weeks etc) between treatments AZD4547 in combination with anastrozole/letrozole versus exemestane alone in patients who are progressing on treatment with either anastrozole or letrozole in the adjuvant or first-line metastatic setting
6. To assess the efficacy based on the tumour response RECIST criteria at all time points between AZD4547 in combination with anastrozole/letrozole versus exemestane alone
7. To assess the efficacy based on the objective response rate (ORR) at all time points between AZD4547 in combination with anastrozole/letrozole versus exemestane alone
8. To assess the efficacy based on progression-free survival (PFS) between AZD4547 in combination with anastrozole/letrozole versus exemestane alone
9. To determine whether FGFR1 amplification is required for any benefit demonstrated based on change in tumour size, RECIST categories, ORR and PFS
10. To assess the safety and tolerability of AZD4547 in combination with anastrozole/letrozole compared with exemestane alone

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

First MREC, 23/12/2011, ref: 11/EM/0393

### Study design

Single-arm Phase IIa study (with combination safety run-in)

### Primary study design

Interventional

### Study type(s)

## Treatment

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

Breast cancer

### Interventions

Current interventions as of 13/07/2017:

#### Safety run-in

Initially, patients continue to receive single agent treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily for 7 days. N.B. this must be preceded by a minimum of 21 days of anastrozole or letrozole treatment prior to study entry. Oral AZD4547 will then be added to this ongoing non-steroidal aromatase inhibitor (either anastrozole or letrozole) therapy twice daily but on an intermittent schedule of one week on /one week off.

#### Phase IIa:

A simple non-randomised single arm design in which patients will continue or restart the NSAI which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily but together with twice daily AZD4547 (80mg); the confirmed dose level for AZD4547 determined during the safety run-in part of the study.

Previous interventions from 15/08/2012 to 13/07/2017:

#### Safety run-in

Initially, patients continue to receive single agent treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily for 7 days. N.B. this must be preceded by a minimum of 21 days of anastrozole or letrozole treatment prior to study entry. Oral AZD4547 will then be added to this ongoing non-steroidal aromatase inhibitor (either anastrozole or letrozole) therapy twice daily but on an intermittent schedule of one week on /one week off.

#### Randomised Phase IIa

Patients will be stratified by FGFR1 FISH level and randomised to receive either:

Arm A: anastrozole or letrozole + AZD4547 in combination (experimental arm)

Arm B: exemestane alone (control arm)

Patients in the experimental arm will continue to receive the treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily but together with twice daily AZD4547. AZD4547 will be given on an intermittent schedule of one week on /one week off. The dose level for AZD4547 will be determined from the safety run-in. Patients must have been on anastrozole or letrozole for a minimum of 28 days prior to study entry.

Patients in the control arm will receive once daily exemestane (25mg).

Original interventions until 15/08/2012:

Initially, patients continue to receive single agent treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily for 7 days. N.B. this must be preceded by a minimum of 21 days of anastrozole or letrozole treatment prior to study entry. Oral AZD4547 will then be added to this ongoing non-steroidal aromatase inhibitor (either anastrozole or letrozole) therapy twice daily but on an intermittent schedule of one week on /one week off.

### Intervention Type

Drug

## Phase

Phase II

## Drug/device/biological/vaccine name(s)

Anastrozole, letrozole, AZD4547, exemestane

## Primary outcome(s)

Current primary outcome measures as of 15/08/2012:

For the Safety Run-in:

Safety and tolerability as assessed by Dose Limiting Toxicities (DLTs)

For the Phase IIa:

Change in tumour size at 12 weeks (or progression if prior to week 12)

Previous primary outcome measures until 15/08/2012:

Change in tumour size at week 12 (or progression if prior to week 12)

## Key secondary outcome(s)

Current secondary outcome measures as of 15/08/2012:

For the Safety Run-in:

1. Pharmacokinetic (PK) parameters of anastrozole or letrozole when given alone and in combination with AZD4547
2. PK parameters of AZD4547 when given in combination with anastrozole or letrozole.
3. Safety and tolerability as assessed by adverse events (AEs)

For the Phase IIa:

1. Change in tumour size at other time points (6 weeks, 20 weeks etc)
2. Tumour response RECIST criteria with 4 categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)
3. Objective response rate (ORR) with 2 categories: CR or PR, SD or PD
4. Progression-free survival (PFS) is time from randomisation to PD (RECIST)

Previous secondary outcome measures until 15/08/2012:

1. Response rate of tumours:
2. Pharmacokinetic parameters of anastrozole or letrozole
3. Pharmacokinetic (PK) parameters of anastrozole or letrozole when given alone and in combination with AZD4547
4. Progression-free survival (PFS)
5. Safety and tolerability of study drug
6. Tumour response

## Completion date

31/12/2017

## Eligibility

### Key inclusion criteria

Current inclusion criteria as of 10/04/2013:

1. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up.
2. Aged 25 years of age or over

3. Post menopausal women
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks
5. Histological confirmation of breast cancer with documented positive oestrogen receptor status (ER+) of primary or metastatic tumour tissue according to local laboratory parameters.
6. Phase IIa only: Mandatory provision of tumour biopsy for AstraZeneca central laboratory confirmation of FGFR1 status by FISH.
7. Fulfils criteria for previous treatment of breast cancer:
  - 7.1. Relapse during a single regimen of adjuvant endocrine therapy with either anastrozole or letrozoleOR
  - 7.2. Progression during first line endocrine therapy with a nonsteroidal AI for advanced breast cancer (metastatic disease or locally advanced disease which is not amenable to treatment with curative intent). Coadministration of a targeted agent with the nonsteroidal AI is permitted providing all toxicities have recovered to CTCAE Grade 1 or below. Safety run-in only: 1 prior regimen of chemotherapy in the advanced setting is permitted. Chemotherapy administered in the adjuvant setting is permitted. Phase IIa only: Chemotherapy administered in the adjuvant setting is permitted.
8. Safety run-in only: At least one lesion (measurable and/or nonmeasurable) that can be accurately assessed by CT/MRI/plain xray at baseline and follow up visits. Phase IIa only: At least one lesion greater than or equal to 10mm in the longest diameter at baseline that can be accurately measured with CT/MRI at baseline and is suitable for accurate repeated measurements.
9. Safety run-in: Study entry must be preceded by a minimum of 21 days of anastrozole or letrozole treatment  
Phase IIa: Study entry must be preceded by a minimum of 28 days of anastrozole or letrozole treatment

Previous inclusion criteria as of 13/08/2012:

1. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up.
2. Aged 25 years of age or over
3. Post menopausal women
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks
5. Histological confirmation of breast cancer with documented positive oestrogen receptor status (ER+) of primary or metastatic tumour tissue according to local laboratory parameters.
6. Phase IIa only: Mandatory provision of tumour biopsy for AstraZeneca central laboratory confirmation of FGFR1 status by FISH.
7. Fulfils criteria for previous treatment of breast cancer:
  - 7.1. Relapse during a single regimen of adjuvant endocrine therapy with either anastrozole or letrozoleOR
  - 7.2. Progression during first line endocrine therapy with a nonsteroidal AI for advanced breast cancer (metastatic disease or locally advanced disease which is not amenable to treatment with curative intent). Coadministration of a targeted agent with the nonsteroidal AI is permitted providing all toxicities have recovered to CTCAE Grade 1 or below. Safety run-in only: 1 prior regimen of chemotherapy in the advanced setting is permitted. Chemotherapy administered in the adjuvant setting is permitted. Phase IIa only: Chemotherapy administered in the adjuvant setting is permitted.
8. Safety run-in only: At least one lesion (measurable and/or nonmeasurable) that can be accurately assessed by CT/MRI/plain xray at baseline and follow up visits. Phase IIa only: At least

one lesion greater than or equal to 10mm in the longest diameter at baseline that can be accurately measured with CT/MRI at baseline and is suitable for accurate repeated measurements.

Previous inclusion criteria until 13/08/2012

4. Eastern Cooperative Oncology Group (ECOG) performance status 01 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks.

8. Safety run-in only: At least one lesion (measurable and/or nonmeasurable) that can be accurately assessed by CT/MRI/plain xray at baseline and follow up visits. Phase IIa only: At least one lesion equal to 10mm in the longest diameter at baseline that can be accurately measured with CT/MRI at baseline and is suitable for accurate repeated measurements.

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

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Sex**

Female

### **Total final enrolment**

52

### **Key exclusion criteria**

1. Treatment with any of the following:

1.1. More than 1 regimen of endocrine therapy for advanced breast cancer

1.2. Previous exposure to any FGFR inhibitor

1.3. Safety run in only: more than 1 prior regimen of chemotherapy for advanced breast cancer; Phase IIa only: any prior chemotherapy for advanced breast cancer;

1.4. Potent inhibitors or inducers of CYP3A4 or CYP2D6, or substrates of CYP3A4 within 2 weeks prior to first dose of study treatment (3 weeks for St Johns Wort);

1.5. Major surgery within 4 weeks prior to first dose of study treatment;

1.6. Radiotherapy with a wide field of radiation within 4 weeks prior to first dose of study treatment;

1.7. Radiotherapy with a limited field of radiation for palliation within 2 weeks before the first dose of study treatment.

2. With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at time of starting study.

3. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

4. Any evidence of severe or uncontrolled systemic diseases or active infection.

5. Any of the following cardiac criteria:

5.1. Mean resting corrected QT interval (QTc) >470 ms obtained from 3 electrocardiograms (ECGs);

5.2. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e. g. complete left bundle branch block, third degree heart block;

5.3. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as

heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.

6. Inadequate bone marrow reserve or organ function as defined by: Haemoglobin < 9.0 g/dL; Absolute neutrophil count (ANC) < 1.5 x 10<sup>9</sup> /L; Platelet count < 100 x 10<sup>9</sup> /L; Alanine aminotransferase > 2.5 x ULN if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases; Aspartate aminotransferase > 2.5 x ULN if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases; Total bilirubin > 1.5 x ULN if no demonstrable liver metastases or > 3 x ULN in the presence of liver metastases; Creatinine > 1.5 times ULN or creatinine clearance <50ml/min; Corrected calcium > ULN; Phosphate > ULN.

7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated IMP or previous significant bowel resection that would preclude absorption of AZD4547 or exemestane or anastrozole or letrozole.

8. History of hypersensitivity to AZD4547 or exemestane or anastrozole or letrozole.

9. History of another malignancy within 5 yrs prior to starting study treatment, except adequately treated basal or squamous cell carcinoma of the skin, carcinoma of the cervix and the disease under study.

10. Any of the following ophthalmological criteria:

10.1. Current evidence or previous history of retinal pigmented epithelium detachment (RPED);

10.2. Previous laser treatment or intraocular injection for treatment of macular degeneration;

10.3. Current evidence or previous history of dry or wet age-related macular degeneration;

10.4. Current evidence or previous history of retinal vein occlusion (RVO);

10.5. Current evidence or previous history of retinal degenerative diseases (e.g.hereditary);

10.6. Current evidence or previous history of any other clinically relevant chorioretinal defect.

11. Concurrent treatment with another investigational agent or use of another investigational agent within 30 days or 5 half lives, whichever is longer, preceding the first dose of study treatment

12. Concurrent treatment with prohibited medications and wash out period for that drug will not have been completed before starting study medication (see Appendix B of protocol)

### **Date of first enrolment**

23/07/2012

### **Date of final enrolment**

31/12/2015

## **Locations**

### **Countries of recruitment**

United Kingdom

England

Scotland

### **Study participating centre**

**Charing Cross Hospital**

London  
United Kingdom  
W6 8RF

**Study participating centre**

**Freeman Hospital**

Newcastle  
United Kingdom  
NE7 7DN

**Study participating centre**

**Addenbrookes Hospital**

Cambridge  
United Kingdom  
CB2 0QQ

**Study participating centre**

**The Beatson Cancer Centre**

Glasgow  
United Kingdom  
G12 0YN

**Study participating centre**

**The Christie**

Manchester  
United Kingdom  
M20 4BX

**Study participating centre**

**Russells Hall Hospital**

Dudley  
United Kingdom  
DY1 2HQ

**Sponsor information**

**Organisation**

Imperial College London (UK)

**ROR**

<https://ror.org/041kmwe10>

**Funder(s)****Funder type**

Charity

**Funder Name**

AstraZeneca (UK)

**Alternative Name(s)**

AstraZeneca PLC, Pearl Therapeutics, AZ

**Funding Body Type**

Government organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

United Kingdom

**Funder Name**

Cancer Research UK

**Alternative Name(s)**

CR\_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

**Results and Publications**

## Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date

## IPD sharing plan summary

Data sharing statement to be made available at a later date

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Abstract results</a>	results abstract	20/05/2017		No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Plain English results</a>			26/10/2022	No	Yes