SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

REGORAFENIB COLORECTAL

PROTOCOL REF: MPHARECO
Version No. 1.0

Approved for use in:

- Metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-based chemotherapy and anti-EGFR-based treatment
- ECOG Performance Status 0 to 1 (PS2 does not meet NHS England criteria)

Indication requires 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)

Continue until progressive disease or unacceptable toxicity

Administration (+/- Counselling Points):

The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.

If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

The tablets should be swallowed whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30 g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of apple juice, and 1 cup of coffee or tea (520 calories, 2 g fat).

Supportive treatments:

Metoclopramide 10mg TDS PRN

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

Dosing in renal and hepatic impairment:

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

Hepatic

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
Less than or equal to 5 x ULN	Any occurrence	Continue regorafenib. Monitor LFT's weekly until returned to less than 3 x ULN or baseline
More than 5 x ULN but less than or equal to 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

	More than 20 x ULN	Any occurrence	Discontinue permanently
	More than 3 x ULN with concurrent bilirubin more than 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 outlined recommendations for the respective observed elevation of ALT and/or AST.

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}).

See SPC for full list www.medicines.org.uk

Main toxicities:

Dose reductions were common in the clinical trials (46% of patients in the consign study)

- Hypertension
- Nausea and vomiting
- Diarrhoea
- Mucositis
- Skin reactions including dry skin, rash, pruritus, Hand-Foot Syndrome and alopecia
- Anorexia and reduced appetite
- Fever
- Headache
- Dysphonia
- Thrombocytopenia
- Reduction in potassium, sodium, calcium, phosphate and magnesium levels
- Abnormal liver function test results (raised bilirubin and transaminases)
- Hypothyroidism

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

Dose Modifications and Toxicity Management:

Complete this guidance in line with SPC/ other protocols or trial protocols

Haematological toxicity (if required):

Proceed on day 1 if-

ANC greater than or equal to 1.0 x 10^9/L	Plt greater than or equal to 100 x 10^9/L

Delay 1 week on day 1 if-

ANC less than or equal to 0.9 x 10^9/L	Plt less than or equal to 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity (if required):

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 2 discontinue on 4th occurrence Grade 3 discontinue on 3rd Occurrence
Grade 4	-	Discontinue

Dose Reduction Level	Dose
1	120mg ONCE daily
2	80mg 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.

References:

Summary of product characteristics accessed 01/01/2023
https://www.medicines.org.uk/emc/product/1263#POSOLOGY

BNF available via: https://bnf.nice.org.uk/

CORRECT trial Lancet 2013 381 (9863): 303 to 312 Grothey et al

CONSIGN study Oncologist 2019 24(2): 185-192 Van Custem et al

Circulation/Dissemination

Date added into Q-Pulse	23rd March 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
February 2023	1.0	**Joanne McCaughey & Dr Zahed Khan**	New Document