

Perjeta[®]



PERTUZUMAB

Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Perjeta 420 mg concentrate for solution for infusion

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 approximately 3.02 mg of pertuzumab for the initial dose and approximately 1.59 mg of pertuzumab for the maintenance dose (see section 6.6).

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 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early breast cancer

Perjeta is indicated for use in combination with trastuzumab 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.

Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (positive nodes).

Metastatic Breast Cancer

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

4.2 Posology and method of administration

Perjeta 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 facilities are immediately available.

Posology

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.

The recommended initial loading dose of pertuzumab 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 infusion. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy (see section 4.4).

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

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

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

When administered with Perjeta, docetaxel can be started at 75 mg/m², and subsequently escalated to 100 mg/m² depending on the chosen regimen and tolerability of the initial dose. Alternatively, docetaxel can be given at 100 mg/m² on a 3 weekly schedule from the start, again depending on the chosen regimen. If a carboplatin-based regimen is used, the recommended dose for docetaxel is 75 mg/m² throughout (no dose escalation). When administered with Perjeta in the adjuvant setting, the recommended dose of paclitaxel is 80 mg/m² once weekly for 12 weekly cycles.

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

Metastatic breast cancer

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

Early breast cancer

In the neoadjuvant setting, Perjeta should be administered for 3 to 6 cycles in combination with trastuzumab and chemotherapy, as part of a complete treatment regimen for early breast cancer (see section 5.1).

In the adjuvant setting, Perjeta should be administered in combination with trastuzumab 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 trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

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

Dose modification

Dose reductions are not recommended for Perjeta or trastuzumab. For details regarding trastuzumab, please refer to the 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 docetaxel and other chemotherapy dose modifications, see relevant prescribing information.

If trastuzumab treatment is discontinued, treatment with Perjeta should be discontinued.

Left ventricular dysfunction

Perjeta and trastuzumab should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. Perjeta should be discontinued if symptomatic heart failure is confirmed (see section 4.4 for more details).

Patients with metastatic breast cancer

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

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

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

Patients with early breast cancer

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

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

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

Elderly patients

No overall differences in efficacy of Perjeta were observed in patients ≥ 65 and < 65 years of age. No dose adjustment is necessary in the elderly population ≥ 65 years of age. Limited data are available in patients > 75 years of age. Please see section 4.8 for assessment of safety of Perjeta in elderly patients.

Renal impairment

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

Hepatic impairment

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment. 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 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 sections 6.2 and 6.6.

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 4.4).

Infusion reactions

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction (see section 4.8). 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.

Hypersensitivity reactions/anaphylaxis

The infusion should be discontinued immediately and permanently if the patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

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 (LVD) [congestive heart failure] was higher in patients treated with Perjeta in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy (see section 4.8).

Perjeta has not been studied in patients with: a pre-treatment LVEF value of $< 50\%$; a prior history of congestive heart failure (CHF); LVEF declines to $< 50\%$ during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial

infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m² of doxorubicin or its equivalent.

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

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

Sequential use of Perjeta (in combination with trastuzumab and a taxane) has been evaluated following the epirubicin or doxorubicin component of many anthracycline-based regimens in the APHINITY and BERENICE studies. However, only limited safety data are available on concurrent use of Perjeta and an anthracycline. In the TRYPHAENA study, Perjeta was given concurrently with epirubicin, as part of the FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen (see sections 4.8 and 5.1). Only chemotherapy-naïve patients were treated and they received low cumulative doses of epirubicin (up to 300 mg/m²). In this study, cardiac safety was similar to that observed in patients given the same regimen but with Perjeta administered sequentially (following FEC chemotherapy).

Infusion reactions

Perjeta has been associated with infusion reactions, including events with a fatal outcome (see section 4.8). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of Perjeta is recommended. If a significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see section 4.2).

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis and events with a fatal outcome, has been observed with Perjeta (see section 4.8). Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use. Perjeta must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.2).

Febrile neutropenia

Patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment (see section 4.8). In the CLEOPATRA trial in metastatic breast cancer, nadir neutrophil counts were similar in Perjeta-treated and placebo-treated patients. The higher incidence of febrile neutropenia in Perjeta-treated patients was associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. No events of febrile neutropenia were reported after cessation of docetaxel.

Diarrhoea

Perjeta may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) have a higher risk of diarrhoea compared with younger patients (< 65 years). Treat diarrhoea according to standard practice and guidelines. Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment with pertuzumab should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with pertuzumab may be reinstated.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic (PK) interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomised, pivotal trial CLEOPATRA in metastatic breast cancer. In addition, in the population PK analysis, no evidence of a drug-drug interaction has been shown between pertuzumab and trastuzumab or between pertuzumab and docetaxel. This absence of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

Five studies evaluated the effects of pertuzumab on the PK of co-administered cytotoxic agents, docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin and erlotinib. There was no evidence of any PK interaction between pertuzumab and any of these agents. The PK of pertuzumab in these studies was comparable to those observed in single-agent studies.

4.6 Fertility, pregnancy and lactation

Contraception

Women of childbearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of pertuzumab.

Pregnancy

There is limited amount of data from the use of pertuzumab in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

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

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 5.2).

Fertility

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. In repeated dose toxicity studies in cynomolgus monkeys, no definitive conclusions could be drawn on the adverse effect on male reproductive organs. No adverse reactions were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, Perjeta has a minor influence on the ability to drive or use machines. Dizziness may occur during treatment with Perjeta (see section 4.8). Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The safety of Perjeta has been evaluated in more than 6,000 patients in Phase I, II, and 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 2]. 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 with concomitant anti-neoplastic agents.

Tabulated list of adverse reactions

Table 2 summarizes the ADRs from the Perjeta-treated groups of the following pivotal clinical trials:

- CLEOPATRA, in which Perjeta was given in combination with docetaxel and trastuzumab to patients with metastatic breast cancer (n=453)

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

In addition, ADRs reported in the post-marketing setting are included in Table 2. As Perjeta was used with trastuzumab and chemotherapy in these trials, it is difficult to ascertain the causal relationship of an adverse event to a particular medicinal product.

The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Within each frequency grouping and SOC, ADRs are presented in the order of decreasing seriousness.

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

Table 2 Summary of ADRs in patients treated with Perjeta in clinical trials[^], and in the Post-marketing setting[†]

| System organ class | <u>Very Common</u> | <u>Common</u> | <u>Uncommon</u> | <u>Rare</u> |
|---|--|---|---|---|
| Infections and infestations | Nasopharyngitis | Paronychia Upper respiratory tract infection | | |
| Blood and lymphatic system disorders | Febrile neutropenia* Neutropenia Leucopenia Anaemia | | | |
| Immune system disorders | Infusion reaction ^{oo} , * | Hypersensitivity ^o , * Drug hypersensitivity ^o , * | Anaphylactic reaction ^o , * | Cytokine release syndrome ^{oo} |
| Metabolism and nutrition disorders | Decreased appetite | | | Tumour lysis syndrome [†] |
| Psychiatric disorders | Insomnia | | | |
| Nervous system disorders | Neuropathy peripheral Headache Dysgeusia Peripheral sensory neuropathy Dizziness Paraesthesia | | | |
| Eye disorders | Lacrimation increased | | | |
| Cardiac disorders | | Left ventricular dysfunction ** | Cardiac failure congestive** | |
| Vascular disorders | Hot flush | | | |
| Respiratory, thoracic and mediastinal disorders | Cough Epistaxis Dyspnoea | | Interstitial lung disease Pleural effusion | |
| Gastrointestinal disorders | Diarrhoea Vomiting | | | |

| System organ class | <u>Very Common</u> | <u>Common</u> | <u>Uncommon</u> | <u>Rare</u> |
|--|---|--------------------------|-----------------|-------------|
| | Stomatitis Nausea Constipation Dyspepsia Abdominal pain | | | |
| Skin and subcutaneous tissue disorders | Alopecia Rash Nail disorder Pruritus Dry skin | | | |
| Musculoskeletal and connective tissue disorders | Myalgia Arthralgia Pain in extremity | | | |
| General disorders and administration site conditions | Mucosal inflammation Oedema peripheral Pyrexia Fatigue Asthenia | Chills Pain Oedema | | |

^ Table 2 shows pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of Perjeta was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of Perjeta was 4, across all treatment arms) and TRYPHAENA (median number of cycles of Perjeta was 3 – 6 across treatment arms) and from the treatment period of APHINITY (median number of cycles of Perjeta was 18).

* ADRs with a fatal outcome have been reported.

** For the overall treatment period across the 4 studies. The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.

° Hypersensitivity/anaphylactic reaction is based on a group of terms.

°° Infusion reaction includes a range of different terms within a time window, see “Description of selected adverse reactions” below.

† ADRs reported in the post marketing setting=

Description of selected adverse reactions

Left ventricular dysfunction (LVD)

In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of LVD during study treatment was higher in the placebo-treated group than in the Perjeta-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta-treated group (1.8% in the placebo-treated group vs. 1.5% in the Perjeta-treated group) (see section 4.4).

In the neoadjuvant trial NEOSPHERE, in which patients received 4 cycles of Perjeta as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the Perjeta, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and trastuzumab-treated group.

In the neoadjuvant trial TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus trastuzumab and FEC (5-fluorouracil, epirubicin, cyclophosphamide) followed by Perjeta plus trastuzumab and docetaxel; 9.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH (docetaxel, carboplatin and trastuzumab). The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC (this excludes a patient who experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus trastuzumab and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel experienced symptomatic LVD.

In 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 doxorubicin and cyclophosphamide (AC) followed by Perjeta plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by

Perjeta plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10% points from baseline and to <50% was <1% (0.8% of Perjeta-treated patients vs 0.4% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 62.5% 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 2.9% of placebo-treated patients, of whom 84.4% of Perjeta-treated patients and 87.0% of placebo-treated patients had recovered at the data cutoff.

Infusion reactions

An infusion 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 trastuzumab and docetaxel to allow for the examination of Perjeta-associated reactions. On the first day when only Perjeta was administered, the overall frequency of infusion 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 reactions ($\geq 1.0\%$) 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 reactions in the Perjeta-treated group ($\geq 1.0\%$) were fatigue, dysgeusia, drug hypersensitivity, myalgia and vomiting (see section 4.4).

In neoadjuvant and adjuvant trials, Perjeta was administered on the same day as other study treatments in all cycles. Infusion reactions occurred in 18.6% - 25.0% of patients on the first day of Perjeta administration (in combination with trastuzumab and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with the majority of reactions being mild or moderate in severity.

Hypersensitivity reactions/anaphylaxis

In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of investigator reported hypersensitivity/anaphylaxis events 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 4.4).

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 the 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 the TRYPHAENA and APHINITY trials, 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 (63.0% of patients in the Perjeta-treated group and 58.3% of patients in the placebo-treated group), of which the majority were neutropenic events (see section 4.4). Febrile neutropenia occurred in 13.7% 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 among 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 (25.8%) compared with the placebo-treated group (11.3%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with trastuzumab 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, trastuzumab 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, trastuzumab and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant trastuzumab 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 trial CLEOPATRA in metastatic breast cancer, diarrhoea occurred in 68.4% of Perjeta-treated patients and 48.7% of placebo-treated patients (see section 4.4). Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 9.3% in Perjeta-treated patients vs 5.1% in placebo-treated patients. The median duration of the longest episode was 18 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, trastuzumab and docetaxel compared with 33.6% of patients treated with trastuzumab 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, trastuzumab 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

In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of Perjeta-treated patients, compared with 38.9% 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.

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta + TCH and 20.0% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given.

In the APHINITY trial, the adverse event of rash occurred in 25.8% of patients in Perjeta arm vs. 20.3% of patients in placebo arm. The majority of rash events were Grade 1 or 2.

Laboratory abnormalities

In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was balanced in the two treatment groups (86.3% of Perjeta-treated patients and 86.6% of placebo-treated patients, including 60.7% and 64.8% Grade 4 neutropenia, respectively).

In the NEOSPHERE trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 74.5% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 84.5% in patients treated with

trastuzumab and docetaxel, including 50.9% and 60.2% Grade 4 neutropenia, respectively. In the TRYPHAENA trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 85.3% in patients treated with neoadjuvant Perjeta + TCH and 77.0% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC, including 66.7% and 59.5% Grade 4 neutropenia, respectively.

In the APHINITY trial, the incidence of NCI-CTCAE v.4 Grade 3-4 neutropenia was 40.6% in patients treated with Perjeta, trastuzumab and chemotherapy compared with 39.1% in patients treated with placebo, trastuzumab and chemotherapy, including 28.3% and 26.5% Grade 4 neutropenia, respectively.

Elderly Patients

The incidence of the following all grade adverse events was at least 5% higher in patients ≥ 65 years of age, compared to patients < 65 years of age: decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhoea. Limited data are available in patients > 75 years of age.

Reporting of suspected adverse reactions

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

Any suspected adverse events should be reported to the Ministry of Health according to the national regulation by using the form <https://sideeffects.health.gov.il/>

4.9 Overdose

The maximum tolerated dose of pertuzumab 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FD02

Mechanism of action

Pertuzumab 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, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumour cells, the combination of pertuzumab and trastuzumab significantly augmented antitumour activity in HER2-overexpressing xenograft models.

Clinical efficacy and safety

The efficacy of Perjeta in HER2-positive breast cancer is supported by a randomised phase III trial and a single-arm phase II trial in metastatic breast cancer, two randomised neoadjuvant phase II trials in early breast cancer (one controlled), a non-randomised neoadjuvant phase II trial, and a randomised phase III trial in the adjuvant setting.

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 trastuzumab and docetaxel

CLEOPATRA (WO20698) 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 4.4). 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 randomised 1:1 to receive placebo + trastuzumab + docetaxel or Perjeta + trastuzumab + docetaxel.

Perjeta and trastuzumab were given at standard doses in a 3-weekly regimen. Patients were treated with Perjeta and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m² as an intravenous infusion every three 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.

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 randomisation to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumour assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT B Quality of Life questionnaire.

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as oestrogen receptor (ER) positive and/or progesterone receptor (PgR) 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 trastuzumab. 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 3. 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 3 Summary of efficacy from CLEOPATRA study

| Parameter | Placebo+ trastuzumab + docetaxel n=406 | Perjeta+ trastuzumab + docetaxel n=402 | HR (95% CI) | p-value |
|---|---|---|--|----------------|
| Progression-Free Survival (independent review) – primary endpoint* | | | | |
| no. of patients with an event | 242 (59%) | 191 (47.5%) | 0.62 | <0.0001 |
| Median months | 12.4 | 18.5 | [0.51;0.75] | |
| Overall Survival - secondary endpoint** | | | | |
| no. of patients with an event | 221 (54.4%) | 168 (41.8%) | 0.68 | 0.0002 |
| Median months | 40.8 | 56.5 | [0.56;0.84] | |
| Objective Response Rate (ORR)^ - secondary endpoint | | | | |
| 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] | | |

* Primary progression-free survival analysis, cutoff date 13th May 2011.

** Event-driven final overall survival analysis, cutoff date 11th February 2014.

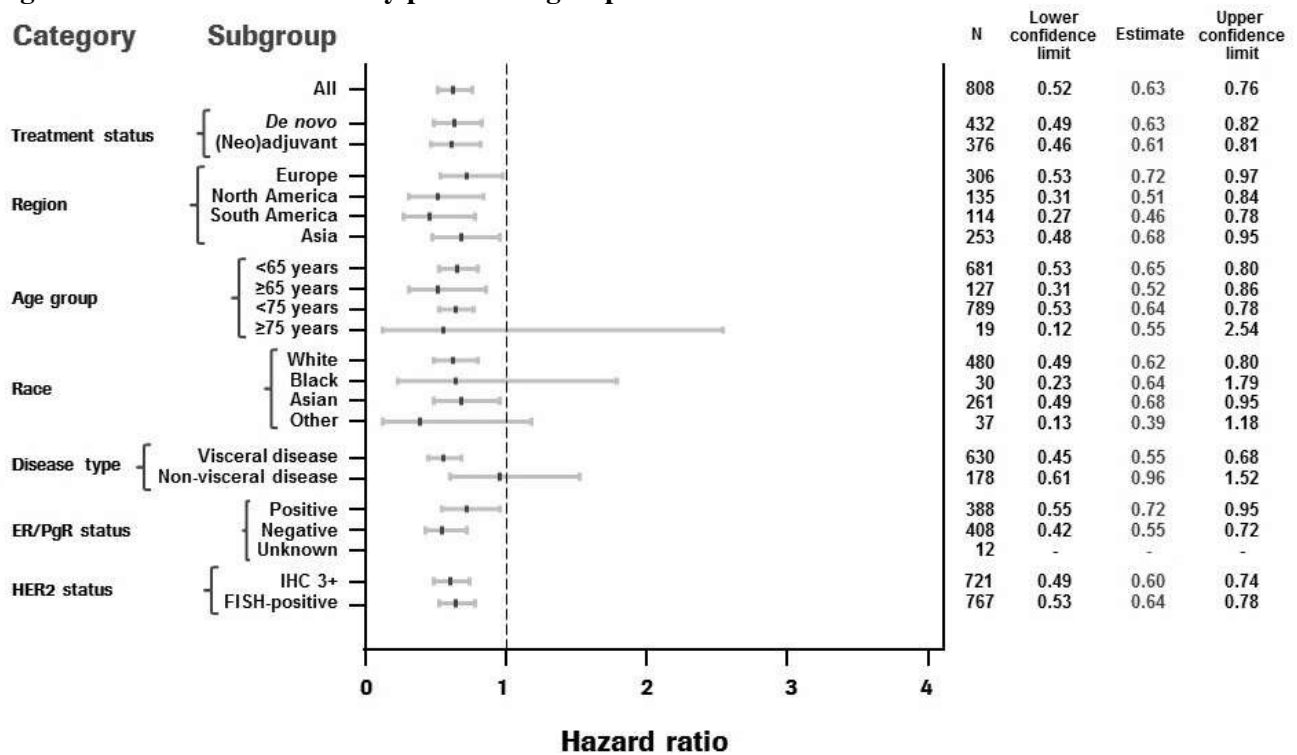
*** Patients with best overall response of confirmed CR or PR by RECIST.

† Evaluated in patients with Best Overall Response of CR or PR.

^ Objective response rate and duration of response are based on IRF-assessed tumour assessments.

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 trastuzumab (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 trastuzumab (n = 288).

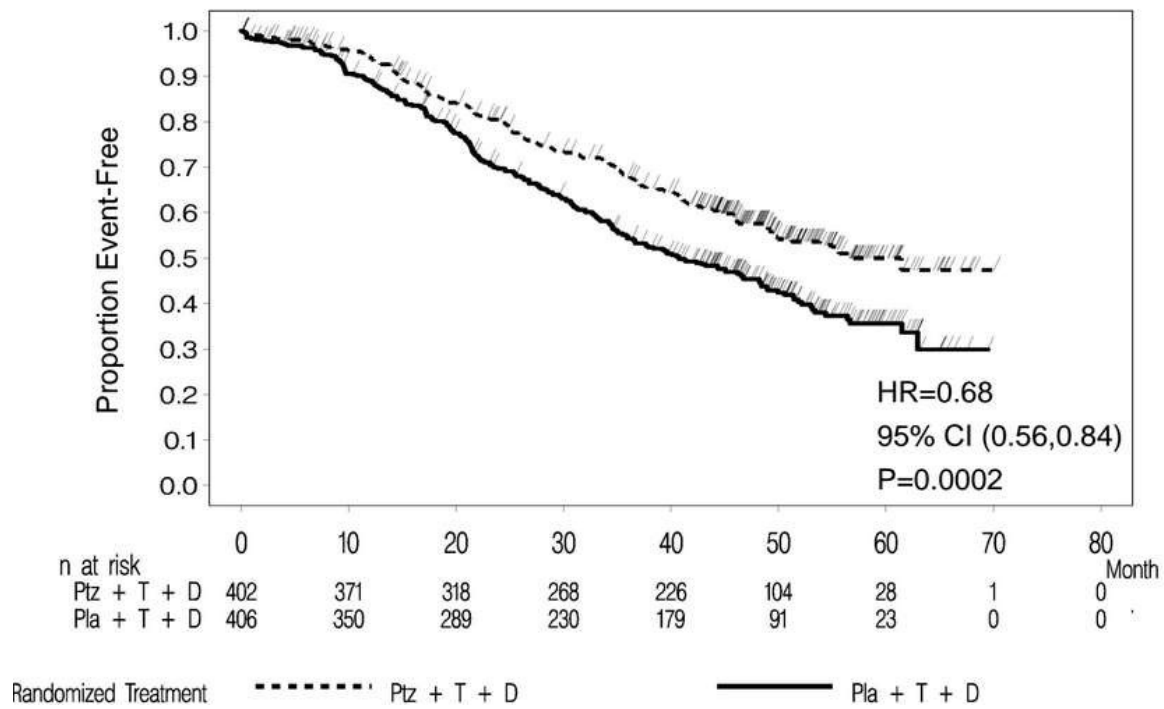
Figure 1 IRF-assessed PFS by patient subgroup



The event-driven final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the Perjeta-treated group). The statistically significant OS benefit in favour of the Perjeta-treated group, previously observed at an interim analysis of OS (performed one year after the primary analysis), was maintained (HR 0.68, $p = 0.0002$ log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the Perjeta-treated group (see Table 3, Figure 2).

A descriptive analysis of OS performed at the end of the study when 515 patients had died (280 in the placebo-treated group and 235 in the Perjeta-treated group) showed that the statistically significant OS benefit in favour of the Perjeta-treated group was maintained over time after a median follow-up of 99 months (HR 0.69, $p < 0.0001$ log-rank test; median time to death 40.8 months [placebo-treated group] versus 57.1 months [Perjeta-treated group]). Landmark survival estimates at 8 years were 37% in the Perjeta-treated group and 23% in the placebo-treated group.

Figure 2 Kaplan-Meier Curve of Event-Driven Overall Survival



HR= hazard ratio; CI= confidence interval; Pla= placebo; Ptz= pertuzumab (Perjeta); T= trastuzumab (Herceptin); D= docetaxel.

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 trastuzumab. Treatment with Perjeta and trastuzumab 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 trastuzumab.

Early Breast Cancer

Neoadjuvant Treatment

In the neoadjuvant setting, locally advanced and inflammatory breast cancers are considered as high-risk irrespective of hormone receptor status. In early stage breast cancer, tumor size, grade, hormone receptor status and lymph node metastases should be taken into account in the risk assessment.

The indication in the neoadjuvant treatment of breast cancer is based on demonstration of an improvement in pathological complete response rate, and trends to improvement in disease-free survival that nevertheless do not establish or precisely measure a benefit with regard to long-term outcomes, such as overall survival or disease-free survival.

NEOSPHERE (WO20697)

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

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

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

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

Pertuzumab was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. Docetaxel was given intravenously at an initial dose of 75 mg/ m² followed by 75 mg/ m² or 100 mg/ m² (if tolerated) every 3 weeks. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m²), epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²) (FEC) given intravenously every three weeks, and trastuzumab administered intravenously every three weeks to complete one year of therapy. Patients who only received Perjeta plus trastuzumab prior to surgery subsequently received both FEC and docetaxel post surgery.

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 tumours only), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypTON0).

Demographics were well balanced (median age was 49-50 years, the majority were caucasian (71%)) and all patients 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 presented in Table 4. A statistically significant improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition. The difference in pCR rate is considered likely to translate into a clinically meaningful difference in long term outcomes and is supported by positive trends in PFS (HR 0.69, 95% CI 0.34, 1.40) and DFS (HR 0.60, 95% CI 0.28, 1.27).

The pCR rates as well as the magnitude of benefit with Perjeta (Perjeta plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel) were lower in the subgroup of patients with hormone receptor-positive tumours (difference of 6% in pCR in the breast) than in patients with hormone receptor-negative tumours (difference of 26.4% in pCR in the breast).

pCR rates were similar in patients with operable versus locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions but the pCR rate was higher in patients who received Perjeta plus trastuzumab and docetaxel.

TRYPHAENA (BO22280)

TRYPHAENA is a multicentre, randomised phase II clinical trial conducted in 225 adult female patients with HER2-positive locally advanced, operable, or inflammatory breast cancer (T2-4d; primary tumour > 2cm in diameter) who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (see section 4.4) or LVEF < 55% were not included. The majority of patients were less than 65 years old. Patients were randomised to receive one of three neoadjuvant regimens prior to surgery as follows:

- 3 cycles of FEC followed by 3 cycles of docetaxel, all given concurrently with Perjeta and trastuzumab
- 3 cycles of FEC alone followed by 3 cycles of docetaxel, with trastuzumab and Perjeta given concurrently
- 6 cycles of TCH in combination with Perjeta.

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

Pertuzumab was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. FEC (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 group treated with Perjeta in combination with TCH, docetaxel was given intravenously at 75 mg/m² (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received trastuzumab to complete one year of therapy.

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

Compared with published data for similar regimens without pertuzumab, high pCR rates were observed in all 3 treatment arms (see Table 4). A consistent pattern of results was observed regardless of pCR definition used. The pCR rates were lower in the subgroup of patients with hormone receptor-positive tumours (range 46.2% to 50.0%) than in patients with hormone receptor-negative tumours (range 65.0% to 83.8%).

pCR rates were similar in patients with operable and locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions.

Table 4 NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Overview of efficacy (Intent to Treat Population)

| Parameter | NEOSPHERE (WO20697) | | | | TRYPHAENA (BO22280) | | |
|---|----------------------------------|---|--|--|--|---|----------------------------|
| | Trastuzumab + Docetaxel N=107 | Perjeta+ Trastuzumab + Docetaxel N=107 | Perjeta+ Trastuzumab N=107 | Perjeta + Docetaxel N=96 | Perjeta+ Trastuzumab + FEC→ Perjeta+ Trastuzumab + Docetaxel N=73 | FEC→ Perjeta+ Trastuzumab + Docetaxel N=75 | Perjeta +TCH N=77 |
| pCR rate in the breast (ypT0/is) n (%) [95% CI] ¹ | 31 (29.0%) [20.6; 38.5] | 49 (45.8%) [36.1; 55.7] | 18 (16.8%) [10.3; 25.3] | 23 (24.0%) [15.8; 33.7] | 45 (61.6%) [49.5; 72.8] | 43 (57.3%) [45.4; 68.7] | 51 (66.2%) [54.6; 76.6] |
| Difference in pCR rates ² [95% CI] ³ | | +16.8 % [3.5; 30.1] | -12.2 % [-23.8; -0.5] | -21.8 % [-35.1; -8.5] | NA | NA | NA |
| p-value (with Simes corr. for CMH test) ⁴ | | 0.0141 (vs. Trastuzumab+ Docetaxel) | 0.0198 (vs. Trastuzumab+ Docetaxel) | 0.0030 (vs Perjeta+ Trastuzumab +Docetaxel) | NA | NA | NA |
| pCR rate in the breast and lymph node (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 Response ⁵ | 79 (79.8%) | 89 (88.1%) | 69 (67.6%) | 65 (71.4%) | 67 (91.8%) | 71 (94.7%) | 69 (89.6%) |

FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab, CMH: Cochran–Mantel–Haenszel

1. 95% CI for one sample binomial using Pearson-Clopper method.

2. Treatment Perjeta+Trastuzumab+Docetaxel and Perjeta+Trastuzumab are compared to Trastuzumab+ Docetaxel while Perjeta+Docetaxel is compared to Perjeta+Trastuzumab+Docetaxel.

3. Approximate 95% CI for difference of two response 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, multicentre, multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage 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 trastuzumab plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

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

Following surgery all patients received Perjeta and trastuzumab intravenously every 3 weeks to complete 1 year of therapy.

The primary endpoint of the BERENICE trial is cardiac safety in the neoadjuvant period of the trial. The primary endpoint of cardiac safety, i.e. the incidence of NYHA Class III/IV LVD and LVEF declines, was consistent with previous data in the neoadjuvant setting (see section 4.4. and 4.8).

Adjuvant Treatment

In the adjuvant setting, based on data from the APHINITY study, HER2-positive early breast cancer patients at high risk of recurrence are defined as those with lymph node-positive or hormone receptor-negative disease.

APHINITY (BO25126)

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

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

Pertuzumab and trastuzumab were administered intravenously (see section 4.2) every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (up to 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 randomisation to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Secondary efficacy endpoints were IDFS including second primary non-breast cancer, overall survival (OS), disease-free survival (DFS), recurrence-free interval (RFI) and distant recurrence-free interval (DRFI).

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 of 45.4 months, the APHINITY study showed a 19% (hazard ratio [HR] = 0.81; 95% CI 0.66, 1.00 p-value 0.0446) reduction in risk of recurrence or death in patients randomised to receive Perjeta compared with patients randomised to receive placebo.

After a median follow-up of 101.2 months (8.4 years), at the third OS interim analysis, the number of deaths in patients randomised to the Perjeta arm was 168 deaths [7.0%] compared with 202 deaths [8.4%] in the placebo arm; HR=0.83, 95% CI [0.68, 1.02].

The efficacy results from the APHINITY trial are summarised in Table 5 and in Figure 3.

Table 5 Overall Efficacy: ITT Population

| | Perjeta + trastuzumab + Chemotherapy N=2400 | Placebo + trastuzumab + Chemotherapy N=2404 |
|---|--|--|
| Primary Endpoint | | |
| Invasive Disease Free Survival (IDFS) * | | |
| Number (%) of patients with event | 171 (7.1%) | 210 (8.7%) |
| HR [95% CI] | 0.81 [0.66, 1.00] | |
| p-value (Log-Rank test, stratified ¹) | 0.0446 | |
| 3 year event-free rate ² [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, stratified ¹) | 0.0430 | |
| 3 year event-free rate ² [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 ¹) | 0.0327 | |
| 3 year event-free rate ² [95% CI] | 93.4 [92.4, 94.4] | 92.3 [91.2, 93.4] |
| Overall Survival (OS)** | | |
| Number (%) of patients with event | 168 (7.0%) | 202 (8.4%) |
| HR [95% CI] | 0.83 [0.68, 1.02] | |

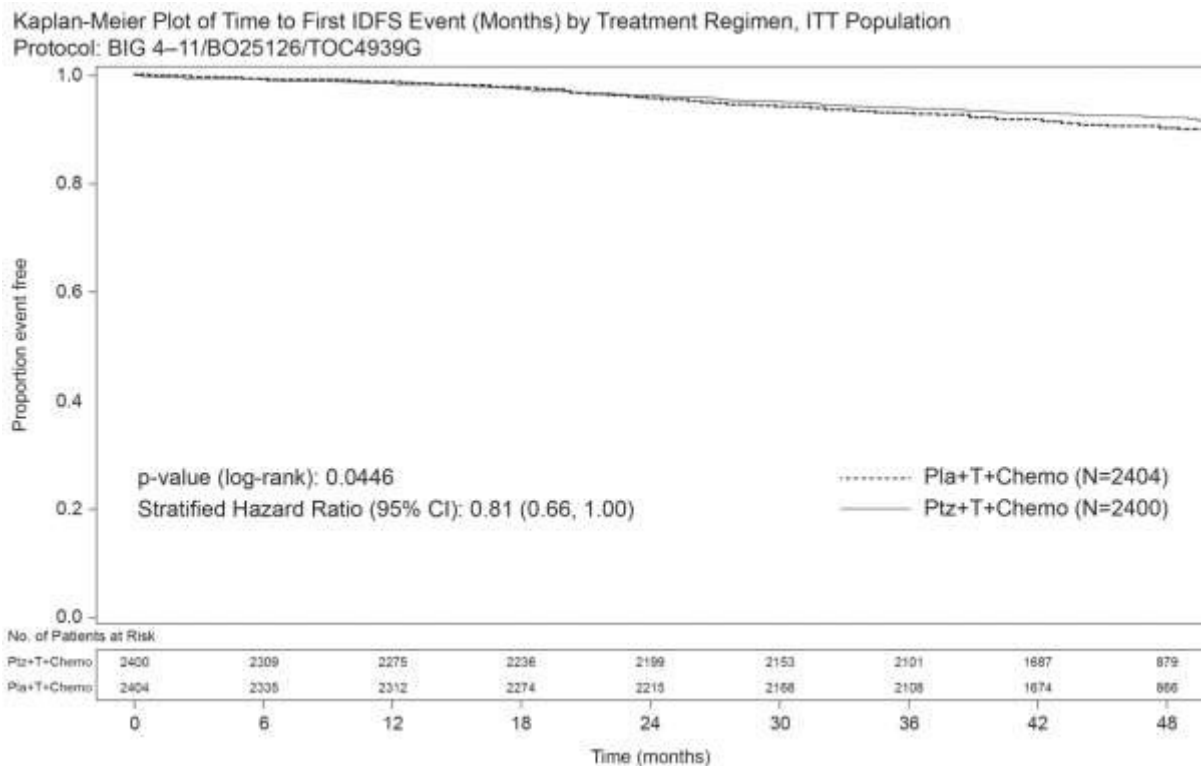
Key to abbreviations (Table 5): HR: Hazard Ratio; CI: Confidence Interval

* Primary Invasive Disease Free Survival analysis, cutoff date 19th December 2016.

** Data from 3rd interim analysis for overall survival, cutoff date 10th January 2022.1. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.

2. 3-year event-free rate derived from Kaplan-Meier estimates.

Figure 3 Kaplan-Meier Curve of Invasive Disease Free Survival



IDFS= invasive disease free survival; CI= confidence interval; Pla= placebo; Ptz= pertuzumab (Perjeta); T= trastuzumab.

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

Results of Subgroup Analysis

At the time of the primary analysis, the benefits of Perjeta were more apparent in subgroups of patients a high risk of recurrence: patients with node-positive or hormone receptor-negative disease (see table 6).

Table 6 Efficacy results in subgroups by nodal status and hormone receptor status¹

| Population | Number of IDFS events/Total N (%) | | Unstratified HR (95% CI) |
|--------------------------------|--------------------------------------|--------------------------------------|--------------------------|
| | Perjeta + trastuzumab + chemotherapy | Placebo + trastuzumab + chemotherapy | |
| Nodal status | | | |
| Positive | 139/1503 (9.2%) | 181/1502 (12.1%) | 0.77 (0.62, 0.96) |
| Negative | 32/897 (3.6%) | 29/902 (3.2%) | 1.13 (0.68, 1.86) |
| Hormone receptor status | | | |
| Negative | 71/864 (8.2%) | 91/858 (10.6%) | 0.76 (0.56, 1.04) |
| Positive | 100/1536 (6.5%) | 119/1546 (7.7%) | 0.86 (0.66, 1.13) |

¹ Prespecified subgroup analyses without adjusting for multiple comparisons, therefore, results are considered descriptive.

Estimates of IDFS rates in the lymph 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 placebo-treated patients, respectively. In the lymph 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-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. In the hormone receptor-positive subgroup estimates of IDFS rates 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.

Patient Reported Outcomes (PRO)

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

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

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

Immunogenicity

Patients in the pivotal trial CLEOPATRA were tested at multiple time-points for anti-drug antibodies (ADA) to Perjeta. 3.3% (13/389 patients) of Perjeta-treated patients and 6.7% (25/372 patients) of placebo-treated patients 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.

5.2 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 pertuzumab doses ranging from 2 to 25 mg/kg administered every 3 weeks as a 30-60 minutes intravenous infusion.

Absorption

Perjeta is administered as an intravenous infusion.

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

Pertuzumab 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 pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

Renal impairment

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

5.3 Preclinical 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-Histidine
Glacial Acetic Acid
Polysorbate 20
Sterile Water for Injection

6.2 Incompatibilities

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The expiry date of the product is indicated on the packaging materials.

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C and up to 30 days at 2°C to 8°C protected from light.

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, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (Type I glass) with a stopper (butyl rubber) containing 14 ml of solution.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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 is for single use only.

The vial must not be shaken. 14 ml of Perjeta concentrate should be withdrawn from the vial using a sterile needle and syringe and diluted into a 250 ml PVC or non-PVC polyolefin infusion bag of sodium chloride 9 mg/ml (0.9%) solution for infusion. After dilution, one ml of solution should contain approximately 3.02 mg of pertuzumab (840 mg/278 ml) for the initial dose where two vials are required and approximately 1.59 mg of pertuzumab (420 mg/264 ml) for the maintenance dose where one vial is required. The bag should be gently inverted to mix the solution in order to avoid foaming.

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used. Once the infusion is prepared it should be administered immediately (see section 6.3).

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

Perjeta is compatible with polyvinylchloride (PVC) or non-PVC polyolefin bags including polyethylene.

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.B 6391, Hod Hasharon 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

149.26.33749.00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland.

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