REGORAFENIB

For third line use in adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) who have resistance or intolerance to imatinib, and resistance to sunitinib

Individual funding must be agreed before treatment may start

Drug/Dosage:	**Regorafenib**	160mg po once daily for 21 days, then 7 days rest
Administration:	Regorafenib is available as 40mg tablets, which should be swallowed whole with water after a light meal that contains less than 30% fat. (An example of a light meal is cereal with skimmed milk, toast and jam, apple juice, and coffee or tea) Grapefruit and grapefruit juice should be avoided while on regorafenib.	
Frequency:	every 4 weeks (3 weeks treatment, followed by one week rest) for as long as there is clinical benefit, or until unacceptable toxicity.	
Main Toxicities:	hand-foot syndrome; hepatotoxicity; diarrhoea; hypertension; dysphonia; fatigue	
Anti- emetics:	mildly emetogenic – anti-emetics not routinely needed	
Regular Investigations:	FBC	every 4 weeks
	LFTs	every 2 weeks for 2 months, then every 4 weeks
	U&Es	every 4 weeks
	Blood pressure	every 2 weeks for 2 months, then every 4 weeks

Comments:

Patients should be advised to apply moisturiser to their hands and feet regularly throughout treatment, and to minimise activities that put pressure on feet or hands if they start to develop sore hands or feet. Recommended moisturisers are Udderly Smooth or urea-containing moisturisers eg Eucerin.

Elimination of regorafenib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St Johns wort) with regorafenib should be avoided, as this may increase the risk of therapeutic failure.

Co-administration with enzyme inhibitors (eg itraconazole, posaconazole, erythromycin, clarithromycin, grapefruit juice) should also be avoided, as their effect on regorafenib exposure has not been studied.

Dose Modifications

Management of suspected adverse drug reactions may require temporary interruption or dose reduction of therapy.
When dose reduction is necessary, regorafenib should be reduced in 40mg steps. The lowest recommended daily dose is 80mg.

Haematological Toxicity:

An increased risk of bleeding may occur while on regorafenib. Discontinue regorafenib if any bleeding event requires medical intervention.

Hypertension:

If hypertension develops, it should be treated and monitored closely until stabilised. It is not a reason to stop regorafenib, unless patient develops severe hypertension.

Reason for Update: new protocol	Approved by Consultant: Dr S Cummins
Version: 1	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: none	Date: 19.11.13
Prepared by: S Taylor	Checked by: C Tucker

Skin Toxicity:

Skin Toxicity	Occurrence	Action
Grade 1	Any	Maintain dosing. Provide supportive measures.
Grade 2	1st occurrence	Decrease dose by 40mg daily. If no improvement at lower dose, interrupt therapy for a minimum of 7 days until resolved to Grade 0-1. Dose re-escalation may be considered.
	No improvement in 7 days or 2nd occurrence	Interrupt therapy until toxicity resolved to Grade 0-1. When re-starting, reduce daily dose by 40mg.
	3rd occurrence	Interrupt therapy until toxicity resolved to Grade 0-1. When re-starting, reduce daily dose by 40mg.
	4th occurrence	Discontinue permanently
Grade 3	1st occurrence	Interrupt therapy for a minimum of 7 days until toxicity resolved to Grade 0-1. When re-starting, reduce daily dose by 40mg.
	2nd occurrence	Interrupt therapy for a minimum of 7 days until toxicity resolved to Grade 0-1. When re-starting, reduce daily dose by 40mg.
	3rd occurrence	Discontinue permanently

Hepatic Impairment: Regorafenib is mainly eliminated via the hepatic route. No dose adjustment is required in patients with mild (Child Pugh A) hepatic impairment.
There is insufficient data for dose recommendation in moderate hepatic impairment (Child Pugh B).
Regorafenib is not recommended in severe hepatic impairment (Child Pugh C)

Hepatotoxicity:

Observed elevation of ALT / AST	Action
Raised, but ≤ 5 x ULN	Continue regorafenib but monitor LFTs weekly until transaminases < 3 x ULN
>5 x ULN but ≤20 x ULN	1st occurrence: Interrupt treatment and monitor transaminases weekly until < 3 x ULN. Treatment may be re-started with dose reduced by 40mg compared to previous dose. LFTs must be monitored weekly for at least 4 weeks. If re-occurs, discontinue permanently.
>3 x ULN with concurrent bilirubin >2 x ULN	Discontinue permanently. Monitor LFTs weekly until recovered. (except for patient with Gilbert's syndrome; then manage according to transaminase levels only)
>20 x ULN	Discontinue permanently

Renal Impairment: No dose adjustment is required in mild or moderate renal impairment. No data are available in patients with CrCl < 30ml/min/1.73m^2. However pharmacokinetic modelling does not predict any change in exposure in these patients.