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NEO21-RS: A prospective study of the outcomes following 21-gene recurrence score directed neoadjuvant therapy in ER-positive, HER2-negative breast cancer

Submission date 08/07/2019	**Recruitment status** Suspended	[X] Prospectively registered [ ] Protocol
Registration date 08/07/2019	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 20/09/2021	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
See https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-palbociclib-and-hormone-therapy-before-surgery-to-remove-breast-cancer-neo12-rs (added 08/01/2021)

Contact information

Type(s)
Scientific

Contact name
Miss Helen Scott

Contact details
Liverpool Clinical Trials Centre
University of Liverpool
Block C, Waterhouse Building
1-3 Brownlow Street
Liverpool
United Kingdom
L69 3GL
+44 (0)151 794 8209
hscott@liverpool.ac.uk

Additional identifiers

EudraCT/CTIS number
2018-000157-41

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS: 37602

Study information

Scientific Title
NEO21-RS: A phase II randomised study of the cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with oestrogen suppression therapy versus oestrogen suppression therapy alone as neoadjuvant therapy in ER-positive intermediate recurrence score primary breast cancer

Acronym
NEO21-RS

Study objectives
The purpose of this study is to look at different breast cancer treatments given to shrink the tumour before having surgery to remove it. Treatment given before surgery is called neoadjuvant therapy and this can be either hormone therapy or chemotherapy.

A test called the Oncotype DX Breast Recurrence Score®, when used after breast surgery can help decide whether chemotherapy is needed to treat the tumour or if hormone therapy alone is the right treatment. Breast cancers with a low recurrence score (RS) are treated with hormone therapy, while for those with a high RS chemotherapy is recommended followed by hormone therapy. In breast cancers that have an intermediate RS it is not known what is the best treatment and if chemotherapy is needed to treat these cancers. Currently, the Oncotype DX® test is not available to patients who need treatment before surgery (neoadjuvant treatment). This study will give patients needing treatment before surgery access to this test. Patients with a low RS will receive hormone therapy, while those with a high RS will be treated with chemotherapy. If the breast cancer has an intermediate RS these will be randomised to compare hormone treatment alone against hormone treatment plus a new drug called Palbociclib. All patients entered will be followed up and how effective the treatment received at shrinking the breast cancer recorded.

There are 2 components to this study:
1. An observational study of the outcomes for patients whose tumours have a low and high RS
2. A randomised trial to compare two different treatments for patients whose tumours have an intermediate RS breast cancer. Half will receive hormone therapy on its own and the other half will have hormone therapy plus a new drug called palbociclib.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/04/2018, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8012; Email: nrescommittee.northwest-haydock@nhs.net)

Study design
Randomised; Both; Design type: Treatment, Drug, Cohort study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Breast cancer

Interventions
This is a multi-centre, phase II randomised, open-label study to assess the efficacy and safety of palbociclib with oestrogen suppression therapy in patients with ER-positive early breast cancer who have an intermediate recurrence score as determined by the Oncotype DX assay.

There are two studies:
1. Multicentre, two-arm parallel group, open-label, neoadjuvant RCT
2. Observational cohort study

Patients considered eligible for study participation will have the following screening assessments carried out within 21 days of randomisation:
1. Provision of study information (PIS and ICF)
2. Signing of Informed Consent Form
3. Assessment of eligibility criteria
4. Patient Registration to trial
5. Review of medical history and past drug history
6. Breast biopsy (up to 28 days prior to registration/randomisation)
7. 21-gene recurrence score (Oncotype Dx, Genomic Health)
8. Haematology and clinical biochemistry – 4 tubes (including FBC, LFT, clotting, glucose, FSH and E2)
9. Collection of Formalin Fixed Paraffin Embedded tissue
10. Pregnancy test (for premenopausal women only)
11. Vital signs (including BP, pulse, height and weight)

Patients who satisfy the minimum eligibility requirements as follows can be enrolled on the study:
1. Received PIS
2. Written informed consent given
3. Trial registration forms signed by PI/co-investigator confirming tumour ≥ 20mm and

neoadjuvant therapy required
4. 21-gene recurrence score request raised (pathology to prepare tissue specimen and send to Genomic Health, PI to forward RS request to LCTU for submission to Genomic Health)

Completion of the remaining screening assessments can be undertaken whilst awaiting 21-gene RS results. Assessments carried out as part of routine care can be used for screening only if within the specified windows.

On receipt of the RS score (within 10-14 days) to LCTU the result will be communicated to site within 24 hours(working day). Notification of Low and High RS results will be forwarded to the clinical team at site, detailing the RS group and value and advising the appropriate standard care pathway of endocrine therapy or chemotherapy.
On receipt of an intermediate RS result to LCTU, the patient's eligibility will be confirmed and the patient randomised to the therapeutic or control arm and sites notified of the RS group (only) and the allocated treatment arm. Intermediate RS values will not be communicated until after surgery so that the clinician remains blinded; this is to avoid clinicians influencing treatment decisions as a result of borderline RS group values.

Patients in the low and high RS groups will be required to attend hospital visits for the following assessments:
Baseline - physical examination, vital signs, breast examination, breast ultrasound, ECOG performance status, haematology and biochemistry blood tests, translational blood sample, dispensing/administration of drug. Tissue prepared for sending for Ki67 testing.
4-weekly visits x5 (at week 4, 8, 12, 16 and 20) - breast examination, breast ultrasound (at week 12 only), concomitant medications check, ECOG performance status and drug dispensed /administered.
End of treatment visit (24 weeks) - breast examination, breast ultrasound, translational blood sample, concomitant medications check, ECOG performance status. Tissue prepared for sending for Ki67 testing.
Surgery Visit - pre-planned breast surgery and core biopsy (as standard of care) and collection of Formalin Fixed Paraffin Embedded Tissue.
4-weeks post surgery visit - collection of data on final treatment delivered.

Patients in the intermediate RS group will be required to attend hospital visits for the following assessments:
Baseline - physical examination, vital signs, breast examination, breast ultrasound, ECOG performance status, haematology and biochemistry blood tests, translational blood samples, concomitant medication check, dispensing/administration of drug, drug diary review. Tissue prepared for sending for Ki67 testing.
2 weeks visit - breast core biopsy, translational blood samples. Tissue prepared for sending for Ki67 testing. Patients receiving palbociclib will also have FBC blood sample taken for standard monitoring of toxicities.
4-weekly visits x5 (at week 4, 8, 12, 16 and 20) - physical examination, breast examination, breast ultrasound (week 12 only), haematology and biochemistry blood sample, translational blood sample, ECOG performance status, concomitant medications check, drug diary review, drug dispensing/administration, adverse event recording.
6 weeks visit (for patients receiving palbociclib only) - FBC blood sample taken for standard monitoring of toxicities.
End of treatment visit (24 weeks) - physical examination, breast examination, breast ultrasound, breast core biopsy, haematology and biochemistry blood samples, translational blood samples, ECOG performance status, concomitant medication check, drug diary review, adverse event recording. Tissue prepared for sending for Ki67 testing.

Surgery visit - pre-planned breast surgery (standard of care) and collection of Formalin Fixed Paraffin Embedded Tissue
4-weeks post surgery visit - collection of data on final treatment and adverse event recording.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
For the RCT (intermediate-risk patients):
The change in level of proliferation marker Ki67 from baseline to 24 weeks

Secondary outcome measures
1. The proportion of patients showing objective radiological response as measured by ultrasound after 24 weeks of treatment according to ECOG criteria
2. The proportion of patients showing objective clinical response after 24 weeks of treatment according to ECOG criteria
3. The proportion of patients who undergo breast conservation after 24 weeks of treatment
4. The proportion of patients with improved surgical outcome after 24 weeks of treatment (Improved surgical outcome is defined as the patient having less extensive surgery than planned at the start of study)
5. The proportion of patients showing pathological complete response (pCR) after 24 weeks of treatment (pathological complete response is defined as no invasive disease in breast and axilla)
6. The proportion of tumours with a Preoperative Endocrine Prognostic Index (PEPI) score of 0 or 1 after 24 weeks of treatment
7. The proportion of patients going on to receive adjuvant chemotherapy

For the observational cohort (low- and high-risk patients) all outcomes are secondary, although the change in level of proliferation marker Ki67 will be assessed:
1. The proportion of patients showing objective radiological response rate as measured by ultrasound after 24 weeks of treatment according to ECOG criteria
2. The proportion of patients showing objective clinical response rate after 24 weeks of treatment according to ECOG criteria
3. The proportion of patients who undergo breast conservation after 24 weeks of treatment
4. The proportion of patients with improved surgical outcome after 24 weeks of treatment
5. The proportion of patients showing pathological complete response (pCR) after 24 weeks of treatment
6. The proportion of tumours with a Preoperative Endocrine Prognostic Index (PEPI) score of 0 or 1 after 24 weeks (low recurrence score group only)
7. The proportion of patients going on to receive adjuvant chemotherapy (low recurrence score group only)
8. The change in level of Ki67 proliferation marker from baseline to 24 weeks

Overall study start date
24/07/2018

Completion date
31/05/2022

Eligibility

Key inclusion criteria
1. 18 years of age or older
2. Histologically confirmed invasive breast cancer
3. ER positive (Allred ≥3)
4. HER2 negative per the 2013 ASCO/CAP guidelines
5. Axillary node negative or positive
6. Tumour measuring ≥15mm in longest diameter as measured clinically or radiologically or any size tumour with axillary node involvement
7. Candidate for neoadjuvant endocrine therapy or chemotherapy
8. Pre- or postmenopausal women. Postmenopausal status will be defined by the presence of any one of the following criteria:
8.1. ≥55 years of age with an intact uterus and amenorrhoea ≥12 months at the time of diagnosis
8.2. <55 years with no menses for at least 12 months prior to study entry and documented or current FSH and oestradiol levels within the postmenopausal range (as per local institutional /laboratory standard)
8.3. >18 years with prior hysterectomy with intact ovaries and with a documented or current FSH and oestradiol level within the postmenopausal range (as per local institutional/laboratory standard)
8.4. >18 years with prior bilateral oophorectomy
9. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2
10. Adequate bone marrow function defined by Hb≥10 g/dl, ANC >1.5 x109/L, PLT≥100 x109/L
11. Adequate renal function defined by a serum creatinine ≤1.5 x ULN. Adequate liver function defined by total bilirubin ≤ 1.5 x ULN (patients with Gilbert's syndrome exempted), either ALT or AST ≤1.5 x ULN and ALP ≤1.5 x ULN
12. No contraindications to receiving palbociclib
13. Written informed consent, able to comply with treatment and follow-up

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 188; UK Sample Size: 188

Key exclusion criteria
1. Inflammatory breast cancer
2. Evidence of metastatic disease prior to 21-gene recurrence score assay testing

3. Any history of invasive malignancy within 5 years of starting study treatment (other than adequately treated basal cell carcinoma or squamous cell carcinoma of the skin and cervical carcinoma in situ)
4. Surgical axillary staging procedure prior to study procedure (with the exception of FNA or core biopsy)
5. Evidence of bleeding diathesis
6. Prior endocrine therapy or chemotherapy for breast cancer
7. Concomitant use (defined as use within 4 weeks prior to entry) of HRT or any other oestrogen-containing medication or supplement (including vaginal oestrogens and phytoestrogens)
8. Uncontrolled abnormalities of serum potassium, sodium, calcium or magnesium levels
9. Use of CYP3A inhibitors or inducers
10. Pregnant or breastfeeding
11. Evidence of uncontrolled active infection
12. Evidence of significant medical condition or laboratory findings which, in the opinion of the investigator, makes it undesirable for the patient to participate in the trial

Date of first enrolment
01/09/2019

Date of final enrolment
31/08/2021

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Wales

Study participating centre
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Belfast City Hospital
Lisburn Road
Belfast
United Kingdom
BT9 7AB

Study participating centre
East Cheshire NHS Trust
Macclesfield District Gen Hospital
Victoria Road
Macclesfield
United Kingdom
SK10 3BL

Study participating centre
Pennine Acute Hospitals NHS Trust
Trust Headquarters
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre
Bolton NHS Foundation Trust
The Royal Bolton Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Wirral University
Teaching Hospital NHS Foundation Trust
Arrowe Park Hospital
Arrowe Park Road
Upton
United Kingdom
CH49 5PE

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester

United Kingdom
M20 4BX

Study participating centre
Countess Of Chester Hospital NHS Foundation Trust
The Countess Of Chester Health Park
Chester
United Kingdom
CH2 1UL

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Velindre NHS Trust
Velindre Cancer Centre
Velindre Road
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Abertawe Bro Margannwg University Health Board
Singleton Hospital
Sketty Lane
Swansea
United Kingdom
SA2 8QA

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Colchester Hospital University NHS Foundation Trust
Colchester District General Hospital
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Maidstone and Tunbridge Wells NHS Trust
Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
University Hospital of South Manchester NHS Foundation Trust
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Sponsor information

Organisation
University of Liverpool

Sponsor details
c/o Alex Astor
Research Support Office - Block D Waterhouse Building
3 Brownlow Street
Liverpool
England
United Kingdom
L69 3GL
-
sponsor@liv.ac.uk

Sponsor type
University/education

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. Protocol paper
2. Peer reviewed scientific journals
3. Internal report
4. Conference presentation
5. Publication on website
6. Submission to regulatory authorities

Intention to publish date
01/05/2023

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