Systemic Anti-Cancer Treatment Protocol

Regorafenib

PROTOCOL REF: MPHAREGGI
(Version No: 2.0)

Approved for use in:

Second line treatment hepatocellular carcinoma for patients that have previously been treated with sorafenib (ECOG PS 0-1)

Treatment of metastatic or unresectable gastrointestinal stromal tumours (GIST) that have progressed on, or intolerant to, imatinib or sunitinib (ECOG PS 0-1)

Both indications require registration with NHSE via the Blueteq website

Dosage:

Drug	Dose	Route	Frequency
Regorafenib	160mg	PO	Once Daily for 21 days (followed by one week break)

Supportive Treatments:

Domperidone 10mg TDS PRN

Loperamide 4mg at onset then 2mg after each loose stool (max.16mg in 24hrs)

Administration

- Regorafenib is available in 40mg tablets
- Regorafenib should be administered after a low fat meal
- The tablets should be swallowed with a glass of water

Main Toxicities

- Nausea and vomiting
- Diarrhoea
- Mucositis
- Skin reactions including dry skin, rash, pruritus, Hand-Foot Syndrome and alopecia

- Anorexia and reduced appetite
- Hypertension
- Fever
- Headache
- Dysphonia
- Thrombocytopenia
- Reduction in potassium, sodium, calcium, phosphate and magnesium levels
- Abnormal liver function test results (raised bilirubin and transaminases)
- Hypothyroidism

Drug Interactions

Strong CYP3A4 inhibitors: can increase exposure to regorafenib by up to 33%. Manufacturer recommends avoiding concomitant use with ketoconazole, itraconazole, voriconazole, clarithromycin and grapefruit juice.

Strong UGT1AP inhibitors: manufacturer recommends avoiding concomitant use of drugs such as mefenamic acid.

CYP3A4 inducers: these can increase metabolism of regorafenib and should be avoided (rifampicin, phenytoin, carbamazepine, phenobarbital and St John's Wort).

BCRP substrates: co-administration of regorafenib can increase exposure to drugs such as rosuvastatin, atorvastatin and methotrexate (as much as 3.8-fold increase in AUC and 4.6-fold increase in C_{max}).

Investigations and Treatment Plan

	Pre	C1	C1 D15	C2	C2 D15	C3	C4	Ongoing
Clinical Assessment	X	X		X		X	X	Once stable, alternate cycles
SACT Assessment	X	X		X		X	X	Every cycle
FBC	X	X		X		X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	Every 2 weeks for the first 2 cycles then every cycle
Phosphate	X	X		X		X	X	Every cycle
Magnesium	X	X		X		X	X	Every cycle
Thyroid function	X							Every 12 weeks
AFP	X	X		X		X	X	Every cycle
CT scan	X							Every 12 weeks
Informed Consent	X							
Blood pressure	X	X		X		X	X	Every cycle
PS recorded	X	X		X		X	X	Every cycle
Toxicities documented	X	X		X		X	X	Every cycle
Height recorded	X							
Weight recorded	X	X		X		X	X	Every cycle

Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L*

Discuss with consultant if:-

ANC ≤ 0.99 x 10^9/L	Platelets ≤ 49 x 10^9/L*

*HCC patients may have longstanding thrombocytopenia which is likely attributed to hypersplenism secondary to portal hypertension rather than being treatment-related. Review of the platelet trend over a period of time is therefore recommended to fully assess

Non-haematological Toxicity

Toxicity (CTC Grade)	Treatment Delay	Dose Reduction
Grade 1	No delay	No reduction
Grade 2 and 3	Delay treatment and refer back to clinician. Hold treatment until Grade 0-1	Reduce down to next level
Grade 4	-	Discontinue

Dose Reduction Level	Dose
1	120mg ONCE daily
2	80mg ONCE daily
3	40mg ONCE daily

Any patient that experiences a non-haematological toxicity that does not have a set management plan in this protocol will need referring back for a clinical review or discussing with the medical team before proceeding with treatment.

Hepatic impairment

Regorafenib is eliminated mainly via the hepatic route. No dose adjustments required for patients with mild (Child-Pugh A) hepatic impairment. There is limited

safety data for patients with moderate (Child-Pugh B) hepatic impairment. Not recommended in severe hepatic impairment.

Observed elevations of ALT and/or AST	Occurrence	Recommended action and dose modification
≤ 5 x ULN	Any occurrence	Continue regorafenib. Monitor LFT's weekly until returned to < 3 x ULN or baseline
> 5 x ULN but ≤ 20 x ULN	1st occurrence	Hold treatment. Monitor LFT's weekly until returned to < 3 x ULN or baseline. Restart: If benefit outweighs risk of hepatotoxicity, re-start but reduce dose by 40 mg (one tablet), and monitor LFTs weekly for at least 4 weeks.
	Re-occurrence	Discontinue permanently
> 20 x ULN	Any occurrence	Discontinue permanently
> 3 x ULN with concurrent bilirubin > 2 x ULN*	Any occurrence	Discontinue permanently. Monitor LFTs weekly until resolution or return to baseline

*** Exception**: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above recommendations for the respective observed elevation for ALT and/or AST.

Renal impairment

No dose adjustments required for patients with mild, moderate or severe renal impairment.

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References:

1. Stivarga 40mg film-coated tablets.
2. Summary of Product Characteristics. Bayer plc, Reading, 26/08/2013. Available from https://www.medicines.org.uk/emc
3. Bruix J et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. Volume 389, no. 10064, p56-66, 7 January 2017