Professional Information

WARNING:

CARDIOMYOPATHY, EMBRYO-FETAL TOXICITY, **and PULMONARY TOXICITY** ***See full prescribing information for complete boxed warning.***

Cardiomyopathy: PHESGO administration can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue PHESGO for cardiomyopathy. (See section 4.4)

Embryo-fetal Toxicity: Exposure to PHESGO can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (See section 4.4 and 4.6)

Pulmonary Toxicity: Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (See section 4.4.)

SCHEDULING STATUS

S4

1 PROPRIETARY NAME AND DOSAGE FORM

Phesgo® 1 200 mg/600 mg solution for subcutaneous injection

Phesgo® 600 mg/600 mg solution for subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): pertuzumab, trastuzumab

Each vial of 15 mL solution contains 1200 mg pertuzumab/600 mg trastuzumab

Each vial of 10 mL solution contains 600 mg pertuzumab/600 mg trastuzumab

Excipients with known effect: sucrose

Contains Sucrose (1 200 mg/600 mg contains 685 mg and 600 mg/600 mg) contains 342 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Phesgo is a clear to opalescent solution, colourless to slightly brownish solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Early Breast Cancer (EBC)

Phesgo is indicated in combination with chemotherapy 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) as part of a complete treatment regimen for early breast cancer

- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Metastatic Breast Cancer (MBC)

Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

4.2 Posology and method of administration

Method of Administration

Phesgo therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Patients currently receiving intravenous pertuzumab and trastuzumab can switch to Phesgo. Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was investigated in study MO40628 (see 4.8 Undesirable Effects and Clinical / Efficacy Studies)
In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Phesgo.

Phesgo is for subcutaneous (SC) use in the thigh only. Do not administer intravenously.

Metastatic and Early Breast Cancer

For Phesgo dose recommendations in early and metastatic breast cancer refer to Table 1

Table 1: Phesgo recommended dosing and administration

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time[ab]
Loading dose	1200 mg pertuzumab/ 600 mg trastuzumab	8 minutes	30 minutes
Maintenance dose (every 3 weeks)	600 mg pertuzumab/ 600 mg trastuzumab	5 minutes	15 minutes

[a]Patients should be observed for injection-related and hypersensitivity reactions

[b]Observation period should start following administration of Phesgo and be completed prior to any subsequent administration of chemotherapy

In patients receiving intravenous pertuzumab and trastuzumab with < 6 weeks since their last dose, Phesgo should be administered as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations. In patients receiving intravenous pertuzumab and trastuzumab with ≥ 6 weeks since their last dose, Phesgo should be administered as a loading dose of 1200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations

The injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch/2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Do not split the dose between two syringes or between two sites of administration. During the treatment course with Phesgo, other medications for SC administration should preferably be injected at different sites.

In patients receiving a taxane, Phesgo should be administered prior to the taxane. When administered with Phesgo, the recommended initial dose of docetaxel is 75 mg/m2.

In patients receiving an anthracycline-based regimen, Phesgo should be administered following completion of the entire anthracycline regimen.

Early Breast Cancer (EBC)

In the neoadjuvant setting (before surgery), it is recommended that patients are treated with Phesgo for three to six cycles depending on the regimen chosen in combination with chemotherapy (see Clinical/ Efficacy Studies).

In the adjuvant setting (after surgery), Phesgo should be administered 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. Phesgo treatment should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see Clinical/Efficacy Studies).

Patients who start Phesgo in the neoadjuvant setting should continue to receive adjuvant Phesgo to complete 1 year of treatment (maximum 18 cycles).

Metastatic Breast Cancer (MBC)

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

Delayed or Missed Doses

If the time between two sequential doses is less than 6 weeks, the 600 mg pertuzumab/ 600 mg trastuzumab maintenance dose of Phesgo should be administered as soon as possible. Do not wait until the next planned dose.

If the time between two sequential injections is 6 weeks or more, the loading dose of 1200 mg pertuzumab/600 mg trastuzumab should be re-adminstered followed by the maintenance dose of 600 mg pertuzumab/ 600 mg trastuzumab every 3 weeks thereafter.

Dose Modifications

No dose reductions of Phesgo are recommended. For chemotherapy dose modifications, see relevant prescribing information.

Injection-related reactions

The injection should be slowed or paused if the patient experiences injection-related symptoms (see 4.4 Special warnings and Precautions).

Hypersensitivity/anaphylaxis

The injection should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see 4.4 Special warnings and Precautions).

Left ventricular dysfunction

See 4.4 Special warnings and Precautions for information on dose recommendations in the event of left ventricular dysfunction.

Special Dosage Instructions

Pediatric use

The safety and efficacy of Phesgo in children and adolescents (<18 years) has not been established.

Geriatric use

No dose adjustment of Phesgo is required in patients ≥65 years of age (see Geriatric Use and Pharmacokinetics in Special populations).

However, with intravenous pertuzumab in combination with trastuzumab, the incidence of the following all grade adverse events were at least 5% higher in patients patients ≥65 years of age (n=418) compared to patients <65 years of age (n=2926): decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea

Renal Impairment

Dose adjustments of Phesgo 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 Phesgo have not been studied in patients with hepatic impairment. No dose recommendation can be made for Phesgo (see Pharmacokinetics in Special populations).

4.3 Contraindications

Phesgo is contraindicated in patients with a known hypersensitivity to pertuzumab, trastuzumab or any of the excipients. (see section 6.1)

4.4 Special warnings and precautions for use

General

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

Sugar

Phesgo contains sucrose. Patients with the rare hereditary conditions of sucrose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Phesgo.

Phesgo contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Left ventricular dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including pertzumab and trastuzumab. The incidence of symptomatic left ventricular systolic dysfunction (LVD [congestive heart failure]) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared to trastuzumb and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy (see 4.8 Undesirable effects).

Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF decreases based on studies with intravenous pertuzumab in combination with trastuzumab and chemotherapy.

Phesgo and/or intravenous pertuzumab and trastuzumab have not been studied in patients with: a pretreatment LVEF value of <55% (EBC) or <50% (MBC); a prior history of congestive heart failure (CHF); conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360 mg/m2 of doxorubicin or its equivalent.

Intravenous pertuzumab in combination with trastuzumab and chemotherapy has not been studied in patients with decreases in LVEF <50% during prior trastuzumab adjuvant therapy.

Assess LVEF prior to initiation of Phesgo and at regular intervals during treatment to ensure that LVEF is within normal limits (see Table 2 below). If the LVEF declines as indicated in Table 2 and has not improved, or has declined further at the subsequent assessment, discontinuation of Phesgo

should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Table 2: Dose recommendations for left ventricular dysfunction

<table>
<tr><th></th><th>Pre treatment LVEF:</th><th>Monitor LVEF every:</th><th colspan="2">Withhold Phesgo for at least 3 weeks for an LVEF decrease to:</th><th colspan="2">Resume Phesgo after 3 weeks if LVEF has recovered to:</th></tr>
<tr><td rowspan="2">Metastatic Breast Cancer[a]</td><td rowspan="2">≥ 50%</td><td rowspan="2">~12 weeks</td><td colspan="2">Either</td><td colspan="2">Either</td></tr>
<tr><td><40 %</td><td>40%-45% with a fall of ≥10%-points below pretreatment value</td><td>>45 %</td><td>40%-45% with a fall of <10%-points below pretreatment value</td></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥ 55%b</td><td rowspan="2">~12 weeks (once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10%-points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥ 50%</td><td>< 10%-points below pretreatment value</td></tr>
</table>

[a]based on intravenous pertuzumab data (CLEOPATRA study)

[b]for patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion ofanthracyclines, before starting Phesgo.

febrile/infusion-related reactions (IRRs)

Phesgo has been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration of Phesgo. Close observation of the patient during and for 30 minutes after administration of the loading dose and during and for 15 minutes following the administration of the maintenance dose of Phesgo is recommended.

If a significant injection-related reaction occurs, the injection should be slowed down or paused 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 injection-related reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see 2.2 Dosage and Administration). Although fatal outcomes resulting from injection-related reactions have not been observed with Phesgo, caution should be exercised as fatal infusion related-reactions have been associated with intravenous pertuzumab
in combination with intravenous trastuzumab and chemotherapy.

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with Phesgo, caution should be exercised as these have been associated with intravenous pertuzumab in combination with trastuzumab and chemotherapy (see 4.8 Undesirable effects).

Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Phesgo is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, or to any of its excipients (see 4.3 Contraindications).

4.5 Interaction with other medicines and other forms of interaction

No formal drug-drug interaction studies have been performed.

Intravenous Pertuzumab

A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug drug interaction between pertuzumab and trastuzumab and between pertuzumab and docetaxel. In

addition, no clinically relevant pharmacokinetic interaction of coadministered docetaxel or trastuzumab on pertuzumab was evident, based on the population pharmacokinetics analysis. This

lack of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

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

Intravenous trastuzumab

There have been no formal drug interaction studies performed with trastuzumab in humans. Clinically significant interactions between trastuzumab and the concomitant medications used in clinical trials have not been observed.

In studies where trastuzumab was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of trastuzumab altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxylpaclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab.

However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab suggested that the

exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

Phesgo should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

No clinical studies of Phesgo in pregnant women have been performed. Pertuzumab administered intraveneously to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death. In the post-marketing setting for trastuzumab, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women.

Based on the aforementioned animal studies and post-marketing data, Phesgo has the potential to cause fetal harm when administered to a pregnant woman. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Phesgo, or if a patient becomes pregnant while receiving Phesgo or within 7 months following the last dose of Phesgo, close monitoring by a multidisciplinary team is desirable.

Breastfeeding

As human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Phesgo therapy and for 7 months after the last dose of Phesgo.

Fertility

No specific fertility studies in animals have been performed to evaluate the effects of Phesgo.

Contraception

Women of childbearing potential including those who are partners of male patients should use effective contraception during treatment with Phesgo and for 7 months following the last dose of Phesgo.

Labour and Delivery

The safe use of Phesgo during labor and delivery has not been established.

4.7 Effects on ability to drive and use machines.

Phesgo has a minor influence on the ability to drive and use machines. Injection-related reactions and dizziness may occur during treatment with Phesgo (see 4.4 Special warnings and Precautions and 4.8 Undesirable effects).

4.8 Undesirable effects

Clinical Trials

Summary of the safety profile

The safety profile of Phesgo is based on data from the Phase III FEDERICA study in which HER2-positive early breast cancer patients were treated with either Phesgo (n=248) or intravenous pertuzumab and trastuzumab (n=252), in combination with chemotherapy .

The most common (≥5%) adverse drug reactions (ADRs) reported in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab were,

injection site reaction, infusion-related reactions, asthenia, fatigue, rash, ejection fraction decreased, and anemia .

The most common (≥1%) serious adverse events (SAEs) reported in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab were febrile neutropenia, pyrexia,

neutropenia, neutropenic sepsis, infusion-related reaction and neutrophil count decreased. SAEs were equally distributed between the Phesgo treatment arm and the intravenous pertuzumab in combination with trastuzumab treatment arm . The following adverse drug reactions were reported with a higher frequency (≥5%) with Phesgo compared to intravenous pertuzumab in combination with trastuzumab [64]: Alopecia 77% vs 70.2%, Dyspnea 10.1% vs 4.4%, and Fatigue 27.8% vs 22.6%.

Tabulated list of adverse drug reactions

The safety profile of Phesgo was overall consistent to the known safety profile of intravenous pertuzumab in combination with trastuzumab and chemotherapy as seen in the pertuzumab and trastuzumab-treated arms of the following pivotal studies (n=3344):

- CLEOPATRA, in which pertuzumab was given in combination with trastuzumab and docetaxel to patients with MBC (n=453)
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which neoadjuvant

pertuzumab was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or EBC

- APHINITY, in which adjuvant pertuzumab was given in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxanecontaining chemotherapy to patients with EBC (n=2364) Table 3 presents ADRs that have been reported in association with the use of

pertuzumab, trastuzumab and chemotherapy in the pivotal clinical trials and in the postmarketing setting.

As pertuzumab and trastuzumab is used in combination with chemotherapy, it is difficult to ascertain the causal relationship of an adverse reaction to a particular drug.

In this section, the following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very

rare (<1/10,000), and unknown (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Summary of adverse drug reactions reported from the pertuzumab, trastuzumab pivotal trials and in and in the post-marketing setting[a]

ADR (MedDRA Preferred Term) System Organ Class	Pertuzumab + trastuzumab + chemotherapy[b] Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Blood and lymphatic system disorders			
Neutropenia	31.4	24.2	Very common
Anemia	24.8	5.7	Very common
Febrile neutropenia[d]	11.9	11.8	Very common
Leukopenia	10.8	6.1	Very common
Cardiac disorders			
Left ventricular dysfunction[e]	1.4	0.3	Common
Cardiac failure congestive[e]	0.1	<0.1	Uncommon
Eye disorders			
Lacrimation increased	12.1	-	Very common
Gastrointestinal disorders			
Diarrhea	67.9	8.9	Very common
Nausea	60.8	1.9	Very common
Vomiting	30.0	1.7	Very common
Stomatitis	24.9	1.6	Very common
Constipation	24.5	0.4	Very common

Dyspepsia	13.2	<0.1	Very common
Abdominal pain	11.7	0.4	Very common
General disorders and administration site conditions			
Fatigue	44.3	3.3	Very common
Mucosal inflammation	23.2	1.5	Very common
Asthenia	20.9	1.5	Very common
Pyrexia	18.9	0.6	Very common
Edema peripheral	16.2	<0.1	Very common
Injection site reactions[f]	12.9	0	Very common
Immune system disorders			
Hypersensitivity	3.3	0.4	Common
Drug hypersensitivity	2.5	0.4	Common
Infections and infestations			
Nasopharyngitis	12.8	<0.1	Very common
Upper respiratory tract infection	9.5	0.3	Common
Paronychia	3.9	<0.1	Common
Metabolism and nutrition disorders			
Decreased appetite	23.1	0.8	Very common
Tumor lysis syndrome[g]	Unknown		
Musculoskeletal and connective tissue disorders			
Arthralgia	24.6	0.7	Very common
Myalgia	24.3	0.8	Very common
Pain in extremity	10.0	0.2	Very common
Nervous system disorders			

Dysgeusia	22.7	<0.1	Very common
Headache	21.8	0.4	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Neuropathy peripheral	14.7	0.7	Very common
Dizziness	11.2	0.1	Very common
Paraesthesia	10.2	0.4	Very common
Psychiatric disorders			
Insomnia	15.9	0.2	Very common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.6	<0.1	Very common
Cough	15.5	<0.1	Very common
Dyspnea	11.5	0.5	Very common
Pleural effusion	0.9	<0.1	Uncommon
Skin and subcutaneous tissue disorders			
Alopecia	63.1	<0.1	Very common
Rash	26.4	0.5	Very common
Nail disorder	12.9	0.3	Very common
Pruritus	12.9	<0.1	Very common
Dry skin	11.7	<0.1	Very common
Vascular disorders			
Hot flush	15.7	0.1	Very common

[a] Table 3 shows pooled data from the overall treatment period in CLEOPATRA; from the neoadjuvant treatment period in NEOSPHERE and TRYPHAENA; and from the treatment period of APHINITY). Additionally, Table 3 shows an ADR specific to the Phesgo route of administration that has been reported in FEDERICA.

[b] In NEOSPHERE, 108 patients received pertuzumab + trastuzumab alone without docetaxel and 94 patients received pertuzumab + docetaxel without trastuzumab.

[c] In CLEOPATRA, 45 patients who were randomized to receive placebo and who had no prior exposure to pertuzumab, had crossed over to receive pertuzumab and are included in the 3344 patients treated with pertuzumab.

[d] In this table this denotes an adverse reaction that has been reported in association with a fatal outcome.

[e]The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA preferred terms reported in the individual studies.

[f] observed with Phesgo only.

[g] identified in the postmarketing setting.

Description of selected adverse drug reactions from clinical trials

Left ventricular dysfunction

In FEDERICA, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was 0.4% of Phesgo treated patients vs 0% of intravenous pertuzumab and trastuzumab-treated patients. Of the patients who experienced symptomatic heart failure, all Phesgo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% (confirmed by secondary LVEF) were reported in 0.4% of Phesgo-treated patients and 0.8% of intravenous pertuzumab and trastuzumab-treated patients, of whom none of the Phesgo-treated patients or intravenous pertuzumab and trastuzumab-treated patients had recovered at the data cutoff.

Injection/infusion-related Reactions

In FEDERICA, an injection/infusion-related reaction was defined as any systemic reaction reported within 24hrs of Phesgo or intravenous pertuzumab in combination with trastuzumab administration.

Injection-related reactions were reported in 1.2% of Phesgo-treated patients and infusion-related reactions were reported in 10.3% of intravenous pertuzumab and trastuzumab-treated patients. Injection site reactions (defined as any local reaction reported within 24 hours of Phesgo) were reported in 12.9% of Phesgo treated patients and were all grade 1 or 2 events.

Hypersensitivity reactions/anaphylaxis

In FEDERICA, the overall frequency of hypersensitivity/anaphylaxis reported events related to HER2-targeted therapy was 1.6% in both the Phesgo-treated patients and intravenous pertuzumab and trastuzumab-treated patients, of which none were NCI-CTCAE (version 4) Grade 3-4 (see 4.4 Special warnings & Precautions).

Laboratory Abnormalities

In FEDERICA, the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the Phesgo and intravenous pertuzumab and trastuzumab groups.

Intravenous Pertuzumab and Trastuzumab

Left ventricular dysfunction

In CLEOPATRA, the incidence of LVD during study treatment was higher in the placebo-treated group than the pertuzumab-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the pertuzumab-treated group (1.8% in the placebo-treated group vs. 1.5% in the pertuzumab-treated group) (see 4.4 Special warnings & Precautions).

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

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with pertuzumab plus trastuzumab and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by pertuzumab plus trastuzumab and docetaxel; 9.3% in the group treated with pertuzumab plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with pertuzumab in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with pertuzumab plus trastuzumab and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving pertuzumab plus trastuzumab and docetaxel) and also 1.3% in the group treated with pertuzumab in combination with TCH. No patients in the group treated with pertuzumab plus trastuzumab and FEC followed by pertuzumab 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 pertuzumab plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by pertuzumab 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 pertuzumab plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by pertuzumab plus trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was <1% (0.6% of pertuzumab-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of pertuzumab-treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% were reported in 2.7% of pertuzumab-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of

pertuzumab-treated patients and 80.6% of placebo-treated patients had recovered at the data cutoff.

Infusion-related reaction

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 CLEOPATRA, the initial dose of pertuzumab was given the day before trastuzumab and docetaxel to allow for the examination of pertuzumab associated reactions. On the first day when only pertuzumab was administered, the overall frequency of infusion-related reactions was 9.8% in the placebo-treated group and 13.2% in the pertuzumab-treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions (≥1.0%) in the pertuzumab-treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion related reactions (≥1.0%) in the pertuzumab-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting (see 4.4 Special warnings & Precautions).

In neoadjuvant and adjuvant trials, pertuzumab was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 18.6% - 25.0% of patients on the first day of pertuzumab administration (in combination with trastuzumab and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate.

Hypersensitivity/anaphylaxis

In CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.3% in the placebo-treated patients and 11.3% in the pertuzumab-treated patients, of which 2.5% and

2.0% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo-treated group and 4 patients in the pertuzumab-treated group experienced anaphylaxis (see 4.4 Special warnings & Precautions).

Overall, the majority of hypersensitivity reactions was 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.

In neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the pertuzumab and docetaxel-treated group experienced anaphylaxis [85]. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the pertuzumab 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

Laboratory Abnormalities

In the pivotal trials CLEOPATRA, NEOSPHERE, and APHINITY the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the pertuzumab-treated and control groups.

Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa)

Switching from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was well tolerated by patients and did not reveal any new or clinically relevant safety concerns and the adverse events experienced were in line with those reported in FEDERICA and in previous studies using intravenous pertuzumab and trastuzumab administration (see Clinical / Efficacy Studies)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Clinical experience

There is no experience with overdose of Phesgo in human clinical trials. The highest Phesgo dose tested is 1200 mg pertuzumab/600 mg trastuzumab.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Antineoplastic agents: recombinant humanized IgG1 monoclonal antibodies ATC code: Not yet assigned:

Mechanism of Action

Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig)G1κ monoclonal antibodies, which target the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes, subdomains II and IV, respectively, without competing and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

Additionally, the Fc portion of both their IgG1 framework provides for potent activation of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, both pertuzumab and trastuzumab ADCC

are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

5.2 Pharmacokinetic properties

Pertuzumab and trastuzumab exposure following subcutaneous administration of Phesgo (1200 mg pertuzumab/600 mg trastuzumab loading dose followed by 600 mg pertuzumab/600 mg trastuzumab every 3 weeks) in the FEDERICA study is shown in Table 4. The pharmacokinetic (PK) results for the primary endpoint of pertuzumab Cycle 7 C_{trough} (i.e., pre-dose cycle 8), showed non-inferiority of pertuzumab within Phesgo (geometric mean 88.7 mcg/mL) compared to intravenous pertuzumab (geometric mean 72.4 mcg/mL) with a geometric mean ratio of 1.22 (90% CI: 1.14–1.31). The lower boundary of the two-sided 90% confidence interval for the geometric mean ratio of pertuzumab within Phesgo and intravenous pertuzumab was 1.14, i.e., greater than the predefined margin of 0.8.

The PK results for the secondary endpoint, trastuzumab Cycle 7 Ctrough (i.e., predose Cycle 8), showed non-inferiority of trastuzumab within Phesgo (geometric mean 58.7 mcg/mL) compared to intravenous trastuzumab (geometric mean 44.1 mcg/mL) with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43).

A population PK model of pertuzumab with linear elimination from the central compartment was constructed using pooled pertuzumab within Phesgo and intravenous pertuzumab PK data from FEDERICA to describe the observed pertuzumab PK concentrations following subcutaneous Phesgo administration and intravenous pertuzumab administration.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled trastuzumab PK data from the phase III study BO22227 (Hannah) of subcutaneous trastuzumab vs. intravenous trastuzumab, to describe the observed PK concentrations following intravenous trastuzumab or subcutaneous trastuzumab administration in HER2 positive EBC patients. The PK analysis using the HANNAH population PK model

demonstrated that there was no impact on the PK of trastuzumab within Phesgo from pertuzumab within Phesgo as consistent PK were observed between trastuzumab within Phesgo and subcutaneous trastusumab.

The population PK predicted pertuzumab and trastuzumab exposures are summarized in Table 5 below .

Table 5: Pertuzumab and trastuzumab exposure (median with 5th-95th Percentiles) following subcutaneous administration of Phesgo or intravenous pertuzumab or trastuzumab.

Parameter		**Pertuzumab within [Phesgo]**	**Intravenous pertuzumab**	**Trastuzumab within [Phesgo][b]**	**Intravenous trastuzumab [b]**
C_{trough} (mcg/mL)	Cycle 5	85.1 (48.7 – 122.5)	74.9 (47.8 - 99.8)	28.2 (14.1 - 44.5)	31.9 (21.6 - 52.0)
	Cycle 7	88.9 (51.8 - 142.5)	78.5 (41.3 - 114.9)	58.4 (28.0 - 93.8)	45.8 (30.0 - 78.1)
C_{max} (mcg/mL)	Cycle 5	106.5 (62.9 - 152.6)	304.8 (191.1- 409.7)	44.9 (31.2 - 64.6)	176.8 (135.7 - 244.7)
	Cycle 7	149.5 (88.5 - 218.5)	225.9 (158.5 - 301.8)	118.6 (73.8 - 167.3)	171.6 (133.2 - 245.3)
$AUC_{0\text{-}21\ days}$ (mcg/mL•day)	Cycle 5	2306.9 (1388.4 - 3376.2)	2519.7 (1898.4 - 3138.9)	1026.3 (639.7 - 1451.8)	1361.2 (1048.1 - 2071.8)
	Cycle 7	2569.3 (1487.4 - 3786.1)	2454.3 (1561.4 - 3346.1)	1864.0 (1034.9 - 2746.8)	1704.9 (1274.2 - 2618.5)

[a]first dose of Phesgo, intravenous pertuzumab and trastuzumab administered at Cycle 5;

[b]Study BO22227 Hannah population PK model used for trastuzumab PK simulation.

Absorption

The median maximum serum concentration (Cmax) of pertuzumab within Phesgo and time to maximal concentration (Tmax) were 157 ug/mL and 3.82 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.712 and the first-order absorption rate (Ka) is 0.348 (1/day).

The median maximum serum concentration (Cmax) of trastuzumab within Phesgo and time to maximal concentration (Tmax) were 117 ug/mL and 3.85 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.771 and the first-order absorption rate (Ka) is 0.404 (1/day).

Distribution

Based on population PK analysis, the volume of distribution of the central (Vc) compartment of pertuzumab within Phesgo in the typical patient, was 2.77 L. Based on population PK analysis, the volume of distribution of the central (Vc) compartment of subcutaneous trastuzumab in the typical patient, was 2.91 L.

Metabolism

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

Elimination

Based on population pharmacokinetic (PK) analysis, the clearance of pertuzumab within Phesgo was 0.163 L/day and the elimination half-life (t1/2) was approximately 24.3 days. Based on population pharmacokinetic (PK) analysis, the linear clearance of subcutaneous trastuzumab was 0.111 L/day. Trastuzumab is estimated to reach concentrations that are <1 µg/mL (approximately

3% of the population predicted Cmin,ss, or about 97% washout) in at least 95% patients 7 months after the last dose.

Pharmacokinetics in Special Populations

Pediatric Population

No studies have been conducted to investigate the pharmacokinetics of Phesgo in the pediatric population.

Geriatric Population

No studies have been conducted to investigate the pharmacokinetics of Phesgo in geriatric patients.

In population PK analyses of pertuzumab within Phesgo and intravenous pertuzumab, age was not found to significantly affect PK of pertuzumab.

In population PK analyses of subcutaneous or intravenous trastuzumab, age has been shown to have no effect on the disposition of trastuzumab.

Renal impairment

No formal PK study of Phesgo has been conducted in patients with renal impairment. Based on population PK analyses of pertuzumab within Phesgo and intravenous pertuzumab, renal impairment was shown not to affect pertuzumab exposure; however, only limited data from patients with severe renal impairment were included in population PK analyses.

In a population pharmacokinetic analysis of subcutaneous and intravenous trastuzumab, renal impairment was shown not to affect trastuzumab disposition.

Hepatic impairment

No formal pharmacokinetic study of Phesgo has been conducted in patients with hepatic impairment.

Summary of clinical/efficacy studies

This section presents the clinical experience from Phesgo and intravenous pertuzumab in combination with trastuzumab patients with HER2-positive early and metastatic breast cancer. HER2 overexpression in all trials outlined below was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥2.0.

Early Breast Cancer

Fixed-dose combination of pertuzumab and trastuzumab Phesgo

FEDERICA WO40324

FEDERICA is an open-label, multicenter, randomized study conducted in 500 patients with HER2-positive early breast cancer that is operable or locally advanced **(**including inflammatory) breast cancer with a tumor size >2 cm or node-positive in the neoadjuvant and adjuvant setting. Patients were randomized to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either Phesgo or intravenous pertuzumab and trastuzumab during cycles 5-8. Investigators selected one of two of the following neoadjuvant chemotherapy regimens for individual patients:

- 4 cycles of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) every 2 weeks followed by paclitaxel (80 mg/m2) weekly for 12 weeks
- 4 cycles of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) every 3 weeks followed by 4 cycles of docetaxel (75 mg/m2 for the first cycle and then 100 mg/m2 at subsequent cycles at the investigator's discretion) every 3 weeks.

Following surgery, patients continued therapy with Phesgo or intravenous pertuzumab and trastuzumab as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles of HER2-targeted therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per local

practice. In the adjuvant setting, substitution of intravenous trastuzumab for subcutaneous trastuzumab SC was permitted at investigator discretion. HER2-targeted therapy was administered every 3 weeks according to Table 6 as follows:

Table 6: Dosing and administration of Phesgo, intravenous pertuzumab, intravenous trastuzumab, and subcutaneous trastuzumab

Medication	Administration	Dose	
		Loading	Maintenance
Phesgo	Subcutaneous injection	1200 mg/600 mg	600 mg/600 mg
pertuzumab	Intravenous infusion	840 mg	420 mg
trastuzumab	Intravenous infusion	8 mg/kg	6 mg/kg
trastuzumab	Subcutaneous injection	600 mg	

FEDERICA was designed to demonstrate non-inferiority of the pertuzumab Cycle 7 (i.e., pre-dose Cycle 8) serum Ctrough of pertuzumab within Phesgo compared with intravenous pertuzumab (primary endpoint). Additional secondary endpoints included non-inferiority of the Cycle 7 serum trastuzumab Ctrough of trastuzumab within Phesgo compared with intravenous trastuzumab, efficacy [total pathological complete response (tpCR)], and safety outcomes. Demographics were well balanced between the two treatment arms and the median age of patients treated in the study was 51 years. The majority of patients had hormone receptor-positive disease (61.2%), node-positive disease (57.6%), and were Caucasian (65.8%).

Non-inferiority of the pertuzumab and trastuzumab exposure from Phesgo was demonstrated (see Pharmacokinetic properties). The analysis of secondary efficacy endpoint, tpCR, defined as an absence of invasive disease in the breast and axilla (ypT0/is, ypN0), is shown in Table 7.

Table 7: Summary of total pathological Complete Response (tpCR)

	Phesgo (n=248)	Intravenous pertuzumab + trastuzumab (n=252)
tpCR (ypT0/is, ypN0)	148 (59.7%)	150 (59.5%)
Exact 95% CI for tpCR Rate1	(53.28, 65.84)	52.18, 65.64)
Difference in tpCR rate (SC minus IV arm)	0.15	
95% CI for the difference in tpCR2 rate	-8.67 to 8.97	

[1] Confidence interval for one sample binomial using Pearson-Clopper method

[2] Hauck-Anderson continuity correction has been used in this calculation.

Intraveneous Pertuzumab and Trastuzumab

Neoadjuvant Treatment

NEOSPHERE (WO20697)

NEOSPHERE is a multicenter, randomized 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, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen (ER) or progesterone (PgR) positivity.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 7 for 4 cycles. 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 three weeks and trastuzumab administered intravenously every three weeks to complete one year of therapy.

Patients in the pertuzumab plus trastuzumab and docetaxel arm received docetaxel every three weeks for four cycles prior to FEC after surgery so that all patients received equivalent cumulative doses of the chemotherapeutic agents and trastuzumab.
The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 only), disease-free survival (DFS), and PFS. Additional
exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

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

The efficacy results are summarized in Table 6. A statistically significant and clinically meaningful improvement in pCR rate (ypT0/is) was observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition.

Pathological complete response (pCR) rates as well as the magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (5.9% to 26.0% and 27.3% to 63.2%, respectively).

TRYPHAENA (BO22280)

TRYPHAENA is a multicenter, randomized Phase II clinical study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer. Patients were

randomized to receive one of three neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with pertuzumab and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, or 6 cycles of TCH in combination with pertuzumab. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and /or PgR positivity.
Pertuzumab and trastuzumab were administered intravenously as outlined in Table 6. 5-Fluorouracil (500 mg/m2), epirubicin (100 mg/m2), cyclophosphamide (600 mg/m2) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m2 IV infusion every three weeks with the option to escalate to 100 mg/m2 at the investigator's discretion if the initial dose was well tolerated. However, in the pertuzumab in combination with TCH arm, docetaxel was given intravenously at 75 mg/m2 and no escalation was permitted and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received trastuzumab to complete one year of therapy, which was administered intravenously every 3 weeks.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see 4.8 Undesirable Effects). Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.
Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (77%)) and all were female. Overall 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer and 69% had operable breast cancer, with approximately half the patients in each treatment group had ER-positive and/or PgR-positive disease.
High pCR rates were observed in all 3 treatment arms (see Table 8). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 8: NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Summary of Efficacy (ITT population)

	NEOSPHERE (WO20697)				**TRYPHAENA (BO22280)**		
Parameter	T+D N=107	Ptz+T+D N=107	Ptz+T N=107	Ptz+D N=96	Ptz+T+FEC/ Ptz+T+D N=73	FEC/ Ptz+T+D N=75	Ptz+TCH N=77
ypT0/is n (%) [95% CI][1]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs Ptz+T+D)	NA	NA	NA
ypT0/is N0 n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]

ypT0 N0 n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]
Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

Key to abbreviations (Table 9): T: Trastuzumab; D: docetaxel; Ptz: Pertuzumab; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab.

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

2. Treatment Ptz+T+D and-Ptz+T are compared with T+D, while Ptz+D is compared with Ptz+T+D

3. Approximate 95% CI for difference of two rates using Hauck-Anderson method.

4. p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

5. Clinical response represents patients with a best overall response of CR or PR during the neoadjuvant period (in the primary breast lesion)

BERENICE (WO29217)

BERENICE is a non-randomized, open-label, multicenter**,** multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer.

The BERENICE study included two parallel groups of patients. Patients considered suitable for neoadjuvant treatment with trastuzumab plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

Cohort A - 4 cycles of two-weekly doxorubicin and cyclophosphamide (dose dense AC) followed

by 4 cycles of pertuzumab in combination with trastuzumab and paclitaxel.
Cohort B - 4 cycles of FEC followed by 4 cycles of pertuzumab in combination with trastuzumab and docetaxel.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 6. Doxorubicin 60 mg/m2 IV and cyclophosphamide 600 mg/m2 IV were administered every 2 weeks (ddAC) for four cycles (Cycles 1-4) with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m2 IV weekly for 12 weeks (Cycles 5-8), with pertuzumab and trastuzumab every 3 weeks during Cycles 5-8 (from the start of paclitaxel; four cycles of pertuzumab and trastuzumab in total during the neoadjuvant period). 5-Fluorouracil (500 mg/m2), epirubicin (100 mg/m2), cyclophosphamide (600 mg/m2) were given intravenously every three weeks for 4 cycles. Docetaxel was given at an initial dose of 75 mg/m2 IV infusion every three weeks with the option to escalate to 100 mg/m2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received pertuzumab and trastuzumab which were administered intravenously every 3 weeks, to complete one year of therapy.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see 4.8 Undesirable Effects). Key secondary endpoints at the time of primary analysis were neoadjuvant safety and pCR rate in the breast and nodes (i.e. ypT0/is ypN0). Longterm clinical and safety outcomes will also be assessed (IDFS, EFS and OS, not yet available).

Demographics of the patients were well balanced between the groups. The median age of the patients was 49 years, the majority of patients were Caucasian (83%) and all but one patient was female. Approximately two-thirds of patients (64.3% [n = 128] in Cohort A and 61.7% [n = 124] in Cohort B) had hormone receptor-positive disease.

High pCR rates were observed in both treatment arms, with pCR (ypT0/is ypN0) rates of 61.8% in Cohort A and 60.7% in Cohort B. A consistent pattern of results was observed regardless of pCR

definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors in both Cohorts (51.6% to 81.5% and 57.3% to 68.0% respectively).

Adjuvant Treatment

APHINITY (BO25126)

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

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

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 6 starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

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

Demographics were well balanced between the two treatment arms. The median age was 51 years, and over 99% of patients were female. The majority of patients had node-positive (63%) and/or hormone receptor-positive disease (64%), and were Caucasian (71%).

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

The efficacy results from the APHINITY trial are summarized in Table 9 and in Figures 1 and 2.

Table 9: Overall Efficacy (ITT Population)

	Pertuzumab + Trastuzumab + chemotherapy N=2400	**Placebo + Trastuzumab + chemotherapy N=2404**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value (Log-Rank test, stratified[2])	0.0446	
3 year event-free rate[3] [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI]	0.82 [0.68, 0.99]	
p-value (Log-Rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
Disease Free Survival (DFS)		
Number (%) of patients with event	192 (8.0%)	236 (9.8%)
HR [95% CI]	0.81 [0.67, 0.98]	
p-value (Log-Rank test, stratified[2])	0.0327	

	Pertuzumab + Trastuzumab + chemotherapy N=2400	**Placebo + Trastuzumab + chemotherapy N=2404**
3 year event-free rate[3] [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
Overall Survival (OS)[4]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value (Log-Rank test, stratified[2])	0.4673	
3 year event-free rate[3] [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]
Recurrence Free Interval (RFI)		
Number (%) of patients with event	138 (5.8%)	173 (7.2%)
HR [95% CI]	0.79 [0.63, 0.99]	
p-value (Log-Rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	95.2 [94.3, 96.1]	94.3 [93.3, 95.2]
Distant recurrence-free interval (DRFI)		
Number (%) of patients with event	119 (5.0%)	145 (6.0%)
HR [95% CI]	0.82 [0.64, 1.04]	
p-value (Log-Rank test, stratified[2])	0.1007	
3 year event-free rate[3] [95% CI]	95.7 [94.9, 96.5]	95.1 [94.3, 96.0]

Key to abbreviations (Table 7): HR: Hazard Ratio; CI: Confidence Intervals

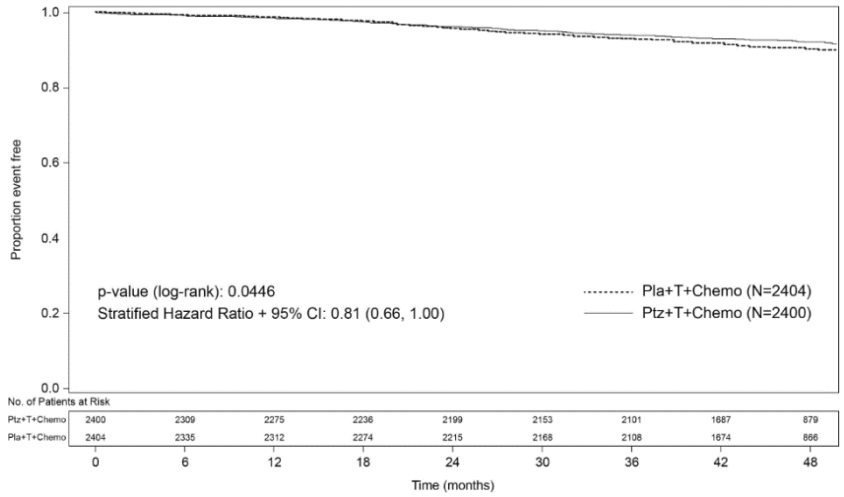
1. Hierarchical testing applied for all secondary endpoints with the exception of RFI and DRFI.

2. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.

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

4. Data from first interim analysis

Figure 1: Kaplan-Meier curve of invasive disease free survival



Pla = placebo; Ptz = pertuzumab; T = trastuzumab

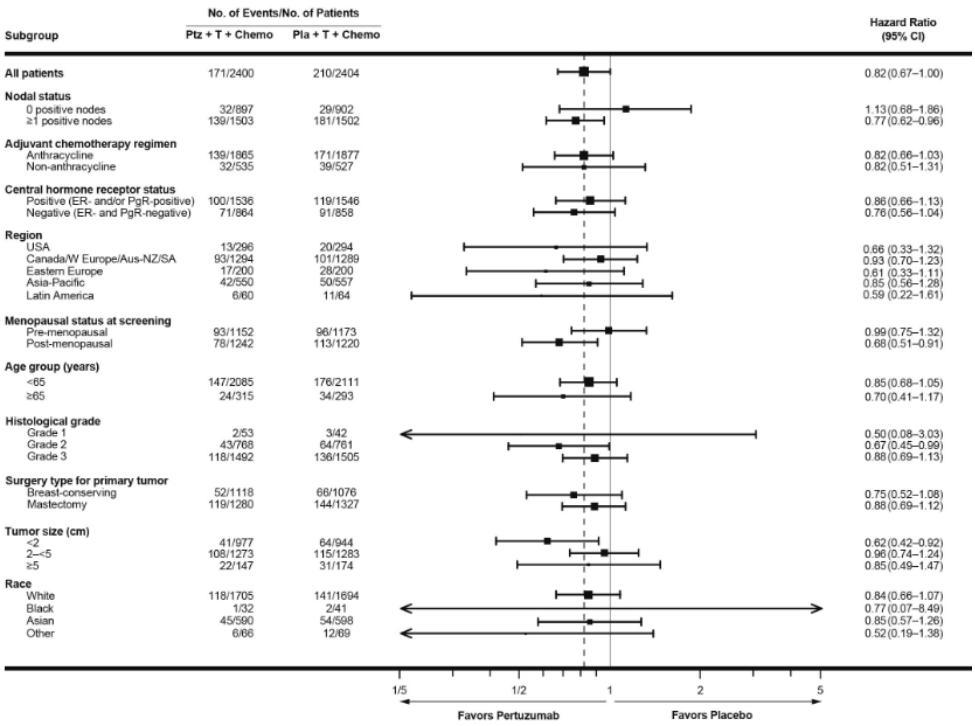
The estimate of IDFS at 4-years was 92.3% in the pertuzumab-treated group versus 90.6% in the placebo-treated group. At the time of the estimate the median follow-up was 45.4 months.

Results of Subgroup Analysis

Consistent results were observed across the majority of pre-specified patient subgroups. The benefits of pertuzumab were more apparent for patients in certain

high risk groups, notably patients with node-positive or hormone receptor-negative disease (see Figure 2 below).

Figure 2: Forest Plot of invasive disease free survival by subgroup



Pla = placebo; Ptz = pertuzumab; T = trastuzumab

Estimates of IDFS rates in the node positive subgroup were 92.0% versus 90.2% at 3 years and 89.9% vs. 86.7% at 4 years in pertuzumab-treated patients versus the placebo-treated patients, respectively. In the node negative subgroup estimates of IDFS rates were 97.5% versus 98.4% at 3 years and 96.2% versus 96.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively.

In the hormone receptor-positive subgroup estimates of IDFS were 94.8% versus 94.4% at 3 years and 93.0% versus 91.6% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the hormone receptor-negative subgroup estimates of IDFS rates were 92.8% versus 91.2% at 3 years and 91.0%versus 88.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively.

Patient Reported Outcomes (PRO)

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

clinically meaningful.

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

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

Metastatic Breast Cancer

CLEOPATRA (WO20698)

CLEOPATRA is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Patients were randomized 1:1 to receive placebo plus trastuzumab and docetaxel (placebo-treated) or pertuzumab plus trastuzumab and docetaxel (pertuzumab-treated). 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.
Pertuzumab and trastuzumab were administered intravenously as outlined in Table 6. Patients were treated with pertuzumab 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 was 16.2 in the placebo treatment group and 19.9 in the pertuzumab-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 tumor 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 questionnaire.

Demographics were well balanced (median age was 54 years old, the majority were Caucasian (59%) and all were female with the exception of 2 patients). Approximately half the patients in each treatment group had hormone receptorpositive disease (defined as estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) and approximately half of the patients in each treatment group had received prior adjuvant or neo-adjuvant therapy (192 patients [47.3%] in the placebo-treated group vs 184 patients [45.8%] pertuzumab-treated group) . 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 pertuzumab-treated group had IRF-confirmed progressive disease or had died within 18 weeks of their last tumor assessment .

At the time of the primary analysis 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 pertuzumab-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 pertuzumab-treated group) (see Figure 3). 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 pertuzumab) (see Table 9). 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 4).

The efficacy results from the CLEOPATRA trial are summarized in Table 10 below

Table 10: Summary of efficacy from CLEOPATRA study

Parameter	**Placebo + Trastuzumab + docetaxel n=406**	**Pertuzumab + Trastuzumab + docetaxel n=402**	**HR (95% CI)**	**p-value**
Primary Endpoint				
Progression-Free Survival (IRF review) No. of patients with an event Median months	242 (59%) 12.4	191 (47.5%) 18.5	0.62 [0.51;0.75]	<0.0001
Secondary Endpoints				
Overall Survival (Final analysis of OS) No. of patients with an event*	221 (54.4%) 40.8	168 (41.8%) 56.5	0.68 [0.56;0.84]	0.0002

Median months				
Progression-Free Survival(investigator assessment) **No. of patients with an event** **Median months**	250 (61.6%) 12.4	201 (50.0%) 18.5	0.65 [0.54;0.78]	<0.0001
Objective Response Rate (ORR) **No. of patients with an event** **Responders**** **95% CI for ORR** **Complete response (CR)** **Partial Response (PR)** **Stable disease (SD)** **Progressive disease (PD)**	336 233 (69.3 %) [64.1; 74.2] 14 (4.2 %) 219 (65.2 %) 70 (20.8 %) 28 (8.3 %)	343 275 (80.2 %) [75.6; 84.3] 19 (5.5 %) 256 (74.6 %) 50 (14.6 %) 13 (3.8 %)	Difference in ORR: 10.8% [4.2,17.5]%	0.0011
Duration of Response ^n= **Median weeks**	233 54.1 [46;64]	275 87.6 [71;106]		

95% CI for Median				

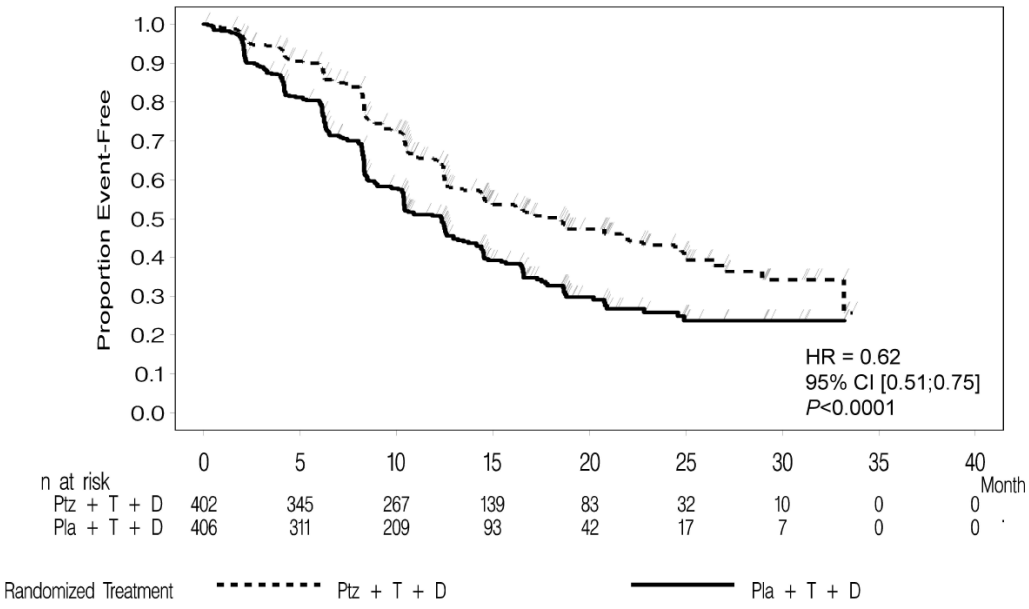
*Final analysis of overall survival, cutoff date 11 Feb 2014

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

^ Evaluated in Patients with Best Overall Response of CR or PR

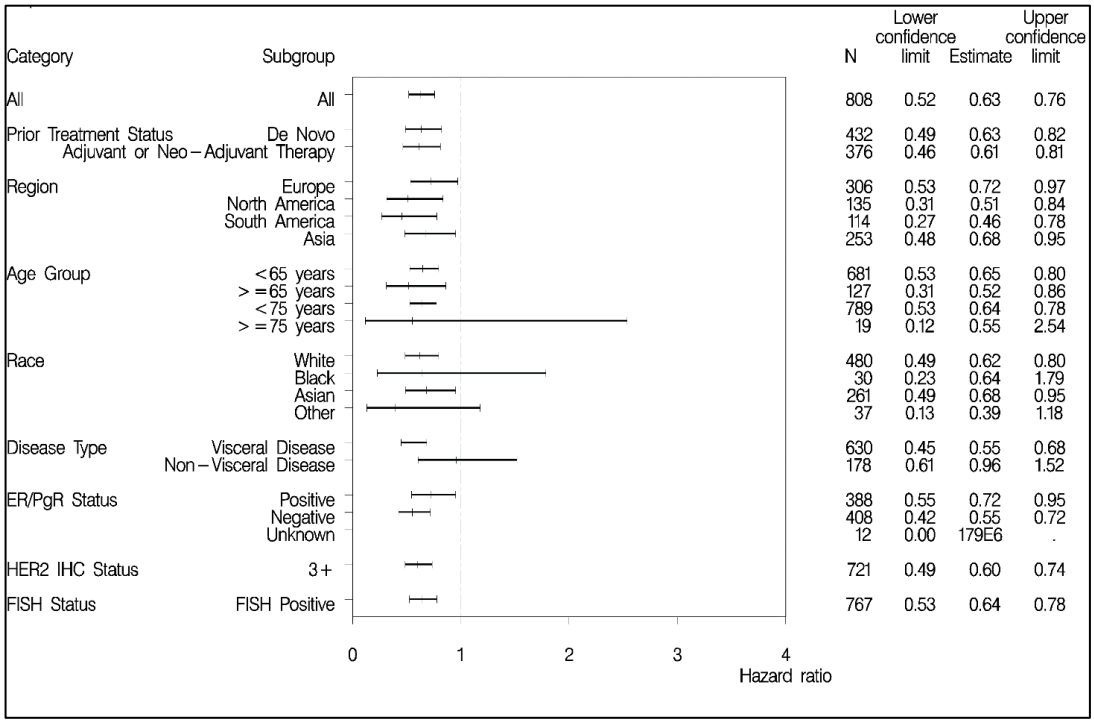
Objective response rate and duration of response are based on IRF-assessed tumor assessments

Figure 3: Kaplan-Meier curve of IRF-assessed progression-free survival



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab; T=trastuzumab

Figure 4: IRF assessed PFS by patient subgroup

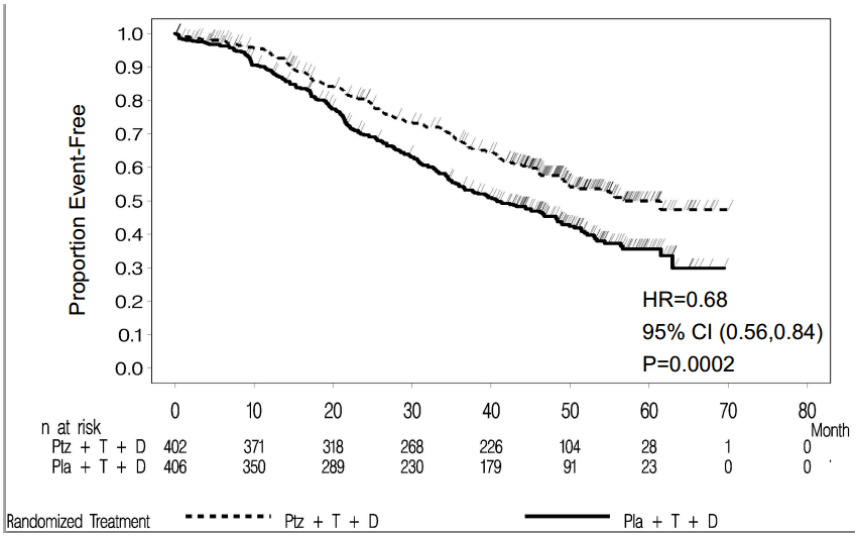


At the primary analysis of efficacy, an interim analysis of OS showed a strong trend suggestive of a survival benefit in favor of the Perjeta-treated group.

An interim analysis of OS performed one year after the primary analysis of efficacy, demonstrated a statistically significant OS benefit in favor of the pertuzumab-treated group (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 pertuzumab-treated group.

The final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the pertuzumab-treated group). The statistically significant OS benefit in favor of the pertuzumab-treated group was maintained (HR 0.68, p = 0.0002 log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the pertuzumab-treated group (see Table 10, Figure 5).

Figure 5: Kaplan-Meier curve of overall survival



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab; T=trastuzumab

There was no statistically significant difference between treatment groups in Health Related Quality of Life as assessed by time to symptom progression on the FACTB TOI-PFB subscale, defined as a 5 point reduction in subscale score (HR =0.97, 95% CI =0.81; 1.16) [137]. In an exploratory analysis, patients treated with pertuzumab in combination with trastuzumab and docetaxel experienced a lower risk of symptom progression on the FACT-B breast cancer subscale (defined as a 2 point reduction in subscale score) compared to those treated with trastuzumab and docetaxel alone (HR =0.78, 95% CI =0.65; 0.94).

PHranceSCa (MO40628)

Study MO40628 investigated the safety of switching from intravenous pertuzumab and trastuzumab to Phesgo (and vice versa) with a primary objective to evaluate patient preference for Phesgo. A total of 160 patients included in this 2-arm, cross-over study: 80 patients were randomized to Arm A (3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of Phesgo) and 80 patients were randomized to Arm B (3 cycles of Phesgo followed by 3 cycles intravenous pertuzumab and trastuzumab). After that, patients could choose to continue their treatment with intravenous pertuzumab and trastuzumab or with Phesgo to complete a total of 18 cycles of HER2-targeted therapy.

At primary analysis, 136 out of 160 patients (85%) reported preferring subcutaneous administration of PHESGO over intravenous pertuzumab and trastuzumab and the most common reason was that administration required less time in the clinic. 22 out of 160 patients (14%) reported preferring intravenous pertuzumab and trastuzumab over PHESGO and the most common reason was feels more comfortable during administration. Two out of 160 patients (1%) had no preference for the route of administration.

Among the patients in Arm A, the incidence of AEs was similar when switching from intravenous pertuzumab and trastuzumab to Phesgo. Within Arm A, the incidence of AEs during Cycles 1-3 (IV) was 77.5% compared to Cycles 4-6 (SC) which was 72.5%. Within Arm B, the incidence of AEs during Cycles 1-3 (SC) was 77.5% compared to Cycles 4-6 (IV) which was 63.8% . The total number of events was higher during Cycles 1-3 compared to Cycles 4-6, regardless of treatment administered**.**

Immunogenicity

As with all therapeutic proteins, there is the potential for immune response in patients treated with Phesgo. 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 treatment-emergent antibodies to Phesgo with the incidence of antibodies to other products may be misleading.

In the FEDERICA study, the incidence of treatment-emergent anti-pertuzumab and antitrastuzumab antibodies was 3% (7/237) and 0.4% (1/237), respectively, in patients treated with intravenous pertuzumab and trastuzumab.

The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and antivorhyaluronidase alfa antibodies was 4.8% (11/231), 0.9% (2/232), and 0.9% (2/225), respectively, in patients treated with Phesgo. The clinical relevance of the development of anti-

pertuzumab, anti-trastuzumab or anti-vorhyaluronidase alfa antibodies after treatment with Phesgo is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phesgo contains vorhyaluronidase alfa (recombinant human hyaluronidase rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, Sucrose, L-methionine, Polysorbate 20 and water for injection.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store at 2°C-8°C.

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

Do not freeze.

Store out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Phesgo 1200 mg/600 mg solution for subcutaneous injection:

One 20 mL type I borosilicate glass vial with fluororesin-laminated rubber stopper laminated with fluororesin containing 15 mL solution of 1200 mg of pertuzumab and 600 mg of trastuzumab.

Pack of 1 vial

Phesgo 600 mg/600 mg solution for subcutaneous injection:

One 15 mL type I borsilicate glass vial with fluororesin-laminated rubber stopper laminated with fluororesin containing 10 mL solution of 600 mg pertuzumab and 600 mg of trastuzumab.

Pack of 1 vial

20 mm, aluminum seal with plastic flip-off cap (cool green flip-off color for the loading dose and orange flip-off color for maintenance dose).

6.6 Special precautions for disposal and other handling

The 1200 mg pertuzumab/600 mg trastuzumab and 600 mg pertzumab/600 mg trastuzumab solution are ready to use solutions for injection which does not need to be mixed with other drugs or diluted.

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Do not shake.

Phesgo solution for injection is for single use only and should be prepared by a healthcare professional using aseptic technique.

From a microbiological point of view, the medicine should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. If not used immediately, preparation should take place in controlled and validated aseptic conditions. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days at 2°C - 8°C or 24 hours at 9°C - 30°C. After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying

of the solution in the needle and not compromise the quality of the medicinal product. Label the syringe with the peel-off sticker.

The hypodermic injection needle must be attached to the syringe immediately prior to administration. Followed by volume adjustment to 10 mL (600 mg pertuzumab/600 mg trastuzumab) or 15 mL (1200 mg pertuzumab/600 mg trastuzumab)

No incompatibilities between Phesgo and polypropylene, polycarbonate, polyurethane, polyethylene, polyvinyl chloride and fluorinated ethylene polypropylene have been observed.

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.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley,

Midrand, Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Phesgo 600 mg/600 mg: 550445

Phesgo 1 200 mg/600 mg: 550444

9. Date of first authorisation/renewal of the authorisation

17 May 2022

10. DATE OF REVISION OF THE TEXT

Last revision: 20 June 2023

Botswana	S2 BOT2203970/1
Namibia	S2 23/26/0013/4
Zimbabwe	PP 2023/9/7/6394/5
Zambia	1361121/221H

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