BC Cancer Protocol Summary for Treatment of Advanced Colorectal Cancer using Fruquintinib

Protocol Code	*UGIAVFRU*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:
Patient must have:
- Unresectable or metastatic colorectal adenocarcinoma or adenocarcinoma of the appendix or small bowel, and
- Prior treatment in the advanced setting with all (or not considered candidates for any) of the following:
    - standard fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy*,
    - an anti-VEGF therapy (e.g., bevacizumab),
    - an anti-EGFR therapy (e.g. PANitumumab, cetuximab) if RAS wild-type, and
    - trifluridine-tipiracil–based therapy,
    - an immune checkpoint inhibitor (if MSI-H or dMMR tumour),
    - a BRAF inhibitor (if BRAF-mutant tumour)

  *One of the prior lines of therapy could previously have been given in the neoadjuvant/adjuvant setting if recurrence occurred during or within 6 months of neoadjuvant/adjuvant treatment
- BC Cancer “Compassionate Access Program” request approval prior to treatment

Patients should have:
- Good performance status
- Adequate hematologic and hepatic function

EXCLUSIONS:
Patients must not have:
- Symptomatic CNS metastases that are neurologically unstable, and/or
- Need for increasing doses of steroids to control CNS disease.

CAUTIONS:
- Patients with thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or a history of stroke and/or transient ischemic attack within the last 12 months
- Uncontrolled hypertension and/or a history of aneurysm
- Concurrent anticoagulant therapy

TESTS:

- Baseline: CBC & Diff, ALT, alkaline phosphatase, total bilirubin, albumin, INR, TSH, dipstick or laboratory urinalysis for protein, blood pressure measurement
- Baseline if clinically indicated: creatinine, CEA, CA 19-9, GGT, ECG
- Every 2 weeks during Cycles 1 and 2: ALT, total bilirubin
- Prior to each cycle: CBC & Diff, ALT, total bilirubin, dipstick or laboratory urinalysis for protein, blood pressure measurement
- If clinically indicated: creatinine, INR weekly, TSH, alkaline phosphatase, sodium, potassium, calcium, magnesium, total cholesterol, triglycerides, ECG, CEA, CA 19-9
- 24-hour urine for protein if laboratory urinalysis for protein is greater than or equal 1 g/L or dipstick urinalysis shows 2+ proteinuria
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle
- Weekly telephone nursing assessment for signs and symptoms of side effects during Cycle 1 (Optional).

PREMEDICATIONS:

- Antiemetics are not usually required

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
fruquintinib	5 mg once daily on Days 1 to 21, then 7 days off	PO

Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Table 1 - Dose Reduction Levels for All Toxicities:

Starting Dose	Dose Level -1	Dose Level -2
5 mg	4mg	3mg

1. **Hepatotoxicity:**

ALT		Total Bilirubin	Management
Less than or equal to 3 x ULN	and/or	Less than or equal to 1.5 x ULN	Continue current dose
Greater than 3 x ULN	or	Greater than 1.5 x ULN	Hold treatment ▪ Once resolved or returned to baseline, resume at the next lower dose level. ▪ For persistent elevations not responding to dose reduction to 3 mg daily, permanently discontinue.
Greater than 3 x ULN	and	Greater than 2 x ULN (in the absence of other causes)	Permanently discontinue
Greater than 20 x ULN	or	Greater than 10 x ULN	Permanently discontinue

ULN = upper limit of normal
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2. **Hypertension:**
   - Initiate antihypertensive therapy if clinically indicated
   - If fruquintinib is held or discontinued, a drop in blood pressure should be anticipated. Antihypertensive dose adjustment or interruption may be required.

Blood Pressure (mmHg)	Management
Systolic blood pressure less than 160 OR Diastolic blood pressure less than 100	▪ Continue with current dose ▪ Start or adjust antihypertensive therapy as clinically indicated
Systolic blood pressure greater than or equal to160 OR Diastolic blood pressure greater than or equal to 100	▪ Start or adjust antihypertensive therapy ▪ If hypertension persists despite optimal management, hold treatment until systolic blood pressure recovers to less than 140 and diastolic blood pressure is less than 90, or baseline ▪ Once controlled, restart at next lower dose level ▪ For persistent hypertension after dose reduction to 3 mg daily, permanently discontinue.
Elevated blood pressure with life-threatening consequences, urgent intervention indicated	Permanently discontinue

3. **Hemorrhagic events:**

Severity*	Management
Grade 2 Moderate symptoms, intervention indicated	▪ Hold treatment until bleeding fully resolves or recovers to Grade 1 (mild symptoms; intervention not indicated) or baseline, then resume at the next lower dose level. ▪ For recurrent Grade 2 hemorrhagic events after dose reduction to 3 mg daily, permanently discontinue.
Grade 3 or 4 Transfusion indicated; invasive intervention indicated; hospitalization or life-threatening consequences; urgent intervention indicated	Permanently discontinue

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4. **Proteinuria:**

Proteinuria	Dose Modification
Negative or 1+ dipstick, or less than 1 g/L lab urine protein	Continue current dose
2+ dipstick or greater, or greater than or equal to 1 g/L lab urine protein	Continue current dose ▪ Obtain 24-hour urine collection ▪ Adjust treatment per table below
4+ dipstick or 3 g/L laboratory urinalysis for protein at baseline or during treatment	Hold treatment ▪ Obtain 24-hour urine collection ▪ Adjust treatment per table below
Nephrotic syndrome	Permanently discontinue

24-Hour Urine Total Protein (g/24 hours)	Management
Less than 2	Continue current dose
Greater than or equal to 2	▪ Hold treatment until proteinuria fully resolves or is less than 1g/ 24 hours ▪ Resume at reduced dose at next lower dose level ▪ If the patient continues to experience greater than or equal to 2 g/ 24 hours proteinuria after dose reduction to 3 mg daily, permanently discontinue
Nephrotic Syndrome	Permanently discontinue

5. **Palmar-plantar erythrodysesthesia (PPE):**

Grade*	Description	Fruquintinib Dose
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Continue current dose
2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Hold treatment ▪ Initiate supportive care treatment ▪ If toxicity fully resolves or recovers to Grade 1 or baseline, then resume at the same dose level.
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	Hold treatment ▪ Initiate supportive care treatment ▪ If toxicity fully resolves or recovers to Grade 1 or baseline, resume at the next lower dose level. ▪ For persistent Grade 3 not responding to 3 mg daily or Grade 4, permanently discontinue.

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6. **Other toxicity:**

Grade*	Dose Modification
3	Delay ▪ If toxicity fully resolves or recovers to Grade 1 or baseline, resume at the next lower dose level. ▪ For persistent Grade 3 reactions not responding to dose reduction to 3 mg daily, permanently discontinue.
4	Discontinue treatment ▪ Consider resuming at next lower dose level **only if** the toxicity is non-life threatening and fully resolves or recovers to Grade 1 or baseline and the potential benefit outweighs the risk.

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PRECAUTIONS:

1. **Hypertension:** The onset of hypertension usually occurs during the first 2 weeks of treatment. Pre-existing hypertension should be controlled prior to initiation of treatment with fruquintinib. Hypertension may be treated with a combination of standard antihypertensive therapy and fruquintinib dose reduction or interruption. Temporary suspension of fruquintinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with fruquintinib may be resumed once hypertension is controlled. Discontinue fruquintinib for hypertensive crisis, or severe and persistent hypertension despite anti-hypertensive therapy. Blood pressure should be monitored daily for the first 2 cycles of treatment. Blood pressure can be monitored either by the patient or by a primary care provider, provided the results are reviewed by treating clinician at each visit.
2. **Hepatotoxicity:** serious liver injury has been reported with fruquintinib. Closely monitor liver function during treatment. Depending on the severity of liver function test abnormalities, fruquintinib treatment may need to be withheld, dose reduced or permanently discontinued.
3. **Hemorrhagic events:** Fruquintinib can cause serious hemorrhagic events which may be fatal. Closely monitor patients who are at risk for bleeding. Monitor the INR levels in patients receiving anticoagulants. Withhold, reduce dose, or permanently discontinue based on severity and persistence of hemorrhage (see Dose Modifications).
4. **Proteinuria** can occur while on fruquintinib. Urine protein monitoring via routine urinalysis is recommended throughout treatment. If proteinuria is detected, dose interruption, adjustment, or discontinuation may be necessary. See Dose Modifications, above. Discontinue fruquintinib for nephrotic syndrome.

5. **Arterial thromboembolic events:** It is recommended to avoid starting treatment in patients with a history of thromboembolic events (including deep vein thrombosis and pulmonary embolism) within the past 6 months or if they have a history of stroke and/or transient ischemic attack within the last 12 months. If arterial thrombosis is suspected, fruquintinib should be permanently discontinued immediately.
6. **Aneurysm and artery dissection:** The use of VEGF pathway inhibitors may promote the formation of aneurysms and/or artery dissections. Before starting treatment with fruquintinib, this risk should be carefully considered in patients with a history of risk factors such as hypertension or aneurysm.
7. **Wound healing complications**: Withhold fruquintinib for 2 weeks before major surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing has occurred.
8. **Infections**: Infections, including fatalities, have been reported in patients treatment with fruquintinib. Do not initiate treatment with fruquintinib in patients with active infections. Monitor for infection during treatment and withhold for Grade 3 or 4 infections or worsening infection of any grade. Resume treatment at the same dose when the infection has resolved.
9. **Posterior reversible encephalopathy syndrome (PRES):** Fruquintinib may rarely cause PRES, also known as r**eversible posterior leukoencephalopathy syndrome (RPLS)**. Symptoms of PRES include seizures, headache, visual disturbances, or cortical blindness, with or without associated hypertension, confusion or altered mental function. Immediately discontinue treatment with fruquintinib if PRES is suspected and do not restart until PRES is ruled out as a cause.
10. **Palmar-plantar erythrodysesthesia (PPE):** is associated with fruquintinib treatment and may require dose interruption and/or adjustment (see dose modifications). Patients should be instructed on importance of preventative measures such as moisturizing and sun protection.
11. **Gastrointestinal (GI) perforation:** Fruquintinib can cause GI perforation. Patients should be monitored for symptoms of GI perforation and discontinue fruquintinib in patients who develop GI perforation or fistula.
12. **Drug interactions:** Avoid concomitant use of fruquintinib with strong CYP3A inducers. See BC Cancer Drug Manual.

Contact the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at 604-930-2098 with any problems or questions regarding this treatment program.

REFERENCES:

1. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA. 2018 Jun 26;319(24):2486-2496.
2. Dasari A, Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023 Jul 1;402(10395):41-53.
3. Kennecke H, Berry S, Maroun J, et al. A retrospective observational study to estimate the attrition of patients across lines of systemic treatment for metastatic colorectal cancer in Canada. Curr Oncol. 2019 Dec;26(6):e748-e754.
4. Fruquintinib (Fruzaqla) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies December 2024; 4(12):1-28.