

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}PERJETA[®]

pertuzumab for injection

Sterile Concentrate for Solution for Infusion, 420mg/14 mL vial

Professed Standard

Antineoplastic

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Date of Initial Authorization:
APR 12, 2013

Submission Control No.: 230602

Date of Revision: February 25, 2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Early Breast Cancer

PERJETA (pertuzumab for injection) in combination with trastuzumab and chemotherapy is indicated for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) (see [14](#) Clinical Trials Section).
- adjuvant treatment of patients with HER2-positive early breast cancer with lymph node positive and/or hormone receptor negative disease (see [14](#) Clinical Trials section).

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.

Selection of Patients/Diagnostic Tests:

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

1.1 Pediatrics

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

1.2 Geriatrics

No overall differences in efficacy of PERJETA were observed between adult patients ≥ 65 and <65 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥ 65 years of age, compared to patients aged <65 years of age: decreased appetite, anemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhea. No dose adjustment is required in the elderly population (≥ 65 years of age).

2 CONTRAINDICATIONS

PERJETA (pertuzumab) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the [Dosage Forms, Strengths, Composition and Packaging](#) section of the product monograph.

- Refer to the Product Monographs of trastuzumab and docetaxel for further information on the contraindications of these drugs.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
<p>Left Ventricular Dysfunction: Subclinical and clinical cardiac failure has been observed in a clinical trial with PERJETA in neoadjuvant setting. Evaluate left ventricular function in all patients prior to and during treatment with PERJETA. For more information, including information on discontinuation criteria, see 7 WARNINGS AND PRECAUTIONS: Cardiovascular, Left Ventricular Dysfunction.</p>
<p>Embryo-Fetal Toxicity: Exposure to PERJETA (pertuzumab) can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception (see 7 WARNINGS AND PRECAUTION: Special Population, Pregnant Women).</p>
<p>Hypersensitivity reactions /anaphylaxis and Infusion-related reactions: PERJETA has been associated with severe hypersensitivity reactions, anaphylaxis and infusion-related reactions. Events with fatal outcomes have been observed (see 7 WARNINGS AND PRECAUTION: Immune). Patients should be evaluated and carefully monitored during and after infusions. Permanent discontinuation should be considered in patients with severe reactions.</p>

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients treated with PERJETA should have HER2-positive tumour status, defined as a score of 3+ by IHC or a ratio of ≥ 2.0 by ISH assessed by a validated test.

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

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose:

Metastatic and Early Breast Cancer

The recommended initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 to 60 minutes. An observation period of 30 to 60 minutes is recommended after completion of each PERJETA infusion. The observation period should be completed prior to any subsequent dose of trastuzumab or chemotherapy (see [7](#) WARNINGS AND PRECAUTIONS: Infusion-related reactions and WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis).

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

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

or

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

In patients receiving a taxane, PERJETA and trastuzumab should be administered prior to the taxane. When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m². If a carboplatin-based regimen is used, the recommended dose for docetaxel is 75 mg/m² throughout (no dose escalation).

In patients receiving an anthracycline-based regimen, PERJETA and trastuzumab should be administered following completion of the anthracycline treatment.

Neoadjuvant treatment of Early Breast Cancer

In the neoadjuvant setting (before surgery), it is recommended that patients are treated with PERJETA for three to six cycles depending on the regimen chosen in combination with trastuzumab and chemotherapy.

PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer:

- Four preoperative cycles of PERJETA in combination with trastuzumab and docetaxel (75 mg/m² with the option to escalate to 100 mg/m² at physician discretion if initial dose is well tolerated), every 3 weeks, followed by 3 postoperative cycles of 5-fluorouracil (600 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (600 mg/m²) (FEC), every 3 weeks, as given in NeoSphere
- Three or four preoperative cycles of FEC (F: 500 mg/m²; E: 100 mg/m²; C: 600 mg/m²) alone, every 3 weeks, followed by 3 or 4 preoperative cycles of PERJETA in combination

with docetaxel (75 mg/m² with the option to escalate to 100 mg/m² at physician discretion if initial dose is well tolerated) and trastuzumab, every 3 weeks, as given in TRYPHAENA and BERENICE, respectively

- Six preoperative cycles of PERJETA in combination with docetaxel (75 mg/m²: escalation of docetaxel above 75 mg/m² is not recommended), carboplatin (AUC 6), and trastuzumab (TCH), every 3 weeks, as given in TRYPHAENA
- Four preoperative cycles of dose-dense doxorubicin and cyclophosphamide (ddAC; A: 60 mg/m²; C: 600 mg/m²) alone, every 2 weeks, followed by 4 preoperative cycles of PERJETA in combination with trastuzumab, every 3 weeks, and paclitaxel (80 mg/m²) every week for 12 weeks, as given in BERENICE

Patients who start PERJETA and trastuzumab in the neoadjuvant setting may at the discretion of the physician continue to receive adjuvant PERJETA and trastuzumab to complete 1 year of treatment.

Adjuvant treatment of Early Breast Cancer

In the adjuvant setting (after surgery), PERJETA should be administered in combination with trastuzumab for a total of one year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. PERJETA and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see [14](#) CLINICAL TRIALS).

Metastatic Breast Cancer

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

In the pivotal clinical trial CLEOPATRA, for the loading dose of PERJETA in Cycle 1, it was administered on the first day; trastuzumab (intravenous formulation) was administered on the following day and followed by docetaxel on the same day. If all three medications could be tolerated in Cycle 1, in the subsequent cycles they could be administered in the same sequence on the same day.

Dose Adjustments:

Dose reductions are not recommended for PERJETA and trastuzumab (see the trastuzumab (intravenous formulation) and trastuzumab (subcutaneous formulation) Product Monographs).

For chemotherapy dose modifications, see relevant Product Monograph.

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 dose modifications, see the Product Monograph for docetaxel. A reduction in docetaxel dose was required in approximately 25% of patients in both treatment arms in the pivotal trial CLEOPATRA.

Infusion-related reactions:

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

Hypersensitivity reactions/anaphylaxis:

The infusion should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see [7](#) WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis).

Left ventricular dysfunction:

See [7](#) WARNINGS AND PRECAUTIONS: Left ventricular dysfunction for information on dose recommendations in the event of left ventricular dysfunction. The Product Monographs for trastuzumab should be referred for further information.

4.3 Reconstitution

Parenteral Products:

Instructions for dilution

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

PERJETA does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion. PERJETA should be prepared by a health professional using aseptic technique.

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

For the preparation of the initial dose of PERJETA (840 mg), dilute the content of two vials of PERJETA (2 x 420 mg) into one 250 mL IV bag. The concentration of the final diluted solution will be approximately 3.02 mg/mL. For the preparation of subsequent PERJETA doses (420 mg), dilute the content of one vial of PERJETA (1 x 420mg) into one 250 mL IV bag. The resulting concentration will be approximately 1.59 mg/mL.

Dextrose (5%) solution should not be used (see Incompatibilities).

The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see [11](#) STORAGE, STABILITY AND DISPOSAL).

Incompatibilities

No incompatibilities between PERJETA and polyvinylchloride, polyethylene or non-PVC polyolefin bags have been observed.

Dextrose (5%) solution should not be used to dilute PERJETA since the drug is chemically and physically unstable in such solutions.

PERJETA should not be mixed or diluted with other drugs.

4.4 Administration

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is PERJETA.

PERJETA therapy should only be administered under the supervision of a health professional experienced in the treatment of cancer patients.

PERJETA must be diluted by a health professional and administered as an intravenous infusion. Do not administer as an intravenous push or bolus.

4.5 Missed Dose

Delayed or Missed doses

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

Table 1 Recommendations Regarding Delayed or Missed Doses

Time between two sequential doses	PERJETA	trastuzumab	
		IV	SC
< 6 weeks	The 420 mg dose of PERJETA should be administered as soon as possible. Do not wait until the next planned dose.	The 6 mg/kg dose of intravenous trastuzumab should be administered as soon as possible. Do not wait until the next planned dose.	The fixed dose of 600mg subcutaneous trastuzumab should be administered as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	The loading dose of 840 mg PERJETA should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered over a period of 30 to 60 minutes every 3 weeks thereafter.	The loading dose of 8 mg/kg of intravenous trastuzumab should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered over a period of 30 or 90 minutes every 3 weeks thereafter.	The interval between subsequent subcutaneous trastuzumab doses should not be less than three weeks.

Treatment discontinuation:

PERJETA should be discontinued if trastuzumab treatment is discontinued.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) infusion	420mg/14 mL	Glacial acetic acid, L-histidine, polysorbate 20, sucrose, water for injection

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence and is a first-in-class human epidermal growth factor receptor 2 (HER) dimerization inhibitor.

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as Drug Identification Number (DIN) and the batch/lot number of the product supplied.

PERJETA is supplied as a single-use vial containing 14 mL preservative free liquid concentrate, at a concentration of 30 mg/mL for dilution for intravenous infusion. Each vial of PERJETA drug product contains a total of 420 mg pertuzumab. Non-medicinal ingredients are (alphabetical order); glacial acetic acid, L-histidine, polysorbate 20, sucrose, water for injection.

Packaging:

Each carton contains one vial of 420 mg PERJETA.

PERJETA is also supplied within a kit (PERJETA®-HERCEPTIN® Combo Pack). Each kit contains one vial of 420 mg PERJETA for intravenous infusion and one vial of 440 mg HERCEPTIN (trastuzumab) lyophilized, sterile powder for intravenous injection and one 20 mL vial of Bacteriostatic Water For Injection (BWFI) containing 1.1% benzyl alcohol. For information on the preparation for administration of trastuzumab intravenous formulation, refer to the package insert within the trastuzumab carton.

PERJETA, trastuzumab or Bacteriostatic Water For Injection (BWFI) should not be used after the expiry date (EXP) shown on the vial.

7 WARNINGS AND PRECAUTIONS

Please see [3](#) SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Therapy with PERJETA should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Cardiovascular

Left ventricular dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. The incidence of symptomatic left ventricular systolic dysfunction (LVD [congestive heart failure]) was higher in patients treated with PERJETA in combination with trastuzumab and chemotherapy compared to treatment with trastuzumab and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who had received anthracycline-based chemotherapy (see [8](#) ADVERSE REACTIONS).

PERJETA has not been studied in patients with: a pre-treatment LVEF value of $\leq 50\%$; a prior history of congestive heart failure (CHF); decreases in LVEF to $<50\%$ during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to $> 360\text{mg}/\text{m}^2$ of doxorubicin or its equivalent.

Prior to the initiation of PERJETA and trastuzumab, candidate patients should undergo thorough baseline cardiac assessment including history and physical exam, electrocardiogram (ECG) and either 2D echocardiogram or multiple gated acquisition (MUGA) scan to ensure that LVEF is within normal limits. A careful risk-benefit assessment should be made before deciding to treat with PERJETA and trastuzumab. Cardiac assessments, as performed at baseline, should be repeated at regular intervals (see Table 3 below). If the LVEF declines as indicated in Table 3 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. Following discontinuation of treatment, cardiac assessments should be performed every 6 months up until 24 months from the last administration of PERJETA and/or trastuzumab.

Table 3 Dose Recommendations for Left Ventricular Dysfunction

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

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

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal

Diarrhea

PERJETA may elicit severe diarrhea (see [8](#) ADVERSE REACTIONS). In case of onset of severe diarrhea an anti-diarrheal treatment should be instituted and interruption of the treatment with PERJETA should be considered if no improvement of the condition is achieved. When the diarrhea is under control the treatment with PERJETA may be reinstated.

Hematologic

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 [8](#) ADVERSE REACTIONS). As nadir neutrophil counts were similar in PERJETA-treated and placebo-treated patients, the higher incidence of febrile neutropenia in PERJETA-treated patients may be related to the higher incidence of mucositis and diarrhea in these patients. Symptomatic treatment for mucositis and diarrhea should be considered.

Hepatic/Biliary/Pancreatic

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

Immune

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed in patients treated with PERJETA (see [8](#) ADVERSE REACTIONS). 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 (ARDS). PERJETA is contraindicated in patients who are hypersensitive to pertuzumab or to any ingredient in the formulation (see [2](#) CONTRAINDICATIONS).

Infusion-related reactions

PERJETA has been associated with infusion-related reactions, including events with fatal outcomes (see [8](#) ADVERSE REACTIONS). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent infusions of PERJETA is recommended. If a significant infusion-related reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see [4](#) DOSAGE AND ADMINISTRATION).

Race

In the pivotal trial WO20698/TOC4129g (CLEOPATRA), an increased incidence of neutropenia and febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, there was no difference in the incidence of neutropenia between the PERJETA-treated group (58.6%) and the placebo-treated group (58.6%). However, the incidence of febrile neutropenia was higher in the PERJETA-treated group (25.8%) compared with the placebo-treated group (11.3%). In the APHINITY trial, the incidence of febrile neutropenia in Asian patients was 15.9% in the PERJETA-treated group and 9.9% in the placebo-treated group. The reason for this difference is not known.

In the MetaPHER study, the Asian population, comprised of only two patients, was too small for any meaningful conclusion and for comparison with the overall patient population. Therefore, it is unknown whether increased exposures resulting from subcutaneous trastuzumab further increases neutropenia/febrile neutropenia in the Asian population.

Renal

The safety and efficacy of PERJETA have not been studied in patients with renal impairment.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death (see [16](#) NON-CLINICAL TOXICOLOGY: Teratogenicity). If PERJETA is administered during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to a fetus (see [7](#) WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).

7.1 Special Populations

7.1.1 Pregnant Women

There are no studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA could cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. PERJETA administered to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death (see [16](#) NON-CLINICAL TOXICOLOGY: Teratogenicity). Women of child-bearing potential should use effective contraception while receiving PERJETA in combination with trastuzumab and for 7 months following the last doses of PERJETA and trastuzumab. Male patients with female partners of child bearing potential should also use effective contraception while receiving PERJETA in combination with trastuzumab and for 7 months following the last dose.

Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of intravenous hydration in the management of oligohydramnios due to PERJETA exposure is not known.

Labour and Delivery: The safe use of PERJETA during labour and delivery has not been established.

7.1.2 Breast-feeding

Nursing Women: Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue nursing or the PERJETA-treatment taking into account the importance to the mother and the elimination half- life of pertuzumab (see [10](#) CLINICAL PHARMACOLOGY: Excretion).

7.1.3 Pediatrics

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

7.1.4 Geriatrics

No overall differences in efficacy of PERJETA were observed between adult patients ≥ 65 and < 65 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥ 65 years of age, compared to patients aged < 65 years of age: decreased appetite, anemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhea. No dose adjustment is required in the elderly population (≥ 65 years of age).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of PERJETA (pertuzumab) has been evaluated in more than 6000 patients in Phase I, II and III clinical trials. Patients in these studies had various malignancies, and were predominantly treated with PERJETA in combination with other antineoplastic agents. Those studies included the pivotal trials WO20698/TOC4129g (CLEOPATRA) (n=808), WO20697 (NeoSphere) (n=417), BO22280 (TRYPHAENA) (n=225) and BO25126 (APHINITY) (n=4804). The safety of PERJETA was generally consistent across studies, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether PERJETA was administered as monotherapy or in combination with other antineoplastic agents.

Early Breast Cancer

Neoadjuvant Treatment of Breast Cancer (NeoSphere)

When PERJETA was administered in combination with trastuzumab and docetaxel for 4 cycles, the most common adverse events (AEs) ($> 30\%$) in the neoadjuvant treatment setting were alopecia (65%), neutropenia (50%), diarrhea (46%) and nausea (39%). The most common NCI-CTCAE (version 3.0) Grade ≥ 3 AEs (occurring in $> 2\%$ of patients) were neutropenia, febrile neutropenia, diarrhea, leukopenia, and alopecia. The most common serious AEs (occurring in $> 2\%$ of patients) were neutropenia and febrile neutropenia. One patient administered PERJETA, trastuzumab and docetaxel discontinued docetaxel due to drug hypersensitivity. Dose interruption/modification was required in 35 patients, most commonly (occurring in $> 2\%$ of patients) related to diarrhea, neutropenia, febrile neutropenia, infusion-related reaction, and mucosal inflammation.

Table 4 summarizes the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA in NeoSphere.

Neoadjuvant Treatment of Breast Cancer (TRYPHAENA)

When PERJETA was administered in combination with trastuzumab and 5-fluorouracil, epirubicin, cyclophosphamide (FEC) for 3 cycles followed by 3 cycles of PERJETA and trastuzumab and docetaxel, the most common AEs (occurring in >30% of patients) in the neoadjuvant treatment setting were diarrhea, nausea, neutropenia, alopecia, vomiting, and fatigue. The most common NCI-CTCAE (version 3.0) Grade ≥ 3 AEs (occurring in >2% of patients) in the neoadjuvant treatment setting were neutropenia, leukopenia, febrile neutropenia, diarrhea, amenorrhea, and drug hypersensitivity. Serious AEs (occurring in >2% of patients) in the neoadjuvant treatment setting included febrile neutropenia, neutropenia, and leukopenia. The incidence of patients with ≥ 1 AEs leading to drug discontinuation in the neoadjuvant treatment period was 5.6%. The incidence of patients with ≥ 1 AEs leading to dose modification was 36.1%, with neutropenia (13.9%) and febrile neutropenia (5.6%) the most common reasons for dose modifications.

When PERJETA was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC, the most common AEs (occurring in >30% of patients) in the neoadjuvant treatment setting were diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE (version 3.0) Grade ≥ 3 AEs (occurring in >2% of patients) in the neoadjuvant treatment setting were neutropenia, leukopenia, febrile neutropenia, diarrhea, anemia, nausea, vomiting, dyspnea, and left ventricular dysfunction. Serious AEs (occurring in >2% of patients) in the neoadjuvant treatment period included febrile neutropenia, neutropenia, diarrhea, vomiting and left ventricular dysfunction. The incidence of patients with ≥ 1 AEs leading to drug discontinuation in the neoadjuvant treatment period was 6.7%, with left ventricular dysfunction the reason for discontinuation in more than one patient. The incidence of patients with ≥ 1 AEs leading to dose modification was 29.3%, with neutropenia (14.7%) and diarrhea (5.3%) the most common reasons for dose modifications.

When PERJETA was administered in combination with docetaxel, carboplatin, trastuzumab (TCH) for 6 cycles, the most common AEs (occurring in >30% of patients) in the neoadjuvant treatment setting were diarrhea, alopecia, neutropenia, nausea, fatigue, vomiting, anemia and thrombocytopenia. The most common NCI-CTCAE (version 3.0) Grade ≥ 3 AEs (occurring in >2% of patients) in the neoadjuvant treatment setting were neutropenia, anemia, febrile neutropenia, diarrhea, leukopenia, thrombocytopenia, vomiting, fatigue, alanine aminotransferase increased, hypokalemia and drug hypersensitivity. Serious AEs (occurring in >2% of patients) in the neoadjuvant treatment setting were febrile neutropenia, diarrhea, thrombocytopenia, pneumonia, mucosal inflammation, and drug hypersensitivity. The incidence of patients with ≥ 1 AEs leading to drug discontinuation in the neoadjuvant treatment setting was 7.9%, with drug hypersensitivity and neutropenia the reason for discontinuation in more than one patient. The incidence of patients with ≥ 1 AEs leading to dose modification was 50.0%, with neutropenia (14.5%), anemia (21.1%), and thrombocytopenia (15.8%) the most common reasons for dose modifications.

Table 5 summarizes the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA in TRYPHAENA.

Neoadjuvant Treatment of Breast Cancer (BERENICE)

When PERJETA was administered in combination with trastuzumab and paclitaxel for 4 cycles following 4 cycles of dose-dense doxorubicin and cyclophosphamide, the most common AEs (occurring in >30% of patients) in the neoadjuvant treatment setting were nausea, diarrhea, alopecia, fatigue, constipation and headache. The most common NCI-CTCAE (version 4.0) Grade ≥ 3 AEs (occurring in >2% of patients) were neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell decreased, anemia, diarrhea, alanine aminotransferase decreased, device related infection, peripheral neuropathy, and hypokalemia. Serious AEs (occurring in >2% of patients) in the neoadjuvant treatment setting included febrile neutropenia and device related infection. AEs leading to discontinuation in two or more patients included ejection fraction decreased, peripheral sensory neuropathy, peripheral neuropathy, diarrhea, cardiac failure, neutropenia, and pneumonia. The incidence of patients with ≥ 1 AEs leading to dose modification (interruption/reduction/delay) was 59.8%, with neutropenia (15.6%), infusion related reactions (10.1%), and diarrhea (7.5%) the most common reasons for dose modifications.

When PERJETA was administered in combination with trastuzumab and docetaxel for 4 cycles following 4 cycles of 5-fluorouracil, epirubicin, cyclophosphamide (FEC), the most common AEs (occurring in >30% of patients) in the neoadjuvant treatment setting were nausea, diarrhea, alopecia, fatigue, asthenia, constipation, mucosal inflammation, vomiting, myalgia and anemia. The most common NCI-CTCAE (version 4.0) Grade ≥ 3 AEs (occurring in >2% of patients) were febrile neutropenia, diarrhea, neutropenia, neutrophil count decreased, stomatitis, fatigue, vomiting, mucosal inflammation, neutropenic sepsis, anemia, bone marrow failure, nausea, and white blood cell count decreased. Serious AEs (occurring in >2% of patients) in the neoadjuvant treatment setting included febrile neutropenia, diarrhea, neutropenic sepsis, and pyrexia. AEs leading to discontinuation in two or more patients in the neoadjuvant treatment setting included infusion related reaction, ejection fraction decreased, and diarrhea. The incidence of patients with ≥ 1 AEs leading to dose modification (interruption/reduction/delay) was 50.0%, with neutropenia (11.1%), diarrhea (8.6%) and infusion related reactions (5.6%) the most common reasons for modification. Table 6 summarizes the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA in BERENICE.

Adjuvant Treatment of Breast Cancer (APHINITY)

When PERJETA was administered in combination with trastuzumab and chemotherapy, the most common ADRs (>30%) were diarrhea, nausea, alopecia, fatigue, and vomiting. The most common NCI-CTCAE (version 4.0) Grade 3-4 ADRs (> 2%) were neutropenia, febrile neutropenia, diarrhea, neutrophil count decreased, anemia, white blood cell count decreased, leukopenia, fatigue, nausea, and stomatitis.

Table 7 and Table 8 summarize the adverse reactions that occurred in patients who received adjuvant treatment with PERJETA in APHINITY.

Metastatic Breast Cancer

Study WO20698/TOC4129g (CLEOPATRA)

Table 9 (see 8.2 Clinical Trial Adverse Reactions) summarizes the adverse drug reactions (ADRs) from the pivotal clinical trial CLEOPATRA in which PERJETA was given in combination with trastuzumab and docetaxel vs placebo with trastuzumab and docetaxel. The most common ADRs (>30%) seen in patients treated with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash and peripheral neuropathy. The most common NCI-CTCAE (version 3) Grade 3-4 ADRs ($\geq 10\%$) were neutropenia, febrile neutropenia and leukopenia. The most common serious adverse reactions were febrile neutropenia, neutropenia and diarrhea. Table 9 and Table 10 summarize the adverse reactions that occurred in patients who received PERJETA in CLEOPATRA.

Study BO17929 in Metastatic Breast Cancer

In the Phase II BO17929 trial, a total of 83 patients (from Cohorts 1, 2 and 3) received treatment with PERJETA in combination with trastuzumab and 29 patients received treatment with PERJETA alone.

In Cohorts 1&2 (PERJETA + trastuzumab; N=66), ADRs reported with a frequency of $\geq 30\%$: diarrhea and fatigue; with a frequency of 20-<30%: nausea, headache, and rash; and with a frequency of 10-<20%: arthralgia, asthenia, constipation, decreased appetite, dizziness, nail disorder, myalgia, nasopharyngitis, pruritus, and vomiting.

In Cohort 3 (PERJETA alone; N=29), ADRs reported with a frequency of $\geq 30\%$: diarrhea and nausea; with a frequency of 20-<30%: vomiting; and with a frequency of 10-<20%: arthralgia, asthenia, decreased appetite, dyspnoea, fatigue, pruritus, and rash.

In Cohort 3 (PERJETA + trastuzumab; N=17), no ADRs with a frequency of $\geq 30\%$ were reported. ADRs reported with a frequency of 20-<30%: diarrhea, nausea, vomiting, and fatigue; and with a frequency of 10-<20%: asthenia, chills, constipation, decreased appetite, dizziness, headache, left ventricular dysfunction, pruritus, rash, and upper respiratory tract infection.

Table 11 summarizes the adverse reactions that occurred in patients who received PERJETA in Study BO17929.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Early Breast Cancer

Neoadjuvant Treatment of Breast Cancer (NeoSphere)

Table 4 summarizes the ADRs from the pivotal clinical trial NeoSphere (n=417), in which PERJETA was given in combination with trastuzumab and docetaxel to patients with locally advanced, inflammatory or early breast cancer.

Table 4 Summary of ADRs Occurring in ≥1% of Patients Receiving PERJETA in the Neoadjuvant Setting in NeoSphere by Treatment Regimen

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 n (%)		PERJETA + trastuzumab + docetaxel n=107 n (%)		PERJETA + trastuzumab n=108 n (%)		PERJETA + docetaxel n=94 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
General disorders and administration site conditions								
Fatigue	29 (27)	0	28 (26)	1 (0.9)	13 (12)	0	24 (26)	1 (1)
Mucosal inflammation	23 (21)	0	28 (26)	2 (2)	3 (3)	0	24 (26)	0
Asthenia	19 (18)	0	22 (21)	2 (2)	3 (3)	0	15 (16)	2 (2)
Pyrexia	11 (10)	0	22 (17)	0	9 (8)	0	8 (9)	0
Infusion Related Reaction	5 (5)	0	7 (7)	0	6 (6)	1 (0.9)	5 (5)	0
Edema peripheral	11 (10)	0	3 (3)	0	1 (0.9)	0	5 (5)	0
Skin and subcutaneous tissue disorders								
Alopecia	70 (66)	0	68 (64)	0	1 (0.9)	0	63 (67)	0
Rash	23 (21)	2 (2)	28 (26)	1 (0.9)	12 (11)	0	27 (29)	1 (1)
Nail disorder	9 (8)	0	5 (5)	0	2 (2)	0	7 (7)	0
Pruritis	8 (7)	0	2 (2)	0	3 (3)	0	4 (4)	0
Dry skin	5 (5)	0	2 (2)	0	3 (3)	0	2 (2)	0
Gastrointestinal disorders								
Diarrhea	36 (34)	4 (4)	49 (46)	6 (6)	30 (28)	0	51 (54)	4 (4)
Nausea	39 (36)	0	41 (38)	0	15 (14)	0	34 (36)	1 (1)

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 n (%)		PERJETA + trastuzumab + docetaxel n=107 n (%)		PERJETA + trastuzumab n=108 n (%)		PERJETA + docetaxel n=94 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Stomatitis	8 (7)	0	19 (18)	0	5 (5)	0	9 (10)	0
Vomiting	13 (12)	0	14 (13)	0	5 (5)	0	15 (16)	2 (2)
Abdominal pain	7 (7)	0	7 (7)	0	4 (4)	0	7 (7)	0
Constipation	8 (7)	0	8 (7)	0	3 (3)	0	3 (3)	0
Dyspepsia	4 (4)	0	4 (4)	0	4 (4)	0	4 (4)	0
Blood and lymphatic system disorders								
Neutropenia	67 (63)	63 (59)	54 (50)	48 (45)	1 (0.9)	1 (0.9)	59 (63)	54 (57)
Leukopenia	23 (21)	12 (11)	10 (9)	5 (5)	0	0	12 (13)	8 (9)
Febrile neutropenia	8 (7)	7 (7)	9 (8)	9 (8)	0	0	7 (7)	7 (7)
Anaemia	7 (7)	0	3 (3)	0	5 (5)	0	6 (6)	2 (2)
Nervous system disorders								
Dysgeusia	11 (10)	0	16 (15)	0	5 (5)	0	7 (7)	0
Headache	12 (11)	0	12 (11)	0	15 (14)	0	12 (13)	0
Peripheral Sensory Neuropathy	13 (12)	1 (0.9)	9 (8)	1 (0.9)	2 (2)	0	10 (11)	0
Neuropathy peripheral	9 (8)	0	5 (5)	0	0	0	4 (4)	0
Dizziness	4 (4)	0	3 (3)	0	6 (6)	0	3 (3)	0
Paraesthesia	4 (4)	0	0	0	0.9	0	3 (3)	0
Musculoskeletal and connective tissue disorders								
Myalgia	24 (22)	0	24 (22)	0	10 (9)	0	19 (20)	0
Arthralgia	9 (8)	0	11 (10)	0	5 (5)	0	9 (10)	0
Pain in extremity	1 (0.9)	0	2 (2)	0	1 (0.9)	0	1 (1)	0

Body System/ Adverse Reactions	Trastuzumab + docetaxel		PERJETA + trastuzumab + docetaxel		PERJETA + trastuzumab		PERJETA + docetaxel	
	n=107 n (%)		n=107 n (%)		n=108 n (%)		n=94 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Metabolism and nutrition disorders								
Decreased appetite	7 (7)	0	15 (14)	0	2 (2)	0	14 (15)	0
Psychiatric disorders								
Insomnia	12 (11)	0	9 (8)	0	4 (4)	0	8 (9)	0
Infections and infestations								
Upper respiratory tract infection	3 (3)	0	5 (5)	0	2 (2)	0	6 (6)	0
Nasopharyngitis	4 (4)	0	4 (4)	0	3 (3)	0	2 (2)	0
Respiratory, thoracic and mediastinal disorders								
Epistaxis	7 (7)	0	10 (9)	0	1 (0.9)	0	6 (6)	0
Cough	5 (5)	0	3 (3)	0	3 (3)	0	8 (9)	0
Dyspnoea	4 (4)	0	5 (5)	0	3 (3)	0	3 (3)	0
Vascular disorders								
Hot flush	7 (7)	0	5 (5)	0	0	0	2 (2)	0
Eye disorders								
Lacrimation increased	2 (2)	0	4 (4)	0	1 (1)	0	4 (4)	0
Cardiac disorders								
Left ventricular dysfunction	1 (1)	0	3 (3)	0	0	0	1 (1)	0
Immune system disorders								
Drug hypersensitivity	2 (2)	0	6 (6)	1 (1)	6 (6)	2 (2)	5 (5)	0

Neoadjuvant Treatment of Breast Cancer (TRYPHAENA)

Table 5 summarizes the ADRs from the clinical trial TRYPHAENA (n=218), in which PERJETA was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or early breast cancer.

Table 5 Summary of Adverse Drug Reactions Occurring in ≥1% of Patients Receiving PERJETA in the Neoadjuvant setting in TRYPHAENA

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel		PERJETA + trastuzumab + docetaxel following FEC		PERJETA + TCH	
	n=72 n (%)		n=75 n (%)		n=76 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
General disorders and administration site conditions						
Fatigue	26 (36)	0	27 (36)	0	32 (42)	3(4)
Mucosal inflammation	17 (24)	0	15 (20)	0	13 (17)	1(1)
Pyrexia	12 (17)	0	7 (9)	0	12 (16)	0
Asthenia	7 (10)	0	11 (15)	1(1)	10 (13)	1(1)
Edema peripheral	8 (11)	0	3 (4)	0	7 (9)	0
Skin and subcutaneous tissue disorders						
Alopecia	35 (49)	0	39 (52)	0	41 (54)	0
Rash	14 (19)	0	8 (11)	0	16 (21)	1(1)
Palmar-plantar erythrodysesthesia syndrome	5 (7)	0	8 (11)	0	6 (8)	0
Dry skin	4 (6)	0	7 (9)	0	8 (11)	0
Nail disorder	7 (10)	0	5 (7)	0	8 (9)	0
Pruritus	2 (3)	0	3 (4)	0	3 (4)	0
Gastrointestinal disorders						
Diarrhea	44 (61)	3(4)	46 (61)	4(5)	55 (72)	9(12)
Nausea	38 (53)	0	40 (53)	2(3)	34 (45)	0

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel		PERJETA + trastuzumab + docetaxel following FEC		PERJETA + TCH	
	n=72 n (%)		n=75 n (%)		n=76 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Vomiting	29 (40)	0	27 (36)	2 (3)	30 (39)	4 (5)
Dyspepsia	18 (25)	1 (1)	6 (8)	0	17 (22)	0
Constipation	13 (18)	0	17 (23)	0	12 (16)	0
Stomatitis	10 (14)	0	13 (17)	0	9 (12)	0
Abdominal pain	3 (4)	0	6 (8)	0	5 (7)	0
Blood and lymphatic system disorders						
Neutropenia	37 (51)	34 (47)	35 (47)	32 (43)	37 (49)	35 (46)
Leukopenia	16 (22)	14 (19)	12 (16)	9 (12)	13 (17)	9 (12)
Anemia	14 (19)	1 (1)	6 (8)	2 (3)	28 (37)	13 (17)
Febrile neutropenia	13 (18)	13 (18)	7 (9)	7 (9)	13 (17)	13 (17)
Thrombocytopenia	5 (7)	0	1 (1)	0	23 (30)	9 (12)
Immune system disorders						
Drug hypersensitivity	7 (10)	2 (3)	1 (1)	0	8 (11)	2 (3)
Hypersensitivity	0	0	0	0	1 (1)	0
Nervous system disorders						
Headache	16 (22)	0	11 (15)	0	12 (17)	0
Dysgeusia	8 (11)	0	10 (13)	0	16 (21)	0
Dizziness	6 (8)	0	6 (8)	1 (1)	12 (16)	0
Neuropathy peripheral	4 (6)	0	1 (1)	0	8 (11)	0
Peripheral sensory neuropathy	3 (4)	0	7 (9)	0	5 (7)	0
Paraesthesia	3 (4)	0	1 (4)	0	4 (5)	0

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel		PERJETA + trastuzumab + docetaxel following FEC		PERJETA + TCH	
	n=72 n (%)		n=75 n (%)		n=76 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Musculoskeletal and connective tissue disorders						
Myalgia	12 (17)	0	9 (11)	1(1)	8 (11)	0
Arthralgia	8 (11)	0	9 (12)	0	5 (7)	0
Pain in extremity	3 (4)	0	5 (7)	0	2 (3)	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	9 (13)	0	6 (8)	2 (3)	8 (11)	1 (1)
Epistaxis	8 (11)	0	8 (11)	0	12 (16)	1 (1)
Cough	7 (10)	0	4 (5)	0	9 (12)	0
Oropharyngeal pain	6 (8)	0	5 (7)	0	9 (12)	0
Metabolism and nutrition disorders						
Decreased appetite	15 (21)	0	8 (11)	0	16 (21)	0
Eye disorders						
Lacrimation increased	9 (13)	0	4 (5)	0	6 (8)	0
Psychiatric disorders						
Insomnia	8 (11)	0	10 (13)	0	16 (21)	0
Investigations						
ALT increased	5 (7)	0	2 (3)	0	8 (11)	3 (4)
Infections and infestations						
Nasopharyngitis	5 (7)	0	5 (7)	0	6 (8)	0
Upper respiratory tract infection	6 (8)	0	3 (4)	0	2 (3)	0
Paronychia	0	0	1 (1)	0	1 (1)	0

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel		PERJETA + trastuzumab + docetaxel following FEC		PERJETA + TCH	
	n=72 n (%)		n=75 n (%)		n=76 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Vascular disorders						
Hot flush	2 (3)	0	4 (5)	0	7 (9)	0
Cardiac disorders						
Left ventricular dysfunction	4 (6)	0	3 (4)	2 (3)	2 (3)	0
Injury, poisoning and procedural complications						
Infusion related reaction	2 (2.8)	0	0	0	2 (2.6)	0

FEC=5-fluorouracil, epirubicin, cyclophosphamide; TCH=docetaxel, carboplatin, and trastuzumab

Neoadjuvant Treatment of Breast Cancer (BERENICE)

Table 6 summarizes the ADRs from the clinical trial BERENICE, in which PERJETA was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or early breast cancer.

Table 6 Summary of ADRs Occurring in ≥1% of Patients Receiving PERJETA in the Neoadjuvant setting in BERENICE

Body System/Adverse Reactions	PERJETA + trastuzumab + paclitaxel following ddAC		PERJETA + trastuzumab + docetaxel following FEC	
	n=199 n (%)		n=198 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
General disorders and administration site conditions				
Fatigue	116 (58)	2 (1)	76 (38)	9 (5)
Asthenia	37 (19)	3 (2)	82 (41)	0
Mucosal inflammation	43 (22)	2 (1)	74 (37)	7 (4)
Pyrexia	30 (15)	0	35 (18)	0
Edema peripheral	18 (9)	0	24 (12)	2 (1)
Skin and subcutaneous tissue disorders				
Alopecia	124 (62)	0	116 (59)	0
Rash	28 (14)	0	21 (11)	0
Dry skin	27 (14)	0	19 (10)	0
Nail discoloration	29 (15)	0	3 (2)	0
Palmar-Plantar Erythrodysesthesia Syndrome	11 (6)	0	20 (10)	1 (0.5)
Nail disorder	14 (7)	0	19 (10)	0
Pruritis	11 (8)	2 (1)	16 (8)	1 (0.5)
Gastrointestinal disorders				
Nausea	141 (71)	5 (3)	137 (69)	4 (2)
Diarrhea	133 (67)	6 (3)	137 (69)	20 (10)
Constipation	69 (35)	1 (0.5)	76 (38)	1 (0.5)

Body System/Adverse Reactions	PERJETA + trastuzumab + paclitaxel following ddAC		PERJETA + trastuzumab + docetaxel following FEC	
	n=199 n (%)		n=198 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Vomiting	45 (23)	2 (1)	69 (35)	8 (4)
Stomatitis	49 (25)	0	54 (27)	10 (5)
Dyspepsia	39 (19)	0	38 (16)	0
Abdominal pain upper	12 (6)	0	26 (13)	0
Abdominal pain	10 (5)	0	20 (10)	0
Gastroesophageal reflux disease	23 (12)	0	4 (2)	0
Blood and lymphatic system disorders				
Anemia	54 (27)	6 (3)	60 (30)	5 (3)
Neutropenia	44 (22)	24 (12)	32 (16)	17 (9)
Febrile neutropenia	14 (7)	14 (7)	34 (17)	34 (17)
Leukopenia	6 (3)	2 (1)	2	2 (1)
Nervous system disorders				
Headache	60 (30)	1 (0.5)	28 (14)	1 (0.5)
Dysgeusia	39 (20)	0	38 (19)	1 (0.5)
Neuropathy peripheral	85 (42)	6 (3)	41 (21)	1 (0.5)
Paresthesia	29 (15)	0	18 (9)	0
Dizziness	23 (12)	0	15 (8)	0
Musculoskeletal and connective tissue disorders				
Myalgia	40 (20)	0	66 (33)	2 (1)
Arthralgia	39 (20)	0	42 (21)	2 (1)
Back pain	20 (10)	0	17 (9)	0
Pain in extremity	20 (10)	0	15 (8)	0

Body System/Adverse Reactions	PERJETA + trastuzumab + paclitaxel following ddAC		PERJETA + trastuzumab + docetaxel following FEC	
	n=199 n (%)		n=198 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Bone pain	23 (12)	1 (0.5)	9 (5)	0
Infections and infestations				
Urinary tract infection	21 (11)	2 (1)	4 (2)	0
Nasopharyngitis	14 (7)	0	17 (9)	0
Upper respiratory tract infection	14 (7)	0	4 (2)	0
Paronychia	1 (0.5)	0	2 (1)	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	50 (25)	0	37 (19)	0
Dyspnea	29 (15)	1 (0.5)	29 (15)	1 (0.5)
Cough	40 (20)	1 (0.5)	17 (9)	0
Oropharyngeal pain	20 (10)	0	15 (8)	1 (0.5)
Metabolism and nutrition disorders				
Decreased appetite	39 (20)	0	45 (23)	0
Eye disorders				
Lacrimation increased	18 (9)	0	36 (18)	0
Psychiatric disorders				
Insomnia	37 (19)	0	25 (13)	0
Vascular disorders				
Hot flush	38 (19)	0	26 (13)	0
Investigations				
White blood cell count decreased	21 (11)	8 (4)	5 (3)	4 (2)
Injury, poisoning and procedural complications				

Body System/Adverse Reactions	PERJETA + trastuzumab + paclitaxel following ddAC		PERJETA + trastuzumab + docetaxel following FEC	
	n=199 n (%)		n=198 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Infusion related reaction	31 (16)	2 (1)	25 (13)	2 (1)
Immune system disorders				
Hypersensitivity	5 (3)	0	4 (2)	1 (0.5)
Drug hypersensitivity	2 (1)	0	0	0

ddAC = dose-dense doxorubicin, cyclophosphamide, FEC=5-fluorouracil, epirubicin, cyclophosphamide

Adjuvant Treatment of Breast Cancer (APHINITY)

Table 7 summarizes the ADRs from the pivotal clinical trial APHINITY, in which PERJETA was given in combination with trastuzumab and chemotherapy or placebo in combination with trastuzumab and chemotherapy. Table 7 reports the ADRs that occurred in at least 1% of patients in the PERJETA-treated group.

Table 7 Summary of Adverse Drug Reactions Occurring in ≥1% of Patients Receiving PERJETA in the Pivotal Clinical Trial APHINITY

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Cardiac disorders				
Cardiac Failure	0.7	0.2	1.4	0.7
General disorders and administration site conditions				
Fatigue	44.3	2.5	48.8	3.9
Mucosal inflammation	18.6	0.7	23.4	1.7
Asthenia	20.8	1.7	21.4	1.4
Pyrexia	19.5	0.7	20.0	0.6
Edema peripheral	20.1	0.2	17.1	-

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy		PERJETA + trastuzumab + chemotherapy	
	n=2405 Frequency rate %		n=2364 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Skin and subcutaneous tissue disorders				
Alopecia	66.9	<0.1	66.7	<0.1
Rash	20.3	0.2	25.8	0.4
Pruritus	9.0	<0.1	14.0	0.1
Palmar-plantar erythrodysesthesia syndrome	6.6	0.4	9.1	1.2
Dry skin	11.1	<0.1	13.2	0.1
Nail disorder	11.8	0.1	11.8	0.2
Gastrointestinal disorders				
Diarrhea	45.2	3.7	71.2	9.8
Nausea	65.5	2.5	69.0	2.4
Vomiting	30.5	1.8	32.5	1.9
Constipation	31.6	0.3	28.9	0.5
Stomatitis	23.8	1.0	28.4	2.2
Dyspepsia	14.2	-	13.7	-
Abdominal pain	10.9	0.6	12.1	0.5
Abdominal pain upper	9.1	0.2	10.4	0.3
Blood and lymphatic system disorders				
Anemia	23.2	4.7	27.7	6.9
Neutropenia	23.4	15.7	24.8	16.3
Febrile neutropenia*	11.1	11.1	12.1	12.1
Leukopenia	9.2	4.4	9.1	4.4
Nervous system disorders				
Dysgeusia	21.5	<0.1	26.0	0.1
Headache	23.4	0.4	22.5	0.3
Peripheral sensory neuropathy	17.5	0.5	18.1	0.6
Neuropathy peripheral	15.3	0.6	15.5	0.5
Parasthesia	10.0	0.2	11.8	0.5
Dizziness	11.4	0.2	11.4	-
Musculoskeletal and connective tissue disorders				
Arthralgia	32.5	1.1	28.7	0.9
Myalgia	29.5	1.3	26.0	0.9
Pain in extremity	10.5	0.2	10.0	0.2
Infections and infestations				
Nasopharyngitis	11.8	0.1	13.4	<0.1

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Upper respiratory tract infection	7.4	0.2	8.1
Paronychia	2.3	<0.1	3.9	0.1
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	13.6	-	18.2	<0.1
Cough	14.6	<0.1	15.8	<0.1
Dyspnea	11.5	0.5	11.9	0.4
Metabolism and nutrition disorders				
Decreased appetite	19.9	0.4	23.9	0.8
Hypokalaemia	4.0	0.6	6.5	1.9
Hypomagnesaemia	3.3	0.1	6.3	0.9
Dehydration	2.1	0.2	4.0	1.2
Hypophosphataemia	0.6	0.2	1.0	0.6
Vascular disorders				
Hot flush	21.2	0.4	20.4	0.2
Eye disorders				
Lacrimation increased	13.4	<0.1	13.1	-
Psychiatric disorders				
Insomnia	16.6	<0.1	17.1	0.3
Investigations				
Neutrophil count decreased	13.7	9.6	13.8	9.6
Weight decreased	3.2	1.1	8.0	4.2
Injury, poisoning and procedural complications				
Radiation skin injury	11.1	0.3	12.6	0.3
Immune system disorders				
Hypersensitivity	2.9	0.4	3.4	0.4
Drug hypersensitivity	0.5	<0.1	1.3	0.2

* In this table this denotes an ADR that has been reported in association with a fatal outcome

Table 8 Summary of ADRs Occurring in ≥1% of Patients Receiving PERJETA in the Pivotal Clinical Trial APHINITY by Treatment Regimen and Chemotherapy Type

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	Placebo + trastuzumab + anthracycline N=1894	Placebo + trastuzumab + non- anthracycline N=510	PERJETA + trastuzumab + anthracycline N=1834	PERJETA + trastuzumab + non- anthracycline N=528
Cardiac disorders				
Cardiac Failure	0.8	0.4	1.6	0.8
General disorders and administration site conditions				
Fatigue	40.9	57.1	45.8	59.5
Mucosal Inflammation	18.4	19.4	23.4	23.1
Asthenia	22.5	14.1	23.9	12.5
Pyrexia	20.6	15.3	21.2	15.9
Oedema Peripheral	18.0	27.8	16.6	18.8
Skin And Subcutaneous Tissue Disorders				
Alopecia	68.0	62.9	69.3	58.0
Rash	20.5	19.4	26.1	24.6
Pruritus	9.0	9.0	13.8	14.6
Palmar-plantar erythrodysesthesia syndrome	7.1	4.5	10.7	3.8
Dry Skin	11.5	9.8	14.3	9.3
Nail Disorder	11.6	12.7	12.1	11.0
Gastrointestinal disorders				
Diarrhoea	40.8	61.6	67.3	84.7
Nausea	65.8	64.3	69.1	69.1

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	Placebo + trastuzumab + anthracycline N=1894	Placebo + trastuzumab + non- anthracycline N=510	PERJETA + trastuzumab + anthracycline N=1834	PERJETA + trastuzumab + non- anthracycline N=528
Vomiting	30.5	30.4	30.4	39.8
Constipation	30.5	35.7	29.7	26.3
Stomatitis	24.6	21.2	30.5	21.0
Dyspepsia	13.4	17.1	13.4	15.0
Abdominal Pain	9.8	14.9	11.0	16.1
Abdominal Pain upper	9.8	6.5	11.1	7.8
Blood And Lymphatic System Disorders				
Anaemia	19.2	37.6	23.0	44.3
Neutropenia	23.3	23.5	24.5	25.9
Febrile Neutropenia	10.8	12.2	12.8	9.7
Leukopenia	10.1	5.9	10.3	5.3
Nervous System Disorders				
Dysgeusia	19.5	28.8	24.6	30.9
Headache	23.3	23.7	22.9	21.0
Peripheral Sensory Neuropathy	16.7	20.6	18.4	16.9
Neuropathy Peripheral	13.3	22.9	14.0	20.6
Paraesthesia	10.1	9.4	13.0	7.6
Dizziness	10.6	14.7	10.7	13.8
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	33.1	30.4	29.9	24.2

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	Placebo + trastuzumab + anthracycline N=1894	Placebo + trastuzumab + non- anthracycline N=510	PERJETA + trastuzumab + anthracycline N=1834	PERJETA + trastuzumab + non- anthracycline N=528
Myalgia	29.7	29.0	27.1	22.3
Pain In Extremity	9.8	12.9	9.7	11.0
Infections And Infestations				
Nasopharyngitis	13.4	6.1	15.3	6.4
Upper Respiratory Tract Infection	6.8	9.6	8.1	8.1
Paronychia	2.4	1.8	4.4	2.5
Respiratory, Thoracic And Mediastinal Disorders				
Epistaxis	13.6	13.3	18.4	17.6
Cough	14.9	13.5	15.9	15.7
Dyspnoea	10.6	15.1	11.1	14.8
Metabolism And Nutrition Disorders				
Decreased Appetite	18.8	23.7	22.8	27.8
Hypokalaemia	2.6	9.8	3.7	16.3
Hypomagnesaemia	1.1	11.6	1.9	22.0
Dehydration	1.0	6.5	1.3	13.4
Hypophosphataemia	0.2	2.2	0.3	3.4
Vascular Disorders				
Hot Flush	21.0	21.8	20.7	19.3
Eye Disorders				
Lacrimation Increased	12.2	17.8	12.1	16.7
Psychiatric Disorders				

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %		PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %	
	Placebo + trastuzumab + anthracycline N=1894	Placebo + trastuzumab + non- anthracycline N=510	PERJETA + trastuzumab + anthracycline N=1834	PERJETA + trastuzumab + non- anthracycline N=528
Insomnia	15.3	21.8	16.2	20.1
Investigations				
Neutrophil Count Decreased	14.9	9.2	15.0	9.8
Weight decreased	3.1	3.5	7.2	11.4
Injury, poisoning and procedural complications				
Radiation Skin Injury	10.7	12.5	12.4	13.3
Immune System Disorders				
Hypersensitivity	2.6	3.9	3.1	4.4
Drug Hypersensitivity	0.5	0.6	0.9	2.5

ADRs reported in patients receiving PERJETA and trastuzumab after discontinuation of chemotherapy

In the pivotal trial APHINITY, the frequency of ADRs decreased during the targeted treatment alone phase. All ADRs in the PERJETA treatment group occurred in <10% of patients with the exception of diarrhea (18.1%), arthralgia (15.3%), radiation skin injury (12.4%), and hot flush (12.1%).

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Table 9 summarizes the adverse drug reactions (ADRs) from the pivotal clinical trial CLEOPATRA in which PERJETA was given in combination with trastuzumab and docetaxel vs placebo with trastuzumab and docetaxel.

Table 9 Summary of Adverse Drug Reactions Occurring in >1% from the Pivotal Clinical Trial CLEOPATRA

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + trastuzumab + docetaxel n =396 Frequency rate %		PERJETA + trastuzumab + docetaxel n =408 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
General disorders and administration site conditions				
Fatigue	37.4	3.3	38.5	2.2
Asthenia	30.8	1.8	28.2	2.7
Edema peripheral	28.0	0.8	25.0	0.5
Mucosal inflammation/Mucositis	19.9	1.0	27.2	1.5
Pyrexia	18.2	0.5	20.8	1.2
Chills	3.8	-	8.3	-
Skin and subcutaneous tissue disorders				
Alopecia	60.6	0.3	60.8	-
Rash	24.2	0.8	38.2	0.7
Nail disorder	23.2	0.3	23.5	1.2
Pruritus	10.1	-	18.4	-
Dry skin	6.3	-	11.5	-
Erythema	5.1	-	5.6	-
Dermatitis acneiform	1.8	-	3.9	0.2
Gastrointestinal disorders				
Diarrhea	48.2	5.1	68.4	9.6
Nausea	42.4	0.5	45.1	1.2
Vomiting	24.5	1.5	27.2	1.5
Constipation	25.5	1.0	16.9	-
Stomatitis	15.9	0.3	20.1	0.5
Dyspepsia	12.1	-	13.5	-
Blood and lymphatic system disorders				
Neutropenia	50.0	46.2	53.4	49.0

Anaemia	19.7	3.5	25.0	2.5
Leukopenia	20.7	14.9	18.4	12.3
Febrile neutropenia*	7.6	7.3	13.7	13.0
Nervous system disorders				
Headache	19.2	1.0	26.0	2.0
Neuropathy peripheral	19.9	1.8	23.3	2.7
Dysgeusia	15.7	-	18.4	-
Peripheral sensory neuropathy	14.9	0.3	12.7	0.5
Dizziness	13.4	-	16.4	0.7
Musculoskeletal and connective tissue disorders				
Myalgia	25.0	0.8	24.0	1.2
Arthralgia	17.9	0.8	20.3	0.2
Infections and infestations				
Upper respiratory tract infection	14.4	-	22.1	0.7
Nasopharyngitis	15.2	0.3	18.6	-
Paronychia	4.0	0.3	7.8	-
Respiratory, thoracic and mediastinal disorders				
Cough	19.9	0.3	24.8	0.5
Dyspnea	15.9	2.0	16.7	1.0
Pleural effusion	5.6	1.3	5.1	0.2
Metabolism and nutrition disorders				
Decreased appetite	26.8	1.5	29.7	1.7
Eye disorders				
Lacrimation increased	13.9	-	14.7	-
Psychiatric disorders				
Insomnia	13.9	-	16.4	-
Cardiac disorders				
Left ventricular dysfunction ¹	8.6	3.3	7.8	1.5
Immune system disorders				
Hypersensitivity	5.3	0.8	7.4	1.2
Drug hypersensitivity	3.8	1.5	4.4	0.5
Anaphylactic reaction	0.5	0.3	1.0	0.5

Infusion-Related Reactions ²	10.1	0.3	13.7	0.2
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* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

¹Including Symptomatic Left Ventricular Systolic Dysfunction (CHF) (1.5% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

²Incidences reflect those occurring on the first day of infusion, when only PERJETA was administered

Table 10 Summary of Adverse Events (AEs) with a ≥2% Higher Incidence in the PERJETA-treated Group Compared to the Placebo-treated Group from the Pivotal Clinical Trial CLEOPATRA

Adverse Event (AE) (MedDRA) System Organ Class	Placebo + trastuzumab + docetaxel n =396		PERJETA + trastuzumab + docetaxel n =408	
	Frequency rate %		Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
General disorders and administration site conditions				
Influenza like illness	2.5	-	5.9	0.2
Gastrointestinal disorders				
Abdominal pain	12.9	0.8	15.7	-
Gastritis	1.8	-	3.9	-
Dysphagia	0.3	-	2.7	0.2
Musculoskeletal and connective tissue disorders				
Pain in extremity	13.1	0.3	18.6	0.5
Back Pain	12.1	1.0	16.7	1.5
Muscle spasms	5.1	-	12.3	0.5
Infections and infestations				
Urinary tract infection	7.6	0.8	10.0	1.0
Pharyngitis	2.3	0.3	5.9	0.2
Cellulitis	3.3	0.5	5.6	2.0
Cystitis	1.5	-	3.9	-
Rash pustular	-	-	2.7	0.5

Adverse Event (AE) (MedDRA) System Organ Class	Placebo + trastuzumab + docetaxel n =396 Frequency rate %		PERJETA + trastuzumab + docetaxel n =408 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Metabolism and nutrition disorders				
Hypokalaemia	5.3	1.3	9.1	1.5
Eye disorders				
Conjunctivitis	4.8	-	7.6	0.2
Dry eye	2.0	-	5.9	-
Investigations				
Weight decreased	4.8	0.5	9.1	0.5
Renal and urinary disorders				
Dysuria	2.8	-	5.6	-
Respiratory, thoracic and mediastinal disorders				
Rhinorrhea	5.8	-	8.1	-
Vascular Disorders				
Hypertension	8.1	1.8	13.0	2.5
Nervous System Disorders				
Hypoaesthesia	2.8	-	5.1	-

QT Prolongation

In the Cleopatra trial; in the Placebo arm, 1.3% of patients experienced AEs suggestive of QT prolongation compared with 3.9% of patients in the PERJETA arm.

AEs including ADRs reported in patients receiving PERJETA and trastuzumab after discontinuation of docetaxel

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 treatment group occurred in <10% of patients with the exception of diarrhea (28.1%), rash

(18.3%), upper respiratory tract infection (18.3%), headache (17.0%), nasopharyngitis (17.0%), pruritus (13.7%), fatigue (13.4%), asthenia (13.4%), nausea (12.7%) and arthralgia (11.4%).

After discontinuation of docetaxel treatment, AEs (regardless of causality) that were reported with a $\geq 2\%$ difference in patients in the PERJETA-treated arm compared with the placebo-treated arm were diarrhea, abdominal pain, gastritis, upper respiratory tract infection, urinary tract infection, herpes zoster, pain in extremity, rash, dermatitis acneiform, pruritus, peripheral neuropathy, headache, hypoaesthesia, fatigue, asthenia, mucosal inflammation, edema, muscle spasms, back pain, musculoskeletal chest pain, paronychia, onycholysis, oropharyngeal pain, hypokalemia, conjunctivitis, hypertension, and lymphoedema.

Study BO17929 in Metastatic Breast Cancer

Table 11 Overview of Safety in Study BO17929

Number (%) of patients with	Cohorts 1 and 2 PERJETA + trastuzumab (N=66)	Cohort 3 PERJETA alone (N=29)	Cohort 3 PERJETA + trastuzumab (N=17)
Any AE	64 (96.9)	27 (93.1)	15 (88.2)
Related	54 (81.8)	20 (69.0)	12 (70.6)
NCI-CTCAE Grade ≥ 3	11 (16.7)	5 (17.2)	4 (23.5)
Related	6 (9.1)	0	2 (11.8)
Serious AE	11 (16.7)	1 (3.4)	1 (5.9)
Related	3 (4.5)	0	1 (5.9)
Events to Monitor			
Symptomatic Cardiac Dysfunction	0 3 (4.5)	0 1 (3.4)	0 1 (5.9)
LVEF decrease ^a (Local Read)	2 (3.0)	1 (3.4)	0
LVEF decrease ^a (Central Read)	42 (63.6)	14 (48.3)	5 (29.4)
All grades diarrhea	2 (3.0)	1 (3.4)	1 (5.9)
CTC Grade 3, 4 or 5 diarrhea ^b	5 (7.6)	0	0
Infusion-related AEs ^c			

^a Decrease of $\geq 10\%$ points to value $<50\%$

^b All cases were Grade 3 diarrhea

^c Infusion-related AEs assessed for first four cycles of treatment only in cohorts 1&2

Left Ventricular Dysfunction in Study BO17929

No symptomatic cardiac AEs were reported in this study. Five patients experienced an asymptomatic decline in LVEF (of at least 10%-points from baseline to an absolute value below 50%).

Additional Supportive Clinical Trial Information

Study BO29159 (MetaPHER) was an open-label, single-arm, multicenter Phase IIIb study designed to evaluate the safety and tolerability of subcutaneous trastuzumab in combination with PERJETA plus docetaxel in patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) who had not previously received systemic non-hormonal anti-cancer therapy in the metastatic setting. The safety profile of subcutaneous trastuzumab+PERJETA+docetaxel based on the MetaPHER final analysis was consistent with the known safety profile of intravenous trastuzumab+PERJETA+docetaxel from the CLEOPATRA trial.

Investigator-assessed injection related reaction events (including local and systemic events) were reported in 5.1% of patients, occurred primarily in Cycles 1 and 2, and were, with the exception of just one Grade 2 event, of Grade 1 intensity only.

Although, the MetaPHER and CLEOPATRA studies both enrolled patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) who had not previously received systemic non-hormonal anti-cancer therapy in the metastatic setting, comparisons of the safety profiles from MetaPHER and CLEOPATRA are limited due to the slightly different enrolment criteria, and some differences in the demographics of the study population. Notably, fewer Asian patients were enrolled in MetaPHER and it is noted that Asian patients were reported to have increased incidence of neutropenia and febrile neutropenia in the CLEOPATRA study (see [7](#) WARNINGS AND PRECAUTIONS, Special Populations, Race).

Metastatic and Early Breast Cancer

Further Information on Selected Adverse Drug Reactions

Left ventricular dysfunction

In the pivotal trial WO20698/TOC4129g (CLEOPATRA), the incidence of LVD during study treatment was 8.6% in the placebo with trastuzumab and docetaxel treated group and 7.8% in the PERJETA with trastuzumab and docetaxel treated group. The incidence of symptomatic LVD was 1.8% in the placebo-treated group and 1.5% in the PERJETA-treated group.

In NeoSphere, in which patients received four cycles of PERJETA as neoadjuvant treatment, the incidence of LVD (defined as events identified under the Preferred Term “Left Ventricular Dysfunction” according to MedDRA) was higher in the PERJETA, trastuzumab and docetaxel-treated group in the neoadjuvant treatment period (2.8% PERJETA, trastuzumab, and docetaxel versus 0.9% trastuzumab and docetaxel) and overall treatment period (7.5% PERJETA, trastuzumab and docetaxel versus 1.9% trastuzumab and docetaxel). There was one case of

symptomatic LVD (NCI CTCAE Grade ≥ 3 and NYHA classification ≥ 2) in the PERJETA and trastuzumab-treated group and no patients in the other 3 arms in the neoadjuvant treatment period or overall treatment period.

In TRYPHAENA with neoadjuvant treated patients, the incidence of LVD (defined as events identified under the Preferred Term “Left Ventricular Dysfunction” according to MedDRA) during the overall treatment period was 8.3% in the group treated with PERJETA plus trastuzumab and 5-fluorouracil, epirubicin and cyclophosphamide (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 docetaxel, carboplatin and trastuzumab (TCH). The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with PERJETA plus trastuzumab and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving PERJETA plus trastuzumab and docetaxel) and also 1.3% in the group treated with PERJETA in combination with TCH. No patients in the group treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel experienced symptomatic LVD.

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

In the pivotal trial APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10% from baseline and to $< 50\%$ or cardiac death was $< 1\%$ (0.7% of PERJETA-treated patients vs 0.3% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of PERJETA-treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cut-off. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10% from baseline and to $< 50\%$ were reported in 2.7% of PERJETA-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of PERJETA-treated patients and 80.6% of placebo-treated patients had recovered at the data cut-off.

Infusion-related reactions

An infusion-related reaction was defined in the pivotal 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, the overall frequency of events was 10.1% in the placebo-treated group and 13.7% in the PERJETA-treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions in

the PERJETA-treated group ($\geq 1.0\%$) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity and vomiting.

During the 2nd cycle when all drugs were administered on the same day, the most common infusion-related reactions in the PERJETA-treated group ($\geq 1.0\%$) were fatigue, dysgeusia, hypersensitivity, myalgia and vomiting (see [7](#) WARNINGS AND PRECAUTIONS: Infusion-related reactions).

In the neoadjuvant and adjuvant trials, PERJETA was administered on the same day as the other study treatment drugs. In the NeoSphere and TRYPHAENA trials, infusion-related reactions occurred in 18.6% - 25.0% of patients on the first day of PERJETA administration (in combination with trastuzumab and chemotherapy). In the APHINITY trial, the incidence of infusion-related reactions (all grades) was 20.9% of patients in the PERJETA-treated group and 18.0% in the placebo-treated group on the first day of administration (in combination with trastuzumab and chemotherapy). The incidence of Grade 3-4 adverse events in the APHINITY trial was 1.2% for the PERJETA-treated group and 0.7% for the placebo-treated group. The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being of mild or moderate severity.

Hypersensitivity reactions/anaphylaxis

In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of events reported as hypersensitivity/anaphylaxis was 9.3% in the placebo-treated patients and 11.3% in the PERJETA-treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) Grade 3-4, respectively. Two (2) patients in the placebo-treated group and 4 patients in the PERJETA-treated group experienced anaphylaxis (see [7](#) WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis). Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment.

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 TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the PERJETA and TCH treated group (13.2% and 7.6% respectively), of which 2.6% and 1.3% of events, respectively, were NCI-CTCAE Grade 3-4. In the APHINITY trial, the incidence of hypersensitivity/anaphylaxis events was 4.9% in the placebo + TCH group, of which 1.6% of events were NCI-CTCAE Grade 3-4.

Febrile neutropenia

In the pivotal trial CLEOPATRA in metastatic breast cancer, no events of febrile neutropenia were reported after cessation of docetaxel. The median total dose of docetaxel was 940.8 mg and 1008.0 mg in the PERJETA-treated and the placebo-treated patients, respectively. Febrile neutropenia occurred in 13.7% of PERJETA-treated patients and 7.6% of placebo-treated patients. 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 APHINITY trial, febrile neutropenia occurred in 12.1% of PERJETA-treated patients and 11.1% of placebo-treated patients.

In the NeoSphere trial, febrile neutropenia occurred in the neoadjuvant treatment period in 8.4% of PERJETA, trastuzumab and docetaxel-treated patients and in 7.5% of trastuzumab and docetaxel-treated patients. In the TRYPHAENA trial, febrile neutropenia occurred in the neoadjuvant treatment period in 18.1% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 9.3% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 17.1% of patients treated with PERJETA in combination with TCH.

Diarrhea

In the pivotal trial CLEOPATRA in metastatic breast cancer, diarrhea occurred in 68.6% of Perjeta-treated patients and 48.2% 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 diarrhea was 9.8% 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. Diarrheal events responded well to proactive management with anti-diarrheal agents.

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 diarrhea 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. The median duration of the longest event was 35 days in the PERJETA+ trastuzumab + chemotherapy arm versus 13 days in the PERJETA + trastuzumab arm. Elderly patients (≥ 65 years) had a higher risk of diarrhea compared with younger patients (< 65 years).

In the NeoSphere trial, diarrhea occurred in the neoadjuvant treatment period in 45.8% of PERJETA, trastuzumab and docetaxel-treated patients and in 33.6% of trastuzumab and docetaxel-treated patients. In the TRYPHAENA trial, diarrhea in the neoadjuvant treatment period occurred in 61.1% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 61.3% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 72.4% of patients treated with PERJETA in combination with TCH. The majority of cases were Grade 1-2 in severity; Grade ≥ 3 diarrhea was experienced by 4%, 5% and 12% of patients in the study groups, respectively.

Rash

In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 52.2% of PERJETA-treated patients, compared with 39.1% 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 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.

In the NeoSphere trial, rash occurred in 26.2% of PERJETA, trastuzumab and docetaxel-treated patients and in 21.5% of trastuzumab and docetaxel-treated patients. The majority of rash events were Grade 1 or 2. In the TRYPHAENA trial, rash occurred in 19.4% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 10.7% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 21.1% of patients treated with PERJETA in combination with TCH. One event of Grade 3 rash was recorded, occurring in the group treated with PERJETA in combination with TCH.

8.3 Less Common Clinical Trial Adverse Reactions

Early Breast Cancer

Neoadjuvant Treatment of Breast Cancer (NeoSphere)

**Listing 1: The following Adverse Drug Reactions were reported in <1% of patients in the PERJETA-treated group in the pivotal clinical trial NeoSphere:
(Ptz=pertuzumab; H=trastuzumab; D=docetaxel)**

Cardiac disorders: Cardiac failure congestive (0.9% in the Ptz+H arm, 0% in H+D arm, 0% in Ptz+H+D arm and 0% in Ptz+D arm)

Infections and infestations: Paronychia (0.9% in the H+D arm, 0.9% in the Ptz+H+D arm, 0% in the Ptz+H arm and 0% in the Ptz+D arm)

Neoadjuvant Treatment of Breast Cancer (BERENICE)

**Listing 2: The following Adverse Drug Reactions were reported in <1% of patients receiving PERJETA in BERENICE:
(D=docetaxel, ddAC= dose-dense doxorubicin and cyclophosphamide, FEC= 5-fluorouracil, epirubicin, cyclophosphamide, H=trastuzumab, P=pertuzumab, T=paclitaxel)**

Cardiac disorders: Cardiac failure congestive (0.5% in ddAC, T+PH v 0% in FEC, D+PH)

Adjuvant Treatment of Breast Cancer (APHINITY)

Listing 3: The following Adverse Drug Reactions were reported in <1% of patients in the PERJETA-treated group in the pivotal clinical trial APHINITY:

Cardiac disorders: Cardiac failure congestive (<0.1% in the PERJETA-treated group vs. <0.1% in the placebo-treated group), left ventricular dysfunction (0.0% in the PERJETA-treated group vs. <0.1% in the placebo-treated group)

Nervous system disorders: Cerebral haemorrhage (All Grades: 0.1% in the PERJETA-treated group vs. 0.0% in the placebo-treated group; Grade ≥ 3 : 0.1% in the PERJETA-treated group vs. 0.0% in the placebo-treated group). One Grade 5 cerebral haemorrhage was reported in the PERJETA-treated group.

Respiratory, thoracic, and mediastinal disorders: Pleural effusion (0.1% in the PERJETA-treated group vs. 0.2% in the placebo-treated group)

Metastatic Breast Cancer

Listing 4: The following adverse reactions were reported at an incidence of < 1% in the pivotal clinical trial CLEOPATRA:

Respiratory, Thoracic and Mediastinal Disorders: Interstitial Lung Disease

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In the pivotal trial CLEOPATRA, the incidence of NCI-CTCAE (version 3) Grade 3-4 leukopenia was higher in the PERJETA-treated group (64.6% of PERJETA-treated patients and 60.7% of placebo-treated patients, including 13.6% and 13.3% Grade 4 leukopenia, respectively).

The incidence of NCI-CTCAE (version 3) Grade 3-4 neutropenia was balanced in the PERJETA-treated and control groups in the pivotal trial CLEOPATRA (82.4% of PERJETA-treated patients and 81.1% of placebo-treated patients, including 57.9% and 60.4% Grade 4 neutropenia, respectively) and in the pivotal trial APHINITY.

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.

In the NeoSphere trial, the incidence of NCI-CTCAE v.3 Grade 3-4 leukopenia was 51.4% (5.6% Grade 4) in patients treated with PERJETA, trastuzumab and docetaxel and 56.1% (5.6% Grade 4) in patients treated with trastuzumab and docetaxel. The incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 78.5% (56.1% Grade 4) in patients treated with PERJETA, trastuzumab and docetaxel and 88.6% (64.8% Grade 4) in patients treated with trastuzumab and docetaxel.

In the TRYPHAENA study, the incidence of NCI-CTCAE v.3 Grade 3-4 leukopenia was 80.6% (29.2% Grade 4) in patients treated with 3 cycles of PERJETA, trastuzumab and 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by 3 cycles of PERJETA, trastuzumab and docetaxel, 67.5% (24.3% Grade 4) in patients treated with 3 cycles of PERJETA, trastuzumab and docetaxel following 3 cycles of FEC, and 62.6% (13.3% Grade 4) in patients treated with 6 cycles

of PERJETA, trastuzumab, docetaxel and carboplatin. The incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 92.9% (70.4% Grade 4), 77.1% (59.5% Grade 4), and 85.4% (66.7% Grade 4) in the groups, respectively.

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

8.5 Post-Market Adverse Reactions

Safety reports from the post-marketing setting are consistent with safety data from clinical trials of PERJETA.

The following adverse drug reaction has been identified from post marketing experience with Perjeta based on spontaneous case reports and literature cases. The adverse drug reaction is listed according to system organ class in MedDRA.

Table 12 Adverse Drug Reactions from Post-Marketing Experience

System Organ Class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Tumour Lysis Syndrome (TLS)	Rare ($\geq 0.01\%$ and $< 0.1\%$) in breast cancer patients

9 DRUG INTERACTIONS

9.1 Drug-Behavioural Interactions

PERJETA has a minor influence on the ability to drive and use machines. Dizziness may occur during treatment with PERJETA. Patients experiencing infusion-related reactions to PERJETA should be advised not to drive and use machines until symptoms abate.

9.2 Drug-Drug Interactions

A sub-study in 37 patients in the pivotal trial WO20698/TOC4129g (CLEOPATRA) showed no evidence of drug-drug interaction between pertuzumab and trastuzumab or between pertuzumab and docetaxel. This lack of drug-drug interaction was confirmed by pharmacokinetic data in a sub-study of 36 patients from the APHINITY study.

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

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody that specifically targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including HER1 (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 anti- tumour activity in HER2-overexpressing xenograft models.

10.2 Pharmacodynamics

Refer to Section 10.1 Mechanism of Action.

10.3 Pharmacokinetics

Across multiple clinical trials in various indications there were no dose-related changes in the pharmacokinetics of pertuzumab at doses ranging from 2-25 mg/kg. In seven clinical trials where PK parameters were obtained, the estimated mean clearance (CL) ranged from 0.232 - 0.329 L/day, the steady-state volume of distribution (V_{ss}) from 3.53 - 7.05 L, and the half-life from 11.1 - 22.3 days.

No differences in pertuzumab PK were observed in patients with early breast cancer compared to patients with metastatic breast cancer.

Absorption: Pertuzumab is administered as an IV infusion.

Distribution: Following intravenous administration, the mean V_{ss} across two dose groups ranged from 3.53 – 4.12 L in metastatic breast cancer patients (Study BO16934), from 4.89 – 7.05 L in advanced solid tumour patients (across 12 dose groups in Studies TOC2297g, JO17076, BO17003 and BO17021), 4.45 – 5.23 L across two dose groups in hormone-resistant prostate cancer patients (Study BO17004) and 4.9 L in one dose group in non-small cell lung cancer patients (Study WO20024).

Metabolism:

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

Elimination:

The mean CL of pertuzumab ranged from 0.247 – 0.270 L/day across two dose groups in metastatic breast cancer patients (Study BO16934), from 0.232 – 0.329 L/day in advanced solid tumour patients (across 12 dose groups in Studies TOC2297g, JO17076, BO17003 and BO17021), 0.253 – 0.270 L/day across two dose groups in hormone-resistant prostate cancer patients (Study BO17004) and 0.240 L/day in one dose group in non-small cell lung cancer patients (Study WO20024).

The mean half-life of pertuzumab ranged from 11.4 – 12.2 days in metastatic breast cancer patients (Study BO16934), 11.1 – 22.3 days in advanced solid tumour patients (Studies TOC2297g, JO17076, BO17003 and BO17021), 13.7 – 19.3 days in hormone-resistant prostate cancer patients (Study BO17004) and 17.9 days in non-small cell lung cancer patients (Study WO20024).

Special Populations and Conditions**Geriatrics**

No dedicated studies have been conducted in geriatric patients with pertuzumab.

Renal Insufficiency

No formal pharmacokinetic study has been conducted in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

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

PERJETA should not be used after the expiry date (EXP) shown on the vial and carton.

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

DO NOT FREEZE. DO NOT SHAKE.

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

The solution of PERJETA for infusion diluted in US Pharmacopeia (USP) polyvinylchloride (PVC) or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection may be stored at 2–8°C (36–46°F) for up to 24 hours prior to use. Diluted PERJETA has been shown to be stable for up to 24 hours (up to 30°C). However, since diluted PERJETA contains no preservative, it should be used immediately. If it is not used immediately the diluted solution should be stored refrigerated (2–8°C) and used within 24 hour

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Any unused medicinal product or waste material should be disposed of in accordance with local medical waste or collection systems.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Product Characteristics:

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues. The molecular mass of intact pertuzumab is approximately 148,088 Daltons for the antibody form with each heavy chain terminating at glycine residue 448 and containing predominantly a G0 oligosaccharide.

PERJETA acts by blocking the association of HER2 with the other HER family members, including HER1 (EGFR), HER3, and HER4. Pertuzumab can also prevent formation of HER2 homodimerization. As a result, pertuzumab inhibits ligand-initiated intracellular signaling pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3 (PI3) kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis.

PERJETA is supplied as a clear to slightly opalescent, colorless to pale brown sterile liquid solution (see [6](#) DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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

Early Breast Cancer

NeoSphere ([WO20697](#))

NeoSphere is a multicenter, randomized, open-label Phase II clinical trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy.

Patients were randomized to receive one of four neoadjuvant regimens prior to surgery as follows:

- trastuzumab plus docetaxel
- PERJETA plus trastuzumab and docetaxel
- PERJETA plus trastuzumab
- PERJETA plus docetaxel.

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

PERJETA and trastuzumab were administered intravenously (see [4](#) DOSAGE AND ADMINISTRATION) every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m² by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be escalated to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received three cycles of 5-fluorouracil (600 mg/m²), epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete one year of therapy. Patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC after surgery.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Additional exploratory pCR rates included nodal status (ypT0/isNO and ypTON0).

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (71%) and all were female). Overall 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer and 61% had operable breast cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER positive and/or PgR positive).

Study BO25126 (APHINITY)

APHINITY is a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumour excised prior to randomization. Patients were randomized to receive PERJETA or placebo, in combination with adjuvant trastuzumab and chemotherapy. Patients were stratified by nodal status, central hormone receptor status, adjuvant chemotherapy regimen and protocol version. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

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

PERJETA and trastuzumab were administered intravenously (see [4](#) DOSAGE AND ADMINISTRATION) every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Secondary efficacy endpoints included, among others, overall survival (OS).

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%). All patients had an ECOG performance score of 0 (88%) or 1 (12%). The number of patients that received anthracycline-based versus non-anthracycline-based chemotherapy was 78% and 22%, respectively.

PERJETA-treated patients and placebo-treated patients both received a median number of 18 cycles of anti-HER2 therapy.

Metastatic Breast Cancer (MBC)

Study WO20698/TOC4129g (CLEOPATRA)

WO20698/TOC4129g (CLEOPATRA) is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 patients with HER2-positive metastatic or unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Patients were randomized 1:1 to receive placebo + trastuzumab + docetaxel or PERJETA + trastuzumab + docetaxel. Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease free interval of at least 12 months before enrolment into the trial.

PERJETA and trastuzumab were administered intravenously as outlined in DOSAGE AND ADMINISTRATION. Patients were treated with PERJETA and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m² IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated.

At the time of the primary analysis, the mean number of cycles of study treatment received in the placebo treatment group was 16.2 and in the PERJETA-treated group was 19.9.

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.

Key secondary efficacy endpoints were overall survival (OS), progression-free survival (investigator-assessed), objective response rate.

Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumour prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumours, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab.

Study BO17929

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

Cohorts 1 and 2: Sixty six patients in cohorts 1 and 2 received at least one dose of PERJETA and trastuzumab. All patients had received prior treatment for metastatic disease; half were receiving second-line treatment for metastatic disease, while 35% were receiving third-line treatment and beyond. In addition, 71% had received neoadjuvant chemotherapy.

Cohort 3: Twenty nine patients received at least one cycle of PERJETA. Of these 29 patients, 12 participated in the single-agent Phase only, and 17 went on to receive PERJETA and trastuzumab treatment when they had documented progression on PERJETA alone. All 29 patients had progressed on first-line therapy in the metastatic setting, and 41.4% had also progressed after second line therapy. All patients in Cohort 3 received at least one full dose of PERJETA. Patients on PERJETA and trastuzumab treatment received a median of 12 cycles overall.

14.2 Study Results

Early Breast Cancer

NeoSphere (WO20697)

The efficacy results are summarized in **Table 13**.

Table 13 NeoSphere: Summary of Efficacy (ITT population)

Parameter	NeoSphere			
	T+D N=107	Ptz+T+D N=107	Ptz+T N=107	Ptz+D N=96
pCR ¹ n (%) [95% CI] ²	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]
p-value ³		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs Ptz+T+D)

ITT: Intention to treat; T:trastuzumab; D: docetaxel; Ptz: PERJETA; CI: Confidence Interval

1. ypT0/is= bpCR, eradication of all invasive cancer from the breast
2. 95% CI for one sample binomial using Pearson-Clopper method.
3. p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

In exploratory analyses of pCR, pCR defined as the absence of invasive carcinoma in the breast and lymph nodes, irrespective of ductal carcinoma *in situ* (ypT0/is ypN0, or total pCR), and absence of invasive carcinoma in the breast and lymph nodes (ypT0 ypN0) were analyzed. The percentage of patients with pCR by ypT0/is ypN0 was 39.3% in patients treated with PERJETA in combination with trastuzumab and docetaxel and 21.5% in patients treated with trastuzumab and docetaxel. The percentage of patients with pCR by ypT0 ypN0 was 32.7% and 12.1% in the groups, respectively.

In an exploratory sub-group analysis, the breast pCR rates and the magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumours compared to patients with hormone receptor-negative tumours. In the Perjeta plus trastuzumab and docetaxel arm, the breast pCR rate was 26.0% in patients with hormone receptor-positive tumours and 63.2% in patients with hormone-receptor negative tumours. In the trastuzumab and doxetaxel arm, the breast pCR rate was 20% in patients with hormone receptor-positive tumours and 36.8% in patients with hormone-receptor negative tumours.

Study BO25126 (APHINITY)

After a median follow-up to 45.4 months, the APHINITY study demonstrated 19% reduction in risk of recurrence or death in patients randomized to receive PERJETA compared with patients randomized to receive placebo, hazard ratio (HR) = 0.81 (95% CI: 0.66, 1.00).

The efficacy results from the APHINITY trial are summarized in **Table 14** and in **Figure 1**.

Table 14 Overall Efficacy from APHINITY Study (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 ¹	0.0446	
3 year event-free rate ² [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints		
Overall Survival (OS)³		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value ¹	0.4673	
3 year event-free rate ² [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]

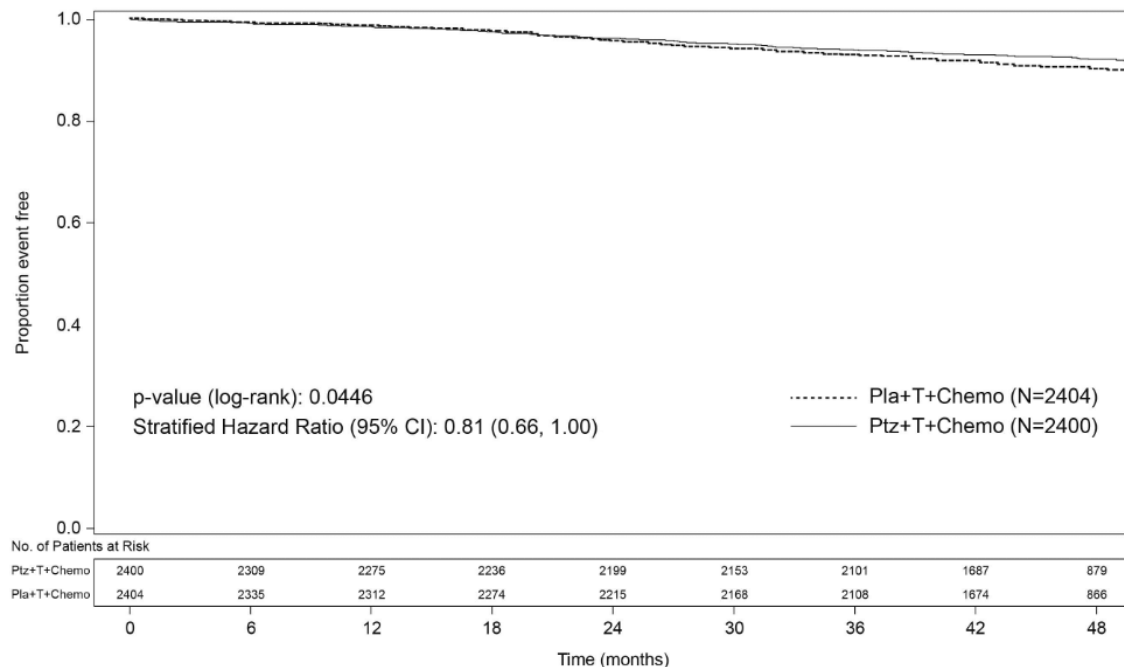
ITT: Intent-to-treat; HR: Hazard Ratio; CI: Confidence Intervals,

¹ Log Rank test, stratified; 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

³ Data from first interim analysis performed at 26% of target events for final OS analysis. Alpha level for OS analysis controlled by the O'Brien Fleming method with Lan-DeMets alpha spending function.

Figure 1 Kaplan-Meier Curve of Invasive Disease Free Survival



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.

Within the anthracycline subgroup, the estimate of IDFS at 4-years was 92.1% in the PERJETA-treated group versus 90.1% in the placebo-treated group. Within the non-anthracycline subgroup, the estimate of IDFS at 4-years was 92.9% in the PERJETA-treated group versus 92.1% in the placebo-treated group.

In a subgroup analysis, the benefits of PERJETA were more apparent for patients with node-positive or hormone receptor-negative disease. The findings for these patients are presented in Table 15.

Table 15 Invasive Disease-Free Survival (IDFS) Efficacy Results by Lymph Node and Hormone Receptor Status from APHINTY Study1

Nodal Status:	Positive		Negative	
	PERJETA + trastuzumab + chemotherapy N=1503	Placebo + trastuzumab + chemotherapy N=1502	PERJETA + trastuzumab + chemotherapy N=897	Placebo + trastuzumab + chemotherapy N=902
Number (%) of patients with event	139 (9.2%)	181 (12.1%)	32 (3.6%)	29 (3.2%)
HR [95% CI]	0.77 (0.62, 0.96)		1.13 (0.68, 1.86)	
3 year event-free rate [95% CI] ²	92.0 (90.6, 93.4)	90.2 (88.6, 91.7)	97.5 (96.5, 98.6)	98.4 (97.6, 99.2)
<hr/>				
Hormone Receptor Status:	Positive		Negative	
	PERJETA + trastuzumab + chemotherapy N=1536	Placebo + trastuzumab + chemotherapy N=1546	PERJETA + trastuzumab + chemotherapy N=864	Placebo + trastuzumab + chemotherapy N=858
Number (%) of patients with event	100 (6.5%)	119 (7.7%)	71 (8.2%)	91 (10.6%)
HR [95% CI]	0.86 (0.66, 1.13)		0.76 (0.56, 1.04)	

Nodal Status:	Positive		Negative	
	PERJETA + trastuzumab + chemotherapy N=1503	Placebo + trastuzumab + chemotherapy N=1502	PERJETA + trastuzumab + chemotherapy N=897	Placebo + trastuzumab + chemotherapy N=902
3 year event-free rate [95% CI] ²	94.8 (93.7, 95.9)	94.4 (93.2, 95.5)	92.8 (91.0, 94.5)	91.2 (89.2, 93.1)

HR: Hazard Ratio; CI: Confidence Intervals

¹ Exploratory analyses of pre-specified subgroups without adjustment for multiple comparisons

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

Metastatic Breast Cancer (MBC)

Study WO20698/TOC4129g (CLEOPATRA)

At the time of the primary progression-free survival analysis, a total of 242 patients (59%) in the placebo-treated group and 191 patients (47.5%) in the PERJETA-treated group had IRF-confirmed progressive disease or had died.

At the time of primary analysis, the study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR] = 0.62, 95% CI = 0.51, 0.75, $p < 0.0001$) in the PERJETA-treated group compared with the placebo-treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo + trastuzumab + docetaxel treated group vs 18.5 months in the PERJETA-treated group) (see Figure 2). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with disease limited to non-visceral metastasis ($n=178$), the hazard ratio was 0.96 (95% CI: 0.61, 1.52) (see Figure 3).

At a second OS analysis performed (confirmatory analysis) one year after the primary analysis of efficacy, 267 patients had died with more deaths occurring in the placebo-treated group compared with the PERJETA-treated group (154 deaths (37.9%) versus 113 deaths (28.1%), respectively). A statistically significant OS benefit in favour of the PERJETA-treated group was demonstrated (HR 0.66, Adjusted (98.62%) CI = 0.49, 0.90, $p = 0.0008$ log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached in the PERJETA-treated group (see Table 16 and Figure 4). OS results in patient subgroups were consistent with those observed for all patients with the exception of the subgroup of patients with disease limited to non-visceral metastases [HR = 1.42 (95% CI: 0.71, 2.84)].

The final analysis of OS was performed when 389 (48.1%) patients had died [221 (54.4%) in the placebo-treated group and 168 (41.8%) in the PERJETA-treated group]. This occurred approximately 21 months after the confirmatory OS analysis. 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 16). The final OS analysis is considered descriptive as confirmatory statistical significance had already been achieved at the second interim analysis.

Duration of IRF-assessed objective response was assessed in the 233 patients in the placebo-treated group and 275 patients in the PERJETA-treated group with a best overall response of CR or PR, as assessed by the IRF. The median duration of response was 12.5 months in the placebo-treated patients compared to 20.2 months in the PERJETA-treated patients. The efficacy results from the CLEOPATRA trial are summarised in Table 16:

Table 16 Summary of Efficacy from CLEOPATRA Study (ITT Population)

Parameter	Placebo + trastuzumab + docetaxel n=406	PERJETA + trastuzumab + docetaxel n=402	HR (95% CI)	p-value
Primary Endpoint:				
Progression-Free Survival (IRF review)				
No. of patients with an event	242 (59%)	191 (47.5%)	0.62	<0.0001
Median PFS (months)	12.4	18.5	[0.51;0.75]	
Secondary Endpoints:				
Overall Survival				
Confirmatory analysis (2 nd Interim analysis)				
No. of patients with an event*	154 (37.9%)	113 (28.1%)	0.66	0.0008*
Median months	37.6	Not reached	[0.49;0.90]#	
Final analysis**				
No. of patients with an event	221 (54.4%)	168 (41.8%)	0.68	[0.56; 0.84]**
Median months	40.8	56.5		
Objective Response Rate (ORR) ^				
No. of patients with measurable disease	336	343		
ORR (CR+PR)	233 (69.3 %)	275 (80.2 %)		

Parameter	Placebo + trastuzumab + docetaxel n=406	PERJETA + trastuzumab + docetaxel n=402	HR (95% CI)	p-value
Complete response (CR)	14 (4.2 %)	19 (5.5 %)		
Partial Response (PR)	219 (65.2 %)	256 (74.6 %)		

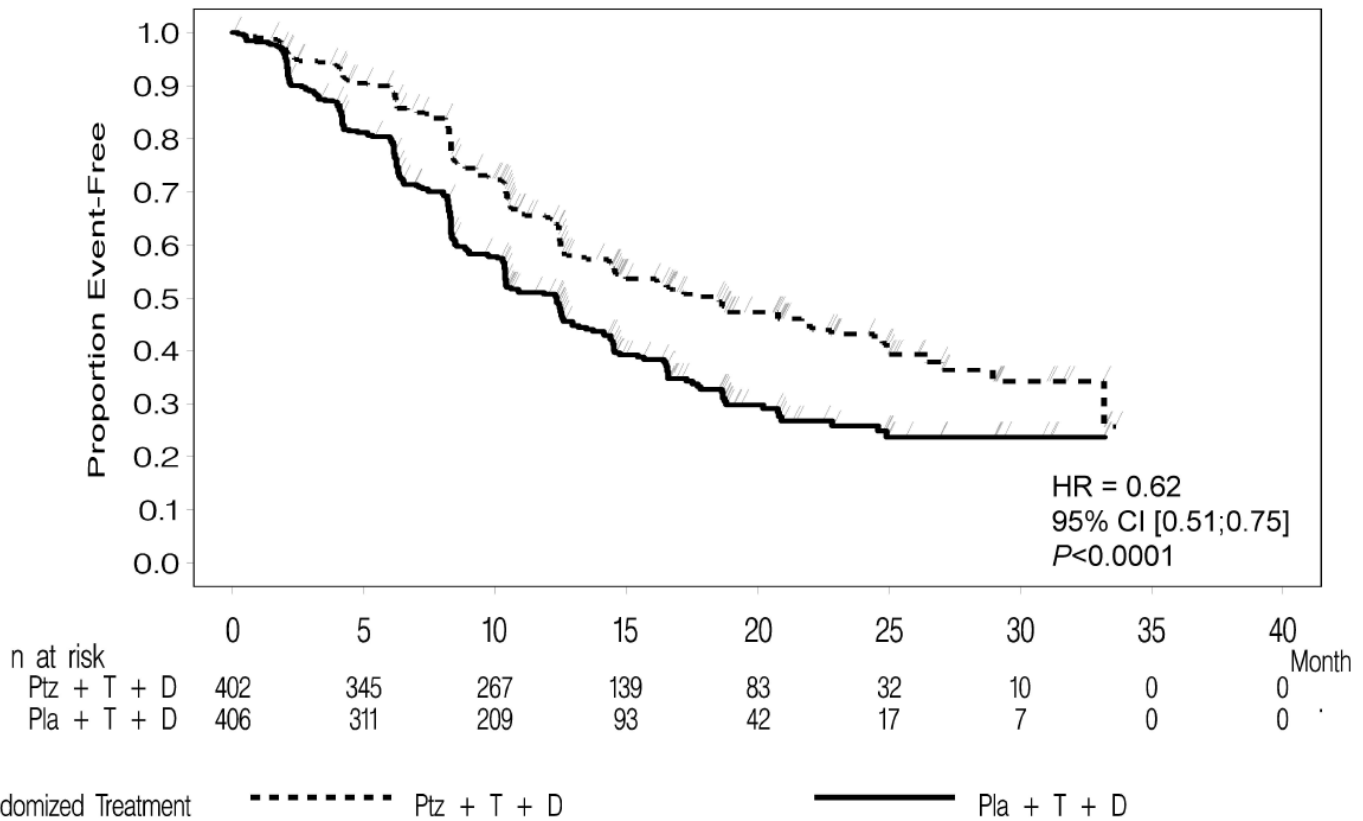
*OS data based upon data with additional 1 year follow up after the primary data cutoff. The p-value met the O'Brien Fleming stopping boundary of the Lan DeMets alpha spending function for the second interim analysis of overall survival ($p \leq 0.0138$). The result was therefore statistically significant.

adjusted CI presented for OS, to reflect the stopping boundary of $p \leq 0.0138$. The interval represents the 98.62% CI

**Final analysis of overall survival, cut-off date 11 Feb 2014. Final OS analysis considered descriptive only as the confirmatory statistical significance had already been achieved at the second interim analysis.

^Objective response rate is based on IRF-assessed tumour assessments

Figure 2 Kaplan-Meier Curve of IRF-assessed Progression-Free Survival (ITT Population)



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

Figure 3 IRF-assessed PFS by Patient Subgroup (ITT Population)

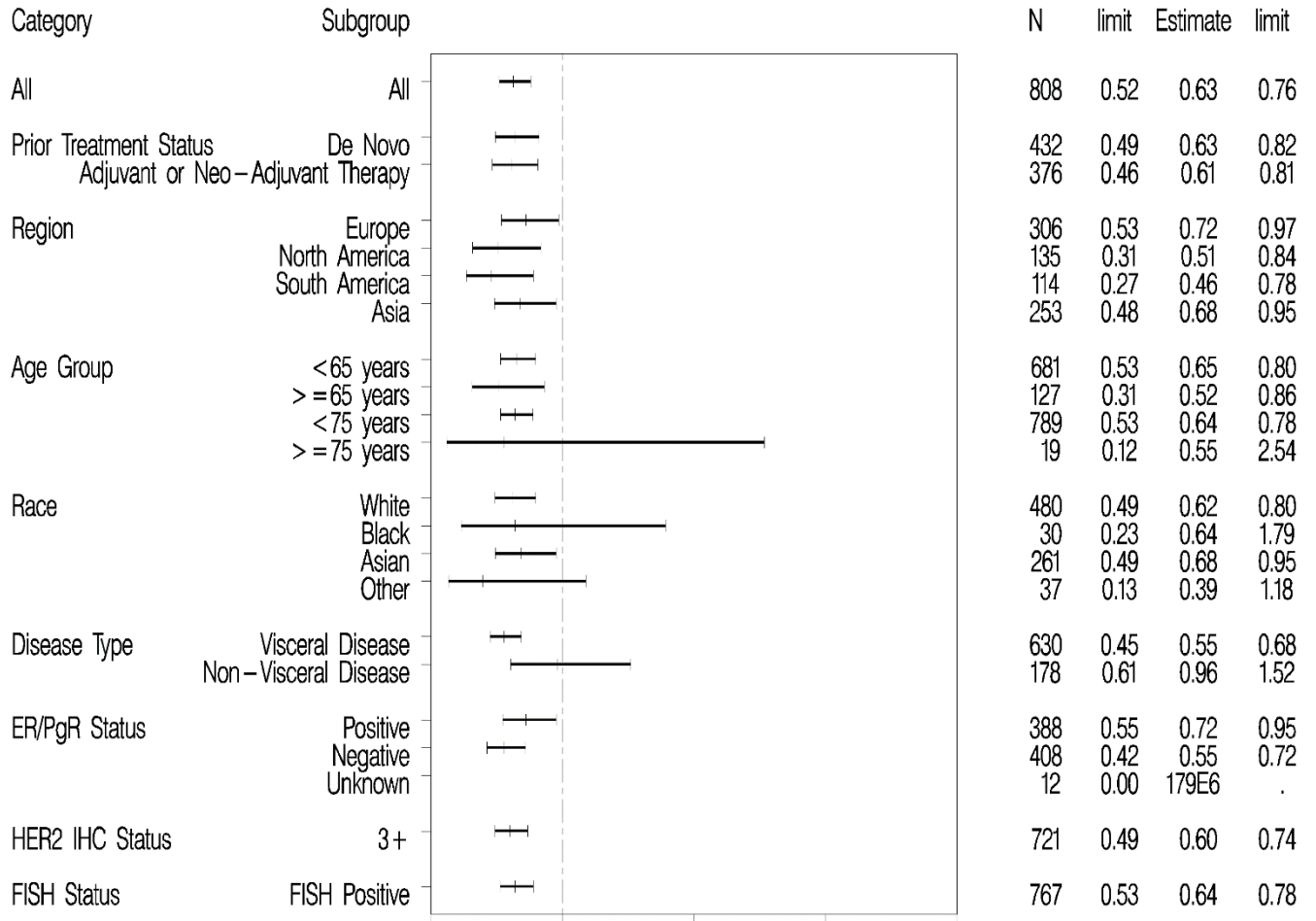
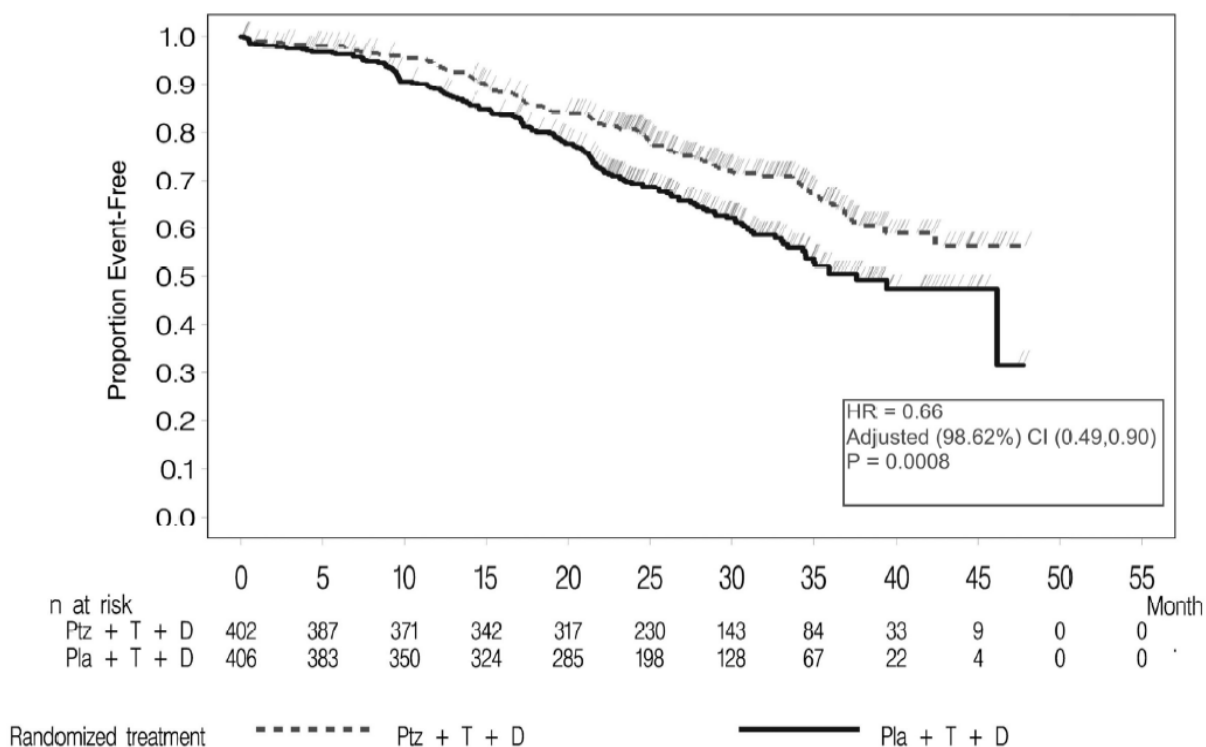


Figure 4 **Kaplan-Meier Curve of Overall Survival (2nd Interim Analysis, ITT Population)**



Study BO17929

Cohorts 1 and 2: At the time of the primary analysis, the median duration of treatment on study was nine cycles (27 weeks). The ORR and CBR at the time of the primary analysis are presented in Table 17. The median PFS and time to progression (TTP) were 24 weeks. Median time to response was 11 weeks, and in those patients with a response, the median duration of response was 25 weeks. Patients who had a CR tended to have had a longer duration of previous trastuzumab therapy (28 months (range 8-76) versus 9 months (range 2-35) for those without CBR). The sum of measurable tumour burden was lower in the CR group (median of 27mm, range 11-46 for CR group; 73mm, range 17-168 for patients without a CBR) although the ranges were wide. Patients with CR tended to have fewer lesions, and correspondingly had fewer lesion sites. Four of this group had target and non-target lesions in lymph nodes only and the fifth had target lesions solely within the lung. Patients who did not experience CBR generally had a greater overall number of lesions at multiple sites.

Cohort 3: Table 17 shows that PERJETA alone had modest activity in patients after failure of trastuzumab (middle column). However, when trastuzumab was added back in, there was an increase in response. These responses occurred in patients whose disease had recently

progressed on each antibody when given separately. In addition 3 patients had stable disease lasting six months or longer for a total clinical benefit rate of 35.3%.

Table 17 Study BO17929: Descriptive Efficacy Data

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

NOTE: >6 months = 8 cycles of therapy

14.3 Comparative Bioavailability Studies

Not applicable.

14.4 Immunogenicity

Not applicable.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

In cynomolgus monkeys, weekly IV 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 diarrhea was noted. Slight increases in BUN, (which did not worsen with chronic dosing, and not associated with any macroscopic or microscopic renal findings), were also observed in repeat dose studies. These BUN abnormalities occurred in the absence of other renal laboratory abnormalities (e.g. creatinine, electrolytes). Chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhea-related dehydration in a subset of monkeys, which were managed with intravenous fluid replacement therapy. In a chronic toxicity study, the poor condition of 3 animals, one of which had to be euthanized, was attributed to dehydration and pre-renal azotemia secondary to frequent diarrhea. Although there was not a consistent correlation, slight increases in BUN may be, at least in part, due to frequent diarrhea in these studies. The presence of diarrhea was a confounding factor that prevented determination of a direct or indirect kidney effect with pertuzumab treatment. Based on the available preclinical data to date and the potential role of HER2 in kidney function, a direct kidney effect caused by pertuzumab treatment could not be ruled out from the preclinical studies.

In the embryo-fetal toxicity study, all fetuses at all dose levels exhibited adverse, renal histopathological changes (i.e., hypoplasia of the glomeruli, renal tubules, collecting tubules and renal pelvis) demonstrating that HER2 plays a role in kidney development.

The findings from the repeat-dose toxicity studies with pertuzumab are summarized in Table 18.

Table 18 Repeat-Dose Toxicity Studies

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg) ^a	Duration of Dosing
99-520-1820	Repeat-Dose Toxicity	Cynomolgus monkey	2/M, 2/F	IV	10, 50, <u>100</u>	4 weeks ^b
Comments: Pertuzumab was well tolerated at doses up to 100 mg/kg administered twice weekly.						
00-377-1821	Repeat-Dose Toxicity	Cynomolgus monkey	4-6/M 4-6/F	IV	15, 50, <u>150</u>	one dose weekly for 7 weeks
Comments: Pertuzumab was generally well tolerated up to the highest dose tested of 150 mg/kg. A pertuzumab-related increase in diarrhea as well as the persistence of diarrhea was noted at doses \geq 15 mg/kg. This finding did not adversely affect the health of the animals and showed evidence of reversibility.						
00-604-1560	Repeat-Dose Toxicity	Cynomolgus monkey	3/F	SC	<u>250</u>	one dose weekly for 4 weeks
Comments: Pertuzumab was well tolerated at the subcutaneous dose of 250 mg/kg/week and did not significantly affect peripheral blood platelet count, morphology, or coagulation times in cynomolgus monkeys. There were no observations of significant pertuzumab related increased incidence of diarrhea in this study.						
01-458-1821	Repeat-Dose Toxicity	Cynomolgus monkey	4-6/M 4-6/F	IV	^c 15, 50, 150	one dose weekly for 26 weeks
Comments: Pertuzumab administered IV for 26 weeks was generally well tolerated up to 150 mg/kg. A pertuzumab related increase in diarrhea as well as the persistence of diarrhea was noted at doses \geq 15 mg/kg. The cause of morbidity leading to early euthanasia for one 50 mg/kg/dose monkey was not determined; however, the findings were consistent with an electrolyte imbalance and dehydration secondary to recurrent and persistent diarrhea. Based on the incidence and persistence of diarrhea and slight elevations in urea nitrogen at all dose levels, a no observable effect level was not determined.						

^a Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

^b 2 doses per week for 4 weeks.

^c NOAEL not determined.

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

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

Impairment of Fertility: No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys. The findings from the repeat-dose toxicity studies with pertuzumab are summarized in Table 18 above.

Reproductive and Developmental Toxicology: Reproductive toxicology studies have been conducted in cynomolgus monkeys at loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg achieving clinically relevant exposures. Intravenous administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) has been shown to be embryotoxic with a dose dependent increase in embryo-fetal deaths between GD 25 to 70. 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. The findings from the reproductive toxicology studies with pertuzumab are summarized in Table 19.

Data from additional toxicology studies are summarized in Table 20.

Table 19 Reproductive and Developmental Toxicity

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg) ^a	Duration of Dosing
07-0925	Reproductive and Developmental Toxicity	Cynomolgus monkey	12/F	IV	^a 30/10, 100/33.3, 150/100	Loading: GD19 Maintenance: GD26-50 (twice weekly)
<p>Comments: Administration of pertuzumab to pregnant cynomolgus monkeys between GD 19 and 50 was generally well tolerated by the dams but was associated with high embryo and fetal lethality and oligohydramnios accompanied by delayed development of the fetal kidneys, as well as some secondary external, visceral, and skeletal abnormalities at clinically relevant concentrations. A fetal no-observable-effect level was not determined.</p>						

^a Loading/Maintenance dose.

Table 20 Other Toxicity Studies

Study No.	Type of Study	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg)	Duration of Dosing
00-562-1821	Hemolytic Potential & Blood Compatibility	Cynomolgus monkey and human blood, serum, and plasma	NA	In vitro	21.6, 10.8, or 5.4 mg/mL	NA
Comments: At concentrations up to 21.6 mg/mL pertuzumab did not cause hemolysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma.						
01-014-1821	Tissue Cross-Reactivity	Human tissue	NA	In vitro	1.0 or 10.0 µg/mL	NA
Comments: Cross-reactivity to pertuzumab was demonstrated in a membranous pattern with normal human tonsil, parathyroid gland, mammary gland, haired skin, ureter, urinary bladder, placenta, and kidney tissues.						
01-015-1821	Tissue Cross-Reactivity	Cynomolgus monkey tissue	NA	In vitro	1.0 or 10.0 µg/mL	NA
Comments: Cross-reactivity to pertuzumab was demonstrated in a membranous pattern with normal epithelium from cynomolgus monkey sweat and sebaceous glands, mammary gland, placenta, kidney, ureter, urinary bladder, and prostate gland.						

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^PPERJETA[®]

pertuzumab for injection

Read this carefully before you start taking **PERJETA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PERJETA**.

Serious Warnings and Precautions

Heart Problems: PERJETA may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure). Your health care provider may run tests to monitor your heart function before and during treatment with PERJETA. Based on test results your doctor may hold or discontinue treatment with PERJETA. See “*Serious side effects*” for more details about signs of heart problems to look out for.

Embryo-Fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have shown a reduction in the amount of amniotic fluid, delayed renal development, and death. Your health care provider will advise you of these risks and the need for effective contraception while you are taking PERJETA in combination with trastuzumab and 7 months after the last dose of treatment because of the length of time PERJETA and trastuzumab can remain in the body.

Hypersensitivity reactions / anaphylaxis and Infusion-related reactions: PERJETA has been associated with severe reactions. Deaths have been reported. You will be observed and carefully monitored during and after infusions. If you have a severe reaction, your doctor may need to completely stop your PERJETA treatment.

What is PERJETA used for?

PERJETA, pronounced “per-JE-tah” is used to treat people with breast cancer when:

- there are a large number of “HER2-positive” cancer cells involved – your doctor will test for this.
- the cancer has spread to other parts of the body (metastasized)
- the cancer may have advanced in one region and has not spread to other parts of the body and treatment is going to be given before surgery (treatment before surgery is called neoadjuvant therapy)
- the cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy)

As well as PERJETA you will also receive trastuzumab and medicines called chemotherapy.

- Information about these medicines is described in separate patient information leaflets. Ask your doctor or nurse to give you information about these other medicines.

How does PERJETA work?

PERJETA is a type of medicine called a “monoclonal antibody” which attaches itself to specific targets in your body.

PERJETA recognizes and attaches to a protein in your body called “human epidermal growth factor 2” or HER2 for short. 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.

What are the ingredients in PERJETA?

Medicinal ingredients: pertuzumab (pronounced per-TOOZ-ue-mab)

Non-medicinal ingredients: glacial acetic acid, L-histidine, polysorbate 20, sucrose, water for injection

PERJETA comes in the following dosage forms:

PERJETA is a clear to slightly pearly (opalescent), colourless to pale brown solution for intravenous (IV) infusion. PERJETA is supplied as a single-use vial containing 14 mL preservative-free liquid concentrate, at a concentration of 30 mg/mL for dilution for intravenous infusion.

Do not use PERJETA if:

- you are allergic to this drug or to any ingredient in the formulation. See **What are the ingredients in PERJETA**. If you are not sure, talk to your doctor or nurse before you are given PERJETA.

PERJETA is not recommended for anyone under the age of 18 years because there is no information on how well it works in this age group.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PERJETA. Talk about any health conditions or problems you may have, including if you:

- You have ever had heart problems (such as heart failure, heart attack, treatment for serious irregular heartbeats, uncontrolled high blood pressure) - 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 anthracycline, e.g. doxorubicin - these medicines can damage heart muscle and increase the risk of heart problems with PERJETA

Other warnings you should know about:**Pregnancy, breast-feeding and contraception**

- Before starting treatment, you must tell your healthcare provider if you are pregnant, think you may be pregnant or are planning to have a baby. You should also tell your healthcare provider if you are breast-feeding.
- Tell your healthcare provider straight away if you get pregnant during treatment with PERJETA and trastuzumab or during the 7 months after stopping treatment.
- Ask your healthcare provider 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 trastuzumab and for 7 months after stopping treatment. If you are a male patient taking PERJETA with a female partner who can become pregnant you should use effective contraception during treatment with PERJETA and trastuzumab and for 7 months after stopping treatment. Talk to your healthcare provider about the best contraception for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

It may take up to 7 months for PERJETA and trastuzumab to be removed from the body. Therefore, you should tell your doctor that you have had PERJETA if you start any new medication in the 7 months after stopping treatment.

How to take PERJETA:**Usual dose:**

PERJETA will be given to you by your healthcare provider 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, second 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), after surgery (adjuvant therapy) or for disease which has spread.
- PERJETA is given with other cancer treatments (trastuzumab and chemotherapy).

The first infusion:

- you will be given 840 mg of PERJETA over 60 minutes
- 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
- you will also be given trastuzumab and chemotherapy

For further information on dosing of trastuzumab and chemotherapy (which can cause side effects as well), please refer to the package insert for these products. If you have questions about these medications, please ask your healthcare provider.

Overdose:

If you think you, or a person you are caring for, have taken too much PERJETA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

You will then return to receiving a dose of 420 mg PERJETA for following infusions.

If you stop having PERJETA

Do not stop having this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your healthcare provider.

What are possible side effects from using PERJETA?

These are not all the possible side effects you may have when taking PERJETA. If you experience any side effects not listed here, tell your healthcare professional.

Unwanted effects are possible with all medicines. Talk to your doctor, nurse or pharmacist if you are worried about side effects or find them very bothersome, and report any new or continuing symptoms to your doctor immediately. Your doctor will be able to tell you what to do and may be able to help you with these side effects.

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

- hair loss
- dizziness
- loss of, or altered, taste
- producing more tears
- headache
- sore throat, red, sore or runny nose, flu-like symptoms and a fever
- feeling sick (nausea, vomiting)

- having less of an appetite
- nail problems
- rash, dry, itchy or acne like skin
- joint or muscle pain, muscle weakness
- weak, numb, tingling or prickling sensations mainly affecting the feet and legs
- pain in the body, arms, legs, and abdomen
- inflammation of your digestive tract (e.g. sore mouth)
- swollen ankles or other body parts due to your body holding onto too much water
- not being able to sleep
- decrease in the number of red and white blood cells – shown in a blood test
- fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- cough
- nose bleeds
- heartburn
- hot flushes
- fatigue

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

- inflammation of the nail bed where the nail and skin meet

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Diarrhea	✓		
Swelling of your face and throat with difficulty breathing, feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, constipation and mouth ulcers.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Swollen ankles or other body parts		✓	
Shortness of breath and cough		✓	
Hot flushes		✓	
Loss of appetite	✓		
Constipation	✓		
COMMON			
Chest pain, nausea, discomfort radiating to the back, jaw, throat, or arm.		✓	
RARE			
Vomiting, muscle cramps, numbness or tingling	✓		
Decreased urination		✓	

This is not a complete list of side effects. For any unexpected effects while taking PERJETA, contact your doctor or pharmacist.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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 vial and carton.
- Store vials in a refrigerator at 2-8°C.
- Keep vial in the outer carton in order to protect from light.
- Do not freeze or shake PERJETA.
- Do not use this medicine if you notice any particles in the liquid or it is the wrong colour (see **PERJETA comes in the following dosage forms**).
- 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.

Keep out of reach and sight of children.

If you want more information about PERJETA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388 .

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Last Revised: February 25, 2021

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