PERTUZUMAB IV & TRASTUZUMAB (ONTRUZANT) IV

a) First-line use, in combination with docetaxel, for HER2 +ve locally advanced or metastatic breast cancer

*Blueteq registration is required before starting treatment with pertuzumab for advanced disease*

b) Neo-adjuvant treatment of HER2 +ve early stage breast cancer at high risk of recurrence (T2-T4b and/or node +ve disease), when used in combination with taxane-containing chemotherapy for early stage breast cancer (i.e. EC-taxane regimens or docetaxel-carboplatin)

c) Adjuvant use for HER2 +ve early stage breast cancer, when used in combination with taxane-containing chemotherapy for early stage breast cancer (i.e. EC-taxane regimens or docetaxel-carboplatin), in patients with lymph node positive disease only

*N.B. Blueteq registration is required before starting treatment with neo-adjuvant pertuzumab, and before starting treatment with adjuvant pertuzumab*

Drugs / Dosage / Administration:

**Loading doses:**
- Paracetamol 1000 mg pre-med 30 minutes before treatment starts
- **Pertuzumab** 840mg in 250ml sodium chloride 0.9% IV over 60 minutes
  - observe for 60 minutes, then:
- **Trastuzumab (Ontruzant)** 8 mg/kg in 250ml sodium chloride 0.9% IV over 90 minutes

**Maintenance Doses:** starting 3 weeks after loading doses, and if loading dose tolerated:
- Pre-medication not routinely needed.
- **Pertuzumab** 420 mg in 250ml sodium chloride 0.9% IV over 30 minutes,
  - observe for 30 minutes, then:
- **Trastuzumab (Ontruzant)** 6 mg/kg in 250ml sodium chloride 0.9% IV over 30 minutes,

Pertuzumab, trastuzumab and taxane may be given in any order, but the preferred order is as above, followed by the taxane.

For Cycle 1 only, give pertuzumab and trastuzumab on Day 1 and give the taxane (+/- carboplatin) on Day 2.

For subsequent cycles, administer the pertuzumab and trastuzumab first, then a short saline flush, followed by the taxane (+/- carboplatin).

Pertuzumab infusion should be slowed or interrupted in the event of an infusion reaction. The guidelines for chemotherapy allergic reactions should be followed. The infusion may be resumed when symptoms resolve. Pertuzumab should be permanently discontinued in the event of a Grade 4 reaction.

Patients should be observed for 6 hours after the start of the first trastuzumab infusion (i.e. 4½ hours post-infusion), and for 30 minutes post-infusion for subsequent doses.

If a decision is made to allow the patient to leave in advance of these times, they must be counselled about the possibility of delayed infusion-related symptoms and instructed to contact the hospital in the event of these occurring.

NB. Trastuzumab infusion-related and pulmonary symptoms may rarely occur more than 6 hours after the start of a trastuzumab infusion. Patients should be warned about this and instructed to contact the hospital if any such symptoms occur.
Re-loading: If the interval between doses is ≥ 6 weeks, a re-loading dose of pertuzumab is required. If the interval between doses is more than 4 weeks, a re-loading dose of trastuzumab is usually required. However, if the delay was due to cardiac toxicity, the doctor may choose not to re-load the patient.

Frequency: Every 3 weeks

**Advanced setting:** administer pertuzumab and trastuzumab until disease progression (docetaxel usually administered with the first 6 cycles)
At each clinical review, note that all pertuzumab and trastuzumab doses are to be prescribed and confirmed up until the next clinical review is due.

**Neo-adjuvant setting:** Up to 4 doses of pertuzumab and trastuzumab IV, with the taxane cycles of EC - taxane regimens.
Up to 6 doses of pertuzumab and trastuzumab IV with docetaxel and carboplatin

**Adjuvant setting:** patients with node positive disease have the option to access pertuzumab and trastuzumab IV, to complete a total of 18 doses (including any neo-adjuvant doses)
Clinical review pre Doses 7 and 13 (once corresponding LVEF result available)

*N.B. patients with node negative disease should be treated with adjuvant trastuzumab monotherapy (usually s/c), to complete a total of 18 trastuzumab doses (including any neo-adjuvant doses).*

Main Toxicities: infusion-related symptoms (usually mild to moderate): e.g. fever; chills; headache; nausea; vomiting; asthenia (due to either agent, and occur mainly with 1st dose); cardiotoxicity (see below)

Antiemetics: mildly emetogenic

Extravasation: non-vesicants

Regular Investigations: FBC, U&Es & LFTs baseline, at 4 and 8 months; then 6 monthly in advanced setting
Echo*/MUGA scan baseline; at 4 and 8 months; then 6 monthly in advanced setting
Patients who develop asymptomatic cardiac dysfunction will require more frequent monitoring e.g. every 6–8 weeks.

Blood pressure**

**baseline, at 4 and 8 months; then 6 monthly in advanced setting

* An echocardiogram is the preferred test, but whichever test is used initially for an individual, should ideally be used throughout

** If blood pressure ≥ 140/90 mmHg, a diagnosis of hypertension needs to be confirmed by asking patient to visit GP for ambulatory or home blood pressure monitoring.

Patients with a confirmed diagnosis of hypertension should be treated with an ACE inhibitor which is also licensed for the treatment of heart failure e.g. ramipril.

Comments:

Neo-adjuvant setting: baseline LVEF ≥ 55%
Adjuvant setting: baseline LVEF > 50%
Advanced setting: baseline LVEF > 50%

Caution should be exercised in treating patients who present with a history of hypertension, coronary artery disease or cardiac arrhythmia. Patients who have received prior anthracycline or prior radiotherapy to the chest area may be at higher risk of LVEF declines.
Dose Modifications: No reductions in the dose of pertuzumab or trastuzumab were made during clinical trials. Patients may continue pertuzumab and trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression.

Cardiotoxicity: Neo-adjuvant and adjuvant use in early stage breast cancer:

In line with the national guidance for trastuzumab¹, and for consistency of management of HER2-induced cardiotoxicity, see table below for indications for interruption of pertuzumab and trastuzumab, initiation of ACE inhibitor therapy, referral to cardiologist and increased monitoring:

<table>
<thead>
<tr>
<th>LVEF</th>
<th>Signs or symptoms</th>
<th>Trastuzumab + Pertuzumab</th>
<th>Start ACE inhibitor</th>
<th>Cardiology referral</th>
<th>Additional monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≥ 50% and &lt; 10 EF points decrease from baseline</td>
<td>None</td>
<td>Continue</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>LVEF 41 – 49% or ≥ 10 EF points decrease from baseline (even if still &gt; 50%)</td>
<td>None</td>
<td>Continue (if in doubt, check with Consultant)</td>
<td>Yes*</td>
<td>*Refer if already on ACEI</td>
<td>After 6-8 weeks</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>Any</td>
<td>Stop</td>
<td>Yes</td>
<td>Refer</td>
<td>Within 6-8 weeks*</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>Stop</td>
<td>Yes</td>
<td>Refer</td>
<td>Within 6-8 weeks*</td>
</tr>
</tbody>
</table>

*Trastuzumab and pertuzumab may be re-initiated if LVEF recovers to > 50%.

Advanced breast cancer:

The above table may be followed, however if in doubt, discuss with Consultant; there may be occasions where the benefits for the individual patient of continuing with trastuzumab and pertuzumab are deemed to outweigh the risks.

Schneeweiss, A et al; Ann Oncol 2013; 24 (9): 2278 – 2284 (neo-adjuvant)
¹Jones, AL et al; Br J Cancer 2009; 100: 684 – 692
Von Minckwitz, G et al; NEJM 2017; 377: 122 – 131 (adjuvant)