Pertuzumab, Trastuzumab and DOCEtaxel Therapy - 21 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pertuzumab is indicated in combination with trastuzumab and 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	00204a	Pertuzumab-ODMS Feb 2014

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 trastuzumab and pertuzumab are administered.

Cycle 1: Pertuzumab and trastuzumab loading doses

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1 or 2	1	Pertuzumab	840mg	IV Observe for 1hr post infusion	250ml 0.9% sodium chloride over 60min
2 or 1	1	Trastuzumab	8mg/kg	IV infusion Observe post infusion[a]	250ml 0.9% sodium chloride over 90min
3	1	DOCEtaxel[b]	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min[c]
[a]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. 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 Use non-PVC equipment					

Cycles 2 and subsequent cycles

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60mins post infusion[c]	250ml 0.9% sodium chloride over 30min if no adverse reactions[d]	Every 21 days
2 or 1	1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[a]	250ml 0.9% sodium chloride over 30 min	Every 21 days
3	1	DOCEtaxel	[e]75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min[b]	Every 21 days for a minimum of 6 cycles
[a]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.						
[b]75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag Use non-PVC equipment						
[c]Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.						
[d]The infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant						
[e]The dose of DOCEtaxel may be escalated to 100 mg/m^2 on subsequent cycles if the initial dose is well tolerated.						
Trastuzumab is incompatible with glucose solution						

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, DOCEtaxel, 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
- Lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, 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
- **Pertuzumab and trastuzumab**
  - None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs.
  - Discontinue pertuzumab if trastuzumab is discontinued.
  - Patient may continue to receive both pertuzumab and trastuzumab if DOCEtaxel is discontinued due to toxicity or after 6-8 cycles and without evidence of disease progression.
- Delayed or missed doses
  - If the time between two sequential infusions is < 6 weeks, the 420 mg dose of pertuzumab should be administered as soon as possible without regard to the next planned dose.
  - Re-load pertuzumab if the time between two sequential infusions is > 6 weeks or more.
  - Re-load trastuzumab if the time between two sequential infusions is > 6 weeks.
  - If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1.
  - The next cycle should follow 21 days from the re-loading dose.

Renal and Hepatic Impairment:

Table 1: Dose modification 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 required	See Table 2 below

Table 2: Dose modification of DOCEtaxel in hepatic impairment.

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

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Pertuzumab and Trastuzumab		
LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value.		Withhold treatment with pertuzumab and trastuzumab. 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 **DOCEtaxel** 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** Low **(Refer to local policy)**
- **Trastuzumab** 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 (5,6)*
- **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

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.

Reference:

- ***NCCP Regimen 00203 Docetaxel Monotherapy 75mg/m^2-21 day cycle***
- ***NCCP Regimen 00200 Trastuzumab Monotherapy -21 day cycle***

for detailed information on adverse effects/regimen specific complications.

DRUG INTERACTIONS:

- 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.
- 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 (7).
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Pertuzumab	-	L01XC13
DOCEtaxel	-	L01CD02
Trastuzumab	-	L01XC03

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Version	Date	Amendment	Approved By
1	18/02/2014		Prof Bryan Hennessy
2	30/05/2015	Modification of premedication regimen	Prof Maccon Keane
3	23/06/2016	Modification to allow for substitution of PACLItaxel for DOCEtaxel where patients are intolerant, have had significant toxicity or are deemed clinically unsuitable for DOCEtaxel.	Prof Maccon Keane
4	09/10/2017	Clarified use of G-CSF and updated administration details.	Prof Maccon Keane
5	18/10/2018	Updated order of administration on treatment table	Prof Maccon Keane
6	13/02/2019	Updated recommendation on number of cycles of DOCEtaxel	Prof Maccon Keane

7	02/05/2019	Updated trastuzumab and pertuzumab infusion time from cycle 2 onwards. Updated emetogenic potential	Prof Maccon Keane
8	10/11/2020	Reviewed	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.