PERJETA®

Pertuzumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent, recombinant humanized IgG1 monoclonal antibody

HER2 dimerization inhibitor

ATC code: L01XC13 pertuzumab

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) infusion.

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Pertuzumab.

Dosage Preparations: Perjeta is supplied as a single-use vial containing 14 mL preservative free liquid concentrate, at a concentration of 30 mg/mL. Each vial of Perjeta drug product contains a total of 420 mg pertuzumab.

Excipients: As registered locally

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION

Metastatic Breast Cancer

Perjeta is indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease

Early Breast Cancer

Perjeta is indicated in combination with Herceptin and chemotherapy for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer (see Dosage and Administration and Clinical Studies).

- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (see 3.1.2 Clinical Studies)

2.2 DOSAGE AND ADMINISTRATION

General

Patients treated with Perjeta should have HER2-positive tumor status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH), assessed by a validated test.

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

For full instructions on assay performance and interpretation, please refer to the package inserts of validated HER2 testing assays.

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.

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 intravenous infusion. Do not administer as an IV push or bolus.

Metastatic and Early Breast Cancer

The recommended initial dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered

over a period of 30 to 60 minutes. 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 dose of Herceptin or chemotherapy (see section 2.4 Warnings and Precautions).

Perjeta and Herceptin should be administered sequentially and can be given in any order. When administered with Perjeta, the recommendation is to follow a 3-weekly schedule for Herceptin administered either as:

- an IV infusion with an initial dose of 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg body weight

  or

- a fixed dose of Herceptin subcutaneous (SC) injection (600mg) for the initial dose and every 3 weeks thereafter irrespective of the patient's body weight.

In patients receiving a taxane, Perjeta and Herceptin should be administered prior to the taxane. When administered with Perjeta, the recommended initial dose of docetaxel is 75 mg/m2.

In patients receiving an anthracycline-based regimen, Perjeta and Herceptin should be administered following completion of the entire anthracycline regimen.

Metastatic Breast Cancer (MBC)

Perjeta should be administered in combination with Herceptin and docetaxel until disease progression or unmanageable toxicity. Treatment with Perjeta and Herceptin 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 Herceptin and chemotherapy (see Section 3.1.2 Clinical/ Efficacy Studies).

In the adjuvant setting (after surgery), Perjeta should be administered in combination with Herceptin 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 Herceptin should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see section 3.1.2 Clinical/Efficacy Studies).

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

Delayed or Missed doses

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

Table 1 Recommendations regarding delayed or missed doses

Time between two sequential doses	Perjeta	Herceptin	
		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.	The 6 mg/kg dose of Herceptin IV should be administered as soon as possible. Do not wait until the next planned dose.	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 of Herceptin 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.	

Dose modifications

Perjeta should be discontinued if Herceptin treatment is discontinued.

Dose reductions are not recommended for Perjeta and Herceptin (see Herceptin prescribing information).

For chemotherapy dose modifications, see relevant prescribing information.

Infusion-related reactions

The infusion rate of Perjeta may be slowed or the administration interrupted if the patient develops an infusion-related 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 2.4 Warnings and Precautions).

Left ventricular dysfunction

See section 2.4 Warnings and Precautions for information on dose recommendations in the event of left ventricular dysfunction.

2.2.1 SPECIAL DOSAGE INSTRUCTIONS

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

Geriatric use: No dose adjustment is required in patients ≥65 years of age (see section 2.5.5 Geriatric Use).

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 3.2.5 Pharmacokinetics in special populations).

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

2.3 CONTRAINDICATIONS

Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 GENERAL

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Left ventricular dysfunction

Decreases in LVEF have been reported with drugs 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 Herceptin and chemotherapy compared with Herceptin and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF. The majority of cases of symptomatic heart failure reported in the

adjuvant setting were in patients who received anthracycline-based chemotherapy (see section 2.6 Undesirable effects).

Perjeta has not been studied in patients with: a pretreatment LVEF value of <50%; a prior history of congestive heart failure (CHF); decreases in LVEF to <50% during prior Herceptin 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/m2 of doxorubicin or its equivalent.

Assess LVEF prior to initiation of Perjeta and at regular intervals during treatment to ensure that LVEF is within normal limits (see Table 2 below). If the LVEF declines as indicated in Table 2 and has not improved, or has declined further at the subsequent assessment, discontinuation of Perjeta and Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Table 2 Dose recommendations for left ventricular dysfunction

<table>
<tr><td></td><td>Pre-treatment LVEF:</td><td>Monitor LVEF every:</td><td colspan="2">Withhold PERJETA and Herceptin for at least 3 weeks for an LVEF decrease to:</td><td colspan="2">Resume PERJETA and Herceptin after 3 weeks if LVEF has recovered to:</td></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 weeks (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 Herceptin

Infusion-related reactions

Perjeta has been associated with infusion-related reactions, including events with fatal outcomes (see section 2.6 Undesirable effects) [72]. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent infusions of Perjeta is recommended. 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 2.2 Dosage and 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 2.6 Undesirable effects) [72]. 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 of its excipients (see section 2.3 Contraindications).

2.4.2 DRUG ABUSE AND DEPENDENCE

No data to report

2.4.3 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 2.6 Undesirable effects).

2.5 USE IN SPECIAL POPULATIONS

2.5.1 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Contraception: Women of child-bearing potential including those who are partners of male patients should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

2.5.2 PREGNANCY

Perjeta should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

There are no studies of Perjeta in pregnant women. Perjeta administered to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death (see section 3.3.4 Reproductive Toxicity) [18]. 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.

Labor and delivery: The safe use of Perjeta during labor and delivery has not been established.

2.5.3 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 the Perjeta-treatment, taking into account the importance to the mother and the elimination half-life of pertuzumab (see section 3.2.4 Elimination) [19].

2.5.4 PEDIATRIC USE

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

2.5.5 GERIATRIC USE

No overall differences in efficacy of Perjeta were observed in patients ≥65 and <65 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged <65 years of age: decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea (see section 2.2 Dosage and administration).

2.5.6 RENAL IMPAIRMENT

(See sections 2.2.1 and 3.2.5 Pharmacokinetics in special populations).

2.5.7 HEPATIC IMPAIRMENT

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

2.6 UNDESIRABLE EFFECTS

2.6.1 CLINICAL TRIALS

The safety of Perjeta has been evaluated in more than 6000 patients in Phase I-III trials in patients with various malignancies, and predominantly treated with Perjeta in combination with other antineoplastic 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 agents.

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

As Perjeta is used with Herceptin 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 diarrhea, 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 + Herceptin + 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
Anemia	24.8	5.7	Very common
Febrile neutropenia*	11.9	11.8	Very common

Leukopenia	10.8	6.1	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			
Diarrhea	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
Edema peripheral	16.2	<0.1	Very common
Immune system disorders			
Hypersensitivity	3.3	0.4	Common
Drug hypersensitivity	2.5	0.4	Common
Infections and infestations			
Nasopharyngitis	12.8	<0.1	Very common
Upper respiratory tract infection	9.5	0.3	Common
Paronychia	3.9	<0.1	Common
Metabolism and nutrition disorders			
Decreased appetite	23.1	0.8	Very common
Musculoskeletal and connective tissue disorders			
Arthralgia	24.6	0.7	Very common
Myalgia	24.3	0.8	Very common
Pain in extremity	10.0	0.2	Very common
Nervous system disorders			
Dysgeusia	22.7	<0.1	Very common
Headache	21.8	0.4	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Neuropathy peripheral	14.7	0.7	Very common

Dizziness	11.2	0.1	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
Dyspnea	11.5	0.5	Very common
Pleural effusion	0.9	<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			
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); 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) [70].

^ ^ 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 3344 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:

Left ventricular dysfunction

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 2.4 Warnings & Precautions).

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, Herceptin and docetaxel-treated group (7.5%) compared to the Herceptin and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and Herceptin-treated group.

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus Herceptin and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by Perjeta plus Herceptin and docetaxel; 9.3% in the group treated with Perjeta plus Herceptin and docetaxel following FEC; and 6.6% 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 Herceptin and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus Herceptin 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 Herceptin and FEC followed by Perjeta plus Herceptin and docetaxel experienced symptomatic LVD.

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 Herceptin and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with Herceptin 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 Herceptin and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus Herceptin 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 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. 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 cutoff.

Infusion-related reactions

An infusion-related reaction was defined in the pivotal trials 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 Herceptin 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 2.4 Warnings & Precautions).

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 Herceptin 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 9.3% in the placebo-treated patients and 11.3% in the Perjeta-treated patients, of which 2.5% and 2.0% 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 2.4 Warnings & Precautions).

Overall, the majority of hypersensitivity reactions was 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, two patients 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.

2.6.2 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	Tumor Lysis Syndrome

Laboratory Abnormalities

Laboratory abnormalities reported from the post marketing setting are consistent with data from clinical trials of Perjeta.

2.7 OVERDOSE

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

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS 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 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.

3 PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 MECHANISM OF ACTION

Perjeta is a recombinant humanized monoclonal antibody that specifically targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) [25] and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4 [26]. As a result, Perjeta inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively [27]. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While Perjeta alone inhibited the proliferation of human tumor cells, the combination of Perjeta and Herceptin significantly augmented anti-tumor activity in HER2-overexpressing xenograft models.

3.1.2 CLINICAL / EFFICACY STUDIES

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.

Metastatic Breast Cancer

Perjeta in combination with Herceptin and docetaxel

CLEOPATRA is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Patients were randomized 1:1 to receive placebo plus Herceptin and docetaxel or Perjeta plus Herceptin 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 Herceptin were administered intravenously as outlined in section 2.2 Dosage and Administration. Patients were treated with Perjeta and Herceptin until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m2 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 tumor 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 questionnaire.

Demographics were well balanced (median age was 54 years old, the majority were 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 estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) and approximately half of the patients in each treatment group had received prior adjuvant or neo-adjuvant therapy (192 patients [47.3%] in the placebo treated group vs 184 patients [45.8%] Perjeta treated group).

At the time of the primary progression-free survival 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 tumor 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). 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 5). 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 5:

Table 5 Summary of efficacy from CLEOPATRA study

Parameter	Placebo + Herceptin + docetaxel n=406	Perjeta + Herceptin + docetaxel n=402	HR (95% CI)	p-value
Primary Endpoint				
Progression-Free Survival (IRF review)				

No. of patients with an event Median months	242 (59%) 12.4	191 (47.5%) 18.5	0.62 [0.51;0.75]	<0.0001
Secondary Endpoints				
Overall Survival (Final analysis of OS) No. of patients with an event* Median months	 221 (54.4%) 40.8	 168 (41.8%) 56.5	 0.68 [0.56;0.84]	 0.0002
Progression-Free Survival (investigator assessment) No. of patients with an event Median months	 250 (61.6%) 12.4	 201 (50.0%) 18.5	 0.65 [0.54;0.78]	 <0.0001
Objective Response Rate (ORR) No. of patients with an event Responders** 95% CI for ORR Complete response (CR) Partial Response (PR) Stable disease (SD) Progressive disease (PD)	 336 233 (69.3 %) [64.1; 74.2] 14 (4.2 %) 219 (65.2 %) 70 (20.8 %) 28 (8.3 %)	 343 275 (80.2 %) [75.6; 84.3] 19 (5.5 %) 256 (74.6 %) 50 (14.6 %) 13 (3.8 %)	 Difference in ORR: 10.8% [4.2,17.5] %	 0.0011
Duration of Response ^ n= Median weeks 95% CI for Median	 233 54.1 [46;64]	 275 87.6 [71;106]		

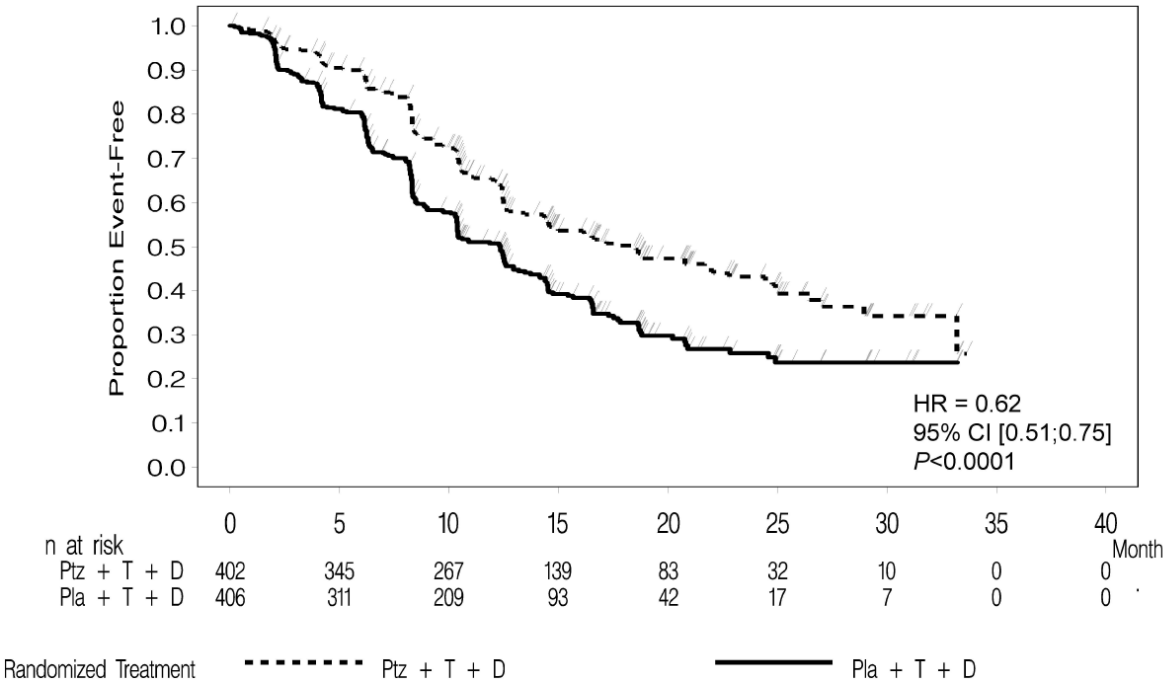
*Final analysis of overall survival, cutoff date 11 Feb 2014

** Patients with best overall response of confirmed CR or PR by RECIST.

^ Evaluated in Patients with Best Overall Response of CR or PR

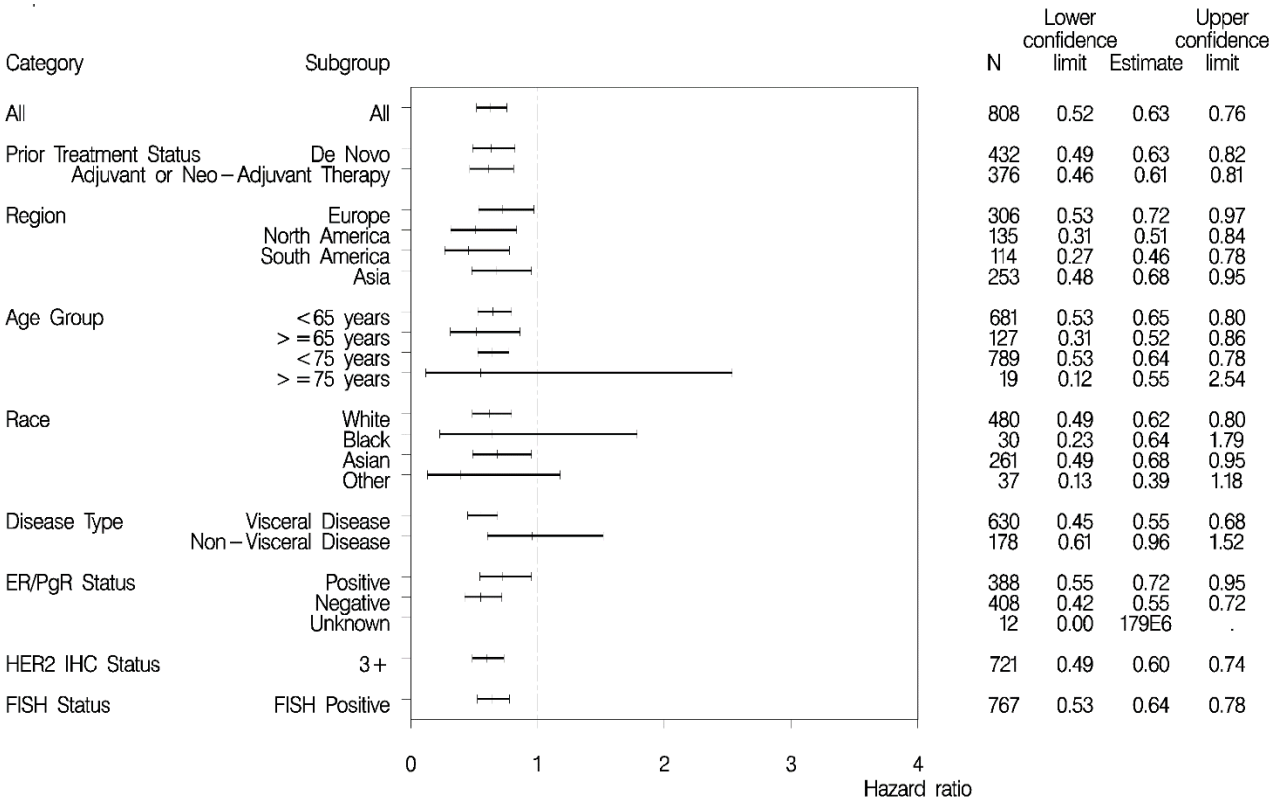
Objective response rate and duration of response are based on IRF-assessed tumor assessments

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



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

Figure 2 IRF assessed PFS by patient subgroup

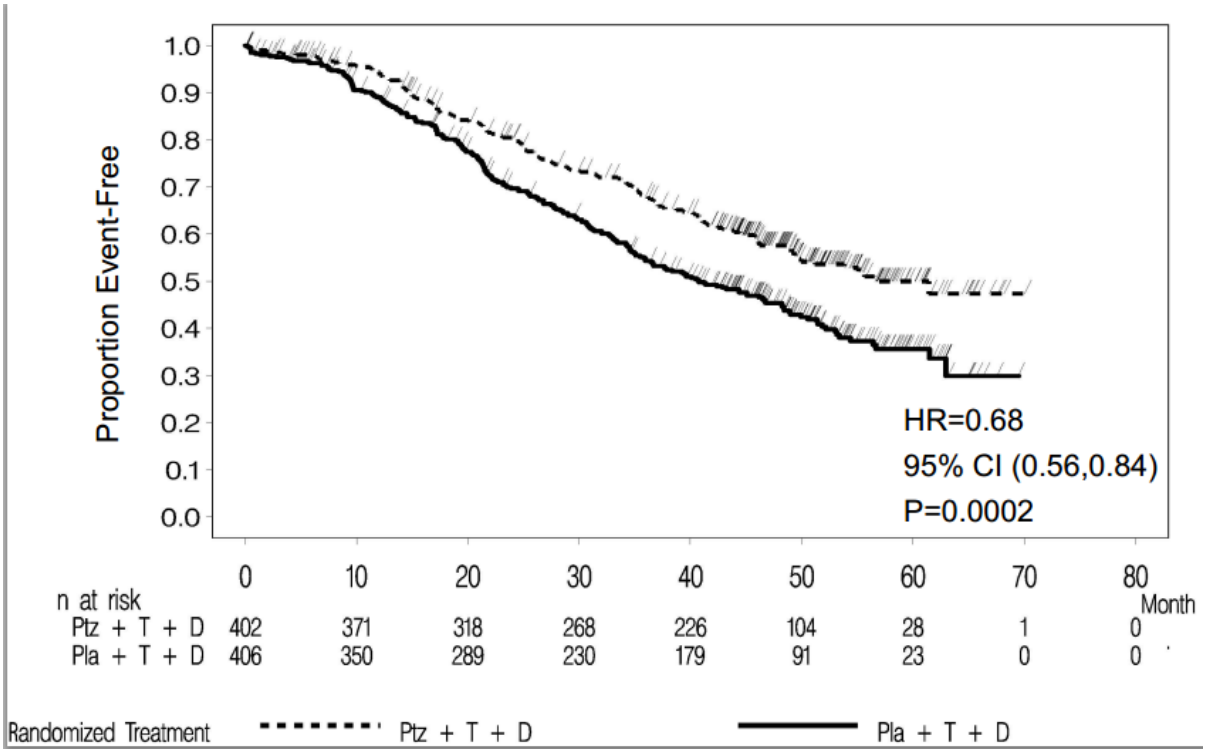


At the primary analysis of efficacy, an interim analysis of OS showed a strong trend suggestive of a survival benefit in favor of the Perjeta-treated group.

An interim analysis of OS performed one year after the primary analysis of efficacy, demonstrated a statistically significant OS benefit in favor of the Perjeta-treated group (HR 0.66, p = 0.0008 log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached in 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 favor 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 5, 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). In an exploratory analysis, patients treated with Perjeta in combination with Herceptin and docetaxel experienced a lower risk of symptom progression on the FACT-B breast cancer subscale (defined as a 2 point reduction in subscale score) compared to those treated with Herceptin and docetaxel alone (HR =0.78, 95% CI =0.65; 0.94).

BO17929 [36]

BO17929 was a Phase II, single arm, non-randomized study with Perjeta and was conducted in patients with HER2-positive MBC who had received prior treatment with Herceptin. The trial was divided into 3 cohorts.

Cohorts 1 and 2: 66 patients in cohorts 1 and 2 received at least one dose of Perjeta and Herceptin (all treated population and all patients had received prior treatment for metastatic disease; half were receiving second-line treatment for metastatic disease, while

35% were receiving third-line treatment and beyond. In addition, 71% had received neoadjuvant chemotherapy). At the time of the primary analysis, the median duration of treatment on study was nine cycles (27 weeks). At the time of the primary analysis, the ORR and CBR are presented in Table 6. The median PFS and time to progression (TTP) were 24 weeks. Median time to response was 11 weeks, and in those patients with a response, the median duration of response was 25 weeks.

Cohort 3: 29 patients received at least one cycle of Perjeta, of these 29 patients, 12 participated in the single-agent Phase only, and 17 went on to receive Perjeta and Herceptin treatment when they had documented progression on Perjeta alone. All 29 patients had progressed on first-line therapy in the metastatic setting, and 41.4% had also progressed after second line therapy. All patients in Cohort 3 received at least one full dose of Perjeta. Patients on Perjeta and Herceptin treatment received a median of 12 cycles overall. Table 6 shows that Perjeta alone had modest activity in patients after failure of Herceptin (middle column). These responses occurred in patients whose disease had recently progressed on each antibody when given separately. In addition 3 patients had stable disease lasting six months or longer for a total clinical benefit rate of 35.3%.

Table 6 Study BO17929: Efficacy data

Response, n (%)	Cohorts 1 and 2 (Perjeta + Herceptin) (n = 66)	Cohort 3 (Perjeta alone) (n = 29)	Cohort 3 (Perjeta + Herceptin) (n = 17)
Complete response (CR)	4 (6.1)	0 (0.0)	0 (0.0)
Partial response (PR)	12 (18.2)	1 (3.4)	3 (17.6)
Objective response rate (ORR)	16 (24.2)	1 (3.4)	3 (17.6)
Stable disease (SD) ≥ 6 months	17 (25.8)	2 (6.9)	3 (17.6)
Clinical benefit response (CBR) rate (CR + PR + SD ≥ 6 months)	33 (50.0)	3 (10.3)	6 (35.3)
Progressive disease (PD)	33 (50.0)	26 (89.7)	9 (52.9)
Missing (no response assessment)	0 (0.0)	0 (0.0)	2 (11.8)

Note :> 6 months = 8 cycles of therapy

Early Breast Cancer

NEOSPHERE (WO20697) [37]

NEOSPHERE is a multicenter, randomized Phase II clinical trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. Patients were randomized to receive one of four neoadjuvant regimens prior to surgery as follows: Herceptin plus docetaxel, Perjeta plus Herceptin and docetaxel, Perjeta plus Herceptin, or Perjeta plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen (ER) or progesterone (PgR) positivity.

Perjeta and Herceptin were administered intravenously (see section 2.2 Dosage and Administration) for 4 cycles. Following surgery all patients received three cycles of 5-Fluorouracil (600 mg/m2), epirubicin (90 mg/m2), cyclophosphamide (600 mg/m2) (FEC) given intravenously every three weeks and Herceptin administered intravenously every three weeks to complete one year of therapy Patients in the Perjeta plus Herceptin 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 Herceptin.

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 [46]. 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).

The efficacy results are summarized in Table 7. A statistically significant and clinically meaningful improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus Herceptin and docetaxel compared to patients receiving Herceptin and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition.

Pathological complete response (pCR) rates as well as the magnitude of improvement with Perjeta were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (5.9% to 26.0% and 27.3% to 63.2%, respectively).

TRYPHAENA (BO22280)

TRYPHAENA is a multicenter, randomized Phase ll 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 Herceptin, 3 cycles of FEC alone followed by 3 cycles of docetaxel and Herceptin in combination with Perjeta, or 6 cycles of TCH in combination with Perjeta. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and /or PgR positivity.

Perjeta and Herceptin were administered intravenously as outlined in section 2.2 Dosage and Administration. 5-Fluorouracil (500 mg/m2), epirubicin (100 mg/m2), cyclophosphamide (600 mg/m2) were given intravenously every three weeks for 3 cycles. Docetaxel was given as 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. However, in the Perjeta in combination with TCH arm, docetaxel was given intravenously at 75 mg/m2 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.

High pCR rates were observed in all 3 treatment arms (see Table 7). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 7 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 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 rates2 [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/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 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 Response5	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 7): T: Herceptin; D: docetaxel; Ptz: Perjeta; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab.

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-randomized, open-label, multicenter, multinational, 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 Herceptin 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 Herceptin and paclitaxel

Cohort B - 4 cycles of FEC followed by 4 cycles of Perjeta in combination with Herceptin and docetaxel.

Perjeta and Herceptin were administered intravenously as outlined in Section 2.2 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 Herceptin every 3 weeks during Cycles 5-8 (from the start of paclitaxel; four cycles of Perjeta and Herceptin 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 Herceptin 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 2.6 Undesirable 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 tumors than in patients with hormone receptor-negative tumors in both Cohorts (51.6% to 81.5% and 57.3% to 68.0% respectively).

APHINITY (BO25126)

APHINITY is a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive Perjeta or placebo, in combination with adjuvant Herceptin 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
- 4 cycles of AC or EC, followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel
- 6 cycles of docetaxel in combination with carboplatin

Perjeta and Herceptin were administered intravenously (see section 2.2 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 standard.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomization 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 randomized to receive Perjeta compared with patients randomized to receive placebo.

The efficacy results from the APHINITY trial are summarized in Table 8 and in Figures 4 and 5.

Table 8 Overall Efficacy (ITT Population)

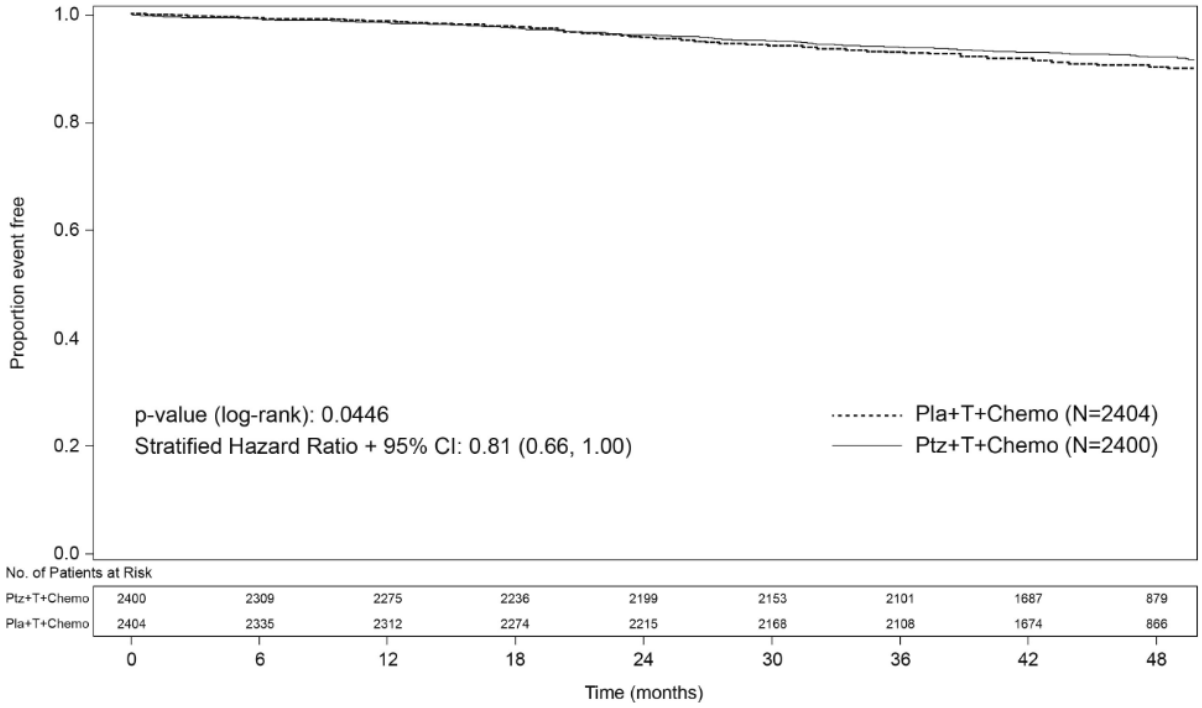
	Perjeta + Herceptin + chemotherapy N=2400	Placebo + Herceptin + chemotherapy N=2404
Primary Endpoint		
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value (Log-Rank test, stratified2)	0.0446	
3 year event-free rate3 [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints1		
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, stratified2)	0.0430	
3 year event-free rate3 [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, stratified2)	0.0327	
3 year event-free rate3 [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, stratified2)	0.4673	
3 year event-free rate3 [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%)

	Perjeta + Herceptin + chemotherapy N=2400	Placebo + Herceptin + chemotherapy N=2404
HR [95% CI]	0.79 [0.63, 0.99]	
p-value (Log-Rank test, stratified2)	0.0430	
3 year event-free rate3 [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, stratified2)	0.1007	
3 year event-free rate3 [95% CI]	95.7 [94.9, 96.5]	95.1 [94.3, 96.0]

Key to abbreviations (Table 8): 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 4 Kaplan-Meier curve of invasive disease free survival



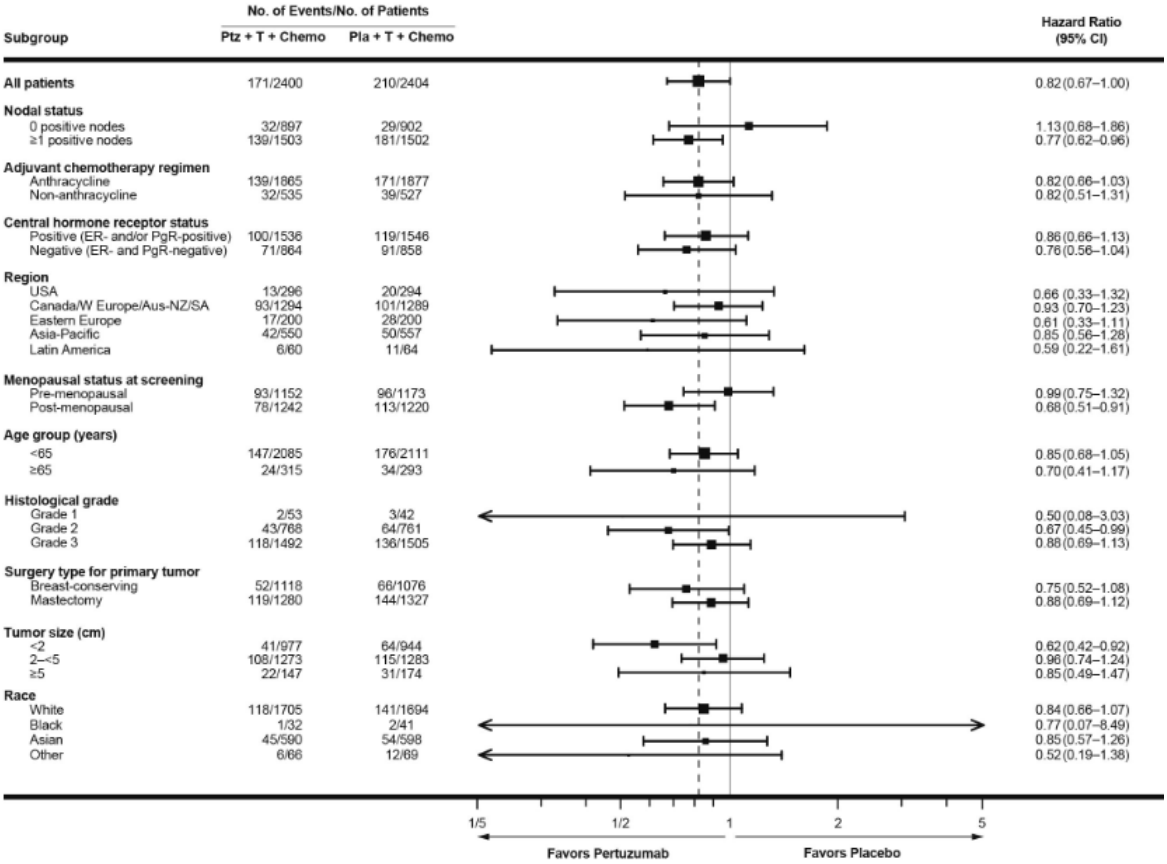
Pla = placebo; Ptz = pertuzumab (Perjeta); T = trastuzumab (Herceptin)

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 (see Figure 5 below).

Figure 5 Forest Plot of invasive disease free survival by subgroup



Pla = placebo; Ptz = pertuzumab (Perjeta); T = trastuzumab (Herceptin)

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 diarrhea 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 diarrhea 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. Diarrhea symptoms returned to baseline after HER2 therapy in the Perjeta-arm. The addition of Perjeta to Herceptin plus chemotherapy did not affect patients' overall role function over the course of the study.

3.1.3 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 ADA. 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.

3.2 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 481 patients, the median clearance (CL) of pertuzumab was 0.235 L/day and the median half-life was 18 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

tumor 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

3.2.1 ABSORPTION

Pertuzumab is administered as an IV infusion.

3.2.2 DISTRIBUTION

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

3.2.3 METABOLISM

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

3.2.4 ELIMINATION

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

3.2.5 PHARMACOKINETICS IN SPECIAL POPULATIONS

Geriatric population: No dedicated studies of pertuzumab have been conducted in geriatric 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.

3.3 NONCLINICAL SAFETY

3.3.1 CARCINOGENICITY

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

3.3.2 GENOTOXICITY

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

3.3.3 IMPAIRMENT OF FERTILITY

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. 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.

3.3.4 REPRODUCTIVE TOXICITY

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 clinically relevant exposures. Intravenous administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) has been shown to be embryotoxic with a dose dependent increase in embryo-fetal deaths between GD 25 to 70. Delayed renal development and oligohydramnios were identified at GD100.

3.3.5 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 diarrhea was noted. In a subset of monkeys chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhea-related dehydration which were managed with intravenous fluid replacement therapy.

4 PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Storage: As registered locally

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.

Shelf-life

As registered locally

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the solution for infusion containing the product

Perjeta drug product does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

The solution of Perjeta for infusion diluted in polyvinylchloride (PVC) or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection, US Pharmacopeia (USP), may be stored at 2°C–8°C (36°F-46°F) 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 stored refrigerated (2°C–8°C).

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Instructions for dilution

Perjeta is for single use only and is administered intravenously by infusion.

Perjeta does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion and should be prepared by a healthcare professional.

Perjeta should be prepared by a healthcare professional using aseptic technique.

14 ml Perjeta liquid concentrate should be withdrawn from the vial and diluted into a 250 mL PVC or non-PVC polyolefin 0.9% sodium chloride infusion bag. Do not withdraw saline out of the infusion bag.

After dilution, the solution should contain a nominal concentration of 3.0mg / mL of pertuzumab for the initial dose where two vials are required and 1.6 mg / mL of pertuzumab for the subsequent dose where one vial is required.

Dextrose (5%) solution should not be used (see 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 discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see section 4.1 Storage).

Incompatibilities

No incompatibilities between Perjeta and polyvinylchloride, polyethylene or non-PVC polyolefin bags have been observed [42, 43].

Dextrose (5%) solution should not be used to dilute Perjeta since it was chemically and physically unstable in such solutions[43] (Dilute formulations of Pertuzumab liquid formulations in D5W IV bags did not maintain stable pH after storage at room temperature (27-33°C) for 24 hours followed by 24 hours at refrigerator temperature (2-8°C)).

Perjeta should not be mixed or diluted with other drugs.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.3 PACKS

Vials 420 mg/14 ml 1

Medicine: keep out of reach of children

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