AUSTRALIAN PRODUCT INFORMATION – Perjeta (pertuzumab)

1. NAME OF THE MEDICINE
Pertuzumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Perjeta 420 mg concentrate for intravenous infusion.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Perjeta is supplied in a single-dose glass vial containing 14mL of clear to opalescent, colourless to slightly brownish solution.

Each vial contains 420 mg of pertuzumab (30 mg/mL).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Neoadjuvant Treatment of Breast Cancer
Perjeta is indicated in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with inflammatory or locally advanced HER2-positive breast cancer as part of a complete treatment regimen.
Note to indication: this approval is based on improvement in pathological complete response rate. No improvement in disease-free, progression-free or overall survival has been shown.

Metastatic Breast Cancer
Perjeta is indicated in combination with trastuzumab and docetaxel for patients with metastatic HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose
General
Substitution by any other biological medicinal product requires the consent of the prescribing physician. In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Perjeta.

DO NOT ADMINISTER PERJETA AS AN IV PUSH OR BOLUS.

Detection of HER2 Protein Overexpression or HER2 Gene Amplification
Patients can only be treated with Perjeta in combination with trastuzumab and must have a HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridization (ISH).

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

HER2 protein overexpression should be detected using an IHC-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using ISH of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH).

For any other method to be used for the assessment of HER2 protein or gene expression, the test method must be precise and accurate enough to demonstrate overexpression of HER2 (it must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) HER2 overexpression).

For full instructions on assay performance and interpretation please refer to the package inserts of validated HER2 testing assays. Official recommendations on HER2 testing may also apply.

Dosage of Perjeta in combination with trastuzumab and chemotherapy

The recommended initial dose of Perjeta is 840 mg, administered as a 60 min IV infusion, followed by, every 3 weeks, a 420 mg dose administered over 30-60 min.

When trastuzumab is administered with Perjeta, the recommendation is to follow a 3-weekly schedule, administered as an IV infusion, with an initial trastuzumab dose of 8 mg/kg followed by every 3 weeks, a dose of 6 mg/kg.

When docetaxel is administered with Perjeta, the recommended initial docetaxel dose is 75 mg/m^2. The dose of docetaxel may be escalated to 100 mg/m^2 if the initial dose is well tolerated.

The medicinal products should be administered sequentially. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, the docetaxel should be administered after Perjeta and trastuzumab.

An observation period of 30-60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel (see section 4.4).

Neoadjuvant Treatment of Breast Cancer

Perjeta should be administered for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for inflammatory or locally advanced HER2-positive breast cancer.

Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment.

The safety of Perjeta as part of a doxorubicin-containing regimen has not been established.

There is insufficient evidence to recommend concomitant administration of an anthracycline with Perjeta.

Duration of treatment

Metastatic Breast Cancer

It is recommended that patients are treated with Perjeta until disease progression or unmanageable toxicity.

Neoadjuvant Treatment of Breast Cancer

It is recommended that patients are treated with Perjeta for three to six cycles depending on the regimen chosen (see section 5.1).

The safety of Perjeta administered for greater than 6 cycles for the neoadjuvant treatment of breast cancer has not been established.

Dose modifications

Perjeta should be discontinued if trastuzumab treatment is discontinued.

If docetaxel is discontinued, treatment with Perjeta and trastuzumab may continue until disease progression or unmanageable toxicity in the metastatic setting.

Dose reductions are not recommended for Perjeta.

Trastuzumab dose reductions are not recommended, see trastuzumab prescribing information.

For docetaxel and other chemotherapy dose modifications, see the product information for each agent.

Infusion-related reactions

The infusion rate of Perjeta may be slowed or interrupted if the patient develops an infusion-associated reaction.

Hypersensitivity reactions/anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction (see section 4.4).

Left ventricular dysfunction

Withhold Perjeta and trastuzumab dosing for at least 3 weeks for either;

- a drop in left ventricular ejection fraction (LVEF) to < 40% or
- LVEF of 40%-45% associated with a fall of ≥10%-points below baseline.

Perjeta and trastuzumab may be resumed if the LVEF has recovered to >45% or 40-45% associated with <10%-points below baseline.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see section 4.4).

Special populations

Elderly

No differences of safety and efficacy of Perjeta were observed between adult patients ≥65 and <65 years of age. No dose adjustment is required in the elderly population.

Paediatric use

The safety and efficacy of Perjeta in children and adolescents below 18 years of age have not been established.

Renal impairment

Dose adjustments of Perjeta are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (see section 5.2).

Hepatic impairment

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment.

Delayed or missed doses

If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta should be administered as soon as possible. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg Perjeta should be re-administered as a 60 min IV infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 to 60 min.

Method of Administration

Instructions for dilution

Perjeta should be prepared by a healthcare professional using aseptic technique. Perjeta does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Initial dose

Dilute 28 mL (two vials, 840 mg) of Perjeta in 250 mL of 0.9% sodium chloride (do not withdraw saline out of the infusion bag). After dilution, of the solution should contain approximately 3.0 mg/mL of pertuzumab.

Subsequent doses

Dilute 14mL (one vial, 420 mg) of Perjeta in 250 mL of 0.9% sodium chloride (do not withdraw saline out of the infusion bag). After dilution the solution should contain approximately 1.6 mg/mL of pertuzumab.

Glucose (5%) solution should not be used (see section 6.2).

The bag should be *gently* inverted to mix the solution in order to avoid foaming.

Parenteral drug products should be inspected visually for particulates and discolouration prior to administration.

Perjeta is for single use in one patient only. Once the infusion is prepared it should be administered immediately (see section 6.4).

4.3 CONTRAINDICATIONS

Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab, Chinese hamster ovary cell proteins or to any other component of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Perjeta therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. Perjeta must be diluted by a healthcare professional and administered as an IV infusion.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record.

Cardiac failure and left ventricular dysfunction

Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2 activity, including Perjeta.

Close clinical and regular radiological monitoring of cardiac function is recommended and any decision regarding commencing Perjeta in patients with cardiac risk factors should be balanced against the risk of possible cardiac dysfunction and necessitating discontinuation of therapy.

Perjeta was associated with an increased risk of left ventricular dysfunction (LVD) in the NEOSPHERE and TRYPHAENA studies. Up to 16% of patients developed LVD in the arm receiving FEC followed by Perjeta plus trastuzumab and docetaxel in the TRYPHAENA study. Congestive heart failure necessitating discontinuation of therapy occurred in a patient with pre-existing cardiac risk factors receiving concurrent neoadjuvant Perjeta and trastuzumab without chemotherapy in the NEOSPHERE study.

In neoadjuvant treated patients (NEOSPHERE –see section 5.1) the incidence of LVD was higher in the Perjeta–treated groups than the trastuzumab and docetaxel treated group. An increased incidence of LVEF declines was observed in patients treated with Perjeta in combination with trastuzumab and docetaxel; LVEF recovered to ≥50% in all patients.

In the pivotal Phase III trial CLEOPATRA, for patients with metastatic breast cancer, Perjeta in combination with trastuzumab and docetaxel was not associated with an increase in the incidence of symptomatic left ventricular systolic dysfunction (LVD[congestive heart failure]) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel (see section 4.8). However, patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

Perjeta has not been studied in patients with a baseline LVEF value of ≤50%; a prior history of congestive heart failure (CHF); decreases in LVEF to <50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360mg/m^2 of doxorubicin (or its equivalent).

Assess LVEF prior to initiation of Perjeta and at regular intervals (e.g. every 3 months in the metastatic setting and every six weeks in the neoadjuvant setting) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is <40% or, 40-45% and ≥10% points below baseline, Perjeta and trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see section 4.2).

Infusion related reactions

Perjeta has been associated with infusion reactions (see section 4.4). Close observation of the patient during, and for 60 min after the first infusion and during, and for 30 min following subsequent infusions, is recommended following the administration of Perjeta. If a significant infusion related reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see section 4.2).

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of Perjeta (see section 4.8). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or to any Perjeta excipients (see section 4.3).

Febrile neutropenia

Patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel. This may be associated with a higher incidence of mucositis and diarrhoea in Perjeta-treated patients. In the CLEOPATRA study in both treatment groups, the proportion of patients who experienced febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment groups compared with patients of other races and from other geographic regions. In the CLEOPATRA study, among Asian patients, the incidence of febrile neutropenia was 26% in the Perjeta-treated group compared with 12% in the placebo-treated group. If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate.

Tumour Lysis Syndrome

Tumour Lysis Syndrome (TLS) refers to the constellation of metabolic disturbances that may be seen after initiation of effective cancer treatment. It usually occurs in patients with high grade, bulky, rapidly proliferating, treatment-responsive tumours and in patients with acute haematological malignancies.

To date, while no cases have been reported from controlled investigational clinical trials in more than 10,000 patients exposed to Perjeta cases suggestive of TLS have been reported in the postmarketing setting. There is no confirmed causal association between TLS and Perjeta in these cases, however patients at risk of tumour lysis syndrome should be monitored closely and appropriate precautions taken.

Paediatric use

The safety and efficacy of Perjeta in children and adolescents below 18 years of age have not been established.

Use in the elderly

No differences of safety and efficacy of Perjeta were observed between adult patients ≥65 and <65 years of age.

Use in renal impairment

The safety and efficacy of Perjeta have not been studied in patients with renal impairment.

Use in hepatic impairment

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment.

Effect on laboratory tests

No text.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug-drug interaction between Perjeta and trastuzumab and between Perjeta and docetaxel. In addition, no clinical relevant pharmacokinetic interaction of co-administered docetaxel or trastuzumab on Perjeta was evident based on the population pharmacokinetics analysis. This lack of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE study.

Four studies have evaluated the effects of Perjeta on the pharmacokinetics of co-administered cytotoxic agents; docetaxel, gemcitabine, erlotinib and capecitabine. There was no evidence of any pharmacokinetics interaction between Perjeta and any of these agents. The pharmacokinetics of Perjeta in these studies was comparable to those observed in single-agent studies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific fertility studies in animals have been performed to evaluate the effect of Perjeta. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys.

Use in pregnancy - Category D

Perjeta is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pertuzumab may cause embryo-fetal harm and death when administered during pregnancy. Confirm pregnancy status prior to the initiation of Perjeta and advice patients of the risks and the importance for contraception during and after treatment. Perjeta should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

There are no studies of Perjeta in pregnant women. Reproductive toxicology studies have been conducted in cynomolgus monkeys at loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg achieving plasma pertuzumab concentrations approximately 2-19 times the clinical Cmax at the loading dose of 800 mg. IV administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) was shown to be embryo- and foetotoxic with a dose dependent increase in embryo-foetal deaths and abortions between GD 25 to 70. Delayed renal development, oligohydramnios and other abnormalities were identified at GD100.

Use in lactation

Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue nursing or Perjeta taking into account the importance to the mother and the elimination half-life of pertuzumab (see section 5.2).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person’s ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of Perjeta has been evaluated in more than 1600 patients the randomised CLEOPATRA (n=808), NEOSPHERE (n=417) and TRYPHAENA (n=225) trials, and in Phase I and II trials conducted in patients with various malignancies, and predominantly treated with Perjeta in combination with other anti-neoplastic agents. The safety of Perjeta in Phase I and Phase II studies was generally consistent with that observed in the CLEOPATRA, NEOSPHERE and TRYPHAENA trials, although the incidence and most

common adverse drug reactions (ADRs) varied depending on whether pertuzumab was administered as monotherapy or in combination with other anti-neoplastic agent(s).

Neoadjuvant Treatment of Breast Cancer
In NEOSPHERE, the most common ADRs (≥50%) seen with Perjeta in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common NCI-CTCAE (version 3) Grade 3-4 ADR (≥10%) was neutropenia.

In TRYPHAENA, when Perjeta was administered in combination with trastuzumab and docetaxel for three cycles following three cycles of FEC, the most common ADRs (≥50%) were diarrhoea, nausea and alopecia. The most common NCI-CTCAE (version 3) Grade 3-4 ADRs (≥10%) were neutropenia and leukopenia. Similarly, when Perjeta was administered in combination with docetaxel, carboplatin and trastuzumab (TCH) for six cycles, the most common ADRs (≥50%) were diarrhoea and alopecia. The most common NCI-CTCAE (version 3) Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia, anaemia, leukopenia and diarrhoea.

Metastatic Breast Cancer
In the pivotal metastatic breast cancer (MBC) trial CLEOPATRA, the most common ADRs (≥50%) seen in Perjeta in combination trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE (version 3) grade 3-4 ADRs (>10%) were neutropenia, febrile neutropenia and leukopenia. After discontinuation of docetaxel, ADRs in the Perjeta and trastuzumab treatment group occurred in <10% of patients with the exception of diarrhoea (28.1%), rash (18.3%), upper respiratory tract infection (18.3%), headache (17.0%), nasopharyngitis (17.05), pruritis(13.750, fatigue (13.4%), asthenia (13.4%), nausea (12.7%), arthralgia (11.4%), pain in extremity (13.4%), back pain (12.1%) and cough (12.1%).

Metastatic Breast Cancer and Neoadjuvant Treatment of Breast Cancer
Table 1 summarizes the ADRs from the treatment arm of the double-blind pivotal clinical trial, CLEOPATRA, in which Perjeta was given in combination with trastuzumab and docetaxel to patients with MBC, and from the neoadjuvant trials NEOSPHERE and TRYPHAENA, in which Perjeta was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or early breast cancer. As Perjeta is used with trastuzumab and chemotherapy, it is difficult to ascertain the causal relationship of an adverse reaction to a particular drug.

The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 1 – Summary of ADR's in patients treated with Perjeta in the Metastatic and Neoadjuvant setting^

ADR (MedDRA Preferred Term) **System Organ Class**	**Perjeta + Herceptin + chemotherapy^^** **n = 980^^^ (100%)** **Frequency rate %**		**Frequency category**
	All Grades %	**Grades 3-4 %**	

ADR (MedDRA Preferred Term) System Organ Class	Perjeta + Herceptin + chemotherapy^^ n = 980^^^ (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Blood and lymphatic system disorders			
Neutropenia	45.2	41.2	Very common
Anaemia	17.1	3.1	Very common
Leukopenia	14.2	9.7	Very common
Febrile neutropenia*	10.7	10.4	Very common
Cardiac disorders			
Left ventricular dysfunction**	4.5	0.8	Common
Cardiac failure congestive**	0.3	0.2	Uncommon
Eye disorders			
Lacrimation increased	9.0	-	Common
Gastrointestinal disorders			
Diarrhoea	58.9	6.6	Very common
Nausea	39.5	0.7	Very common
Vomiting	23.4	1.3	Very common
Stomatitis	15.2	0.2	Very common
Constipation	12.3	-	Very common
General disorders and administration site conditions			
Fatigue	31.5	1.4	Very common
Mucosal inflammation	21.5	0.9	Very common
Asthenia	18.6	1.7	Very common
Pyrexia	15.6	0.5	Very common
Oedema peripheral	12.4	0.2	Very common
Immune system disorders			
Drug hypersensitivity	5.2	0.9	Common
Hypersensitivity	3.1	0.4	Common
Infections and infestations			
Upper respiratory tract infection	11.7	0.3	Very common
Nasopharyngitis	10.8	-	Very common
Paronychia	3.8	-	Common
Metabolism and nutrition disorders			
Decreased appetite	19.6	0.7	Very common
Musculoskeletal and connective tissue disorders			
Myalgia	18.6	0.6	Very common
Arthralgia	13.2	0.1	Very common
Nervous system disorders			
Headache	19.3	0.7	Very common
Dysgeusia	14.1	-	Very common
Neuropathy peripheral	11.6	1.1	Very common
Dizziness	9.9	0.4	Common
Peripheral sensory neuropathy	8.9	0.3	Common
Psychiatric disorders			
Insomnia	12.2	-	Very common
Respiratory, thoracic and mediastinal disorders			
Cough	13.6	0.2	Very common

ADR (MedDRA Preferred Term) System Organ Class	Perjeta + Herceptin + chemotherapy^^ n = 980^^^ (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Dyspnoea	9.8	0.7	Common
Pleural effusion	2.2	0.1	Common
Skin and subcutaneous tissue disorders			
Alopecia	51.0	-	Very common
Rash	27.1	0.6	Very common
Nail disorder	13.5	0.5	Very common
Pruritus	9.2	-	Common
Dry skin	7.7	-	Common

^ Table 1 shows pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of Perjeta was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of Perjeta was 4, across all treatment arms) and TRYPHAENA (median number of cycles of Perjeta was 3 in the FEC/Ptz+T+D arm and 6 in the Ptz+T+FEC/Ptz+T+D and Ptz+TCH arms).
^^ In NEOSPHERE, 108 patients received Perjeta + Herceptin alone without docetaxel and 94 patients received Perjeta + docetaxel without Herceptin.
^^^ In CLEOPATRA, 45 patients who were randomized to receive placebo and who had no prior exposure to Perjeta, had crossed over to receive Perjeta and are included in the 980 patients treated with Perjeta.
* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome.
** The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.

Further information on selected adverse drug reactions:

Cardiac failure and left ventricular dysfunction

In NEOSPHERE, in which patients received four cycles of Perjeta as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the Perjeta, trastuzumab and docetaxel-treated group (8.4%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and trastuzumab--treated group. In NEOSPHERE there was no central review of cardiac imaging result (see section 4.4).

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 6.9% in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel; 16.0% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC; and 10.5% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus trastuzumab and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel experienced symptomatic LVD. In TRYPHAENA cardiac imaging results were reviewed centrally (see section 4.4).

In the pivotal trial CLEOPATRA, the incidence of LVD during study treatment was higher in the placebo--treated group than the Perjeta-treated group (8.6% and 6.6%, respectively). The

incidence of symptomatic LVD was also lower in the Perjeta treated group (1.8% in the placebo--treated group vs. 1.5% in the Perjeta-treated group) (see section 4.4).

Infusion related reactions

An infusion related reaction was defined in the pivotal trial as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion, or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of Perjeta was given the day before trastuzumab and docetaxel to allow for the examination of Perjeta associated reactions. On the first day, when only Perjeta was administered, the overall frequency of infusion related reactions was 9.8% in the placebo treated group and 13. 2% in the Perjeta treated group, with the majority of reactions being mild or moderate. The most common infusion related reactions (≥1.0%) in the Perjeta treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity and vomiting.

During the second cycle, when all drugs were administered on the same day, the most common infusion related reactions (≥1.0%) in the Perjeta treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia and vomiting (see section 4.4).

In NEOSPHERE and TRYPHAENA, Perjeta was administered on the same day as the other study treatment drugs. Infusion-related reactions were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate.

Hypersensitivity reactions/anaphylaxis

In the pivotal trial CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.1% in the placebo treated patients and 11.0% in the Perjeta treated patients, of which 2.5% and 2% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo treated group and 4 patients in the Perjeta treated group experienced anaphylaxis (see section 4.4).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to study treatment, most reactions were assessed as secondary to docetaxel infusions.

In NEOSPHERE and TRYPHAENA, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, one patient in the Perjeta and docetaxel treated group experienced anaphylaxis. In TRYPHAENA, the overall frequency of hpersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2%), of which 2.65 were NCI-CTCAE (version 3) grade 3-4.

Post marketing Experience

The following adverse drug reaction has been identified from post marketing experience with Perjeta based on spontaneous case reports and literature cases. The adverse drug reaction is listed according to system organ class in MedDRA.

Table 2: Adverse Drug Reactions from Post marketing Experience

System Organ Class	Adverse reaction
Metabolism and nutrition disorders	Tumour Lysis Syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems .

4.9 OVERDOSE

There is no experience with overdosage in human clinical trials. Single doses higher than 25 mg/kg (1727 mg) have not been tested.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre call on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC13

Mechanism of Action

Pertuzumab binds to the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. It inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).While pertuzumab alone inhibited the proliferation of human tumour cells, the anti-tumour activity was significantly augmented when pertuzumab was used in combination with trastuzumab in HER2-overexpressing xenograft models.

Clinical trials

Neoadjuvant Treatment of Breast Cancer

NEOSPHERE (WO20697)

NEOSPHERE is a phase II, multicentre, multinational randomized controlled trial with Perjeta and was conducted in 417 adult female patients with newly diagnosed, early, inflammatory or locally advanced HER2-positive breast cancer (T2-4d; primary tumour > 2cm in diameter) who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (see section 4.4) or LVEF < 55% were not included. The majority of patients were less than 65 years old.

Patients were randomised to receive one of the following neoadjuvant regimens for 4 cycles prior to surgery:

- Trastuzumab plus docetaxel
- Perjeta plus trastuzumab and docetaxel
- Perjeta plus trastuzumab
- Perjeta plus docetaxel.

Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER or PgR positivity. HER2 overexpression was centrally confirmed and defined as an IHC score of 3+, or ISH amplification ratio ≥2.0.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks for four cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks for four cycles. Following surgery all patients received three cycles of 5-Fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), cyclophosphamide (600 mg/m^2) (FEC) given intravenously every three weeks and trastuzumab administered intravenously every three weeks to complete one year of therapy. Patients in the Perjeta plus trastuzumab and docetaxel arm received docetaxel every three weeks for four cycles prior to FEC after surgery so that all patients received equivalent cumulative doses of the chemotherapeutic agents and trastuzumab.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 only), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (71%) and all were female. Overall 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer and 61% had operable breast cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER positive and/or PgR positive). Pathological assessment of lymph nodes at baseline occurred in 5 patients.

The efficacy results are summarised in Table 1. A statistically significant improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition.

The pCR rates as well as the magnitude of benefit with Perjeta (for patients receiving Perjeta plus trastuzumab and docetaxel compared with trastuzumab and docetaxel) were lower in the subgroup of patients with hormone receptor-positive tumours (difference of 6% in pCR in the breast) than patients with hormone receptor-negative tumours (difference of 26.4% in pCR in the breast). pCR rates were similar in patients with operable versus locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions but the pCR rate was higher in patients who received Perjeta plus trastuzumab and docetaxel.

TRYPHAENA (BO22280)
TRYPHAENA is a multicenter, randomized Phase II clinical study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer. Breast tumour specimens were required to show HER2 over expression defined as a score of 3+ by IHC or ISH amplification by ≥ 2.0 as determined by a central laboratory.

Patients were randomized to receive one of three neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with Perjeta and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with Perjeta or 6 cycles of TCH in combination with Perjeta. There is insufficient evidence to recommend concomitant administration of an anthracycline with Perjeta.

Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and /or PgR positivity.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (600 mg/m^2) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every three weeks with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the Perjeta in combination with TCH arm, docetaxel was given intravenously at 75 mg/m^2 and no escalation was permitted and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received Herceptin to complete one year of therapy, which was administered intravenously every 3 weeks.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (77%) and all were female. Overall 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer and 69% had operable breast cancer, with approximately half the patients in each treatment group had ER-positive and/or PgR-positive disease.

pCR rates were observed in all 3 treatment arms (see Table 2). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumours than in patients with hormone receptor-negative tumours (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 3: NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Summary of Efficacy (ITT population)

	NEOSPHERE (WO20697)				**TRYPHAENA (BO22280)**		
Parameter	**T+D N=107**	**Ptz+T+D N=107**	**Ptz+T N=107**	**Ptz+D N=96**	**Ptz+T+FEC/ Ptz+T+D N=73**	**FEC/ Ptz+T+D N=75**	**Ptz+TCH N=77**
ypT0/is N0* n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]
ypT0/is* n (%) [95% CI][1]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs Ptz+T+D)	NA	NA	NA
ypT0 N0 * n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]

Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

Key to abbreviations (Table 4): T: trastuzumab; D: docetaxel; Ptz: Perjeta; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab.
* baseline lymph node status was determined histologically in <2 % of patients
1. 95% CI for one sample binomial using Pearson-Clopper method.
2. Treatment Ptz+T+D and-Ptz+T are compared with T+D, while Ptz+D is compared with Ptz+T+D
3. Approximate 95% CI for difference of two rates using Hauck-Anderson method.
4. p-value from Cochran-Mantel-Haenszel -test, with Simes multiplicity adjustment
5. Clinical response represents patients with a best overall response of CR or PR during the neoadjuvant period (in the primary breast lesion)

Metastatic Breast Cancer

Perjeta in combination with trastuzumab and docetaxel
WO20698/TOC4129g (CLEOPATRA)

CLEOPATRA is a multicentre, randomized, double-blind, placebo-controlled phase III clinical trial conducted in 808 patients with HER2-positive metastatic (n=789) or locally recurrent unresectable breast cancer (n=19) who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Breast tumour specimens were required to show HER2 overexpression defined as a score of 3+ by IHC or ISH amplification ratio ≥ 2.0 as determined at a central laboratory. Patients were randomized 1:1 to receive placebo + trastuzumab and docetaxel or Perjeta + trastuzumab and docetaxel. Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease free interval of at least 12 months before enrolment into the trial.

Perjeta was given intravenously as an initial dose of 840 mg, followed every three weeks thereafter by a dose of 420 mg. Trastuzumab was given intravenously as an initial dose of 8 mg/kg, followed every three weeks thereafter by 6 mg/kg. Patients were treated with Perjeta and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

At the time of the primary analysis, the mean number of cycles of study treatment received was 16.2 in the placebo treatment group and 19.9 in the Perjeta treated group.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumour assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT-B QoL (Functional Assessment of Cancer Therapy–Breast, Quality of Life) questionnaire.

Demographics were well balanced (median age was 54 years old, majority Caucasian (59%) and all were female with the exception of 2 patients). Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as oestrogen receptor positive and/or progesterone receptor positive), approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant therapy (192 patients [47.3%] in

the placebo treated group vs. 184 patients [45.8%] in the Perjeta treated group), and approximately 11 % of patients had received prior trastuzumab (41 patients [10.1%] in the placebo treated group vs. 47 patients [11.7%] in the Perjeta treated group). Of the 19 patients categorized as having locally recurrent, unresectable disease, 6 patients (2 in the placebo group and 4 in the Perjeta group) had metastases on their baseline assessment.

At the time of the primary PFS analysis, a total of 242 patients (59%) in the placebo treated group and 191 patients (47.5%) in the Perjeta treated group had IRF-confirmed progressive disease or had died within 18 weeks of their last tumour assessment.

At the time of the primary analysis, the CLEOPATRA study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR] = 0.62, 95% CI = 0.51, 0.75, p<0.0001) in the Perjeta treated group compared with the placebo treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo treated group vs. 18.5 months in the Perjeta treated group) (see Figure 1). At the time of the primary analysis, the results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS (median PFS was 12.4 months for placebo vs 18.5 months for Perjeta) (see Table 2). Consistent results were observed across pre-specified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see Figure 2).

The efficacy results from the CLEOPATRA trial are summarized in Table 3 below:

Table 4: Summary of efficacy from CLEOPATRA study

Parameter	**Placebo + trastuzumab + docetaxel (n=406)**	**Perjeta + trastuzumab + docetaxel (n=402)**	**HR (95% CI)**	**p-value**
Primary Endpoint:				
Progression-Free Survival (Independent review facility assessment) – primary endpoint*			0.62 [0.51;0.75]	<0.0001
No. of patients with an event	242 (59%)	191 (47.5%)		
Median months	12.4	18.5		
Secondary Endpoints:				
Overall Survival (Final analysis of OS)**			0.68 [0.56;0.84]	0.0002
No. of patients with an event*	221 (54.4%)	168 (41.8%)		
Median months	40.8	56.5		
Progression-Free Survival (investigator assessment)			0.65 [0.54;0.78]	<0.0001
No. of patients with an event	250 (61.6%)	201 (50.0%)		
Median months	12.4	18.5		
Objective Response Rate (ORR)				
No. of patients with an event	336	343		
Responders***	233 (69.3 %)	275 (80.2 %)	Difference in ORR: 10.8% [4.2,17.5]%	0.0011
95% CI for ORR	[64.1; 74.2]	[75.6; 84.3]		
Complete response (CR)	14 (4.2 %)	19 (5.5 %)		
Partial Response (PR)	219 (65.2 %)	256 (74.6 %)		
Stable disease (SD)	70 (20.8 %)	50 (14.6 %)		
Progressive disease (PD)	28 (8.3 %)	13 (3.8 %)		
Duration of Response ^#				

n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;64]	[71;106]		

* Primary progression-free survival analysis, cutoff date 13 May 2011
** Final analysis of overall survival, cutoff date 11 February 2014
*** Patients with best overall response of confirmed CR or PR by RECIST.
^ Evaluated in patients with best Overall Response of CR or PR
# Objective response rate and duration of response are based on IRF-assessed tumour assessments

Figure 1: Kaplan-Meier curve of IRF-assessed progression-free survival

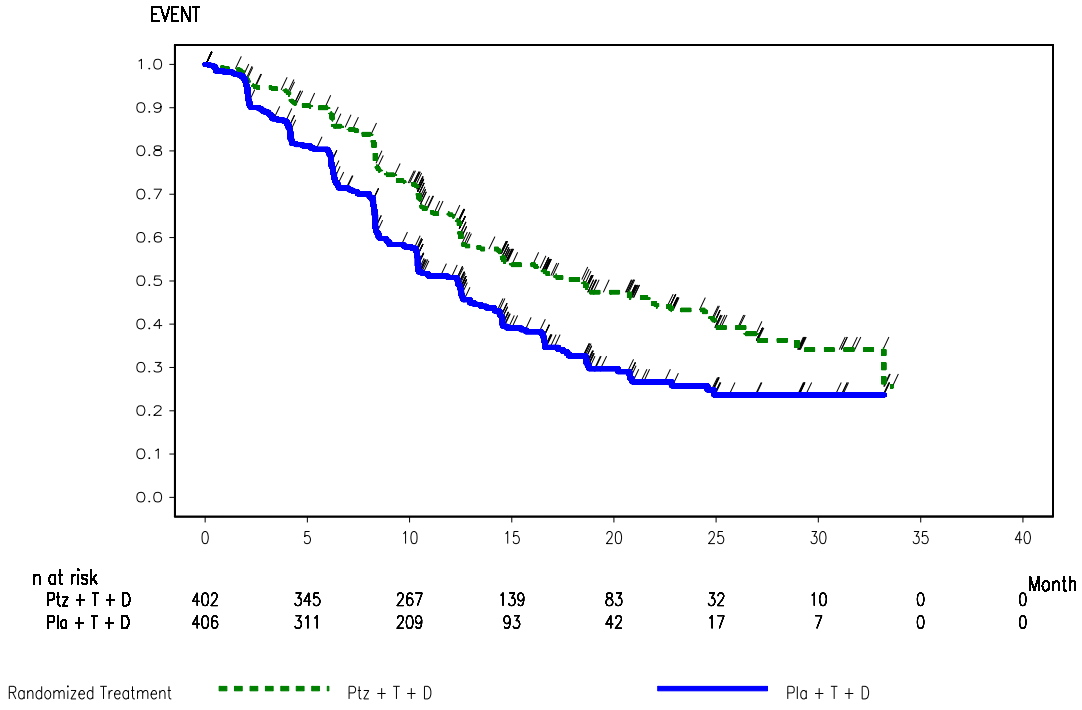
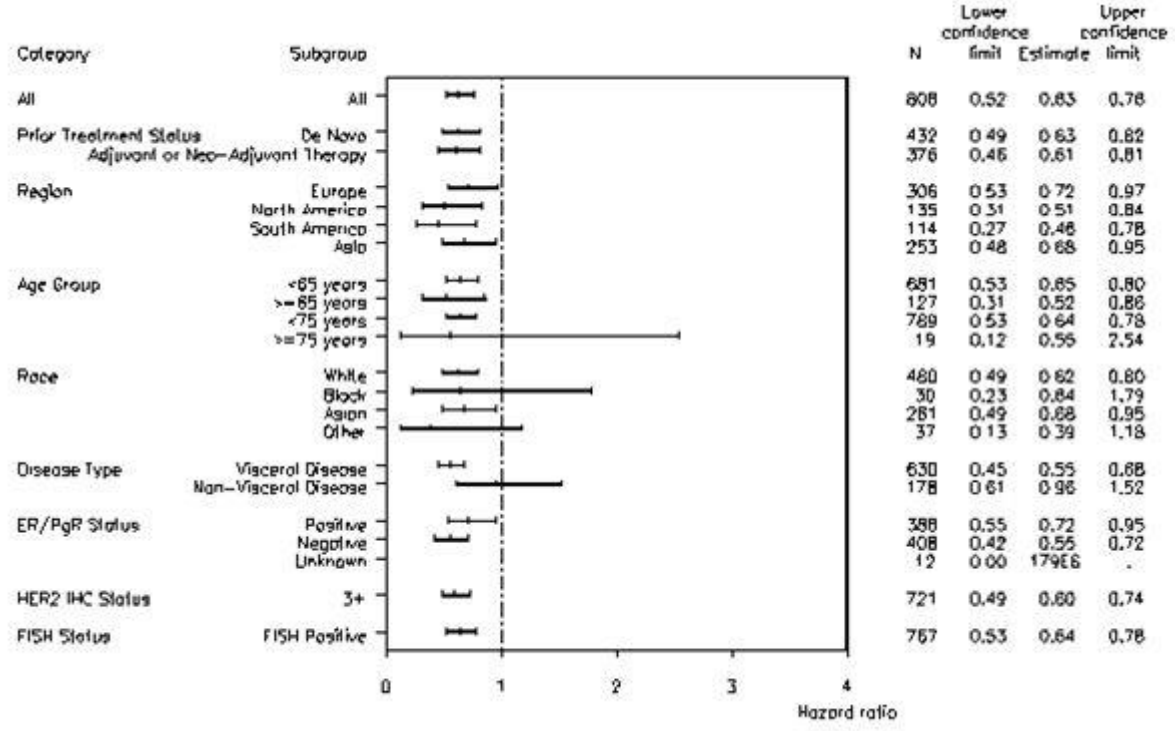


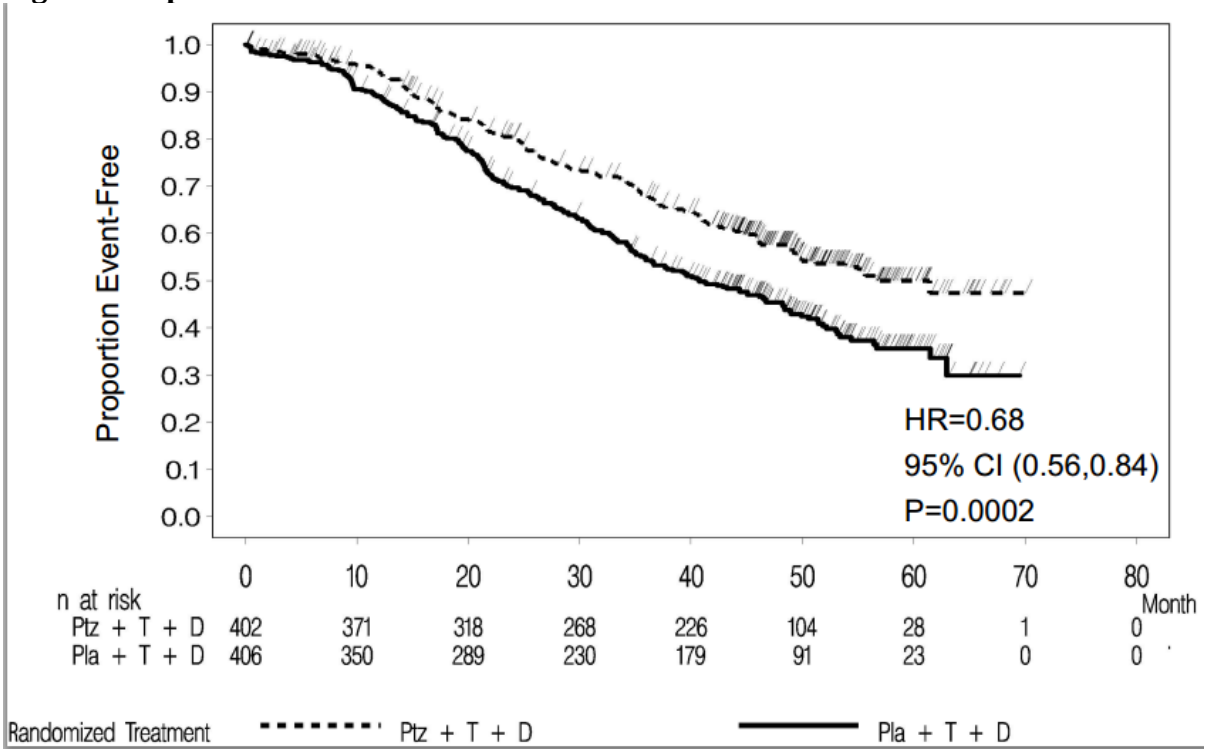
Figure 2: IRF assessed PFS by patient subgroup



At the primary analysis of efficacy an interim analysis of OS showed a strong trend suggestive of a survival benefit in favour of the Perjeta treated group.

The final analysis of OS was performed when 389 patients had died (221 in the Placebo-treated group and 168 in the Perjeta-treated group). The statistically significant OS benefit in favour of the Perjeta-treated group was maintained (HR 0.68, p = 0.0002 log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the Perjeta-treated group (see Table 3, Figure 3).

Figure 3 Kaplan-Meier curve of overall survival



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab (Perjeta); T=trastuzumab (Herceptin);

There was no statistically significant difference between treatment groups in Health Related Quality of Life as assessed by time to symptom progression on the FACT-B TOI-PFB subscale, defined as a 5 point reduction in subscale score (HR =0.97, 95% CI =0.81; 1.16).

Immunogenicity

Patients in the pivotal trial CLEOPATRA were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Perjeta. Approximately 6.2% (23/372) of patients in the placebo treated group and 2.8% (11/386) of patients in the Perjeta treated group tested positive for ATA. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to ATA.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Perjeta with the incidence of antibodies to other products may be misleading.

5.2 PHARMACOKINETIC PROPERTIES

Across multiple clinical trials, in various indications, there was no change in clearance of pertuzumab at doses of 2-25 mg/kg. Based on a population PK analysis that included 444 patients, the median clearance (CL) of pertuzumab was 0.239 L/day and the median half-life was 17.2 days.

The population PK analysis suggested no PK differences based on age, gender and ethnicity (Japanese versus non-Japanese). Baseline albumin and lean body weight were the most significant covariates influencing CL. Clearance decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses performed at the recommended dose and schedule of Perjeta showed that at the extreme values of these two covariates, there was no significant impact on the ability to

achieve target steady-state concentrations identified in preclinical tumour xenograft models. Therefore, there is no need to adjust the dosage of pertuzumab based on these covariates.

The PK results of pertuzumab in the NEOSPHERE study were consistent with the predictions from the previous population PK model.

Absorption

Pertuzumab is administered as an intravenous (IV) infusion. There have been no studies performed with other routes of administration.

Distribution

Across all clinical studies, the volume of distribution of the central (Vc) and the peripheral (Vp) compartment in the typical patient, was 3.11L and 2.46L, respectively.

Metabolism

The metabolism of pertuzumab has not been directly studied. Antibodies are cleared principally by catabolism.

Excretion

The median clearance (CL) of pertuzumab was 0.235 L/day and the median half-life was 18 days.

Pharmacokinetics in special populations

Elderly

No dedicated pertuzumab studies have been conducted in elderly patients. In a population PK analysis, age was not found to significantly affect PK of pertuzumab. In the population PK analysis, 32.5% (n=143) patients were ≥65 years of age and 9.1% (n=40) patients were ≥75 years of age.

Renal Impairment

No formal PK study has been conducted in patients with renal impairment. Based on the population PK analysis, renal impairment is not expected to influence pertuzumab exposure; however, only limited data from patients with moderate and severe renal impairment were included in the population PK analysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies have not been performed to evaluate the mutagenic potential of pertuzumab.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab.

Other

In cynomolgus monkeys, weekly IV administration of pertuzumab at doses up to 150 mg/kg/dose were generally well tolerated. With doses of 15 mg/kg and higher intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhoea-related dehydration which were managed with IV fluid replacement therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Sucrose
Polysorbate 20
Histidine
Acetic acid, glacial

6.2 INCOMPATIBILITIES
No incompatibilities between Perjeta and polyvinylchloride (PVC), polyethylene or non-PVC polyolefin bags have been observed.

Glucose (5%) solution should not be used to dilute Perjeta since it is chemically and physically unstable (diluted formulations of pertuzumab concentrate solution in Glucose (5%) IV bags did not maintain stable pH after storage at room temperature (27-33°C) for 24 hours followed by 24 hours at 2-8°C).

Perjeta should not be mixed or diluted with other drugs.

6.3 SHELF LIFE
Unopened vial
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Diluted solution
The Perjeta infusion solution, diluted in PVC or non-PVC polyolefin bags, may be stored at 2°C–8°C for up to 24 hours prior to use. Diluted Perjeta has been shown to be stable for up to 24 hours (up to 30°C) however, since diluted Perjeta contains no preservative, the diluted solution should be refrigerated (2°C–8°C).

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store vials in a refrigerator at 2°C-8°C. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

6.5 NATURE AND CONTENTS OF CONTAINER
Vial (Type I glass) with a stopper (butyl rubber) containing 14 ml of solution.

Pack of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
The release of medicines into the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

For instructions on dilution of the product before administration, see section 4.2.

6.7 PHYSIOCHEMICAL PROPERTIES
CAS: 380610-27-5

Perjeta (pertuzumab) is a recombinant humanized monoclonal antibody. The antibody is based upon the human IgG_1 kappa framework sequence, with a molecular weight of ~

148kDa and composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

6 May 2013

10. DATE OF REVISION OF THE TEXT

25 July 2018

Summary table of changes

Section Changed	Summary of new information
All sections	New PI format, changes to cross references, new mandatory text added
8	Updated sponsor address
4.8	Addition of Post marketing sub heading and adverse reaction of tumour lysis syndrome