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Safety of AZD4547 in breast cancer patients

Submission date 27/04/2012	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 27/04/2012	**Overall study status** Completed	
Last Edited 26/10/2022	**Condition category** Cancer	

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

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Additional identifiers

Clinical Trials Information System (CTIS)
2011-000454-32

ClinicalTrials.gov (NCT)
NCT01791985

Protocol serial number

11456

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 letrozole
OR
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 letrozole
OR
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 109 /L; Platelet count < 100 x 109 /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?
Abstract results	results abstract	20/05/2017		No	No
HRA research summary			28/06/2023	No	No
Plain English results			26/10/2022	No	Yes