Systemic Anti Cancer Treatment Protocol

Everolimus in Renal Cell Cancer

PROTOCOL REF: MPHAREVER
(Version No: 2.1)

The protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

Advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Must be registered on Blueteq

Dosage:

Drug	Dosage	Route	Frequency
Everolimus	10mg	oral	Once daily

Every 28 days until disease progression or unacceptable toxicity

Supportive treatments:

Domperidone 10mg oral tablets, up to three times a day as required

Dosing in renal and hepatic impairment:

Renal:

No dose adjustment is required

Hepatic:

Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.

Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily.

Severe hepatic impairment (Child-Pugh C) –only recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg daily must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Assessing a child pugh score for an adult

Parameter	Score		
	1	2	3
Ascites	None	Mild to moderate Easily treated	Moderate to severe
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4
Bilirubin (micromol/L)	< 35	35 to 50	> 50
Albumin (g/L)	35	28 to 35	< 28
INR	< 1.7	1.8 to 2.3	> 2.3

Child Pugh score 5 to 6 = Grade A; well-functioning liver
Child Pugh score 7 to 9 = Grade B; significant functional compromise
Child Pugh score 10 to 15 = Grade C; decompensate liver

Administration (+/- Counselling Points):

Everolimus should be administered orally once daily at the same time every day, consistently either with or without food.

Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

Drug Interactions

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 – concomitant use increases risk for angioedema.

7.0 Main Toxicities:

Neutropenia, fatigue, dyspnoea, anaemia, thrombocytopenia, stomatitis, skin reaction, headaches, nausea, pneumonitis, oedema, hyperglycaemia.

Please refer to the SPC for more information on toxicities.

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	C5	Ongoing
Informed Consent	X						
Clinical Assessment	X		X	X			1ST three cycles and then three monthly thereafter
SACT assessment (to include PS and toxicities)		X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	Every cycle
Fasting lipids and cholesterol	X				X		monitor periodically
CT scan	X				X		Every 12 weeks
Weight recorded	X	X	X	X	X	X	Every cycle
Height recorded	X						1ST cycle
Random glucose	X						monitor periodically

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets > 75 x 10^9/L

If platelets 50 to 75 x 10^9/L, and/or neutrophils 0.5 to 1.0 x 10^9/L then interrupt treatment until recovered to > 75 x 10^9/L and > 1.0 x 10^9/L and re-initiate at previous dose.
If below these levels then re-initiate at reduced dose of 5mg daily.

Non-haematological toxicity

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.

10.0 References:

Electronic medicines compendium. *Afinitor 10mg tablets.* Available from https://www.medicines.org.uk/emc/product/6658/smpc

NICE. Everolimus for advanced renal cell carcinoma after previous treatment. https://www.nice.org.uk/guidance/ta432/resources/everolimus-for-advanced-renal-cell-carcinoma-after-previous-treatment-pdf-82604720798917