LONDON CANCER ALLIANCE West and South

Breast Pathway Group – Everolimus in Advanced Breast Cancer

Indication:	Hormone receptor positive, HER2 negative advanced breast cancer National Cancer Drug Fund criteria: • ER+ve, HER2 –ve metastatic breast cancer • No symptomatic visceral diease • In combination with exemestane • Previous treatment with a non-steroidal aromatase inhibitor • No previous treatment with exemestane for metastatic breast cancer • No more than one-line of chemotherapy for the treatment of advanced breast cancer Ensure funding has been approved prior to starting treatment.
Regimen details:	Everolimus 10mg once daily PO Continuous In combination with exemestane
Administration:	Everolimus taken orally once daily. Tablets should be swallowed whole with a glass of water, at the same time each day, consistently either with or without food. Do not crush or chew. Tablets available as 2.5mg, 5mg or 10mg.
Frequency:	Dosing is continuous. Treatment is prescribed every 28 days until disease progression or unacceptable toxicity
Pre-medication:	Not routinely required
Anti- emetics:	Low emetogenicity Follow Local Anti-emetic Policy
Supportive medication:	Mouthcare as per local policy

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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

Regular investigations:

Prior to Cycle 1:

Hepatitis serology	Baseline
Fasting serum glucose	Baseline & periodically as appropriate
Lipids	Baseline & periodically as appropriate
Proteinuria	Baseline & periodically as appropriate
CT	Every 2-3 cycles to assess disease

Prior to Day 1 (all cycles):

FBC	Monthly
LFTs	Monthly
U&Es	Monthly
Respiratory examination*	

*patients with new respiratory findings should have a chest CT

Toxicities: Anaemia, hypercholesterolaemia, hyperglycaemia, diabetes mellitus, lymphopenia, hypophosphatemia, hypertension, haemorrhage, thrombocytopenia, neutropenia, cough, raised creatinine, proteinuria, raised AST and ALT, infection, fatigue, anorexia, nausea, vomiting, stomatitis, mucositis, diarrhoea, dysgeusia, headache, rash, pneumonitis, hypersensitivity reactions, impaired wound healing

DOSE MODIFICATIONS

Dose levels	**Dose and schedule**
Starting dose	10mg once a day
Decrease one level	5mg once a day
Decrease two dose levels	5mg every other day

Haematological Toxicity

NCI CTCAE Grade	**Platelets (x 10^9/L)**	**Dose**
1	≥ 75	10mg once daily
2	50-74	Withhold everolimus until recovery to ≤ Grade 1 and resume therapy at 10mg daily. For 2nd recurrence, delay everolimus until recovery to ≤ Grade 1 and reduce by one dose level.
3	25-49	Withhold everolimus until recovery to ≤ Grade 1 and reduce by one dose level. For 2nd occurrence, discontinue therapy.
4	< 25	Discontinue everolimus

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NCI CTCAE Grade	Neutrophils (x 10^9/L)	Dose
1	≥ 1.5	10mg once daily
2	≥ 1.0	10mg once daily
3	0.5 – 0.9	Withhold everolimus until recovery to ≤ Grade 1 and resume therapy at 10mg daily. For 2nd occurrence, delay therapy until neutrophil count ≥ 1.5 x 10^9/L and reduce by one dose level. For 3rd recurrence, discontinue everolimus.
4	< 0.5	Withhold everolimus until recovery to ≤ Grade 1 and reduce by one dose level. For 2nd recurrence, discontinue everolimus.

Non-haematological Toxicities

Renal Impairment No dose adjustment required.

Hepatic Impairment

Hepatic impairment	Dose
Mild (Child-Pugh A)	7.5mg daily
Moderate (Child-Pugh B)	5mg daily
Severe (Child-Pugh C)	Not recommended. Discuss with the consultant, consider discontinuation or max 2.5mg daily

Child-Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	< 34	34 - 50	> 50
Albumin	> 35	28 - 35	< 28
PT (s prolonged)	< 4	4 - 6	> 6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

If there is primary biliary cirrhosis or sclerosing cholangitis then bilirubin is classified as < 68 = 1; 68 – 170 = 2; > 170 = 3.

The individual scores are summed and then grouped as:

< 7 = A

7 – 9 = B

> 9 = C

Dose modifications for other toxicities as appropriate

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NCI CTCAE Grade	Dose
Grade 2 (except pneumonitis – see below)	If the toxicity is tolerable, maintain the same dose. If toxicity is intolerable, withhold everolimus until recovery to Grade ≤ 1 then resume everolimus at 10mg daily. For recurrence, withhold everolimus until recovery to ≤ Grade 1 and reduce by one dose level.
Grade 3 (except hyperlipidemia)	Withhold everolimus until recovery to ≤ Grade 1 and reduce by one dose level. For 2nd recurrence, discontinue everolimus.
Grade 3 hyperlipidemia ONLY	No dose interruption of everolimus required. Use standard medical therapies
Grade 4	Discontinue everolimus

NCI CTCAE Grade:	Management of Non-infectious Pneumonitis	Dose
1 (Asymptomatic radio-logical changes)	No therapy required	100% dose
2 (Symptomatic, not interfering with ADL*)	Symptomatic ONLY. Prescribe corticosteroids if cough is troublesome	Reduce by one dose level until recovery to ≤ Grade 1. Consider interruption of therapy if symptoms troublesome.
3 (interfering with ADL*, oxygen indicated)	Prescribe corticosteroids if infective origin ruled out. Taper as medically indicated	Withhold everolimus until recovery to ≤ Grade 1. Consider restarting at reduced dose level if recovered within 28 days and evidence of clinical benefit.
4	Prescribe corticosteroids if infective origin ruled out. Taper as medically indicated	Discontinue everolimus

*ADL: activities daily living

Location of regimen delivery: Outpatient setting

Comments: To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorbtion should not take everolimus.

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Drug interactions:	ACE inhibitors: angioedema has been reported with concomitant use Food: a high-fat meal slightly reduces the exposure to everolimus Potent CYP3A4/P-glycoprotein inhibitors (ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin): concomitant use not recommended Moderate CYP3A4/P-glycoprotein inhibitors (aprepitant, erythromycin, verapamil, diltiazem, fluconazole, ciclosporin oral): use with caution and consider dose reduction to 5mg daily or 5mg every other day. Monitor side effects Grapefruit or grapefruit products: avoid concomitant use Potent CYP3A4 inducers: (dexamethasone, rifampicin, carbamazepine, phenobarbital, phenytoin): avoid concomitant use St John's Wort (*Hypericum perforatum*): should not be used Avoid live vaccines during treatment with everolimus

References:

Novartis Pharmaceuticals UK Ltd. 2013. Summary of product characteristics: Afinitor (everolimus).Available at www.medicines.org.uk [accessed 07/11/2013]

Baselga et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2012;366:520-9.

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