PERTUZUMAB IV & TRASTUZUMAB (HERCEPTIN) IV

a) First-line use, in combination with docetaxel, for HER2 +ve locally advanced or metastatic breast cancer, and LVEF > 50%.

b) Neo-adjuvant treatment of locally advanced, inflammatory or early breast cancer at high risk of recurrence, when used in combination with docetaxel-containing chemotherapy for early stage breast cancer (i.e. EC-docetaxel regimens or TCH) and LVEF ≥ 55%.

Blueteq registration is required before starting treatment with 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 o*bserve for 60 minutes, then:*
	Trastuzumab (Herceptin)	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, o*bserve for 30 minutes, then:*
	Trastuzumab (Herceptin)	6 mg/kg in 250ml sodium chloride 0.9% IV over 30 minutes,

Pertuzumab, trastuzumab (Herceptin) and docetaxel may be given in any order, but the preferred order is as above, followed by the docetaxel.
For Cycle 1 only, give pertuzumab and trastuzumab on Day 1 and give docetaxel on Day 2.
For subsequent cycles, administer the pertuzumab and trastuzumab first, then a short saline flush, followed by the docetaxel.
(N.B. For use with neo-adjuvant TCH, for Cycle 1 only, give pertuzumab on day 1, and give s/c Herceptin as part of TCH on Day 2)

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.

Reason for Update: neo-adjuvant indication added	Approved by Consultant: Dr A Neal
Version: 4	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 3	Date: 5.12.16
Prepared by: S Taylor	Checked by: C Tucker

Neo-adjuvant setting: Up to 4 doses of pertuzumab and Herceptin IV, with the docetaxel cycles of EC-docetaxel regimens.
Up to 6 doses of pertuzumab with TCH *(with s/c Herceptin instead of IV herceptin)*
After surgery, patients should be treated with adjuvant trastuzumab (Herceptin), to complete a total of 18 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)

Anti-emetics: 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:
Advanced setting: baseline LVEF should be > 50%.
Neo-adjuvant setting: baseline LVEF needs to be ≥ 55%.
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: Pertuzumab and trastuzumab should both be withheld for at least 3 weeks for any of the following:
- signs and symptoms suggestive of congestive heart failure
- a drop in LVEF to < 40%
- LVEF of 40 - 45% associated with a fall of ≥ 10 ejection fraction points below pre-treatment values.

Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to > 45%, or 40-45% associated with < 10 ejection fraction points below pre-treatment value.
If LVEF has not improved, or has declined further, after 3 weeks, discontinuation of treatment should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.
If symptomatic cardiac failure develops during treatment, it should be treated with standard medications for this purpose.

References:
Baselga, J et al; NEJM 2012; 366 (2): 109 – 119
Gianni, L et al; Lancet Oncology 2012; 13 (1): 25 – 32
Schneeweiss, A et al; Ann Oncol 2013; 24 (9): 2278 - 2284