PERTUZUMAB in Advanced or Metastatic Breast Cancer

Indication: First line treatment of locally advanced or metastatic breast cancer

NCDF criteria to be met:
- Locally advanced or metastatic breast cancer
- HER2 3+ or FISH positive
- PS 0 or 1
- Prior adjuvant HER2 therapy completed more than 12 months prior to metastatic diagnosis
- No prior treatment with chemotherapy or HER2 therapy for metastatic disease
- To be given as first line treatment in combination with docetaxel and trastuzumab

NOTE: not to be used beyond first disease progression

Cancer drug fund application and approval is required before starting treatment.

Regimen details: 3-weekly regimen

Loading dose: Pertuzumab  840mg  IV  D1  cycle 1
Maintenance dose: Pertuzumab  420mg  IV  D1  cycle 2 onwards

Dose modifications are not recommended.

Pertuzumab is given in combination with trastuzumab and docetaxel; docetaxel should be given for 6 cycles (see separate protocol); pertuzumab and trastuzumab may be continued until progressive disease. If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

Due to the potential for hypersensitivity reactions: for cycle 1 only, give pertuzumab on day 1, trastuzumab on day 2 and docetaxel on day 3.
From cycle 2 onwards, administer pertuzumab and trastuzumab sequentially (in any order) first, followed by docetaxel on day 1.

See separate protocol for trastuzumab in the metastatic setting for details of doses, monitoring and ongoing treatment.

See separate protocol for docetaxel in the metastatic setting for details of doses, monitoring and ongoing treatment.

Missed doses: If the time between two sequential infusions is less than 6 weeks, the 420mg dose should be given as soon as possible.

If the time between two sequential infusions is greater than 6 weeks, the patient should receive a re-loading dose of 840mg given over 60 minutes.

Administration: Pertuzumab in 250ml sodium chloride 0.9% infuse over 30-60 minutes

Frequency: 3-weekly cycle until disease progression or unacceptable toxicity
Anti-emetics: Low emetogenicity  
Follow local anti-emetic policy

Regular investigations:  
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>FBC</td>
<td>Baseline and every 3 cycles</td>
</tr>
<tr>
<td>LFTs</td>
<td>Baseline and every 3 cycles</td>
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<tr>
<td>U&amp;Es</td>
<td>Baseline and every 3 cycles</td>
</tr>
<tr>
<td>MUGA/ ECHO, LVEF</td>
<td>Baseline and every 3 cycles</td>
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(see monitoring of toxicities section - cardiac function assessment)  
NOTE: see additional investigations required when co-administered with docetaxel and trastuzumab – see separate protocols

Supportive medication: Hydrocortisone, chlorphenamine and paracetamol can be given for chills / fever / rigor during the infusion if required.

Extravasation: Non vesicant

Toxicities:  
Infusion related symptoms (mild to moderate in severity, occur mainly with first dose): pyrexia, chills, headache, asthenia, hypersensitivity/anaphylaxis and vomiting.

Infusion related symptoms (subsequent cycles): fatigue, dysgeusia, hypersensitivity/anaphylaxis, myalgia.

As pertuzumab is given with trastuzumab and docetaxel, it is difficult to ascertain a causal relationship to a particular medicinal product (see separate protocol for trastuzumab and docetaxel): upper respiratory tract infection, neutropenia including febrile neutropenia, anaemia, insomnia, peripheral neuropathy, increased lacrimation, stomatitis, dyspepsia, alopecia, nail disorder, dry skin and pruritis, arthralgia, pleural effusion, interstitial lung disease (uncommon).

Common events (≥10%) reported in pertuzumab monotherapy patients: headache, decreased appetite, dyspnoea, cough, diarrhoea, vomiting, nausea, constipation, rash, pain, oedema, fatigue, asthenia, cardiotoxicity.

Infusion related reactions

Pertuzumab has been associated with infusion and hypersensitivity reactions. Close observation during and for 60 minutes after the first infusion, and during and for 30-60 minutes for subsequent infusions is recommended prior to starting the next agent.

If infusion-related symptoms such as fever and chills occur, the infusion should be slowed down or interrupted and the necessary supportive medication (see above) should be administered.

For more severe infusion-related symptoms, discontinue the infusion immediately and follow the local anaphylaxis policy.

Cardiotoxicity

A baseline left ventricular ejection fraction (LVEF) above the lower limit of normal (> 50%) is required for the treatment to go ahead (measured on echocardiography or multiple gated acquisition, ECHO or MUGA).

Cardiac monitoring is carried out at baseline and every three cycles during treatment.
**Guideline for stopping treatment in the event of reduced cardiac function**

Discuss with the consultant:
If LVEF is <40%, or 40-45% and associated with ≥10% ejection points from baseline pertuzumab and trastuzumab should be withheld and a repeat LVEF should be performed in 3 weeks. If there is no improvement discuss with consultant and seek cardiology opinion. Discuss with consultant before re-starting.

**Haematological Toxicity**

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.

Patients may continue pertuzumab and trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression but should be carefully monitored for complications of neutropenia.

After discontinuing docetaxel, it is recommended to perform full blood count at the same time as cardiac monitoring (every 3 cycles).

**Renal Impairment**

Dose adjustments are not needed in patients with mild or moderate renal impairment.

It is recommended to perform renal function tests at the same time as the cardiac monitoring (every 3 cycles)

**Hepatic Impairment**

The safety and efficacy of pertuzumab has not been studied in patients with hepatic impairment.

It is recommended to perform liver function tests at the same time as the cardiac monitoring (every 3 cycles)

**References:**

