Everolimus

Indication
Treatment of advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy
Metastatic breast cancer (in combination with exemestane)
Unresectable or metastatic neuroendocrine tumours

Regimen details
Everolimus 10mg orally once daily

Cycle frequency
Treatment is continuous, dispense monthly

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Patients should avoid consuming grapefruit and grapefruit juice.
Tablets may be taken with or without food but must always be taken the same way

Pre-medication
Nil

Emetogenicity
No routine antiemetics required

Additional supportive medication
None

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Fasting glucose	14 days
Lipids	14 days
Blood pressure	14 days
ECG	14 days

Blood pressure must be controlled before initiating everolimus

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST)
Repeat fasting glucose, lipids and blood pressure as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ ULN
AST	≤ ULN

Dose modifications

Adverse reaction	Severity[1]	Dose adjustment
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	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	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.
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.

[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0

Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	EVEROLIMUS Dose Adjustment
Grade 1	CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required	Administer 100% of everolimus dose.
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce everolimus dose until recovery to ≤ Grade 1. Everolimus may also be interrupted if symptoms are troublesome. Discontinue everolimus if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is required *	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is required *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

Renal impairment

No dose modifications are required in renal impairment.

Cases of renal failure have been reported in patients receiving everolimus. Renal function should be monitored. Patients with acute renal failure should stop treatment until the cause has been investigated and treated.

Hepatic impairment

Everolimus is mainly excreted via hepatic elimination. Doses adjustments should be made as per table below if patient's hepatic status changes during treatment

Degree of hepatic impairment	Everolimus dose
Mild (Child Pugh A)	7.5mg OD
Moderate (Child Pugh B)	5mg OD
Severe (Child Pugh C)	Not recommended – if used dose must not exceed 2.5mg OD

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Venous thromboembolism
Impaired wound healing
Teratogenicity
Infertility (males)
ARDS

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Hyperlipidaemia
Myelosuppression
Rash
Pneumonitis (patients should report any new or worsening respiratory symptoms)
Stomatitis/Mucositis
Hyperglycaemia

- **Other side effects**

Taste disturbances
Fatigue
Headache
Insomnia
Weight loss

Significant drug interactions

– for full details consult product literature/ reference texts

Potent CYP3A4 and PgP inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration - may increase plasma concentrations of everolimus. Risk of toxicity.

Moderate CYP3A4 and PgP inhibitors (e.g. erythromycin, imatinib, ciclosporin, verapamil, diltiazem, grapefruit juice): co administration with caution and close monitoring/consider dose reduction of everolimus.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of everolimus.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, dexamethasone, St Johns Wort): avoid co-administration - may reduce exposure to everolimus. Risk of therapeutic failure.

ACE inhibitors: caution, increased risk of angioedema

Additional comments

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

References

Afinitor SPC - https://www.medicines.org.uk/emc/product/7733/smpc

South West Clinical Network SACT protocols - http://www.swscn.org.uk/guidance-protocols/cancer-protocols/

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, DESIGNATED LEAD CLINICIAN FOR KIDNEY CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: September 2020
Review: September 2022
VERSION: 8