BC Cancer Protocol Summary for Palliative Treatment of Metastatic Colorectal Cancer using Irinotecan, Oxaliplatin, Fluorouracil, Leucovorin, and Bevacizumab

***Protocol Code*:**	*GIAVFIROXB*
***Tumour Group*:**	*Gastrointestinal*
***Contact Physician*:**	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and
  - No prior chemotherapy in the advanced setting, or
  - Received prior immunotherapy if MMR deficient/MSI-H metastatic colorectal adenocarcinoma.

Note:

- Use of first-line GIAVFIROXB precludes the use of irinotecan and oxaliplatin based chemotherapy in any subsequent line of therapy

Patients should have:

- Good performance status
- Adequate marrow reserve, renal and liver function

EXCLUSIONS:

Patient must not have:

- Major surgery within 28 days of administration of therapy
- Untreated CNS metastases
- Congenital long QT syndrome
- Progression on or within 6 months of adjuvant treatment completion

CAUTIONS:

- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, renal disease including proteinuria, bleeding disorders, previous anthracycline exposure, prior radiation to the chest wall or other serious medical illness
- Patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Patients with symptomatic peripheral neuropathy
- Patients with recent (less than 6 months) arterial thromboembolic events
- Patients with baseline hyperbilirubinemia (greater than 26 micromol/L) not explained by degree of liver metastases

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), dipstick or laboratory urinalysis for protein, blood pressure measurement
- Baseline if clinically indicated: CEA, CA 19-9, GGT, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, blood pressure measurement
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG
- Prior to each *even* numbered cycles: dipstick or laboratory urinalysis for protein
- 24 hour urine for protein if occurrence of proteinuria dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1 g/L
- Blood pressure measurement to be taken pre and post dose for first 3 cycles only and then pre-therapy with each subsequent visit.
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see precautions)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia
- If Grade 1 or 2 oxaliplatin hypersensitivity reactions:
  - 45 minutes prior to oxaliplatin:
    - dexamethasone 20 mg IV in 50 mL NS over 15 minutes
  - 30 minutes prior to oxaliplatin:
    - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
- Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.
- Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.

TREATMENT:

A cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
oxaliplatin*	85 mg/m^2	IV in 250 to 500 mL D5W over 2 hours
leucovorin†	400 mg/m^2	IV in 250 mL D5W over 1 hour 30 minutes**
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 minutes**
fluorouracil†	400 mg/m^2	IV push, after leucovorin, THEN
bevacizumab	5 mg/kg††§	IV in 100 mL NS over 10 minutes‡
fluorouracil	2400 mg/m^2§	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ***

Repeat every 14 days until disease progression or unacceptable toxicity.

* Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.

** Irinotecan and leucovorin may be infused at the same time by using a Y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag

† fluorouracil IV push is optional in the advanced setting:

fluorouracil IV push	leucovorin administration options
fluorouracil IV push given	• leucovorin given as IV infusion OR • leucovorin given as 20 mg/m^2 IV push
fluorouracil IV push omitted	• leucovorin omitted OR • leucovorin given as IV infusion OR • leucovorin given as 20 mg/m^2 IV push

†† The bevacizumab dose should be recalculated for patients who experience more than a 10% change in body weight. Select dose per Dose Banding Table (appendix).

‡ Observe for fever, chills, rash, pruritus, urticaria or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted then it should be given at an initial rate of 60 minutes or longer.

If acute hypertension (increase in BP measurement of greater than 20 mm Hg diastolic or greater than 160/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at ½ the original rate of infusion if blood pressure returns to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab and subsequent infusions of bevacizumab should be given over 3 hours. Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

Line should be flushed with Normal Saline pre and post dose as bevacizumab should not be mixed with dextrose solutions.

§ Select dose per Dose Banding Table (appendix).

*** *A*lternative administration:

- Inpatients: 1200 mg/m^2/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for the management of diarrhea.

DOSE MODIFICATIONS (A, B & C):

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

A. Dose Modifications for NEUROLOGIC Toxicity
B. Dose Modifications for HEMATOLOGIC Toxicity
C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Table 1 - Dose Reduction Levels for All Toxicity

Agent	Starting Dose	Dose Level -1	Dose Level -2*
oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
leucovorin	No dose modifications. ▪ If fluorouracil push is omitted, leucovorin may also be omitted or given as 20 mg/m^2 IV push ▪ If oxaliplatin is omitted, leucovorin may be given as 20 mg/m^2 IV push		
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
fluorouracil push	400 mg/m^2	320 mg/m^2	200 mg/m^2
fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2

* For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.

Table 2 - Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with Oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

A. Dose Modifications for oxaliplatin NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 to 7 days	Greater than 7 days	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	1st time: ↓ 1dose level 2nd time: ↓ 1dose level	Discontinue
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Increase duration of infusion to 6 hours	N/A	N/A

B. Dose Modifications for HEMATOLOGIC Toxicity based on Day 1 CBC
NOTE: Dose reductions should be maintained for subsequent cycles.

<table>
<tr><th rowspan="2"></th><th rowspan="2">CYCLE DELAY</th><th colspan="3">DOSE REDUCTION</th></tr>
<tr><th>irinotecan</th><th>oxaliplatin</th><th>leucovorin/
fluorouracil</th></tr>
<tr><td>ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L</td><td>No cycle delay</td><td colspan="3">No dose reduction</td></tr>
<tr><td rowspan="2">ANC greater than or equal to 1.0 x 10^9/L and less than 1.5 x 10^9/L</td><td rowspan="2">Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L

If no recovery in 2 weeks, discontinue the treatment*.</td><td>1st episode: dose reduction to 150 mg/m^2

2nd episode: maintain dose at 150 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: no dose reduction

2nd episode: dose reduction to 65 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level

2nd episode – eliminate the IV push fluorouracil and leucovorin infusion and maintain infusional fluorouracil at dose level -1

3rd episode: discontinue the treatment</td></tr>
<tr><td colspan="3">NOTE: Dose reductions should be maintained for subsequent cycles.</td></tr>
</table>

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<tr><th rowspan="2"></th><th rowspan="2">CYCLE DELAY</th><th colspan="3">DOSE REDUCTION</th></tr>
<tr><th>irinotecan</th><th>oxaliplatin</th><th>leucovorin/
fluorouracil</th></tr>
<tr><td rowspan="2">ANC greater than or equal to 0.5 10^9/L and less than 1.0 x 10^9/L</td><td rowspan="2">Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L

GCSF support should be considered

If no recovery in 2 weeks, discontinue the treatment.</td><td>1st episode: dose reduction to 150 mg/m^2

2nd episode: dose reduction to 120 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: no dose reduction

2nd episode: dose reduction to 65 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: eliminate the IV push fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level

2nd episode: maintain the reduced dose

3rd episode: discontinue the treatment</td></tr>
<tr><td colspan="3">NOTE: Dose reductions should be maintained for subsequent cycles.</td></tr>
<tr><td rowspan="2">ANC less than 0.5 x 10^9/L</td><td rowspan="2">Delay the treatment until ANC greater than or equal to 1.5 x 10^9/L

GCSF support should be considered

If no recovery in 2 weeks, discontinue the treatment.</td><td>1st episode: dose reduction to 150 mg/m^2

2nd episode: dose reduction dose at 120 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: dose reduction to 65mg/m2

2nd episode: dose reduction to 50 mg/m^2

3rd episode: discontinue the treatment</td><td>1st episode: eliminate the IV push fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level

2nd episode: maintain the reduced dose

3rd episode: discontinue the treatment</td></tr>
<tr><td colspan="3">NOTE: Dose reductions should be maintained for subsequent cycles.</td></tr>
</table>

	CYCLE DELAY	DOSE REDUCTION		
		irinotecan	**oxaliplatin**	**leucovorin/ fluorouracil**
Platelets greater than or equal to 50 x 10^9/L and less than 75 x 10^9 /L	Delay the treatment until recovery (platelets greater than or equal to 75 x 10^9/L). If no recovery in 2 weeks, **discontinue the treatment**.	**1st episode**: no dose reduction **2nd episode**: reduce the dose to 150 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: dose reduction to 65 mg/m^2 **2nd episode**: maintain the reduced dose **3rd episode**: **discontinue the treatment**	**1st episode**: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level **2nd episode**: maintain the reduced dose **3rd episode: discontinue the treatment**
		NOTE: Dose reductions should be maintained for subsequent cycles.		
Platelets less than 50 x10^9 /L	Delay the treatment until recovery (platelets greater than or equal to 75 x 10^9/L). If no recovery in 2 weeks, **discontinue the treatment**.	**1st episode**: no dose reduction **2nd episode**: dose reduction to 150 mg/m^2 **3rd episode**: **discontinue the treatment**	**1st episode**: dose reduction to 65 mg/m^2 **2nd episode**: dose reduction to 50mg/m2 **3rd episode**: **discontinue the treatment**	**1st episode**: reduce the IV push fluorouracil and the infusional fluorouracil by one dose level **2nd episode** – eliminate the IV push fluorouracil and leucovorin infusion and maintain the infusional fluorouracil at dose level -1 **3rd episode**: **discontinue the treatment**
		NOTE: Dose reductions should be maintained for subsequent cycles.		

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	**Diarrhea**	
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of irinotecan and infusional fluorouracil. Discontinue IV push fluorouracil and leucovorin.
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level of oxaliplatin and infusional fluorouracil. Discontinue irinotecan, IV push fluorouracil and leucovorin.
	Grade	**Stomatitis**	
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level of IV push and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of oxaliplatin, irinotecan and infusional fluorouracil. Discontinue IV push fluorouracil and leucovorin.

Proteinuria:

There are 3 different measures of proteinuria that may be used to assess the need for modification of Bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24 hour urine collections for protein (measured in g/24 hours)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each even numbered cycle of therapy:

Degree of Proteinuria	
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer Bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer Bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust Bevacizumab treatment based on the table below.
If urine dipstick shows 4+ at baseline or during treatment	Withhold Bevacizumab and proceed with 24 hour urine collection

24-Hour Urine Total Protein (g/24 hours)	**Bevacizumab Dose**
Less than or equal to 2	100%
Greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2 g/24 hour
Greater than 4	Discontinue Therapy

Hypertension:

Blood Pressure (mm Hg)	Bevacizumab Dose
Less than or equal to 160/100	100%
Greater than 160/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy*
Hypertensive Crisis	Discontinue Therapy

- Antihypertensive therapy may include hydroCHLOROthiazide 12.5 to 25 mg PO once daily, ramipril (ALTACE®) 2.5 to 5 mg PO once daily, or amlodipine (NORVASC™) 5 to 10 mg PO once daily.

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required (see table below). For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication. See Premedications.

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

2. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	Pharyngo-laryngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with oxaliplatin. Supportive care is required. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed **oxaliplatin should be discontinued.**
4. **Diarrhea:** may be life threatening and requires prompt, aggressive treatment.
   - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
   - **Late diarrhea** has an onset of 5 to 11 days post-treatment, a duration of 3 to 7 days and must be treated promptly with **loperamide** (eg, IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
     - **4 mg stat**
     - **then 2 mg every 2 hours until diarrhea-free for 12 hours**
     - may take 4 mg every 4 hours at night
   - The use of drinks such as GATORADE® or POWERADE® to replace fluid & body salts is recommended.

- Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.

5. **Other cholinergic symptoms:** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
6. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
7. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. **GCSF support should be initiated for further cycles after an episode of febrile neutropenia.**
8. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
9. **Hepatic dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or ALT greater than 3x the upper limit of normal if no liver metastases, or ALT greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17 to 35 micromol/L.
10. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.
11. **Gastrointestinal perforations and wound dehiscence**: Can be fatal. Typical presentation is reported as abdominal pain associated with symptoms such as constipation and vomiting. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.
12. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue Bevacizumab. Patients with significant bleeding diatheses should not receive Bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of Bevacizumab. COX-2 inhibitors are permissible. For patients on warfarin, see under Thrombosis.
13. **Thrombosis:** A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with Bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary embolus arises, hold Bevacizumab for 2 weeks, then consider resumption of Bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue Bevacizumab. Patients on warfarin should have INR checked frequently, at least once per cycle, while receiving Bevacizumab. In patients receiving warfarin with an elevated INR, it is recommended to **hold the bevacizumab if INR is greater than 3.0.**

14. **Proteinuria**: Has been seen in all clinical trials with Bevacizumab to date and is likely dose-dependent. If proteinuria of greater than or equal to 2g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
15. **Hypertension**: Has been seen in all clinical trials with Bevacizumab to date and is likely dose-dependent. The most commonly used therapies are Calcium Channel Blockers, ACE Inhibitors and Diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue Bevacizumab.
16. **Reversible Posterior Leukoencephalopathy Syndrome:** Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
17. **Congestive Heart Failure:** Has been reported in up to 3.5% of patients treated with Bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.
18. **Myocardial** ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
19. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
20. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
21. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
22. **Venous Occlusive Disease** is a rare but serious complications that has been reported in patients (0.02%) receiving Oxaliplatin in combination with Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
23. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, Oxaliplatin should be permanently discontinued.
24. **Potential Drug Interactions:** Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. carbamazepine, phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.

25. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of fluorouracil, repeat INR weekly for one month.
26. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.

Call 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. Cremolini C, Antoniotti C, Stein A, et al. Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer. J Clin Oncol. 2020 Aug 20:JCO2001225.
2. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020 Apr;21(4):497-507.
3. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015 Oct;16(13):1306-15.
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Appendix. Dose Bands

BEVACIZUMAB DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 188		**Pharmacy prepares specific dose**
188	221.49	**200**
221.5	236.49	**225**
236.5	260.49	**250**
260.5	286.49	**275**
286.5	332.49	**300**
332.5	387.49	**350**
387.5	443.49	**400**
443.5	474.49	**450**
474.5	554.49	**500**
554.5	665.49	**600**
665.5	776.49	**700**
776.5	887.49	**800**
887.5	999.49	**900**
999.5	1099.49	**1000**
1099.5	1199.49	**1100**
1199.5	1299.49	**1200**
1299.5	1399.49	**1300**
1399.5	1499.49	**1400**
1499.5	1599.49	**1500**
1599.5	1699.49	**1600**
1699.5	1799.49	**1700**
1799.5	1899.49	**1800**
1899.5	1999.49	**1900**
1999.5	2099.49	**2000**
2099.5	2199.49	**2100**
2199.5	2299.49	**2200**
2299.5	2399.49	**2300**
More than 2399.49		**Pharmacy prepares specific dose**

FLUOROURACIL DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg) for INFUSOR
From:	To:	
Less than 3000		**Pharmacy prepares specific dose**
3000	3400	**3200 mg**
3401	3800	**3600 mg**
3801	4200	**4000 mg**
4201	4600	**4400 mg**
4601	5000	**4800 mg**
5001	5500	**5250 mg**
More than 5500		**Pharmacy prepares specific dose**