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A clinical trial exploring a new imaging technique for assessing response to anti-cancer treatments in post-menopausal women with breast cancer

Submission date
19/09/2024

Recruitment status
Recruiting

Registration date
10/12/2024

Overall study status
Ongoing

Last Edited
13/02/2025

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Breast cancer is the most common cancer in UK women. Medical imaging like mammography (taking X-ray pictures) and ultrasound (using sound waves) are used to track changes in size of tumour over time. Unfortunately, it can take many weeks before changes large enough to tell if treatments are working are seen.
Tumour cells act differently to regular cells. Some of these differences can be used to get an earlier look at whether a treatment is working. Knowing a treatment isn't working early on allows for quicker adjustments, increasing the chance of a good outcome and reducing the time patients suffer with side effects from ineffective treatments.
One thing that sets tumour cells apart is how they use sugar. Tumour cells take in more sugar from the blood and use it in a unique way. This leads to many types of tumours having lots of a natural substance called lactate.
In this proposed trial, AKTivate, we will use a new type of imaging called Hyperpolarised C13 Magnetic Resonance Imaging (MRI). This allows us to see lactate build-up in breast cancers. If a drug treatment is working well, the amount of lactate should fall. This usually happens at an earlier stage than changes in size.

AKTivate will assess if hyperpolarized C13 MRI can reliably assess whether capivasertib and exemestane are working within just 2 weeks. Funding is through a collaboration with AZ.

Who can participate?
60 women with early-stage oestrogen-positive (ER+) breast cancer will participate.

What does the study involve?
Participants will have hyperpolarised C13 MRI scans and cancer biopsies before and after 2 weeks of treatment in what we call a window of opportunity trial. All women will receive the drug capivasertib. Capivasertib has worked well in trials for advanced and metastatic breast cancer. AKTivate will gather information to help assess if it might work well against early-stage

breast cancer. Half will also get a drug called exemestane. This is commonly used in early and advanced ER+ breast cancer.

What are the possible benefits and risks of participating?
Benefits:
By joining this trial, you may help improve treatments for women with similar types of breast cancer in the future. Specifically, the trial will help us to understand more about whether Hyperpolarised C13 pyruvate MRI can reliably be used to tell if breast cancer treatments are working at an early stage. You might feel better from your breast cancer symptoms or see an improvement in your condition, but we can't promise that you will directly benefit from taking part in this trial.
Risks:
All Adverse Events will be checked as per visit schedule outlined in the protocol and participants will be regularly followed up for any adverse events until resolution. In order to mitigate these side effects, the trial team will be encouraged to prescribe medication to ease side effects of the trial medication experienced by the participants.
Dose interruptions are permitted, as well as dose reductions to manage toxicities related to trial medication. In case of severe reactions, trial treatment will be discontinued. Participants will be given contact details of their site study team, printed on the Participant Information Sheet and also receive a Participant ID card with local contact details on. These contact details will also include an Out of Hours service, in line with local site arrangements. Participants will be asked to self-administer oral medication once or twice a day, depending on the treatment arm they are randomised to. There is a risk that participants may lose the medication or overdose/underdose. For that, participants will be given a diary with clear instructions and will be asked to keep a record of the tablets they take. Participants will be contacted by the site study team at regular intervals, where the diary will be checked and/or talked through. Participants will also be asked to return used and unused or empty medication bottles for trial drug reconciliation purposes.
Participants are asked to attend 7 trial appointments which could be reduced to 6 depending on their availability and clinic arrangements.
The longest appointments are the two imaging and biopsy visits. We have identified waiting time for the biopsy appointment as the major cause of potential prolonged visits. We have involved a named radiology senior fellow to carry out the biopsies to minimise waiting time. We have engaged our local NIHR unit to ensure the area the participants are waiting is away from the main hospital and ensured food is available. We will actively monitor for opportunities to further reduce the time participants spend in hospital.
Participants are asked to undergo two MRI scans. Some MRI scans will coincide with scans that patients would have as part of their routine care (dependent on standard of care practice at local sites). There are few risks attached to having a MRI scan and participants will already be familiar with the procedure while joining the study. The use of contrasts (Gadolinium and the 13C pyruvate) is part of the scan procedure. They are considered safe to the body unless participants have severe kidney impairment (in such case scan with contrasts will not be performed). A venous cannula will be inserted for the administration of the pyruvate and another cannula will be inserted into one arm for administration of the gadolinium during imaging; the injection will last around 10 seconds and may feel cold, patients sometimes experience a metallic taste in the mouth. Participants may experience mild pain and/or bruising from where a trial blood sample is taken.
Three research biopsies are required as part of the trial, before patient start trial treatment, at the end of the trial treatment and at surgery. Biopsies can cause discomfort and carry some risks (for example bleeding and infection) which participants will be aware of from their diagnostic biopsy procedure. As those biopsies for this study will be done at a specific time points, those may be an additional procedures for some participants as there is a chance they would not need a biopsy as part of their normal care. However, a repeat biopsy (i.e. a biopsy sometime after the

initial diagnostic biopsy) is often something doctors would advise to have as part of active surveillance follow-up of patients, so it could be incorporated in normal pattern of care. In addition, a repeat biopsy at the end of the study will provide important information on how effective the treatment has been in controlling the growth of the cancer. All procedures performed during the participation in the trial and risks related are described in the PIS. Participants will not be able to participate in any other interventional research studies with concomitant, systemic or investigational anti-cancer agents. Also, the protocol lists a number of medications and trial restrictions which must not be taken whilst receiving the trial medication or discontinued prior to participation in the trial. The study team will be asked to consider the participant's current medications and any new medications required before trial participation to ensure the safety of participants. Also, the participant's treating clinician will be able to withdraw them from the trial if they believe their patient should take the contraindicated medication instead of the trial medication. Whole Genome Sequencing data generated in this trial might be shared with the oncogenomic review board upon patient consent. All cases will be de-identified through the use of ID numbers.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2024 to November 2027

Who is funding the study?
AstraZeneca UK

Who is the main contact?
Dr Jean Abraham, ja344@medschl.cam.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1009061

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CCTU0441, IRAS 1009061

Study information

Scientific Title
Randomised Phase II open-label window of opportunity trial AKTivate - Identifying target engagement and biomarkers of response, including an imaging biomarker, in participants receiving Capivasertib plus Exemestane and Capivasertib alone in post-menopausal participants with oestrogen receptor positive (ER+) early-stage breast cancer

Acronym
AKTivate

Study objectives
In this proposed trial, we will use a special type of imaging called Hyperpolarised C13 Magnetic Resonance Imaging (MRI) to assess the tumour response in patients taking the Capivasertib only and in those taking Capivasertib and exemestane.

Target-product engagement of capivasertib +/- exemestane will be assessed by a reduction in the hyperpolarized 13C-labelled lactate/ pyruvate ratio (LAC/PYR).

Secondary objectives:
To compare the degree of target engagement between capivasertib only and in combination with exemestane ,using hyperpolarised MRI at baseline and at end of treatment; to measure the change in tumour proliferation for participants receiving capivasertib only and those receiving with exemestane between baseline, end of treatment and at surgery; to compare the change in tumour proliferation for participants receiving capiva only versus with exemestane between baseline and at end of treatment; to correlate changes in engagement seen using hyper MRI, with changes in tumour proliferation markers at baseline and at end of treatment; to assess the safety and tolerability of capiva and in combination with exemestane when given in 2 weeks; to measure engagement of capiva with or without exemest in PI3K/AKT/PTEN pathway-altered and

non-altered tumours, using hyperpolarised 13C MRSI techniques at baseline and following 10d of capiva treatment; to show if engagement can be seen its effect on FOXM1.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 07/12/2024, North East - Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne , NE2 4NQ, United Kingdom; +44 (0)20 710 48120; tyneandwearsouth.rec@hra.nhs.uk), ref: 24/NE/0180

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Breast Cancer oestrogen positive (ER+) and HER 2 negative

Interventions
Arm A: Capivasertib (AZD5363) orally 400mg twice a day on Days 1 to 4 and Days 8 to 11 of a 14-day treatment period between diagnosis and starting standard of care treatment (surgery or neoadjuvant chemotherapy).

Arm B: Capivasertib (AZD5363) orally 400mg twice a day on Days 1 to 4 and Days 8 to 11 of a 14-day treatment period + Exemestane orally 25 mg ONCE a day on Days -4 to 11, of a 15-day treatment period between diagnosis and starting standard of care treatment (surgery or neoadjuvant chemotherapy).

The randomisation process will occur once written informed consent is received from the participant, and eligibility is confirmed. Randomisation can occur at any time during the screening phase but must be complete prior to the start of any trial treatment(s). Eligible participants will be randomised via a web-based central randomisation system and assigned to treatment arm A or treatment arm B in a 1:1 ratio using random permuted blocks. The web-based central randomisation system will allocate participant treatment arm and trial numbers sequentially in the order in which the participants are randomised.

The stratification factors are:
-Tumour grade – 2 or 3
-Known histological involvement of the lymph nodes – Yes or No
In terms of follow up, participants will be seen four weeks after finishing capivasertib and follow your progress for a year after they have surgery.

Intervention Type
Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)
Capivasertib, exemestane

Primary outcome(s)
1. To determine whether the combination of capivasertib and exemestane, administered over two weeks, demonstrates target engagement that can be seen using hyperpolarized 13C MRSI techniques following an early-stage ER+ breast cancer diagnosis and before surgery
2. Target-product engagement of capivasertib +/- exemestane will be assessed by the reduction in the hyperpolarized 13C-labelled lactate/pyruvate (LAC/PYR) ratio between baseline and following at least ten days after initiation of capivasertib

Key secondary outcome(s))
At baseline (before treatment starts), at the last day of the medicines treatment and also at surgery (for some of the endpoints):
1. Effects on tumour proliferation will be assessed by Ki67 IHC, measuring the percentage change (%) between baseline, following at least ten days after initiation of capivasertib and at surgery
2. Changes in the hyperpolarized 13C-labelled lactate: pyruvate ratio between baseline and following at least ten days after initiation of capivasertib will be correlated with alterations observed in tumour proliferation markers during the same time frame
3. Changes in the hyperpolarized 13C-labelled lactate: pyruvate ratio, Ki67 as well as any relevant biomarker changes between baseline and following at least ten days after initiation of capivasertib will be compared between the two arms
4. A subgroup analysis is planned to assess changes in the hyperpolarized 13C-labelled lactate: pyruvate ratio, Ki67 as well as any relevant biomarker changes between baseline and following at least ten days after initiation of capivasertib in PI3K/AKT/PTEN pathway-altered tumours and non-altered tumours. Tumours will be categorised on the basis of whole-genome sequencing results
5. Change in FOXM1 status will be measured via its effects on LDHA expression using MRSI of hyperpolarized [1-13C] pyruvate metabolism
6. Safety and tolerability of capivasertib +/- exemestane will be assessed using the incidence of Serious Adverse Events (SAEs) and the incidence of Adverse Events (AEs), measured according to CTCAE v5.0 criteria

Completion date
30/11/2027

Eligibility

Key inclusion criteria
1. Female sex as assigned at birth
2. Aged between 18 and 79 years
3. Post-menopausal
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1
5. ER-positive, HER2-negative invasive breast cancer
6. Intermediate or high-risk of breast cancer recurrence (grade 2 or 3 and Ki67 ≥10%)
7. Clinical stage T1c-4, NX or N0-N3, M0 (primary breast cancer ≥15mm)
8. Adequate bone marrow, renal and hepatic function
9. Capable of giving written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
79 years

Sex
Female

Key exclusion criteria
1. Metastatic , inoperable locally advanced or recurrent disease
2. History of another primary malignancy except for malignancy treated with curative intent
3. Persistent toxicities caused by previous anticancer therapy, excluding alopecia
4. Diabetes mellitus type 1
5. Diabetes mellitus type 2
6. Haemoglobin ≥7.0% at screening
7. Some cardiac conditions as: mean resting QT interval at screening, arrhythmia, history of QT prolongation associated with medications that required discontinuation of that medication, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives
8. Hypotension at screening
9. Known HIV infection that is not well controlled
10. Known active hepatitis B or C infection
11. Known active tuberculosis infection
12. Known contraindication or inability to tolerate MRI
13. Known hypersensitivity or contraindications to aromatase inhibitors, capivasertib or any of the excipients of exemestane or capivasertib
14. Received any prior treatment for either this breast cancer or a previous breast cancer diagnosis
15. Prior exposure to any chemotherapy or anti-cancer agents without appropriate washout period before randomization/enrolment 16) Hormone therapy including hormone replacement therapy (HRT) use in the 6 months prior to screening
16. Radiotherapy within 14 days prior to the first dose of study intervention
17. Major surgical procedure or significant traumatic injury within 28 days of the first dose of capivasertib
18. Previous treatment in the AKTivate study
19. Participation in another clinical study with a study intervention or investigational medicinal device administered in the 28 days prior to first dose of study intervention or concurrent enrolment in another clinical study
20. Women of childbearing potential, women who are currently pregnant or breastfeeding, women who are planning to become pregnant, or women who are lactating during the study

period
21. Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements
22. Body mass index < 18.5 kg/m² at the time of screening

Date of first enrolment
01/10/2025

Date of final enrolment
30/11/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
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Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca UK

Alternative Name(s)
AstraZeneca UK Limited, AZ

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date