NCCP Chemotherapy Regimen

Pertuzumab and Trastuzumab and DOCEtaxel Therapy - 21 day cycle

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td>00204a</td>
<td>Pertuzumab-ODMS Feb 2014</td>
</tr>
</tbody>
</table>

If a reimbursement indicator (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not gone have not been assessed through the formal HSE reimbursement process.

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 patient's 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

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pertuzumab</td>
<td>840mg</td>
<td>IV Observe for 1hr post infusion</td>
<td>250ml 0.9% sodium chloride over 60min</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Trastuzumab</td>
<td>8mg/kg</td>
<td>IV infusion Observe post infusion³</td>
<td>250ml 0.9% sodium chloride over 90min</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>DOCEtaxel⁵</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>'250ml 0.9% sodium chloride or 5% glucose over 60min</td>
</tr>
</tbody>
</table>

³Recommended 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.

⁵Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications)
Cycles 2 and subsequent cycles

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pertuzumab</td>
<td>420mg</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 60min. Reduce to 30 mins on subsequent doses if no adverse reactions.</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 60min</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>DOCEtaxel</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride or 5% glucose over 60min</td>
<td>Every 21 days up to maximum of 8 cycles</td>
</tr>
</tbody>
</table>

ELIGIBILITY:
- Indications as above
- HER2 positive as demonstrated by a validated test method
- Life expectancy > 3 months
- 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 10⁹/L
- Pregnancy
- Lactation

Please see Protocol 00226a for further details on dose modifications and adverse events associated with PACLItaxel

NCCP Regimen: Pertuzumab Trastuzumab and DOCEtaxel Therapy– 21 day cycle
Published: 30/05/2015
Review: 09/10/2019
Version number: 4

Tumour Group: Breast
NCCP Regimen Code: 00204
ISMO Contributor: Prof Bryan Hennessy, Prof Maccon Keane
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**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.
  - 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 3: Dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>No dose reduction required for mild or moderate renal impairment. No dose recommendations for severe impairment due to limited data.</td>
<td>No specific dose recommendations. Has not been studied in patients with hepatic impairment.</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>No dose reduction required.</td>
<td>No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.</td>
</tr>
<tr>
<td>DOCETaxel</td>
<td>No dose reduction required.</td>
<td>See Table 3 below</td>
</tr>
</tbody>
</table>

Table 4: Dose modification of DOCETaxel in hepatic impairment.

<table>
<thead>
<tr>
<th>Alkaline Phosphatase</th>
<th>AST and/or ALT</th>
<th>Serum Bilirubin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.5 ULN</td>
<td>and</td>
<td></td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>&gt; 6 ULN</td>
<td>and/or</td>
<td>&gt; 3.5 ULN (AST and ALT)</td>
<td>Stop treatment unless strictly indicated and should be discussed with a Consultant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; ULN</td>
<td></td>
</tr>
</tbody>
</table>

Management of adverse events:

Table 5: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab and Trastuzumab</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>LVEF &lt; 40% or 40-45% associated with ≥10% points below the pretreatment value.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>NCI-CTCAE Grade 4 hypersensitivity reactions</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>DOCETaxel</td>
<td></td>
<td>Decrease dose of DOCETaxel to 60mg/m². If the patient continues to experience these reactions at 60 mg/m², treatment with docetaxel should be discontinued</td>
</tr>
<tr>
<td>Grade &gt;2 peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 skin reaction</td>
<td></td>
<td>Docetaxel will be reduced from 75 to 60 mg/m².</td>
</tr>
<tr>
<td>Grade ≥3 stomatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: 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 (2,3)**
- **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 Protocol 00203 Docetaxel Monotherapy 75mg/m²-21 day cycle,
NCCP Protocol 00200 Trastuzumab Monotherapy -21 day cycle and
NCCP Protocol 00261 Carboplatin Monotherapy
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:

<table>
<thead>
<tr>
<th></th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>L01XC13</td>
</tr>
<tr>
<td>DOCEtaxel</td>
<td>L01CD02</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>L01XC03</td>
</tr>
</tbody>
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REFERENCES:


Version| Date| Amendment| Approved By
---|---|---|---
1| 18/02/2014| Modification of premedication regimen| Prof Bryan Hennessy
2| 30/05/2015| 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
3| 23/06/2016| Clarified use of G-SCF and updated administration details. | Prof Maccon Keane
4| 09/10/2017| | Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
NCCP Chemotherapy Regimen

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfomedonc/cdmp/

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