# 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

**Protocol number 1.3**

**29 SEPTEMBER 2021**


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| **Study Sites:** | 1. Princess Alexandra Hospital, Brisbane<br>2. St Vincent's Hospital, Sydney |

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# 1 SYNOPSIS AND SCHEMA

**PROTOCOL SYNOPSIS**

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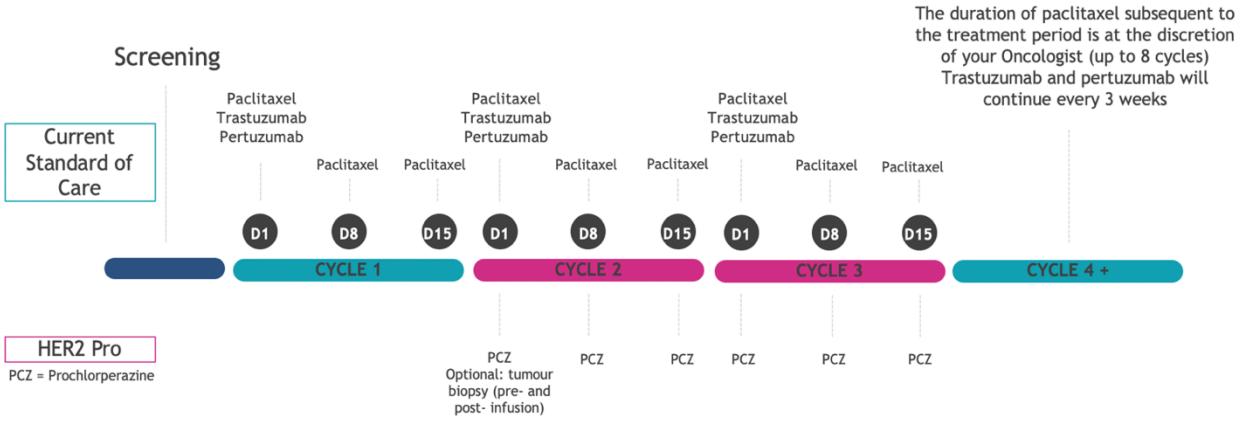
|---|---|
| Background | Inhibition of dynamin-mediated endocytosis such as with prochlorperazine (PCZ) has been shown to increase the efficacy of trastuzumab and other monoclonal antibodies in preclinical models. Current standard therapy for metastatic HER2-positive breast cancer is paclitaxel in combination with trastuzumab and pertuzumab, followed by continuation of HER2-directed therapy until progression. The addition of PCZ has the potential for enhanced anticancer effect, but this novel combination needs to be assessed for feasibility and safety. |
| General aim | To evaluate the feasibility and safety of PCZ in combination with paclitaxel, trastuzumab, and pertuzumab in patients with HER2-positive metastatic breast cancer |
| Objectives | To determine the: |
| Primary | 1. Recommended phase 2 dose (RP2D) |
| Secondary | 1. Frequency and severity of adverse events (CTCAE v5.0)<br>2. Rate of absolute >10% reduction from baseline to less than 50% in left ventricular ejection fraction (LVEF)<br>3. Objective response rate (ORR, RECIST 1.1)<br>4. Duration of response (DOR, RECIST 1.1)<br>5. Progression-free survival (PFS, RECIST 1.1) |
| Tertiary | 1. Measures of immune system activation, such as by peripheral blood fluorescence-activated cell sorting (FACS)<br>2. Receptor trafficking analysis on research biopsy pre and 2 hours post treatment<br>3. Development of patient-derived xenograft models |
| | Single-arm phase 1 multicentre clinical trial |
| Study population | Patients with previously untreated metastatic HER2-positive breast cancer that are suitable for receiving study treatments |
| Interventions | Standard treatment with paclitaxel 80mg/m$^2$ weekly and loading dose trastuzumab 8mg/kg and pertuzumab 840mg. From cycle 2, paclitaxel 80mg/m$^2$ weekly, trastuzumab 6mg/kg and pertuzumab 420mg every 3 weeks in combination with de-escalating doses of PCZ given as 6 weekly treatments. |
| Study assessments | Clinical assessment and adverse events at baseline and weekly on treatment, then at 3- and 6-weeks post-treatment. |
| Sample size | Between 6 and 12 patients will be recruited based on the 3+3 dose de-escalation study design |

# STUDY SCHEMA




Eligible patients with metastatic HER2-positive breast cancer

↓

**First cycle:**
Pertuzumab 840 mg
Trastuzumab 8 mg/kg
Paclitaxel 80 mg/m$^2$ q1w

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**Cycles 2 and 3**
**Dose de-escalation:**
Pertuzumab 420 mg q3w
Trastuzumab 6 mg/kg q3w
Paclitaxel 80 mg/m$^2$ q1w
PLUS
Prochlorperazine q1w at dose levels in absence of DLT:
Dose level 1 = 0.8 mg/kg
Dose level -1 = 0.7 mg/kg
Dose level -2 = 0.6 mg/kg

↓

Monitor for DLT and adjust dose levels as per protocol
Extend to cycles 4 and 5 if no SAE

↓

RP2D is the highest dose level achieved where < 33% of enrolled patients experience DLT. Patients will be monitored for 6 weeks following treatment discontinuation.

## 2 BACKGROUND

Monoclonal antibodies (mAbs) represent a major class of anti-cancer therapies. The efficacy of therapeutic mAbs capable of antibody dependent cell cytotoxicity (ADCC) is highly dependent on its ability to remain surface bound long enough for interaction between the mAb Fc region and immune effector cells which leads to tumour clearance (1). Inhibition of HER2 internalisation via inhibition of ubiquitination, dynamin inhibition or even caveolin-1 depletion has been shown to increase the effectiveness of trastuzumab, a HER2 directed mAb, to target HER2-positive tumours and thus increase the level of trastuzumab-mediated ADCC (2, 3). We have demonstrated that inhibition of dynamin-mediated endocytosis such as with prochlorperazine has been shown to increase the efficacy of trastuzumab and other monoclonal antibodies through enhanced immune cell mediated tumour killing in preclinical models (2). The paradigm changing work published in the journal *Cell* demonstrates a fundamental principal to improve how we utilise cancer antibody therapy.

Current standard therapy for metastatic HER2-positive breast cancer is taxane induction chemotherapy in combination with trastuzumab and pertuzumab, followed by continuation of HER2-directed therapy until progression (4). Prochlorperazine co-administered with the EGFR-directed mAb cetuximab was safe in the Phase 1b dose escalation safety trial CESTEM-1 (ACTRN 12619001527156) of head and neck squamous cell carcinoma and EGFR-expressing triple negative breast cancer (unpublished data). In this study of 15 patients, no serious adverse events, grade 3/4 toxicities or haematological toxicities were observed. Grade 1 sedation, akathisia and orthostatic hypotension related to prochlorperazine resolved within 24 hours. Significantly the cetuximab-induced rash, which is correlated with positive response, was observed in 70% of patients, as opposed to a maximal response rate of 15% when cetuximab is used as a monotherapy.

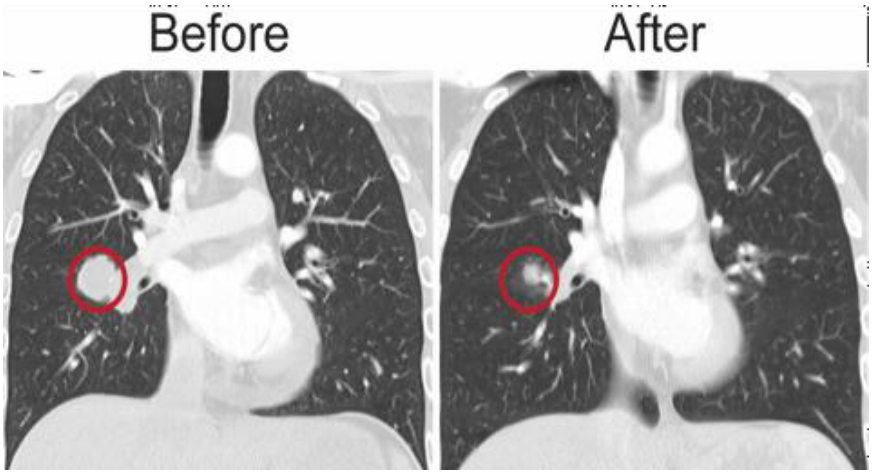


Figure 1. MRI scans of a patient demonstrating shrinkage of a lung metastases after 6 weeks of cetuximab and prochlorperazine treatment.

This study was underpinned by a Phase 1 proof of mechanism trial at the Princess Alexandra Hospital (HREC/15/QPAH/048) which demonstrated that prochlorperazine was well tolerated by patients, even those considered “frail” (unpublished). In this study, consenting patients supplied pre-infusion tumour biopsies for analysis of surface EGFR levels (Figure 2). Patients underwent a 20-minute infusion with high dose prochlorperazine and a second biopsy was collected 90 minutes later. This demonstrated enhanced surface EFFR expression levels in their tumours post-infusion (Figure 2) and strong EGFR clustering.

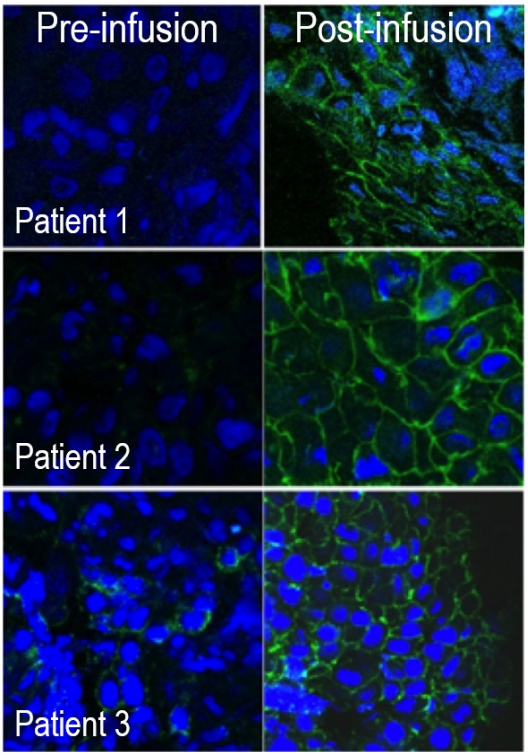


Figure 2. Pre- and post-prochlorperazine infusion in live patient tumour biopsies surface labelled with EGF-488 (green) and nuclear stain (blue). Confocal images.

Building on these results, we hereby propose a similar phase 1 trial to evaluate the addition of prochlorperazine to the current standard of care HER2-directed mAbs trastuzumab and pertuzumab after induction chemotherapy in patients with HER2-positive metastatic breast cancer. This early phase trial will pave the way for the subsequent evaluation of this treatment combination in a larger phase 2/3 trial.

# 3 AIM AND OBJECTIVES

**Aim** – To evaluate the feasibility and safety of PCZ in combination with paclitaxel, trastuzumab, and pertuzumab in patients with HER2-positive metastatic breast cancer

**Objectives** – to determine the:

**Primary:**

1) Recommended phase 2 dose (RP2D)

**Secondary:**

1) Frequency and severity of adverse events (CTCAE v5.0)
2) Rate of absolute >10% reduction from baseline to less than 50% in left ventricular ejection fraction (LVEF)
3) Objective response rate (ORR, RECIST 1.1)
4) Duration of response (DOR, RECIST 1.1)
5) Progression-free survival (PFS, RECIST 1.1)

**Tertiary:**

1) Measures of immune system activation, such as by peripheral blood fluorescence-activated cell sorting (FACS)
2) Receptor trafficking analysis on research biopsy pre and 2 hours post treatment
3) Development of patient-derived xenograft models

# 4 DESIGN

Single-arm, multicentre, phase 1 trial

# 5 SUBJECT POPULATION

Patients must meet all the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. All enquiries about eligibility should be addressed by contacting the trial management committee.

## 5.1 Target population

Patients with previously untreated HER2-positive locally advanced or metastatic breast cancer who are suitable for treatment with the combination of prochlorperazine and standard systemic therapy with paclitaxel, pertuzumab, and trastuzumab systemic therapy.

## 5.2 Inclusion criteria

1. Patients aged ≥ 18 years with HER2-positive advanced breast cancer, defined as:
    - Breast cancer that is metastatic or not amenable to resection or radiation therapy with curative intent; and
    - Histologically and/or cytologically confirmed invasive breast cancer that is HER2-positive by local laboratory according to ASCO/CAP (American Society of Clinical Oncology / College of American Pathologists) guidelines.
    - Patients can be any oestrogen receptor / progesterone receptor status
2. Consent for fresh biopsy at baseline and 2 hours following first prochlorperazine treatment if deemed safe to do so by the investigator. If a fresh biopsy is deemed unsafe by the

investigator, patients must agree to provide archival tissue taken at the time of or after the diagnosis of advanced breast cancer.

3. ECOG performance status 0 or 1.
4. For women of child-bearing potential, negative serum pregnancy test (beta-hCG) within 72 hours before starting study treatment and agreement to use a highly effective form of contraception (per local institutional guidelines) during study treatment and for 6 months after the end of treatment.
5. Adequate bone marrow and organ function as defined by the following laboratory values:
    - Absolute neutrophil count ≥ 1.5 x $10^9$ / L
    - Platelets ≥ 100 x $10^9$/L
    - Haemoglobin ≥ 90 g/L
    - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) below 3 x ULN. If the patient has liver metastases, ALT and AST below 5 x ULN.
    - Serum creatinine < ULN or creatinine clearance ≥ 60 mL/min/1.73$m^2$ by Cockcroft-Gault formula for patients with serum creatinine ≥ ULN.
    - Total serum bilirubin < 1.5 x ULN (or conjugated bilirubin < ULN).
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) < 1.5x ULN, unless on therapeutic anticoagulation.
6. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by either ECHO or MUGA. If the patient is registered, the same method of LVEF assessment must be used throughout the study and, to the extent possible, be obtained at the same institution.
7. Patients with a history or presence of asymptomatic CNS metastases are eligible provided they meet all of the following criteria:
    - No history of intracranial haemorrhage or spinal cord haemorrhage.
    - Not requiring anticonvulsants for symptomatic control.
    - Minimum of 3 weeks between completion of CNS radiotherapy and study commencement and recovery from significant (Grade ≥ 3 by CTCAE v5.0) acute toxicities with no ongoing requirement for corticosteroids.
8. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
9. Signed written informed consent.

## 5.3 Exclusion criteria

1. History of anticancer therapy for advanced breast cancer with the possible exception of one prior endocrine therapy regimen (such as an aromatase inhibitor or tamoxifen, with or without goserelin).
2. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin or liposomal doxorubicin > 360 mg/$m^2$
    - Epirubicin > 720 mg/$m^2$
3. Peripheral neuropathy of Grade ≥ 2 at baseline by CTCAE v5.0.
4. Prior radiotherapy or surgery within 14 days of study registration.
5. Unwilling to avoid driving or operating machinery for up to 24 hours after administration of study medication.

6. Current chronic daily treatment with corticosteroids at a dose > 10mg/day prednisolone equivalent, excluding inhaled steroids.
7. Known hypersensitivity or prior intolerable adverse reaction to prochlorperazine, paclitaxel, trastuzumab, or pertuzumab.
8. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 50 mmHg in two consecutive blood pressure readings within the 1 hour prior to study drug administration.
9. Parkinson disease or other chronic extrapyramidal condition.
10. Clinically significant cardiovascular disease ≤ 1 year prior to enrolment, including myocardial infarction, unstable angina, symptomatic congestive heart failure, and/or serious uncontrolled cardiac arrhythmia.
11. History of prolonged QT interval, QTcF > 450ms on baseline ECG, and/or taking medications or supplements with a known risk of prolonging the QT interval or inducing Torsades de Pointes.
12. History of interstitial lung disease, such as pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on previous imaging.
13. Significant prior or concurrent malignancy. Note that malignancies with very low risk of interfering with either participation or endpoint interpretation are permitted, such as adequately treated carcinoma-in-situ of the cervix, or basal cell or squamous cell carcinoma of the skin.
14. Pregnant or lactating women.
15. Serious medical or psychiatric condition that might limit the ability of the patient to consent to the study and/or comply with the protocol.

## 5.4 Screening

Written informed consent must be signed and dated by both the potential participant and the investigator prior to any study-specific screening investigations being performed; CT and WBBS performed before consent will be accepted if performed ≤ 28 days prior to registration.

## 5.5 Registration

For registration to this study, potential participants must meet all the inclusion criteria and none of the exclusion criteria. There will be no exceptions made to these eligibility requirements at the time of registration.

All participants must be registered before starting study treatment. Treatment should be planned to start within 7 days of registration. Registration should be done only after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility and signed the completed registration form.

Once the registration has been completed, the participant will be assigned a study number and written confirmation of registration will be provided to the study site.

# 6 TREATMENT PLAN

## 6.1 Administration of study treatments

### 6.1.1 Prochlorperazine - Investigational Product (IP)

Prochlorperazine will be administered as an intravenous infusion at a given dose level over 20 minutes, 60 minutes following the administration of cycle 2 of the standard treatment regimen of pertuzumab, trastuzumab and paclitaxel. The reason for this is that dexamethasone, which may impact ADCC, is not required from cycle 2 of the treatment.

On completion of the prochlorperazine infusion, the intravenous line will be flushed with 100ml 0.9% normal saline. The standard reconstitution of prochlorperazine is within a solution of the mesylate salt in 5% dextrose. As the dose per infusion varies depending on body size and dose level, the concentration of the infusion will differ: for instance, an expected dose of prochlorperazine would be 50-100mg diluted in 250ml for a 1-2mg/5ml concentration solution running over 20 minutes.

Prochlorperazine is given over 6 weeks, starting from day 1 of cycle 2. See the Schedule of Assessments in Section 7.1 for more details. If there are no treatment associated serious adverse events, patient will continue 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 for Cycle 2 Day 1, however with only one blood test per week.

Prochlorperazine should not be co-administered with dexamethasone during this trial. Dexamethasone will be weaned as per guidelines with 8mg in Week 1 of Cycle 1 and 4mg in Week 2 of Cycle 1. Dexamethasone should then be ceased, providing the patient has not experienced any adverse drug reactions. If the trial patient experiences an adverse drug reaction and necessitates administration of dexamethasone after Week 2 – the participant cannot proceed with the trial and will require a replacement in the cohort.

The treating clinician will assess each participant's current medication list at the screening visit to ensure no significant potential interactions exist. If there is the concern for a significant drug interaction, the patient would be advised not to participate in the trial. Common medications which would be considered to have a potential drug interaction with prochlorperazine include:

- Amitriptyline
- Buprenorphine
- Buproprion
- Citalopram
- Clozapine
- Escitalopram
- Haloperidol
- Methadone
- Metoclopramide
- Moxifloxacin
- Sotalol
- Tramadol
- Topiramate

### 6.1.2 Pertuzumab, trastuzumab, and paclitaxel

As standard-of-care therapies, the pertuzumab, trastuzumab, and paclitaxel will be obtained, handled, stored, and administered according to local institutional guidelines.

### 6.1.3 Dose limiting toxicity (DLT) and dose de-escalation

The DLT window will be 0-64 days following commencement of prochlorperazine at a given dose level. The first dose of study treatment for the first 2 patients treated at each dose level will be

staggered by at least 24 hours. A patient will be considered evaluable for DLT if they have completed at least 1 infusion of prochlorperazine.

Adverse events will be graded using CTCAE v5.0. Any DLT must be a toxicity that is considered related to the study drug prochlorperazine, including as a potential exacerbator of chemotherapy toxicity. For this study, DLTs are defined as:

***Haematologic dose limiting toxicity***

- Grade 4 neutropenia lasting > 5 days
- Febrile neutropenia lasting > 48 hours or associated with haemodynamic compromise or objective evidence of infection
- Grade 4 thrombocytopenia of any duration
- ≥ Grade 3 thrombocytopenia associated with clinically significant bleeding

***Non-haematologic dose limiting toxicity***

- ≥ Grade 3 ALT or AST rise, ≥ Grade 3 bilirubin rise, or likely drug-induced liver injury per Hy's law, defined as all of:
    - ALT or AST ≥ 3x ULN; and
    - Total bilirubin ≥ 2x ULN; and
    - No alternative aetiology can be identified.
- Grade 3 syncope or ≥ Grade 3 hypotension.
- ≥ Grade 3 constipation, only if not resolving to ≤ Grade 1 within 14 days with medical therapy.
- ≥ Grade 2 urinary retention.
- ≥ Grade 3 fatigue lasting > 7 days.
- ≥ Grade 3 cardiac arrhythmia, including Torsades de Pointes.
- ≥ Grade 3 psychosis.
- ≥ Grade 3 extrapyramidal disorder lasting > 5 days, such as acute dystonia including oculogyric crisis, tardive dyskinesia, torticollis, akathisia.

The starting dose is DL1. If at any time, there are 2 or more DLTs at any given dose level, further accrual to that cohort will be ceased. Notice will be sent at re-initiation of accrual at the next lower dose. If the first 2 patients enrolled in DL-2 experience a DLT, the study will either cease or continue with an alternative treatment schedule.

If more than 33% DLT evaluable patients in a DL cohort experience a DLT, further enrolment to that cohort will stop and a lower DL will be explored. If less than 33% DLT-evaluable patients in a DL cohort experience a DLT, the cohort will then be expanded to include 3 additional patients before the recommended phase 2 dose (RP2D) is declared, for additional safety exploration.

| **Dose level (DL)** | **Dose of pertuzumab, trastuzumab, and paclitaxel** | **Dose of prochlorperazine** | **Minimum number of patients** |
|---|---|---|---|
| 1 (starting) | See below | 0.8 mg/kg | 3 |
| -1 | See below | 0.7 mg/kg | 3 |
| -2 | See below | 0.6 mg/kg | 3 |

The other medications pertuzumab, trastuzumab, and paclitaxel are given at the same dose regardless of prochlorperazine dose level. For the first cycle, these doses are pertuzumab 840 mg every 3 weeks, trastuzumab 8 mg/kg every 3 weeks, and paclitaxel 80 mg/m$^2$ every week.

For subsequent cycles, these doses are pertuzumab 420 mg every 3 weeks, trastuzumab 6 mg/kg every 3 weeks, and paclitaxel 80 mg/m$^2$ every week.

The RP2D will be the highest dose level achieved with prochlorperazine in combination with pertuzumab, trastuzumab, and paclitaxel where less than 33% patients enrolled have experienced a DLT.

## 6.2 Dose modifications and delays

### 6.2.1 Prochlorperazine

Any evidence of extrapyramidal reactions following administration of prochlorperazine requires immediate withdrawal from treatment and no further infusions of prochlorperazine. In the unlikely event of a reaction to prochlorperazine, benztropine and diazepam will be available at the start of the infusion.

Prochlorperazine dose modifications and delays are not permitted.

### 6.2.2 Pertuzumab and trastuzumab

Pertuzumab and trastuzumab may be delayed due to toxicities. If pertuzumab and trastuzumab is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment.

Pertuzumab or trastuzumab dose modifications are not permitted.

### 6.2.3 Paclitaxel

Paclitaxel may be delayed due to toxicities. If paclitaxel is delayed for more than 3 weeks with no recovery, the patient should be withdrawn from paclitaxel treatment. If paclitaxel needs to be permanently discontinued, the patient will continue on prochlorperazine, pertuzumab, and trastuzumab.

Dose modifications for paclitaxel will be performed as clinically appropriate based on the investigator's medical judgment; details in this section can be used as guidance, though only the specific dose levels shown should be used.

| **Dose level** | **Paclitaxel** |
|---|---|
| Starting dose | 80 mg/m$^2$ |
| First dose reduction | 60 mg/m$^2$ |
| Second dose reduction | 40 mg/m$^2$ |
| Third dose reduction | Discontinue |

## 6.3 Concomitant medications

### 6.3.1 Permitted

Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, premedications, antiemetics, etc., according to standard of care when necessary. All protocol-permitted medications taken by the patient should continue as necessary during the study and be reported in the case report form (CRF).

### 6.3.2 Prohibited

The following medications and treatments should NOT be used during the study:

- Radiotherapy
- Corticosteroids at > 10 mg/day prednisolone equivalent*
- Drugs that are known to prolong the QT interval

*Corticosteroids at these doses are not permitted during the study period.

As stated in Section 6.1.1 - If the trial patient experiences an adverse drug reaction and necessitates administration of dexamethasone after Week 2 of Cycle 1 – the participant cannot proceed with the trial and will require a replacement in the cohort.

## 6.4 Compliance

Medication compliance will be determined by participant attendance for study treatment administration. The participant will be counselled appropriately if significant non-compliance is determined.

## 6.5 Study discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease is documented by a site investigator.
- Unacceptable toxicity
- Occurrence of an exclusion criterion affecting patient safety.
- Required use of a concomitant treatment that is not permitted.
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a person has failed to attend scheduled assessments in the study, the investigator must determine the reasons and document the circumstances as completely and accurately as possible in the medical record and CRF.
- The patient declines further study treatment or withdraws their consent to participate in the study.

Patients are permitted to continue weekly prochlorperazine at their own discretion, upon consultation with their treating Oncologist.

## 6.6 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient’s clinician. This can include, if appropriate, ongoing trastuzumab and pertuzumab.

# 7 ASSESSMENT PLAN

## 7.1 Schedule of assessments

| | | | | | On treatment; cycle = 21 days | | | | | | Post-treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Cycle 4 | Safety C5D1 | C6D1 and ongoing | Survival follow-up |
| Procedure | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | | | |
| | <=28 days | | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | Every 3 weeks (±3 days) | As per standard follow up |
| Informed consent | X | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | | | | |
| Medical history / demographics | X | | | | | | | | | | | | | |
| Concomitant medications | X | X | | | X | X | X | X | X | X | X | X | | |
| Confirm eligibility | | X | | | | | | | | | | | | |
| Clinical assessment | X | X | | | X | X | X | X | X | X | X | X | X[a] | |
| Adverse events | X | X | | | X | X | X | X | X | X | X | X | | |
| Paclitaxel (SOC) | | X | X | X | X | X | X | X | X | X | X[b] | X[b] | | |
| Trastuzumab + pertuzumab (SOC) | | X | | | X | | | X | | | X | X | X | |
| Prochlorperazine administration | | | | | X | X | X | X | X | X | | | | |
| Blood tests | X | X | | | X | X | X | X | X | X | X | X | X[a] | |
| Ca15.3 | X | X | | | X | | | X | | | X | X | X[a] | |
| Pregnancy test | X | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Translational bloods | X | X | | | X | X | X | X | X | X | X | | | |
| Translational biopsy | X | | | | X[c] | | | | | | | | | |
| HRQOL form | | | | | | | | | | | | | | |
| Imaging (CT and WBBS) | X | | | | | | | | | | | X | X[a] | |
| MUGA / echocardiogram | X | | | | | | | | | | | X | | |
| Electrocardiogram (ECG) | X | | | | X | X | X | X | X | X | | | | X |
| Survival follow-up | | | | | | | | | | | | | | X |

[a]Frequency of clinical assessment and progress imaging subsequent to treatment period is at discretion of the investigator.

[b]Number of paclitaxel doses given subsequent to treatment period is at discretion of the investigator (up to 8 cycles).

[c]Biopsy of an accessible lesion will be performed at 1.5 hours (±30 minutes) after the administration of prochlorperazine

## 7.2 Details of assessments

### 7.2.1 Clinical assessment

Clinical assessment includes history, physical examination, and performance status. Participants will be reviewed by their study investigator weekly during the prochlorperazine infusions, then every 3 weeks. Subsequent clinical assessment frequency is at the discretion of the investigator.

### 7.2.2 Imaging

CT chest, abdomen, and pelvis, as well as $^{99m}$Tc bone scan will be performed at screening, then at the safety visit (week 13 ± 3 days). Subsequent imaging frequency is at the discretion of the investigator.

### 7.2.3 Blood collection

Local pathology laboratories will be used for routine blood tests. Blood will be taken every week during the treatment period, then every 3 weeks, with additional assessments as clinically indicated. Subsequent standard-of-care blood test frequency will be at the discretion of the investigator.

Translational blood tests are performed before and after each administration of prochlorperazine. (Section 8.7).

### 7.2.4 Tissue collection

Information and consent obtained if appropriate. If a biopsy hasn't already been undertaken, a biopsy and 4ml blood plasma sample will be taken as part of standard care and transported straight to the laboratory for examination of immune status. If appropriate, biopsies may be taken under image guidance (ultrasound or computed tomography).

Either that day or on the next available appointment (depending on patient availability) patient will be taken to the Oncology Day Unit where a Registered Nurse can monitor the patient and take blood samples. Here an intravenous line is inserted. This remains until the patient is discharged from the Oncology Day Unit. Subject receives 0.8mg/kg intravenous dose of prochlorperazine over 20-30 mins. A biopsy will be collected approximately 90 minutes post the administration of intravenous prochlorperazine.

Patient will only be able to transfer from site if blood pressure is stable. They will be advised not to use machinery or drive for a further 24 hours. Transportation home will need to occur via a carer.

### 7.2.5 Cardiac assessment

Cardiac assessment with MUGA or echocardiogram should be performed during screening, then at the safety visit (cycle 5 or week 13 ± 3 days), then every 12 weeks subsequently, with other assessments as clinically indicated. Left ventricular ejection fraction (LVEF) assessment by echocardiography is preferred. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor.

An electrocardiogram (ECG) will be performed on initial screening visit, during each prochlorperazine infusion and at the end of treatment and 21-day safety assessment.

## 7.3 End of treatment and 21-day safety assessment

An end of treatment and safety assessment should be performed at 21 days after the last dose of study treatment to identify any adverse events occurring within this time. In the event of unresolved toxicity, participants should continue to be followed.

## 7.4 Follow up after treatment

Study-specific follow-up assessments after treatment should be completed at the specified time points (± 7 days). Subjects who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, state-based cancer registries and/or the national mortality registry (AIHW).

For patients who have been lost to follow-up, Medicare may be used to provide updated contact information and/or hospitalisations and the AIHW may be used to collect mortality information.

# 8 OUTCOMES, ENDPOINTS, AND OTHER MEASURES

## 8.1 Recommended phase 2 dose (RP2D)

The primary objective is to determine the RP2D, defined as the highest dose level achieved with prochlorperazine in combination with pertuzumab, trastuzumab, and paclitaxel where less than 33% patients enrolled have experienced a DLT.

## 8.2 Frequency and severity of adverse events

The CTCAE v5.0 will be used to classify and grade the intensity of adverse events observed during the study period.

## 8.3 Rate of reduction in LVEF

Rate of reduction in left ventricular ejection fraction (LVEF) is defined as the proportion of participants with reduction in LVEF, defined as an absolute fall of at least 10% from baseline to a new LVEF of less than 50%.

## 8.4 Objective response rate (ORR)

Objective response rate (ORR) is defined as the proportion of participants with objective response, defined as a complete response (CR) or partial response (PR) according to RECIST v1.1 recorded from enrolment until disease progression or death due to any cause. Patients not recording CR or PR and patients with inadequate data for tumour assessment are considered non-responders in the ORR analysis.

## 8.5 Duration of response (DOR)

Duration of response (DOR) is defined as the time from the first documentation of objective response (CR or PR) to the first documentation of objective tumour progression or death due to any cause, whichever occurs first. DOR data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who do not die due to any cause while on study. DOR will only be calculated for the subgroup of patients with an objective response.

## 8.6 Progression-free survival (PFS)

Progression-free survival (PFS) is defined as the time from enrolment to the date of the first documentation of progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who do not die due to any cause while on study. Participants lacking an evaluation of tumour response after enrolment will have their PFS time censored on the date of enrolment with the duration of one day.

## 8.7 Measures of immune system activation

10ml of blood will be collected at baseline and within 2 hours of each administration of intravenous prochlorperazine. Bloods will be transported to the Translational Research Institute (Brisbane site) or stored (St Vincent's Hospital, Sydney) for transfer to the Brisbane site. PBMC will be prepared from blood samples and subjected to a 16 channel (colour) Symphony FACS panel which will record immune cell number and immune cell activation as well as select cytokine levels to determine the activation state of the immune system for correlation with patient clinical response. A portion of tumour biopsy will be analysed in the same way to determine immune cell infiltration.

## 8.8 Receptor trafficking analysis

Tumour biopsies will be collected pre- and post-PCZ administration and will be subjected to timed uptake of trastuzumab prior to fixation, as described by our team (5). Tumours will be fixed and separated into two sets. One set will be labelled with fluorescent secondary anti-human antibodies and the other with HRP-anti-human antibodies. The fluorescent set will be imaged by confocal and 3D-SIM light microscopy, the HRP-set will be transported to IMB (Parton laboratory) for analysis by electron microscopy.

## 8.9 Development of patient-derived xenograft models

Where research biopsies are obtained, fresh or frozen tissue will be utilised to develop Patient Derived Xenografts (PDXs) in the Connie Johnson Laboratory as per published protocols.

# 9 SAFETY REPORTING

## 9.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).
- Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (i.e. the subject is at risk of death at the time of the event),
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect,
- Other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected, i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the drug caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

For the purposes of this study, hospitalisations related to disease progression are not reported as SAEs.

## 9.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the trial management committee within 24 hours of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 12 weeks from the end of study treatment.

The trial management committee will be responsible for providing reports to the Lead HREC. The trial management committee will provide SUSAR reports and SAE line listings to investigators for submission to Human Research Ethics Committees (HRECs) as required. The investigator must notify the local HREC as required.

The trial management committee will submit 'reportable safety events' to the TGA in Australia in time to comply with the requisite specified regulatory time windows (usually 7 days for fata/life-threatening events with an 8-day follow-up report, and 15 days for other SUSARs).

The following information will be recorded for each Serious Adverse Event:

- Event description including classification according to NCI CTCAE v5.0
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity / Worst Grade
- Attribution to study intervention prochlorperazine
- Expectedness (listed in IB/product information)
- Action taken with study intervention prochlorperazine, including rechallenge (if done)
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE, including end date if recovered

## 9.3 Pregnancy

Pregnancy occurring in a participant during and up to 90 days after the completion of the study treatment should also be reported to the investigator and the trial management committee. The investigator should counsel the patient and their partner regarding the risks of continuing with the pregnancy and the possible effects on the foetus.

The trial management committee must be notified within 24 hours and the participant followed during the entire course of the pregnancy and the postpartum period. After obtaining participant and partner consent, parental and neonatal outcomes will be recorded even if they are completely normal.

# 10 CENTRAL STORAGE OF BIOSPECIMENS

## 10.1 Central blood collection

The Translational Research Institute, Brisbane, will be used to conduct translational research studies including biomarker analyses. Translational research bloods will be collected and initially processed and stored at each site. Samples will later be shipped to the Translational Research Institute, Brisbane, for translational research and storage. Refer to the biological sampling manual for procedures.

## 10.2 Central tissue collection

Archival tissue may be collected for translational research from consenting participants. Samples will be shipped to central laboratories for translational research and storage. Refer to the biological sampling manual for procedures.

# 11 TREATMENT SUPPLY AND ACCOUNTABILITY

## 11.1 Study treatment - prochlorperazine

Prochlorperazine is a phenothiazine with a piperazine moiety in the side chain. It possesses strong antiemetic and antipsychotic activity with less sedative action than chlorpromazine.

As with other phenothiazines, prochlorperazine has actions on several neurotransmitter systems:

- Antidopamine action, which probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.
- $\alpha$-Adrenoreceptor antagonism, which contributes to cardiovascular side effects such as orthostatic hypotension and reflex tachycardia.
- Potentiation of noradrenaline by blocking its reuptake into nerve terminals.
- Weak anticholinergic action.
- Weak antihistamine action.
- Weak serotonin antagonism.

Prochlorperazine is available in injection ampoules at a concentration of 12.5mg/ml. Each ampoule contains a 12.5mg dose (1ml). This supply will be identical at both trial sites.

## 11.2 Drug accountability

The pharmacy department at participating institutions will maintain a record of prochlorperazine supply and use, as well as subsequent returns. The pharmacy will also maintain a record of drug receipt and drug destruction as appropriate.

# 12 STATISTICAL CONSIDERATIONS

## 12.1 Sample size

The sample size will be between 6 and 12 patients based on a 3+3 dose de-escalation design.

## 12.2 Statistical analysis

Safety analyses will include all participants who received at least one dose of study treatment.

Efficacy analyses will be by intention-to-treat and include all participants recruited, regardless of whether they received study treatment.

Time to event data will be summarised using the Kaplan Meier method including all participants recruited.

Measures of effect will be reported with 2-sided 95% confidence intervals calculated with appropriate methods.

Suitable regression models will be used to test the effects of baseline characteristics on key endpoints, e.g. PSA response, pain response, etc. Logistic regression will be used for dichotomous endpoints. Cox proportional hazards models will be used for time-to-event endpoints. Linear regression will be used for HRQL data, using models for repeated measures data as appropriate.

Sensitivity analyses will be used to assess effects on the findings and conclusions of excluding participants who were deemed ineligible, unevaluable, or did not receive study treatment.

## 12.3 Interim analyses

No interim analyses are planned for this study.

# 13 STUDY COMMITTEES

## 13.1 Trial management committee

The trial management committee (TMC) will consist of Professor Elgene Lim, Professor Euan Walpole and Dr Katharine Cuff. The TMC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The TMC will consider recommendations from the SDMC about whether to continue the study as planned, modify, or stop it, based on information arising during the course of the study.

## 13.2 Data and Safety Monitoring Board (DSMB)

This study has a Data and Safety Monitoring Board (DSMB).

The DSMB will provide independent assessment of patient safety and trial progress, making recommendations to the TMC about the continuation of the trial based on data made available by the trial statistician.

Agreed terms of reference for the DSMB will be developed with the TMC.

The DSMB will be supplied with:

- Interim analysis report(s)
- Cumulative list of SAEs after the completion of treatment for each dose cohort
- Information about the study's progress including accrual rates
- Medical, ethical or other information that might influence decisions to continue the study

# 14 ADMINISTRATIVE ASPECTS

## 14.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct

of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance, the principal investigator and HREC must be advised immediately.

## 14.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Kinghorn Cancer Centre or the PAH / TRI sites and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

## 14.3 Protocol amendments

Changes and amendments to the protocol can only be made by the trial management committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

## 14.4 Data handling and record keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

a. Subject’s name, contact information and protocol identification.
b. The date that the subject entered the study, and subject number.
c. A statement that informed consent was obtained (including the date).
d. Relevant medical history
e. Dates of all subject visits and results of key trial parameters.
f. Occurrence and status of any adverse events.
g. The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 15 years following completion of the study.

## 14.5 Study monitoring

Data from this study will be monitored by TMC or their delegates according to local SOPs. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The TMC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorised TMC staff direct access to their medical records and the study data.

## 14.6 Audit and inspection

This study may be subject to audit or inspection by representatives of the Sponsor or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA)).

## 14.7 Publication policy

The TMC will be responsible for decisions regarding presentations and publications arising from this trial according to the sponsor guidelines. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group led by the coordinating principal investigator in conjunction with participating clinicians and scientists. Authorship recognizes the intellectual contributions of investigators and others to a study, and is defined as per ICMJE guidelines (www.icmje.org). Publications and abstracts must be presented to the TMC for review and approved prior to submission. Authorship of any secondary publications (e.g. relating to various biological studies) will reflect the intellectual and time input into these studies and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the trial without the prior written permission of the TMC.

## 14.8 Insurance and indemnity

Indemnity is being sought from The University of Queensland who will also act as the study sponsor.

# 15 REFERENCES


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5. Joseph SR, Lum B, Banushi B, Barry R, Panizza B, Walpole E, et al. Antibody/Ligand-Target Receptor Internalization Assay Protocol Using Fresh Human or Murine Tumor Ex Vivo Samples. STAR Protoc. 2020;1(2):100087.

# 16 APPENDIX