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 List of Excipients.

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

Early Breast Cancer
Perjeta is indicated in combination with trastuzumab and chemotherapy for:

- the neoadjuvant treatment of patients with HER2-positive inflammatory or locally advanced, or early stage (either > 2 cm in diameter or node positive) breast cancer as part of a complete treatment regimen for early breast cancer
- the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

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

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.

DO NOT ADMINISTER PERJETA AS AN IV PUSH OR BOLUS.

Metastatic and Early Breast Cancer

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. An observation period of 30-60 minutes is recommended after completion of each Perjeta infusion. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy (see section 4.4 Special Warnings and Precautions for Use).

Perjeta and trastuzumab should be administered sequentially and not mixed in the same infusion bag. Perjeta and trastuzumab can be given in any order. When administered with Perjeta the recommendation is to follow a 3 weekly schedule for trastuzumab administered as either:

- an IV infusion with an initial loading dose of trastuzumab 8 mg/kg body weight followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight
- a fixed subcutaneous dose of trastuzumab by injection (600 mg) every 3 weeks irrespective of the patient's body weight

In patients receiving a taxane, Perjeta and trastuzumab should be administered prior to the taxane.

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.

In patients receiving an anthracycline-based regimen, Perjeta and trastuzumab should be administered following completion of the entire anthracycline regimen (see section 4.4. Special Warnings and Precautions for Use).

Duration of treatment

Metastatic Breast Cancer (MBC)

Perjeta should be administered in combination with trastuzumab and docetaxel until disease progression or unmanageable toxicity. Treatment with Perjeta and trastuzumab may continue even if treatment with docetaxel is discontinued.

Early Breast Cancer (EBC)

In the neoadjuvant setting (before surgery) it is recommended that patients are treated with Perjeta for three to six cycles depending on the regimen chosen, in combination with trastuzumab and chemotherapy, as part of a complete regimen for early breast cancer (see section 5.1 Pharmacodynamic Properties).

In the adjuvant setting (after surgery), Perjeta should be administered in combination with trastuzumab for a total of one year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity,

whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline and/or taxane-based chemotherapy. Perjeta and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see section 5.1 Pharmacodynamic Properties).

Patients who start Perjeta and trastuzumab in the neoadjuvant setting, should continue to receive adjuvant Perjeta and trastuzumab to complete one year of treatment (maximum 18 cycles).

Dose modifications

Perjeta should be discontinued if trastuzumab treatment is discontinued.

Dose reductions are not recommended for Perjeta.

Trastuzumab dose reductions are not recommended (see trastuzumab prescribing information).

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

Infusion-related reactions

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

Hypersensitivity reactions/anaphylaxis

The infusion should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see section 4.4 Special Warnings and Precautions for Use).

Left ventricular dysfunction

Perjeta and trastuzumab should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. Perjeta should be discontinued if symptomatic heart failure is confirmed.

See section 4.4 Special Warnings and Precautions for Use for further information on dose recommendations in the event of left ventricular dysfunction.

Special populations

Elderly

No overall differences in efficacy and safety of Perjeta were observed in patients ≥65 and <65 years of age with the exception of diarrhoea, which had an increased incidence in patients ≥65 years of age. No dose adjustment is required in the elderly population (≥65 years of age). Limited data are available in patients >75 years of age (see section 4.4 Special Warnings and Precautions for Use).

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 Pharmacokinetic Properties).

Hepatic impairment

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

Delayed or missed doses

For recommendations on delayed or missed doses, please refer to Table 1 below.

Table 1 – Recommendations for delayed or missed doses

Time between two Sequential doses	Perjeta	Trastuzumab	
		IV	SC
< 6 weeks	The 420 mg dose of Perjeta IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The 6 mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The fixed dose of 600mg Herceptin SC should be administered as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	The loading dose of 840 mg Perjeta IV should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered over a period of 30 to 60 minutes every 3 weeks thereafter.	The loading dose of 8 mg/kg trastuzumab IV should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered over a period of 30 or 90 minutes every 3 weeks thereafter.	

Method of Administration

Instructions for dilution

Perjeta should be prepared by a healthcare professional using aseptic technique. Use a sterile needle and syringe to prepare Perjeta. 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% or alternatively 0.45% sodium chloride (do not withdraw saline out of the infusion bag). After dilution 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% or alternatively 0.45% 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 Incompatibilities).

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 Special Precautions for Storage).

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. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

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

Cardiac failure and left ventricular dysfunction

Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Perjeta. The incidence of symptomatic left ventricular systolic dysfunction (LVD) [congestive heart failure] was higher in patients treated with Perjeta in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy (see section 4.8 Adverse Effects (Undesirable Effects)).

Perjeta has not been studied in patients with: a pre-treatment LVEF value of < 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or 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 > 360 mg/m^2 of doxorubicin or its equivalent.

Assess LVEF prior to initiation of Perjeta and at regular intervals during treatment with Perjeta (e.g. once during neoadjuvant treatment and every 12 weeks in the adjuvant or metastatic setting) to ensure that LVEF is within normal limits. If the LVEF has declined as indicated in section 4.2 Dose and Method of Administration and has not improved, or has declined further at the subsequent assessment, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Perjeta with an anthracycline. Based on the pharmacological actions of HER2-targeted agents and anthracyclines, the risk of cardiac toxicity might be expected to be higher with concomitant use of Perjeta and anthracyclines than with sequential use.

Sequential use of Perjeta (in combination with trastuzumab and a taxane) has been evaluated following the epirubicin or doxorubicin component of many anthracycline-based regimens in the APHINITY and BERENICE studies. However, only limited safety data are available on concurrent use of Perjeta and an anthracycline. In the TRYPHAENA study, Perjeta was given concurrently with epirubicin, as part of the FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen (see section 4.8 Adverse Effects (Undesirable Effects) and section 5.1 Pharmacodynamic Properties). Only chemotherapy-naive patients were treated and they received low cumulative doses of epirubicin (up to 300 mg/m^2).

In this study, cardiac safety was similar to that observed in patients given the same regimen but with Perjeta administered sequentially (following FEC chemotherapy).

Table 2 – Dose Modifications for Left Ventricular Dysfunction

<table>
<tr><th></th><th>Pre-treatment LVEF:</th><th>Monitor LVEF every:</th><th colspan="2">Withhold Perjeta and trastuzumab for at least 3 weeks for an LVEF decrease to:</th><th colspan="2">Resume Perjeta and trastuzumab after 3 weeks if LVEF has recovered to:</th></tr>
<tr><td rowspan="2">Metastatic Breast Cancer</td><td rowspan="2">≥50%</td><td rowspan="2">~ 12 weeks</td><td colspan="2">Either</td><td colspan="2">Either</td></tr>
<tr><td><40%</td><td>40%-45% with a fall of ≥ 10% points below pre-treatment value</td><td>>45%</td><td>40%-45% with a fall of <10% points below pre-treatment value</td></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥55%*</td><td rowspan="2">~ 12 week
(once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10% points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥50%</td><td>< 10% points below pre-treatment value</td></tr>
</table>

*for patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines before starting Perjeta and trastuzumab

Patients with metastatic breast cancer

Patients should have a pre-treatment left ventricular ejection fraction (LVEF) of ≥ 50%. Perjeta and trastuzumab should be withheld for at least 3 weeks for:

- a drop in LVEF to less than 40%
- a LVEF of 40-45% associated with a fall of ≥ 10% points below pre-treatment value.

Perjeta and trastuzumab may be resumed if the LVEF has recovered to > 45%, or to 40-45% associated with a difference of < 10% points below pre-treatment values.

Patients with early breast cancer

Patients should have a pre-treatment LVEF of ≥ 55% (≥ 50% after completion of the anthracycline component of chemotherapy, if given). Perjeta and trastuzumab should be withheld for at least 3 weeks for:

- a drop in LVEF to less than 50% associated with a fall of ≥ 10% points below pre-treatment values.

Perjeta and trastuzumab may be resumed if the LVEF has recovered to ≥ 50%, or to a difference of < 10% points below pre-treatment values.

Infusion related reactions

Perjeta has been associated with infusion related reactions, including events with fatal outcomes (see 4.8 Adverse Effects (Undesirable Effects)). 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 Dosage and Method of Administration).

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes have been observed in patients treated with Perjeta (see section 4.8 Adverse Effects (Undesirable Effects)). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. The infusion should be discontinued immediately and permanently if the patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.2 Dose and Method of Administration (Undesirable Effects)). Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or to any Perjeta excipients (see section 4.3 Contraindications).

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 post-marketing 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.

Diarrhoea

Perjeta may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (> 65 years) may have a higher risk of diarrhoea compared with younger patients (< 65 years). Treat diarrhoea according to standard practice and guidelines. Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment with Perjeta

should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with Perjeta may be reinstated.

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 overall differences of safety and efficacy of Perjeta were observed in patients ≥65 and <65 years of age with the exception of diarrhoea, which had an observed increase in incidence in patients ≥65 years of age (see section 4.2 Dose and Method of Administration).

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 pertuzumab and trastuzumab and between pertuzumab and docetaxel. In addition, no clinically relevant pharmacokinetic interaction of co-administered docetaxel or trastuzumab on pertuzumab was evident based on the population pharmacokinetics analysis. This lack of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

Five studies have evaluated the effects of pertuzumab on the pharmacokinetics of co-administered cytotoxic agents; docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin and erlotinib. There was no evidence of any pharmacokinetics interaction between pertuzumab and any of these agents. The pharmacokinetics of pertuzumab 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.

Contraception: Women of child-bearing potential, including those who are partners of male patients should use effective contraception while receiving Perjeta and for 7 months following the last dose of

Perjeta in combination with trastuzumab. This is the length of time trastuzumab can remain in the body after stopping treatment.

There are no studies of Perjeta in pregnant women, however Perjeta is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy.

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. Therefore, based on these animal studies and the mechanism of action Perjeta is considered to have the potential to cause fetal harm when administered to a pregnant woman.

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 Pharmacokinetic Properties).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

. Perjeta has a minor influence on the ability to drive and use machines. Dizziness may occur during treatment with Perjeta ((see section 4.8 Adverse Effects (Undesirable Effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of Perjeta has been evaluated in more than 6000 patients in Phase I- III trials conducted in patients with various malignancies, and predominantly treated with Perjeta in combination with other anti-neoplastic agents. Those studies included the pivotal trials CLEOPATRA (n=808), NEOSPHERE (n=417), TRYPHAENA (n=225) and APHINITY (n=4804) (pooled in Table 3). The safety of Perjeta was generally consistent across studies, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether Perjeta was administered as monotherapy or in combination with other anti-neoplastic agent(s).

Metastatic and Early Breast Cancer

Table 3 summarizes the ADRs from the Perjeta-treatment arms of the following pivotal clinical trials:

- CLEOPATRA, in which Perjeta was given in combination with trastuzumab and docetaxel to patients with MBC (n=453)
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which neoadjuvant Perjeta was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or EBC
- APHINITY, in which adjuvant Perjeta was given in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxane-containing chemotherapy to patients with EBC (n=2364)

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).

The most common ADRs (≥30%) from this pooled data were diarrhoea, alopecia, nausea, fatigue, neutropenia, and vomiting. The most common NCI-CTCAE Grade 3-4 ADRs (≥10%) were neutropenia and febrile neutropenia.

Table 3 – Summary of adverse drug reactions in patients treated with Perjeta ^

ADR (MedDRA Preferred Term) **System Organ Class**	**Perjeta + trastuzumab + chemotherapy^^** **n = 3344^^^ (100%)** **Frequency rate %**		**Frequency category**
	All Grades %	**Grades 3-4 %**	
Blood and lymphatic system disorders			
Neutropenia	31.4	24.2	Very common
Anaemia	24.8	5.7	Very common
Leukopenia	10.8	6.1	Very common
Febrile neutropenia*	11.9	11.8	Very common
Cardiac disorders			
Left ventricular dysfunction**	1.4	0.3	Common
Cardiac failure congestive**	0.1	<0.1	Uncommon
Eye disorders			
Lacrimation increased	12.1	-	Very common
Gastrointestinal disorders			
Diarrhoea	67.9	8.9	Very common
Nausea	60.8	1.9	Very common
Vomiting	30.0	1.7	Very common
Stomatitis	24.9	1.6	Very common
Constipation	24.5	0.4	Very common
Dyspepsia	13.2	<0.1	Very common
Abdominal pain	11.7	0.4	Very common
General disorders and administration site conditions			
Fatigue	44.3	3.3	Very common
Mucosal inflammation	23.2	1.5	Very common
Asthenia	20.9	1.5	Very common
Pyrexia	18.9	0.6	Very common
Oedema peripheral	16.2	<0.1	Very common
Chills	4.7	-	Common
Pain	6.0	0.2	Common
Oedema	6.1	0.1	Common
Immune system disorders			
Infusion related reaction	3.7	<0.1	Common
Drug hypersensitivity	2.5	0.4	Common

ADR (MedDRA Preferred Term) System Organ Class	Perjeta + trastuzumab + chemotherapy^^ n = 3344^^^ (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Hypersensitivity	3.3	0.4	Common
Anaphylactic reaction	0.2	0.1	Uncommon
Cytokine release syndrome	<0.1	-	Rare
Infections and infestations			
Upper respiratory tract infection	9.5	0.3	Common
Nasopharyngitis	12.8	<0.1	Very common
Paronychia	3.9	<0.1	Common
Metabolism and nutrition disorders			
Decreased appetite	23.1	0.8	Very common
Musculoskeletal and connective tissue disorders			
Myalgia	24.3	0.8	Very common
Arthralgia	24.6	0.7	Very common
Pain in extremity	10.0	0.2	Very common
Nervous system disorders			
Headache	21.8	0.4	Very common
Dysgeusia	22.7	<0.1	Very common
Neuropathy peripheral	14.7	0.7	Very common
Dizziness	11.2	0.1	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Paraesthesia	10.2	0.4	Very common
Psychiatric disorders			
Insomnia	15.9	0.2	Very common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.6	<0.1	Very common
Cough	15.5	<0.1	Very common
Dyspnoea	11.5	0.5	Very common
Pleural effusion	0.9	<0.1	Uncommon
Interstitial lung disease	0.1	<0.1	Uncommon
Skin and subcutaneous tissue disorders			
Alopecia	63.1	<0.1	Very common
Rash	26.4	0.5	Very common
Nail disorder	12.9	0.3	Very common
Pruritus	12.9	<0.1	Very common
Dry skin	11.7	<0.1	Very common
Vascular disorders			

ADR (MedDRA Preferred Term) System Organ Class	Perjeta + trastuzumab + chemotherapy^^ n = 3344^^^ (100%) Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Hot flush	15.7	0.1	Very common

^ Table 3 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); and from the treatment period of APHINITY (median number of cycles of Perjeta was 18).

^^ In NEOSPHERE, 108 patients received Perjeta + trastuzumab alone without docetaxel and 94 patients received Perjeta + docetaxel without trastuzumab.

^^^ 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 Special Warnings and Precautions for Use).

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 6.9% in the group treated with Perjeta plus trastuzumab and 5-fluorouracil, epirubicin and cyclophosphamide (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 Special Warnings and Precautions for Use).

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 Special Warnings and Precautions for Use).

In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense AC followed by Perjeta plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (PT ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by Perjeta plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was <1% (0.6% of Perjeta-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of Perjeta-treated patients and 66.8% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cut-off. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% were reported in 2.7% of Perjeta-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of Perjeta-treated patients and 80.6% of placebo-treated patients had recovered at the data cut-off.

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 Special Warnings and Precautions for Use).

In neoadjuvant and adjuvant trials, Perjeta was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 18.6% - 25.0% of patients on the first day of Perjeta administration (in combination with trastuzumab and chemotherapy). The type and severity of events 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 Special Warnings and Precautions for Use).

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 neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, one patient in the Perjeta and docetaxel treated group experienced anaphylaxis. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2% and 7.6%, respectively), of which 2.6% and 1.3% of events respectively were NCI-CTCAE grade 3-4.

Laboratory Abnormalities
In the pivotal trials CLEOPATRA, NEOSPHERE and APHINITY the incidence of NCI-CTCAE grade 3-4 decreases in neutrophil counts were balanced in the Perjeta-treated and control groups.

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 4: 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

HER2 overexpression was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥2.0 in the trials outlined below.

Early 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 Special Warnings and Precautions for Use) 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.

Perjeta and trastuzumab were administered intravenously (see section 4.2 Dose and Method of Administration) for 4 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 5. 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.

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 and trastuzumab were administered intravenously as outlined in section 4.2 Dose and Method of Administration. 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 5). 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 5: 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]

	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* 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: 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)

BERENICE (WO29217)
BERENICE is a non-randomised, open-label, multi-center, multi-national, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer.

The BERENICE study included two parallel groups of patients. Patients considered suitable for neoadjuvant treatment with trastuzumab plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

- Cohort A - 4 cycles of two weekly doxorubicin and cyclophosphamide (dose dense AC) followed by 4 cycles of Perjeta in combination with trastuzumab and paclitaxel
- Cohort B - 4 cycles of FEC followed by 4 cycles of Perjeta in combination with trastuzumab and docetaxel

Perjeta and trastuzumab were administered intravenously as outlined in DOSAGE AND ADMINISTRATION. Doxorubicin 60 mg/m2 IV and cyclophosphamide 600 mg/m2 IV were administered every 2 weeks (ddAC) for four cycles (Cycles 1-4) with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m2 IV weekly for 12 weeks (Cycles 5-8), with Perjeta and trastuzumab every 3 weeks during Cycles 5-8 (from the start of paclitaxel; four cycles of Perjeta and trastuzumab in total during the neoadjuvant period). 5-Fluorouracil (500 mg/m2), epirubicin (100 mg/m2), cyclophosphamide (600 mg/m2) were given intravenously every three weeks for 4 cycles. Docetaxel was given at an initial dose of 75 mg/m2 IV infusion every three weeks with the option to escalate to 100 mg/m2 at the investigator's discretion if

the initial dose was well tolerated. Following surgery all patients received Perjeta and trastuzumab which were administered intravenously every 3 weeks, to complete one year of therapy.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (*see ADVERSE EFFECTS*). Key secondary endpoints at the time of primary analysis were neoadjuvant safety and pCR rate in the breast and nodes (i.e. ypT0/is ypN0). Long-term clinical and safety outcomes will also be assessed (iDFS, EFS and OS, not yet available).

Demographics of the patients were well balanced between the groups. The median age of the patients was 49 years, the majority of patients were Caucasian (83%) and all but one patient was female. Approximately two-thirds of patients (64.3% [n=128] in Cohort A and 61.7% [n=124] in Cohort B) had hormone receptor-positive disease.

High pCR rates were observed in both treatment arms, with pCR (ypT0/is ypN0) rates of 61.8% in Cohort A and 60.7% in Cohort B. 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 in both Cohorts (51.6% to 81.5% and 57.3% to 68.0% respectively).

APHINITY (BO25126)
APHINITY is a multicenter, randomised, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumour excised prior to randomisation. Patients were then randomised to receive Perjeta or placebo, in combination with adjuvant trastuzumab and chemotherapy. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

- 3 or 4 cycles of FEC or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel, or
- 4 cycles of AC or EC, followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel, or
- 6 cycles of docetaxel in combination with carboplatin

Perjeta and trastuzumab were administered intravenously (see DOSAGE AND ADMINISTRATION) every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical practice.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomisation to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause.

Demographics were well balanced between the two treatment arms. The median age was 51 years, and over 99% of patients were female. The majority of patients had node-positive (63%) and/or hormone receptor-positive disease (64%), and were Caucasian (71%).

After a median follow-up to 45.4 months, the APHINITY study demonstrated 19% (hazard ratio [HR] = 0.81) reduction in risk of recurrence or death in patients randomised to receive Perjeta compared with patients randomised to receive placebo.

The efficacy results from the APHINITY trial are summarised in Table 6 and in Figures 1 and 2.

Table 6: Overall Efficacy (ITT Population)

	Perjeta + trastuzumab + chemotherapy n=2400	**Placebo + trastuzumab + chemotherapy n=2404**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value (Log-Rank test, stratified[2])	0.0446	
3 year event-free rate[3] [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI]	0.82 [0.68, 0.99]	
p-value (Log-Rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
Disease Free Survival (DFS)		
Number (%) of patients with event	192 (8.0%)	236 (9.8%)
HR [95% CI]	0.81 [0.67, 0.98]	
p-value (Log-Rank test, stratified[2])	0.0327	
3 year event-free rate[3] [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
Overall Survival (OS)[4]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value (Log-Rank test, stratified[2])	0.4673	
3 year event-free rate[3] [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]
Recurrence Free Interval (RFI)		
Number (%) of patients with event	138 (5.8%)	173 (7.2%)
HR [95% CI]	0.79 [0.63, 0.99]	
p-value (Log-Rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	95.2 [94.3, 96.1]	94.3 [93.3, 95.2]
Distant recurrence-free interval (DRFI)		
Number (%) of patients with event	119 (5.0%)	145 (6.0%)
HR [95% CI]	0.82 [0.64, 1.04]	
p-value (Log-Rank test, stratified[2])	0.1007	
3 year event-free rate[3] [95% CI]	95.7 [94.9, 96.5]	95.1 [94.3, 96.0]

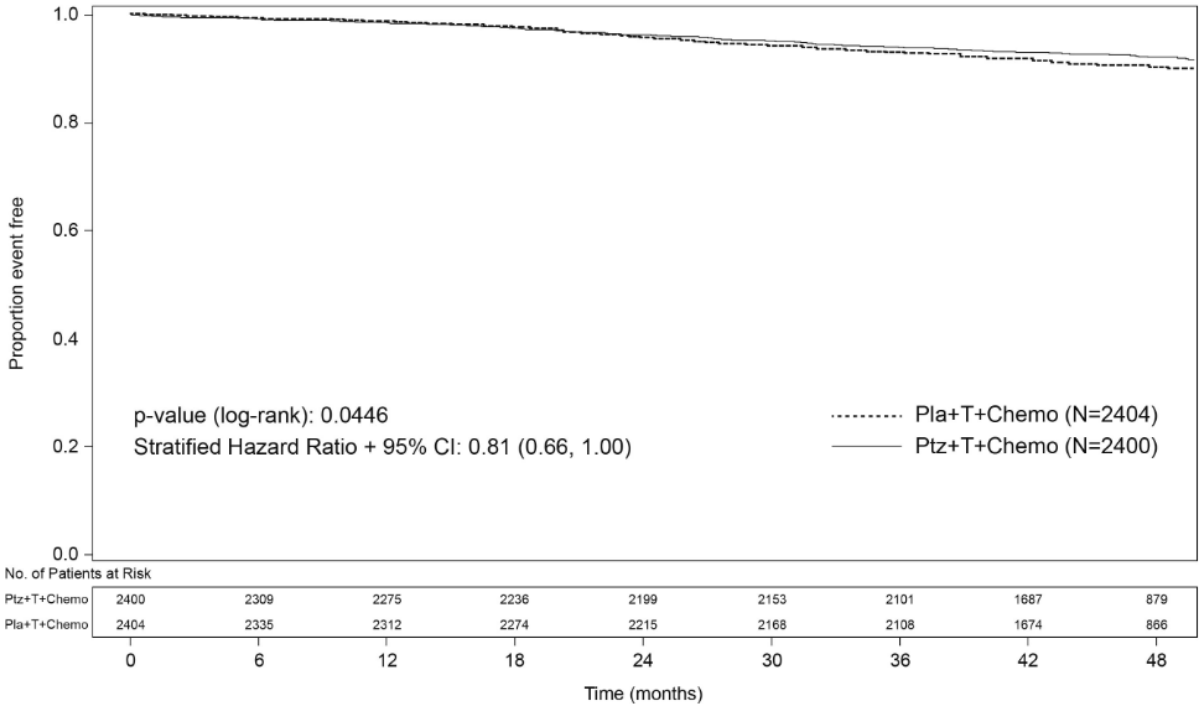
Key to abbreviations: HR: Hazard Ratio; CI: Confidence Intervals

1. Hierarchical testing applied for all secondary endpoints with the exception of RFI and DRFI

2. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen

3. 3-year event-free rate derived from Kaplan-Meier estimates
4. Data from first interim analysis

Figure 1: Kaplan-Meier curve of invasive disease free survival

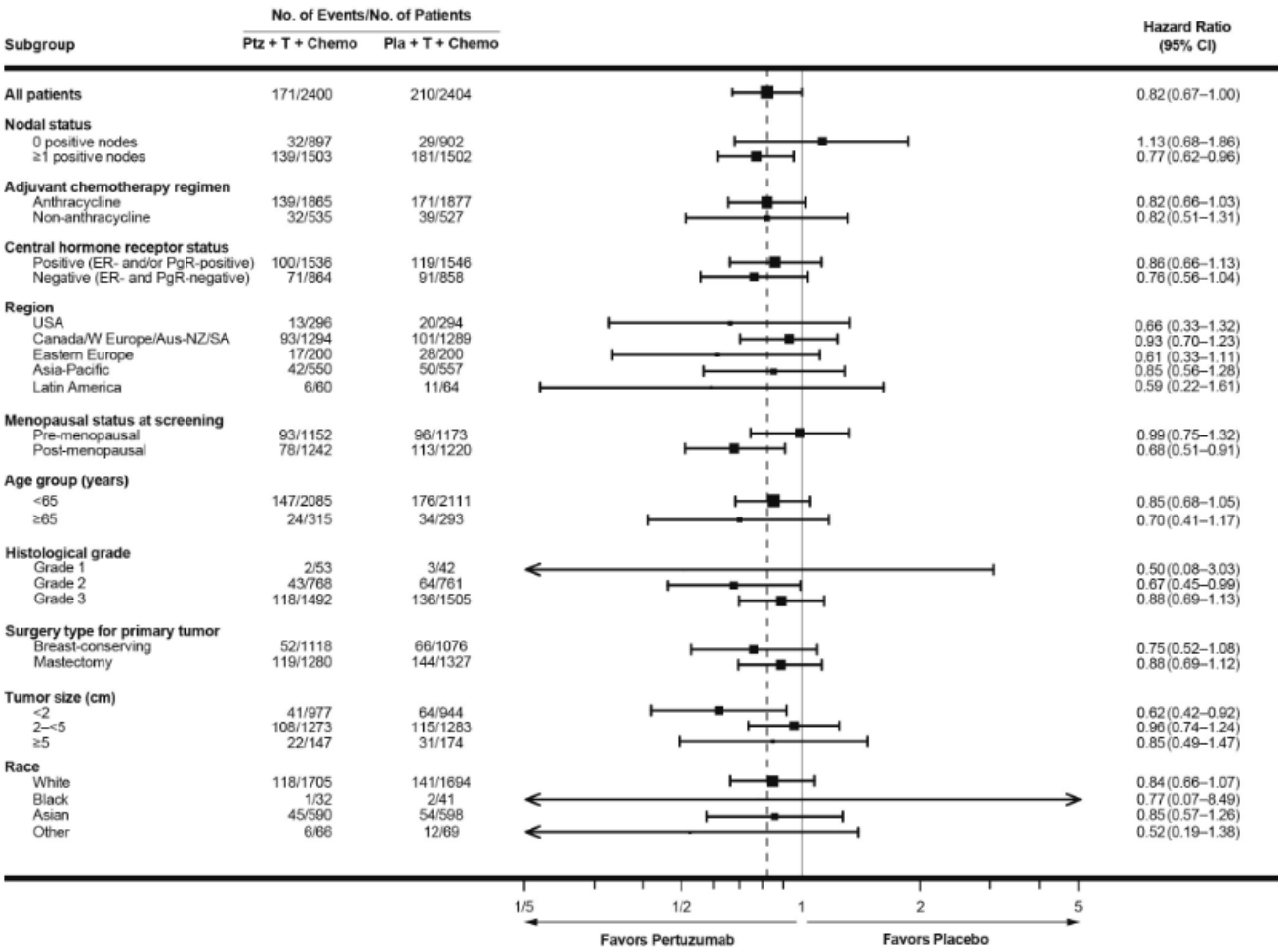


Pla = placebo; Ptz = Perjeta; T = trastuzumab

The estimate of IDFS at 4-years was 92.3% in the Perjeta-treated group versus 90.6% in the placebo-treated group. At the time of the estimate the median follow-up was 45.4 months.

Results of Subgroup Analysis
Consistent results were observed across the majority of pre-specified patient subgroups. The benefits of Perjeta were more apparent for patients in certain high risk groups, notably patients with node-positive or hormone receptor-negative disease.

Figure 2: Forest plot of invasive disease free survival by subgroup



Pla = placebo; Ptz = Perjeta; T = trastuzumab

Estimates of IDFS rates in the node positive subgroup were 92.0% versus 90.2% at 3 years and 89.9% vs. 86.7% at 4 years in Perjeta-treated patients versus the placebo-treated patients, respectively. In the node negative subgroup estimates of IDFS rates were 97.5% versus 98.4% at 3 years and 96.2% versus 96.7% at 4 years in Perjeta-treated patients versus placebo-treated patients, respectively. In the hormone receptor-positive subgroup estimates of IDFS were 94.8% versus 94.4% at 3 years and 93.0% versus 91.6% at 4 years in Perjeta-treated patients versus placebo-treated patients, respectively. In the hormone receptor-negative subgroup estimates of IDFS rates were 92.8% versus 91.2% at 3 years and 91.0% versus 88.7% at 4 years in PERJETA-treated patients versus placebo-treated patients, respectively.

Patient Reported Outcomes (PRO)

Secondary endpoints included the assessment of patient-reported global health status, role and physical function, and treatment symptoms using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. In the analyses of patient-reported outcomes, a 10-point difference was considered clinically meaningful.

Patients' physical function, global health status and diarrhoea scores showed a clinically meaningful change during chemotherapy in both treatment arms. The mean decrease from baseline at that time for physical function was -10.7 (95% CI-11.4, -10.0) in the Perjeta arm and -10.6 (95% -11.4, -9.9) in the placebo arm; global health status was -11.2 (95% CI -12.2, -10.2) in the Perjeta arm and -10.2 (95% CI -11.1,-9.2) in the placebo arm. Change in diarrhoea symptoms increased to +22.3 (95% CI 21.0, 23.6) in the Perjeta arm versus +9.2 (95% CI 8.2, 10.2) in the placebo arm.

Thereafter in both arms, physical function and global health status scores returned to baseline levels during targeted treatment. Diarrhoea symptoms returned to baseline after HER2 therapy in the Perjeta-arm. The addition of Perjeta to trastuzumab plus chemotherapy did not affect patients' overall role function over the course of the study.

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. 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 and trastuzumab were administered intravenously as outlined in section 4.2 Dose and Method of Administration. 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 3). 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 7). 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 4).

The efficacy results from the CLEOPATRA trial are summarized in Table 7 below:

Table 7: 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	
95% CI for ORR	[64.1; 74.2]	[75.6; 84.3]	in ORR:	
Complete response (CR)	14 (4.2 %)	19 (5.5 %)	10.8%	0.0011
Partial Response (PR)	219 (65.2 %)	256 (74.6 %)	[4.2,17.5]%	
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 3: Kaplan-Meier curve of IRF-assessed progression-free survival

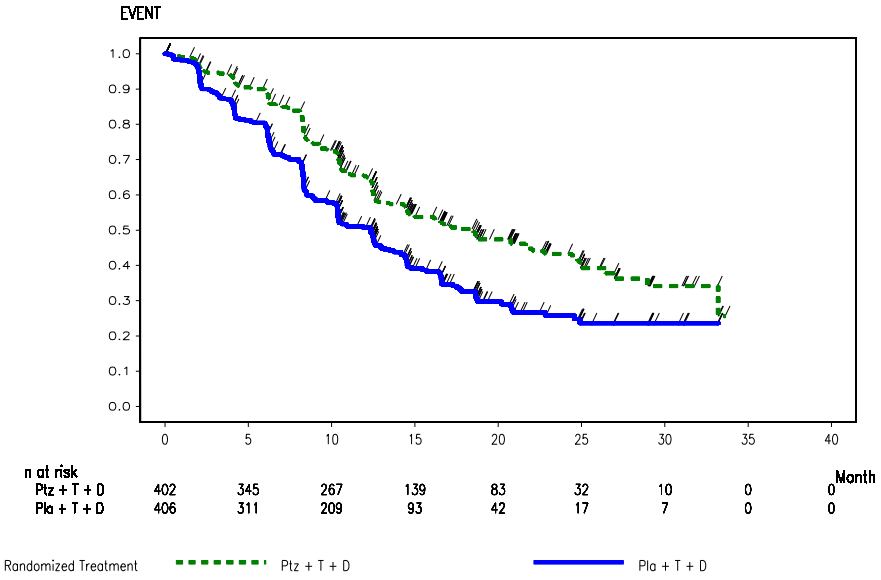
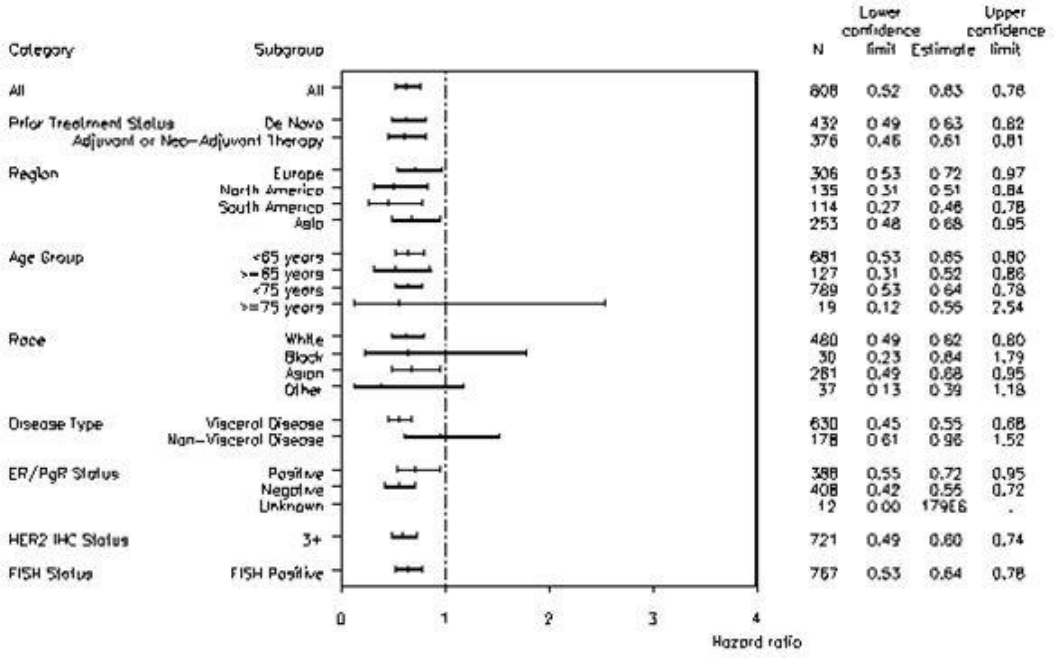


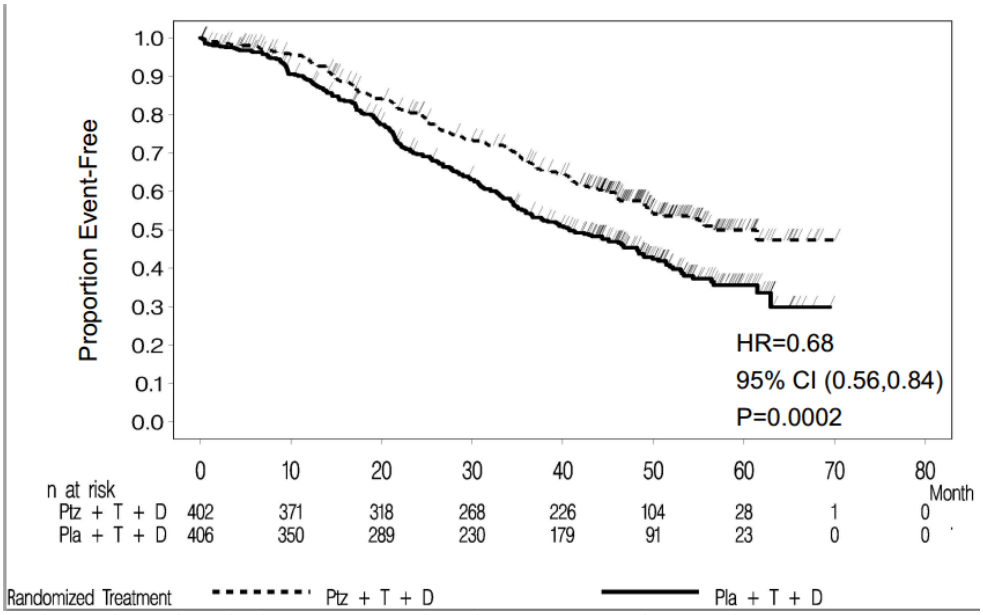
Figure 4: IRF assessed PFS by patient subgroup



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 7, Figure 5).

Figure 5 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-drug antibodies (ADA) to Perjeta. 6.7% (25/372) of patients in the placebo treated group and 3.3% (13/389) of patients in the Perjeta treated group tested positive for ADTA. In BERENICE, 4.1% (16/392) of the patients treated with Perjeta tested positive for ADA. None of these patients experienced anaphylactic/hypersensitivity reactions that were clearly related to ADA.

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 and APHINITY studies were consistent with the predictions from the previous population PK model. No differences in pertuzumab PK were observed in patients with early breast cancer compared to patients with metastatic breast cancer.

Absorption
Pertuzumab is administered as an intravenous (IV) infusion.

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 Dosage and Method of Administration.

6.7 PHYSIOCHEMICAL PROPERTIES

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.

CAS: 380610-27-5

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

31 October 2025

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of 0.45% NaCl diluent option