Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Princess Alexandra Hospital

Title	HER2Pro 1b: Addition of prochlorperazine to paclitaxel, trastuzumab and pertuzumab for previously untreated HER2-positive metastatic breast cancer: a phase 1 dose de-escalation study
Project Funded by	The University of Queensland, Metro South Health and The Princess Alexandra Research Foundation
Coordinating Principal Investigator/ Principal Investigators	*Professor Elgene Lim* *Professor Euan Walpole* *Associate Professor Fiona Simpson* *Doctor Katharine Cuff*
Associate Investigator(s)	*Dr Caroline Cooper* *Dr Rasha Cosman* *Dr Emma-Anne Karlsen* *Professor Christopher Pyke* *Dr Shannon Joseph* *Dr Blerida Banushi* *Mr Benedict Lum* *Miss Priscila Oliveira de Lima* *Mrs Lilia Merida de Long*
Location	Princess Alexandra Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have specific type of breast cancer that expresses human epidermal growth factor receptor 2 (HER2). The research project is designed to test whether participants treated with a high dose of an anti-nausea drug called *prochlorperazine* in addition to their standard anti-cancer will have improved outcomes. Prochlorperazine is an anti-nausea drug that can affect the brain and nervous system and can sometimes help to reduce the symptoms of nausea and dizziness during an illness.

By administering a high dose of prochlorperazine as an infusion directly into your veins over a short period of time (20-30 minutes), the process by which cells absorb molecules may be blocked. When this absorption process is blocked, it is thought that individuals may respond better to one of the drugs used to treat HER2-positive breast cancer.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you do not wish to take part, you do not have to. You will receive the best possible care whether you take part or choose not to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read.
- Consent to take part in the research project.
- Consent to have the tests and treatments that are described.
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Patients with HER2-positive breast cancer receive treatment of their cancer with a therapeutic antibody (a treatment drug) such as the antibody trastuzumab, which is used in this study. Antibodies are proteins produced in the immune component of blood called plasma which help to detect foreign objects such as bacteria and viruses in your body. Trastuzumab is an antibody which can recognise cancer cells as foreign.

Trastuzumab is used to treat HER2-positive breast cancer and other cancers in conjunction with chemotherapy and, if applicable, radiotherapy. In metastatic breast cancer it can be administered in combination with another therapeutic antibody (pertuzumab) and chemotherapy (paclitaxel) in patients who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

Approximately 20-25% of patients who receive this treatment combination (Trastuzumab, Pertuzumab and Paclitaxel) do not respond to treatment. Research suggests a potential reason for this is that the protein receptor that trastuzumab targets may be inside the cancer cell and therefore, the drug cannot get to the trastuzumab target and kill the cancer cell. Laboratory tests on mice have shown that a drug commonly used for nausea and dizziness called prochlorperazine may help the cancer cells to be killed by trastuzumab.

A previous study has demonstrated that a high dose (0.8 mg/kg) of prochlorperazine can move the trastuzumab target to the surface of HER2-positive cancer cells. The study dose (0.8mg/kg) of prochlorperazine is higher than the currently approved dose in Australia. Prochlorperazine is used for nausea and dizziness, but the effect of prochlorperazine on the trastuzumab target has not been investigated before. The same dose of prochlorperazine was given in a similar study conducted by the investigators. None of the 13 participants in this study experienced a serious adverse event above Grade 2 thought to be related to the drug.

If you take part in this trial and your tumour is easy to access, we will ask you if we can perform a biopsy before and after the prochlorperazine infusion. This is entirely optional and will be discussed with you by your treating specialist. Only these two tissue samples would be required. Research Scientists will look at each of these tissue samples to determine if the prochlorperazine has moved the trastuzumab target in the tumour so we can match this with any potential outcomes.

A blood sample will be taken from you at times over the course of therapy. This will be used by Research Scientists to see what changes are occurring in your immune system.

Prochlorperazine is approved in Australia to treat nausea, vomiting and dizziness due to various causes. However, it is not approved as a treatment during anti-cancer treatment to improve outcomes in people with breast cancer. Therefore, in this research project it is being used as an experimental treatment to assist in the movement of a drug target to the surface of a cancer cell to improve cancer treatment outcomes.

This research has been initiated by Associate Professor Elgene Lim (St Vincent's Hospital, Sydney) in collaboration with Professor Euan Walpole, Dr Katharine Cuff and Associate Professor Fiona Simpson.

This research has been funded by The University of Queensland, Metro South Health and The Princess Alexandra Research Foundation. Samples of tissue and blood will be collected by the Cancer Services Department at the Princess Alexandra Hospital and transport them to research scientists at the Translational Research Institute on the same campus.

3 What does participation in this research involve?

Your doctor will tell you whether you are eligible to participate in this study. Eligibility is based on several criteria. The most important thing is that you have a diagnosis of metastatic HER2-positive breast cancer.

Importantly, you need to be aware that since the dose of prochlorperazine we give you may cause drowsiness you will have to ensure that you have someone to take you home afterwards. You will not be able to drive or operate heavy machinery for at least 24 hours after each dose of prochlorperazine.

Once consent is given, we will organise a screening visit at a time suitable to you. Once the screening is completed, you will receive your first cycle of standard treatment consisting of paclitaxel, trastuzumab and pertuzumab. The timing of this will be arranged via the Oncology Day Unit in conjunction with your treating medical oncologist who will supervise your treatment on this study. On Day 1 of the **second cycle** of your treatment, you will, in addition, have the first intravenous infusion of prochlorperazine, and two tissue biopsies will be taken if you have consented to the optional biopsies.

Once at the Oncology Day Unit you will be attended by a Registered Nurse who will monitor you throughout the trial. A small cannula will be placed into a vein in your hand or arm and a blood sample will be taken from this cannula. A small 3-8mm tissue biopsy of your tumour will be collected by the study doctor if you are in the accessible tumour group. In some circumstances, this biopsy may be taken by our Radiology colleagues, under ultrasound or CT guidance. The cannula will then have a line attached to it so that the trial drug, prochlorperazine can be infused into your vein (0.8mg / kg) over 20-30 minutes. Your blood pressure and pulse will be monitored every 30 minutes and a 4 ml blood sample from your other arm at 30 minutes, 45 minutes and 60 minutes from the start of the infusion.

While prochlorperazine is routinely given to patients, this trial will be giving prochlorperazine in higher doses than normal. As mentioned above, this same dose of prochlorperazine has been given in a previous study without a serious adverse event. It is expected that you will feel drowsy after the infusion. For 24 hours after the infusion of prochlorperazine it is normal to feel mildly agitated and restless. We can manage this with additional medication, in discussion with the trial doctor, if required. Please inform your treating doctor if you have a prior history of anxiety or panic attacks so that adequate support can be provided. We expect that all side effects will resolve within 24 hours as the prochlorperazine clears your system.

A second tissue biopsy of your tumour will be collected by the study doctor 2 hours after the infusion has finished if you are in the accessible tumour group. <u>No further tissue biopsies will be collected on this study.</u>

Upon completion of the infusion and an observation period of a minimum of four hours in the Day Oncology Unit you will be discharged to go home.

You will not be able to drive or operate machinery for at least 24 hours. Therefore, it is important that you have someone responsible to drive you home. You may not be able to work for 24 hours depending on your field of work.

You will come back into the hospital one week later for your second dose of prochlorperazine, in combination with your standard treatment. The procedure for this will be the same as described above, **without** the collection of tissue biopsies in any group but **with** blood sampling.

This process will be repeated weekly for a total of six weeks of prochlorperazine in combination with your standard treatment.

There are no additional costs associated with participating in this research project. Medication, tests and medical care required as part of the research project will be provided to you with no out-of-pocket fees, provided that you are eligible for Medicare. Your standard of care treatment is covered by the Pharmaceutical Benefits Scheme (PBS).

4 What do I have to do?

Once you have signed the consent form, a screening visit will be organised for you. This visit will occur up to two weeks before you commence anti-cancer treatment (standard treatment). At this and every study visit you will be asked how you are feeling and if you have had any changes in your health since you signed the informed consent form(s) or at any time during this visit. It will be very important to tell the study staff about anything that has changed so that it can be properly recorded. These changes will not necessarily keep you from continuing in the study so you should provide the study team with as much information as possible.

The following study procedures will occur:

Screening Visit (Before starting treatment)

- Recording of demographic characteristics including date of birth, gender.
- Review of inclusion and exclusion criteria.
- Recording of medical/malignancy history.
- Conduct of a full physical examination (an examination of each body system/part, including measurement of height and weight) by the study doctor.
- An assessment by the study doctor of how your disease is progressing and how it is affecting your daily life.
- You will be asked about any prior or current medications that you are taking
- Measurement of vital signs (respiratory rate, sitting pulse rate, temperature and sitting blood pressure);
- Collection of blood (approximately 10 mL or 2 teaspoons) from a vein in your arm with a needle and syringe (which is called venepuncture) to perform the following tests to assess your general health (these tests will be called “Standard blood tests” in the remainder of this document:
    - Haematology (a count of the different cells in your blood);
    - Biochemistry (including kidney and liver function tests);
- A urine sample will be collected for a pregnancy test (for females of child-bearing potential only).
- Electrocardiogram (ECG) which involves the placement of painless sticky pads (or electrodes) onto your chest, arms and legs to assess the electrical activity of your heart;
- A computed tomography (CT) scan of your head, neck, chest, abdomen and pelvis will be performed up to 28 days prior to Day 1 to assist with determining your overall tumour burden

Cycle 1 Day 1 - Study procedures:

Your medical oncologist will organise for you to commence anti-cancer treatment.

- Physical examination, weight and vital signs;
- Standard blood tests
- Collection of an additional blood sample (approximately 5ml or 1 teaspoon) to determine a “normal” picture of your blood before you commence therapy.

Cycle 2 Day 1 - Study procedures:
This will be done at the Day Oncology Unit and an appointment for this visit will be provided at the start of treatment.

- Vital signs
- An indwelling cannula (a flexible, small plastic tube) will be inserted into a vein in your hand or forearm for collection of blood samples and for infusion of prochlorperazine.
- Standard blood tests
- Collection of an additional blood sample (approximately 5ml or 1 teaspoon) to determine a “normal” picture of your blood before you commence therapy
- If accessible, a tissue biopsy of your tumour will be taken before infusion of prochlorperazine
- Infusion of prochlorperazine through the cannula in your arm. This will take approximately 30 minutes
- If accessible a second biopsy of your tumour will be taken 2 hours after the prochlorperazine infusion is finished

You will need to stay in the Oncology Day Unit for 4 hours after the infusion of prochlorperazine has finished.

You must be sure that you have someone to take you home after the treatment. Please be aware that if you are still in the workforce you will not be able to return to work that day.

Cycle 2 Day 8 (and weekly for a total of 6 weeks)

- You will be reviewed by the medical oncologist supervising your care
- Your weekly anti-cancer treatment dose will be organised by your cancer doctor and treatment will again occur in the Oncology Day Unit.
- Vital signs will be measured.
- An indwelling cannula will be inserted into a vein in your hand or forearm.
- Standard blood tests
- Infusion of prochlorperazine through the cannula in your arm. This will take approximately 30 minutes.

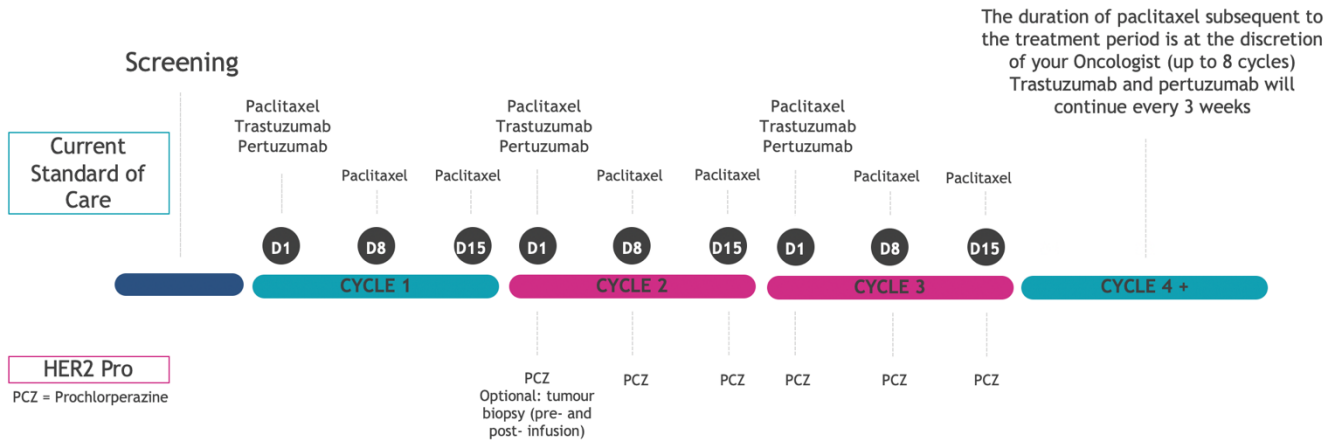
Each week, you will need to stay in the Oncology Day Unit for 4 hours after the infusion of prochlorperazine has finished.
You must be sure that you have someone to take you home after the trial. Please be aware that if you are still in the workforce you will not be able to return to work that day.

After 6 weeks of therapy, you will have a CT scan of your head, neck, chest, abdomen and pelvis. This will be organised by the study team and will be performed within 4 weeks of completing treatment.

If there are no treatment associated serious adverse events, you will be eligible for an additional 6 weeks of anti-cancer treatment and prochlorperazine. The procedure for these additional 6 weeks of therapy will be the same as described above for Day 8, but there will be only one blood test per week.

Please note that blood samples will be taken every week during the treatment period, then every 3 weeks, with additional tests as clinically indicated. In addition, blood samples will be taken before and within 2 hours of completing each dose of prochlorperazine.

Proposed timeline:



5 Other relevant information about the research project

This is a small early phase safety study to determine whether the treatment of metastatic HER2-positive breast cancer patients with prochlorperazine in combination with trastuzumab, paclitaxel and pertuzumab is safe and well tolerated. There will only be a total of 12 participants in the whole trial, and all participants will receive intravenous prochlorperazine.

The results of this trial will inform us as to whether we are justified in moving to a larger phase 2 randomised clinical trial of prochlorperazine plus trastuzumab, paclitaxel and pertuzumab.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision to participate or not, or to participate and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Princess Alexandra Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Participation in this trial is entirely voluntary and is in addition to the standard treatment you will receive for your tumour.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research.

A possible benefit is that the addition of prochlorperazine would enhance the efficacy of the standard therapies used to treat your cancer, pertuzumab and trastuzumab.

9 What are the possible risks and disadvantages of taking part?

This is an experimental study where the dosages of one of the drugs will be varied. This is a test of safety and efficacy and as such there are risks involved as described below.

Medical treatments and procedures often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these

side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

If you do not wish to participate in this study, you will be offered current approved and standard therapies. In addition, there may be other clinical trial options open to you, which you can discuss with your treating Oncologist.

Infusion of prochlorperazine:
Medical treatments often cause side effects. You may have none or may display varying levels of severity. Prochlorperazine has been used in clinical practice for over 20 years and most patients who experience nausea, vomiting or dizziness as a result of an illness receive an oral form which they take at home unsupervised. For this study we will be giving you an intravenous infusion of prochlorperazine that is higher than typically used, and currently licensed in Australia, and higher than recommended in the product information. However, these doses have been reported in the clinical literature as being well tolerated.

There is a possibility that you may display:

- Drowsiness
- Lowered blood pressure
    - The lowered blood pressure may make you feel faint if you stand up quickly so we would ask that you remain seated throughout the trial or ask for assistance from the nurse if you need to stand up or use the bathroom.
    - We will check the blood pressure of all participants following the infusion and prior to discharge home. For the patients with a symptomatic drop in blood pressure, we may give them extra fluid intravenously and will keep them under observation until their blood pressure recovers and they are asymptomatic, and ensure that they were then escorted to their car for pickup.
- Dry mouth
- Headache.

0.5-1% of patients may display some involuntary jerky movements, known as extrapyramidal symptoms, with the currently approved dose of prochlorperazine. This typically self-resolves, however, additional medication can be given to relieve these symptoms. If you were to experience extrapyramidal symptoms, you will be withdrawn from this research project and no further infusions of prochlorperazine will be given. Whilst prochlorperazine is commonly used by patients we will be prepared for any unexpected side effect so please tell the nurse if you feel anything unusual.

A doctor will be available at all times and if you display any unexpected side effect they will make sure the proper treatments are administered. If the side effects are pronounced, then a decision may be made to stop future doses of the treatment. Be aware if you have any unexpected side effect that you will be advised to stay under medical care until it is safe for you to be discharged.

Tumour biopsy:
A biopsy of tumour(s) will be conducted only on Day 1 of Cycle 2 of the study to collect tissue samples from the tumours. Depending on where your tumour is, you may receive a local anaesthetic to numb the biopsy site if required. This is usually given by injection with a thin needle or a spray. The numbing medication can cause a burning sensation in the skin for a few seconds. Afterward, the biopsy site is numb, and you should not feel any pain or discomfort during the punch biopsy. The study doctor uses a circular tool to remove a small, round section of skin including deeper layers. The area removed is about the size of a pencil-top eraser (3-5 mm). The procedure involves using an ultrasound to give the biopsy needle to the site of the tumour. A dressing or adhesive bandage may then placed over the site to protect the wound

and prevent bleeding. The biopsy area may be tender for a few days afterward and can be treated with analgesic medications.

A skin biopsy is a generally safe procedure but there are risks that include the following: bleeding, bruising, scarring and infection.

Insertion of an indwelling cannula:
The insertion of an intra-venous cannula for the collection of blood samples is very safe, but there are potential risks associated with this:

- There is a risk that a clot will form in the vein, which may take several weeks to resolve.
- There is a small risk of infection, although the techniques used and the cleaning with antiseptic solutions prior to insertion of the cannula minimises this risk.
- There is the possibility of bruising and discomfort around the site of an intravenous cannula, although this is generally minor and resolves within a few days.
- There is a very small risk that a nerve could be damaged during insertion of a cannula, however, the site is carefully chosen to minimise this risk. Nerve damage may persist indefinitely, but usually resolves within 6-12 months.
- There is also a small chance the cannula becomes dislodged from the vein, which can cause minor bleeding.

Infusion of Trastuzumab, Paclitaxel and Pertuzumab:
Trastuzumab has been used clinically as a HER2 targeting antibody therapy in combination with pertuzumab and paclitaxel to treat metastatic HER2-positive breast cancer in patients who have not received chemotherapy for their disease. Therefore, the potential side effects of these treatments are well documented.

Risks and side effects related to the **trastuzumab** treatment include the following:
Likely (occurring in > 20% of patients)

- Chills
- Fever
- Body pain

Less likely (occurring in < 20% of patients)

- Headache
- Diarrhea
- Abdominal pain
- Back pain
- Infection
- Flu-like symptoms
- Vomiting
- Cough
- Shortness of breath
- Rhinitis or pharyngitis – Runny nose and sore throat
- Insomnia
- Rash
- Dizziness
- Swelling (usually of the feet, ankles or hands)
- Weakness
- Nausea

Rare but serious (occurring in < 3% of patients)

- Allergic reactions that may include itching and rash, shortness of breath or even a drop in your blood pressure. Most of these events occur within 24 hours of infusion. However, delayed reactions have occurred. If a person experiences severe allergic reaction, trastuzumab will be discontinued.
- Interference with the pumping action of the heart leading to heart failure. The incidence of heart problems (heart failure) increases in people with heart disease or other risk factors such as radiation to the chest, advancing age, and use of other heart-toxic drugs (such as epirubicin and cyclophosphamide). Your doctor will check your heart function before you start taking Trastuzumab and will monitor your heart closely during your treatment. Trastuzumab will be discontinued if symptoms of heart failure appear.

Risks and side effects related to the **paclitaxel** treatment include the following:
Likely (occurring in > 20% of patients)

- Fatigue
- Hair loss
- Pain, numbness, tingling, swelling, or muscle weakness in hands and/or feet (neuropathy). These symptoms usually get better or go away without medication within 3 weeks of stopping treatment.

- You may get joint and muscle pain a few days after your treatment. These symptoms usually disappear in a few days

Less Likely (occurring in < 20% of patients)

- Nausea (feeling as if you're about to throw up) or vomiting (throwing-up)
- Low blood pressure
- Shortness of breath Cough
- Inflammation or irritation of the mucous membranes in the mouth or throat.
- Heart burn
- Diarrhea
- Low white blood cell counts which may make you more susceptible to infection
- Low platelet counts which may make you bruise more easily and bleed longer if injured
- Low red blood cell counts which may cause tiredness, shortness of breath or fatigue
- Abnormal blood tests reflecting problems with liver function

Rare but serious (occurring in < 3% of patients)

- Liver failure including brain and nervous system damage that occurs as a complication of liver disorders.
- Severe heart problems including chest pain, high blood pressure, and abnormal heart rhythms that prevent the heart from pumping blood normally and could be life threatening
- Blood clots in the lungs
- Damage to the eyes resulting in decreased vision.
- Serious, sometimes life threatening gastrointestinal (GI) perforations have occurred rarely. A GI perforation is the development of an opening or hole in the wall of the bowel or stomach that may require surgery to repair.

Risks and side effects related to the **pertuzumab** treatment include the following:
Please note that pertuzumab is not used alone and the following side effects were observed when it was used in combination with trastuzumab and paclitaxel chemotherapy.

Likely (occurring in > 20% of patients).

- Diarrhea
- Hair loss
- Low white blood cell count
- Nausea
- Fatigue
- Rash
- Peripheral neuropathy (numbness & tingling in hands and feet)

Less likely (occurring in <20% of patients).

- Decreased appetite
- Mouth irritation or mouth sores
- Weakness
- Anaemia
- Swelling
- Muscle aches
- Nail changes
- Joint aches
- Shortness of breath
- Headache
- Fever
- Abnormal taste
- Upper respiratory tract infection
- Vomiting
- Itching
- Watery eyes
- Difficulty sleeping
- Dizziness
- Abdominal pain
- Dry skin
- Allergic reactions / hypersensitivity reactions

Rare but serious (occurring in < 3% of patients)

- Hypersensitivity reactions, anaphylaxis, and allergic reactions.
- Interference with the pumping action of the heart leading to heart failure.

<u>Blood Collection:</u>
You may experience side effects related to having a blood sample taken.
Side effects may include:

- Pain
- Bruising
- Bleeding.

It is anticipated that should you experience a side effect that it will be mild.
Please notify the nurses or doctors if you notice any worrying side effects.

Electrocardiogram (ECG)
As a result of the patches that are put on your skin when performing the ECG, there is the possibility a rash or minor irritation of the skin may result.

Computed Tomography
A computed Tomography (CT) scan of your tumour(s) will be performed as part of your standard of care therapy.

This research study involves exposure to an amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is up to about 23 mSv. The benefits from the study should be weighed against the possible detrimental effects of the additional radiation exposures, including an increased risk of cancer induction. In this particular study, the risk is low and the estimated risk of such harm is up to about 1 in 270.

Have you been involved in any other research studies that involve radiation? If so, please tell us.

Please keep information contained within the Patient Information and Consent Form about your exposure to radiation in this study, including the radiation dose. You will be required to provide this information to researchers of any future research projects involving radiation.

Tumour biopsy:
A biopsy of tumour(s) will be conducted only on Day 1 of Cycle 2 of the study to collect tissue samples from the tumours. Depending on where your tumour is, you may receive a local anaesthetic to numb the biopsy site if required. This is usually given by injection with a thin needle or a spray. The numbing medication can cause a burning sensation in the skin for a few seconds. Afterward, the biopsy site is numb, and you should not feel any pain or discomfort during the punch biopsy. The study doctor uses a circular tool to remove a small, round section of skin including deeper layers. The area removed is about the size of a pencil-top eraser (3-5 mm). The procedure involves cutting into the top layer of fat beneath the skin, so a stitch may be needed to close the wound. A dressing or adhesive bandage may then placed over the site to protect the wound and prevent bleeding. The biopsy area may be tender for a few days afterward.

A skin biopsy is a generally safe procedure but there are risks that include the following:

- Bleeding
- Bruising
- Scarring
- Infection

If appropriate, this biopsy may be taken under ultrasound or CT guidance.

10 What will happen to my test samples?

Your blood and tissue samples will be transported from the Princess Alexandra Hospital to the Translational Research Institute. There are three main research questions we wish to answer.

The first is whether the dosing of patients with prochlorperazine is well tolerated when added with standard treatment of trastuzumab, paclitaxel and pertuzumab.

The second is whether the dose of prochlorperazine is sufficient to move the trastuzumab target onto the surface of the cancer cells.

The third thing we would like to determine is how your blood concentration of prochlorperazine affects the movement of the trastuzumab target on the cancer cells.

Your blood and tissue samples will be used for this research project only. They will not be transferred or sold later.

11 What if new information arises during this research project?

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

Also, upon receiving new information, your study doctor might consider that it is on your best interest to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for you to continue your regular medical care.

12 Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments, as this may impact on your eligibility and may cause adverse reactions with the trial medication.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you do not wish for any samples that have been taken to be used please let the study doctor know and we will ensure your samples are discarded. Your decision regarding participation in this trial or to withdraw from this trial is entirely your choice and your decision will not affect your ongoing treatment or care. If you withdraw from this trial, you will still be able to access standard of care therapy.

The Investigator will make every reasonable effort to keep each patient on study and final assessments will be performed, if possible. If a participant wishes to withdraw from the study, they need to notify the investigator/treating clinician and sign a withdrawal form. They will not have to attend for further data collection.

Patients who are removed from the study due to adverse experiences (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to withdraw a patient from study:

- unacceptable toxicity
- unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable.
- SAE requiring discontinuation of treatment.
- withdrawal of consent - where patient is not evaluable, additional patients will be recruited to replace them.
- serious violation of the study protocol (including persistent patient attendance failure and persistent non-compliance).
- withdrawal by the Investigator for clinical reasons not related to the study drug treatment
- evidence of disease progression (other than the re-accumulation of ascites or pleural effusion).

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable, unexpected or severe side effects

15 What happens when the research project ends?

Post-treatment follow-up:

- After the trial treatments (prochlorperazine infusion) have stopped, your anti-cancer treatment will continue. If you are still benefiting from the trastuzumab and pertuzumab infusions you will continue to receive these every 21 days. Your oncologist will advise you on the best treatment for your cancer.
- At these visits, you will be examined to monitor the response of the tumour to treatment and any side effects you may have experienced. A CT scan may also be performed at these visits.
- Once the study follow-up is complete, you will continue to be followed up by your doctor at regular intervals.
- This type of follow up is routine even in patients who are not participating in the trial.

Once the trial is complete, the researchers will analyse all the data and determine whether the drug was able to move the trastuzumab target to the cancer cell surface and if the combination of the two therapies is safe. If it did then the results of this trial will support the design of a larger clinical trial in which prochlorperazine, trastuzumab, paclitaxel and pertuzumab will be administered together to see if they can improve response rates and long-term survival of patients with HER2-positive breast cancer.

Part 2 How is the research project being conducted?

16 What will happen to the information about me?

By signing the consent form, you consent to the collection and use of personal information by the study doctor and relevant research staff for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission.

All information gathered will be coded in such a way that a particular participant can be re-identified at any time. This is to ensure that if any clinically relevant information is identified during the project, you and your doctors can be notified.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to allow the study team to access the health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Translational Research Institute and the institution relevant to this Participant Information Sheet, the Princess Alexandra Hospital. By signing the Consent Form, you authorise the release or access of this confidential information to the relevant study personnel and regulatory authorities, as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. At no point will your individual identifying features be published, and for most of the report, only collective results will be reported, not individual cases.

Information about your participation in this research project may be recorded in your health records.

In accordance with the privacy and other relevant laws of Australia and/or Queensland, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member listed at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, without out-of-pocket payments, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by the Princess Alexandra Hospital, the University of Queensland and the Translational Research Institute and is being funded by The University of Queensland, Metro South Health and The Princess Alexandra Research Foundation.

By participating in this research project, you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to the Translational Research Institute.

The University of Queensland and the Translational Research Institute may directly or indirectly benefit financially from knowledge acquired through analysis of your samples.

You will not benefit financially from your involvement in this research project even if, for example, the knowledge acquired from analysing your samples proves to be of commercial value to the University of Queensland and the Translational Research Institute. If knowledge acquired through this research leads to discoveries that are of commercial value to the University of Queensland and the Translational Research Institute, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

This project is partially funded by the National Health and Medical Research Council Ideas Grant and Centre for Translational Breast Cancer Research (TransBCR): delivering laboratory discoveries to the clinic NHMRC APP 1153049.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages). Associate Professor Simpson currently holds patents on the use of prochlorperazine as a dynamin inhibitor in combination with monoclonal antibody therapy.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Metro South Health Service District Human Research Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor by email on katharine.cuff@health.qld.gov.au or any of the following people:

Clinical contact person

Name	*Dr Katharine Cuff*
Position	*Medical Oncologist, Division of Cancer Care*
Telephone	*(07) 3176 6577, (07) 3176 2111*
Email	*katharine.cuff@health.qld.gov.au*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*Patient Liaison Officer*
Telephone	*(07) 3176 5598*
Email	*PAH_PLO@health.qld.gov.au*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*Metro South HREC*
HREC Coordinator	*HREC Coordinator*
Telephone	*(07) 3443 8049*
Email	*EthicsResearch.PAH@health.qld.gov.au*

Consent Form - *Adult providing own consent*

Title	HER2Pro 1b: Addition of prochlorperazine to paclitaxel, trastuzumab and pertuzumab for previously untreated HER2-positive metastatic breast cancer: a phase 1 dose de-escalation study
Project Funded by	The University of Queensland, Metro South Health, the National Health and Medical Research Council and The Princess Alexandra Research Foundation
Coordinating Principal Investigator/ Principal Investigators	*Professor Elgene Lim* *Professor Euan Walpole* *Associate Professor Fiona Simpson* *Doctor Katharine Cuff*
Associate Investigator(s)	*Dr Caroline Cooper* *Dr Rasha Cosman* *Dr Shannon Joseph* *Dr Blerida Banushi* *Professor Christopher Pyke* *Dr Emma-Anne Karlsen* *Mr Benedict Lum* *Miss Priscila Oliveira de Lima*
Location	*Princess Alexandra Hospital*

Declaration by Participant

I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.
I understand the purposes, procedures and risks of the research described in the project.
I have had an opportunity to ask questions and I am satisfied with the answers I have received.
I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
I understand that I will be given a signed copy of this document to keep.
I consent to the optional two (2) tissue biopsies pre- and post-prochlorperazine infusion:

☐ Yes ☐ No

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	HER2Pro 1b: Addition of prochlorperazine to paclitaxel, trastuzumab and pertuzumab for previously untreated HER2-positive metastatic breast cancer: a phase 1 dose de-escalation study
Project Funded by	The University of Queensland, Metro South Health, the National Health and Medical Research Council and The Princess Alexandra
Coordinating Principal Investigator/ Principal Investigators	*Professor Elgene Lim* *Professor Euan Walpole* *Associate Professor Fiona Simpson* *Doctor Katharine Cuff*
Associate Investigator(s)	*Dr Caroline Cooper* *Dr Rasha Cosman* *Dr Shannon Joseph* *Dr Blerida Banushi* *Dr Emma-Anne Karlsen* *Professor Christopher Pyke* *Mr Benedict Lum* *Miss Priscila Oliveira de Lima*
Location	*Princess Alexandra Hospital*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Princess Alexandra Hospital.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.