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Combination treatment for early hormone-positive HER-positive breast cancer

Submission date 06/04/2023	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/11/2023	**Overall study status** Ongoing	
Last Edited 05/02/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
This is a study where patients with early breast cancer will be given a combination of medications before they have their operation to remove the breast cancer. We want to look at whether this combination of drugs may be successful as a treatment for early breast cancer. We will be looking at post-menopausal women with early breast cancer that is ER-positive, PgR-positive and HER2-positive, and who are eligible for surgery. Breast cancer that has a significant number of receptors for either oestrogen (ER+) or progesterone (PgR+) is considered hormone-receptor positive and can be treated with either hormone therapy alone or chemotherapy followed by hormone therapy. ER+ breast cancers are routinely treated with hormone therapy that blocks the oestrogen receptor, this type of therapy is more effective when combined with another drug which blocks a molecule called CDK4/6. About 15% of all breast tumours have higher levels of a protein known as HER2, called HER2-positive (HER2+) breast cancers. These cancers tend to grow and spread faster than breast cancers that are HER2-negative, but are much more likely to respond to routine treatment with drugs that target the HER2 protein. 50% of HER2+ breast cancers are also ER+. Research has shown that the combination of HER2 therapy with hormone therapy is more active than hormone therapy alone.

Who can participate?
Patients aged 18 years and over with early breast cancer that is ER+, PgR+ and HER2+

What does the study involve?
Participants receive a combination of treatments: letrozole to block oestrogen receptor (ER), plus trastuzumab and tucatinib to block HER2 and palbociclib to block CDK4/6.

What are the possible benefits and risks of participating?
The study enables the avoidance of chemotherapy and all its potential side effects and issues while allowing access to a neoadjuvant regimen with agents which have previously shown evidence of clinical activity. The treatment may benefit the patient by reducing the size of their tumour and hence reducing the extent of surgery including breast preservation. The information we get from this study may help us to improve the future treatment of patients with ER+, PgR+ and HER2+ breast cancer. The results from this study will be used to help us improve treatments for postmenopausal women with ER+, PgR+ and HER2+ early breast cancer who require

neoadjuvant therapy. Participants will attend additional visits, whether for screening or for treatment that falls outside of standard care. There may be associated costs of travel and availability of time for patients (e.g. taking annual leave). Additional tests and procedures will be required as part of the trial including taking blood at five additional timepoints, two additional research breast biopsies and two additional breast scans. This will be explained in the patient information sheet including the risks of these procedures. Patients may experience adverse events that may be painful, life-threatening or cause death. All possible mitigations have been put in place to protect patients including stringent inclusion and exclusion criteria and patient monitoring. Patients will be informed of possible adverse events and directed to where to find more information in the patient information sheet.

Where is the study run from?
The University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
April 2023 to January 2026

Who is funding the study?
1. Seagen (USA)
2. Pfizer (USA; Donation of palbociclib)

Who is the main contact?
3-pillars@liverpool.ac.uk, Liverpool Clinical Trials Centre (UK)

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-palbociclib-letrozole-trastuzumab-and-tucatinib-before-surgery-for-breast-cancer

Contact information

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Additional identifiers

EudraCT/CTIS number
2021-006077-34

IRAS number
1004806

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
UoL001650, IRAS 1004806, CPMS 58079

Study information

Scientific Title
3-Pillars Study: a phase II open label study of the cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole, trastuzumab plus tucatinib as neoadjuvant treatment for ER-positive, PgR-positive and HER2-positive early breast cancer in post-menopausal women

Acronym
3-Pillars Study

Study objectives
Primary objective:
To assess the pathological complete response rate after 24 weeks of palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib

Secondary objectives:
1. To assess change in Ki67 proliferation index after 2 weeks and 23 weeks of palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib
2. To assess the radiological response rate as measured by ultrasound/MRI/mammogram after 24 weeks of palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib
3. To assess objective clinical response rate after 24 weeks of Palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib
4. To assess the proportion of tumours with a Preoperative Endocrine Prognostic Index (PEPI) score of 0 or 1 after 24 weeks of palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib
5. To assess the safety and tolerability of palbociclib treatment in combination with letrozole, trastuzumab plus tucatinib as neoadjuvant treatment for ER-positive, HER2-positive early breast cancer

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/09/2023, Seasonal REC (Health Research Authority) (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 800; seasonal.rec@hra.nhs.uk), ref: 23/LO/0388

Study design
Single-arm open-label non-randomized study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See trial outputs table

Health condition(s) or problem(s) studied
ER-positive, PgR-positive and HER2-positive early breast cancer

Interventions
3-Pillars is a single-arm trial so participants will not be randomised. All participants taking part in the 3-Pillars trial will receive the same treatment as follows:
1. Tucatinib (300mg tablet taken orally twice daily for 24 weeks or until surgery)
2. Palbociclib (75mg/day on a 28 day schedule of 21 days on and 7 days off for a total of 24 weeks)
3. Letrozole (2.5mg tablet taken orally once daily for 24 weeks or until surgery)
4. Trastuzumab (600mg subcutaneous injection every 3 weeks for 24 weeks or until surgery)

Dose reductions are permissible for tucatinib as follows:
1. Tucatinib – 300mg starting dose, 250mg first dose reduction, 200mg second dose reduction, 150mg third dose reduction
2. Palbociclib – no dose reduction
3. Letrozole – no dose reduction
4. Trastuzumab – no dose reduction

No dose reductions are permissible for palbociclib, letrozole and trastuzumab. Participants will receive a 4-week post-surgery follow-up for a translational blood sample and adverse event recording.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tucatinib, palbociclib, letrozole, trastuzumab

Primary outcome measure
The pathological complete response (PCR) rate after completion of study treatment as defined as the complete absence of invasive carcinoma in the breast and axillary lymph nodes on histological examination at the time of definitive surgery irrespective of in situ carcinoma in the breast (ypT0/ypTis, ypN0). Measured after 24 weeks of treatment.

Secondary outcome measures
1. The difference in the proliferation marker Ki67 (% positive tumour cells) as tested by IHC from baseline to 2 weeks of treatment and from baseline to after 23 weeks of treatment.
2. The objective radiological response rate as defined as the sum of Partial Responses (PR) and Complete Responses (CR) according to RECIST v1.1, as per Investigator's assessments by breast USS, mammogram or MRI after completion of study treatment. Measured after 24 weeks of treatment.
3. The objective clinical response rate after 24 weeks of treatment as per tumour overall objective response rate (ORR), defined as the sum of Partial Responses (PR) and Complete Responses (CR) according to RECIST v1.1 as per Investigator's assessments by breast USS, mammogram or MRI after completion of study treatment. Measured after 24 weeks of treatment.
4. The proportion of tumours with a Preoperative Endocrine Prognostic Index (PEPI) score of 0 or 1 after completion of study treatment. Measured after 24 weeks of treatment.
5. Safety and tolerability in terms of:
5.1. Defined Grade 1 and 2 toxicities as classified by NCI-CTCAE v5.0 recorded at each visit from

start of trial treatment until 4-week post-surgery visit
5.2. Grade 3+ toxicity as classified by NCI-CTCAE v5.0 recorded at each visit from start of trial treatment until 4-week post-surgery visit
5.3. Serious Adverse Events (SAEs) recorded at each visit from start of trial treatment until 4-week post-surgery visit
5.4. Withdrawal from trial treatment due to toxicity recorded at End of Treatment
5.5. Delays to scheduled surgery (due to treatment related toxicities as determined by the investigator) recorded at the Surgery visit

Overall study start date
04/04/2023

Completion date
31/01/2026

Eligibility

Key inclusion criteria
Patients eligible for the trial must comply with all of the following at registration:
1. 18 years old and greater
2. Newly diagnosed (no previous history of invasive breast cancer) histologically confirmed breast cancer
3. Tumour measuring ≥15 mm in longest diameter by ultrasound (US), mammogram or MRI or any size with axillary lymph node involvement
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
5. Postmenopausal as defined by one of the following criteria:
5.1. Prior bilateral oophorectomy
5.2. Age ≥55 years with an intact uterus and EITHER amenorrhoeic for >12 month OR have recorded Follicle-Stimulating Hormone (FSH) and oestradiol levels within the post-menopausal range within the last 12 months
5.3. Age <55 years with an intact uterus, amenorrhoeic for >12 month AND Follicle-Stimulating Hormone (FSH) and oestradiol levels within the post-menopausal range within the last 12 months
5.4. Women who have had a hysterectomy with intact ovaries with FSH and estradiol levels in the postmenopausal range (as per local reference ranges)
6. ER-positive defined as a Quick Allred Score of ≥6
7. PgR-positive defined as a Quick Allred Score of ≥6
8. HER2-positive defined by immunohistochemistry - 3+ by Herceptest/similar assay or gene amplification as determined by FISH/CISH/D-DISH and the ratio of HER2 to CEP17 probes >2.0
9. Adequate bone marrow function defined by all of the following:
9.1. Haemoglobin (Hb) ≥10 g/dl
9.2. White cell count ≥3.0x10^9
9.3. Absolute Neutrophil Count (ANC) >1.5 x10^9/L
9.4. Platelets ≥100 x10^9/L
10. Adequate renal function defined by a serum creatinine ≤1.5 x Upper Limit of Normal (ULN) (according to local reference ranges)
11. Adequate liver function defined by:
11.1. Total bilirubin ≤1.5 ULN (except for patients with clearly documented Gilbert’s syndrome)
11.2. Alanine transaminase (ALT) or aspartate transaminase (AST) ≤1.5 ULN
11.3. Alkaline phosphatase ≤1.5 ULN
12. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial

thromboplastin time (aPTT) ≤1.5 X ULN, unless on medication known to alter INR and PTT/aPTT (values within acceptable ranges as per local protocol)
13. Left ventricular ejection fraction (LVEF) of 50% or higher (determined by echocardiography or multiple-gated acquisition scanning)
14. Available paraffin-embedded tumour block taken at diagnostic biopsy for central assessment of Ki67
15. Able to swallow capsules
16. Provided written informed consent

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Female

Target number of participants
90

Key exclusion criteria
Any patient meeting any of the criteria listed below will be excluded from study participation:
1. Inflammatory or inoperable breast cancer
2. Evidence of bilateral invasive breast cancer
3. Clinically or radiological evidence of metastatic disease (staging to be done in accordance with local guideline)
4. Concomitant use (defined as use within 12 weeks prior to entry) of Hormone Replacement Therapy (HRT) or any other oestrogen-containing medication or supplementation
5. Any prior treatment with any CDK 4/6 inhibitor
6. Use of a strong CYP3A4 or CYP2C8 inhibitor, or food or drugs that are known CYP3A4 inhibitors, within 2 weeks of starting study treatment and during study (See Appendix 3)
7. Use of a strong CYP3A4 or CYP2C8 inducer, or drugs known to be CYP3A4 inducers, within 5 days of starting study treatment and during study (See Appendix 2 and Appendix 3)
8. No plan to commence treatment with CYP3A substrates within 2 weeks of starting study treatment and during study (See Appendix 1)
9. Any prior treatment with HER2-directed therapy
10. Previous investigational medicinal products for any condition within 4 weeks of registration date
11. Any prior history of invasive malignancy within 5 years of starting treatment where there is a medium or high risk of reoccurrence (other than treated basal cell carcinoma or squamous cell carcinoma of the skin and cervical carcinoma in situ or cancers treated with surgery alone).
12. QTc >480 msec or a family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP)
13. Significant cardiovascular disease including but not limited to:
13.1. History of documented congestive cardiac failure
13.2. Angina pectoris requiring anti-anginal medication
13.3. Evidence of transmural infarction on ECG

13.4. Poorly controlled hypertension or uncontrolled asymptomatic hypertension as determined by the investigator
13.5. Clinically significant valvular heart disease
13.6. Ventricular significant arrhythmia requiring therapy
13.7. High-risk uncontrolled arrhythmias or sudden cardiac arrest
14. Has significant gastro-intestinal disease including but not limited to active inflammatory bowel disease, chronic diarrhoea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection which would preclude the adequate oral absorption of medications.
15. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging (e.g., hypocalcaemia, hypokalaemia, hypomagnesemia)
16. Evidence of bleeding diathesis
17. Active bacterial infection (as defined by the use of oral or IV antibiotics at the time of study registration or systemic fungal infection
18. Known human immunodeficiency virus (HIV) positivity (screening HIV is not required for study enrolment)
19. Known active or inactive hepatitis carrier, for example, hepatitis B surface antigen (HBsAg) positive (screening hepatitis B or C is not required for study enrolment)
20. Recent vaccination with a live virus defined as within 28 days of study registration
21. Known hypersensitivity to letrozole, palbociclib, trastuzumab or tucatinib, or to any of the excipients.

Date of first enrolment
29/08/2024

Date of final enrolment
01/03/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Clatterbridge Cancer Centre
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Study participating centre
Nottingham University Hospitals NHS Trust - City Campus
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Study participating centre
University Hospitals Bristol and Weston NHS Foundation Trust
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Study participating centre
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Study participating centre
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Sponsor type
University/education

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http://www.liv.ac.uk/

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Industry

Funder Name
Pfizer

Alternative Name(s)
Pfizer Inc., Pfizer Consumer Healthcare, Davis, Charles Pfizer & Company, Warner-Lambert, King Pharmaceuticals, Wyeth Pharmaceuticals, Seagen

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on a website
4. Other publication
5. Submission to regulatory authorities
6. Access to raw data and right to publish freely by all investigators in the study or by the Independent Steering Committee on behalf of all investigators

Intention to publish date
31/01/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Liverpool Clinical Trials Centre, LCTC@liverpool.ac.uk.

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers.
Patient identifiable data will only be shared with external researchers if the participants have consented to this onward disclosure in accordance with the Common Law Duty of Confidentiality, or if the external researchers obtain approval to waive this Common Law requirement (i.e. Section 251 Approval via the Confidentiality Advisory Group (CAG) / approval from the Public Benefit & Privacy Panel for Health & Social Care (PBPP)) or if the IPD has been fully anonymised prior to sharing.
All requests for access to the IPD will be assessed by the Sponsor and must be agreed upon by all Data Controller organisations.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.0	21/11/2022	26/04/2023	No	Yes
Participant information sheet	Adult PISC version 1.0	06/02/2023	26/04/2023	No	Yes
Participant information sheet	version 3.0	28/03/2024	05/02/2025	No	Yes