# Pertuzumab and Trastuzumab (Phesgo®) and DOCEtaxel Therapy - 21 day cycle

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Pertuzumab/ trastuzumab (Phesgo®) is indicated in combination with DOCEtaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti- HER2 therapy or chemotherapy for their metastatic disease. | C50 | 00796a | Pertuzumab/Trastuzumab (Phesgo®): ODMS 20/12/2022<br>DOCEtaxel: Hospital |

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

Treatment is administered every 21 days in responding patients until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti cancer therapy (SACT) is administered.

**Cycle 1: Pertuzumab and trastuzumab (Phesgo ®) loading dose**

| Order of Admin | Day | Drug | Dose | Route | Diluent & Rate |
|---|---|---|---|---|---|
| 1 | 1 | Pertuzumab/ Trastuzumab (Phesgo®) | 1200mg/600mg | SC<br>Observe for 30 minutes post injection[a] | Over 8 mins |
| 2 | 1 | DOCEtaxel[b] | 75mg/m$^2$ | IV infusion | 250ml 0.9% sodium chloride over 60min[c] |
| [a]Patients should be observed for injection-related reactions and hypersensitivity reactions. Observation period should start following administration of Phesgo® and be completed prior to any subsequent administration of chemotherapy. Any deviation should be noted in local policies. | | | | | |
| [b]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications(See Adverse Effects/Regimen Specific Complications) | | | | | |
| [c]75-185mg dose use 250mL infusion bag.For doses> 185mg use 500mL infusion bag<br>Use non-PVC infusion equipment | | | | | |

**Cycle 2 and subsequent cycles**

| Order of Admin | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 1 | Pertuzumab/ Trastuzumab (Phesgo®) | 600mg/600mg | SC<br>Observe for 15 minutes post injection[a] | Over 5 mins if no adverse reactions | Every 21 days |
| 2 | 1 | DOCEtaxel[b] | [c]75mg/m$^2$ | IV infusion | 250ml 0.9% sodium chloride over 60min[d] | Every 21 days for a minimum of 6 cycles |
| [a]Patients should be observed for injection-related reactions and hypersensitivity reactions. Observation period should start following administration of Phesgo® and be completed prior to any subsequent administration of chemotherapy. Any deviation should be noted in local policies. | | | | | | |
| [b]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications) | | | | | | |
| [c]The dose of DOCEtaxel may be escalated to 100 mg/m2 on subsequent cycles if the initial dose is well tolerated. | | | | | | |
| [d]75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag<br>Use non-PVC infusion bag. | | | | | | |

## ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of ≥ 55%
- Adequate organ function

## EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, DOCEtaxel, murine proteins or any of the excipients
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction with trastuzumab
- Significant hepatic dysfunction, contraindicating DOCEtaxel
- Baseline neutrophil count < 1.5 x $10^9$/L
- Pregnancy or breastfeeding

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

## TESTS:

**Baseline tests**:

- Blood, renal and liver profile
- HER2 positive as demonstrated by a validated test method
- Cardiac function (LVEF using ECHO or MUGA scan)

**Regular tests**:

- FBC, renal and liver profile before each cycle
- MUGA scan or echocardiogram every 12 weeks during treatment with pertuzumab/ trastuzumab (Phesgo®) and at completion of therapy. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

**Disease monitoring:**

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

**Pertuzumab/ trastuzumab (Phesgo®)**

- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing with pertuzumab/trastuzumab (Phesgo®) after a dose delay or missed doses.
    - Doses are held or discontinued if unacceptable toxicity occurs.
    - Patient may continue to receive pertuzumab/trastuzumab (Phesgo®) if DOCEtaxel is discontinued due to toxicity or after 6-8 cycles and without evidence of disease progression.

**Table 1: Delayed or missed doses for pertuzumab and trastuzumab (Phesgo®)**

| Time between two sequential infusions | Dose modification |
|---|---|
| <6 weeks | The maintenance dose of pertuzumab/trastuzumab (Phesgo®) 600 mg/600 mg should be administered as soon as possible. Thereafter, continue with the 3-weekly schedule. |
| ≥6 weeks | A loading dose of pertuzumab/trastuzumab (Phesgo®) 1200 mg/600 mg should be re-administered followed by maintenance dose of pertuzumab/trastuzumab (Phesgo®) 600 mg/600 mg every 3 weeks thereafter. |

**Table 2: Switching from intravenous pertuzumab and trastuzumab administration to Phesgo®**

| Time since last dose | Dose of Phesgo® |
|---|---|
| <6 weeks | Administer as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations |
| ≥6 weeks | 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. |

## Renal and Hepatic Impairment:

**Table 3: Dose modification in renal and hepatic impairment**

| Drug | Renal Impairment | Hepatic Impairment |
|---|---|---|
| **Pertuzumab/ trastuzumab (Phesgo®)** | Dose adjustments 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 (PK) data available. | The safety and efficacy have not been studied in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment. No specific dose adjustment are recommended. |
| **DOCEtaxel** | No dose reduction required | See Table 4 below |

**Table 4: Dose modification of DOCEtaxel in hepatic impairment.**

| Alkaline Phosphatase | | AST and/or ALT | | Serum Bilirubin | Dose |
|---|---|---|---|---|---|
| > 2.5 x ULN | and | > 1.5 x ULN | | | 75 mg/m$^2$ |
| > 6 x ULN | and/or | > 3.5 x ULN (AST and ALT) | and | > ULN | Stop treatment unless strictly indicated and should be discussed with a Consultant. |

## Management of adverse events:

**Table 5: Dose modification schedule based on adverse events**

| Adverse reactions | Discontinue | Recommended dose modification |
|---|---|---|
| **Pertuzumab/trastuzumab (Phesgo®)** | | |
| LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value. | | Withhold treatment with pertuzumab/trastuzumab (Phesgo®). Repeat LVEF within 3 weeks. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist. |
| Symptomatic heart failure | Discontinue | |
| NCI-CTCAE Grade 4 hypersensitivity reactions | Discontinue | |
| **DOCEtaxel** | | |
| Grade >2 peripheral neuropathy | | Decrease dose of **D**OCEtaxel to 60mg/m$^2$. If the patient continues to experience these reactions at 60 mg/m$^2$, treatment with DOCEtaxel should be discontinued. |
| Grade 3 skin reaction | | |
| Grade ≥3 stomatitis | | DOCEtaxel will be reduced from 75 to 60 mg/m$^2$. |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

**Pertuzumab/trastuzumab (Phesgo®):** Minimal **(Refer to local policy)**
**DOCEtaxel:** Low(**Refer to local policy)**

### PREMEDICATIONS:

- **DOCEtaxel:** dexAMETHasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexAMETHasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer.
- **Pertuzumab/trastuzumab (Phesgo®):** Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered. Patient should be educated about the possibility of delayed infusion-related symptoms.

**OTHER SUPPORTIVE CARE**: No specific recommendations

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

**Pertuzumab/trastuzumab (Phesgo®):**

- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Left ventricular dysfunction (including congestive heart failure):** 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 trastuzumab and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines based on studies with intravenous pertuzumab in combination with trastuzumab and chemotherapy. Phesgo® has not been studied in patients with: a pre-treatment 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/m$^2$ of DOXOrubicin or its equivalent. In addition, 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 (e.g. once during neoadjuvant treatment and every 12 weeks in the adjuvant and metastatic setting) to ensure that LVEF is within normal limits. If the LVEF has declined 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. Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Phesgo® with an anthracycline. Based on the pharmacological actions of HER2-targeted agents and anthracyclines, the risk of cardiac toxicity might be expected to be higher with concomitant use of Phesgo and anthracyclines than with sequential use.
- **Injection-related reactions/infusion-related reactions (IRRs):** Phesgo® has been associated with

injection-related reactions. 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. 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. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed with pertuzumab in combination with trastuzumab and chemotherapy. The majority of anaphylactic reactions occurred within the first 6-8 cycles of treatment when pertuzumab and trastuzumab were given in combination with chemotherapy. Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use. Phesgo® must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome. Phesgo is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab or to any of its excipients.
- **Diarrhoea:** Phesgo® may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) have a higher risk of diarrhoea compared with younger patients (< 65 years). Treat diarrhoea according to standard practice and guidelines. Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment with Phesgo® should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with Phesgo® may be reinstated.
- **Pulmonary events:** Severe pulmonary events have been reported with the use of trastuzumab. These events have occasionally been fatal. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Phesgo®. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

**Docetaxel:**

- **Neutropenia**: Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent blood count monitoring should be conducted in all patients treated with DOCEtaxel. DOCEtaxel should be administered when the neutrophil count is ≥ 1.5 x $10^9$cells/L.
- **Neutropenic Enterocolitis:** A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France. This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people.
- **Fluid Retention**: dexAMETHasone premedication must be given to reduce the incidence and severity of fluid retention. It can also reduce the severity of the hypersensitivity reaction.
- **Hypersensitivity Reactions:** Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes

following the initiation of the infusion of DOCEtaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCEtaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCEtaxel.

- **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated (Refer to local extravasation guidelines).
- **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.

## DRUG INTERACTIONS:

- A possible interaction with warfarin has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.
- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 20/12/2022 | | Prof Maccon Keane |
| 2 | 10/08/2023 | Updated emetogenic potential of pertuzumab/trastuzumab (Phesgo) | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.