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**INF-PER-2021 02**

# Perjeta®

Pertuzumab

## 1.1 NAME OF THE MEDICINAL PRODUCT

Perjeta concentrate for solution for infusion 420mg/14ml

## 1.2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml.

After dilution, one ml of solution contains 3.36 mg of pertuzumab for the initial dose and 1.68 mg of pertuzumab for the maintenance dose (see section 4.2).

Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

For the full list of excipients, see section 4.3.

## 1.3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear to slightly opalescent, colourless to pale yellow, liquid.

## 2. CLINICAL PARTICULARS

### 2.1 Therapeutic indications

Metastatic Breast Cancer (MBC)

Perjeta is indicated for use in combination with Herceptin and docetaxel for the treatment of adult 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 for use in combination with Herceptin and chemotherapy for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival.
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (see section 3.1.2).

### 2.2 Posology and method of administration

General

Perjeta is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation service is immediately available.

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

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures. For full instructions on assay performance and interpretation please refer to the package leaflets of validated HER2 testing assays.

Posology

*Metastatic and Early Breast Cancer*

The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance 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*).

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 (600 mg) 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/m$^2$, and administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m$^2$ on subsequent cycles if the initial dose is well tolerated. 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).

In the adjuvant setting, Perjeta should be administered in combination with Herceptin for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include 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).

*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).

Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. For chemotherapy dose modifications, see relevant prescribing information.

*Left ventricular dysfunction*

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**

| | Pre-treatment LVEF: | Monitor LVEF every: | Withhold PERJETA and Herceptin for at least 3 weeks for an LVEF decrease to: | | Resume PERJETA and Herceptin after 3 weeks if LVEF has recovered to: | |
|---|---|---|---|---|---|---|
| **Metastatic Breast Cancer** | ≥ 50% | ~12 weeks | Either | | Either | |
| | | | <40% | 40%-45% with a fall of ≥10%-points below pre-treatment value | >45% | 40%-45% with a fall of <10%-points below pre-treatment value |
| **Early Breast Cancer** | ≥ 55%* | ~12 weeks (once during neoadjuvant therapy) | <50% with a fall of ≥10%-points below pre-treatment value | | Either | |
| | | | | | ≥50% | < 10% points below pre-treatment value |

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

*Infusion reactions*

The infusion rate of Perjeta may be slowed or the administration interrupted if the patient develops an infusion reaction (see section 2.6). The infusion may be resumed when symptoms abate. Treatment including oxygen, beta agonists, antihistamines, rapid i.v. fluids and antipyretics may also help alleviate symptoms. 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 2.4).

*Elderly patients*

Limited data are available on the safety and efficacy of pertuzumab in patients ≥ 65 years of age. No dose adjustment is required in patients ≥ 65 years of age (see section 2.5). Very limited data are available in patients > 75 years of age.

*Patients with 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).

*Patients with hepatic impairment*

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment. No specific dose recommendations can be made.

*Paediatric population*

The safety and efficacy of Perjeta in children and adolescents below 18 years of age have not been established. There is no relevant use of Perjeta in the paediatric population in the indication of metastatic breast cancer.

Method of administration

Perjeta is administered intravenously by infusion. It should not be administered as an intravenous push or bolus. For instructions on dilution of Perjeta prior to administration, see section 4.2.

For the initial dose, the recommended infusion period is 60 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes to 60 minutes (see section 2.4).

### 2.3 Contraindications

Hypersensitivity to pertuzumab or to any of the excipients listed in section 4.3.

### 2.4 Special warnings and precautions for use

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

*Left ventricular dysfunction (including congestive heart failure)*

Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Perjeta. The incidence of symptomatic left ventricular systolic dysfunction (LVSD [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 had received anthracycline-based chemotherapy (see section 2.6).

Cardiac risk should be carefully considered and balanced against the medical need of the individual patients 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.

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 Herceptin 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.

*Infusion-related reactions*

Perjeta has been associated with infusion-related reactions including events with fatal outcomes (see section 2.6). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions is recommended following the administration of Perjeta. If an 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. Perjeta must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 2.2).

*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). 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).

*Febrile neutropenia*

Patients treated with Perjeta, Herceptin and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, Herceptin and docetaxel, especially during the first 3 cycles of treatment (see section 2.6). As nadir neutrophil counts were similar in Perjeta-treated and placebo-treated patients, the higher incidence of febrile neutropenia in Perjeta-treated patients may be associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. In the pivotal trial, CLEOPATRA, no events of febrile neutropenia were reported after cessation of docetaxel. However, 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. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (26%) compared with the placebo-treated group (12%).

### 2.4.1 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). Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

### 2.5 Use in Special Populations

Females and Males of Reproductive Potential

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

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). 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. Verify the pregnancy status of females of reproductive potential prior to the initiation of Perjeta.

Breast-feeding

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 breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of Perjeta therapy for the woman (see section 3.2).

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 < 65 years of age: decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea (see section 2.2).

### 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 event 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 |
| **Injury, Poisoning and Procedural Complications** | | | |
| Infusion reaction | 3.7 | <0.1 | Common |
| **Immune system disorders** | | | |
| Hypersensitivity | 3.3 | 0.4 | Common |
| Drug hypersensitivity | 2.5 | 0.4 | Common |
| Anaphylactic reaction | 0.2 | 0.1 | Uncommon |
| **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 |
| 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** | | | |
| 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).

^ ^ 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.

Description of selected adverse 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).

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 groups (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 (regardless of causality) described 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 infusion 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 medicinal products were administered on the same day, the most common infusion related reactions in the Perjeta-treated group (> 1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia and vomiting.

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 (not including acute infusion reactions/cytokine release syndrome) during the entire treatment period was 9.3% in the placebo-treated group and 11.3% in the Perjeta-treated group, of which 2.5% and 2.0% were NCI-CTCAE Grade 3-4, respectively. Overall, 2 patients in the placebo-treated group and 4 patients in the Perjeta-treated group experienced events described as anaphylaxis by the investigator (see section 2.4).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to the 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 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.

*Febrile neutropenia*

In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (62.4% of patients in the Perjeta-treated group and 58.2% of patients in the placebo-treated group), of which the majority were neutropenic events. Febrile neutropenia occurred in 13.8% of Perjeta-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing 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. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (26%) compared with the placebo-treated group (12%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with Herceptin and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant Herceptin and docetaxel.

In the APHINITY trial, febrile neutropenia occurred in 12.1% of Perjeta-treated patients and 11.1% of placebo-treated patients. As in the CLEOPATRA, TRYPHAENA, and NEOSPHERE trials, a higher incidence of febrile neutropenia was observed among Perjeta-treated Asian patients compared with other races in the APHINITY trial (15.9% of Perjeta-treated patients and 9.9% of placebo-treated patients).

*Diarrhoea*

In the pivotal clinical trial CLEOPATRA, diarrhoea occurred in 66.8% of Perjeta-treated patients and 46.3% of placebo-treated patients. Most events were mild-moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 7.9% in Perjeta-treated patients vs 5.0% in placebo-treated patients. The median duration of the longest episode was 17 days in Perjeta-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents.

In the NEOSPHERE trial, diarrhoea occurred in 45.8% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel compared with 33.6% of patients treated with Herceptin and docetaxel.

In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. In both studies most events were mild to moderate in severity.

In the APHINITY trial, a higher incidence of diarrhoea was reported in the Perjeta-treated arm (71.2%) compared to the placebo arm (45.2%). Grade ≥ 3 diarrhoea was reported in 9.8% of patients in the Perjeta arm vs. 3.7% in the placebo arm. The majority of the reported events were Grade 1 or 2 in severity. The highest incidence of diarrhoea (all Grades) was reported during the targeted therapy+taxane chemotherapy period (61.4% of patients in the Perjeta arm vs. 33.8% of patients in the placebo arm).The incidence of diarrhoea was much lower after chemotherapy cessation, affecting 18.1% of patients in the Perjeta arm vs. 9.2% of patients in the placebo arm in the post-chemotherapy targeted therapy period.

*Rash*

Rash occurred in 45.2% of Perjeta-treated patients, compared with 36.0% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne.

*Laboratory abnormalities*

In the pivotal trials CLEOPATRA, NEOSPHERE, and APHINITY the incidence of NCI-CTCAE Grade 3-4 neutropenia was 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 |

### 2.7 Overdose

The maximum tolerated dose of Perjeta has not been determined. In clinical trials, single doses higher than 25 mg/kg (1727 mg) have not been tested.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

### 2.8. Interaction 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 Herceptin and between Perjeta and docetaxel. In addition, no clinically relevant pharmacokinetic interaction of co-administered docetaxel or Herceptin on Perjeta 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 Perjeta on the pharmacokinetics of coadministered cytotoxic agents, docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin, and erlotinib. There was no evidence of any pharmacokinetics interaction between Perjeta and any of these agents. The pharmacokinetics of Perjeta in these studies was comparable to those observed in single-agent studies.

## 3. PHARMACOLOGICAL PROPERTIES

### 3.1 Pharmacodynamic properties

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

### 3.1.1 Mechanism of action

Perjeta is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, Perjeta 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, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While Perjeta alone inhibited the proliferation of human tumour cells, the combination of Perjeta and Herceptin significantly augmented antitumour 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.

The efficacy of Perjeta in HER2-positive breast cancer is supported by a randomised phase III comparative trial in metastatic breast cancer and two phase II studies (one single-arm trial in metastatic breast cancer and one randomised comparative trial in the neoadjuvant setting).

<u>*Metastatic breast cancer*</u>

*Perjeta in combination with Herceptin and docetaxel*

CLEOPATRA is a multicentre, randomised, double-blind, placebo-controlled phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer. Patients with clinically important cardiac risk factors were not included (see section 2.4). Due to the exclusion of patients with brain metastases no data are available on Perjeta activity on brain metastases. There is very limited data available in patients with unresectable locally recurrent disease. Patients were randomized 1:1 to receive placebo + Herceptin + docetaxel or Perjeta + Herceptin + docetaxel.

Perjeta and Herceptin were administered intravenously as outlined in *section 2.2*. 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/m$^2$ as an intravenous infusion every three 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.

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.

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as oestrogen receptor positive and/or progesterone receptor positive) and approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant therapy. Most of these patients had received prior anthracycline therapy and 11% of all patients had received prior Herceptin. A total of 43% of patients in both treatment groups had previously received radiotherapy. Patients' median LVEF at baseline was 65.0% (range 50% – 88%) in both groups.

The efficacy results from the CLEOPATRA study are summarised in Table 5. At the time of the primary analysis, a statistically significant improvement in IRF-assessed PFS was demonstrated in the Perjeta-treated group compared with the placebo-treated group. The results for investigator-assessed PFS were similar to those observed for IRF-assessed PFS.

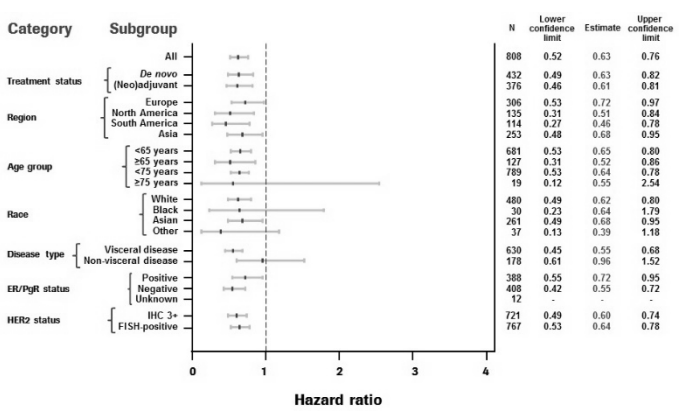
**Table 5 Summary of efficacy from CLEOPATRA study**

| Parameter | Placebo+ Herceptin + docetaxel n=406 | Perjeta+ Herceptin + docetaxel n=402 | HR (95% CI) | p-value |
|---|---|---|---|---|
| **Primary Endpoint:** | | | | |
| **Progression-Free Survival (independent review)** | | | | |
| no. of patients with an event | 242 (59%) | 191 (47.5%) | 0.62 [0.51;0.75] | <0.0001 |
| Median months | 12.4 | 18.5 | | |
| **Secondary Endpoints:** | | | | |
| **Overall Survival (Final analysis of OS)** | | | | |
| No. of patients with an event* | 221 (54.4%) | 168 (41.8%) | 0.68 [0.56;0.84] | 0.0002 |
| Median months | 40.8 | 56.5 | | |
| **Objective Response Rate (ORR)^** | | | | |
| no. of patients with measurable disease | 336 | 343 | Difference in ORR: 10.8% [4.2,17.5]% | 0.0011 |
| Responders** | 233 (69.3%) | 275 (80.2%) | | |
| 95% CI for ORR | [64.1; 74.2] | [75.6; 84.3] | | |
| Complete response (CR) | 14 (4.2%) | 19 (5.5%) | | |
| Partial Response (PR) | 219 (65.2%) | 256 (74.6%) | | |
| Stable disease (SD) | 70 (20.8%) | 50 (14.6%) | | |
| Progressive disease (PD) | 28 (8.3%) | 13 (3.8 %) | | |
| **Duration of Response †^** | | | | |
| n= | 233 | 275 | | |
| Median weeks | 54.1 | 87.6 | | |
| 95% CI for Median | [46;64] | [71;106] | | |

*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 tumour assessments.

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 1). A post hoc exploratory analysis revealed that for patients who had received prior Herceptin (n = 88), the hazard ratio for IRF-assessed PFS was 0.62 (95% CI 0.35, 1.07), compared with 0.60 (95% CI 0.43, 0.83) for patients who had received prior therapy which did not include Herceptin (n = 288).

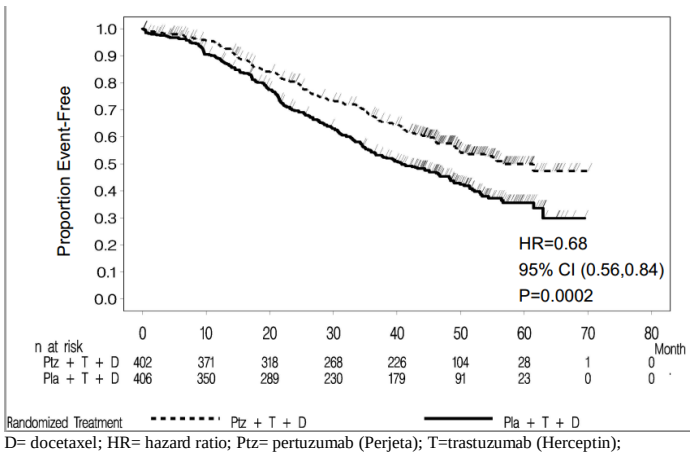
**Figure 1 IRF-assessed PFS by patient subgroup**




An interim analysis of OS performed one year after the primary analysis of efficacy, demonstrated a statistically significant overall survival benefit in favour of the Perjeta-treated group (see Figure 2). OS results in patient subgroups were consistent with those observed for IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-visceral metastasis [HR=1.42 (95% CI:0.71,2.84)]

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 2).

**Figure 2 Kaplan-Meier Curve of Overall Survival**




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

No statistically significant differences were found between the two treatment groups in Health Related Quality of Life as assessed by FACT-B TOI-PFB scores.

*Additional supportive clinical trial information*

**BO17929** - single-arm trial in metastatic breast cancer

BO17929 was a phase II, non-randomised study in patients with metastatic breast cancer whose tumours had progressed during treatment with Herceptin. Treatment with Perjeta and Herceptin resulted in a response rate of 24.2%, with a further 25.8% of patients experiencing stabilisation of disease lasting at least 6 months, indicating that Perjeta is active following progression on Herceptin.

*Early Breast Cancer*

**NEOSPHERE (WO20697)**

NEOSPHERE is a multicentre, randomized Phase II clinical trial conducted in 417 patients with operable, newly diagnosed, early, inflammatory, locally advanced HER2-positive breast cancer (T2-4d) who had not received prior Herceptin 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*) 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 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. 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 summarised in Table 6. 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 tumours than in patients with hormone receptor-negative tumours (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*. 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.

High pCR rates were observed in all 3 treatment arms (see Table 6). 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 6 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 | 31 | 49 | 18 | 23 | 45 | 43 | 51 |
| n (%) | (29.0%) | (45.8%) | (16.8%) | (24.0%) | (61.6%) | (57.3%) | (66.2%) |
| [95% CI][1] | [20.6; 38.5] | [36.1; 55.7] | [10.3; 25.3] | [15.8; 33.7] | [49.5; 72.8] | [45.4; 68.7] | [54.6; 76.6] |
| Difference in pCR rates[2] | | +16.8 % | -12.2 % | -21.8 % | NA | NA | NA |
| [95% CI][3] | | [3.5; 30.1] | [-23.8; -0.5] | [-35.1; -8.5] | | | |
| 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 | 23 | 42 | 12 | 17 | 41 | 41 | 49 |
| n (%) | (21.5%) | (39.3%) | (11.2%) | (17.7%) | (56.2%) | (54.7%) | (63.6%) |
| [95% CI] | [14.1; 30.5] | [30.3; 49.2] | [5.9; 18.8] | [10.7; 26.8] | [44.1; 67.8] | [42.7; 66.2] | [51.9; 74.3] |
| ypT0 N0 | 13 | 35 | 6 | 13 | 37 | 34 | 40 |
| n (%) | (12.1%) | (32.7%) | (5.6%) | (13.2%) | (50.7%) | (45.3%) | (51.9%) |
| [95% CI] | [6.6; 19.9] | [24.0; 42.5] | [2.1; 11.8] | [7.4; 22.0] | [38.7; 62.6] | [33.8; 57.3] | [40.3; 63.5] |
| Clinical Response[5] | 79 (79.8%) | 89 (88.1%) | 69 (67.6%) | 65 (71.4%) | 67 (91.8%) | 71 (94.7%) | 69 (89.6%) |

**Key to abbreviations (Table 6):** T: Herceptin; D: docetaxel; Ptz: Perjeta; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and Herceptin.
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 (with primary tumours >2cm in diameter or node-positive disease).

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*. Doxorubicin 60 mg/m$^2$ IV and cyclophosphamide 600 mg/m$^2$ 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/m$^2$ 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/m$^2$), epirubicin (100 mg/m$^2$), cyclophosphamide (600 mg/m$^2$) were given intravenously every three weeks for 4 cycles. Docetaxel was given at 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. 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.

The pCR (ypT0/is ypN0) rates were 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 (51.6% in Cohort A and 57.3% in Cohort B) than in patients with hormone receptor-negative tumors (81.5% in Cohort A and 68% in Cohort B.

**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*) 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 7 and in Figures 3 and 4.

**Table 7 Overall Efficacy (ITT Population)**

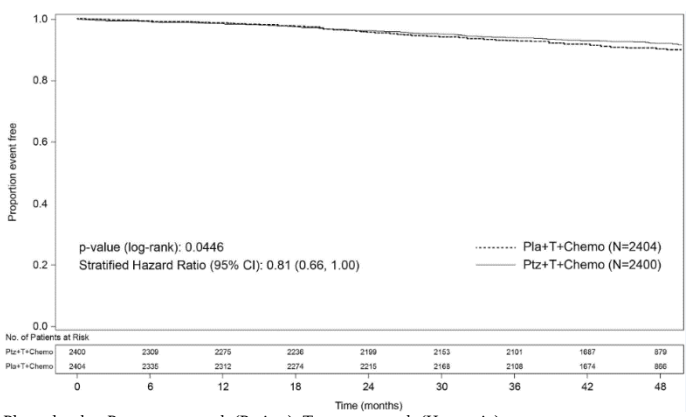
| | **Perjeta + Herceptin + chemotherapy** **N=2400** | **Placebo + Herceptin + chemotherapy** **N=2404** |
|---|---|---|
| **Primary Endpoint** | | |
| **Invasive Disease Free Survival (IDFS)** Number (%) of patients with event | 171 (7.1%) | 210 (8.7%) |
| HR [95% CI] | 0.81 [0.66, 1.00] | |
| p-value (Log-Rank test, 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] | |

| | Perjeta + Herceptin + chemotherapy N=2400 | Placebo + Herceptin + chemotherapy N=2404 |
|---|---|---|
| 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 (Table 7):** ITT: Intent-to-treat; 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 3 Kaplan-Meier curve of invasive disease free survival**



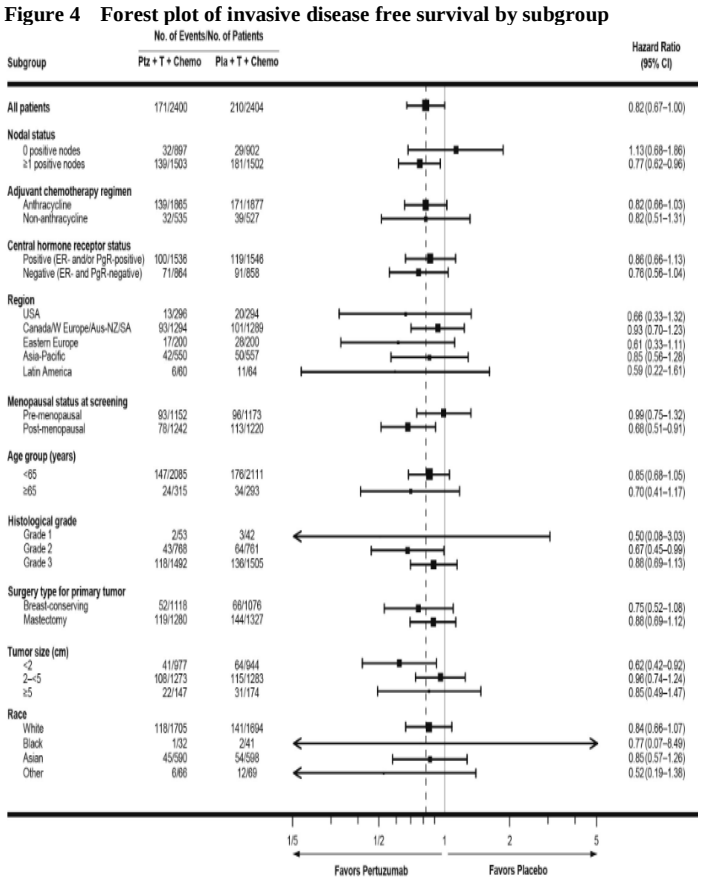

Pla = placebo; Ptz = pertuzumab (Perjeta); T = trastuzumab (Herceptin)

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. At the time of the primary analysis, the benefits of Perjeta were more apparent in subgroups of patients with high risk of recurrence patients with node-positive or hormone receptor-negative disease (see Figure 4).

**Figure 4 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 to ADA. In the 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.

## 3.2 Pharmacokinetic properties

A population pharmacokinetic analysis was performed with data from 481 patients across different clinical trials (phase I, II and III) with various types of advanced malignancies who had received Perjeta as a single agent or in combination at doses ranging from 2 to 25 mg/kg administered every 3 weeks as a 30-60 minutes intravenous infusion.

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*

Perjeta is administered as an intravenous infusion.

*Distribution*

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

*Biotransformation*

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

*Elimination*

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

*Linearity/non-linearity*

Perjeta displayed linear pharmacokinetics within the recommended dose range.

*Elderly patients*

Based on the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of Perjeta between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

*Patients with renal impairment*

No dedicated renal impairment trial for Perjeta has been conducted. Based on the results of the population pharmacokinetic analysis, Perjeta exposure in patients with mild (creatinine clearance [CLcr] 60 to 90 ml/min, N=200) and moderate renal impairment (CLcr 30 to 60 ml/min, N=71) was similar to that in patients with normal renal function (CLcr greater than 90 ml/min, N=200). No relationship between CLcr and Perjeta exposure was observed over the range of CLcr (27 to 244 ml/min).

*Other special populations*

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. CL 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 Perjeta based on these covariates.

## 3.3 Nonclinical safety data

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No definitive conclusion on adverse effects can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study.

Reproductive toxicology studies have been conducted in pregnant cynomolgus monkeys (Gestational Day (GD) 19 through to GD 50) at initial doses of 30 to 150 mg/kg followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on $C_{max}$. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-foetal death between GD25 to GD70. The incidences of embryo-foetal loss were 33, 50, and 85% for pregnant female monkeys treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on $C_{max}$). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. In addition, consistent with foetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 in 30 mg/kg and 1 of 2 in 100 mg/kg groups), ventricular septal defects (1 of 6 in 30 mg/kg group), thin ventricular wall (1 of 2 in 100 mg/kg group) and minor skeletal defects (external - 3 of 6 in 30 mg/kg group) were also noted. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

In cynomolgus monkeys, weekly intravenous administration of pertuzumab at doses up to 150 mg/kg/dose was 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 severe secretory diarrhoea. The diarrhoea was managed (with the exception of euthanasia of one animal, 50 mg/kg/dose) with supportive care including intravenous fluid replacement therapy.

# 4. PHARMACEUTICAL PARTICULARS

## 4.1 Storage

Store vials in a refrigerator at 2°C-8°C.

**DO NOT FREEZE. DO NOT SHAKE.**

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section *Shelf life*.

**Shelf life**

*Unopened Vials*

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

*Diluted solution*

Perjeta 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).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 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 of Perjeta liquid concentrate should be withdrawn from the vial using a sterile needle and syringe 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 3.0 mg/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 discolouration prior to administration. If particulates or discolouration are observed, the solution should not be used. Once the infusion is prepared it should be administered immediately (see section 4.1 *Storage*).

***Incompatibilities***

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

Dextrose (5%) solution should not be used to dilute Perjeta since it was chemically and physically unstable in such solutions.

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 List of excipients

Acetic acid, glacial
L-Histidine
Sucrose
Polysorbate 20
Water for Injections

## 4.4 Packs

Vials 420mg/14ml 1

**Medicine: keep out of reach of children**

Current at February 2021

F. Hoffmann-La Roche Ltd