DOCETAXEL CARBOPLATIN 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/) (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

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.

Cycle 1

Day 1 *PERTUZUMAB with TRASTUZUMAB 1800mg SC over 8 minutes
(if previous neoadjuvant dose <6 weeks ago reduce dose to 1200mg maintenance dose)
(1800mg equivalent to pertuzumab 1200mg and trastuzumab 600mg (1200/600mg vial)).
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^2 in 250ml sodium chloride 0.9% IV infusion over 60 minutes
CARBOPLATIN	AUC 5 (if CrCl used maximum 700mg) in 500ml glucose 5% IV infusion over 30 minutes Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.

Cycles 2 to 6

Day 1 *PERTUZUMAB with TRASTUZUMAB 1200mg SC over 5 minutes
(1200mg equivalent to pertuzumab 600mg and trastuzumab 600mg (600/600mg vial)).
Premedication: Dexamethasone 8mg BD starting 24 hours before chemotherapy (or 20mg IV on day of chemotherapy) and 8mg bd post-chemotherapy for 2 days (for patients who are unable to tolerate high doses of steroids 4mg doses may be considered)

DOCETAXEL	75mg/m^2 in 250ml sodium chloride 0.9% infusion over 60 minutes
CARBOPLATIN	AUC 5 (if CrCl used maximum 700mg) in 500ml glucose 5% IV infusion over 30 minutes Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.

Cycles 7 to 18

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 maximum 6 cycles
Trastuzumab monotherapy continues from cycle 7 up to cycle 18
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

Moderate risk day 1 cycles 1 to 6
Minimal risk day 1 cycles 7 to 18

CONCURRENT MEDICATION REQUIRED

Carboplatin	Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus H_2 antagonist Carboplatin should be given at a slower rate e.g. 2-4 hours.
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 to be added if delays / neutropenic sepsis.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin - irritant
Docetaxel – exfoliant

Filter not required
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs cycles 1 to 6
FBC every 3 months cycles 7 to 18
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥100
Baseline weight and every cycle for cycles 1 to 6, 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 TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
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: PHESGO 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 PHESGO 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.

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)).

Haematological

Docetaxel

In patients who experienced either febrile neutropenia, neutrophil count $<0.5x10^9$/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/m². If the patient continues to experience these reactions at 60mg/m², 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 with 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^2 is give 75mg/m^2
Bilirubin >ULN and ALT and AST >3.5xULN with ALP >6xULN	should not be used unless strictly indicated.

Renal impairment

Carboplatin

GFR/ calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment	contraindicated

REFERENCES

1. APHINITY Trial NEJM 2017: 377:122-131
2. TRYPHAENA trial Annals of Oncology 24: 2278–2284, 2013
3. NEOSPHERE trial Lancet Oncol 2012; 13: 25–32