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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

Adult Information Sheet for 3-PILLARS Trial

- You have been invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. **Part 1** tells you the purpose of the study and what will happen to you if you take part. **Part 2** gives you more detailed information about the conduct of the study.
- You can ask a member of your clinical team if there is anything that is not clear, or if you would like more information.
- If you wish you can discuss it with friends, relatives and/or get independent advice via your local Patient Advice and Liaison Service (PALS) or equivalent.
- Taking part is voluntary. If you don't want to take part then you don't need to give a reason.
- 3-Pillars is a study of early breast cancer to investigate if a combination of neoadjuvant treatments will result in clinically meaningful activity.
- In the study cyclin-dependent kinase 4/6 inhibitor Palbociclib will be administered in combination with letrozole, trastuzumab plus tucatinib as neoadjuvant treatment for ER-positive, PgR-positive and HER2-positive breast cancer.
- Patients that might be able to take part will be postmenopausal women with ER-positive, PgR-positive andHER2-positive early breast cancer who require neoadjuvant therapy and be aged 18 years or over.
- The study aims to recruit 90 women for 24 months at up to 10 UK sites.

How to contact the study team:

If you have any questions about this study please talk to your research team:

- **<Add contact details for PI/RN, i.e. name and telephone number>**

PART 1: Purpose of the study and what will happen if you take

Why are we doing the 3-Pillars study?

The purpose of this study is to find out whether a combination of treatments given before surgery can benefit patients with your type of breast cancer. These different treatments block different ways the cancer cell can grow and spread. The use of treatment before surgery is called neoadjuvant therapy and is given to try and shrink the tumour.

If your breast cancer has a significant number of receptors for either oestrogen or progesterone, it is considered hormone-receptor positive. Early oestrogen receptor positive (ER+) and progesterone receptor positive (PgR+) breast cancer can be treated with either:

- hormone therapy alone or;
- chemotherapy followed by hormone therapy

Some of these treatments can be given after surgery to reduce the risk of the breast cancer returning or before surgery to help shrink the breast cancer as well as reduce the risk of the breast cancer returning.

It is known that ER+ breast cancers generally respond less well to chemotherapy and that not all such cancers need chemotherapy. Given all the possible side effects of chemotherapy it is important we try to avoid treating women in whom it will provide little or no benefit. ER+ breast cancers are routinely treated with hormone therapy that block the oestrogen receptor. It is known that such hormone 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 treatment with drugs that target the HER2 protein. Such treatments are key for HER2+ breast cancer and are routinely used. 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.

This study will treat patients with early breast cancer that is ER+, PgR+ and HER2+ and will consist of a combination of treatments: letrozole to block oestrogen receptor (ER), plus trastuzumab and tucatinib to block HER2 and palbociclib to block CDK4/6.

This study will take place in 10 hospitals across England, Wales and Scotland and 90 patients will take part over a period of 2 years.

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.

Why have I been chosen?

You have been invited to take part in this study because you have been diagnosed with ER+, PgR+ and HER2+ breast cancer and your doctor wants to give you some treatment before you have surgery to shrink your breast cancer.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not you want to take part.

If you decide not to take part then you will still receive the usual treatment your hospital offers. Your doctor can provide you with more information on this.

If you decide to take part you can also choose to stop at any time without giving a reason.

The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future.

What are the drug(s) being tested?

All patients registered to the 3-Pillars trial will receive the same treatment. There are four drugs being investigated in this trial: Palbociclib, Letrozole, Tucatinib and Trastuzumab.

Palbociclib

Palbociclib is a drug which is licensed for the treatment of advanced or secondary breast cancer when used with hormone therapy. It works by blocking two proteins in the cancer cell called cyclin dependant kinase 4 and 6, this results in a slowing of the growth of the breast cancer cells. In advanced breast cancer the combination of hormone therapy plus palbociclib is more effective than hormone therapy alone. Palbociclib is not licenced in early breast cancer and can only be used as part of approved clinical trials. Therefore, it is an 'investigational' medicinal product in terms of this study and its use in combination with neoadjuvant hormone therapy is only available to participants in the 3-Pillars study. Palbociclib has been tested in other clinical trials of neoadjuvant therapy and has shown some promising activity.

Palbociclib is a tablet which is taken orally once a day, for 21 days followed by 7 days off (i.e. 3 weeks on and 1 week off). You will receive treatment for 24 weeks. The tablet should be swallowed whole with a glass of water. Do not chew or crush it. Ideally it should be taken at the same time each day and with food if possible.

Palbociclib comes in a carton containing 3 blister strips of 7 tablets each. You will be prescribed with enough of the drug to last until your next appointment and a repeat prescription provided as required. Any remaining tablets should be returned to hospital at your scheduled appointment.

Letrozole

Letrozole is a drug used for treating breast cancer and can also help prevent breast cancer coming back. It works to lower the level of estrogen in the blood stream by blocking an enzyme called aromatase, which converts the male sex hormones to female sex hormones.

Letrozole is a tablet which is taken orally once a day. You will receive treatment for 24 weeks. The tablet should be swallowed whole with a glass of water. Do not chew or crush it. Ideally it should be taken at the same time each day and with food if possible.

Tucatinb

Tucatinib is a drug that blocks the protein HER2. HER2 causes breast cancer cells to grow and so blocking HER2 can result in a reduction in the growth of a tumour and kill breast cancer cells.

Tucatinib is a tablet which is taken orally twice a day. You will receive treatment for 24 weeks. The tablet should be swallowed whole with a glass of water. Do not chew or crush it. Ideally it should be taken at the same time each day and with food if possible.

Trastuzumab

Trastuzumab is a drug that blocks the effects of HER2 and encourages the immune system to attack and kill cancer cells.

Trastuzumab is given every 3 weeks during hospital visits by subcutaneous injection, which is an injection into your thigh that takes a few minutes.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign an informed consent form. You will be given a copy of the consent form and the information sheet to keep. Your consent form may be viewed by the funder, Seagen. Once you have signed the consent form, we will check and confirm that this study is suitable for you and you will be asked to follow the study plan (see study timeline). You will then be asked to have some tests to assess your condition and to ensure that you are eligible to participate. These are called screening tests. It is likely that some of these tests would be done if you decide not to take part in the study, and would not be considered extra to your standard care. Some of these tests may have already been done. These include physical examination, measuring your height and weight, reviewing any medication you are currently taking and blood tests. These are explained later in this information sheet. Only after all these tests are completed we will be able to confirm if you can take part in the study. If the results of any of these tests show that it is not appropriate for you to take part in the 3-Pillars study, your doctor will discuss with you the routine treatment options available. Once registered all patients will receive the same treatment of Palbociclib in combination with Letrozole, Trastuzumab plus Tucatinib as neoadjuvant treatment.

Samples:

As part of being on the 3-Pillars study we will collect blood and tissue samples from you. The use of samples helps us to answer important scientific questions about your condition and how it responds to treatment. The samples will be used for investigating your condition and for use in this study, samples may also be collected for future analysis. They will not be used for commercial purposes.

Blood samples:

As part of the screening assessments before you start any treatment, you will have some blood taken for haematology (full blood count and to check blood clotting ability) and biochemistry (to check liver function, blood sugar levels and hormone levels) screening. These results will also be used to determine your eligibility to be included in the study and should occur within 28 days before you are registered to take part on the study. You will have these bloods taken again at the start of weeks 2, 4, 8, 12, 16, 20 and at end of treatment (week 24). Where possible any study blood samples will be taken at the same time that you have your standard blood tests performed so that you will not have to undergo any extra procedures. We would also like to take some extra experimental blood samples and complete some blood tests (3 tubes) at Baseline (Day 0), the start of weeks 2, 12, 24 and at your follow-up visit (4 weeks post-surgery). Samples will be transferred to the University of Liverpool for storage and analysis.

Breast Tumour Tissue samples:

We would like to collect samples of your breast tumour tissue. Participants will be required to have a biopsy at screening and at the time of surgery as part of standard of care treatment. Participants will also be required to have an ultrasound guided core breast biopsy at weeks 2 and 23 as a research sample. All samples will be transferred to the University of Liverpool for evaluation and storage. Further details are given about this aspect in Part Two of this information sheet.

Previously taken samples:

As part of your diagnosis you underwent a biopsy. This sample will be stored or 'archived' at your local hospital. With your permission, we will request this tissue sample. It will be transferred to the University of Liverpool for evaluation and storage. As this is a previously taken and stored sample you will not need to attend extra visits or undergo any extra procedures.

Further details about the blood and tissue samples are given in Part Two of this information sheet.

Screening Assessments for all patients

All patients will have the following assessments:

- Breast biopsy done as standard of care (which can be up to 40 days prior to start of treatment-Day 0) and tissue collected.
- Breast scan and tumour size measurement done as standard of care (ultrasound, mammogram or MRI)
- Samples will be taken for blood tests
- Your medical history and past drug history will be reviewed
- Eligibility criteria will be assessed
- Vital signs including temperature, blood pressure, pulse, height and weight will be taken

Only after all these tests are completed will we be able to confirm if you can take part in the study. After screening tests have been completed and you have been registered, your doctor and the research nurse will explain your treatment plan and when to attend hospital for the study visits. If the results of any of these tests show that it is not appropriate for you to take part in the 3-Pillars study, your doctor will discuss with you the routine treatment options available.

Procedures for all eligible patients

At your first visit the doctor or research nurse will explain fully the treatment you are to receive and then hospital visits and assessments will be carried out as follows:

Start of treatment (up to 7 days from registration)

- Translational blood samples
- Receive prescription/administration of the relevant drug(s)

Start of week 2 Visit

- Breast biopsy done for research sample and tissue collected.
- Samples taken for blood tests
- Translational blood samples
- Any side effects reported

Trastuzumab Visits (Start of weeks 3, 6, 9, 15, 21)

- Receive prescription/administration of the relevant drug(s)
- Any side effects reported
- Samples taken for blood tests (Start of week 6 only)

Palbociclib Visits (Start of weeks 4, 8, 16, 20)

- Review of medications
- Samples taken for blood tests
- Breast examination (to measure tumour size)
- Liver function tests
- Drug diary dispensing
- Review drug diary
- Receive prescription/administration of the relevant drug(s)
- ECOG Performance Status (a questionnaire to check quality of life)
- Any side effects reported

Start of week 12 Visit

- Physical examination
- Review of medications
- Samples taken for blood tests
- Translational blood samples
- Breast scan (ultrasound, mammogram or MRI)
- Breast examination (involved calliper measurement)
- Drug diary dispensing
- Review drug diary
- Receive prescription/administration of the relevant drug(s)
- ECOG Performance Status
- Any side effects reported

Start of week 18 Visit

- Receive prescription/administration of the relevant drug(s)
- Any side effects reported
- Heart scan (echocardiogram or MUGA)

Start of week 23 Visit

- Breast biopsy done for research sample and tissue collected
- Any side effects reported

End of Treatment Visit (Start of week 24)

- Physical examination
- Review of medications
- Samples taken for blood tests
- Translational blood samples
- Breast scan (ultrasound, mammogram or MRI)
- Breast examination (involved calliper measurement)
- Review drug diary
- Receive prescription/administration of the relevant drug(s)
- ECOG Performance Status
- Any side effects reported

Surgery (up to +21 days from the end of the last cycle of palbociclib)

- During your planned breast surgery, a tissue sample will be collected

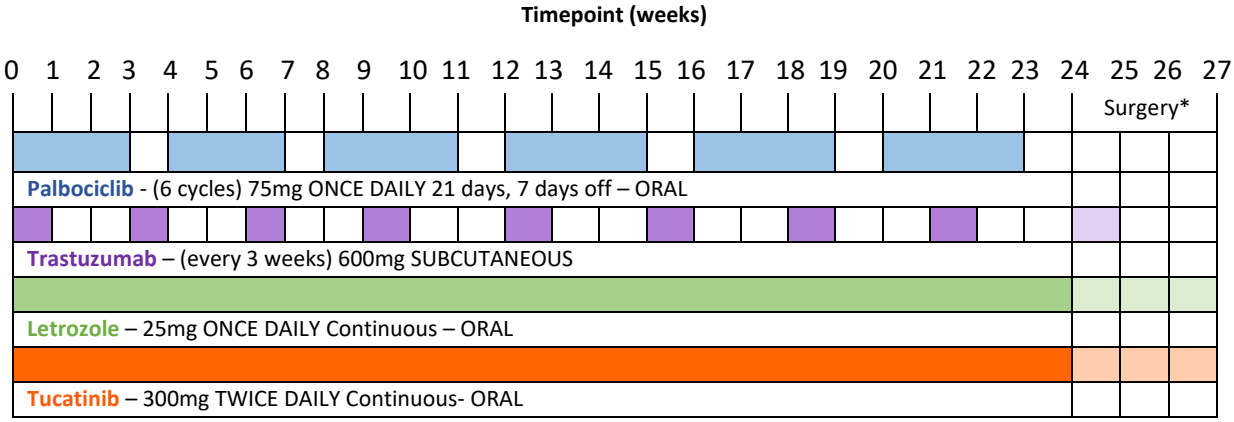
4-weeks Post Surgery Visit

- Translational blood samples
- Any side effects reported

You may also receive a CT scan of your chest at any point during your treatment if you begin to experience any shortness of breath or chest discomfort.

Procedure	**Description**	**Research Treatment or Standard of care**
Investigational medicine	*Once registered onto the trial you will be prescribed the following drugs:* • Palbociclib *(75mg tablets, once daily – 21 days on, 7 days off for 6 cycles)* • Letrozole *(25mg tablets: once daily)* • Tucatinib *(300mg tablets: twice daily)* • Trastuzumab *(600mg subcutaneous injection – administered during visit: every 3 weeks)*	***Research Treatment***
Scans (Imaging)	You will come in to hospital to see your study doctor or nurse 12 weeks after your 1st dose. You will have some scans, either an ultrasound, MRI or mammogram. You will also have a scan of your heart at your 18 week appointment. This will either be an echocardiogram or a MUGA scan. These will be the same as when you started the study.	**Standard of Care**
Surgery	You will come into hospital within 21 days of finishing your final cycle of Palbociclib. You will have surgery to remove your tumour and a tissue sample will be collected.	**Standard of Care**

Treatment Schedule



* Up to 21 days after last palbociclib cycle. Palbociclib will be stopped at 24 weeks. Letrozole, Tucatinib and Trastuzumab will be continued until surgery, and so may be taken beyond 24 weeks.

How will I know which treatment I'm going to have?

All patients will receive Palbociclib in combination with Letrozole, Trastuzumab plus Tucatinib as treatment before surgery.

What are the alternatives for treatment?

You are under no obligation to take part in the 3-Pillars study. If you decide not to take part or are unsuitable for the study, your doctor will discuss the routine treatment options available to you.

What are the benefits and risks of taking part?

We do not know if the study drug will help you. The information we get from this study may help us to improve the future treatment of patients with ER+, PgR+ and HER2+ breast cancer.

You will be required to make additional visits to the hospital as part of your treatment plan and being a participant in a clinical trial. Some of the assessments or procedures may cause discomfort or present a risk.

Blood tests are required in this study. Sometimes after a blood test you may experience a small amount of bruising on your skin where the needle went in. Occasionally a larger area of bruising may appear. Bruises can be painful but are usually harmless.

Medicines

Like all medicines, Palbociclib, Letrozole, Tucatinib and Trastuzumab can cause side effects, although not everybody will experience them. Nobody can tell you which side effects you may experience or how severe they will be. Therefore, all problems need to be reported to the clinical team (doctor or research nurse) looking after you at each visit, or by calling your study doctor immediately.

Palbociclib

The most common side effects of Palbociclib reported (may affect more than 1 in 10 people):

• Infections • Reduced white blood cells, red blood cells or blood platelets • Feeling of tiredness (fatigue)	• Inflammation of the mouth/lips • Nausea, vomiting, diarrhoea • Rash • Hair loss Decreased appetite

Other side effects that have been reported (may affect up to 1 in 10 people) include:

• Fever with a drop in white blood cell count • Blurred vision, increased tearing, dry eye • Abnormalities in liver blood tests • Alteration in taste	• Nosebleed • Dry skin • Weakness • Fever

Other reported side effects are inflammation of the lungs and interstitial lung disease (scarring of the lung tissue). Your team will monitor you closely for any signs and symptoms of these.

Letrozole

The most common side effects of Letrozole reported (may affect more than 1 in 10 people):

• Hot flushes • Excessive sweating • Joint stiffness • Feeling of tiredness (fatigue)	• High cholesterol • Vaginal dryness • Reduced secual interest

Other side effects that have been reported (may affect up to 1 in 10 people) include:

• Decrease or increase in appetite • Depression • Anxiety • Irritability • Headache • Dizziness • Palpitations • High blood pressure • Nausea • Vaginal bleeding • Swelling of hands and legs • Chest pain	• Constipation • Abdominal pain • Diarrhoea • Vomiting • Hair loss • Rash • Dry skin • Muscle and bone pain • Osteoporosis • Bone fractures • Arthritis • Weight increase

Tucatinib

Reported side effects of Tucatinib are:

• Nausea, Diarrhoea and vomiting • Dyspepsia (indigestion) • Constipation • Feeling of tiredness (fatigue) • Dry mouth	• Reduced white blood cells, red blood cells or blood platelets • Muscle pain • Headache • Rash

• Abdominal pain • Swelling of hands and legs • Abnormalities in liver blood tests • Abnormalities in kidney blood tests • Pain in extremity	• Dry skin • Decrease appetite • Alteration in taste • Headache • Nose bleed

Trastuzumab

The most common side effects of Trastuzumab reported (may affect more than 1 in 10 people):

• Infection or cold • Anaemia • Low white blood cells and platelet count decreased • Weight loss • Insomnia • Tremor, dizziness, headache • Pins and needles • Altered taste • Conjunctivitis, teary eyes • Changes in blood presure • Irregular heartbeat • Hot flush • Shortness of breath, cough • Runny nose, nose bleeds • Diarrhoea or constipation	• Vomiting • Nausea • Lip swelling, mouth sores, facial swelling • Abdominal pain • Skin rash • Alopecia • Nail disorder • Swelling and blistering to hands and feet • Joint stiffness • Muscle pain and stiffness • Feeling of tiredness (fatigue) • Weakness • Chest pain • Flu-like symtpoms • Pain and fever • Pain and swelling in extremities

Other side effects that have been reported (may affect up to 1 in 10 people) include:

• Penumonia, lung disorder • Asthma • Acne, dry skin • Dry eye • Bruising • Excessive sweating • Itchy skin • Breast swelling/mastitis • Swelling • Hypersensitivity • Anxiety/depression • Pain in extremities	• Drowsiness • Heart issues, palpitation • Haemorrhoids • Dry mouth • Abnormalities in liver blood tests • Inflammation of the liver, liver tenderness • Abnormalities in kidney blood tests • Arthritis • Back pain, neck pain • Bone pain • Muscle spasms

At each visit you will be asked about any unusual symptoms and if any serious side effects occur the study medication may be reduced or stopped. You will be checked regularly for improvements and recommencement of the study medication only instigated if appropriate.

Details of any side effects associated with the standard of care treatments as provided above can be discussed with your doctor.

We hope that the results from the study will help doctors and patients in the future when making decisions about treatment.

Tests and procedures

Not all patients will receive all of the tests and procedures as many are used for specific clinical reasons. Your doctor will discuss with you what procedures you will have. Some of the tests and procedures may cause discomfort or present risk**.** Here is a summary of the risks:

Ultrasound scan:

An ultrasound scan uses high-frequency sound waves to create an image of part of the inside of the body. An ultrasound can be used to diagnose a condition or guide a surgeon during certain procedures. There are no known risks from the sound waves used in an ultrasound and the procedure is painless.

Ultrasound-guided breast biopsy:

An ultrasound-guided breast biopsy is used to remove a sample of breast tissue for testing. You will feel a quick sting from the needle if you have a local anesthetic to numb the biopsy area and you may feel some pressure when the biopsy needle is put in. You may experience buising and swelling around the biopsy site which may be painful but is usually harmless.

Mammogram scan:

Mammograms are part of your routine care and are designed to look only at breast tissue. Mammograms use very small doses of ionising radiation - lower doses than usual X-rays. If you take part in this study you will undergo two extra scans that may be either a mammogram, MRI or ultrasound. Ionising radiation may cause cancer many years or decades after the exposure.

Magnetic Resonance Imaging (MRI) scan:

The MRI scan uses strong magnetic fields to take detailed images of your body. Because the MRI uses a strong magnet it may disrupt certain medical devices that are implanted in the body, such as pacemakers or drug pumps. MRI scans are not usually recommended for people with these devices.

The radiographer will ask you a number of questions to determine if you are suitable for a MRI. There is no evidence to suggest that the magnetic waves used in the MRI pose any health risks. Due to the confined space, you may experience some anxiousness or claustrophobia. You should let the radiographer know if you do experience this.

Echocardiogram:

An echocardiogram, or echo, is a type of ultrasound scan which uses sound waves to build up a detailed picture of your heart. An echo is a simple, painless and safe procedure and there is no side effects from the scan, although the lubricating gel may feel cold and you may experience some minor discomfort when the electrodes are removed from your skin at the end of the test.

Multiated Acquisition (MUGA) Scan:

A MUGA scan is used to check the health of your heart and shows if there are any problems with the way the heart is pumping. A small amount of radioactive contrast tracer is injected into a vein. The tracer is like a dye that bonds to your red blood cells. The MUGA camera picks up the radiation from the tracer as it travels through the heart. In rare cases a serious allergic reaction to the tracer can occur. You will only undergo a MUGA scan if your clinician does not think an echocardiogram is suitable for you, this will be explained to you.

Computerised Tomography (CT) scan:

If you take part in this study you might have a chest CT scan if you begin to experience any shortness of breath or chest pains.

CT scans use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure.

Some CT scans require a contrast dye to be used to make the images of the scan clearer. You may get a small bruise or swelling around the area where they inject the dye. Rarely, people have an allergic reaction to the dye, such as a rash or itchy skin, headache or feeling sick. Tell your radiographer immediately if you feel unwell.

Ionising Radiation

Mammograms, MUGA and CT scans use ionising radiation. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to you as a consequence of taking part in this study are about 0.13%.

What happens if I change my mind?

If at any point you decide to stop taking part in the study you will still receive treatment and the follow up usually offered by your hospital.

If you do decide to stop taking part we will ask you if you would like to:

- continue to complete follow up visits for the study **or**
- stop taking part with no more study visits.

Information on how we will handle your information and samples in the event of you withdrawing is detailed in Part 2 of this Information Sheet.

What if new information becomes available?

Sometimes during the course of a research project, important new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What happens when the study stops?

Once you have completed your treatment and attended your last study visit (4 weeks post-surgery), you will continue to be followed by your doctor in the normal way.

The study drug will not be available to you once the study has ended.

It is intended that the results of the study will be presented at conferences and published in medical journals so that we can explain to the medical community and patients what our research results have shown. They may also be used to apply to the regulatory authorities to make the drug widely available and/or for research related to the development of pharmaceutical products, diagnostics or medical aids. Confidentiality will be ensured at all times and you will not be identified in any publication.

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form and donating tissue and/or blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information is given in Part 2 of this information sheet.

Will my taking part in the study be kept confidential?

Yes. All the confidential information about your participation in this study will be kept confidential. Detailed information on this is given in Part 2.

PART 2: Detailed Information about the conduct of the study

Who is running the study?

The University of Liverpool is the Sponsor of this study and is responsible for managing it. They are based in the United Kingdom. They have asked that the day to day running of the study is carried out by a team based at the Liverpool Clinical Trials Centre (LCTC, part of the University of Liverpool) and sample collection is overseen by the Liverpool Good Clinical Practice Laboratory Facility (the central study team).

The study has been reviewed by the Medicines and Healthcare Products, the Health Research Authority and the National Research Ethics Service Committee to make sure that the study is scientifically and ethically acceptable.

This study is funded by the biotechnology company, Seagen. Seagen have awarded a grant to fund the study and are providing the Tucatinib drug.

The study has been reviewed by representatives of a patient advocate group. A patient advocate and representative will sit on the Trial Steering Committee to provide ongoing input for the duration of the trial.

Your doctor will not receive any personal payment for including you in this study. The hospital may receive additional funding to help with any extra costs that supporting this study might incur.

How will my information be collected and handled?

The University of Liverpool is the Data Controller for this study and will need to use information from your medical records for this research project.

This information will include your:

- initials
- name
- month and year of birth

People will use this information to do the research or to check your records to make sure that the research is being done properly.

Individuals from The University of Liverpool, the LCTC and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Data will be sent from your hospital / GP and central laboratories to the LCTC.

Safety information will be provided confidentially and securely to the company who supply Tucatinib (Seagen) and the company who supply Palbociclib (Pfizer) . Information on patients who are lactating will also be provided confidentially and securely to the company.

We will notify your GP that you will be taking part in the study for their information.

We will keep all information about you safe and secure.

Some of your information will be sent to the funder of this trial, Seagen, who are based in the **USA**. This will be safety information regarding Tucatinib and will help the safety profile of the drug. They must follow our rules about keeping your information safe. Once we have finished the study, we will keep the data for 25 years, so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from your hospital / GP. If you do not want this to happen, tell us and we will stop. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Information sharing for other research

When you agree to take part in a research study, the information about your health and care may be beneficial to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research, or equivalent standards**.**

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can I find out more about how my information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients
- by asking one of the research team
- by sending an email to <site **email**>, or
- by ringing us on <site **phone number**>
- in the Health Research Authority leaflet available from www.hra.nhs.uk/patientdataandresearch
- by contacting the University of Liverpool Data Protection Officer on LegalServices@liverpool.ac.uk
- In the LCTC's "Privacy Notice" available from: https://www.lctc.org.uk/privacy

If you are not happy with the way your information is being handled, or with the response received from us, you have the right to lodge a complaint with the Information Commissioner's Office at Wycliffe House, Water Lane, Wilmslow, SK9 5AF (www.ico.org.uk).

What will happen to the samples I give?

Some of your samples will be analysed at your hospital for the purpose of your treatment.

Others will be sent to The University of Liverpool Good Clinical Practice (GCP) laboratory and the hisopathology department at University Hospitals Birmingham NHS Foundation Trustfor analysis. These samples will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good reason to do so. We will maintain

this information so that we can properly manage the samples. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

If you choose to withdraw from the study, we won't collect any more samples from you, but we will continue to store and use the samples we have already collected. If you do not want us to do this, please let us know and we will stop. It may however not be possible to destroy some of your samples if they have already been used up as part of the study analysis.

Samples taken for this trial may be used to investigate genetic changes by analysing the DNA of your tumour and/or blood samples. The intention is not to identify DNA sequences that you received from your parents that may have increased your risk of breast cancer and which you could pass down to your children (e.g. in the BRCA1 gene), but it is possible (although unlikely) that we will find such sequences while looking for something else, in which case your clinician will be informed.

With your permission, we would also like to collect extra samples so they can be used in future research. If you agree, coded samples will be sent to the LCTC Post-trial Tissue Bank (at The University of Liverpool) for storage. Some of the data we collect about you in this study will be provided alongside your samples – this too will be coded. Samples will only be used according to the terms of your completed consent form. These researchers work closely with other scientists in the UK and elsewhere and may transfer your samples to these research collaborators for use in future scientific studies.

These objectives of future studies include genetic analysis but only if permission has been given to extract genetic material including DNA/RNA from stored samples.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient Advice and Liaison Service (PALS) or equivalent. Members of your local hospital team should be able to provide this information to you.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project of the study Sponsor (University of Liverpool), compensation may be available and you may have to pay your related legal costs. Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the study and the study Sponsor accepts no liability for negligence on the part of your hospital's employees. However, if you are harmed and this is due to someone's negligence at the hospital, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Participant Study Number			
Participant Initials:		Participant Month and Year of Birth:	/

Adult Consent Form

To be completed by the participant:

Once you have read and understood each statement please enter your initials in each box.	Initial
1. I have read and understood the information sheet for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my care or legal rights being affected. However, the study team may need to collect some limited information for safety reasons.	
3. I agree to take part in the above study.	
4. I give permission for a copy of this fully completed consent form to be sent to the Liverpool Clinical Trials Centre (LCTC) (where it will be kept in a secure location) to allow confirmation that my consent was given.	
5. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the central study team and representatives of the Sponsor, regulatory authorities and the local NHS Trust. I give permission for these individuals to have access to my records and data.	
6. I agree to my GP being informed of my participation in the study.	
7. I agree for the relevant data on my NHS hospital admissions and treatment to be collected from hospital database for the purposes of this study.	
8. I understand that my data will be kept by the Data Controller and all others archiving data and at my hospital/research site in a confidential manner for 25 years from the end of the study.	
9. I consent to samples of my blood/tissue to be taken and used for this study – this will involve genetic testing of the tumour sample.	
10. I consent to samples of my blood/tissue to be taken and used for this study .	
The statements below are optional (you can still take part in the study even if you do not wish to agree to these):	
11. I agree to allow information and data or results arising from this study to be used in future healthcare and/or medical research providing my confidentiality is maintained.	
12. I consent for samples of my blood/tissue to be collected for future research and to be transferred along with a copy of this Consent Form to the LCTC Post-Trial Tissue Bank	
13. I consent to samples of my blood/tissue to be taken and used for future research which may involve genetic testing of the tumour sample.	
14. I consent to samples of my blood/tissue to be taken and used for future research which may involve transfer out of the UK.	

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Participant Study Number			
Participant Initials:		Participant Month and Year of Birth:	/

Adult Consent Form

15. I agree that I may be contacted in the future in relation to this or other related studies. ☐
(if you agree to this statement provide your details below):

Telephone number:	
Email address:	

To be completed by the participant:

Your full name (please print):			
Your signature:		Date:	

To be completed by the Researcher (after participant has completed the form):

Researcher full name (please print):			
Researcher signature:		Date:	

Please file the original wet-ink copy in the 3-Pillars Investigator Site File, and make three copies: one for the participant, one for the medical notes and one to be sent to the LCTC.