Fruquintinib

Indication

Fruquintinib can be used as an option at third line or later if trifluridine– tipiracil with bevacizumab is not suitable, to treat metastatic colorectal cancer in adults when previous treatment has included:

• fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without anti-vascular endothelial growth factor (VEGF) treatment, and

• anti-epidermal growth factor receptor (EGFR) treatment if the cancer is RAS wild-type, unless this was not suitable.

Regimen details

Day	Drug	Dose	Route
1-21	Fruquintinib	5mg once daily	po

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity

Administration

Available as 1mg and 5mg capsules

Women of childbearing age must use effective contraception during, and up to 4 weeks after treatment

Male and female patients of childbearing potential must use highly effective contraception methods during treatment, and for at least 4 weeks following the last dose of fruquintinib.

Pregnancy status should be confirmed at each SACT assessment.

Missed dose: If less than 12 hours – take the current dose, and resume usual dosing the next day If more than 12 hours – omit the current dose, and resume usual dosing the next day

Vomiting: If vomiting occurs after a dose, the dose should not be repeated on the same day, resume the usual dose as scheduled on the following day

Pre-medication

None

Emetogenicity

This regime has low emetogenic potential

Additional supportive medication

Metoclopramide 10mg oral tablets up to three times a day when required

Loperamide 4mg initially then 2mg after each loose stool, max daily dose of 16mg

Extravasation

Not applicable

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
Calculated Creatinine Clearance	14 days
Calcium	14 days
LFT (including AST)	14 days
Blood pressure	14 days
Thyroid function tests	14 days
Urine dipstick for proteinuria	14 days
Hepatitis B serology (HBsAG, HBcAb)	none

Pre-existing high blood pressure must be controlled before starting treatment

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating fruquintinib, this risk should be carefully considered in patients with a history of risk factors such as hypertension or aneurysm.

Dosing in renal and hepatic impairment:

Renal

No dose adjustment is required for mild, moderate or severe renal impairment

Hepatic

Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change in treatment. Discuss deteriorating organ function with consultant.

Liver function	Fruquintinib dose
ALT/AST/ALP ≤ 2.5 x ULN Bilirubin <1.5x ULN	100%
** with liver metastases** ALT/AST/ALP ≤5 x ULN Bilirubin <1.5x ULN	100%
Not recommended in severe liver impairment	Discuss with consultant

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure, urine dipstick for proteinuria

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Bilirubin	≤ 1.5 x ULN
ALT/AST/ALP	≤ 2.5 x ULN (see recommendations)
Hb	≥ 95 g/L
Blood pressure	<150/100 mmHg

If only Hb is low (below 95g/dl) please contact doctor to arrange for blood transfusion but continue with treatment

Dose modifications and toxicity management

Haematological toxicity

Proceed on day 1 if ANC ≥ 1.5 x 10^9 /L and Plt ≥ 100x 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.

Dose Modifications:

Dose Modification	Dose and Regimen	Capsules
Level 0 (original dose)	5mg OD 3 weeks ON/ 1 week OFF	1mgx5 / dose
Level -1 (first dose reduction)	4mg OD 3 weeks ON/ 1 week OFF	1mgx4 / dose
Level -2 (second dose reduction)	3mg OD 3 weeks ON/ 1 week OFF	1mgx3 / dose

Each 28-day cycle

CTCAE v5.0 toxicity grading	Action
Grade 1 or 2[a]	None
Grade 3	Interrupt the dose until toxicity resolves to ≤ grade 1 or baseline level within 14 days, then reduce to a lower dose level
Grade 4	Discontinue permanently

a. If amylase/lipase are elevated, further evaluation for pancreatitis should be performed

b. Including Grade 3 diarrhoea and stomatitis, that are ineffectively treated with drug therapies

Adverse reaction	Dose adjustment
Gastrointestinal perforation	Discontinue fruquintinib
Arterial Thrombosis	Discontinue fruquintinib
Delayed wound healing	Follow general guidance for dose interruptions/reductions/ discontinuations
Reversible Posterior leukoencephalopathy Syndrome (RPLS)	If suspected RPLS, discontinue fruquintinib

Toxicities

Fruquintinib	
Delayed diarrhoea	Once a liquid stool occurs loperamide 4mg should be taken immediately, followed by 2mg every 2 hours for at least 12 hours, and for 12 hours following the last liquid stool. • Patients should be instructed to drink large volumes of water or electrolytes. • Do not continue high dose loperamide for longer than 48 hours • Any concomitant fever or vomiting will require hospitalisaton for rehydration • If diarrhoea persists after 48 hours then patients should be hospitalised for further management and treatment review.
Haemorrhagic events	Close monitoring of haematology parameters and coagulation profile - Original dose can be continued for Grade 1 haemorrhagic events - Temporarily discontinue once Grade 2 occurred, reduce dose - Discontinue permanently if develop Grade 3

Hypertension	- Temporarily discontinue if BP >160/100mmHg, and last more than 7 days after use of anti-hypertensive agents. Consider dose reductions. Please refer to parent team for management.
Posterior reversible encephalopathy syndrome (PRES)	- Discontinue fruquintinib, and perform CT/MRI imaging with neurologist referral
Palmar-plantar erythrodysesthesia (PPE)	- Grade 1 or 2 : symptomatic treatment + topical NSAIDs or oral NSAIDs (diclofenac) - Grade ≥ 3 :interrupt treatment temporarily, and reintroduce at reduced dose after toxicity returns to Grade 1 within 14 days
Proteinuria	24-hour urine for urine protein test - 24-hour urine protein <1g : close observation - 24-hour urine 1g-2g : temporarily discontinue fruquintinib - 24-hour urine > 2g : dose reduction if toxicity returns to Grade 1 within 2 weeks. If not, permanent discontinuation.
Gastrointestinal perforation	- Seek urgent medical attention at local A+E

Proteinuria:

1+ or 2+ on dipstick (0.3 – 2.9g/L)	3+ on dipstick (3 - 19g/L)	4+ on dipstick (≥ 20g/L)
Continue with Fruquintinib. No additional evaluation required	May have dose of Fruquintinib as scheduled, but will need 24 hour urine collection to measure protein a few days before next cycle due. **If 24hr protein result < 2g** Continue with Fruquintinib. With continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to < 1g/24hr, return to dipstick analysis. **If 24hr protein result ≥ 2g** Withhold Fruquintinib until repeat 24 hour urine collection shows < 2g protein. Then re-introduce Fruquintinib, with continued proteinuria monitoring via 24 hour urine.	Withhold Fruquintinib. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Hypertension

Baseline blood pressure <150/100 mmHg	
Diastolic increase >20mmHg above baseline, or BP rises > 150/100mmHg	Antihypertensive therapy may need needed. Refer to parent team for management
Blood pressure > 180/110mmHg	Hold Fruquintinib until blood pressure is controlled

Adverse effects –

for full details consult product literature/ reference texts

Fruquintinib
- **Hypertension** - **Asthenia / Weakness** - **Reduced appetite** - **Diarrhoea** - **Voice changes** - **Abdominal pain** - Haemorrhagic events - VTE risk (severe chest pain, shortness of breath, numbness/weakness-esp. unilateral, sudden severe headache, dizziness, loss of balance, sudden vision loss) - GI perforation - Increased infection risk - Hypothyroidism - Fatigue - Hand-foot-syndrome - Abdominal pain - Nausea - Proteinuria - Constipation - Dysphonia - Increased risk of IO-myocarditis - Thrombocytopenia / Leukopenia / Neutropenia - Stomatitis / Oral pain - Arthralgia - Posterior reversible encephalopathy (PRES) - Delayed wound healing – stop taking fruquintinib 2 weeks before planned surgery

Interactions-

Fruquintinib
- Rifampicin - Efavirenz Limited data, please check with pharmacist if concerned

Additional comments

Patients should not have received systemic anticancer therapies (including chemotherapy, TKIs, endocrine therapy) within 2 weeks prior to first dose of fruquintinib

Uncontrolled hypertension. Do not proceed if BP >140/90mmHg with/without antihypertensive agents; or if needs 2 or more antihypertensive agents to control BP

Unresolved toxicities- Ensure resolution of toxicities from previous antitumour treatment, to Grade 1 (CTCAE 5.0), except alopecia and neurotoxicity Grade ≤ 2

Do not start treatment within 60 days of major surgery or have had any other minor surgery or invasive procedure within last 4 weeks –

Caution with significant cardiovascular events (MI, unstable angina) and thromboembolic events (DVT, PE) within past 6 months, or history of stroke and/or TIA within last 12 months –

Previous medical history of HBV infection may need further liver function monitoring

Contraindicated in Females who are lactating or breastfeeding or with a positive urine/serum hCG test

Contraindicated in Hypersensitivity to fruquintinib and inactive ingredients (azo dye Tartrazine)

References

- FRESCO-2 global phase 3 trial : Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study - The Lancet 2023
- Fruquintinib Summary of Product Characteristics https://www.medicines.org.uk/emc/product/15999/smpc#gref (accessed 9th July 2025)
- Fruquintinib for previously treated metastatic colorectal cancer NICE appraisal TA11280 available at https://www.nice.org.uk/guidance/indevelopment/gid-ta11280 accessed 9 July 2025

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON, DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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