BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer using Irinotecan, Fluorouracil, Leucovorin, and Bevacizumab

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

ELIGIBILITY:

Patient must have:

- Locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and for adenocarcinoma of the appendix and small bowel, and
  - No prior chemotherapy in the advanced setting, or
  - Previously not been suitable for therapy with bevacizumab but whose bevacizumab contraindication has since resolved, or
  - Received prior immunotherapy with UGIAVPEM or UGIAVPEM6 if MMR deficient metastatic colorectal adenocarcinoma, or
  - Received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy, or
  - Progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired, or
  - Left-sided* colorectal adenocarcinoma, previously treated with GIFFOXPAN or GIFFIRPAN

  * Left-sided = splenic flexure to rectum

Patients should have:

- ECOG performance status less than or equal to 2
- Adequate marrow reserve, renal and liver function

Notes:

- Consideration of first line oxaliplatin-based therapy (GIFFOXB) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities
- Patients with metastatic colorectal cancer without left-sided primary may receive either bevacizumab or PANitumumab based treatment, but not sequential use of these agents

EXCLUSIONS:

Patients must not have:

- Major surgery within 28 days of administration of therapy
- Untreated CNS metastases

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 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
- At the beginning of 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.

PREMEDICATIONS:

- Antiemetic protocol for moderately 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.

TREATMENT:

A Cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 min*
leucovorin†	400 mg/m^2	IV in 250 mL D5W over 1 hour 30 min*
fluorouracil†	400 mg/m^2	IV push
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 until disease progression.

* 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.

** 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 than160/100 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 than180/110 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.

† 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

**** *A*lternative 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/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:

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.

Dose Levels for Toxicities

Agent	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2	Dose Level –3
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	Discontinue Therapy
leucovorin	No dose modifications. ▪ If fluorouracil push is omitted, leucovorin may also be omitted or given as 20mg mg/m^2 IV push ▪ If irinotecan is omitted, leucovorin may be given as 20 mg/m^2 IV push			
fluorouracil push	400 mg/m^2	320 mg/m^2	240 mg/m^2	Discontinue Therapy
fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue Therapy

A. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**irinotecan**	**fluorouracil**
▪ If ANC less than 1.5 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.5 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 1.5 after 2 weeks, discontinue treatment.	1	Greater than or equal to 1.5	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.5	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	↓ 1 dose level
	4	Less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia & greater than or equal to Grade 2 fever		↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Platelets ($x10^9$/L)**	**irinotecan**	**fluorouracil**
▪ 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	↓ 1 dose level
	4	Less than 10	↓ 2 dose levels	↓ 2 dose levels

B. Dose Modifications for NON-HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Diarrhea**	**irinotecan**	**fluorouracil**
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any 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	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	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	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Stomatitis**	**irinotecan**	**fluorouracil**
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any 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	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Maintain dose level	↓ 2 dose levels

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	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. **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.
2. **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.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

4. **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.
5. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. 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.
6. **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 on warfarin with an elevated INR, it is recommended to **hold the bevacizumab if INR is greater than 3.0**
7. **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.
8. **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.
9. **Reversible Posterior Leukoencephalopathy Syndrome:** Rarely, patients receiving bevacizumab 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.
10. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
11. **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.
12. **Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely. Supportive care is required.
13. **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.
14. **Stomatitis**: Sucking ice chips may be considered for patients experiencing stomatitis. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches, which subside quickly.
15. **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.

16. **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.
17. **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.
18. **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.
19. **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. Tournigand C, et al. FOLFIRI followed by FOLFOX versus FOLFOX followed by FOLFIRI in metastatic colorectal cancer (MCRC): Final results of a phase III study. Proc Am Soc Clin Oncol 2001;20:abstract 494.
2. Tournigand C, et al. Results of a strategic phase III study in metastatic colorectal cancer: FOLFIRI then FOLFOX or inverse aequence? Proc Int Cong Anti-Cancer Treat 2002:137.
3. Douillard JY, et al. Irinotecan combined with Fluorouracil compared with Fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355(9209):1041-7.
4. Wasserman E, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8(10):1049-51.
5. Mathijssen RHJ, et al. Effects of St. John's wort on Irinotecan metabolism. J Natl Cancer Inst 2002;94(16):1247-9.
6. Tournigand C, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22(2):229-37.
7. Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil and leuocovorin for metastatic colorectal cancer. N Engl J Med 2004;350(23):2335-42.
8. Kabbinavar F, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:1-9.
9. Kabbinavar F, et al. Combined analysis of efficacy: the addition of Bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer J Clin Oncol 2005;23:3697-3705.
10. Saltz LB, et al. Simplification of bevacizumab (bev) administration: Do we need 90, 60, or even 30 minute infusion times? J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):3542.
11. Peng C, Saffo S, Shusterman M, et al. Analysis of the Impact of Eliminating Bolus 5-fluorouracil in Metastatic Colorectal Cancer. J Clin Onc. 2023 Feb 1;41 (4): Suppl.59
12. Peng C, Saffo S, Oberstein PE, et al. Omission of 5-Fluorouracil Bolus From Multidrug Regimens for Advanced Gastrointestinal Cancers: A Multicenter Cohort Study. J Natl Compr Canc Netw. 2024 Sep 5;22(8):521-527.
13. CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Review. Provisional Funding Algorithm. Metastatic colorectal cancer. May 2024.