BC Cancer Protocol Summary for Therapy of Advanced Colorectal Cancer using Trifluridine-Tipiracil and Bevacizumab

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

ELIGIBILITY:

Patients must have:

- Unresectable or metastatic colorectal adenocarcinoma or adenocarcinoma of the appendix or small bowel, and
- Prior treatment in the advanced setting* which must include:
  - Fluoropyrimidine, irinotecan, oxaliplatin, and
  - Anti-VEGF monoclonal antibody (e.g., bevacizumab) and/or an anti-EGFR monoclonal antibody (e.g. PANitumumab, cetuximab) for RAS wild-type disease

  * One of the prior lines of therapy could previously have been given in the neoadjuvant/adjuvant setting if recurrence occurred during or within 6 months of neoadjuvant/adjuvant treatment

Note: the following patients are eligible if other criteria are met:

- Patients previously treated with raltitrexed due to intolerance of fluoropyrimidine,
- Patients not suitable for irinotecan (e.g., due to concerns of bowel toxicity) or oxaliplatin (e.g., severe peripheral neuropathy),
- Patients who were previously not suitable for bevacizumab but whose bevacizumab contraindication has since resolved

Patients should have:

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

EXCLUSIONS:

Patients must not have:

- Major surgery within 28 days of administration of therapy,
- Unstable 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 recent (less than 6 months) arterial thromboembolic events

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, dipstick or laboratory urinalysis for protein, blood pressure measurement
- Baseline if clinically indicated: CEA, 19-9, GGT, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, dipstick or laboratory urinalysis for protein, blood pressure measurement
- Blood pressure measurement to be taken pre and post dose for first 3 bevacizumab doses only and then pre-therapy with each subsequent visit
- Day 15 of Cycle 1, and in subsequent cycles if trifluridine-tipiracil dose modification: CBC & Diff
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG, 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
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy protocols for trifluridine-tipiracil (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
bevacizumab	5 mg/kg* on Days 1 and 15	IV in 100 mL NS over 15 minutes**
trifluridine-tipiracil	35*** mg/m^2 BID on Days 1 to 5 and Days 8 to 12	PO

* 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 blood pressure measurement of greater than 20 mm Hg diastolic or greater than 160/100 mmHg 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 blood pressure measurement of greater than 180/110 mmHg that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

*** based on the trifluridine component; up to maximum of 80 mg/dose. Round trifluridine-tipiracil dose to nearest 5 mg

Repeat every 28 days (one cycle) until progression or unacceptable toxicity.

Suggested trifluridine-tipiracil Dose Dispensing Table:

Dose (mg)* (given BID)	Number of Tablets per Dose	
	15 mg Tablet	20 mg Tablet
20	0	1
25	**See note, below	
30	2	0
35	1	1
40	0	2
45	3	0
50	2	1
55	1	2
60	0	3
65	3	1
70	2	2
75	1	3
80	0	4

* based on the trifluridine component; up to maximum of 80 mg/dose.
15 mg tablet = trifluridine-tipiracil 15 mg-6.14 mg tablet
20 mg tablet = trifluridine-tipiracil 20 mg-8.19 mg tablet

**A total daily dose of trifluridine-tipiracil 50 mg should be taken as 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening

DOSE MODIFICATIONS:

- Patients who are intolerant/unable to continue bevacizumab may continue trifluridine-tipiracil monotherapy. Bevacizumab monotherapy should not be continued without trifluridine-tipiracil

Dose Levels trifluridine-tipiracil (based on the trifluridine component)**:**

Starting dose	Dose level -1	Dose level -2	Dose level -3
35 mg/m^2	30 mg/m^2	25 mg/m^2	20 mg/m^2

- Do not re-escalate trifluridine-tipiracil dose after it has been reduced

- Round trifluridine-tipiracil dose to nearest 5 mg

1. Hematological:

Day 1:

ANC (x 10^9/L)		Platelets (x 10^9/L)	trifluridine-tipiracil	bevacizumab
Greater than or equal to 1.5	and	Greater than or equal to 75	100%	100%
1.0 to less than 1.5	or	50 to less than 75	▪ Delay until ANC 1.5 and platelets 75, then ▪ Restart at previous dose	Delay until trifluridine-tipiracil restarts, then 100%
0.5 to less than 1.0	or	25 to less than 50		
Less than 0.5	or	Less than 25	▪ Delay until ANC 1.5 and platelets 75, then ▪ Reduce one dose level when restarting*	
Febrile neutropenia				

* do not re-escalate dose after it has been reduced

Day 15 (if ordered):

- trifluridine-tipiracil doses are complete on Day 12 of each cycle. Day 15 labs provide guidance regarding trifluridine-tipiracil dose for next cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose for Next Cycle: trifluridine-tipiracil	bevacizumab
Greater than or equal to 1.5	and	Greater than or equal to 75	100% of previous cycle dose	100%
1.0 to less than 1.5	or	50 to less than 75		
0.5 to less than 1.0	or	25 to less than 50		
Less than 0.5	or	Less than 25	Reduce next cycle dose by one dose level*	

* do not re-escalate dose after it has been reduced

2. Renal dysfunction:

- Monitor for increased hematologic toxicity if Creatinine Clearance (CrCl) less than 60 mL/min

CrCl (mL/min)	Trifluridine-tipiracil Dose (Twice Daily on Days 1 to 5 and 8 to 12)	Bevacizumab Dose
Greater than or equal to 60	100%	100%
30 to 59	100%	
15 to 29	20* mg/m^2	
Less than 15	Do not use. No information found.	Do not use without trifluridine-tipiracil

* based on trifluridine component. Reduce dose to 15 mg/m^2 in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2. Do not re-escalate dose after it has been reduced. Permanently discontinue in patients who are unable to tolerate a dose of 15 mg/m^2

3. Proteinuria (bevacizumab):

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)

Degree of Proteinuria	Management
Negative 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

4. Hypertension (bevacizumab):

Blood Pressure (mmHg)	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

- 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.

5. Hepatic dysfunction:

Total bilirubin	Trifluridine-tipiracil Dose	Bevacizumab Dose
Less than or equal to 1.5 x ULN	100%	100%
Greater than 1.5 x ULN	Do not use	Do not use without trifluridine-tipiracil

PRECAUTIONS:

1. **Myelosuppression** can be severe and life-threatening. Fatal events related to neutropenic infection, sepsis, or septic shock have occurred. Monitor closely for signs of infection and treat as indicated.
2. **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.
3. **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 nonsteroidal anti-inflammatory drugs (NSAIDS), including ASA at doses greater than

325 mg/day, should be discontinued prior to institution of bevacizumab. Cyclooxygenase-2 inhibitors (COX-2) inhibitors are permissible. For patients on warfarin, see under Thrombosis.

4. **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.**
5. **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 2 g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
6. **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, angiotensin-converting enzyme (ACE) inhibitors and diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
7. Patients who received **prior radiotherapy** may be at higher risk of hematological and myelosuppression related adverse reaction to trifluridine-tipiracil including febrile neutropenia. Prior chest wall radiation is a risk factor for heart failure, a possible adverse effect of bevacizumab. Caution is advised.
8. **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** 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.

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. Prager GW, Taieb J, Fakih M, et al.; SUNLIGHT Investigators. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med. 2023 May 4;388(18):1657-1667.
2. Trifluridine-Tipiracil (Lonsurf) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies Mar 2024; 4(3): 1-26.
3. CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Review. Provisional Funding Algorithm. Metastatic colorectal cancer. May 2024.