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NAME OF THE MEDICINE

PERJETA®

Pertuzumab

CAS: 380610-27-5

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody. The antibody is based upon the human IgG_1 kappa framework sequence, with a molecular weight of ~ 148kDa and composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues.

DESCRIPTION

PERJETA is supplied as a single-use vial containing 14 mL of preservative-free concentrate solution. Each vial contains 420 mg of pertuzumab (30 mg/mL) with the following excipients; sucrose, polysorbate 20, histidine and acetic acid, glacial.

PHARMACOLOGY

Pharmacodynamics

Pertuzumab binds to 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 EGFR, HER3 and HER4. It inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).While pertuzumab alone inhibited the proliferation of human tumour cells, the anti-tumour activity was significantly augmented when pertuzumab was used in combination with trastuzumab in HER2-overexpressing xenograft models.

Pharmacokinetics

Across multiple clinical trials, in various indications, there was no change in clearance of pertuzumab at doses of 2-25 mg/kg. Based on a population PK analysis that included 444 patients, the median clearance (CL) of pertuzumab was 0.239 L/day and the median half-life was 17.2 days.

The population PK analysis suggested no PK differences based on age, gender and ethnicity (Japanese versus non-Japanese). Baseline albumin and lean body weight were the most significant covariates influencing CL. Clearance decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses performed at the recommended dose and schedule of PERJETA showed that at the extreme values of these two covariates, there was no significant impact on the ability to achieve target steady-state concentrations identified in preclinical tumour xenograft

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models. Therefore, there is no need to adjust the dosage of pertuzumab based on these covariates.

Absorption

Pertuzumab is administered as an intravenous (IV) infusion. There have been no studies performed with other routes of administration.

Distribution

Following IV administration, the volume of distribution of the central compartment (3.07 L) approximates serum volume. The central compartment volume and steady state volume values indicate distribution is restricted to the serum compartment.

Metabolism

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

Excretion

The clearance of pertuzumab is approximately 0.239 L/day with an elimination t½ of approximately 17.2 days.

Pharmacokinetics in special populations

Elderly: No dedicated pertuzumab studies have been conducted in elderly patients. In a population PK analysis, age was not found to significantly affect PK of pertuzumab. In the population PK analysis, 32.5% (n=143) patients were ≥65 years of age and 9.1% (n=40) patients were ≥75 years of age.

Renal Impairment: No formal PK study has been conducted in patients with renal impairment. Based on the population PK analysis, renal impairment is not expected to influence pertuzumab exposure; however, only limited data from patients with moderate and severe renal impairment were included in the population PK analysis.

CLINICAL TRIALS

Metastatic Breast Cancer

PERJETA in combination with trastuzumab and docetaxel

WO20698/TOC4129g (CLEOPATRA)

CLEOPATRA is a multicentre, randomized, double-blind, placebo-controlled phase III clinical trial conducted in 808 patients with HER2-positive metastatic (n=789) or locally recurrent unresectable breast cancer (n=19) who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Breast tumour specimens were required to show HER2 overexpression defined as a score of 3+ by IHC or ISH amplification ratio ≥ 2.0 as determined at a central laboratory. Patients were randomized 1:1 to receive placebo + trastuzumab and docetaxel or PERJETA + trastuzumab and docetaxel. Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients

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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 was given intravenously as an initial dose of 840 mg, followed every three weeks thereafter by a dose of 420 mg. Trastuzumab was given intravenously as an initial dose of 8 mg/kg, followed every three weeks thereafter by 6 mg/kg. 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/m^2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

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

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumour assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT-B QoL (Functional Assessment of Cancer Therapy–Breast, Quality of Life) questionnaire.

Demographics were well balanced (median age was 54 years old, majority Caucasian (59%) and all were female with the exception of 2 patients). Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as oestrogen receptor positive and/or progesterone receptor positive), approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant therapy (192 patients [47.3%] in the placebo treated group vs. 184 patients [45.8%] in the PERJETA treated group), and approximately 11 % of patients had received prior trastuzumab (41 patients [10.1%] in the placebo treated group vs. 47 patients [11.7%] in the PERJETA treated group). Of the 19 patients categorized as having locally recurrent, unresectable disease, 6 patients (2 in the placebo group and 4 in the PERJETA group) had metastases on their baseline assessment.

At the time of the primary PFS analysis, a total of 242 patients (59%) in the placebo treated group and 191 patients (47.5%) in the PERJETA treated group had IRF-confirmed progressive disease or had died within 18 weeks of their last tumour assessment.

The CLEOPATRA study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR] = 0.62, 95% CI = 0.51, 0.75, p<0.0001) in the PERJETA treated group compared with the placebo treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo treated group vs. 18.5 months in the PERJETA treated group) (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS (median PFS was 12.4 months for placebo vs 18.5 months for PERJETA) (see Table 1). Consistent results were observed across pre-specified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see Figure 2).

The efficacy results from the CLEOPATRA trial are summarized in Table 1 below:

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Table 1: Summary of efficacy from CLEOPATRA study

Parameter	Placebo + trastuzumab + docetaxel (n=406)	PERJETA + trastuzumab + docetaxel (n=402)	HR (95% CI)	p-value
Primary Endpoint:				
Progression-Free Survival (Independent review facility assessment)			0.62 [0.51;0.75]	<0.0001
No. of patients with an event	242 (59%)	191 (47.5%)		
Median months	12.4	18.5		
Secondary Endpoints:				
Overall Survival (second interim)			0.66 [0.52;0.84]	0.0008*
No. of patients with an event*	154 (37.9%)	113 (28. 1%)		
Median months	37.6	Not reached		
Progression-Free Survival (investigator assessment)			0.65 [0.54;0.78]	<0.0001
No. of patients with an event	250 (61.6%)	201 (50.0%)		
Median months	12.4	18.5		
Objective Response Rate (ORR)				
No. of patients with an event	336	343		
Responders**	233 (69.3 %)	275 (80.2 %)	Difference in ORR: 10.8% [4.2,17.5]%	0.0011
95% CI for ORR	[64.1; 74.2]	[75.6; 84.3]		
Complete response (CR)	14 (4.2 %)	19 (5.5 %)		
Partial Response (PR)	219 (65.2 %)	256 (74.6 %)		
Stable disease (SD)	70 (20.8 %)	50 (14.6 %)		
Progressive disease (PD)	28 (8.3 %)	13 (3.8 %)		
Duration of Response ^				
n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;54]	[71;106]		

* Second interim overall survival analysis performed one year after the primary analysis: the p-value met the O'Brien Fleming stopping boundary of the Lan DeMets alpha spending function for the interim analysis ($p \leq 0.0138$). The result was therefore statistically significant.

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

^ Evaluated in patients with best Overall Response of CR or PR

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

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

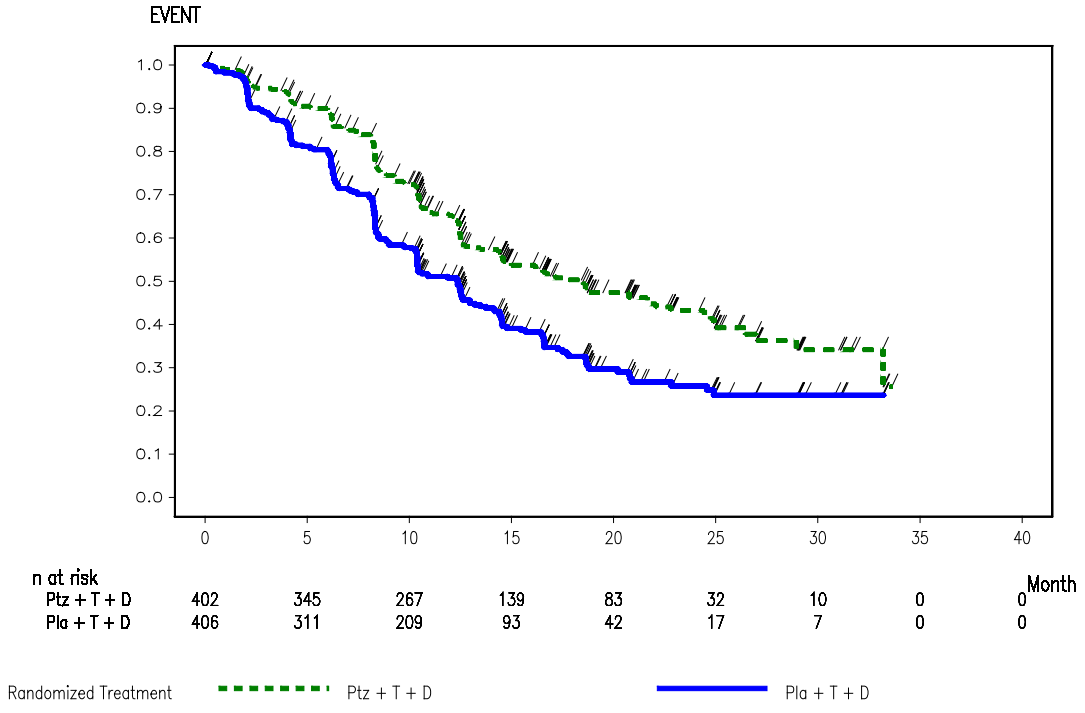
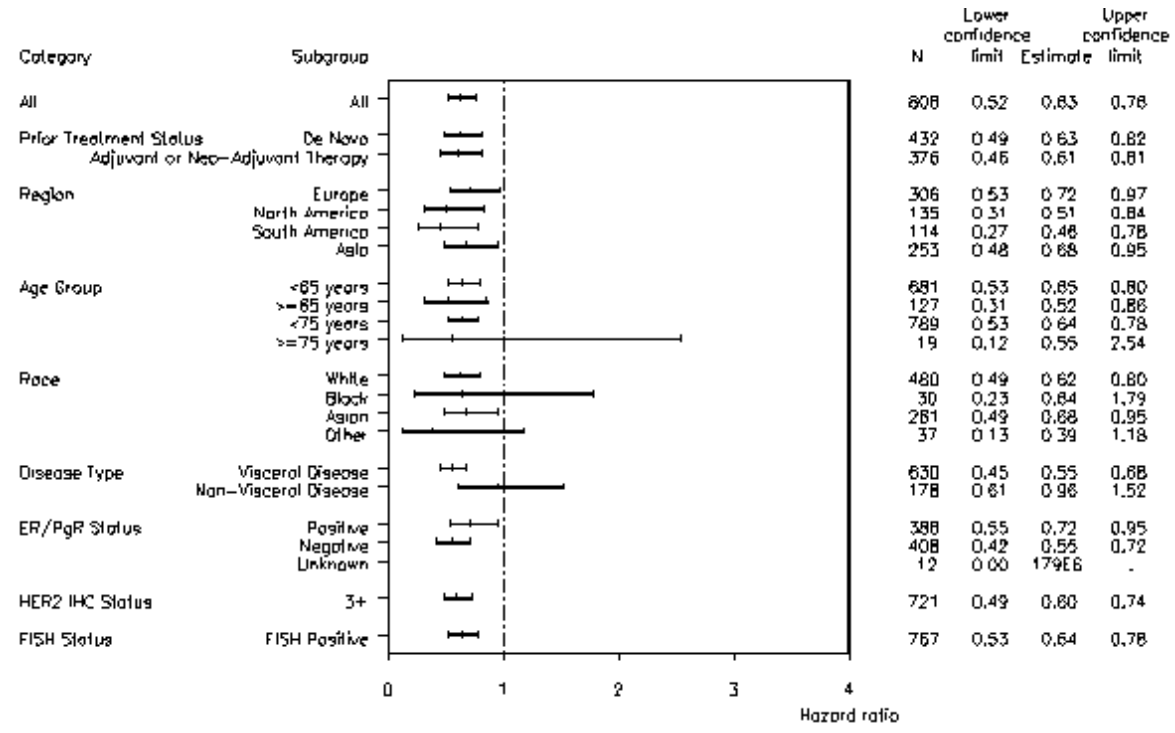


Figure 2: IRF assessed PFS by patient subgroup



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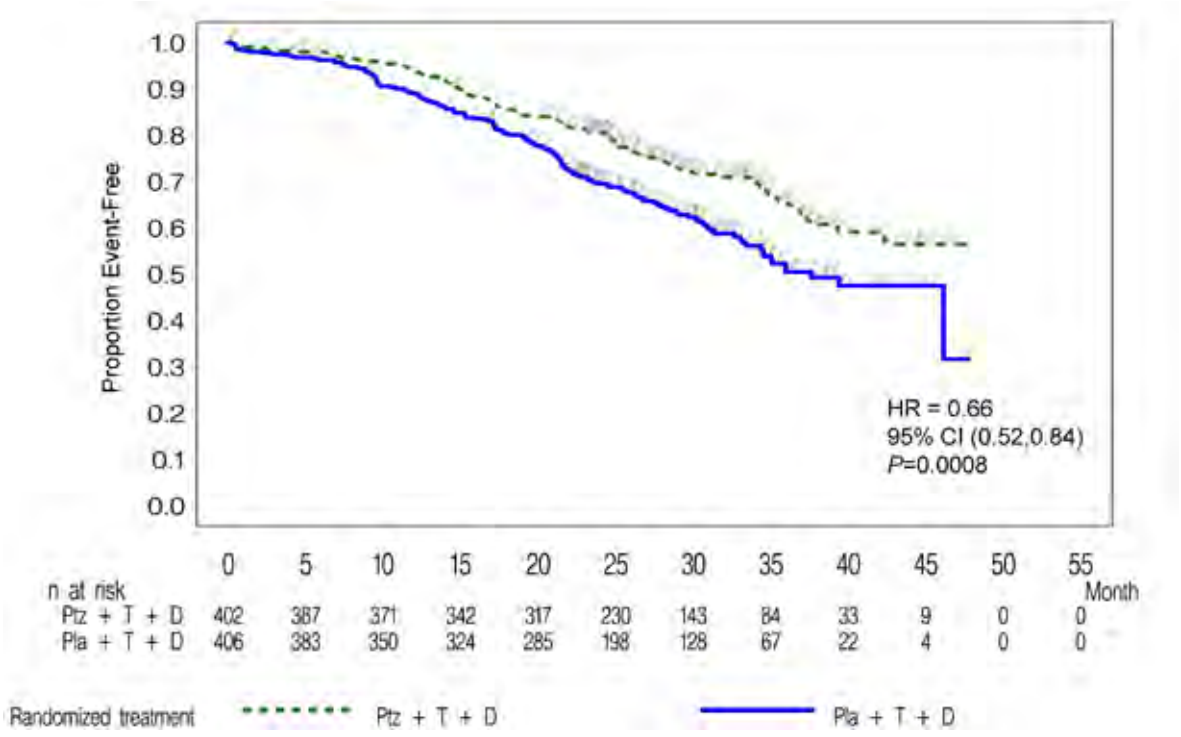
At the primary analysis of efficacy an interim analysis of OS showed a strong trend suggestive of a survival benefit in favour of PERJETA treated group.

At an OS analysis performed 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%) vs. 113 deaths (28.1%) respectively). A statistically significant OS benefit in favour of the PERJETA-treated group was demonstrated (HR 0.66, p = 0.0008 log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached in the PERJETA treated group (see Figure 3).

Figure 3: Kaplan-Meier curve of overall survival



There was no statistically significant difference between treatment groups in Health Related Quality of Life as assessed by time to symptom progression on the FACT-B TOI-PFB subscale, defined as a 5 point reduction in subscale score (HR =0.97, 95% CI =0.81; 1.16).

Immunogenicity

Patients in the pivotal trial CLEOPATRA were tested at multiple time-points for anti-therapeutic antibodies (ATA) to PERJETA. Approximately 6.2% (23/372) of patients in the placebo treated group and 2.8% (11/386) of patients in the PERJETA treated group tested

positive for ATA. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to ATA.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to PERJETA with the incidence of antibodies to other products may be misleading.

INDICATIONS

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

CONTRAINDICATIONS

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab, chinese hamster ovary cell proteins or to any other component of the product.

PRECAUTIONS

General

PERJETA therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. PERJETA must be diluted by a healthcare professional and administered as an IV infusion.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record.

Left ventricular dysfunction

Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2 activity, including PERJETA. In the pivotal trial CLEOPATRA, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel (*see ADVERSE EFFECTS)*. However, patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

PERJETA has not been studied in patients with a baseline LVEF value of ≤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 >360mg/m^2 of doxorubicin (or its equivalent).

Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g. every 3 months) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is <40% or, 40-45% and ≥10% points below baseline, PERJETA and trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the

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LVEF has not improved, or has declined further, discontinuation of PERJETA and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (*see DOSAGE AND ADMINISTRATION)*.

Infusion-associated reactions and hypersensitivity reactions/anaphylaxis

PERJETA has been associated with infusion and hypersensitivity reactions (*see ADVERSE EFFECTS*). Close observation of the patient during, and for 60 min after the first infusion and during, and for 30 min following subsequent infusions, is recommended following the administration of PERJETA. If a significant infusion-associated 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 DOSAGE AND ADMINISTRATION)*.

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. This may be associated with a higher incidence of mucositis and diarrhoea in PERJETA-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was 26% in the PERJETA-treated group compared with 12% in the placebo-treated group.

Effects on fertility

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

Use in pregnancy - Category D

PERJETA should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA.

There are no studies of PERJETA in pregnant women. 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 plasma pertuzumab concentrations approximately 2-19 times the clinical Cmax at the loading dose of 800 mg. IV administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) was shown to be embryo- and foetotoxic with a dose dependent increase in embryo-foetal deaths and abortions between GD 25 to 70. Delayed renal development, oligohydramnios and other abnormalities were identified at GD100.

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Use in lactation

Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue nursing or PERJETA taking into account the importance to the mother and the elimination half-life of pertuzumab (*see Excretion)*.

Paediatric use

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

Use in the elderly

No differences of safety and efficacy of PERJETA were observed between adult patients ≥65 and <65 years of age.

Genotoxicity

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

Carcinogenicity

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

Effect on laboratory tests

No text.

Other

In cynomolgus monkeys, weekly IV administration of pertuzumab at doses up to 150 mg/kg/dose were generally well tolerated. With doses of 15 mg/kg and higher intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhoea-related dehydration which were managed with IV fluid replacement therapy.

Use in renal impairment

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

Use in hepatic impairment

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

INTERACTIONS WITH OTHER MEDICINES

A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug-drug interaction between PERJETA and trastuzumab and between PERJETA and docetaxel. In addition, no clinical relevant pharmacokinetic interaction of co-administered docetaxel or trastuzumab on PERJETA was evident based on the population pharmacokinetics analysis.

Four studies have evaluated the effects of PERJETA on the pharmacokinetics of co-administered cytotoxic agents; docetaxel, gemcitabine, erlotinib and capecitabine. There was

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no evidence of any pharmacokinetics interaction between PERJETA and any of these agents. The pharmacokinetics of PERJETA in these studies were comparable to those observed in single-agent studies.

ADVERSE EFFECTS

The safety of PERJETA has been evaluated in more than 1400 patients either in the pivotal trial CLEOPATRA or in phase I and II trials conducted in patients with various malignancies and predominantly treated with PERJETA in combination with other anti-neoplastic agents.

Table 2 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 in combination with trastuzumab and docetaxel. As PERJETA is used with trastuzumab and docetaxel it is difficult to ascertain the casual relationship of an adverse reaction to a particular drug. The safety of PERJETA in Phase I and II studies was generally consistent with that observed in the CLEOPATRA trial, though the incidence and most common ADRs varied depending on whether pertuzumab was administered as monotherapy or on the concomitant anti-neoplastic agent(s) studied. The most common ADRs (>50%) seen in PERJETA in combination trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE (version 3) grade 3-4 ADRs (>10%) were neutropenia, febrile neutropenia and leukopenia.

Table 2: ADR's occurring in >10% of patients in the PERJETA treated group

ADR	Placebo + trastuzumab + docetaxel n =397		PERJETA + trastuzumab + docetaxel n =407	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
General disorders and administration site conditions				
Fatigue	36.8	3.3	37.6	2.2
Asthenia	30.2	1.5	26.0	2.5
Oedema peripheral	30.0	0.8	23.1	0.5
Mucosal inflammation	19.9	1.0	27.8	1.5
Pyrexia	17.9	0.5	18.7	1.2
Skin and subcutaneous tissue disorders				
Alopecia	60.5	0.3	60.9	-
Rash	24.2	0.8	33.7	0.7
Nail disorder	22.9	0.3	22.9	1.2
Pruritus	10.1	-	14.0	-
Dry skin	4.3	-	10.6	-
Gastrointestinal disorders				
Diarrhoea	46.3	5.0	66.8	7.9
Dyspepsia	12.1	-	12.0	-
Nausea	41.6	0.5	42.3	1.2
Vomiting	23.9	1.5	24.1	1.5
Constipation	24.9	1.0	15.0	-
Stomatitis	15.4	0.3	18.9	0.5
Blood and lymphatic system disorders				
Neutropenia	49.6	45.8	52.8	48.9
Anaemia	18.9	3.5	23.1	2.5
Leukopenia	20.4	14.6	18.2	12.3

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ADR	Placebo + trastuzumab + docetaxel n =397		PERJETA + trastuzumab + docetaxel n =407	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Febrile neutropenia[#]	7.6	7.3	13.8	13.0
Nervous system disorders				
Neuropathy peripheral	20.2	1.8	21.1	2.7
Headache	16.9	0.5	20.9	1.2
Dysgeusia	15.6	-	18.4	-
Peripheral sensory neuropathy	14.1	0.3	12.0	0.5
Dizziness	12.1	-	12.5	0.5
Musculoskeletal and connective tissue disorders				
Myalgia	23.9	0.8	22.9	1.0
Arthralgia	16.1	0.8	15.5	0.2
Pain in extremity	11.8	0.3	15.2	0.5
Infections and infestations				
Upper respiratory tract infection	13.4	-	16.7	0.7
Nasopharyngitis	12.8	0.3	11.8	-
Respiratory, thoracic and mediastinal disorders				
Cough	18.6	0.3	21.4	0.5
Dyspnoea	15.6	2.0	14.0	1.0
Metabolism and nutrition disorders				
Decreased appetite	26.4	1.5	29.2	1.7
Eye disorders				
Lacrimation increased	13.9	-	14.0	-
Psychiatric disorders				
Insomnia	13.4	-	13.3	-

[#] An adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant ADRs were reported in <10% of patients in the PERJETA treated group;

General disorders: Pain (5.5% in the placebo treated group / 5.9% in the PERJETA treated group).

Infections and infestations: Paronychia (3.5 % in the placebo treated group / 7.1% in the PERJETA treated group).

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5.8% in the placebo treated group / 5.2% in the PERJETA treated group).

Cardiac disorders: Left ventricular dysfunction (8.3% in the placebo treated group / 4.4% in the PERJETA treated group) including symptomatic left ventricular systolic dysfunction (CHF) (1.8% in the placebo treated group / 1.0% in the PERJETA treated group).

Immune system disorders: Hypersensitivity (5.0% in placebo treated group / 6.4% in the PERJETA treated group). Drug hypersensitivity (3.8% in the placebo treated group / 4.4% in the PERJETA treated group).

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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 in both treatment arms. After discontinuation of docetaxel in the PERJETA-treated group (i.e. during treatment with PERJETA and trastuzumab alone), all ADRs occurred in <10% of patients with the exception of diarrhoea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%), fatigue (11.1%) and pain in the extremity (10.1%).

Further information on selected adverse drug reactions:

Infusion-associated reactions, hypersensitivity reactions/anaphylaxis

An infusion-associated reaction was defined in the pivotal trial as any ADR occurring during an infusion, or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of PERJETA associated reactions. On the first day, when only PERJETA was administered, the overall frequency of infusion-associated reactions was 14.2% in the placebo treated group and 19.2% in the PERJETA treated group, with the majority of reactions being mild or moderate. The most common infusion-associated reactions (≥1.5%) in the PERJETA treated group were nausea, pyrexia, diarrhoea, chills, fatigue and headache.

During the second cycle, when all drugs were administered on the same day, the most common infusion-associated reactions (≥1.5%) in the PERJETA treated group were alopecia, nausea, and decreased appetite, fatigue, constipation, diarrhoea, stomatitis and drug hypersensitivity.

In the pivotal trial CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis events was 9.1% in the placebo treated patients and 10.8% in the PERJETA treated patients, of which 2.5% and 2% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo treated group and 4 patients in the PERJETA treated group experienced anaphylaxis (*see PRECAUTIONS*).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to study treatment, most reactions were assessed as secondary to docetaxel infusions.

Laboratory Abnormalities

The incidence of NCI-CTCAE (version 3) grade 3-4 decreases in neutrophil counts were balanced in the two treated groups.

DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician. In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is PERJETA.

DO NOT ADMINISTER PERJETA AS AN IV PUSH OR BOLUS.

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Detection of HER2 Protein Overexpression or HER2 Gene Amplification

Patients can only be treated with PERJETA in combination with trastuzumab and must have a HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH).

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

HER2 protein overexpression should be detected using an IHC-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using ISH of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH).

For any other method to be used for the assessment of HER2 protein or gene expression, the test method must be precise and accurate enough to demonstrate overexpression of HER2 (it must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) HER2 overexpression).

For full instructions on assay performance and interpretation please refer to the package inserts of validated HER2 testing assays. Official recommendations on HER2 testing may also apply.

Dosage of PERJETA in combination with trastuzumab and docetaxel

The recommended initial dose of PERJETA is 840 mg, administered as a 60 min IV infusion, followed by, every 3 weeks, a 420 mg dose administered over 30-60 min.

When trastuzumab is administered with PERJETA, the recommendation is to follow a 3-weekly schedule, administered as an IV infusion, with an trastuzumab initial dose of 8 mg/kg followed by every 3 weeks, a dose of 6 mg/kg.

When docetaxel is administered with PERJETA, the recommended initial docetaxel dose is 75 mg/m^2. The dose of docetaxel may be escalated to 100 mg/m^2 if the initial dose is well tolerated.

The medicinal products should be administered sequentially. PERJETA and trastuzumab can be given in any order. When the patient is receiving docetaxel, the docetaxel should be administered after PERJETA and trastuzumab.

An observation period of 30-60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel (*see PRECAUTIONS*).

It is recommended that patients are treated with PERJETA until disease progression or unmanageable toxicity.

Dose modifications

PERJETA should be discontinued if trastuzumab treatment is discontinued.

If docetaxel is discontinued, treatment with PERJETA and trastuzumab may continue until disease progression or unmanageable toxicity.

Dose reductions are not recommended for PERJETA

Trastuzumab dose reductions are not recommended, see trastuzumab prescribing information.

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For docetaxel dose modifications, see docetaxel prescribing information.

Infusion-related reactions

The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-associated reaction. The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction (*see PRECAUTIONS).*

Left ventricular dysfunction

Withhold PERJETA and trastuzumab dosing for at least 3 weeks for either;

- a drop in left ventricular ejection fraction (LVEF) to < 40% or
- LVEF of 40%-45% associated with a fall of ≥10%-points below baseline.

PERJETA and trastuzumab may be resumed if the LVEF has recovered to >45% or 40-45% associated with <10%-points below baseline.

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

Special populations

Elderly: No differences of safety and efficacy of PERJETA were observed between adult patients ≥65 and <65 years of age. No dose adjustment is required in the elderly population.

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

Renal impairment: Dose adjustments of PERJETA are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (*see Pharmacokinetics in special populations)*.

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

Delayed or missed doses

If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of PERJETA should be administered as soon as possible. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg PERJETA should be re-administered as a 60 min IV infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 to 60 min.

Instructions for dilution

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

Withdraw all the contents from the PERJETA vial and dilute in 250 mL 0.9% sodium chloride.

After dilution, one mL of solution should contain approximately 3.36mg of pertuzumab (840mg/250mL) for the initial dose and 1.68 mg of pertuzumab (420mg/250mL) for the subsequent dose. The concentration of the final PERJETA solution should be kept at

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approximately 3.36 mg/mL (840mg/250mL) for the initial dose and 1.68 mg/mL (420mg/250mL) for the subsequent dose.

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

The bag should be *gently* inverted to mix the solution in order to avoid foaming.

Parenteral drug products should be inspected visually for particulates and discolouration prior to administration.

PERJETA is for single use in one patient only. Once the infusion is prepared it should be administered immediately (*see Storage conditions)*.

Incompatibilities

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

Dextrose (5%) solution (D5W) should not be used to dilute PERJETA since it is chemically and physically unstable (diluted formulations of pertuzumab concentrate solution in D5W IV bags did not maintain stable pH after storage at room temperature (27-33°C) for 24 hours followed by 24 hours at 2-8°C).

PERJETA should not be mixed or diluted with other drugs.

OVERDOSAGE

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

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

PERJETA is supplied in a single-dose glass vial containing 14mL of clear to opalescent, colourless to slightly brownish solution. Each vial contains 420 mg of pertuzumab (30 mg/mL).

Storage conditions

Store vials in a refrigerator at 2°C-8°C. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

Shelf-life of PERJETA solution for infusion

PERJETA does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

The PERJETA infusion solution, diluted in PVC or non-PVC polyolefin bags, may be stored at 2°C–8°C for up to 24 hours prior to use. Diluted PERJETA has been shown to be stable for up to 24 hours (up to 30°C) however, since diluted PERJETA contains no preservative, the diluted solution should be refrigerated (2°C–8°C).

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Disposal of unused/expired medicines

The release of medicines into the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4. Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

6 May 2013