PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Everolimus and Exemestane Advanced Breast Cancer

PROTOCOL REF: MPHAEVEXBR
(Version No. 1.1)

Approved for use in:

Postmenopausal women with ER positive, HER2 negative advanced breast cancer

No symptomatic visceral disease

Following progression/recurrence after non-steroidal aromatase inhibitor

NOTE: Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy. Radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered.

***********Requires blueteq registration**********

Dosage:

Drug	Dose	Route	Frequency
Everolimus	**10mg daily**	Oral	Continuous, supply will be every 28 days
Exemestane	**25mg daily**	Oral	Continuous, supply will be via GP

Until disease progression or unacceptable toxicity. If everolimus is discontinued due to toxicity then exemestane can continue.

Administration:

Everolimus is available as 2.5 mg, 5 mg and 10 mg tablets.

It is administered orally once daily at the same time every day, consistently either with or without food.

If a dose is missed, the patient should not take an additional dose, but take the next prescribed dose as usual.

Extravasation risk:

Not applicable .

Supportive Treatments:

Metoclopramide 10mg tablets, to be taken up to three times a day as required for nausea and vomiting for maximum 5 consecutive days.

Dosing in renal and hepatic impairment:

Renal	Everolimus	No adjustments required Elevations of serum creatinine, usually mild, and proteinuria have been reported

Hepatic	Everolimus	**Parameters**	**1 point**	**2 points**	**3 points**
		Total bilirubin (µmol/L)	< 34	34–50	> 50
		Serum albumin (g/L)	> 35	28–35	< 28
		Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
		Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)

Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

Child-Pugh Class	Recommended Daily Dose
A (5-6 points)	7·5mg
B (7-9 points)	5mg
C (10 or more points)	2.5mg

INR: International Normalised Ratio.
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Interactions:

Radiotherapy:- Serious and severe radiation reactions, including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. In addition there is a risk of RRS, refer to the 'NOTE' on page 1 for full details.

Everolimus is metabolized by the cytochrome CYP3A4 pathway and therefore drugs that induce or inhibit this enzyme should be avoided where possible.

INDUCERS (lowers everolimus levels): Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

INHIBITORS (increases everolimus levels): Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

ACE inhibitors (e.g. Ramipril, Enalapril etc)– concomitant use increases risk for angioedema.

For more detailed interactions please refer to the SPC

https://www.medicines.org.uk/emc/product/12240/smpc

Main toxicities:

Note: exemestance side effects not included

Everolimus	
Haematological	Neutropenia, anaemia, thrombocytopenia,
Gastrointestinal	Nausea, vomiting, diarrhoea, mucositis
Respiratory	Pneumonitis, dyspnoea
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Renal and urinary disorders	Proteinuria, blood creatinine increased, renal failure in very rare cases
Skin and subcutaneous tissue disorders	Skin rash Oedema
General disorders and administration site conditions	Hyperglycaemia Headaches Infertility, early menopause

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	x					
Clinical Assessment	x			x		every 3 months or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	x	x	x	x	x	Every cycle
Fasting Lipids and cholesterol	x			x		Every 12 weeks
CrCl (Cockcroft and Gault)	x	x	x	x	x	Every cycle
CT scan	x					Every 12 weeks and if clinically indicated
ECG						If clinically indicated
Full observations	x	x	x	x	x	Every cycle*
Weight recorded	x	x	x	x	x	Every cycle
Random glucose	x		x	x	x	Every cycle
Height	x					

*A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Toxicity	Severity	Everolimus dose adjustment
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.

Non- Haematological toxicity:

Toxicity	Severity	Everolims dose adjustment
Non-infectious pneumonitis	Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Consider interruption of therapy until symptoms improve to Grade ≤1 (asymptomatic; clinical or diagnostic observations only; intervention not indicated). Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self care ADL; oxygen indicated	Interrupt treatment until symptoms resolve to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.

	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.

References:

1. Everolimus tablets SmPC, Novartis Pharmaceuticals UK Ltd. Last updated 21st October 2021.
2. NICE TA421. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy. Published Dec 2016
3. Baselga et al (2012) BOLERO-2: Everolimus in postmenopausal hormone receptor positive advanced breast cancer.*NEJM* 366:520-529
4. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.NICE: CG121 Lung cancer: diagnosis and management. Published date: April 2011.

Circulation/Dissemination

Date added into Q-Pulse	9th January 2023
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Helen Flint Consultant Pharmacist	New Regimen Protocol V1.0
		Gabriella Langton Breast SRG Pharmacist	Routine protocol update V1.1