LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – Pertuzumab in Advanced Breast Cancer

Indication: First line treatment of locally advanced or metastatic breast cancer

National Cancer Drug Fund criteria:

- Locally advanced or metastatic breast cancer
- HER2 3+ or FISH positive
- PS 0 or 1
- Prior adjuvant HER2 therapy completed more than 12 months prior to metastatic diagnosis
- No prior treatment with chemotherapy or HER2 therapy for metastatic disease
- To be given as first line treatment in combination with docetaxel and trastuzumab

NOTE: not to be used beyond first disease progression

Ensure funding has been approved prior to starting treatment.

Regimen details:

Loading dose:	Pertuzumab	840mg	IV	Day 1	cycle 1
Loading dose:	Trastuzumab	8mg/kg	IV	Day 2	cycle 1
	Docetaxel	75mg/m^2	IV	Day 2	cycle 1
Maintenance dose:	Pertuzumab	420mg	IV	Day 1	cycle 2 onwards
Maintenance dose:	Trastuzumab	6mg/kg	IV	Day 1	cycle 2 onwards
	Docetaxel	75mg/m^2	IV	Day 1	cycle 2 onwards

Pertuzumab is given in ***combination*** with intravenous trastuzumab and docetaxel; docetaxel should be given for 6 cycles
Due to the potential for hypersensitivity reactions: for **cycle 1 only**, give pertuzumab on day 1, give trastuzumab followed by docetaxel on day 2.

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Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016

From cycle 2 onwards, administer pertuzumab and trastuzumab sequentially (in any order) first, followed by docetaxel on day 1. Pertuzumab and trastuzumab may be continued until progressive disease. However if trastuzumab treatment is discontinued for any reason, treatment with pertuzumab should be discontinued.

See separate protocol for trastuzumab in the advanced setting for details of doses, monitoring and ongoing treatment.

See separate protocol for docetaxel in the advanced setting for details of doses, monitoring and ongoing treatment.

Administration:	Pertuzumab in 250ml sodium chloride 0.9% infuse over 30-60 minutes Close observation during and for 60 minutes after the first infusion, and during and for 30-60 minutes for subsequent infusions is recommended prior to starting the next agent. Infusion-related hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, dyspnoea and fever or chills following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered. Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.
Missed doses:	If the time between two sequential infusions is less than 6 weeks, the 420mg dose should be given as soon as possible. If the time between two sequential infusions is greater than 6 weeks, the patient should receive a re-loading dose of 840mg given over 60 minutes.
Frequency:	Day 1, every 21 day, until disease progression or unacceptable toxicity
Pre-medication:	Paracetamol / Chlorphenamine / Hydrocortisone can be given for infusion-related reactions such as chills / fever.
Anti- emetics:	Low emetogenicity

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	Follow Local Anti-emetic Policy
Supportive medication:	Loperamide can be used to manage diarrhoea
Extravasation:	Non-vesicant

Regular investigations:

FBC	Baseline, at 4 and 8 months then 4 to 6 monthly thereafter
LFTs	Baseline, at 4 and 8 months then 4 to 6 monthly thereafter
U&Es	Baseline, at 4 and 8 months then 4 to 6 monthly thereafter
LVEF (MUGA/ECHO)	Baseline, at 4 and 8 months then 4 to 6 monthly thereafter (see cardiac monitoring)

NOTE: see additional investigations required when co-administered with docetaxel and trastuzumab – see separate protocols

Toxicities:

Infusion related symptoms (mild to moderate in severity, occur mainly with first dose): pyrexia, chills, headache, asthenia, hypersensitivity/anaphylaxis and vomiting.
Infusion related symptoms (subsequent cycles): fatigue, dysgeusia, hypersensitivity/anaphylaxis, myalgia.
As pertuzumab is given with trastuzumab and docetaxel, it is difficult to ascertain a causal relationship to a particular medicinal product (see separate protocol for trastuzumab and docetaxel): upper respiratory tract infection, neutropenia including febrile neutropenia, anaemia, insomnia, peripheral neuropathy, increased lacrimation, stomatitis, dyspepsia, alopecia, nail disorder, dry skin and pruritis, arthralgia, pleural effusion , interstitial lung disease (uncommon).
Common events (≥10%) reported in pertuzumab monotherapy patients: headache, decreased appetite, dyspnoea, cough, diarrhoea, vomiting, nausea, constipation, rash, pain, oedema, fatigue, asthenia, cardiotoxicity.

DOSE MODIFICATIONS

Haematological Toxicity

Dose modifications are not recommended.
Patients may continue pertuzumab and trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression but should be carefully monitored for complications of

neutropenia. Patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment, the higher incidence of febrile neutropenia in pertuzumab treated patients may also be associated with higher incidence of mucositis and diarrhoea.

Non-haematological Toxicities

Renal Impairment

Dose adjustments are not needed in patients with mild or moderate renal impairment.
It is recommended to perform renal function tests at the same time as the cardiac monitoring.

Hepatic Impairment

The safety and efficacy of pertuzumab has not been studied in patients with hepatic impairment.
It is recommended to perform liver function tests at the same time as the cardiac monitoring.

Dose modifications for other toxicities as appropriate

Cardiac monitoring

A left ventricular ejection fraction (LVEF) above the lower limit of normal (> 50%) is required for the treatment to go ahead (measured on echocardiography, ECHO or multigated acquisition, MUGA).
SmPC suggests cardiac monitoring every 3 cycles, data suggest there is no increased risk of cardiac toxicity therefore cardiac monitoring may be carried out at baseline, at 4 and 8 months then 4 to 6 monthly thereafter as clinically indicated after discussion with the consultant.

Guideline for stopping treatment in the event of reduced cardiac function

If LVEF is <40%, or 40-45% and associated with ≥10% ejection points from baseline, pertuzumab and trastuzumab should be withheld and a repeat LVEF should be performed in 3 weeks. If there is no improvement discuss with consultant and seek cardiology opinion. Discuss with consultant before re-starting.

Location of regimen delivery:	Outpatient setting. Availability of resuscitation equipment must be ensured as a standard precaution.
Comments:	None
Drug interactions:	No pharmacokinetic interactions were observed between pertuzumab and trastuzumab, docetaxel, gemcitabine, erlotinib and capecitabine.

References:

Roche. Summary of product characteristics: Perjeta. Date of authorisation: 04Mar2013. Available at www.medicines.org.uk [accessed 03May2013]
Micromedex: pertuzumab. Available at http://www.micromedexsolutions.com/home/dispatch [Accessed 03May2013]
Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med* 2012;366:109-19

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