Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

Drug regimen
Regorafenib

Indications for use
Third line metastatic GIST
Second line locally advanced or metastatic hepatocellular carcinoma

Regimen

Regorafenib
Dose: 160mg orally once daily for 3 weeks.
Cycle to be repeated every 4 weeks until disease progression

Regorafenib should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat

Investigation prior to initiating treatment
FBC
U&E
LFT/Bone profile

BP monitoring required fortnightly

Caution
Check LFT before starting chemotherapy
See below for dose modifications

Contraindications
Contains lecithin which is derived from soya. Avoid in patients with very severe soya allergy

Investigations and consultations prior to each cycle
FBC, U&E
Check LFTs every 2 weeks for the first 2 months
LFTs must be available before each cycle.

Consultation every cycle

Acceptable levels for treatment to proceed
(If outside these delay one week or contact consultant): see LFT results below.

No dose adjustment is required in patients with mild or moderate renal impairment

Side Effects
Severe and fatal liver toxicity has been reported.
Serious side effects, in less than one percent of patients: liver damage, severe bleeding, blistering and peeling of skin, severe hypertension requiring emergency treatment, acute coronary syndromes and intestinal perforations. Common side effects: weakness or fatigue, loss of appetite, hand-foot syndrome, diarrhea, mucositis, weight loss, infection, high blood pressure, and changes in voice volume or quality (dysphonia).

Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.

For recommended dose modifications and measures in case of hand-foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia syndrome see Table 1.

Table 1: Recommended dose modifications and measures for HFSR

Skin toxicity grade	**Occurrence**	**Recommended dose modification and measures**
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	4th occurrence	Discontinue treatment with Regorafenib permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).

	3rd occurrence	Discontinue treatment with Regorafenib permanently.

For recommended measures and dose modifications in case of worsening of liver function tests considered related to treatment with Regorafenib see Table 2

Table 2: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	**Occurrence**	**Recommended measures and dose modification**
≤5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue Regorafenib treatment. Monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.
>5 times ULN ≤20 times ULN (Grade 3)	1st occurrence	Interrupt Regorafenib treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start Regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with Regorafenib permanently.
>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with Regorafenib permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with Regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

THIS PROTOCOL HAS BEEN DIRECTED BY DR FYFE, CLINICIAN FOR GIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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