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A Phase II, randomised, placebo-controlled study of paclitaxel in combination with the AKT inhibitor AZD5363 in triple-negative advanced or metastatic breast cancer

Submission date
26/09/2014

Recruitment status
No longer recruiting

Registration date
26/09/2014

Overall study status
Completed

Last Edited
09/02/2024

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/trials/trials-search/a-trial-chemotherapy-drug-AZD5363-triple-negative-breast-cancer-come-back-spread-pakt

Contact information

Type(s)
Scientific

Contact name
Prof Peter Schmid

Contact details
Centre for Experimental Cancer Medicine, LG floor
Old Anatomy Building Charterhouse Square
London
United Kingdom
EC1M 6BQ
-
bci-Pakt@qmcr.qmul.ac.uk

Additional identifiers

EudraCT/CTIS number
2013-001521-43

IRAS number

ClinicalTrials.gov number
NCT02423603

Secondary identifying numbers
16095

Study information

Scientific Title
A Phase II, randomised, placebo-controlled study of paclitaxel in combination with the AKT inhibitor AZD5363 in triple-negative advanced or metastatic breast cancer

Acronym
PAKT

Study objectives
The term triple-negative breast cancer (TNBC) is generally used to define tumours that do not express oestrogen receptors (ER), progesterone receptors (PR) and HER2 receptors. This subtype comprises 10-15% of all breast cancers.

TNBC has an aggressive clinical course, shares features with basal-like tumours, and has a poorer outcome compared with other subtypes. Clinically, TNBCs are a challenge to treat because there is no role for endocrine or HER2-directed therapy. Chemotherapy is effective, but neoadjuvant studies have shown that despite initial chemo-sensitivity, TNBCs still had a worse outcome, particularly in women in whom a pathologically confirmed complete response was not achieved. Consequently, there is a clear need to develop specific treatment strategies for the subgroup of TNBCs both in the early and advanced disease setting.

AZD5363 is a potent, selective inhibitor of the kinase activity of the serine/threonine AKT/PKB (protein kinase B) that is being developed as a potential treatment for solid and haematological malignancies. AKT is part of the AGC family of kinases. Mammalian cells express three closely related AKT isoforms: AKT1 (PKBa), AKT2 (PKBß) and AKT3 (PKB?), all encoded by different genes.

This is a placebo-controlled, multicentre, 2-arm randomised phase II trial of paclitaxel + AZD5363 versus paclitaxel + placebo in patients with triple-negative (ER-negative, PR-negative/unknown, HER2-negative) advanced or metastatic breast cancer.

Patients will be randomised into either of the Arms Paclitaxel + Placebo OR Paclitaxel + AZD5363.

Randomisation will be stratified by the following criteria:

Number of metastatic sites (<3, =3)

(Neo)Adjuvant chemotherapy (end of (neo)adjuvant chemotherapy =12 months ago, end of (neo) adjuvant chemotherapy >12 months or no prior (neo)adjuvant chemotherapy).

The Primary Objective is to estimate the clinical benefit of the patients on the Research Arm of the study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
14/LO/0121; First MREC approval date 06/02/2014

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Topic: Cancer; Subtopic: Breast Cancer; Disease: Breast

Interventions
AZD5363/Placebo., Capsules/Tablets; Chemotherapy, Paclitaxel; Study Entry : Registration and One or More Randomisations

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Estimate the clinical benefit of paclitaxel + AZD5363 relative to paclitaxel + placebo, as measured

Secondary outcome measures
Not provided at time of registration

Overall study start date
14/05/2014

Completion date
01/01/2017

Eligibility

Key inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Written informed consent prior to admission to this study
2. Women, age = 18 years
3. Histologically confirmed breast cancer
4. Metastatic or locally recurrent disease; locally recurrent disease must not be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential downstaging with study treatment are not eligible).
5. Patients must have
5.1. at least one lesion, not previously irradiated, that can be measured accurately at baseline as =10 mm in the longest diameter (except lymph nodes which must have short axis =15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements, or
5.2. lytic or mixed (lytic + sclerotic) bone lesions in the absence of measurable disease as defined above; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible
6. Radiological or clinical evidence of recurrence or progression
7. Triple-negative disease, defined as tumour cells being
7.1. negative for ER with <1% of tumour cells positive for ER on IHC or IHC score (Allred) of =2
7.2. negative for PR with <1% of tumour cells positive for PR on IHC or IHC score (Allred) of =2 or PR unknown, and
7.3. negative for HER2 with 0,1+ or 2+ intensity on IHC and no evidence of amplification on ISH.
8. Formalin fixed, paraffin embedded tumour sample from the primary or recurrent cancer must be available for central testing
9. Patients must be able to swallow and retain oral medication
10. Haematologic and biochemical indices within the ranges shown below. These measurements must be performed within one week prior to randomisation
10.1. ANC = 1.5x 109/L, and platelet count = 100 x 109/L
10.2. Serum creatinine < 1.5 times the upper limit of normal (ULN)
10.3. Bilirubin level < 1.5 x ULN
10.4. AST or ALT <2.5 x ULN or <5 x ULN in the presence of liver metastases
11. ECOG performance status 0-2
12. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had a hysterectomy, bilateral oopheroctemy, bilateral tubular ligation or is postmenopausal (total cessation of menses for = 1 year; if the patient is of childbearing potential, she must have a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception (for example, intrauterine device [IUD], birth control pills unless clinically contraindicated, or
barrier device) beginning 2 weeks before the first dose of investigational product and for 30 days after the final dose of
investigational product.
13. Willing and able to provide written informed consent

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex
Female

Target number of participants
Planned Sample Size: 140; UK Sample Size: 140

Total final enrolment
140

Key exclusion criteria
Patients meeting any of the following exclusion criteria are not to be enrolled in the study.
1. Patients with confirmed brain metastases or a history of primary central nervous system tumors or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases. Patients with treated brain metastases that are asymptomatic and have been clinically stable for 3 months will be eligible for protocol participation
2. Prior chemotherapy for metastatic breast cancer
3. Radiotherapy with a wide field of radiation (greater than or equal to 30% marrow or whole pelvis or spine) within 4 weeks before the first dose of study medication (AZD5363/placebo)
4. Prior treatment with PI3K inhibitors, AKT inhibitors or mTOR inhibitors.
5. Prior treatment with paclitaxel or docetaxel in the (neo)adjuvant setting within 12 months from inclusion into this study
6. Preexisting sensory or motor polyneuropathy = Grade 2 according to NCI CTC
7. Malabsorption syndrome or other condition that would interfere with enteral absorption
8. Clinically significant pulmonary dysfunction
9. Prolongation defined as a QTc interval >470 msecs or other significant abnormalities in rhythm, conduction or morphology of resting ECG including 2nd degree (type II) or 3rd degree AV block or bradycardia (ventricular rate <50 beats/min)
10. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, 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.
11. Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Grade =2, or Cardiac ejection fraction outside institutional range of normal or <50%
12. Clinically significant abnormalities of glucose metabolism as defined by any of the following
12.1. Diagnosis of diabetes mellitus type I or II (irrespective of management).
12.2. Glycosylated haemoglobin (HbA1C) =8.0% at screening (64 mmol/mol) (conversion equation for HbA1C [IFCCHbA1C (mmol/mol) = [DCCTHbA1C (%) 2.15] x 10.929)
12.3. Fasting Plasma Glucose = 7.0mmol/L (126 mg/dL) at screening. Fasting is defined as no caloric intake for at least 8 hours.
13. Exposure to potent inhibitors or inducers or substrates of CYP3A4 or substrates of CYP2D6 within 2 weeks before the first dose of study treatment (3 weeks for St Johns Wort)
14. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational
drug within 30 days prior to study entry.
15. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigators opinion, gives reasonable suspicion of a disease or condition

that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
16. Psychological, familial, sociological or geographical conditions that do not permit compliance with the study protocol.
17. Detained persons or prisoners
18. Pregnant or nursing women

Date of first enrolment
14/05/2014

Date of final enrolment
01/01/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Centre for Experimental Cancer Medicine, LG floor
London
United Kingdom
EC1M 6BQ

Sponsor information

Organisation
Queen Mary University of London (UK)

Sponsor details
R&D Office, Queen Mary University of London , Barts & London School of Medicine The QMI building, 5 Walden Street
London
England
United Kingdom
E1 2EF

Sponsor type
University/education

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca UK Limited; CTAAC; Grant Codes: A16202

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	10/02/2020	22/07/2020	Yes	No
HRA research summary			28/06/2023	No	No
Plain English results			09/02/2024	No	Yes