REGORAFENIB (Stivarga)

INDICATION (ICD10) C18, C20, C22, C26, C49

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (REG2) (REG1) (REG3)

1. The second line of tyrosine kinase inhibitor systemic therapy of Child-Pugh A locally advanced or metastatic **hepatocellular** carcinoma previously treated with sorafenib (or cabozantinib which had to be stopped within 3 months solely as a result of dose limiting toxicity in the absence of disease progression). PS 0 or 1. (TA555)
2. The treatment of previously treated unresectable or metastatic **gastrointestinal stromal tumours** following disease progression on or intolerance to imatinib and to sunitinib. PS 0 or 1. (TA488)
3. Monotherapy or patients with metastatic **colorectal** adenocarcinoma cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-based chemotherapy and anti-EGFR-based treatment. PS 0 or 1. (TA866)

REGIMEN

Days 1 to 21	**REGORAFENIB**	160mg	oral	once daily followed by a 7 day rest

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression.

ANTI-EMETICS

Low emetic risk (none usually required)

CONCURRENT MEDICATION REQUIRED

Regorafenib	-

ADMINISTRATION

Regorafenib	Available as 40mg tablets. Swallowed whole with water after a light low fat meal.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration

FBC and U&E Neutrophils ≥1.0x10^9/L Platelets ≥50x10^9/L	baseline and every cycle
LFTs	baseline then every 2 weeks for first 2 cycles then every cycle
Thyroid function	baseline and every 12 weeks
Serum creatinine (and calculated CrCl)	baseline and every cycle
Hepatitis B exposure (refer to hepatology for lamivudine therapy)	before starting treatment
Blood pressure	Baseline and every cycle
ECG (possible ECHO) if patient has pre-existing cardiac disease	baseline
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Regorafenib	Diarrhoea Hepatotoxicity Hypertension Mucositis Skin reactions– apply moisturizer to hands and feet regularly

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Regorafenib	Anticoagulants and heparins may increase risk of bleeding. Strong CYP3A4 inhibitors - can increase exposure to regorafenib by up to 33%. Avoid concomitant use with ketoconazole, itraconazole, voriconazole, clarithromycin and grapefruit juice. Strong UGT1AP inhibitors - avoid concomitant use of drugs such as mefenamic acid. CYP3A4 inducers - can increase metabolism of regorafenib avoid (rifampicin, phenytoin, carbamazepine, phenobarbital and St John's Wort). BCRP substrates: can increase exposure to drugs such as rosuvastatin, atorvastatin and methotrexate.

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

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

Non-haematological

Regorafenib

Hepatotoxicity ALT and/or AST ≤5xULN (maximum Grade 2) Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to <3xULN (grade 1) or baseline.
ALT and/or AST >5xULN-≤20xULN (grade 3) 1st occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until return to <3xULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start regorafenib treatment, reduce dose by 40mg (one tablet), and monitor liver function weekly for at least 4 weeks.
ALT and/or AST >5xULN-≤20xULN (grade 3) Re-occurrence	Discontinue treatment with regorafenib permanently.
ALT and/or AST >20xULN (grade 4) Any occurrence	Discontinue treatment with regorafenib permanently.
ALT and/or AST >3xULN (grade 2 or higher) with concurrent bilirubin >2xULN 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.

Skin toxicity

Grade 1 Any occurrence	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2 1st occurrence	Decrease dose by 40mg (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.
Grade 2 No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Grade 2 3rd occurrence	Interrupt therapy until toxicity resolves to grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Grade 2 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 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Grade 3 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 40mg (one tablet).
Grade 3 3rd occurrence	Discontinue treatment with regorafenib permanently.

Hepatic impairment
Regorafenib
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)

Renal impairment
Regorafenib
No dose adjustment is required in mild, moderate or severe renal impairment.

REFERENCES
1. Bruix, J et al; Lancet 2017; 389 (10064): 56–66
2. Ann Oncol. 2016 Sep;27(9):1794-9. doi: 10.1093/annonc/mdw228. Epub 2016 Jul 1.
Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ben-Ami E1, Barysauskas CM2, von Mehren M3, Heinrich MC4, Corless CL5, Butrynski JE1, Morgan JA1, Wagner AJ1, Choy E6, Yap JT7, Van den Abbeele AD8, Solomon SM1, Fletcher JA9, Demetri GD10, George S11.

Assessments

	Pre	Cycle 1	Cycle 1 day 15	Cycle 2	Cycle 2 day 15	Cycle 3	Cycle 4	Ongoing
Informed consent	x							
Clinical assessment	x			Pre-C2		x	x	Once stable, alternate cycles
SACT assessment (PS and toxicities)	x	x		x		x	x	Every cycle
FBC	x	x		x			x	Every cycle
U&E & LFTs (including AST and ALP), phosphate & magnesium	x	x	x	x	x	x	x	Every cycle
Thyroid function	x							Every 12 weeks
CrCl	x	x		x			X	Every cycle
Blood pressure	x	x		x		x	x	Every bevacizumab dose
Urinalysis for proteinuria								Every bevacizumab dose
CT scan	x							Every 12 weeks
Weight recorded	x	x		x			x	Every cycle
Height	x	x		x			x	Every cycle