Pertuzumab + Trastuzumab + DOCEtaxel

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</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>C50</td>
<td>00204a</td>
</tr>
</tbody>
</table>

ELIGIBILITY:

- Indications as above.
- HER-2-positive tumour status, defined as a score of 3+ by immuno- histochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test.
- Life expectancy > 3months.
- ECOG status 0-1.
- LVEF > 50%

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months).
- Severe liver impairment.
- Baseline neutrophil count < 1,500 cells/mm³.
- 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 or lactation.
- Hypersensitivity to pertuzumab, trastuzumab, DOCEtaxel or any of the excipients.

TESTS:

Baseline tests: FBC, U&Es, LFTs.
Cardiac function every 3 months (LVEF using ECHO or MUGA scan).
Regular tests: FBC, U&Es, LFTs prior to each cycle. Cardiac function every 3 cycles or as clinically indicated. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

Disease monitoring/assessment:
Disease monitoring/assessment should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

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.

Due to the potential for hypersensitivity reactions pertuzumab is administered on day 1, trastuzumab on day 2 and DOCEtaxel on day 2 for cycle 1 only.

**Cycle 1: Pertuzumab (day 1) and trastuzumab (day 2) loading doses**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<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>Trastuzumab</td>
<td>8mg/kg</td>
<td>IV infusion Observe post infusion*</td>
<td>250ml 0.9% sodium chloride over 90min</td>
</tr>
<tr>
<td>2</td>
<td>DOCEtaxel</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride or 5% glucose over 60min</td>
</tr>
</tbody>
</table>

From cycle 2 onwards, all drugs may be administered on the same day if cycle 1 is tolerated. Pertuzumab and trastuzumab should be administered sequentially (in any order) first, followed by DOCEtaxel on the same day.
Cycle 2 and subsequent cycles:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>420mg</td>
<td>IV infusion</td>
<td>Observe for 30-60mins post infusion&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 and further cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250ml 0.9% sodium chloride over 60min. Reduce to 30 mins on subsequent doses if no adverse reactions.</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV infusion</td>
<td>Observe post infusion&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2 and further cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250ml 0.9% sodium chloride over 60min. Reduce to 30 mins on subsequent doses if no adverse reactions.</td>
<td></td>
</tr>
<tr>
<td>DOCEtaxel&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 60min.</td>
<td>2 up to max cycle 8</td>
</tr>
</tbody>
</table>

<sup>a</sup>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.

<sup>b</sup>75-185 mg dose use 250mL infusion bag. For doses > 185mg use 500mL infusion bag Use non-PVC equipment.

<sup>c</sup>Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.

<sup>d</sup>The dose of DOCEtaxel may be escalated to 100 mg/m<sup>2</sup> on subsequent cycles if the initial dose is well tolerated.

<sup>e</sup>Where patients are intolerant of, have had significant toxicity to or are deemed clinically unsuitable for DOCEtaxel, PACLItaxel may be substituted at a dose of 80mg/m2 weekly until progression or unacceptable toxicity. Consideration may be given to discontinuing treatment with PACLItaxel in patients who are progression-free at 6 months at the discretion of the treating clinician. Trastuzumab and pertuzumab should be continued to progression of disease. Please see Protocol 00226a for further details on dose modifications and adverse events associated with PACLItaxel.

** Trastuzumab is incompatible with glucose solution

**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.
  - Weight monitored at each visit and dose adjusted accordingly.
  - Discontinue pertuzumab if trastuzumab is discontinued.
o 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
  o 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.
  o Re-load pertuzumab if the time between two sequential infusions is > 6 weeks or more.
  o Re-load trastuzumab if the time between two sequential infusions is > 6 weeks.
  o If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1.
  o The next cycle should follow 21 days from the re-loading dose.

DOCEtaxel
Hepatic Dysfunction:

<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></td>
<td></td>
<td></td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>&gt; 2.5 ULN</td>
<td>&gt; 1.5 ULN</td>
<td></td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>&gt; 6 ULN</td>
<td>&gt; 3.5 ULN (AST and ALT)</td>
<td>&gt; ULN</td>
<td>Stop treatment unless the benefits are judged to outweigh the risks after discussion with a consultant.</td>
</tr>
</tbody>
</table>

Table 1: 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>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>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 40% or 40-45% associated with ≥10% points below the pretreatment value.</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>
<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>
</tbody>
</table>

DOCEtaxel

Grade 3 skin reaction
Reduce dose from 100 mg/m² to 75 mg/m² and/or from 75 mg/m² to 60mg/m²

Grade >2 peripheral neuropathy

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer). This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoprotocols](http://www.hse.ie/NCCPchemoprotocols).
Grade 3 or 4 stomatitis | Decrease dose to 60 mg/m²

**SUPPORTIVE CARE:**
**EMETOGENIC POTENTIAL:** Low. Refer to local policy

**PREMEDICATIONS:**
- Not usually required for pertuzumab and trastuzumab 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.
- For DOCEtaxel dexamethasone 8 mg PO should be administered 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 (1,2).*

**TAKE HOME MEDICATIONS:**
None usually required.

**OTHER SUPPORTIVE CARE:**
Not usually required.

**ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS**
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac toxicity:**
  - Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab. However, pertuzumab does not seem to further increase the incidence of symptomatic congestive heart failure or...
decreased LVEF when used in combination with trastuzumab and DOCEtaxel.

- 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.

- Pertuzumab and trastuzumab should be withheld for at least 3 weeks for any of the following:
  - signs and symptoms suggestive of congestive heart failure (pertuzumab should be discontinued if symptomatic heart failure is confirmed).
  - a drop in left ventricular ejection fraction (LVEF) to less than 40%.
  - a LVEF of 40%-45% associated with a fall of ≥ 10% points below pretreatment values.

Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with < 10% points below pretreatment value. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

- The half-life of trastuzumab is approximately 4-5 weeks

- **Pertuzumab or trastuzumab infusion-associated symptoms**, usually chills and fever may occur. Stop infusion and consider antihistamine cover. When symptoms have resolved the infusion may be recommenced. For serious reactions, discontinue the trastuzumab or pertuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.

- **Pulmonary events**: Severe pulmonary adverse reactions 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.

- **Fluid Retention**: Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention with DOCEtaxel. It can also reduce the severity of the hypersensitivity reaction.

- **DOCEtaxel 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).*
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Patients treated with pertuzumab, trastuzumab and DOCEtaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and DOCEtaxel, especially during the first 3 cycles of treatment. The higher incidence of febrile neutropenia in pertuzumab treated patients may also be associated with higher incidence of mucositis and diarrhoea. Asian patients may be at higher risk of *febrile neutropenia* than general population when pertuzumab is used with chemotherapy.
- Patients may continue pertuzumab and trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression but should be carefully monitored for complications of neutropenia. DOCEtaxel should be administered when the neutrophil count is > 1500cells/mm³.
- **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.

**DRUG INTERACTIONS:**
- A possible interaction with warfarin and trastuzumab 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 (3).
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
Pertuzumab - L01XC13
Trastuzumab - L01XC03
DOCETaxel - L01CD02

REIMBURSEMENT CATEGORY:
Pertuzumab is available for use in public hospitals and is currently available for reimbursement through the Oncology Hospital Drugs Management System (February 2014). Trastuzumab and DOCETaxel are funded through local hospital budgets (Nov. 2013).

PRESCRIPTIVE AUTHORITY:
Medical Oncologist

REFERENCES:


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18/02/2014</td>
<td>Modification of premedication regimen</td>
<td>Prof Bryan Hennessy</td>
</tr>
<tr>
<td>2</td>
<td>30/05/2015</td>
<td>Modification to allow for substitution of PACLItaxel for DOCEtaxel where patients are intolerant, have had significant toxicity or are deemed clinically unsuitable for DOCEtaxel.</td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>23/06/2016</td>
<td></td>
<td>Dr Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie