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.
- Consideration of first line oxaliplatin-based therapy (UGIFFOXB) should be given for those patients who have Gilbert’s Syndrome or who may be compromised by potential irinotecan toxicities.
- Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line 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/combotherapy is desired.
- Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L).
- Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; ALT and Alkaline Phosphatase less than or equal to 5 x ULN).
- Caution in 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.
- Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy).
- Caution in patients with recent (less than 6 months) arterial thromboembolic events.

EXCLUSIONS:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions).

TESTS AND MONITORING:

- **Baseline**: CBC and differential, Platelets, Creatinine, LFTs (Bilirubin, ALT, Alkaline Phosphatase), dipstick or laboratory urinalysis for protein, Blood Pressure measurement and appropriate imaging study. Optional: CEA, CA 19-9.
- **Recommended Baseline Tests**: sodium, potassium and albumin.
- **Prior to each cycle**: CBC and differential, Platelets, Blood Pressure measurement.
- **Each time seen by physician**: LFT’s (Bilirubin, ALT, Alkaline Phosphatase), Creatinine, sodium, potassium, Albumin.
- **If clinically indicated**: CEA, CA 19-9.
- **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.
- 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)
- 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:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>irinotecan*</td>
<td>180 mg/m²</td>
<td>IV in 500 mL of D5W over 1 hour 30 min</td>
</tr>
<tr>
<td>leucovorin*</td>
<td>400 mg/m²</td>
<td>IV in 250 mL D5W over 1 hour 30 min</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>400 mg/m²</td>
<td>IV push, after Leucovorin, THEN</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>5 mg/Kg**</td>
<td>IV in 100 ml NS over 10 minutes***</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>2400 mg/m²</td>
<td>IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ****</td>
</tr>
</tbody>
</table>

Repeat every 14 days for 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 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.

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

**DOSAGE MODIFICATIONS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Level 0 (Starting Dose)</th>
<th>Dose Level –1</th>
<th>Dose Level –2</th>
<th>Dose Level –3</th>
</tr>
</thead>
<tbody>
<tr>
<td>irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
<td>Discontinue Therapy</td>
</tr>
<tr>
<td>leucovorin*</td>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td>Discontinue Therapy</td>
</tr>
<tr>
<td>fluorouracil IV push</td>
<td>400 mg/m²</td>
<td>320 mg/m²</td>
<td>240 mg/m²</td>
<td>Discontinue Therapy</td>
</tr>
<tr>
<td>fluorouracil infusion</td>
<td>2400 mg/m²</td>
<td>2000 mg/m²</td>
<td>1600 mg/m²</td>
<td>Discontinue Therapy</td>
</tr>
</tbody>
</table>

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

- Maintain dose level
- Maintain dose level

### B. Dose Modifications for NON-HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1) | Toxicity | Dose Level For Subsequent Cycles
--- | --- | ---
| Grade | Platelets ($x10^9$/L) | irinotecan | fluorouracil |
| 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 |

### Diarrhea

- If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum
- Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output

- Maintain dose level
- Maintain dose level

---

BC Cancer Protocol Summary GIFFIRB

Activated: 1 Jan 2006  |  Revised: 6 May 2019 (Eligibility and treatment duration)

Warning: The information contained in these documents is a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/legal.htm
Prior to a Cycle (Day 1) | Toxicity | Dose Level For Subsequent Cycles
--- | --- | ---
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. | 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**
--- | --- | ---

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stomatitis</th>
<th>irinotecan</th>
<th>fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema, edema, or ulcers but can eat</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>3</td>
<td>Painful erythema, edema, ulcers, and cannot eat</td>
<td>Maintain dose level</td>
<td>↓ 1 dose level</td>
</tr>
<tr>
<td>4</td>
<td>As above but mucosal necrosis and/or requires enteral support, dehydration</td>
<td>Maintain dose level</td>
<td>↓ 2 dose levels</td>
</tr>
</tbody>
</table>

**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

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

**24-Hour Urine Total Protein (G/24 hours)**

<table>
<thead>
<tr>
<th>24-Hour Urine Total Protein (G/24 hours)</th>
<th>Bevacizumab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than or equal to 2</td>
<td>100%</td>
</tr>
<tr>
<td>greater than 2 to 4</td>
<td>Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24 hour</td>
</tr>
<tr>
<td>greater than 4</td>
<td>Discontinue Therapy</td>
</tr>
</tbody>
</table>

**Hypertension:**

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>Bevacizumab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than or equal to 160/100</td>
<td>100%</td>
</tr>
<tr>
<td>greater than 160/100</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Notify physician and start or adjust antihypertensive therapy*</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>Discontinue Therapy</td>
</tr>
</tbody>
</table>

- **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. **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 to 1.2 mg IV or SC. 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 to 0.6 mg IV or SC. This dose may be repeated at the physician’s discretion. Blood pressure and heart rate should be monitored. 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.

1. **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.

5. **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**

6. **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.

7. **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.

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. **Pulmonary toxicity**: Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely. Supportive care is required.

11. **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.

12. **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.

13. **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.

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. **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.
16. **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.

17. **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. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

**References**
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-.