Indication	**Upper GI:** Previously treated (with imatinib and sunitinib) Gastrointestinal stromal tumour (GIST) Second line systemic therapy of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma previously treated with sorafenib*. *patients can have received previous treatment with cabozantinib if treatment stopped **within 3 months** of its start, solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression. **Colorectal:** For the treatment of metastatic adenocarcinoma of the colon or rectum which has been previously treated with, or the patient is not considered a candidate for, available therapies including fluoropyrimidine-based chemotherapy and anti-EGFR-based treatment. No prior treatment with regorafenib is permitted.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 4 weeks Continue until progression of disease or unacceptable toxicity
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor LFT's prior to treatment and at least every 2 weeks during the first 2 cycles. Thereafter, prior to each cycle and as clinically indicated. • Monitor FBC & U&Es prior to each cycle. • If neuts <1.0 and/or PLT <50 d/w consultant • **Hepatic Impairment:** No dose reduction is required in mild hepatic impairment (Child-Pugh A). For moderate hepatic impairment (Child-Pugh B) d/w consultant, not recommended in severe hepatic impairment (Child-Pugh C). For patients with observed worsening liver function related to treatment, dose modification and monitoring advice should be followed. See table 2 for further details. • **Renal impairment**: No dose adjustment required. • Monitor BP before first cycle and monitor BP every week during first 6 weeks of treatment. Hypertension should be managed according to usual medical management. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the physician. • **Dose modifications** are made in 40mg steps. The lowest recommended daily dose is 80mg. See also tables below. • Discontinuation of regorafenib is recommended in patients developing gastrointestinal perforation or fistula. • Regorafenib may interfere with wound healing, interrupt treatment if patient undergoing surgical procedure. Discontinue 2 weeks before the elective surgical procedure, and resume 4 weeks after (or at clinician's discretion). • Monitor for clinical signs and symptoms of cardiac ischaemia, especially in patients with cardiac risk factors and/or history of coronary artery disease. In the case of patients developing cardiac ischaemia, interrupt and review. • Monitor for signs and symptoms of infection.

	• Monitor coagulation if patient predisposed to bleeding or if patient on medication which increases risk of bleeding. Patients on anti-coagulants should be closely monitored (INR/PT). • Posterior reversible encephalopathy syndrome (PRES) has been reported. If PRES develops, discontinue regorafenib and manage hypertension. • See Table 1 for recommended dose modifications and measures for hand-foot skin reaction (HSFR). • **Drug interactions:** o Avoid concomitant treatment with potent CYP3A4 inhibitors (e.g ketoconazole, itraconazole, clarithromycin, erythromycin) or inducers (e.g rifampicin, dexamethasone, phenytoin, carbamazepine) o Regorafenib may increase the plasma concentrations of BCRP substrates (methotrexate, fluvastatin, atorvastatin). It is recommended to monitor patients closely for signs/symptoms of increased exposure to BRCP substrates. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Cancerbackup information sheet
References	KMCC protocol UGI-048v3 SPC accessed online 24.11.22 CDF list accessed online 24.11.22

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Recommended dose modifications and measures for hand-foot skin reaction (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

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.

Repeat every 4 weeks

TTO	Drug	Dose	Route	Directions
Day 1	**REGORAFENIB** **(available as 40mg tablets)**	**160mg**	PO	**OD as a single dose for 3 weeks followed by 1 week rest period.** Tablets should be swallowed whole with water after a light (not high fat) meal. Should not be taken with grapefruit juice. If a dose is missed, then it should be taken on the same day as soon as possible. Two doses should not be taken on the same day to make up for a missed dose. In case of vomiting after administration, no additional tablets should be taken. Dispense 3x28 tablets per cycle.
	Metoclopramide	10mg	PO	TDS when required. Do not take for more than 5 days continuously. (dispense 28 tablets on cycle 1, then only if specified)
	Loperamide	2mg	PO	Take two capsules initially then one capsule after each loose stool when required (max. 16mg a day) (dispense 30 capsules on cycle 1 then only if specified)