DOCEtaxel, CARBOplatin and Pertuzumab/Trastuzumab (Phesgo®)(TCHP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory or early breast cancer at high risk of recurrence.	C50	00789a	CARBOplatin and DOCEtaxel: N/A Pertuzumab/trastuzumab (Phesgo®): ODMS 20/12/22

* This is for post 2012 indications only.

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®), DOCEtaxel and CARBOplatin are administered once every 21 days for 6 cycles or until disease progression or unacceptable toxicity develops.

Following surgery, adjuvant trastuzumab treatment continues once every 21 days for a further 12 cycles, continuing for a total of one year from date of first dose (usually 18 doses of trastuzumab in total, including the initial loading dose). Refer to NCCP Regimens 00200 Trastuzumab IV Monotherapy -21 days or 00285 Trastuzumab SC - 21 days.

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

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

Order of Admin:	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/ trastuzumab (Phesgo®)	1200mg/600mg	SC (Observe for 30 minutes post injection [a])	Over 8 minutes	Cycle 1 only
2	1	DOCEtaxel[b]	75mg/m^2	IV infusion	250mL 0.9% NaCl over 60 minutes[c]	Cycle 1 only
3	1	CARBOplatin	AUC 6	IV infusion	500mL glucose 5% over 30 minutes	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]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications. (See Adverse Effects/Regimen Specific Complications)

[c]Concentration of final volume should be <0.74mg/mL. Use non-PVC infusion bag.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Cycles 2 - 6:

Order of Admin:	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/ trastuzumab (Phesgo®)	600mg/600mg	SC (Observe for 15 minutes post injection[a])	Over 5 minutes if no adverse reactions	Every 21 days
2	1	DOCEtaxel[b]	75mg/m^2	IV infusion	250mL 0.9% NaCl over 60 minutes[c]	Every 21 days
3	1	CARBOplatin	AUC 6	IV infusion	500mL glucose 5% over 30 minutes	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]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications. (See Adverse Effects/Regimen Specific Complications)

[c]Concentration of final volume should be <0.74mg/mL. Use non-PVC infusion bag.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

CARBOplatin dose:

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

Dose (mg) = target AUC (mg/mL x minute) x (GFR mL/minute +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/minute.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; 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.*

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

2. *SCr measured using Jaffe assay*

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

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

COCKCROFT-GAULT FORMULA

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication as above
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* here.
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of ≥ 55% (≥ 50% after completion of the anthracycline component of chemotherapy, if given)
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, murine proteins, DOCEtaxel, 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
- Significant hepatic dysfunction, contraindicating DOCEtaxel

- Baseline neutrophil count < 1.5 x 10^9/L
- ≥ Grade 2 sensory or motor neuropathy
- Uncontrolled hypertension
- Pregnancy or breastfeeding

*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:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC, renal and liver profile before each cycle
- Cardiac function (MUGA or ECHO) every 12 weeks. 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.

Trastuzumab and Pertuzumab:

- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing pertuzumab/trastuzumab (Phesgo®) 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: Dose modifications of pertuzumab/trastuzumab (Phesgo®) for delayed or missed doses

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.

Haematological:

- Doses are adjusted based on Day 1 counts and previous cycle febrile neutropenia.
- No dose reduction for nadir counts.
- **No reduction of pertuzumab/trastuzumab (Phesgo®) dose for haematologic toxicity.**

Table 3: Dose modification of DOCEtaxel and CARBOplatin for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose of DOCEtaxel and CARBOplatin	G-CSF option
≥ 1.5	**and**	≥ 100	100%	
1 -1.49	**and**	≥ 100	75%	100% regimen
< 1.0	**or**	< 100	Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75%	Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 100%

Febrile Neutropenia:

Table 4: Dose modification for febrile neutropenia

Event	Dose reduction option	G-CSF option
1st event	75% of previous cycles dose if Day 1 ≥ 1.5 and platelets ≥ 100	100% regimen
2nd event	50% of original cycle dose if Day 1 ≥ 1.5 and platelets ≥ 100	75% regimen
3rd event	Discontinue regimen or switch to G-CSF option	50% regimen

Renal and Hepatic Impairment:

Table 5: Dose modification of pertuzumab, trastuzumab, DOCEtaxel and CARBOplatin 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	Renal impairment: No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected	**See Table 6 below**
CARBOplatin	See note below[a]	No dose modification required

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60mL/minute are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30mL/minute, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20mL/minute, 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 hours 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.

DOCEtaxel and hepatic dysfunction:

- DOCEtaxel doses shall be modified for hepatic toxicity. If DOCEtaxel is delayed due to hepatic toxicity, other drugs being used in combination at that time shall also be delayed and administered when DOCEtaxel is resumed.
- Since no data in patients with abnormal bilirubin level treated with lower dose of DOCEtaxel are available, in the event that bilirubin levels are abnormal during the study, the next cycle will be delayed by a maximum of two weeks. If no recovery, the patient should be taken off chemotherapy. Treatment with pertuzumab/trastuzumab (Phesgo®) may continue.
- In the event that AST and/or ALT and/or alkaline phosphatase and/or bilirubin levels are abnormal in the absence of relapse, the following dose modifications should apply (Table 6).
- Once the dose is reduced due to impaired liver function, no further dose reduction is recommended if no worsening of the parameters is observed.
- In case of recovery of liver function tests on the following cycle, the dose should be re-escalated to the previous dose level.

Table 6: Dose Modification of DOCEtaxel based on hepatic dysfunction

AST Values		ALT Values		Alkaline Phosphatase Values		Bilirubin	Dose Modification
> 1.5–5 x ULN	AND/OR	> 1.5–5 x ULN	AND	> 2.5–5 x ULN	AND	Normal	Consider 75% of the original dose
> 5–10 x ULN	OR	> 5–10 x ULN	AND	< 6 x ULN	AND/OR	≤ 1–1.5 x ULN	Consider 50% of the original dose
> 10 x ULN	OR	> 10 x ULN	OR	> 6 x ULN	OR	> 1.5 x ULN	Not recommended

Non-Haematological Toxicity:

Table 7**: Dose modification of pertuzumab/trastuzumab (Phesgo®), DOCEtaxel and CARBOplatin based on adverse events**

Adverse reactions	Recommended dose modification
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 discuss with consultant and consider referral to cardiology.
Symptomatic heart failure	Discontinue
Grade 4* hypersensitivity reactions	Discontinue
Grade > 2 peripheral neuropathy	Decrease dose of DOCEtaxel to 60mg/m^2. If the patient continues to experience these reactions at 60mg/m^2, treatment with DOCEtaxel should be discontinued.
Grade ≥ 3 Stomatitis	Decrease dose of DOCEtaxel to 60mg/m^2. If despite dose reduction, stomatitis still occurs at grade ≥ 3, DOCEtaxel will be further reduced from 60 to 50 mg/m^2. No further dose reduction is planned.
*NCI-CTCAE Grading	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

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

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

PREMEDICATIONS:

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.

DOCEtaxel: dexAMETHasone 8mg 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.

OTHER SUPPORTIVE CARE:

- Women of childbearing potential must use effective method of contraception during treatment and for 2 months after cessation of treatment with DOCEtaxel.
- Men must use effective method of contraception during treatment and for 4 months after cessation of treatment with DOCEtaxel.

ADVERSE EFFECTS:

Please refer to the relevant Summary of Product Characteristics (SmPC).

DRUG INTERACTIONS:

Consult current drug interaction databases and relevant SmPC.

REFERENCES:

1. Hurvitz SA et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2018 Jan;19(1):115-126. doi: 10.1016/S1470-2045(17)30716-7. Epub 2017 Nov 23. PMID: 29175149.
2. Schneeweiss A et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer. 2018 Jan;89:27-35. doi: 10.1016/j.ejca.2017.10.021. Epub 2017 Dec 8. PMID: 29223479.

3. Schneeweiss A et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013 Sep;24(9):2278-84. doi: 10.1093/annonc/mdt182. Epub 2013 May 22. PMID: 23704196.
4. Appropriate chemotherapy dosing for obese adult patients with cancer:American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13) 1553-1561.
5. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
6. NCCN CARBOplatin Dosing in Adults available here https://www.nccn.org/docs/default-source/clinical/order-templates/appendix_b.pdf?sfvrsn=6286822e_6
7. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
8. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
9. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
10. Chouhan et al. Single premedication dose of dexamethasone 20mg IV before DOCEtaxel administration. J Oncol Pharm Practice 2010;17(3): 155–159
11. Rogers ES et al. Efficacy and safety of a single dose of dexamethasone pre DOCEtaxel treatment: The Auckland experience. Annals of Oncology (2014) 25 (suppl_4): iv517-iv541
12. Fatal Neutropenic Enterocolitis With DOCEtaxel in France by Aude Lecrubier. Available at: http://www.medscape.com/viewarticle/876014
13. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin®) treatment JAMA 1999;282:2299-301.
14. Pertuzumab and Trastuzumab (Phesgo®) Summary of Product Characterisitics. Last updated: 02/03/2022. Accessed 22.04.2024. Available at: https://www.ema.europa.eu/en/documents/product-information/phesgo-epar-product-information_en.pdf
15. DOCEtaxel Summary of Product Characteristics. Last updated: 14/12/2023. Accessed 22.04.2024. Available at: https://www.ema.europa.eu/en/documents/product-information/taxotere-epar-product-information_en.pdf
16. CARBOplatin Summary of Product Characteristics. Last updated: 08/02/2024. Accessed 22/04/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_08022024123309.pdf

Version	Date	Amendment	Approved By
1	15/12/2022		Prof Maccon Keane
2	10/10/2023	Updated standard wording for renal dysfunction and CARBOplatin . Updated exclusions section and emetogenic potential of pertuzumab/trastuzumab (Phesgo®).	Prof Maccon Keane
3	07/06/2024	Regimen reviewed. - Updated information regarding HER2 and LVEF information in Eligibility section - Updated Regular tests section	Prof Maccon Keane

		- Updated Dose Modifications of DOCEtaxel in renal and hepatic impairment (Tables 5 and 6) - Added contraceptive advice in the Other Supportive Care section - Adverse Effects and Drug Interactions sections removed and replaced with standard wording - NCCP Standardisation	

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.