EC DOCETAXEL PERTUZUMAB (Perjeta) TRASTUZUMAB IV (adjuvant)

INDICATION (ICD10) C50
Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)
Pertuzumab in combination with intravenous trastuzumab and chemotherapy as adjuvant therapy for axillary node positive HER2-positive early breast cancer and with NO preceding neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab (PER3) where the following criteria have been met:
2. Histologically documented breast cancer which is HER2 3+ by immunohistochemistry and/or has a ratio of ≥2.0 by in situ hybridisation.
3. Early breast cancer and this has been adequately excised.
4. Pathologically confirmed axillary lymph node involvement. Pertuzumab in combination with trastuzumab as adjuvant treatment is only NICE-recommended and commissioned in patients with pathologically documented axillary lymph node involvement.
5. Due to commence adjuvant chemotherapy in combination with pertuzumab and trastuzumab and will receive one of the standard adjuvant anthracycline- and/or taxane-based chemotherapy regimens as set out in pertuzumab’s Summary of Product Characteristics.
6. 3-4 cycles of EC followed by 3-4 cycles of docetaxel (or 12 cycles of weekly paclitaxel). If a patient has a severe allergic reaction to the docetaxel part of the treatment combination, the patient can be switched to a trial of weekly paclitaxel. Pertuzumab and trastuzumab should commence with the first taxane cycle. Pertuzumab and trastuzumab are not commissioned in combination with other adjuvant chemotherapy regimens.
7. A maximum of 18 cycles of pertuzumab plus trastuzumab will be administered as adjuvant treatment.
8. The trastuzumab will be given intravenously and that best value intravenous trastuzumab is being used. Subcutaneous trastuzumab is not commissioned in combination with pertuzumab.
9. ECOG performance status of 0 or 1.
10. The pre-treatment left ventricular ejection fraction was ≥55% and if anthracyclines were given that the LVEF was ≥50% after completion of the anthracycline component of the adjuvant chemotherapy.
11. Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle
12. Pertuzumab will be otherwise used as set out in its Summary of Product Characteristics
REGIMEN

Cycles 4 to 21 drugs can be given in any order or any day ie 1 or 2 (but wait 30 minutes after pertuzumab before administering other SACT agents)

Cycles 1 to 3
Day 1 EPIRUBICIN 100mg/m² IV bolus
    CYCLOPHOSPHAMIDE 500mg/m² IV bolus

Cycle 4
Day 1 TRASTUZUMAB 8mg/kg in 250ml sodium chloride 0.9% IV infusion
Day 2 PERTUZUMAB 840mg in 250ml sodium chloride 0.9% IV infusion
    Premedication: Dexamethasone 8mg BD starting 24 hours before chemotherapy (or 20mg IV on day of chemotherapy) and 8mg bd post-chemotherapy for 2 days
    DOCETAXEL 75mg/m² in 250ml sodium chloride 0.9% IV infusion over 60 minutes

Cycles 5 to 7
Day 1 TRASTUZUMAB 6mg/kg in 250ml sodium chloride 0.9% IV infusion
    PERTUZUMAB 420mg in 250ml sodium chloride 0.9% IV infusion
    Premedication: Dexamethasone 8mg BD starting 24 hours before chemotherapy (or 20mg IV on day of chemotherapy) and 8mg bd post-chemotherapy for 2 days
    DOCETAXEL 75mg/m² in 250ml sodium chloride 0.9% IV infusion over 60 minutes

Cycles 8 to 21
Day 1 TRASTUZUMAB 6mg/kg in 250ml sodium chloride 0.9% IV infusion
    PERTUZUMAB 420mg in 250ml sodium chloride 0.9% IV infusion

NB Trastuzumab SPC states patients need to be monitored for 6 hours after the start of the first dose and 2 hours after the start of subsequent doses.

Cycle 1 - administer trastuzumab over 90 minutes. Monitor for 3.5 hours post start of infusion (2 hours after completion) of the first dose.
Subsequent cycles - if the initial loading dose was well tolerated (no signs of hypersensitivity), the 2nd dose can be administered as a 30 minute infusion (otherwise to continue to be administered over 90 minutes), and subsequent infusions can be administered over 30 minutes.
If the first cycle was well tolerated, following the 2nd and 3rd cycles patients should be observed on the ward / day unit for 30 minutes after the completion of trastuzumab infusion.
If the 2nd and 3rd cycles were well tolerated, after the 4th and subsequent cycles patients do not need to be observed following completion of trastuzumab infusion.

Patients should be warned of the possibility of delayed reactions and instructed to seek medical advice immediately should this occur.

CYCLE FREQUENCY AND NUMBER OF CYCLES
Combination every 21 days for 7 cycles
Pertuzumab and trastuzumab IV every 21 days from cycle 8 up to cycle 21

ANTI-EMETICS
High risk day 1 cycles 1 to 3
Low risk day 1 cycles 4 to 7
Minimal risk day 1 cycles 8 to 21
CONCURRENT MEDICATION REQUIRED

<table>
<thead>
<tr>
<th>Medication</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Ensure premedication given before docetaxel. This can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Loperamide prn every docetaxel cycle</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.</td>
</tr>
<tr>
<td>GCSF</td>
<td>GCSF for 7 days starting at least 24 hours after chemotherapy</td>
</tr>
</tbody>
</table>

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cyclophosphamide – neutral
Docetaxel – exfoliant
Epirubicin – vesicant
Pertuzumab - neutral
Trastuzumab - neutral

Filters not required
Central line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle cycles 1 to 7 FBC every 3 months cycles 7 to 21

- Neutrophils x 10⁹/L ≥1.5 (<1.5 on the day of chemo go ahead with GCSF support as per local policy, no chemo dose reductions).
- <0.8 wait until neutrophils ≥ 0.8.
- Platelets x 10⁹/L ≥100

Baseline weight and every cycle for cycles 1 to 7, then 3 monthly weight.
Monitor cardiac function according to network guidelines

MAIN TOXICITIES AND ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Toxicities / Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>may irritate bladder, drink copious volumes of water.</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Cardiotoxicity – monitor cardiac function. Epirubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Cutaneous reactions, peripheral neuropathy or fluid retention, hypersensitivity reactions</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Cardiotoxicity - monitor cardiac function. Trastuzumab infusion related chills and/or fevers are commonly observed during the first infusion (but infrequently with subsequent infusions). Other symptoms may include nausea, hypertension, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. Some adverse reactions to trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, supraventricular tachycardia, reduced oxygen saturation and respiratory distress can be serious and potentially fatal. If symptoms of back ache, nausea or vomiting, do a set of obs. Give hydrocortisone 100mg IV, chlorphenamine 10mg IV.</td>
</tr>
</tbody>
</table>
INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

<table>
<thead>
<tr>
<th>Interacting Agent</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Cytochrome P450 enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, St Johns Wort, corticosteroids): may increase active cyclophosphamide metabolites. Allopurinol, Cimetidine and protease inhibitors: may increase active metabolites. Aprepitant, Ciprofloxacin, Fluconazole, Itraconazole: may reduce activation of cyclophosphamide and alter the effectiveness of treatment. Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS
Delay more than 6 weeks since last dose
The 840 mg loading dose of pertuzumab should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered every 3 weeks thereafter.
The loading dose of 8 mg/kg of trastuzumab IV should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered every 3 weeks thereafter.

Epirubicin maximum lifetime dose
= 650mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 1000mg/m² (with normal cardiac function)

Haematological
Previous neutropenic sepsis, Symptoms including diarrhoea, mucositis and leucopenia, discuss with Registrar or Consultant

Docetaxel
In patients who experienced either febrile neutropenia, neutrophil count <0.5x10⁹/L for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Pertuzumab
Dose reductions are not recommended for Pertuzumab. Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. If trastuzumab treatment is discontinued, treatment with Pertuzumab should be discontinued.

Trastuzumab
No dose reduction or cessation of Trastuzumab is required if patient has acute reversible neutropenia.
Non-haematological
Docetaxel
Discuss dose reductions if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.

Trastuzumab and pertuzumab
Continuation and discontinuation of pertuzumab and trastuzumab based on interval LVEF assessment as per network guidelines

### Hepatic impairment

**Docetaxel**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST &gt;1.5xULN and ALP &gt;2.5xULN</td>
<td>SPC contains dose recommendations for 100mg/m² only therefore Clinician discretion</td>
</tr>
<tr>
<td>Bilirubin &gt;ULN and ALT and AST &gt;3.5 x ULN with ALP &gt;6 x ULN</td>
<td>should not be used unless strictly indicated.</td>
</tr>
</tbody>
</table>

**Epirubicin**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin 24-50micromol/L</td>
<td>give 50% dose</td>
</tr>
<tr>
<td>Bilirubin 51-85micromol/L</td>
<td>give 25% dose</td>
</tr>
<tr>
<td>Bilirubin &gt;85micromol/L</td>
<td>omit</td>
</tr>
</tbody>
</table>

### Renal impairment

**Cyclophosphamide**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt;20ml/min</td>
<td>give 100% dose</td>
</tr>
<tr>
<td>GFR 10-20ml/min</td>
<td>give 75% dose</td>
</tr>
<tr>
<td>GFR &lt;10ml/min</td>
<td>give 50% dose</td>
</tr>
</tbody>
</table>

**Epirubicin**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR severe renal impairment (GFR &lt;30ml/min)</td>
<td>Dose reduce</td>
</tr>
</tbody>
</table>

### REFERENCES

2. APHINITY Trial NEJM 2017: 377:122-131