Pertuzumab/Trastuzumab (Phesgo®), PACLitaxel and CARBOplatin Therapy (TRAIN-2)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.	C50	00790a	Pertuzumab/Trastuzumab (Phesgo®): ODMS 20/12/2022 CARBOplatin and PACLitaxel: 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.

Pertuzumab/trastuzumab (Phesgo®), and CARBOplatin are administered on day 1 and PACLitaxel is administered on day 1 and 8 of a 21 day cycle for 6 cycles or until disease progression or unacceptable toxicity develops.

Following surgery, patients should be treated with adjuvant therapy (e.g. trastuzumab OR trastuzumab emtansine as appropriate) to complete 1 year of treatment.

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

Cycle 1: Pertuzumab/trastuzumab (Phesgo®) loading dose

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/trastuzumab (Phesgo®)	1200mg/600mg	SC (Observe for 30 minutes post injection[a])	Over 8 mins	Cycle 1 only
2	1, 8	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCl over 1hr[b]	Cycle 1 only
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30min	Cycle 1 only
[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]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

Cycle 2-6

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/trastuzumab (Phesgo®)	600mg/600mg	SC (Observe for 15 minutes post injection[a])	Over 5 mins if no adverse reactions	Every 21 days
2	1, 8	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCl over 1hr[b]	Every 21 days
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30 min	Every 21 days
[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] PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR** (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, the formulae may not give accurate results and measured GFR is recommended.
    - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered.
    - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{\text{S} \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ≥ 18 years
- ECOG status 0-1
- LVEF ≥ 50%
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, PACLitaxel, CARBOplatin* 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
- Pregnancy / Breast feeding
- Baseline neutrophil count < $1.5x10^9$ cells/L
- Severe hepatic impairment

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- HER2 positive as demonstrated by a validated test method
- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation

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 pertuzumab and trastuzumab after a dose delay or missed doses.
- Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

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.

PACLitaxel and CARBOplatin:

Table 3: Dose Reduction Levels for PACLitaxel and CARBOplatin

	Starting Dose	Dose Level -1	Dose Level -2
PACLitaxel	80mg/m^2	70mg/m^2	60mg/m^2
CARBOplatin	AUC 6	AUC 5	AUC 4

Haematological:

Table 4: Dose modification of CARBOplatin and PACLitaxel in haematological toxicity

Day	ANC (x10^9/L)		Platelets (x10^9/L)	CARBOplatin Dose	PACLitaxel Dose
Day 1	≥1	and	≥ 75	100% Dose	100% Dose
	<1	and/or	<75	Delay treatment until recovery[a]	Delay treatment until recovery[a]
Day 8, 15	<0.5	and/or	<50		Omit day 8 and day 15 PACLitaxel dose
Day 1	Febrile Neutropenia			Decrease CARBOplatin dose by one dose level	
	<0.5 for ≥ 7 days	or	<10		
			10 to 50 with bleeding tendencies		
	Treatment delay for haematological toxicity > 1 week 1st occurrence			Decrease CARBOplatin dose by one dose level to AUC 5	
	2nd occurrence			Decrease CARBOplatin dose further for subsequent cycles to AUC 4	

[a]Treatment may be delayed for a maximum of 3 weeks.

Renal and Hepatic Impairment:

Table 5: 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.			
PACLitaxel	No dose modifications necessary	**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
		< 10 x ULN	and	≤ 1.25 x ULN	80mg/m^2
		< 10 x ULN	and	1.26-2 x ULN	60mg/m^2
		< 10 x ULN	and	2.01-5 x ULN	40mg/m^2
		≥10 x ULN	and/or	>5 x ULN	Not recommended
CARBOplatin	See note below*	No dose modification required			

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution.
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 6: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Pertuzumab and Trastuzumab (Phesgo®)	
Reduction in LVEF to <50% - associated with a fall of ≥ 10% points below pre-treatment values	Withhold treatment with pertuzumab/trastuzumab (Phesgo®) for at least 3 weeks. Pertuzumab/trastuzumab (Phesgo®) may be resumed if the LVEF has recovered to ≥50% or to a difference of <10% points below pre-treatment values. 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
PACLitaxel	
Grade ≥2 motor or sensory neuropathy First Occurrence Persistent Grade ≥2 or 2nd occurrence	 Decrease dose of PACLitaxel by 10mg/m^2. Decrease dose of PACLitaxel by a further 10mg/m^2
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ Grade 3 reaction	Discontinue

Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pertuzumab/trastuzumab (Phesgo®): Minimal **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**
CARBOplatin: High **(Refer to local policy)**

PREMEDICATIONS:

Trastuzumab/pertuzumab(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.

PACLitaxel:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs

of hypersensitivity. Any hypersensitivity should be managed as per local policy.
- Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 7 outlines the suggested premedications prior to treatment with PACLitaxel.

Table 7: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	dexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	dexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.
- G-CSF support may be required **(refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Hypersensitivity**: Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug. Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

Pertuzumab/trastuzumab (Phesgo®)

- **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.

PACLitaxel

- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Hepatic dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Cardiac conduction abnormalities**: If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.

CARBOplatin

- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

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 PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- 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 exclusions and emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.