DOCEtaxel, CARBOplatin, Trastuzumab (S/C) and Pertuzumab (TCH(S/C)P) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory or early breast cancer at high risk of recurrence	C50	00731a	Trastuzumab, CARBOplatin and DOCEtaxel: Hospital Pertuzumab: ODMS 01/07/2020

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.

Trastuzumab, pertuzumab, 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 loading dose

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	840mg	IV Observe for 1hr post infusion	250ml 0.9% sodium chloride over 60min	Cycle 1 only
2 or 1	1	Trastuzumab	600mg	SC[a, b] over 2-5 mins		Cycle 1 only
3	1	DOCEtaxel[c]	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min[d]	Cycle 1 only
4	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30 min	Cycle 1 only

[a]The injection site should be alternated between the left and right thigh.
New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard.
During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.

[b]Patients should be observed for 30 minutes after the first injection and for 15 minutes after subsequent injections for signs or symptoms of administration-related reactions. Any deviation should be noted in local policies.

[c]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications).

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

Cycles 2 - 6:

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60mins post infusion[a]	250ml 0.9% sodium chloride over 30min if no adverse reactions[b]	Every 21 days
2 or 1	1	Trastuzumab	600mg	SC[c, d] over 2-5 mins		Every 21 days
3	1	DOCEtaxel[e]	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min[f]	Every 21 days
4	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 30min	Every 21 days

[a]Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.

[b]The infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant.

[c]The injection site should be alternated between the left and right thigh.
New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard.
During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.

[d]Patients should be observed for 30 minutes after the first injection and for 15 minutes after subsequent injections for signs or symptoms of administration-related reactions. Any deviation should be noted in local policies.

[e]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications).

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

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. (7) 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

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication as above
- HER2 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, 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 breast feeding

*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
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- FBC, renal and liver profile
- 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 trastuzumab 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.

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 of pertuzumab after a dose delay or missed doses.
  - If the patient misses a dose of subcutaneous trastuzumab, it is recommended to administer the next 600mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive trastuzumab subcutaneous formulation administrations should not be less than three weeks.
- Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.
- If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

Table 1: Dose modifications of pertuzumab for delayed or missed doses

Time between two sequential infusions	Pertuzumab
<6 weeks	The 420mg dose of pertuzumab should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.
≥6 weeks	The 840mg loading dose of pertuzumab should be re-administered as a 60min infusion, followed by a maintenance dose of 420mg IV administered every 3 weeks thereafter.

Haematological:

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

Table 2: Dose modification for haematological toxicity

ANC ($x\ 10^9/L$)		Platelets ($x\ 10^9/L$)	Dose 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 3: 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 4: Dose modification of pertuzumab, trastuzumab, DOCEtaxel and CARBOplatin in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Pertuzumab	No dose reduction required for mild or moderate renal impairment. No dose recommendations for severe impairment due to limited data.	No specific dose recommendations. Has not been studied in patients with hepatic impairment.
Trastuzumab	No dose reduction required.	No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.
DOCEtaxel	No dose reduction necessary	**See Table 5 below**
CARBOplatin	• See note below[a]	No dose modification required.

[a]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.

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 trastuzumab may continue.
- In the event that AST and/or ALT and/or alkaline phosphatase levels are abnormal in the absence of relapse, the following dose modifications should apply (Table 5).
- 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 5: Dose Modification of DOCEtaxel based on hepatic dysfunction

AST / ALT Values	Alkaline Phosphatase Values	Dose Modification
≤ 1.5 x ULN	≤ 5 x ULN	No dose modification
> 1.5 x ULN to ≤2.5 x ULN	≤ 2.5 x ULN	No dose modification
> 2.5 x ULN to ≤5 x ULN	≤ 2.5 x ULN	Reduce dose of DOCEtaxel from 75 to 60mg/m^2
> 1.5 x ULN to ≤ 5 x ULN	> 2.5 x ULN to ≤ 5 x ULN	Reduce dose of DOCEtaxel from 75 to 60 mg/m^2
> 5 x ULN	> 5 x ULN	Dose delay by a maximum of 2weeks. If no recovery to the above figures, patient should go off chemotherapy.

Non-Haematological Toxicity:

Table 6: Dose modification of pertuzumab, trastuzumab, 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 and trastuzumab for at least 3 weeks. Pertuzumab and trastuzumab 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
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:

Pertuzumab: Minimal **(Refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**
DOCEtaxel: Low **(refer to local policy)**
CARBOplatin: High **(refer to local policy)**

PREMEDICATIONS:

Trastuzumab and pertuzumab: 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: 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.

- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. DOCEtaxel should only be administered when the neutrophil count is ≥ $1.5x10^9$cells/L.

Pertuzumab

- **Ventricular dysfunction (including congestive heart failure):** The incidence of symptomatic left ventricular systolic dysfunction (LVD) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy.
  Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy.
  Pertuzumab has not been studied in patients with: a pre-treatment LVEF value of < 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360mg/m^2 of DOXOrubicin or its equivalent.
  Assess LVEF prior to initiation of pertuzumab and at regular intervals during treatment with pertuzumab (e.g. every 12 weeks in the adjuvant 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 pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.
- **Infusion reactions, hypersensitivity reactions/anaphylaxis:** Pertuzumab has been associated with infusion and hypersensitivity reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of pertuzumab is recommended. If a significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.
  Pertuzumab must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity

reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome.

- **Diarrhoea:** Pertuzumab may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) may have a higher risk of diarrhoea compared with younger patients (< 65 years). 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 pertuzumab should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with pertuzumab may be reinstated.

Trastuzumab

- **Cardiac toxicity**:
  - Trastuzumab has been associated with moderate to severe cardiac failure. Baseline and 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - If LVEF drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be withheld and a repeat LVEF assessment carried out within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
  - Trastuzumab and anthracyclines should not be given concurrently in combination due to cardiotoxicity risk.
  - Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.
- **Administration-related reactions (ARRs):** Cases of ARRs have been reported with trastuzumab subcutaneous formulation. Patients should be observed for ARRs for 30 minutes after the first injection and for 15 minutes after subsequent injections. They can be treated with an analgesic/antipyretic such as paracetamol, or an antihistamine such as diphenhydramine. Pre-medication may be used to reduce risk of occurrence of ARRs. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR. Therefore, these patients should not be treated with trastuzumab.
- **Pulmonary events:** Severe pulmonary adverse reactions can occur in association with the use of trastuzumab and have been associated with a fatal outcome. These events may occur as part of an infusion-related reaction or with a delayed onset. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

DOCEtaxel:

- **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.
- **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.
- **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.

CARBOplatin:

- **Hypersensitivity:** 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.
- **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 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.
- 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	22/04/2022		Prof Maccon Keane
2	10/08/2023	Reviewed. Updated CARBOplatin infusion time, standard wording for renal dysfunction and and exclusions section for CARBOplatin. Updated emetogenic potential of pertuzumab.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.