

## EC DOCETAXEL PERTUZUMAB / TRASTUZUMAB (Phesgo) SC (neoadjuvant node negative or unknown nodal status)

### 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/](http://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)) (PER2b)

1. Neoadjuvant pertuzumab in patients who are HER2 3+ NODE NEGATIVE or of UNKNOWN NODAL STATUS for previously untreated neoadjuvant treatment of locally advanced, inflammatory or early breast cancer at high risk of recurrence (stage T2-T4b and M0 disease) in combination with taxane chemotherapy. (TA424)

### REGIMEN

Cycles 4 to 7 drugs can be given on any day ie 1 or 2. When given in combination with a taxane on the same day the pertuzumab and trastuzumab should be administered 30 minutes before the taxane.

#### Cycles 1 to 3

Day 1 EPIRUBICIN 100mg/m<sup>2</sup> IV bolus  
CYCLOPHOSPHAMIDE 500mg/m<sup>2</sup> IV bolus

#### Cycle 4

Day 1 \*PERTUZUMAB with TRASTUZUMAB 1800mg SC over 8 minutes  
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/m<sup>2</sup> in 250ml sodium chloride 0.9% IV infusion over 60 minutes

#### Cycles 5 to 7

Day 1 \*PERTUZUMAB with TRASTUZUMAB 1200mg SC over 5 minutes  
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/m<sup>2</sup> in 250ml sodium chloride 0.9% IV infusion over 60 minutes

#### Cycles 8 to 21

Day 1 \*\*TRASTUZUMAB 600mg SC

\*For patients unable to receive SC pertuzumab / trastuzumab (phesgo) see the pertuzumab trastuzumab IV substitution regimen for IV pertuzumab plus IV trastuzumab doses, observation times etc.

\*\*For patients unable to receive SC trastuzumab see the trastuzumab monotherapy regimen for IV trastuzumab doses, observation times etc.

Pertuzumab / Trastuzumab loading dose - observation time post injection 30 minutes

Pertuzumab / Trastuzumab maintenance doses - observation time post injection 15 minutes

Trastuzumab - observation time post injection 30 minutes after the first injection and for 15 minutes after subsequent injections.

## CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 7 cycles

Trastuzumab monotherapy every 21 days from cycle 8 up to cycle 21

It is acknowledged that in patients whose blood counts have not recovered post neoadjuvant chemotherapy and there is a consequent delay to surgery, such patients may receive additional cycles of pertuzumab plus trastuzumab pre-surgery in order to ensure there is no break in anti-HER2 therapy.

It is also acknowledged that such patients may continue with pertuzumab plus trastuzumab after surgery pending determination of status as to axillary nodal involvement or not and pathological complete remission or not, before switching to trastuzumab monotherapy.

## ANTI-EMETICS

High risk day 1 cycles 1 to 3 (consider aprepitant)

Low risk day 1 cycles 4 to 7

Minimal risk day 1 cycles 8 to 21

## CONCURRENT MEDICATION REQUIRED

Docetaxel	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
Pertuzumab with Trastuzumab	Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.
Trastuzumab	Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.
GCSF	GCSF for 7 days starting at least 24 hours after chemotherapy

## EXTRAVASATION AND TYPE OF LINE / FILTERS Cyclophosphamide – neutral

Docetaxel – exfoliant

Epirubicin – vesicant

Filters not required

Central (or peripheral) line

## INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E and LFTs every cycle cycles 1 to 7

Neutrophils x 10<sup>9</sup>/L ≥1.0 (0.8-1.0 on the day of chemo go ahead with GCSF support as per local policy).

Platelets x 10<sup>9</sup>/L ≥100

Baseline weight and every cycle for cycles 1 to 7, then 3 monthly weight.

Monitor cardiac function according to network guidelines. Baseline LVEF greater than or equal to 55% or if anthracyclines were given that the LVEF was greater than or equal to 50% after completion of the anthracycline component of the neo-adjuvant chemotherapy.

## MAIN TOXICITIES AND ADVERSE REACTIONS

Cyclophosphamide	may irritate bladder, drink copious volumes of water.
Epirubicin	Cardiotoxicity – monitor cardiac function. Epirubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Docetaxel	Cutaneous reactions, peripheral neuropathy or fluid retention, hypersensitivity reactions
Pertuzumab with Trastuzumab	Cardiotoxicity - monitor cardiac function. Injection related chills, fevers or headache, slow the rate of injection or pause and appropriate medical therapies administered (Treatment including oxygen, beta agonists, antihistamines, rapid intravenous fluids and antipyretics may also help alleviate systemic symptoms.). For severe injection related reactions discontinue permanently. Other symptoms may include nausea, hypertension, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. Febrile neutropenia, diarrhea, pulmonary events Cardiomyopathy: Pertuzumab with trastuzumab administration can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue pertuzumab with trastuzumab for cardiomyopathy.
Trastuzumab	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 tachyarrhythmia, 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.

## INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Cyclophosphamide	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.
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## DOSE MODIFICATIONS

### Pertuzumab with trastuzumab

Delay more than 6 weeks since last dose

The loading dose of pertuzumab with trastuzumab 1800mg SC (equivalent to pertuzumab 1200mg and trastuzumab 600mg (1200/600mg vial)) should be readministered for 1 dose then followed by maintenance doses of pertuzumab with trastuzumab 1200mg SC (equivalent to pertuzumab 600mg and trastuzumab 600mg (600/600mg vial)).

### Epirubicin maximum lifetime dose

= 650mg/m<sup>2</sup> (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

= 1000mg/m<sup>2</sup> (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 <0.5x10<sup>9</sup>/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 60mg/m<sup>2</sup>. If the patient continues to experience these reactions at 60mg/m<sup>2</sup>, the treatment should be discontinued.

## Non-haematological

### Docetaxel

Discuss dose reductions if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.

### Pertuzumab with Trastuzumab

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

## Hepatic impairment

### Docetaxel

ALT and/or AST >1.5xULN and ALP >2.5xULN	recommended SPC dose for 100mg/m <sup>2</sup> is give 75mg/m <sup>2</sup>
Bilirubin >ULN and ALT and AST >3.5xULN with ALP >6xULN	should not be used unless strictly indicated.

### Epirubicin

Bilirubin 24-51micromol/L	give 50% dose
Bilirubin 52-85micromol/L or AST >4xULN	give 25% dose
Bilirubin >86micromol/L or Child Pugh C	not recommended

## Renal impairment

### Cyclophosphamide

CrCl 10-29ml/min	Consider giving 75% dose
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## REFERENCES

1. Effects of Chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. EBCTG. Lancet 2005; 365: 1687–1717
2. APHINITY Trial NEJM 2017; 377:122-131