

BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, Leucovorin, and Bevacizumab

Protocol Code:

GIFFOX B

Tumour Group:

Gastrointestinal

Contact Physician:

GI Systemic Therapy

ELIGIBILITY:

- First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation and for adenocarcinoma of the appendix and small bowel.
- Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for pre-operative therapy with bevacizumab
- Note: Patients with relapsed or refractory disease with first line anti-EGFR therapy will not be eligible for second line bevacizumab therapy or third line anti-EGFR therapy.
- No major surgery within 28 days of administration of therapy
- No untreated CNS metastases
- ECOG performance status less than or equal to 2
- Patients who have received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy.
- Patients who have progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired.

EXCLUSIONS:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid oxaliplatin in patients with congenital long QT syndrome.

CAUTIONS:

- **Adequate marrow reserve, renal and liver function**
- 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

TESTS AND MONITORING:

- **Baseline:** CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), albumin, sodium, potassium, magnesium, calcium, dipstick or laboratory urinalysis for protein, Blood Pressure measurement and appropriate imaging study. Optional: CEA, CA 19-9
- **Prior to each cycle:** CBC and differential, platelets, creatinine, LFT's (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium, albumin, Blood Pressure measurement
- If clinically indicated: CEA, CA 19-9
- **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 1g/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.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.
- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.

PREMEDICATIONS:

- Antiemetic protocol for high-moderate emetogenic chemotherapy (see SCNAUSEA)
- **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 of D5W over 2 hours
leucovorin*	400 mg/m ²	IV in 250 mL D5W over 2 hours
fluorouracil	400 mg/m ²	IV push, after Leucovorin, THEN
bevacizumab	5 mg/Kg†	IV in 100 mL NS over 15 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 for until disease progression.

** Oxaliplatin and Leucovorin may be infused over the same two hour period by using a Y- site connector placed immediately before the injection site. Oxaliplatin and Leucovorin should not be combined in the same infusion bag. Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline. Leucovorin dose remains at 400 mg/m² IV over 2 hours when concurrent oxaliplatin is omitted.*

† The Bevacizumab dose should be recalculated for patients who experience more than a 10% change in body weight.

‡ 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.

** Alternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside dose banding range are prepared as ordered):**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m²/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.

DOSAGE MODIFICATIONS (A, B & C)

- 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
fluorouracil IV 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

If IV push fluorouracil is delayed/omitted, leucovorin may also be delayed/omitted or reduced to 20 mg mg/m² IV push.

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

***** The recommended starting doses are based on the modified FOLFOX6 regimen which is widely accepted but has not been studied in comparison to the original FOLFOX6 regimen. Patients may start with oxaliplatin 100 mg/m² as per FOLFOX6 at the discretion of their physician.***

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 – 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	1 st time: ↓ 1 dose level 2 nd time: ↓ 1 dose level	1 st time: ↓ 1dose level 2 nd time: ↓ 1dose level	Discontinue
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Maintain dose level	N/A	N/A

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x10 ⁹ /L)	oxaliplatin	fluorouracil
<ul style="list-style-type: none"> ▪ If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). ▪ If ANC remains less than 1.2 after 2 weeks, discontinue treatment. 	1	greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	Maintain dose level
	4	less than 0.5	↓ 1 dose level	omit IV push and ↓ 1 infusion dose level
	Grade	Platelets (x10 ⁹ /L)	oxaliplatin	fluorouracil
<ul style="list-style-type: none"> ▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). ▪ If platelets remain less than 75 after 2 weeks, discontinue treatment. 	1	greater than or equal to 75	Maintain dose level	Maintain dose level
	2	50 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 1 dose level	Maintain dose level
	4	less than 10	↓ 2 dose levels	Maintain dose level

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

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Diarrhea	
<ul style="list-style-type: none"> ▪ 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 IV push and infusional fluorouracil
	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, IV push and infusional fluorouracil
	Grade	Stomatitis	
<ul style="list-style-type: none"> ▪ 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, IV push and infusional fluorouracil

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 2g/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 25mg PO once daily, ramipril (ALTACE®) 2.5 to 5 mg PO once daily, or amlodipine (NORVASC™) 5 to 10mg 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 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:

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)

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 SCOXR: 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. **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.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **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.
6. **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.
7. **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.**
8. **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.
9. **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.
10. **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.
11. **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.
12. **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.
13. **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.

14. **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.
15. 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.
16. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
17. **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.
18. 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.
19. **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.
20. **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:

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