

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

Metastatic Breast Cancer

Perjeta is indicated for use in combination with trastuzumab and docetaxel in 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.

Neoadjuvant Treatment of Breast Cancer

Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1)

4.2 Posology and method of administration

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 facilities are 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

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.

When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.

When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m², administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m² on subsequent cycles if the initial dose is well tolerated (the docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and Perjeta).

The medicinal products should be administered sequentially and not mixed in the same infusion bag. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, this should be administered after Perjeta and trastuzumab. An observation period of 30 to 60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel (see section 4.4).

Metastatic Breast Cancer

Patients should be treated with Perjeta and trastuzumab until disease progression or unmanageable toxicity.

Neoadjuvant Treatment of Breast Cancer

Perjeta should be administered for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment (see section 5.1).

Delayed or missed doses

If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta should be administered as soon as possible without regard to the next planned dose.

If the time between two sequential infusions is 6 weeks or more, the initial loading dose of 840 mg Perjeta should be re-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.

Dose modification

Dose reductions are not recommended for Perjeta.

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 summary of product characteristics (SmPC).

For trastuzumab, dose reductions are not recommended, see trastuzumab summary of product characteristics (SmPC).

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

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

Left ventricular dysfunction

Perjeta and trastuzumab should be withheld for at least 3 weeks for any of the following:

- signs and symptoms suggestive of congestive heart failure (Perjeta should be discontinued if symptomatic heart failure is confirmed)
- a drop in left ventricular ejection fraction (LVEF) to less than 40%
- a LVEF of 40%-45% associated with a fall of $\geq 10\%$ points below pre-treatment values.

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

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

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).

Elderly patients

Limited data are available on the safety and efficacy of Perjeta in patients ≥ 65 years of age. No significant differences in safety and efficacy of Perjeta were observed between elderly patients aged 65 to 75 years and adult patients aged < 65 years. No dose adjustment is necessary in the elderly population ≥ 65 years of age. 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 5.2).

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 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).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and 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. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. In the pivotal trial CLEOPATRA in patients with metastatic breast cancer, Perjeta in combination with trastuzumab and docetaxel was not associated with a greater incidence of symptomatic left ventricular systolic dysfunction (LVD) or LVEF declines compared with placebo and trastuzumab and docetaxel (see section 4.8).

In the neoadjuvant period of NEOSPHERE, the incidence of LVD was higher in the Perjeta-treated groups than in those who did not receive Perjeta. An increased incidence of LVEF declines was also observed in patients treated with Perjeta in combination with trastuzumab and docetaxel; LVEF recovered to $\geq 50\%$ in all patients. Findings were similar in other neoadjuvant trials (see section 5.1).

Perjeta has not been studied in patients with: a pre-treatment LVEF value of $\leq 50\%$; 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 $> 360 \text{ mg/m}^2$ of doxorubicin or its equivalent.

Assess LVEF prior to initiation of Perjeta and during treatment with Perjeta (every 3 cycles in the metastatic setting and every 2 cycles in the neoadjuvant setting) to ensure that LVEF is within the institution's normal limits. If LVEF is $< 40\%$ or 40% - 45% associated with $\geq 10\%$ points below the pretreatment value, Perjeta and trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see section 4.2).

Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Perjeta with an anthracycline. There are limited safety data available from the TRYPHAENA study concerning sequential or concomitant administration of Perjeta with epirubicin, as part of the FEC regimen (see sections 4.8 and 5.1). Cardiac safety data from the BERENICE study, in which patients were treated sequentially with either epirubicin or doxorubicin followed by Perjeta and trastuzumab, were consistent with previous data in the neoadjuvant setting (see section 4.8).

Based on the pharmacological actions of pertuzumab and anthracyclines an increased risk of cardiac toxicity might be expected from concomitant use of these agents compared with sequential use, although not seen in the TRYPHAENA study. In this study, only chemotherapy-naïve subjects, not

receiving additional chemotherapy after surgery, were treated with low cumulative dose of epirubicin, i.e. up to 300 mg/m².

Infusion reactions

Perjeta has been associated with infusion reactions (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, has been observed in clinical trials with Perjeta (see section 4.8). Medications 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). Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients (see section 4.3).

Febrile neutropenia

Patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, 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

Pertuzumab may elicit severe diarrhoea. In case of onset of severe diarrhoea an anti-diarrhoeal treatment should be instituted and interruption of the treatment with pertuzumab should be considered if no improvement of the condition is achieved. When the diarrhoea is under control the 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 trial in the neoadjuvant setting.

Four studies have evaluated the effects of pertuzumab on the PK of co-administered cytotoxic agents, docetaxel, gemcitabine, erlotinib and capecitabine. 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 Perjeta.

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. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, Perjeta is not expected to influence the ability to drive or use machines. 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 2,000 patients in the randomized trials CLEOPATRA (n=808), NEOSPHERE (n=417), and TRYPHAENA (n=225) and in Phase I and phase II trials conducted in patients with various malignancies and predominantly treated with Perjeta in combination with other antineoplastic agents. The safety of Perjeta in Phase I and II studies (including the BERENICE trial) was generally consistent with that observed in the CLEOPATRA, NEOSPHERE and TRYPHAENA trials (pooled in table 1), 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.

Metastatic Breast Cancer

In the pivotal clinical trial CLEOPATRA, 408 patients received at least one dose of Perjeta in combination with trastuzumab and docetaxel. The most common ADRs ($\geq 50\%$) seen with Perjeta in combination with trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs ($> 10\%$) were neutropenia, febrile neutropenia and leucopenia, and the most common serious adverse events were febrile neutropenia, neutropenia and diarrhoea. Treatment-related deaths occurred in 1.2% of patients in the Perjeta-treated group and 1.5% of patients in the placebo-treated group and were mainly due to febrile neutropenia and/or infection.

In the pivotal trial CLEOPATRA, ADRs were reported less frequently after discontinuation of docetaxel treatment. After discontinuation of docetaxel, ADRs in the Perjeta and trastuzumab treated group occurred in < 10% of patients with the exception of diarrhoea (28.1%), upper respiratory tract infection (18.3%), rash (18.3%), headache (17.0%), fatigue (13.4%), nasopharyngitis (17.0%), asthenia (13.4%), pruritus (13.7%), arthralgia (11.4%), nausea (12.7%), pain in extremity (13.4%), back pain (12.1%) and cough (12.1%).

Neoadjuvant Treatment of Breast Cancer

In the neoadjuvant trial NEOSPHERE, the most common ADRs ($\geq 50\%$) seen with Perjeta in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADR ($\geq 10\%$) was neutropenia.

In the neoadjuvant trial TRYPHAENA, when Perjeta was administered in combination with trastuzumab and FEC (5-fluorouracil, epirubicin, cyclophosphamide) for 3 cycles followed by 3 cycles of Perjeta, trastuzumab and docetaxel, the most common ADRs ($\geq 50\%$) were neutropenia, diarrhoea and nausea. The most common NCI-CTCAE v.3 Grade 3-4 ADRs ($\geq 10\%$) were neutropenia, febrile neutropenia and leucopenia. When Perjeta was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide), the most common ADRs ($\geq 50\%$) were diarrhoea, nausea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs ($\geq 10\%$) were neutropenia and leucopenia. Similarly, when Perjeta was administered in combination with TCH (docetaxel, carboplatin and trastuzumab) for 6 cycles, the most common ADRs ($\geq 50\%$) were diarrhoea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs ($\geq 10\%$) were neutropenia, febrile neutropenia, anaemia, leucopenia and diarrhoea. The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established.

In the BERENICE trial, when Perjeta was administered in combination with trastuzumab and paclitaxel for four cycles following four cycles of two weekly doxorubicin and cyclophosphamide (dose dense AC), the most common ADRs ($\geq 50\%$) were nausea, diarrhoea, fatigue and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADR ($\geq 10\%$) was neutropenia. When Perjeta was administered in combination with trastuzumab and docetaxel for four cycles following four cycles of FEC the most common ADRs ($\geq 50\%$) were nausea, diarrhea and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADRs ($\geq 10\%$) were febrile neutropenia and diarrhoea. The overall safety profile seen in BERENICE is consistent with that observed in previous data in the neoadjuvant setting for NEOSPHERE and TRYPHAENA.

Tabulated list of adverse reactions

Table 1 summarizes the ADRs from the pivotal trial CLEOPATRA, in which Perjeta was given in combination with docetaxel and trastuzumab to patients with metastatic breast cancer, and from the neoadjuvant trials NEOSPHERE and TRYPHAENA, in which Perjeta was given in combination with trastuzumab and chemotherapy to patients with early breast cancer. As Perjeta is used with trastuzumab and chemotherapy, 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, adverse reactions are presented in the order of decreasing seriousness.

Table 1 Summary of ADRs in patients treated with Perjeta in the metastatic and neoadjuvant setting[^]

System organ class	<u>Very Common</u>	<u>Common</u>	<u>Uncommon</u>
Infections and infestations	Upper respiratory tract infection Nasopharyngitis	Paronychia	
Blood and lymphatic system disorders	Febrile neutropenia* Neutropenia Leucopenia Anaemia		
Immune system disorders	Hypersensitivity/anaphylactic reaction ^o Infusion reaction/cytokine release syndrome ^{oo}		
Metabolism and nutrition disorders	Decreased appetite †		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral Headache † Dysgeusia	Peripheral sensory neuropathy Dizziness	
Eye disorders		Lacrimation increased	
Cardiac disorders		Left ventricular dysfunction † (including congestive heart failure)**	
Respiratory, thoracic and mediastinal disorders	Cough †	Pleural effusion Dyspnoea †	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea † Vomiting † Stomatitis Nausea † Constipation † Dyspepsia		
Skin and subcutaneous tissue disorders	Alopecia Rash † Nail disorder	Pruritus Dry skin	
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia		

System organ class	<i>Very Common</i>	<i>Common</i>	<i>Uncommon</i>
General disorders and administration site conditions	Mucositis/mucosal inflammation Pain † Oedema † Pyrexia Fatigue † Asthenia †	Chills	

[^] Table 1 shows pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of Perjeta was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of Perjeta was 4, across all treatment arms) and TRYPHAENA (median number of cycles of Perjeta was 3 – 6 across treatment arms)

* Including adverse reactions with a fatal outcome.

** For the overall treatment period across the 3 studies.

† Except for febrile neutropenia, neutropenia, leucopenia, lacrimation increased, interstitial lung disease, paronychia, and alopecia, all events in this table were also reported in at least 1% of patients participating in Perjeta monotherapy trials, although not necessarily considered causally related to Perjeta by the investigator. Very common events (reported in $\geq 10\%$ of Perjeta monotherapy-treated patients) are marked in the Table with a †.

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

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

Description of selected adverse reactions

Left ventricular dysfunction

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 (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. 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.

Infusion reactions

An infusion reaction was defined in the pivotal trial CLEOPATRA in metastatic breast cancer 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 the NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, Perjeta was administered on the same day as the other study treatment drugs in all cycles. Infusion reactions were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with a majority of reactions being mild or moderate.

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 NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In TRYPHAENA, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2%), of which 2.6% were NCI-CTCAE v.3 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. 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.

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. 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.

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.

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.

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. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in [Appendix V](#)**.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 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 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).

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

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive) and approximately half of the patients in each treatment group had received prior adjuvant or 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 2. 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 2 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.

** Final analysis of overall survival, cutoff date 11th February 2014.

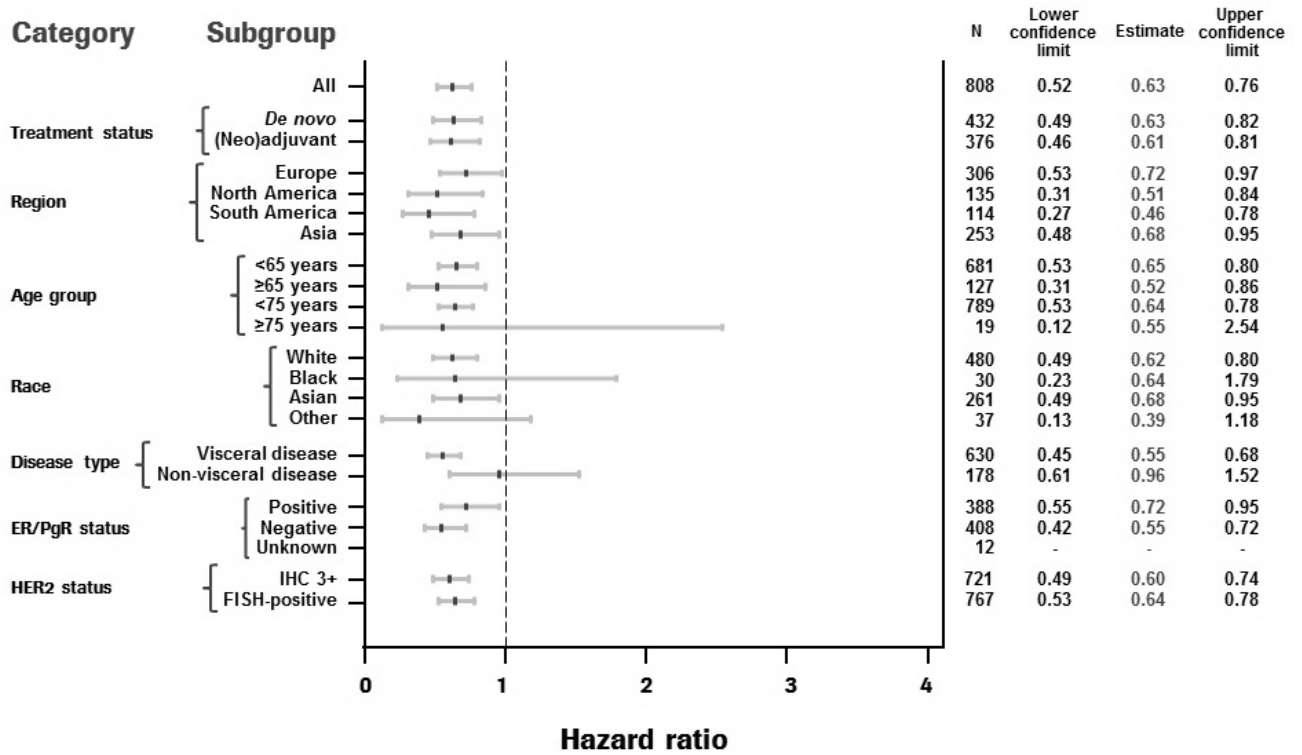
*** Patients with best overall response of confirmed CR or PR by RECIST.

† 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.

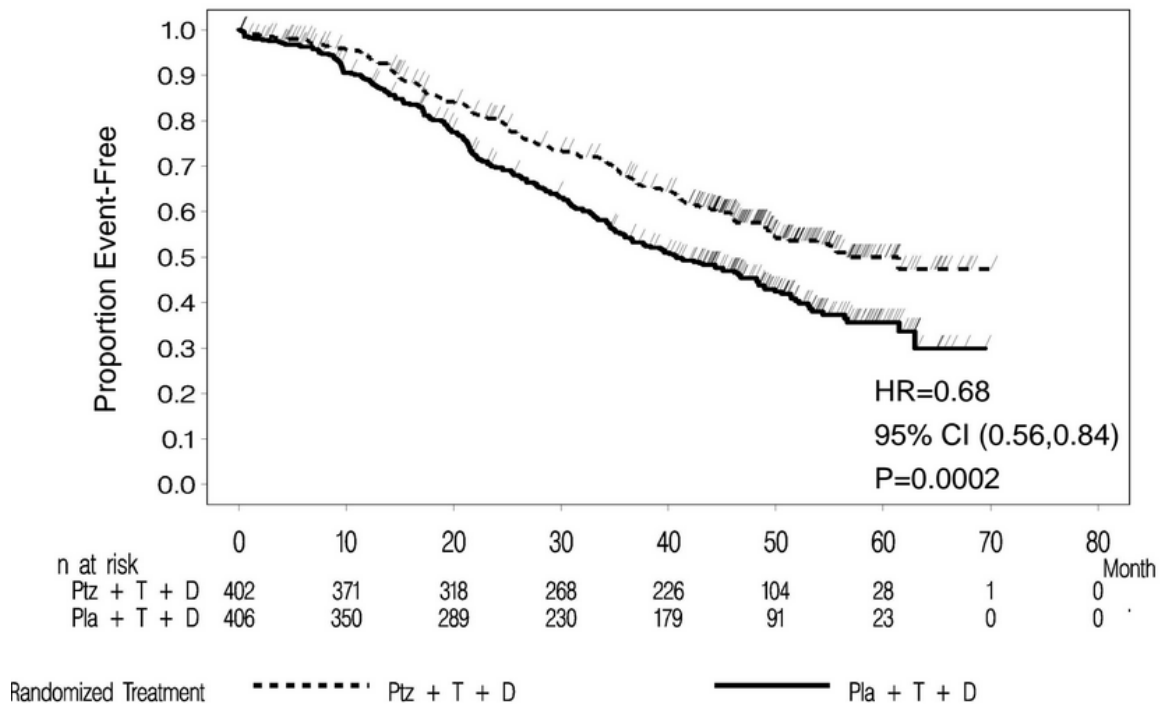
Consistent results were observed across pre-specified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see Figure 1). A post hoc exploratory analysis revealed that for patients who 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 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 2, Figure 2).

Figure 2 Kaplan-Meier Curve of 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.

Neoadjuvant Treatment of Breast Cancer

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

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

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

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

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. 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 ypT0N0).

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 3. 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.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. 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 3). 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 3 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]

	NEOSPHERE (WO20697)				TRYPHAENA (BO22280)		
Parameter	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
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).

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 ADAs. Of these 38 patients, none experienced severe (NCI-CTCAE Grade 4) infusion or hypersensitivity reactions (anaphylaxis) that were clearly related to ADA. In the neoadjuvant part of the BERENICE trial, 0.3% (1/383) of the patients treated with Perjeta tested positive for ADA. This patient did not experience any anaphylactic or hypersensitivity reactions. However, Grade 3 hypersensitivity reactions associated with detectable ADAs occurred in 2 of 366 (0.5%) Perjeta-treated patients in phase I and II studies. There are currently insufficient data to evaluate the effects of ADA on the efficacy of Perjeta in combination with trastuzumab and docetaxel.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Perjeta in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

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 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. There have been no studies performed with other routes of administration.

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 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 [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 Perjeta 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 Perjeta based on these covariates.

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

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

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

6.2 Incompatibilities

No incompatibilities between Perjeta and polyvinylchloride (PVC) or non-PVC polyolefin bags including polyethylene have been observed. 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 vial
2 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°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, 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 and is administered intravenously by infusion.

The vial must not be shaken. 14 ml of Perjeta concentrate should be withdrawn from the vial 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 discoloration 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.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/813/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance(s)

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA 95688-9431
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
MO28047 (PERUSE) A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer	September 2020
Post-authorisation efficacy study (PAES): In order to provide long-term efficacy data in terms of DFS and OS, the MAH should submit the results of study BO25126 (APHINITY), a randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	September 2017

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Perjeta 420 mg concentrate for solution for infusion
pertuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
420 mg/14 ml
1 x 14 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Do not shake
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
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Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/813/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Perjeta 420 mg concentrate for solution for infusion
pertuzumab
IV

2. METHOD OF ADMINISTRATION

For intravenous use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

420 mg/14 ml

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Perjeta 420 mg concentrate for solution for infusion

Pertuzumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start being given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Perjeta is and what it is used for
2. What you need to know before you are given Perjeta
3. How you are given Perjeta
4. Possible side effects
5. How to store Perjeta
6. Contents of the pack and other information

1. What Perjeta is and what it is used for

Perjeta contains the active substance pertuzumab and is used to treat adult patients with breast cancer when:

- The breast cancer has been identified to be of the “HER2-positive” form – your doctor will test you for this.
- The cancer has spread to other parts of the body (metastasised) and has not previously been treated with anticancer medicines (chemotherapy) or other medicines designed to attach to HER2, or else the cancer has come back in the breast after previous treatment.
- The cancer has not spread to other parts of the body and treatment is going to be given before surgery takes place (treatment before surgery is called neoadjuvant therapy)

As well as Perjeta you will also receive trastuzumab and the chemotherapy medicine docetaxel for advanced (metastatic) breast cancer. If you are having Perjeta before surgery, you may also receive other chemotherapy as part of your overall treatment. Information about these medicines is described in separate package leaflets. Ask your doctor or nurse to give you information about these other medicines.

How Perjeta works

Perjeta is a type of medicine called a “monoclonal antibody” which attaches itself to specific targets in your body and on the cancer cells.

Perjeta recognises and attaches to a target called “human epidermal growth factor receptor 2” (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When Perjeta attaches to the HER2 cancer cells, it may slow or stop the cancer cells from growing, or may kill them.

2. What you need to know before you are given Perjeta

You must not be given Perjeta

- If you are allergic to pertuzumab, or to any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you are given Perjeta.

Warnings and precautions

Talk to your doctor or nurse before you are given Perjeta if:

- You have ever had heart problems (such as heart failure, treatment for serious irregular heartbeats, uncontrolled high blood pressure, recent heart attack) – your doctor will run tests to check if your heart is working properly.
- You have ever had heart problems during previous treatment with trastuzumab.
- You have ever had a chemotherapy medicine from the class called anthracyclines, e.g. doxorubicin or epirubicin – these medicines can damage heart muscle and increase the risk of heart problems with Perjeta.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Perjeta.

Infusion reactions

Infusion reactions, allergic or anaphylactic (more severe allergic) reactions can happen. Your doctor or nurse will check for side effects during your infusion and for 30 to 60 minutes afterwards. If you get any serious reaction, your doctor may stop treatment with Perjeta. See section 4 “Serious side effects” for more details about infusion reactions to look out for during the infusion and thereafter.

Heart problems

Treatment with Perjeta may affect the heart. Therefore, your heart function will be checked before and during treatment with Perjeta. See section 4 “Serious side effects” for more details about signs of heart problems to look out for.

Febrile neutropenia (Low white blood cells with fever)

When Perjeta is given with other cancer treatments (trastuzumab and chemotherapy), the number of white blood cells may drop and fever (raised temperature) may develop. If you have inflammation of the digestive tract (e.g. sore mouth or diarrhoea) you may be more likely to develop this side effect.

Diarrhoea

Treatment with Perjeta may cause severe diarrhoea. Diarrhoea is a condition where your body produces more watery stools than normal. If you experience severe diarrhoea while receiving your anti-cancer treatment, your doctor may start you on anti-diarrhoeal treatment and may stop your treatment with Perjeta until the diarrhoea is under control.

Use in children and adolescents

Perjeta should not be given to patients under the age of 18 years because there is no information on how it works in this age group.

Other medicines and Perjeta

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy and breast-feeding

Before starting treatment, you must tell your doctor or nurse if you are pregnant or breast-feeding, or if you think you may be pregnant or are planning to have a baby. They will advise you about the benefits and risks for you and your baby of taking Perjeta while you are pregnant.

- Tell your doctor straight away, if you get pregnant during treatment with Perjeta or during the 6 months after stopping treatment.
- Ask your doctor about whether you can breast-feed during or after treatment with Perjeta.

Perjeta may harm the unborn baby. You should use effective contraception during treatment with Perjeta and for 6 months after stopping treatment. Talk to your doctor about the best contraception for you.

Driving and using machines

Perjeta is unlikely to affect you being able to drive or use machines. However, if you get any infusion reactions, allergic or anaphylactic reactions, wait until these have gone away before driving or using machines.

3. How you are given Perjeta

Being given this medicine

Perjeta will be given to you by a doctor or nurse in a hospital or clinic.

- It is given by a drip into a vein (intravenous infusion) once every three weeks.
- The amount of medicine you are given and how long the infusion will last are different for the first dose and following doses.
- The number of infusions you will be given depends on how you respond to treatment and whether you are receiving treatment before surgery (neoadjuvant therapy) or for disease which has spread.
- Perjeta is given with other cancer treatments (trastuzumab and chemotherapy).

For the first infusion:

- You will be given 840 mg of Perjeta over 60 minutes. Your doctor or nurse will check for side effects during your infusion and for 60 minutes afterwards.
- You will also be given trastuzumab and chemotherapy.

For all following infusions, if the first infusion was well tolerated:

- You will be given 420 mg of Perjeta over 30 to 60 minutes. Your doctor or nurse will check for side effects during your infusion and for 30 to 60 minutes afterwards.
- You will also be given trastuzumab and chemotherapy.

For further information on dosing of trastuzumab and chemotherapy (both of which can cause side effects as well), please refer to the package leaflet for these products in order to understand the use of these medicines. If you have questions about these medicines, please ask your doctor or nurse.

If you forget to have Perjeta

If you forget or miss your appointment to receive Perjeta make another appointment as soon as possible. If it has been 6 weeks or more since your last visit a higher Perjeta dose of 840 mg will be given to you.

If you stop having Perjeta

Do not stop having this medicine without talking to your doctor first. It is important that you are given all the infusions that have been recommended.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell a doctor or nurse straight away, if you notice any of the following side effects:

- The most common side effects which may occur in about 2 out of 3 patients are diarrhoea, hair loss and a decrease in the number of your white blood cells (shown in a blood test) with or without fever.
- In approximately 13 out of 100 patients infusion reactions can occur, which may include feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite. Allergic and anaphylactic (more severe allergic) reactions can happen in about 1 out of 10 patients. These may include swelling of your face and throat, with difficulty in breathing.
- Symptoms of heart problems (heart failure) have been observed in about 5 out of 100 patients and can include cough, shortness of breath when sleeping flat and swelling (fluid retention) in your legs or arms.

Tell a doctor or nurse straight away, if you notice any of the side effects above.

Other side effects include:

Very common (may affect more than 1 in 10 people):

- Fever
- Not being able to sleep
- Decrease in the number of red blood cells – shown in a blood test
- Sore throat, red, sore or runny nose, flu-like symptoms and fever
- Weak, numb, tingling or prickling sensations mainly affecting the feet and legs
- Nail problems
- Loss of or altered taste
- Feeling sick or being sick
- Reduced appetite
- Constipation
- Rash
- Joint or muscle pain, muscle weakness
- Pain (bone, neck, chest, abdominal pain)
- Inflammation of your digestive tract (e.g. sore mouth)
- Swollen ankles or other body parts due to your body retaining too much water

Common (may affect up to 1 in 10 people):

- Feeling dizzy
- Shortness of breath
- Producing more tears
- Dry, itchy or acne like skin
- Fluid on the lungs causing difficulty in breathing
- Inflammation of the nail bed where the nail and skin meet
- Condition in which the left ventricle of the heart is functionally impaired with or without symptoms

Uncommon (may affect up to 1 in 100 people):

- Chest symptoms such as a dry cough or breathlessness (possible signs of interstitial lung disease, a condition of damage to the tissues around the air sacs in the lungs)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

If you experience any of the above symptoms after treatment with Perjeta has been stopped, you should consult your doctor immediately and inform him or her that you have previously been treated with Perjeta.

Some of the side effects which you get may be due to your breast cancer. If you are given Perjeta with trastuzumab and chemotherapy at the same time, some side effects may also be due to these other medicines.

5. How to store Perjeta

Perjeta will be stored by the health professionals at the hospital or clinic. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not use this medicine if you notice any particles in the liquid or it is the wrong colour (please see section 6).
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Perjeta contains

- The active substance is pertuzumab. Each vial contains a total of 420 mg pertuzumab at a concentration of 30 mg/ml
- The other ingredients are glacial acetic acid, L-histidine, sucrose, polysorbate 20 and water for injections

What Perjeta looks like and contents of the pack

Perjeta is a concentrate for solution for infusion. It is a clear to slightly pearly (opalescent), colourless to pale yellow liquid. It is supplied in a glass vial containing 14 ml concentrate. Each pack contains one vial.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>